Congreso Solaci, Sao Paolo, Brasil, Julio 2013
Curso Fellow de Cardiologia Intervencionista

Percutaneous Mitral Valve Insufficiency Correction
Where We Are Now?

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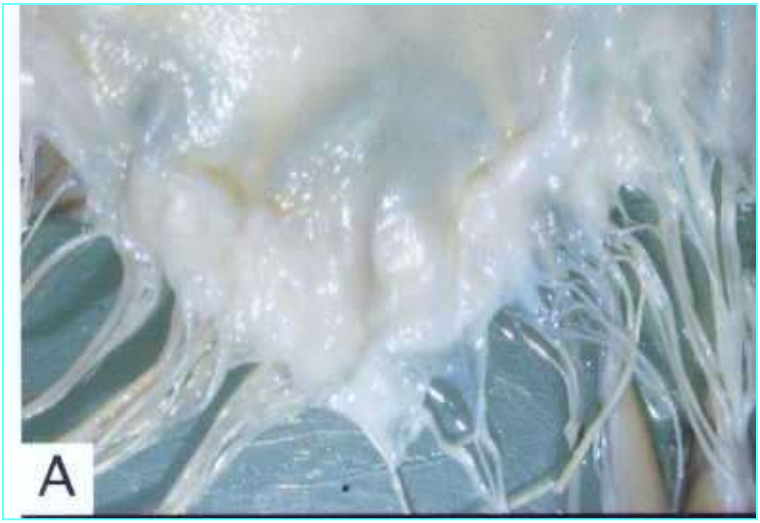
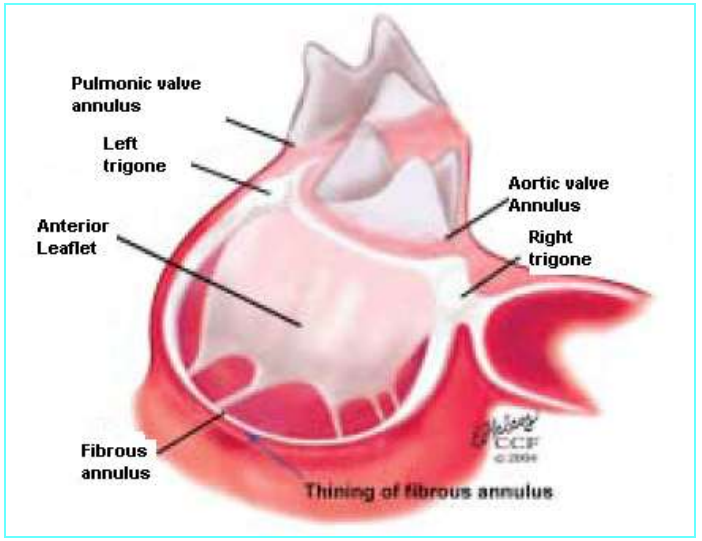
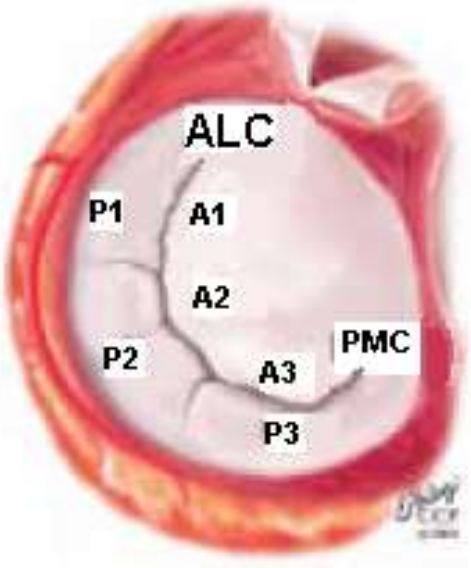
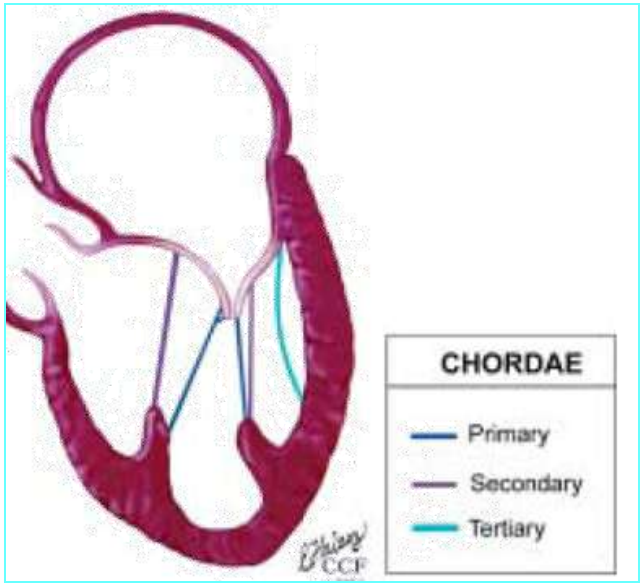
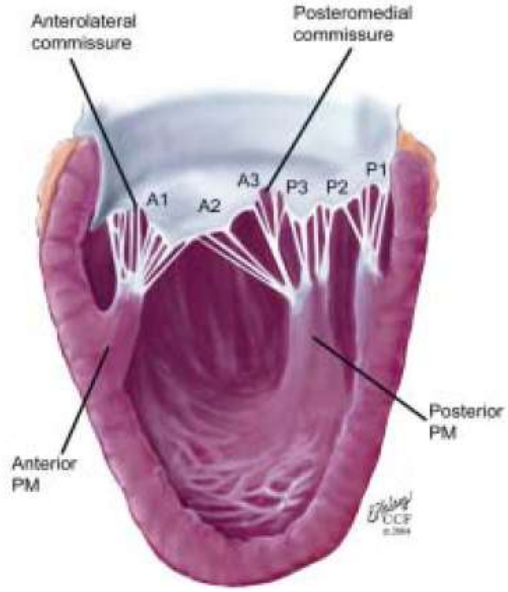
We need to know the anatomy









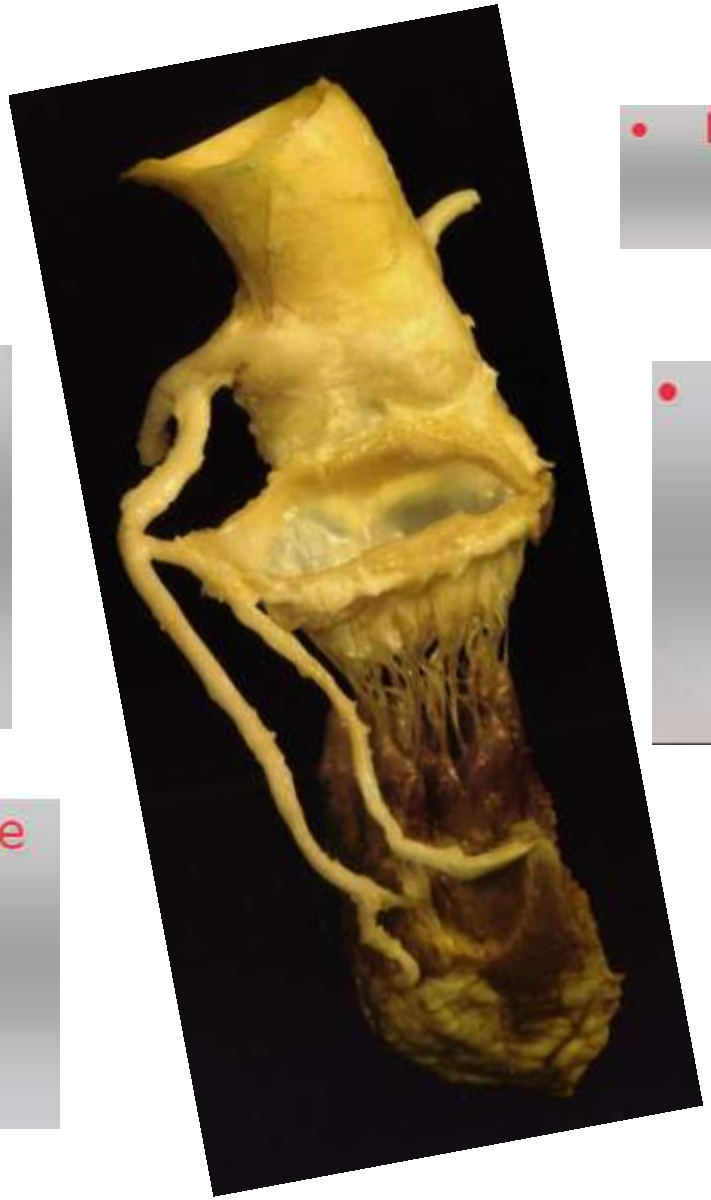


Mechanisms of Mitral Regurgitation

- Mitral Annulus
  - Dilatation
  - Calcification

- Leaflets
  - Perforation
  - Cleft
  - Redundancy
  - Prolapse
  - Thickening
  - Commissural fusion

- Papillary Muscle
  - Elongation
  - Ischemia
  - Fibrosis
  - Rupture
  - Replacement



- LA cavity
  - Posterior wall distension
  - Lack of contraction

- Chordae Tendineae
  - Abnormal insertion
  - Elongation
  - Shortening
  - Rupture
  - Fusion
  - Thickening

- LV Free Wall
  - Lateral distension
    - Ischemia

Mitral Regurgitation

Mitral regurgitation (MR) results from a lack of leaflet coaptation between the two leaflets of the mitral valve—the valve found between the left atrium and left ventricle of the heart. In a normally functioning mitral valve, blood flows in a single direction between the left atrium and left ventricle. MR is characterized by systolic retrograde flow from the left ventricle into the left atrium. Over time, MR may lead to heart failure.

Causes

- Degenerative MR (also known as primary or organic MR), is usually caused by an anatomic defect of one or more structures comprising the mitral valve apparatus.
- Functional MR (also known as secondary MR), is the result of left ventricular (LV) dysfunction and dilation, which causes otherwise normal valve components to fail and produce MR.

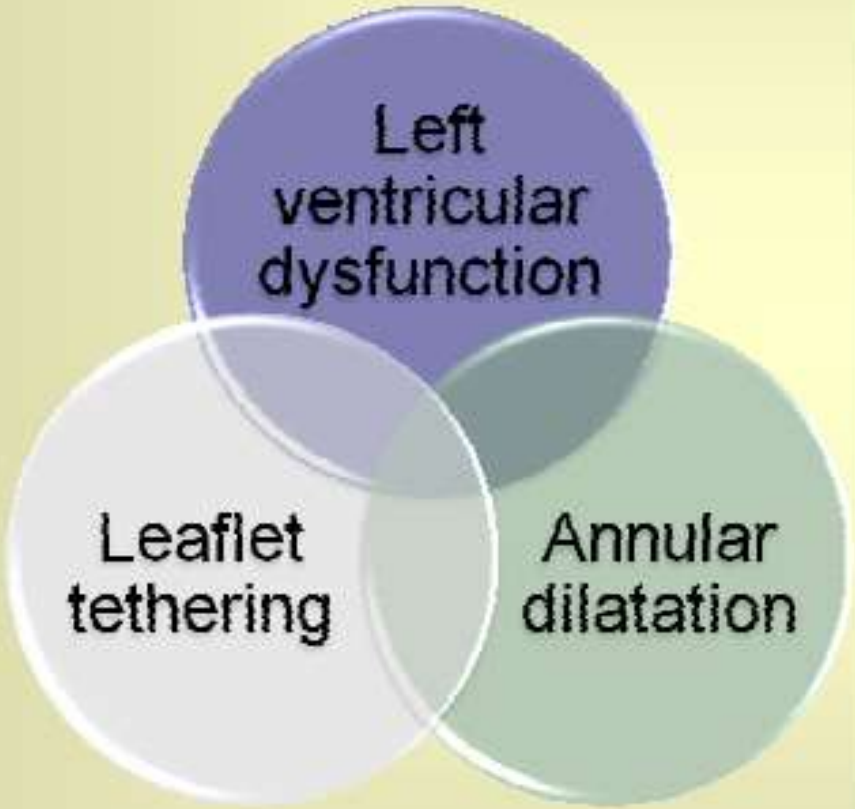
Treatment Options

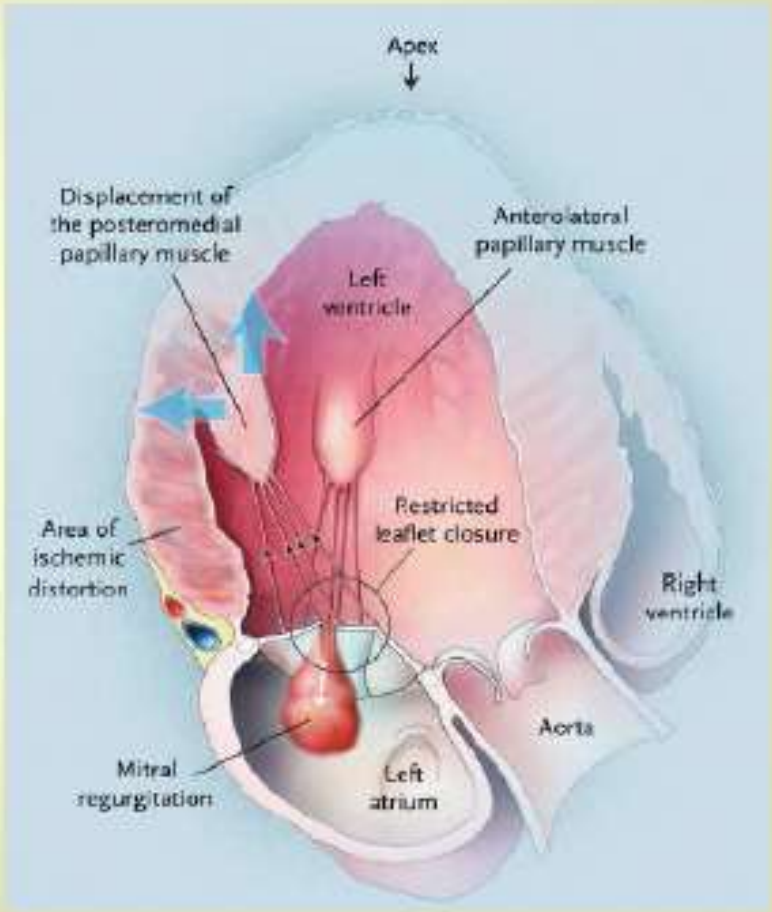
Medical: There are no medications that are indicated to treat MR, but there are medications used to manage patient symptoms.

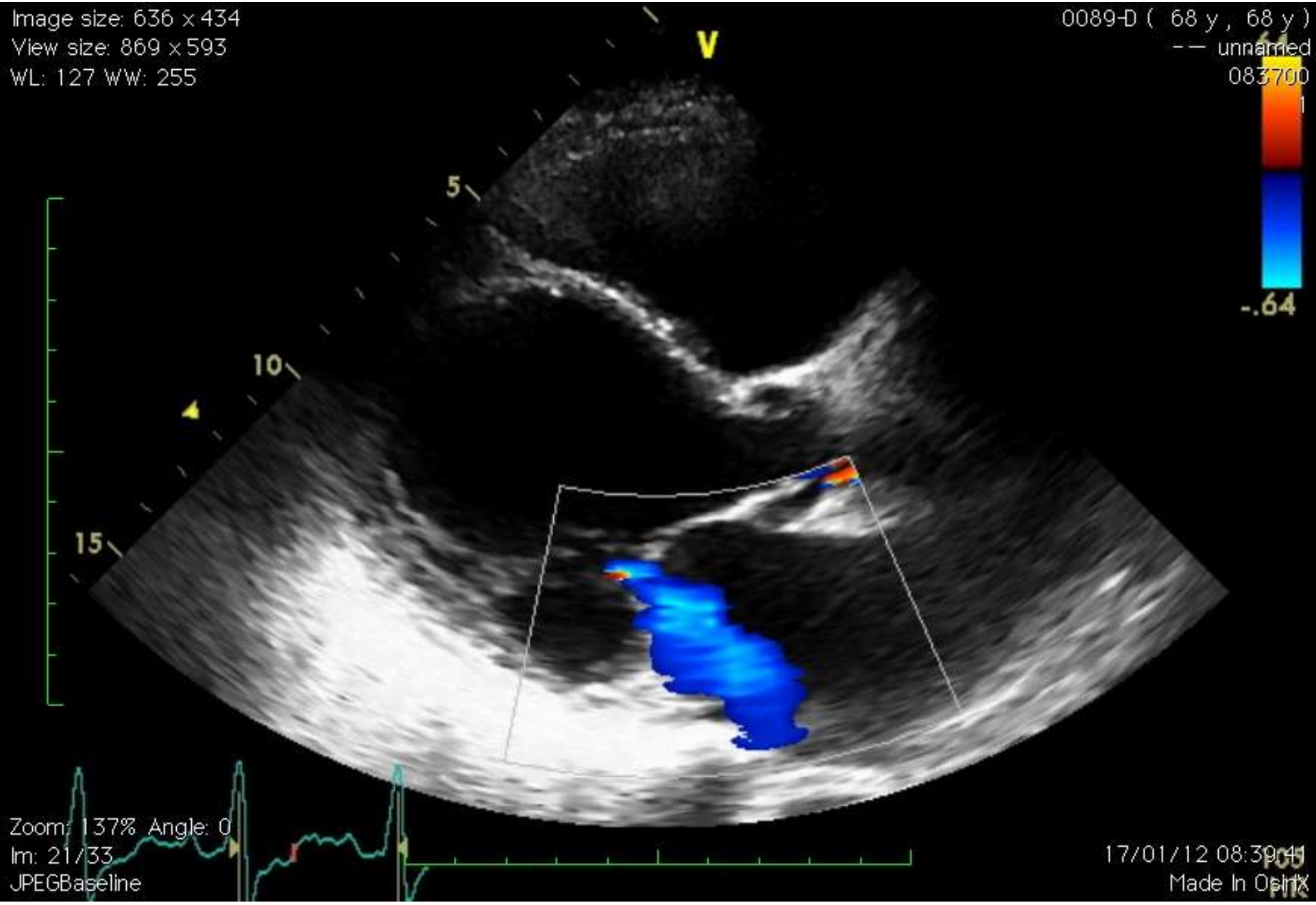
Surgical: For symptomatic patients diagnosed with moderate–severe or severe MR, surgery is generally recommended to repair or replace the mitral valve. Mitral valve repair or replacement typically involves open-heart surgery while on cardiopulmonary bypass. Patients recovering from mitral valve surgery may take several months to regain normal physical function and activity.

Percutaneous mitral valve repair: The MitraClip procedure is a minimally invasive catheter-based therapy. This new treatment increases the options for selected patients with MR. It has been shown to reduce MR, reverse left ventricular remodeling, improve NYHA functional class, and improve quality of life.[6]

Functional Mitral Regurgitation: A combination of many factors



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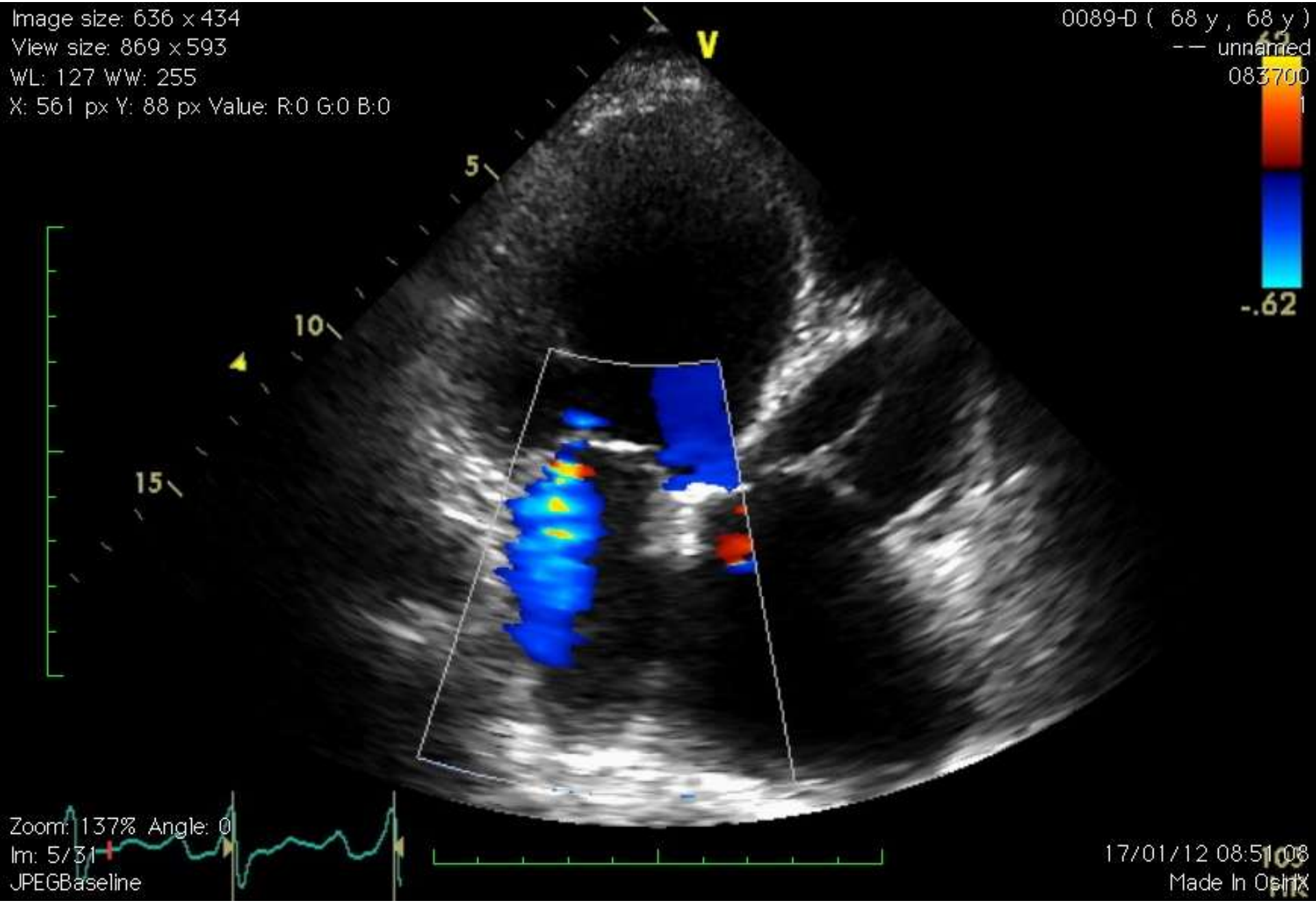
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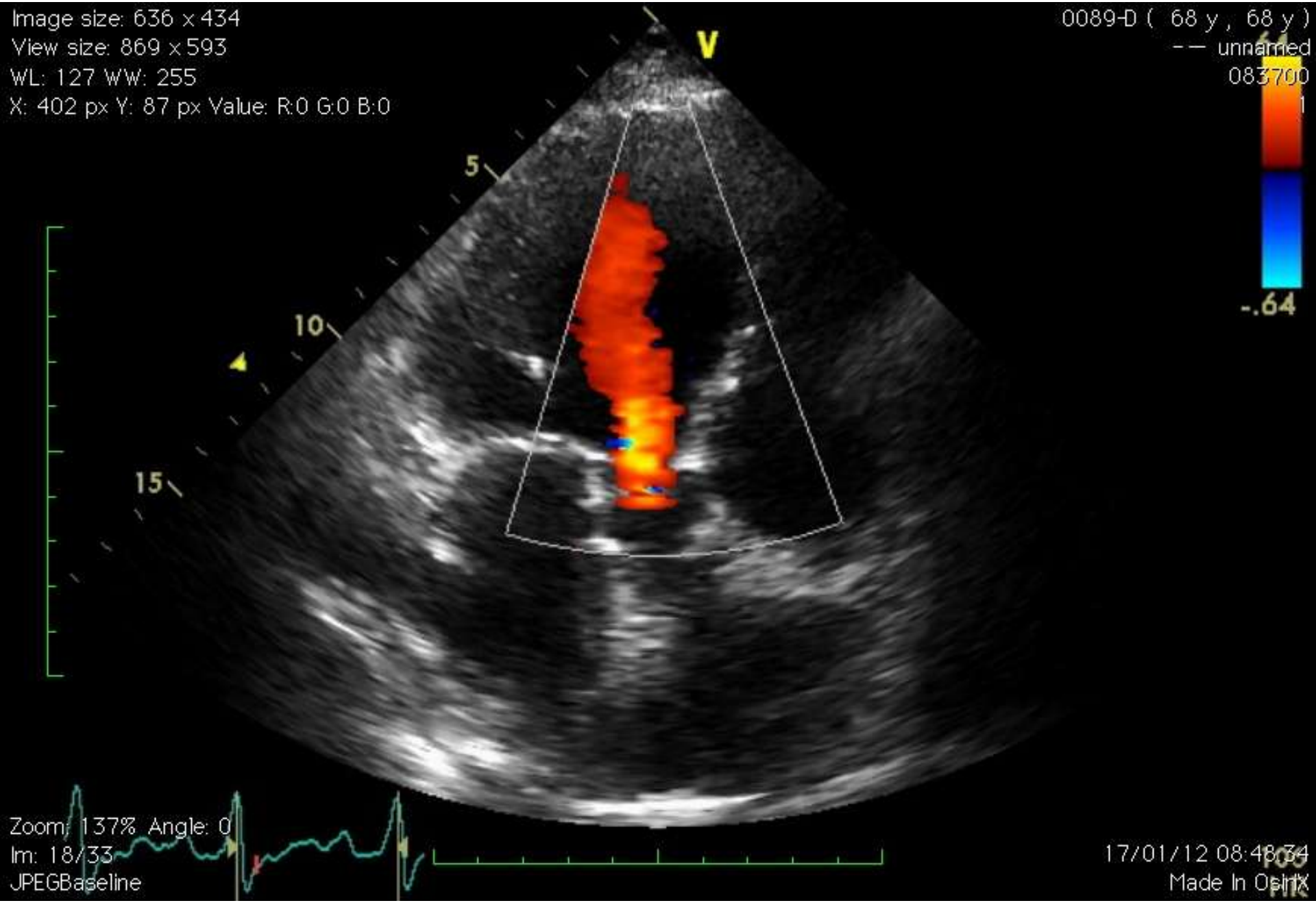
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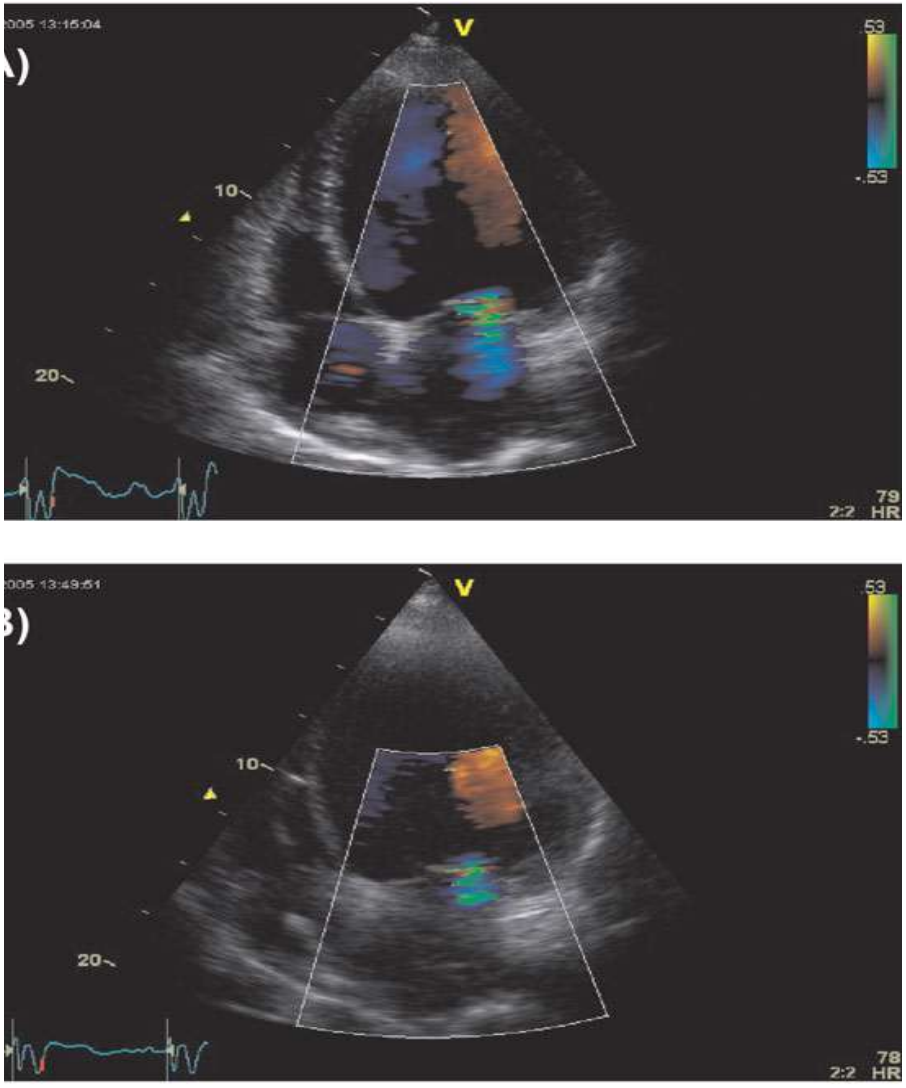
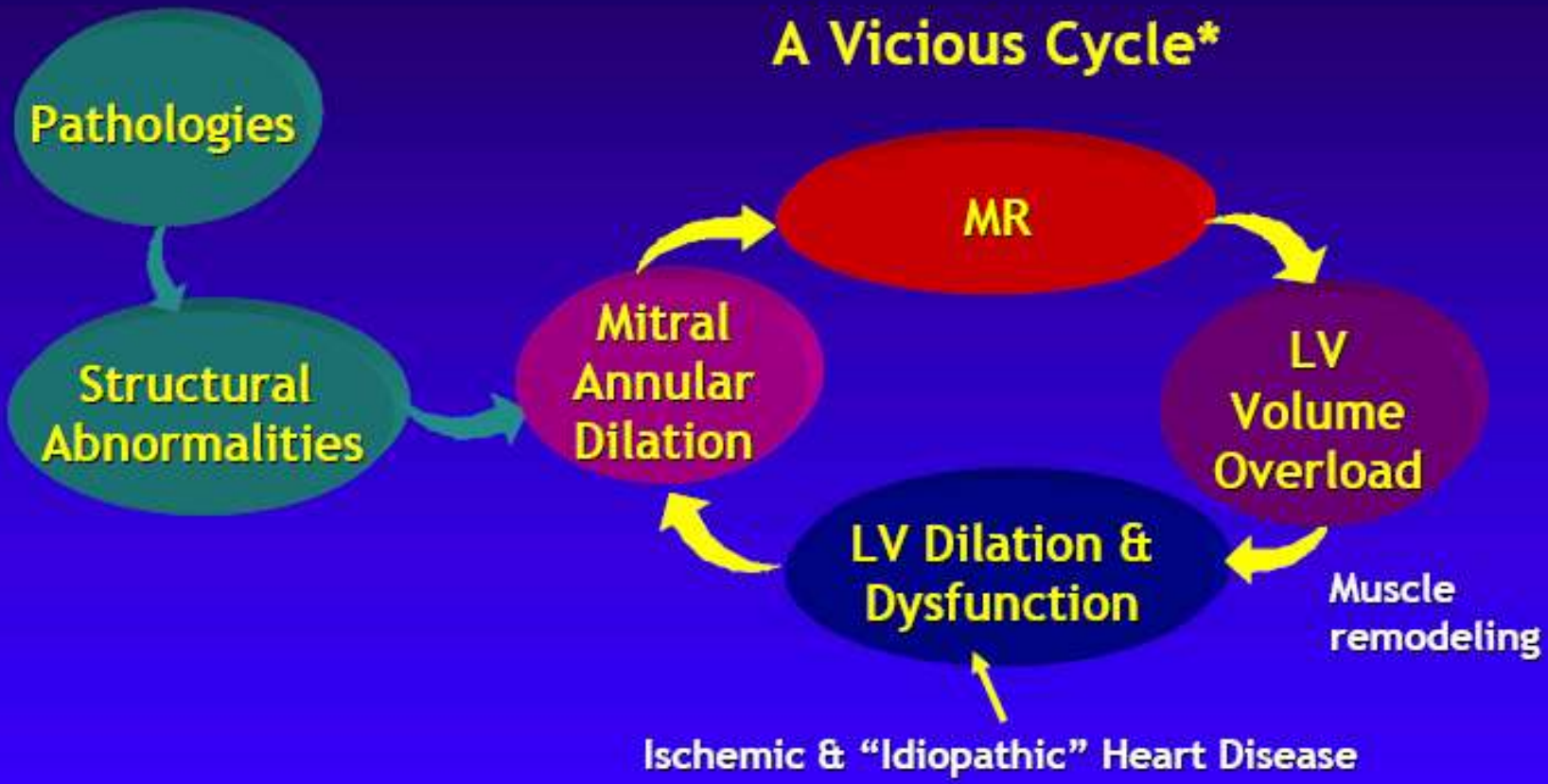
Mitral regurgitation with RCT



C Ypenburg et al. European Heart Journal (2008) 29. 757-765

Clinical Background: Relationship Between (MR) & CHF

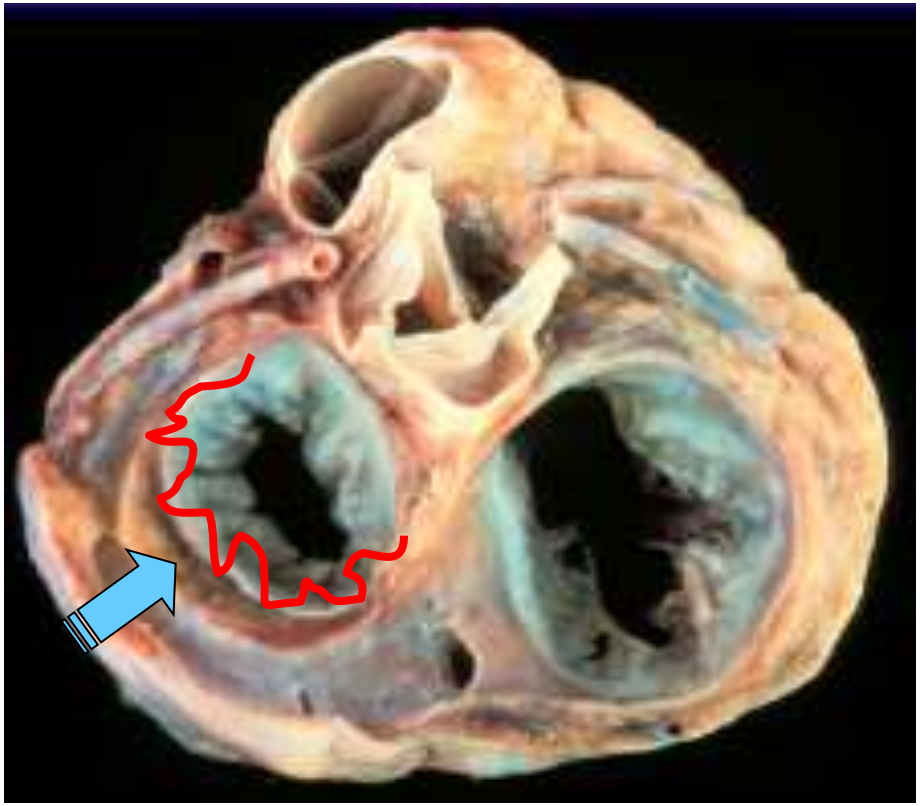


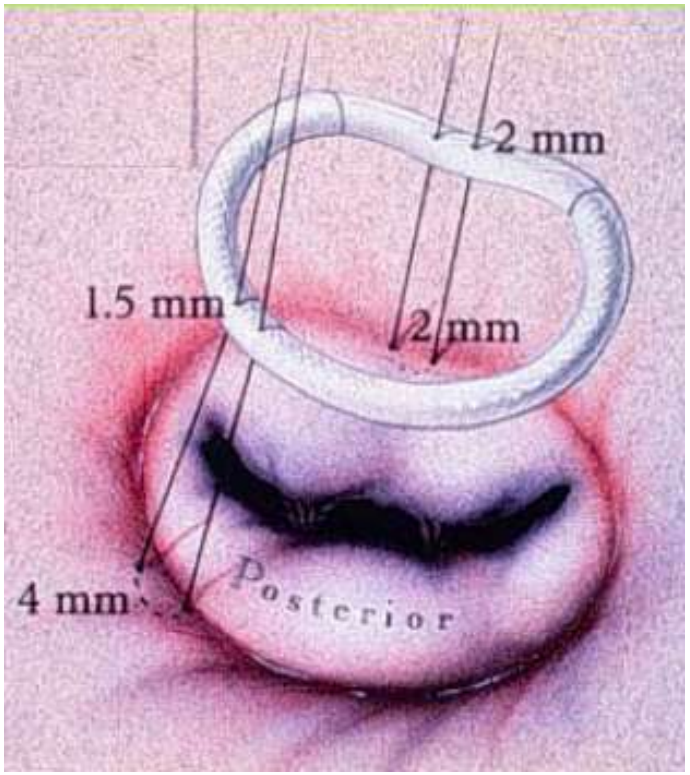
MR: independent predictor of mortality in pts with LV dysfunction

Mitral Valve Repair

- Mitral valve replacement (68% of cases)
  - Biological or mechanical prosthesis
- Mitral valve repair (32%) including one or more of the following:
  - Repositioning and reshaping of the leaflets
  - Annuloplasty
  - Edge to Edge repair technique
  - Replacement or repair of the chordae
  - Manipulation of the papillary muscles
- These options require open arrested heart surgery.

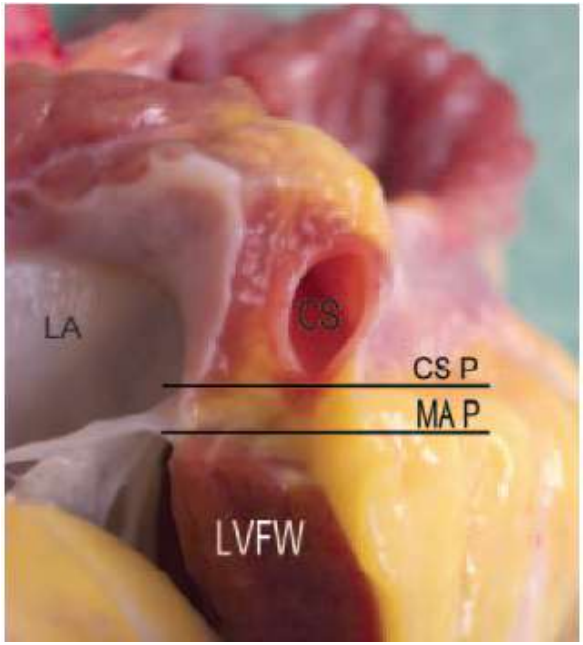
Mitral Annuloplasty Rings





- Reduce posterior annular circumference
- Push posterior leaflet forward for better coaptation

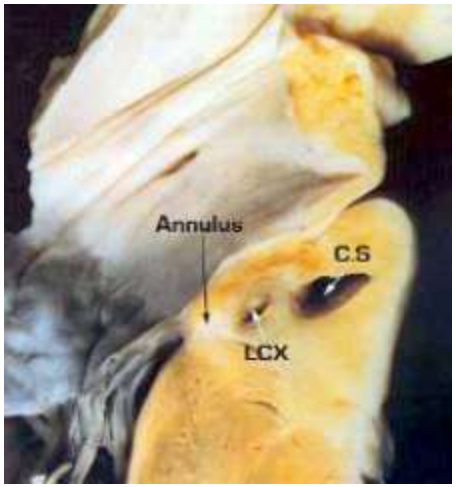
Distance between CS and MVA

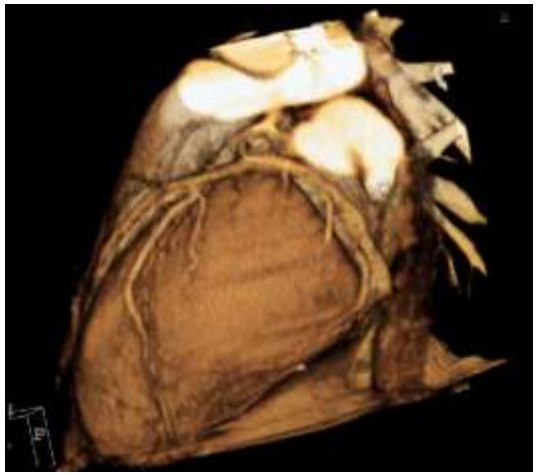


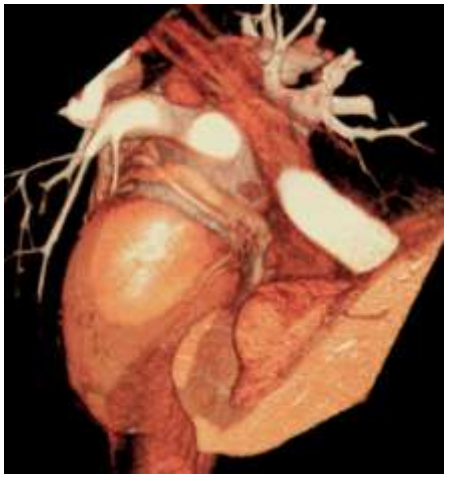
Proximal 5,7 ± 3.3 mm

Distal 9.7 ± 3.2 mm

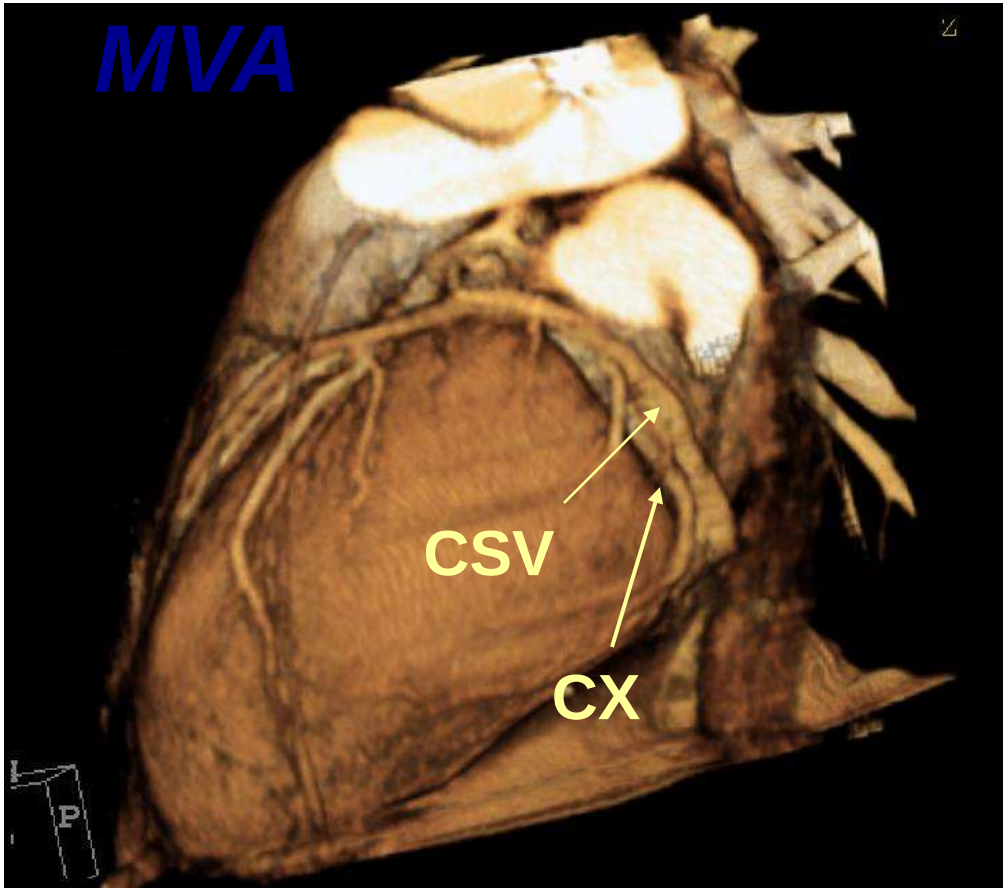
Maselli et all Circulation 2006;114:377-380

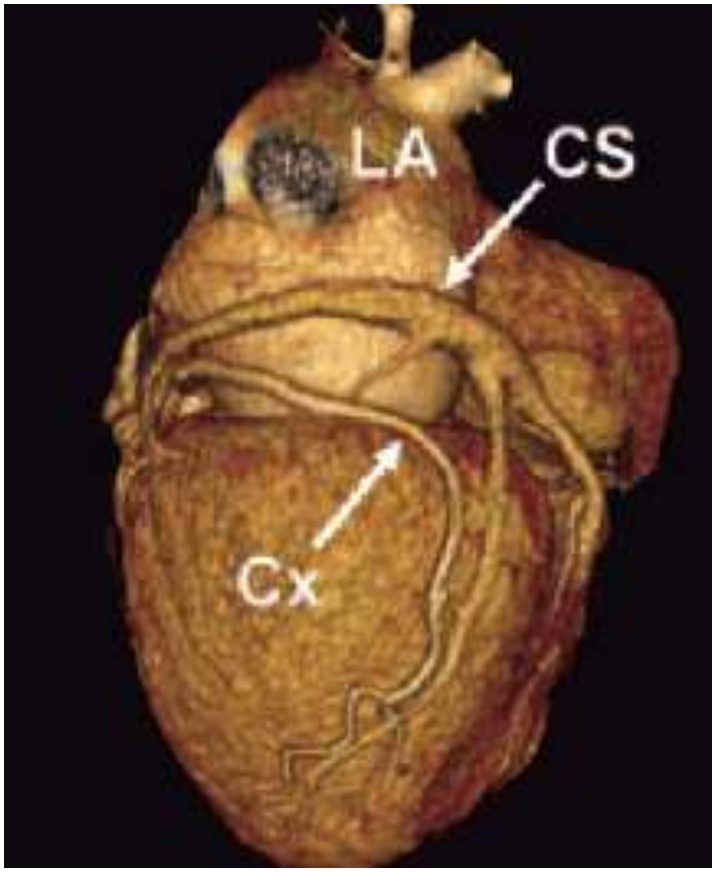






LCX course between CS and MVA





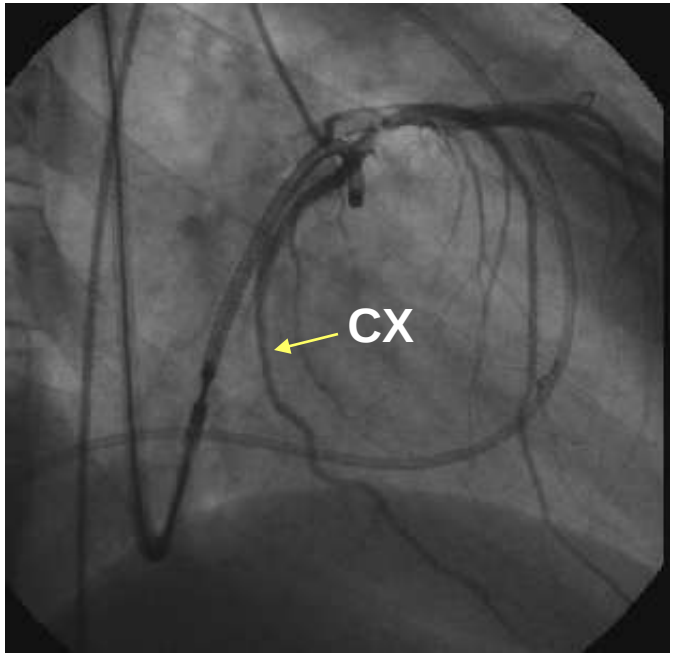
63.9% in 61 Cadaveric Human Heart,

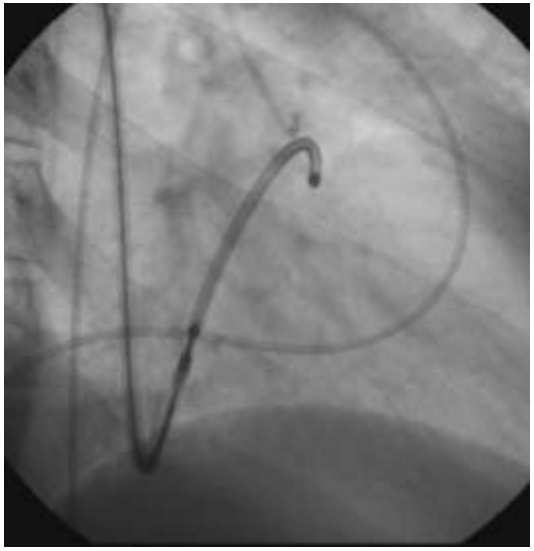
Maselli et all Circulation 2006;114:377-380

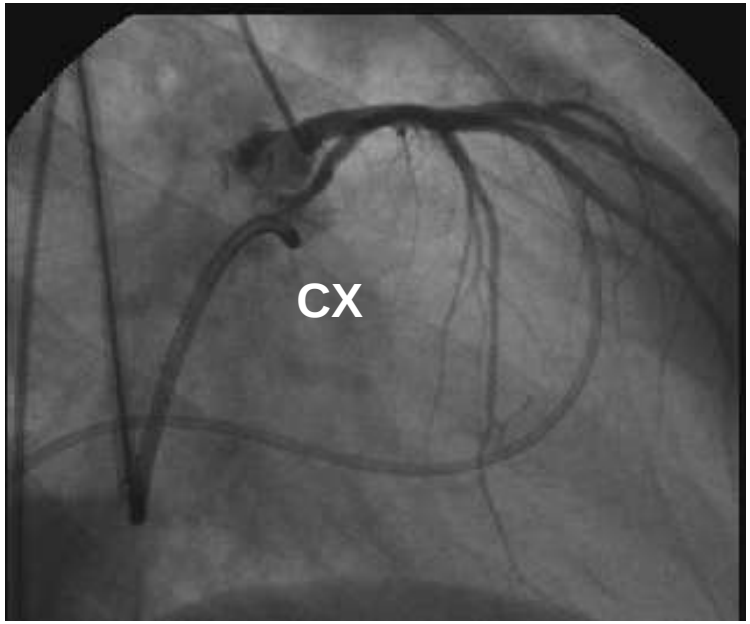
68% IN 105 Human Heart By MSCT,

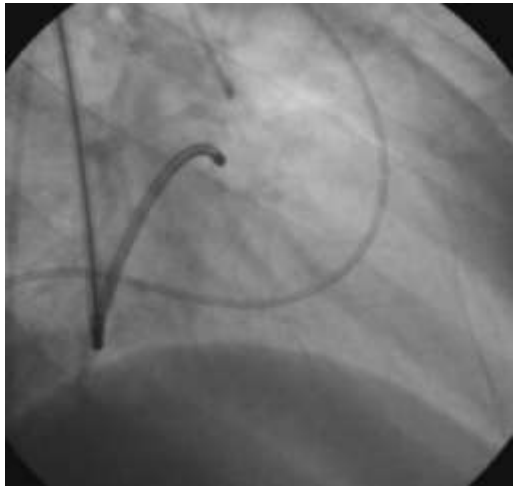
Tops et al, Circulation. 2007;115:1426-1432

Coronary left Circunflex, cinching and ocluded

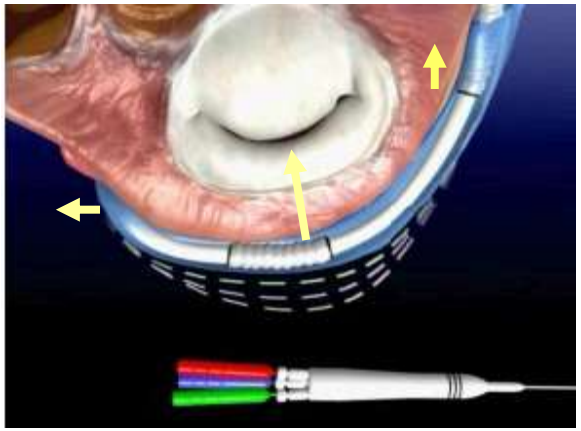




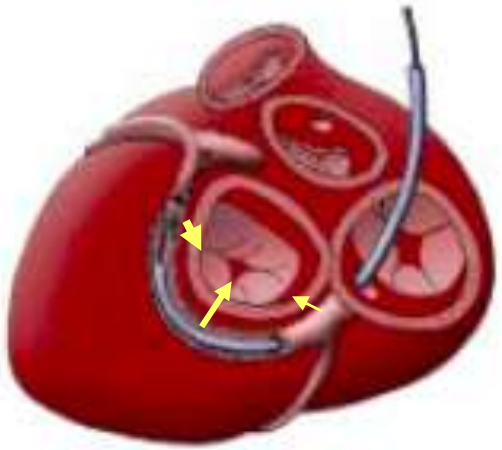


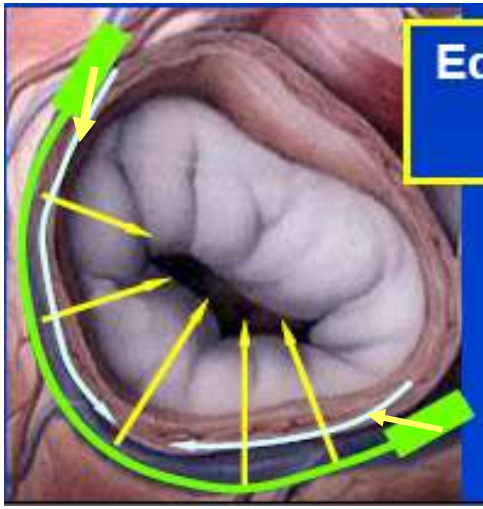


VIACOR



CARDIAC DIMENSIONS

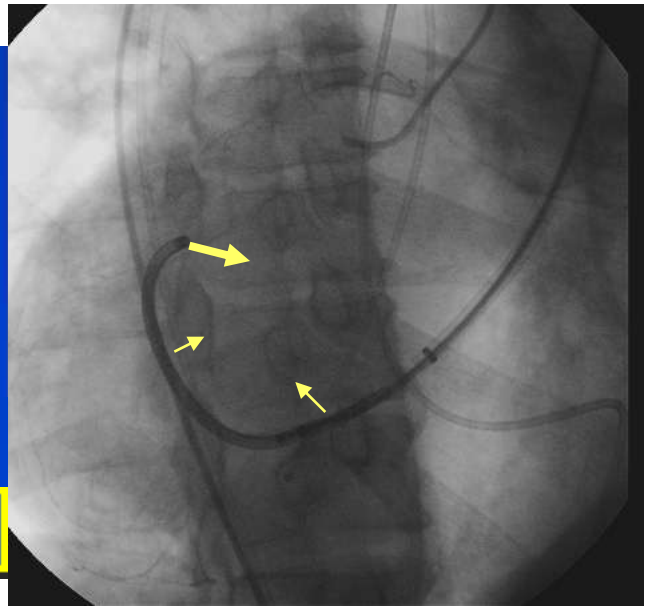




Edwards Life Sciences:

Stent Collar

Mitral Life: Annular ring

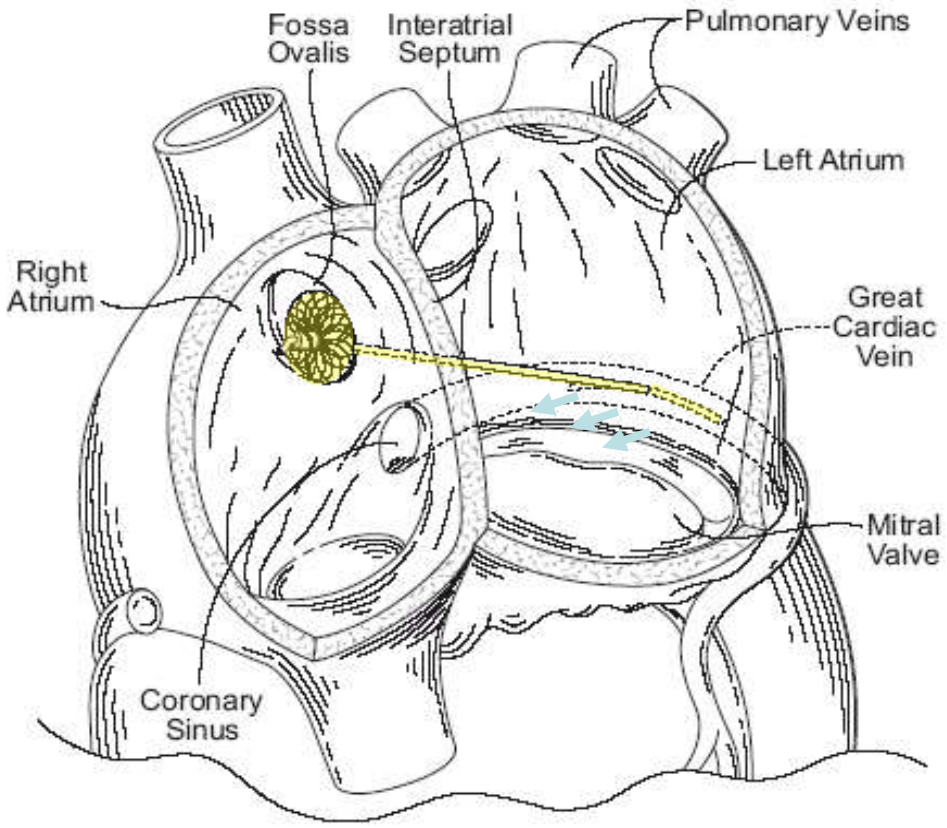


Percutaneous Treatment of Mitral Regurgitation

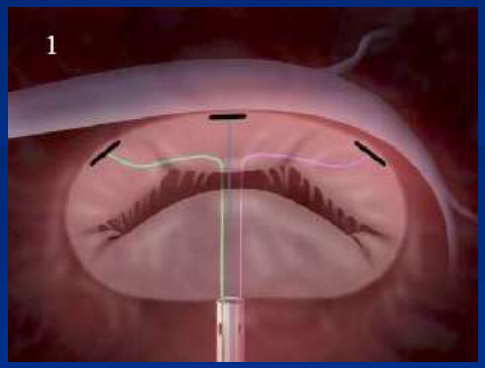
- Issues with CS approach
  - Ability to reduce annulus (CS over LA)
    - Mitral annular calcification?
    - Worsened leaks at commisures
  - Potential pinching of circumflex coronary artery
  - Risk of CS thrombosis/occlusion
  - Risk of CS erosion/perforation over long term
  - Very congested IP space

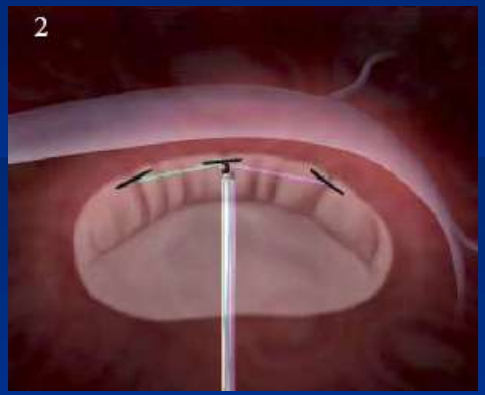
The PS³ System

Percutaneous
Septal-**S**inus **S**hortening

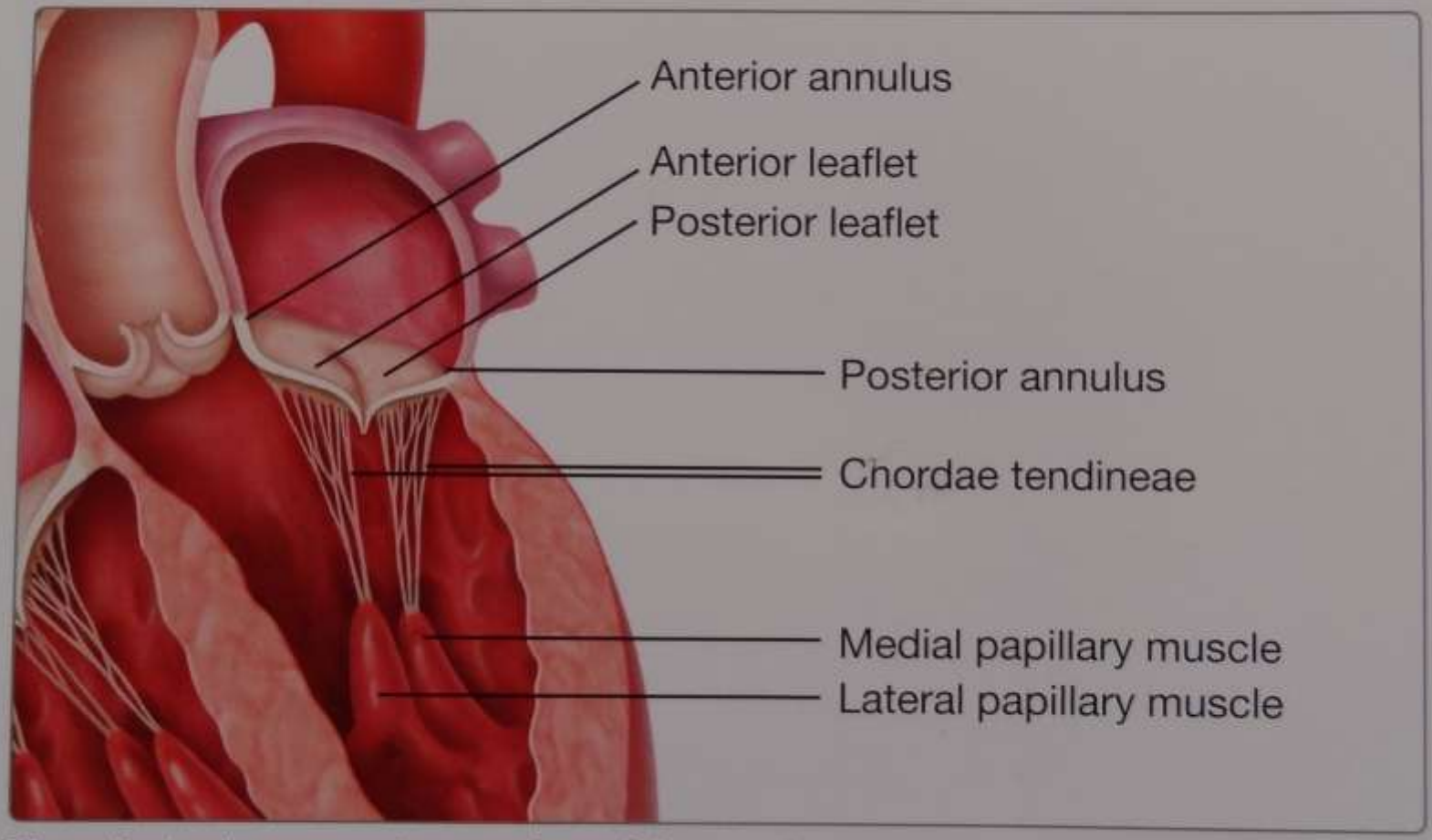


Transventricular suture-based approach

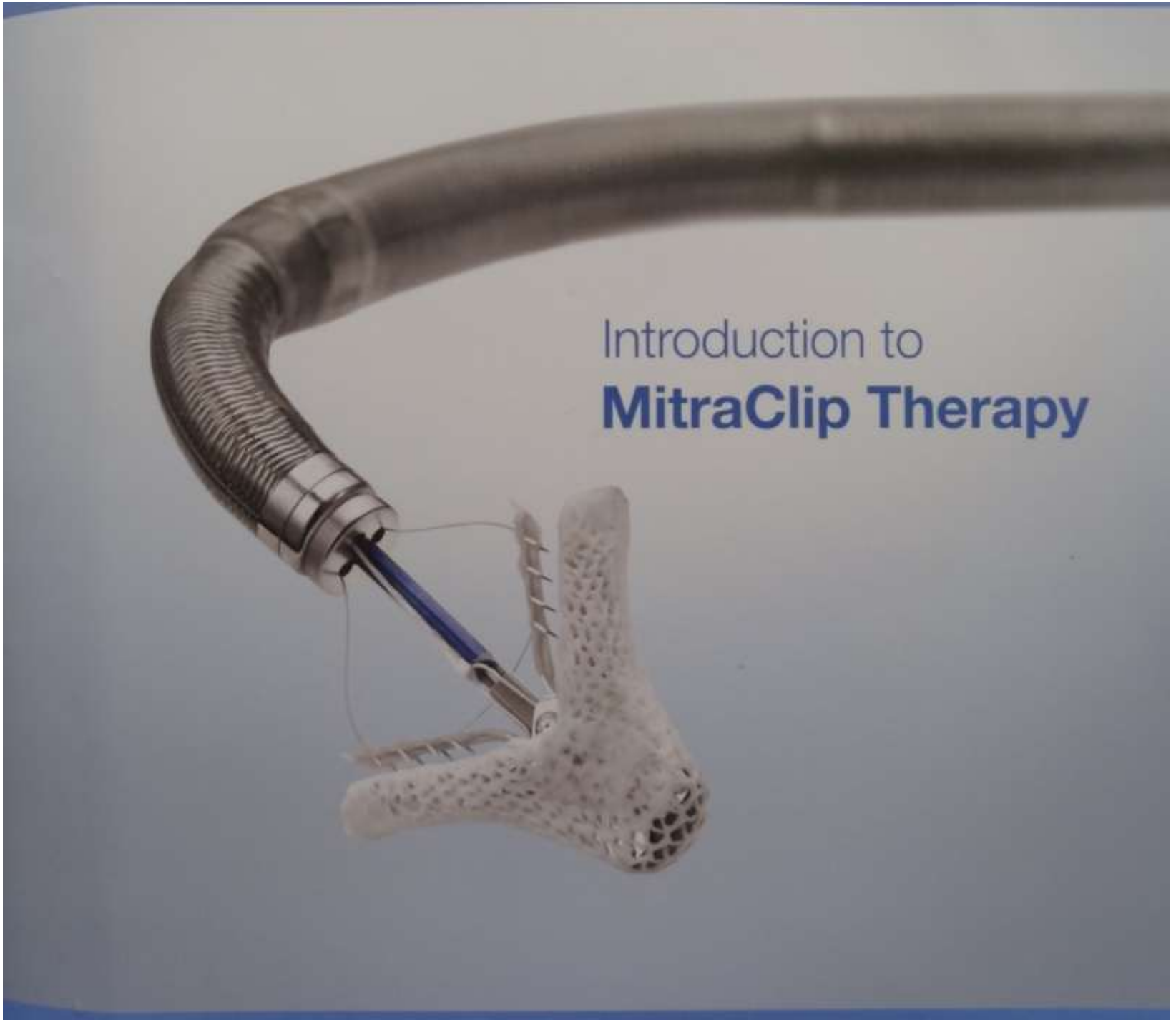




Mitral Valve Anatomy

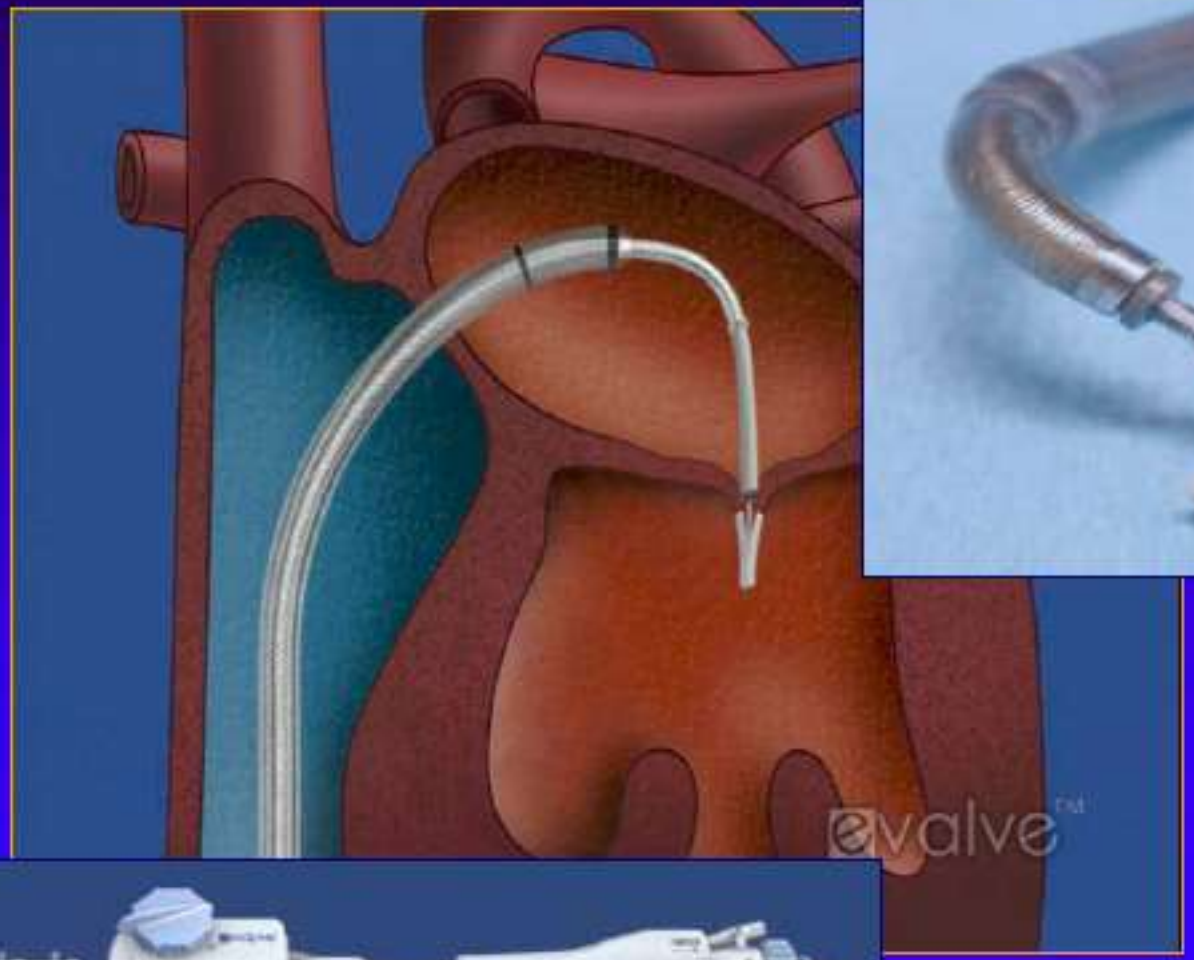


The mitral valve apparatus consists of the annulus, the leaflets, the chordae tendineae, and papillary muscles.

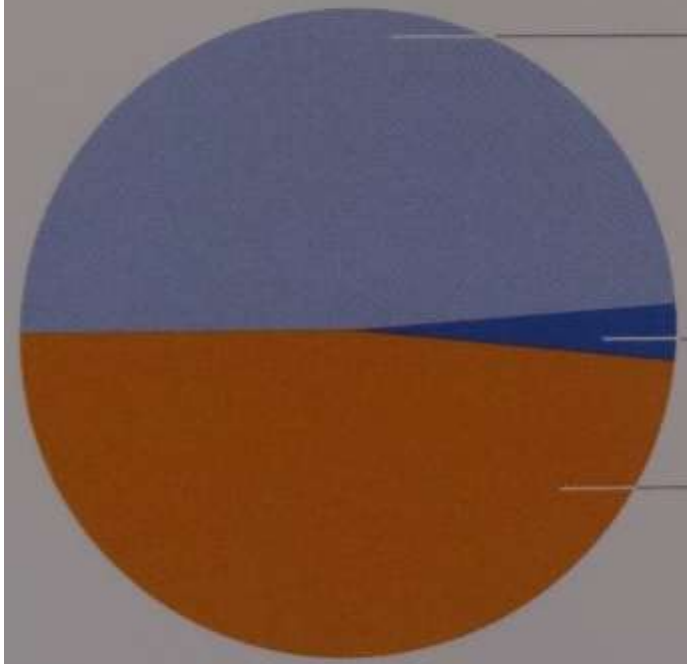

Introduction to
MitraClip Therapy

Evalve : Edge to Edge Mitral Valve

Endovascular Mitral Repair System



U.S. MR Patient Population (2009) [1,7-11]



N=1,740,000

Surgical Candidates 49%

Of surgical candidates, up to 50% of patients are not referred to surgery, even if a surgical indication exists[3-5]

Surgical Patients 2%

High-Risk Patients* 49%

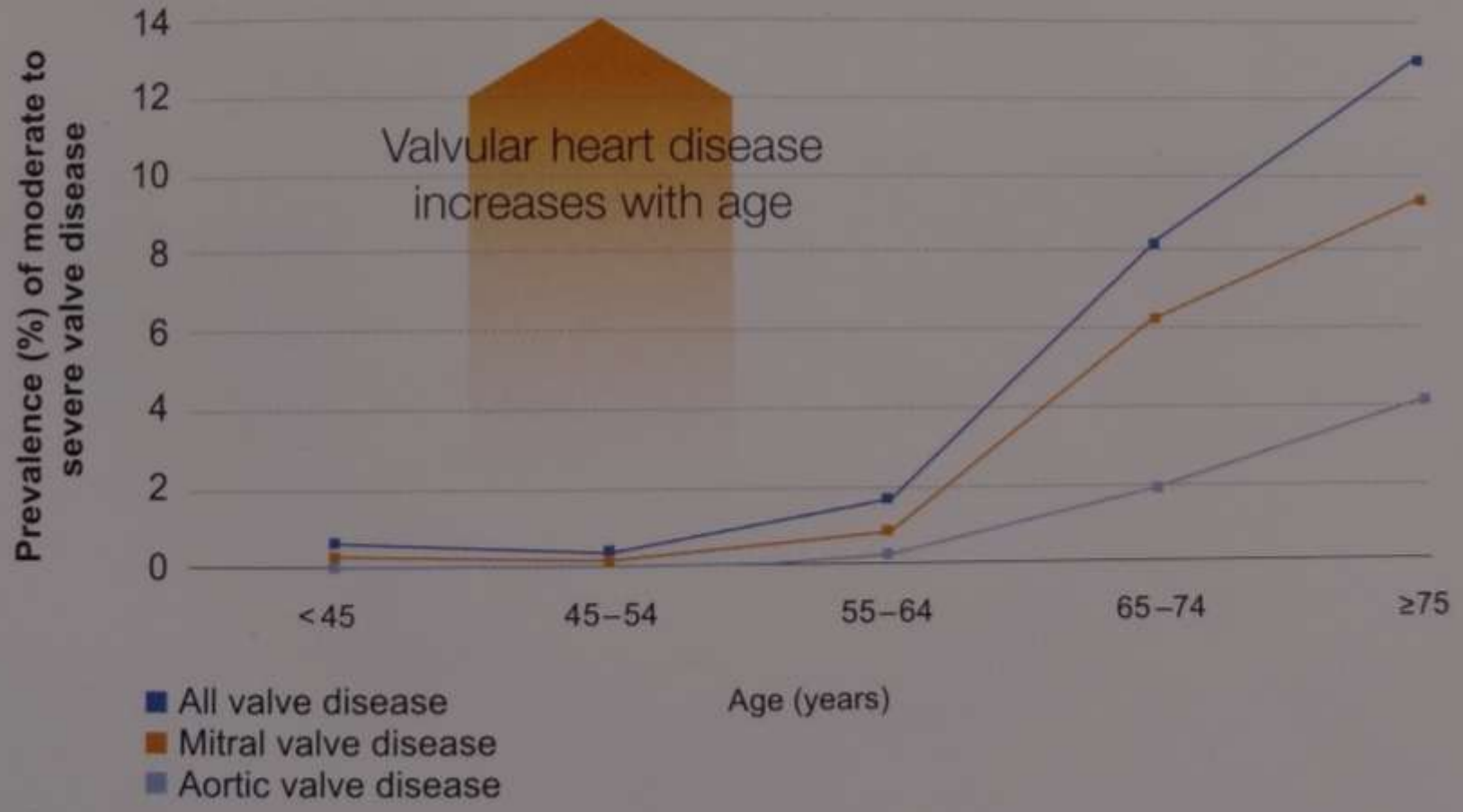
Factors prohibiting surgery include impaired LVEF, high operative risk, multiple comorbidities and advance age[4]

* High risk was defined as patients with EF <35% and/or age of 75+.

Unmet Need

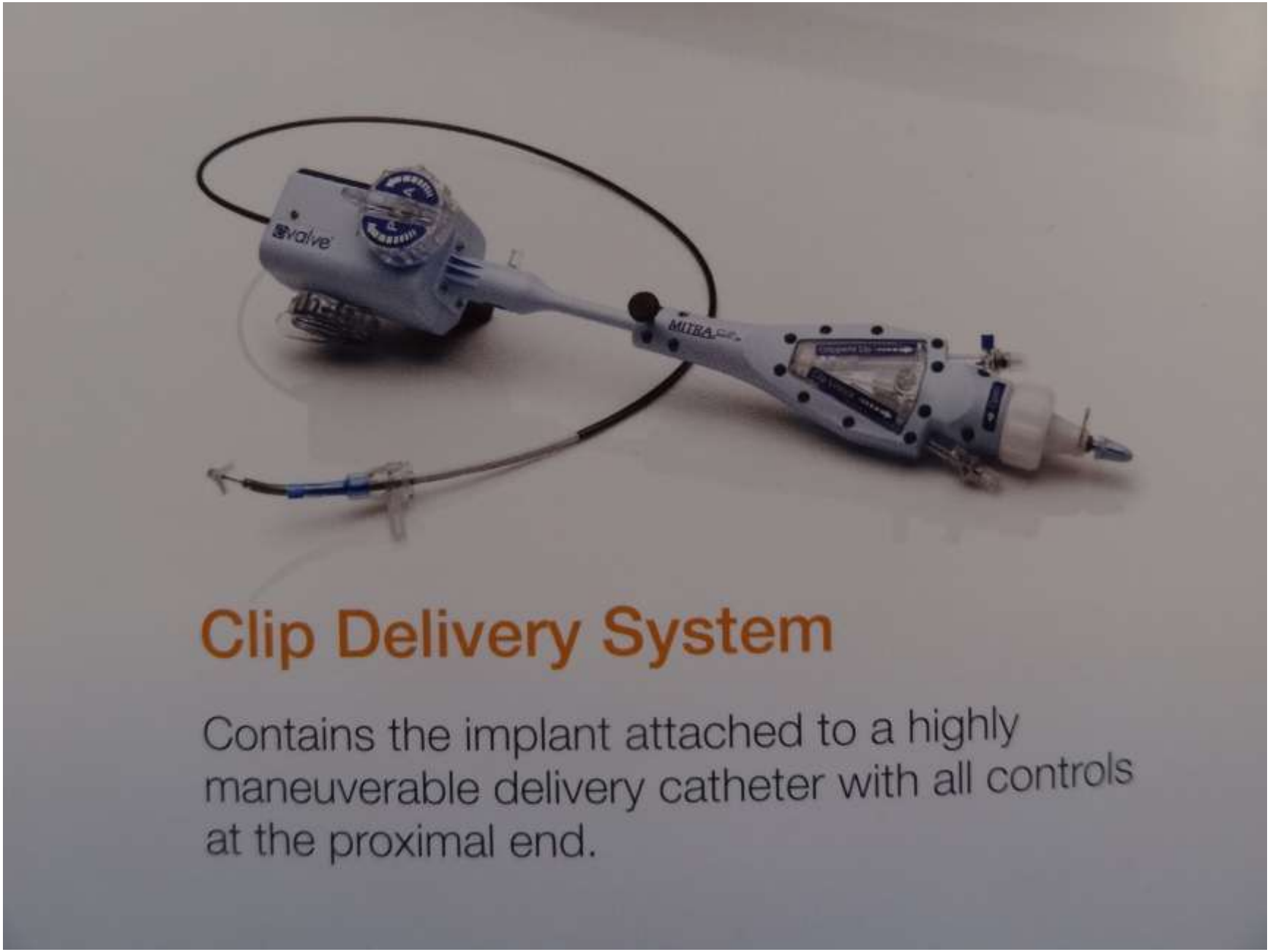
Although moderate to severe MR is common, it is an undertreated disease. In 2009, only approximately 2% of the estimated 1.7 million patients with MR ≥ 3+ were treated with surgical intervention.[1,8-11] Reasons for denying surgery include impaired left ventricular ejection fraction (LVEF), multiple comorbidities, and advanced age, all of which are determinants for high operative risk.[3,7]

Prevalence of Valvular Heart Disease by Age



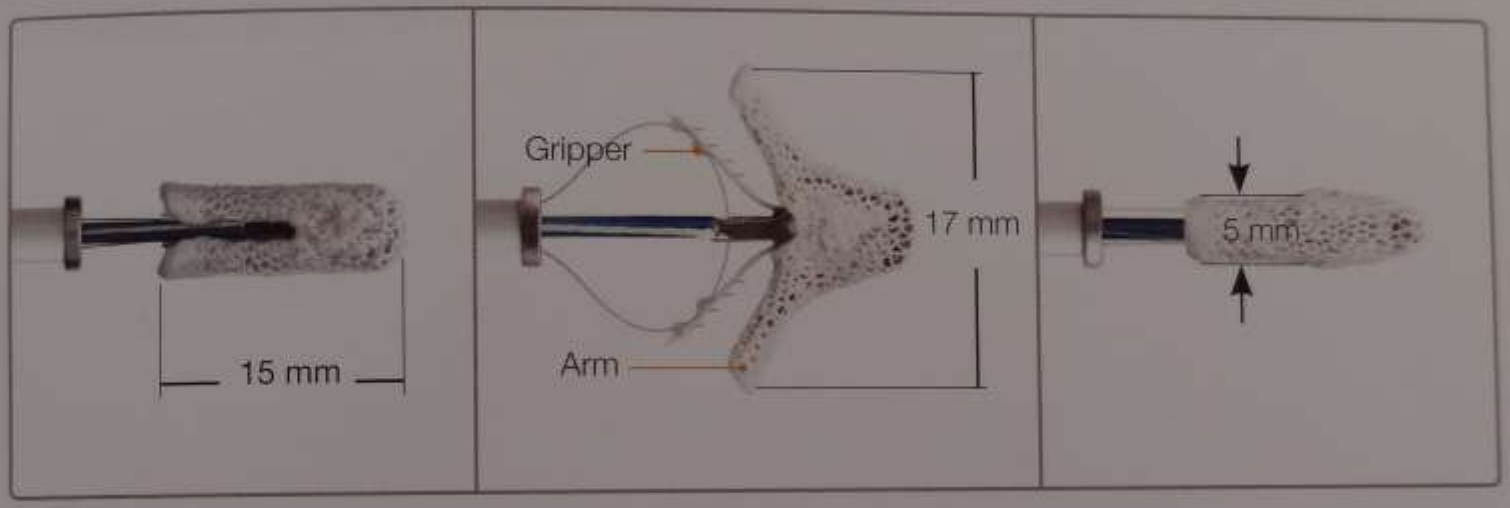
Steerable Guide Catheter

- 24 French steerable catheter
- Percutaneous venous access



Clip Delivery System

Contains the implant attached to a highly maneuverable delivery catheter with all controls at the proximal end.



MitraClip Device (Implant)

- Cobalt chromium construction
- Polyester cover designed to promote tissue growth
- Magnetic resonance conditional to 3 Tesla*

* Static magnetic field up to 3 Tesla; maximum spatial gradient in static field of 2500 gauss/cm or less; maximum whole–body averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of scanning.

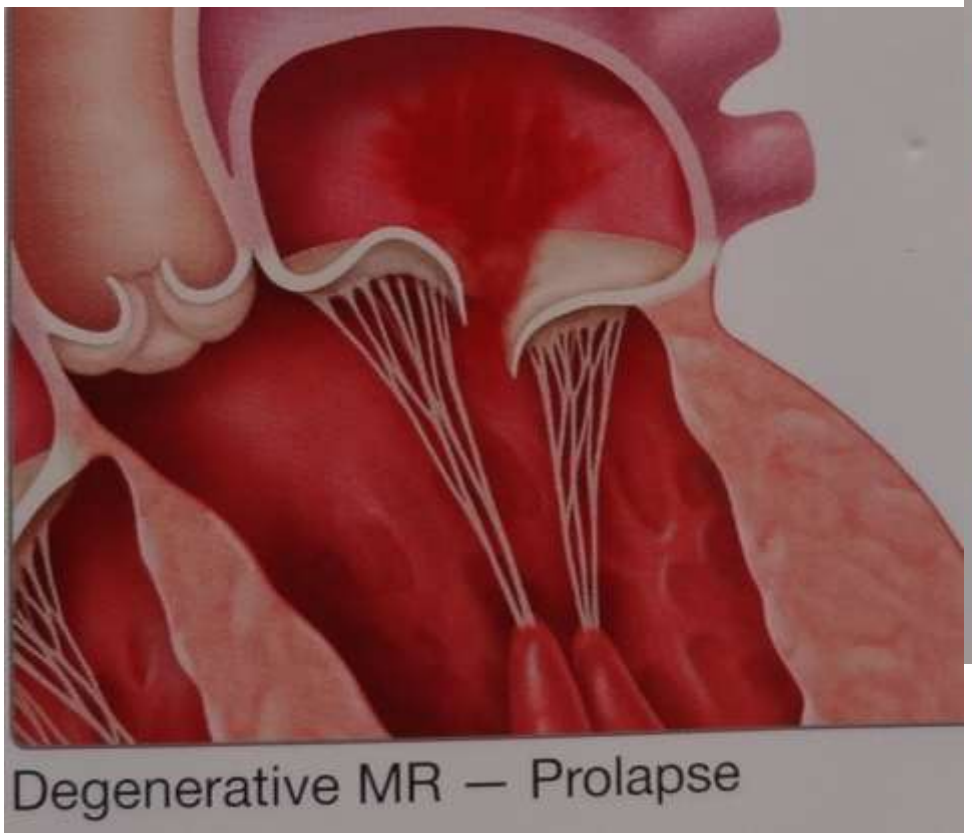
MitraClip System

The MitraClip System performs **percutaneous mitral valve repair** by creating a vertical line of coaptation, forming a double-orifice valve.

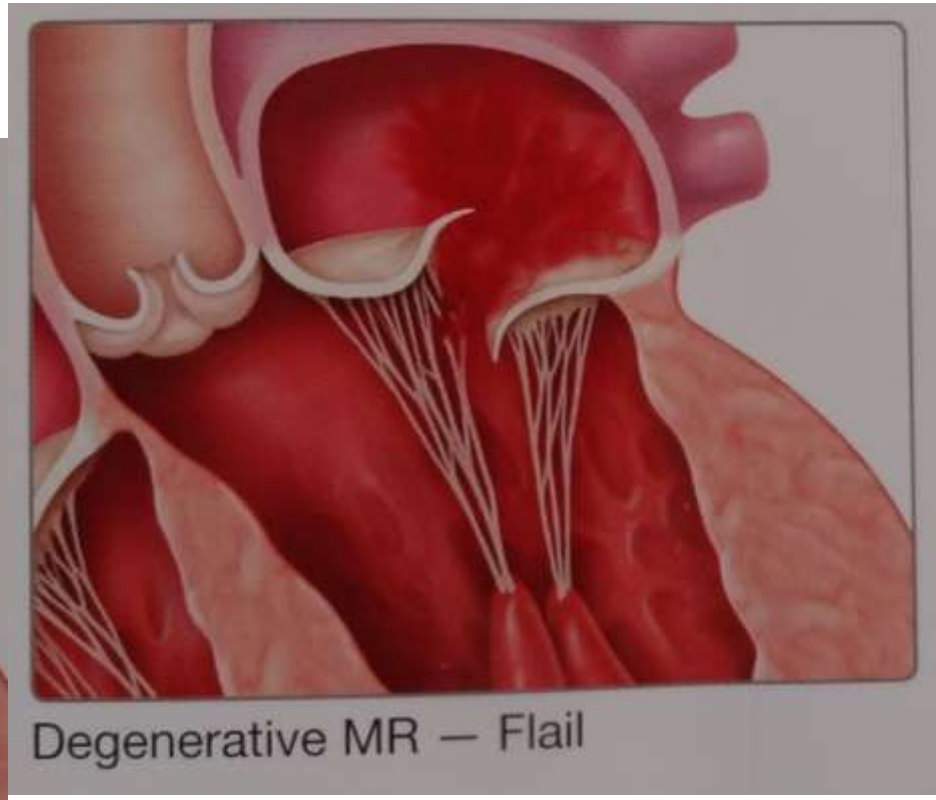
- Beating heart procedure—no cardiopulmonary bypass
- Allows for real-time positioning and repositioning to optimize MR reduction
- Designed to preserve surgical options

- The following considerations should be accounted for:
  - TEE probe will be in place for an extended period of time
  - Intubation under general anesthesia
  - 24 French sheath in right femoral vein
  - Bladder/urinary catheter in place
  - Heparinization during procedure to ACT > 250
- System is prepared by removing all the air in the lumens of the Clip Delivery System and Steerable Guide Catheter
- System is functionally tested prior to use

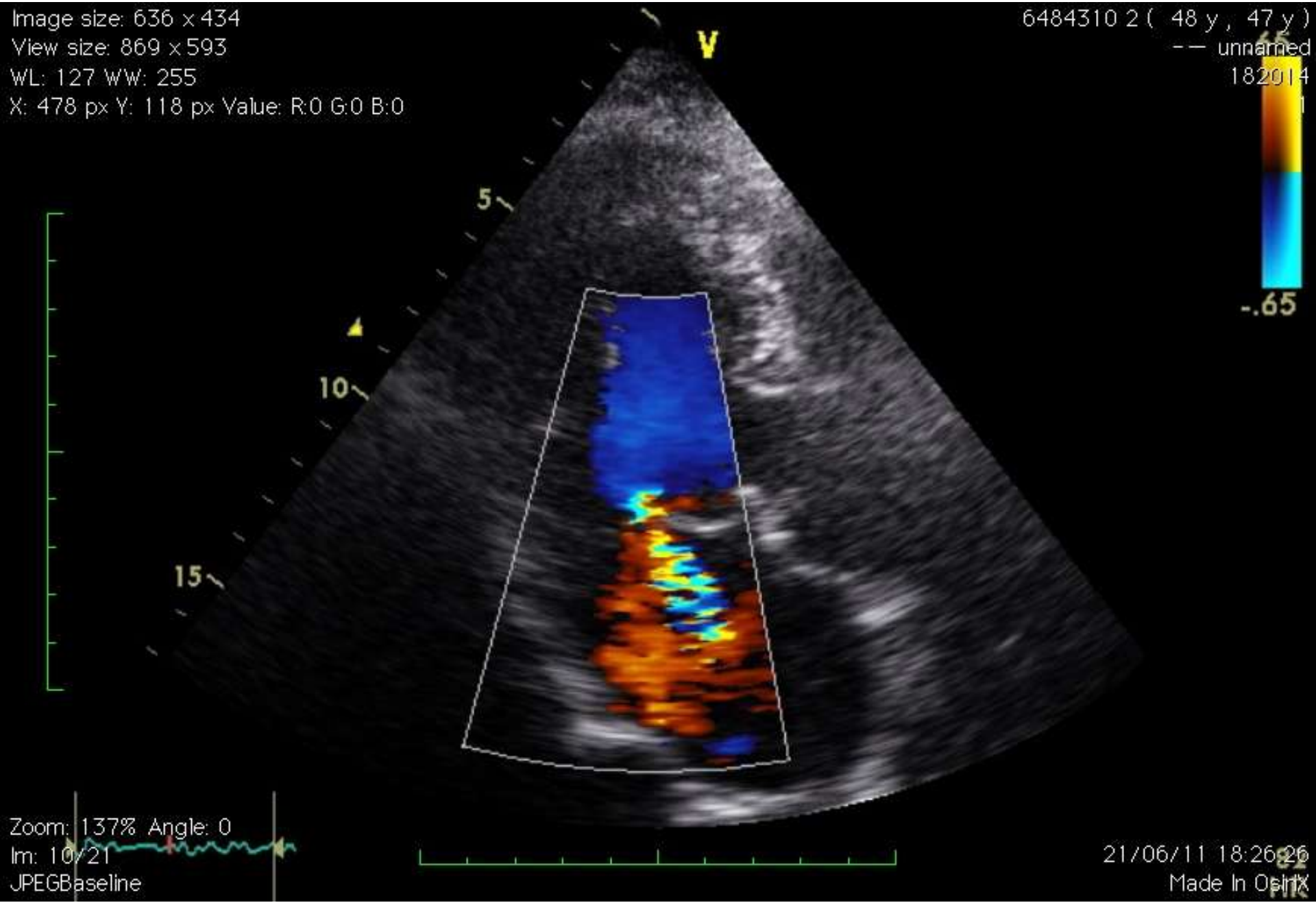
Degenerative MR



Degenerative MR — Prolapse



Degenerative MR — Flail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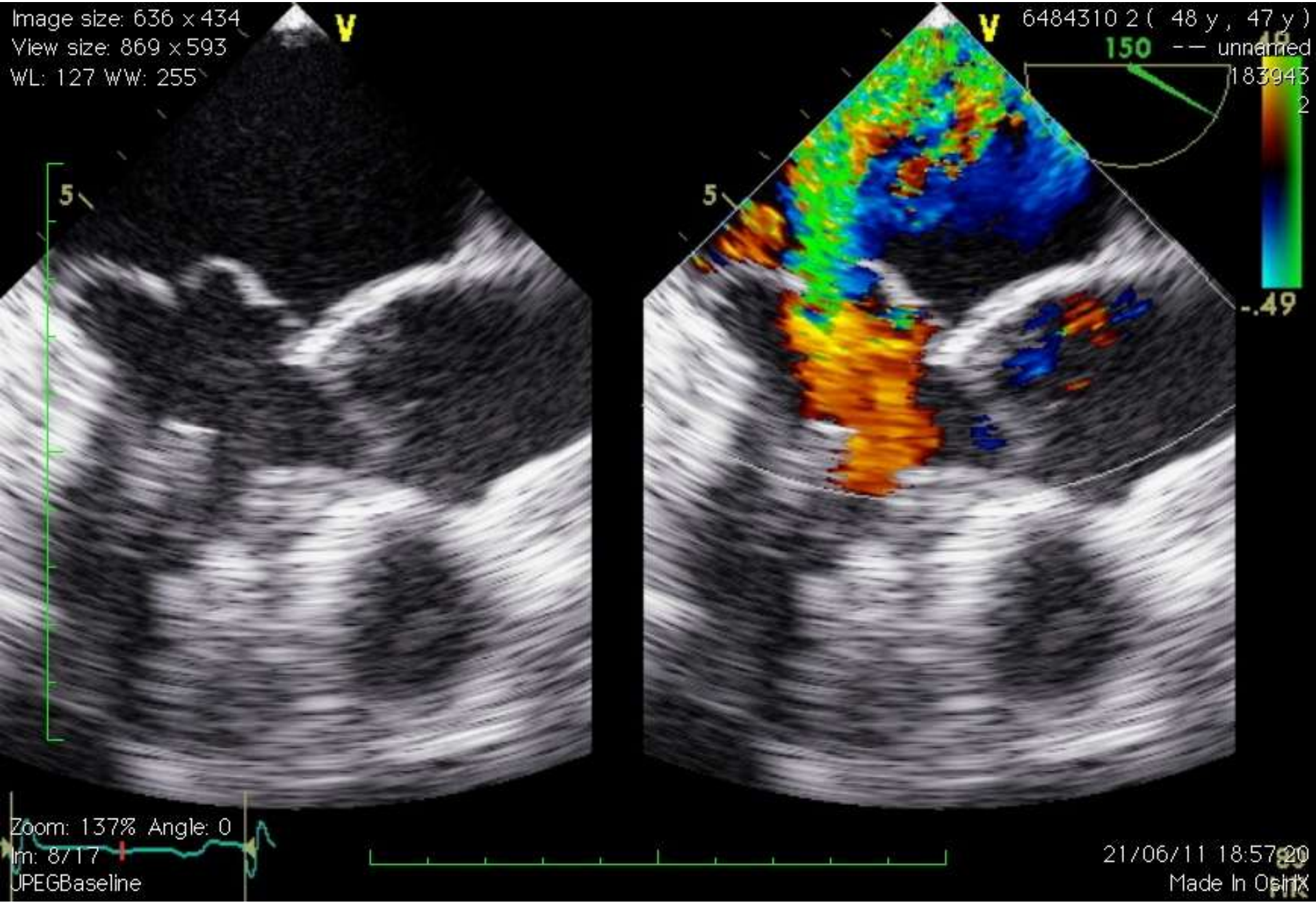
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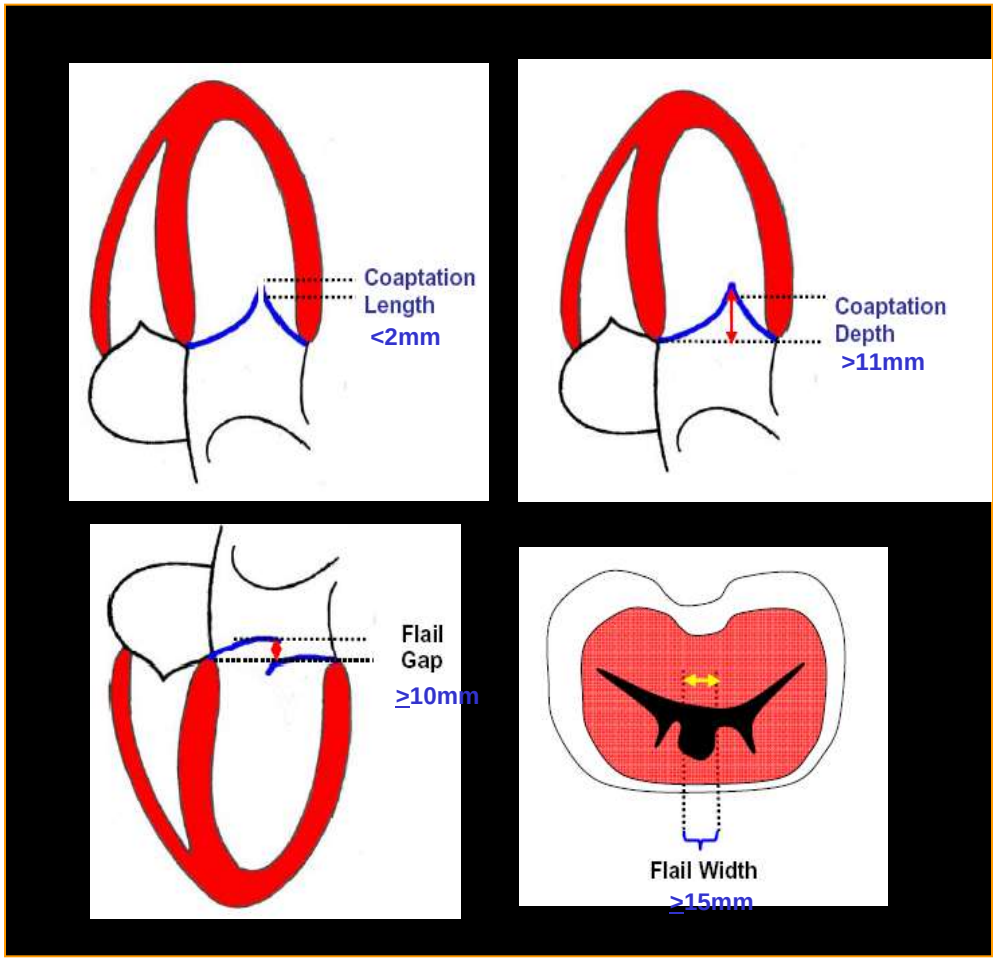
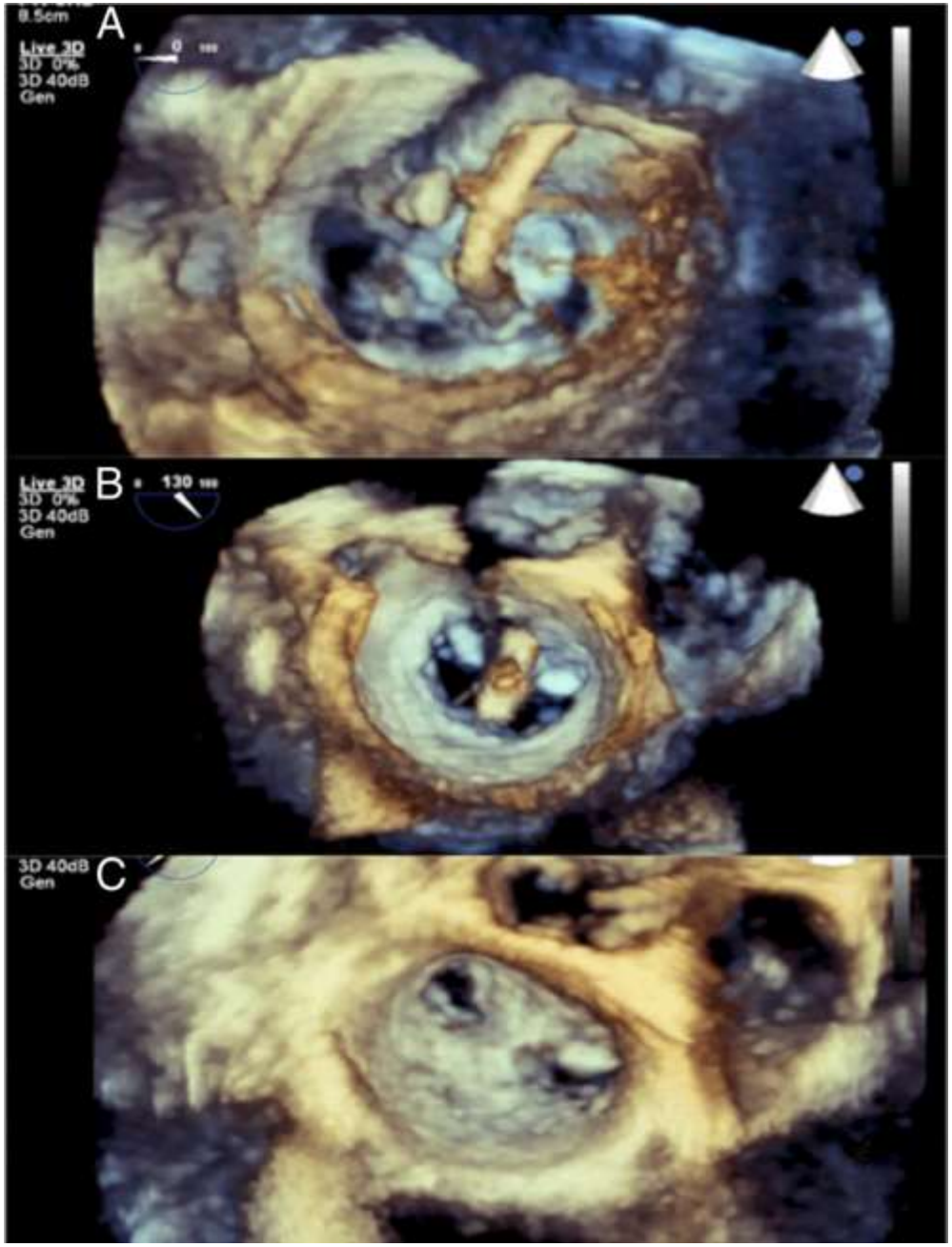
Anatomic Eligibility

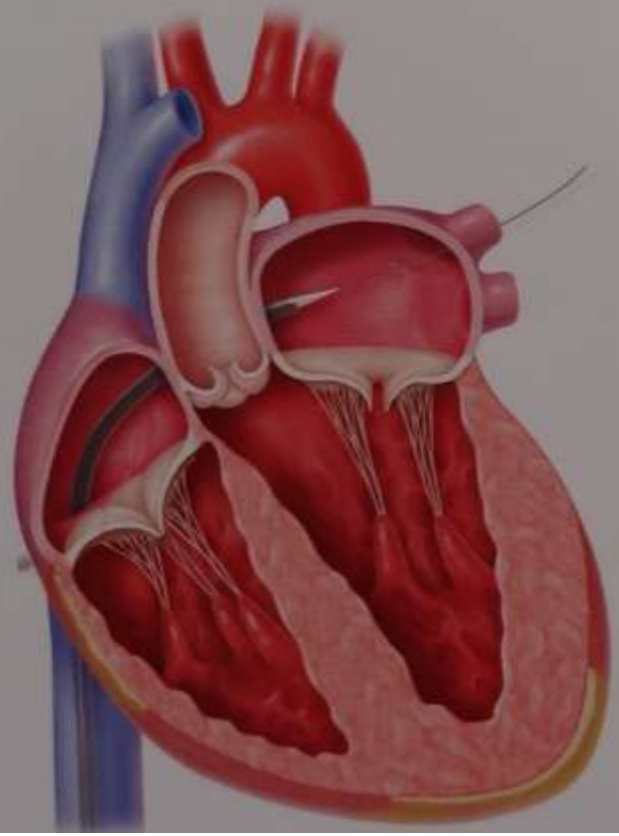
Leaflet mal-coaptation resulting in MR

- Sufficient leaflet tissue for mechanical coaptation
- Non-rheumatic/endocarditic valve morphology
- Protocol anatomic exclusions
  - Flail gap >10mm
  - Flail width >15mm
  - LVIDs > 55mm
  - Coaptation depth >11mm
  - Coaptation length < 2mm



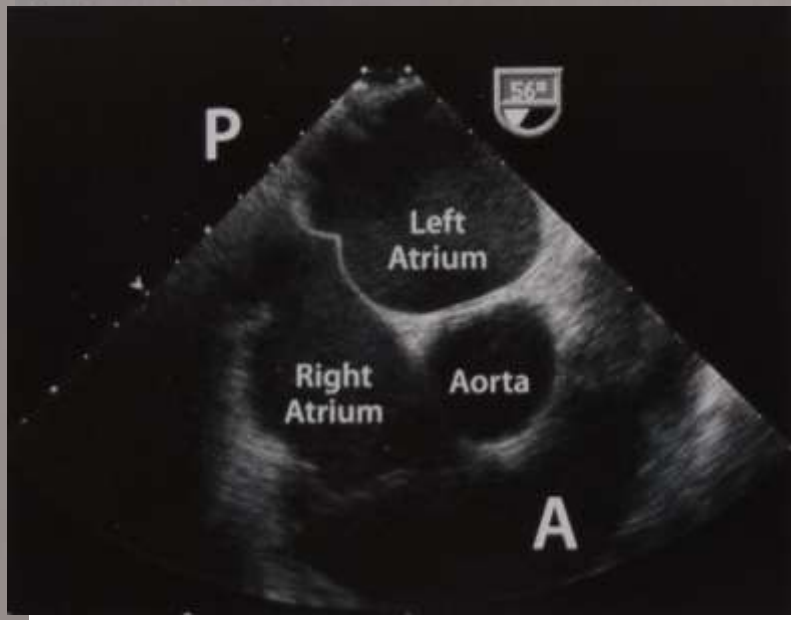

8.5cm
A
Live 3D
3D 0%
3D 40dB
Gen
0
B
Live 3D
3D 0%
3D 40dB
Gen
130
3D 40dB
Gen
C

Transseptal Crossing and Guide Insertion

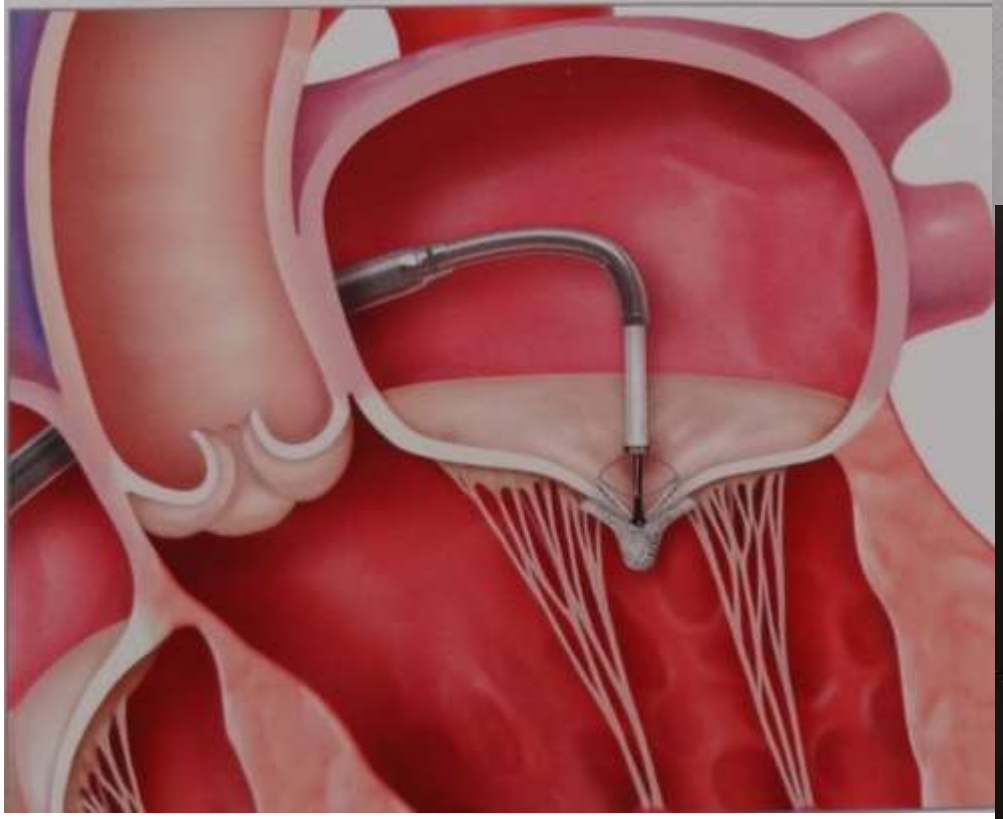


Imaging involved in this step:

- Bicaval
- SAX at Base
- 4 Chamber

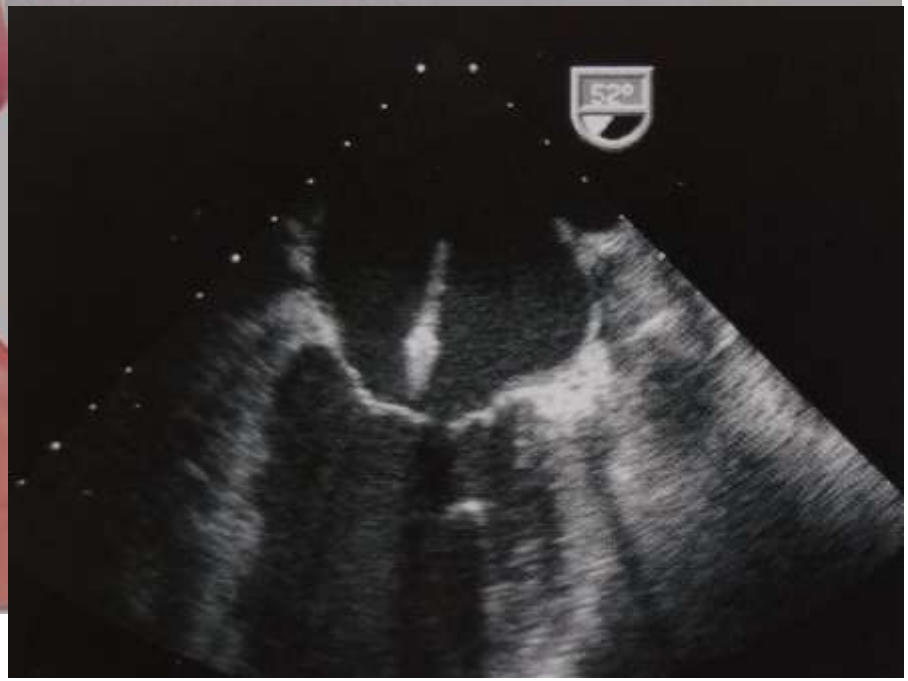


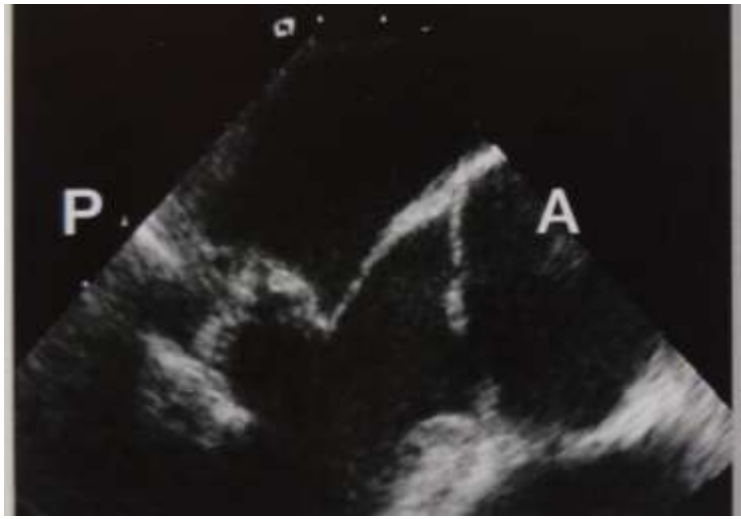
Advancing into Left Ventricle and Leaflet Grasping



Imaging involved in this step:

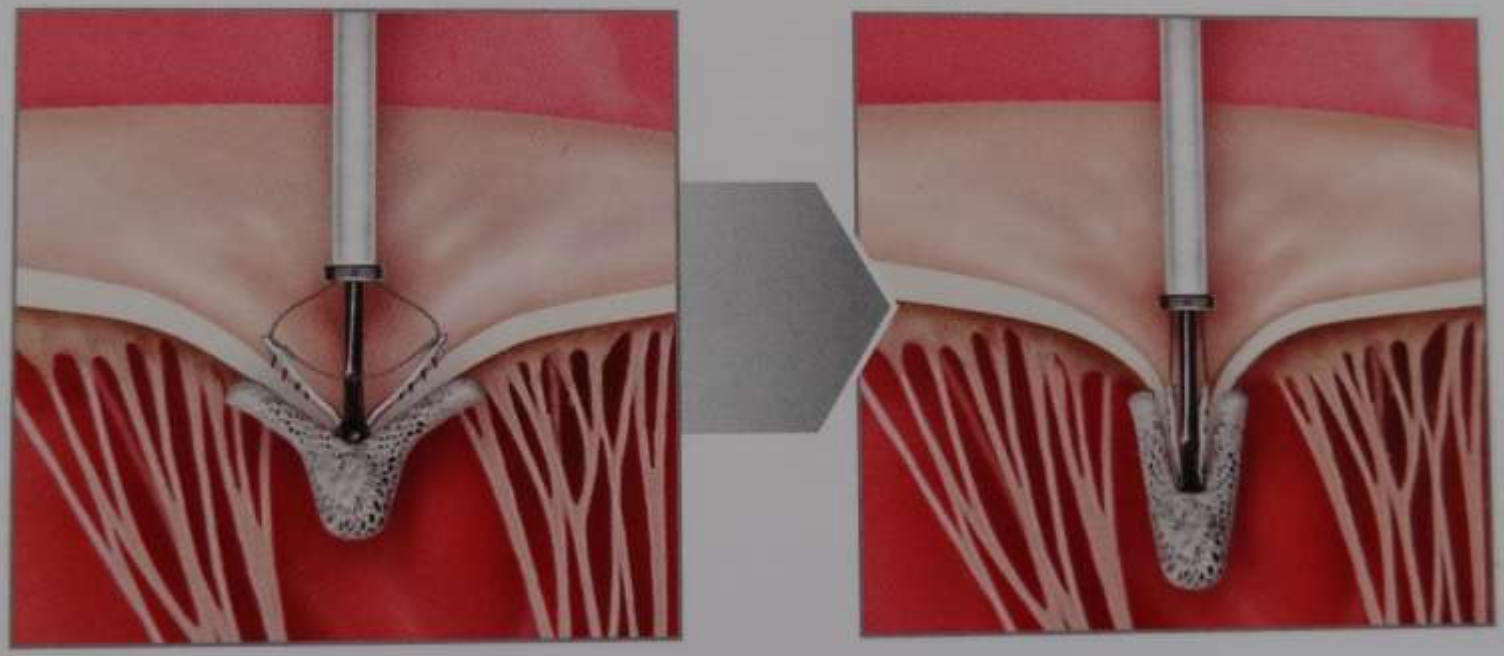
- Intercommissural–2 Chamber
- LVOT
- Transgastric SAX
- Fluoroscopy





Imaging involved in this step:

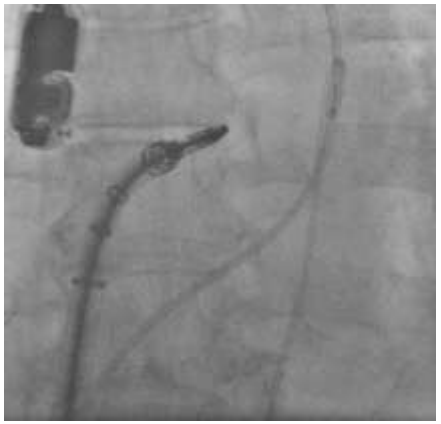
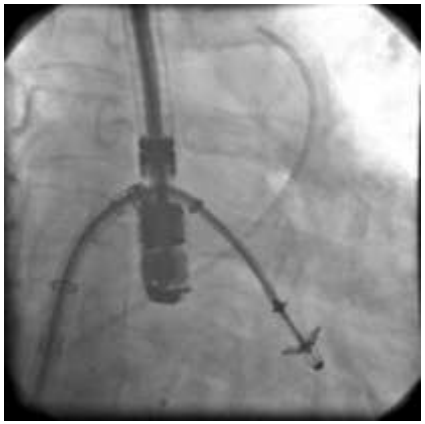
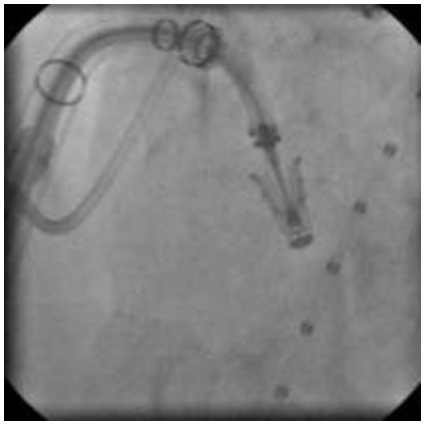
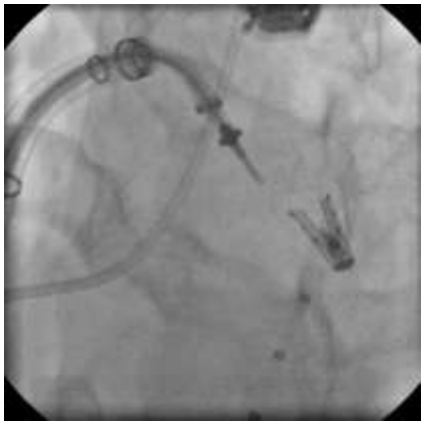
- LVOT
- Fluoroscopy

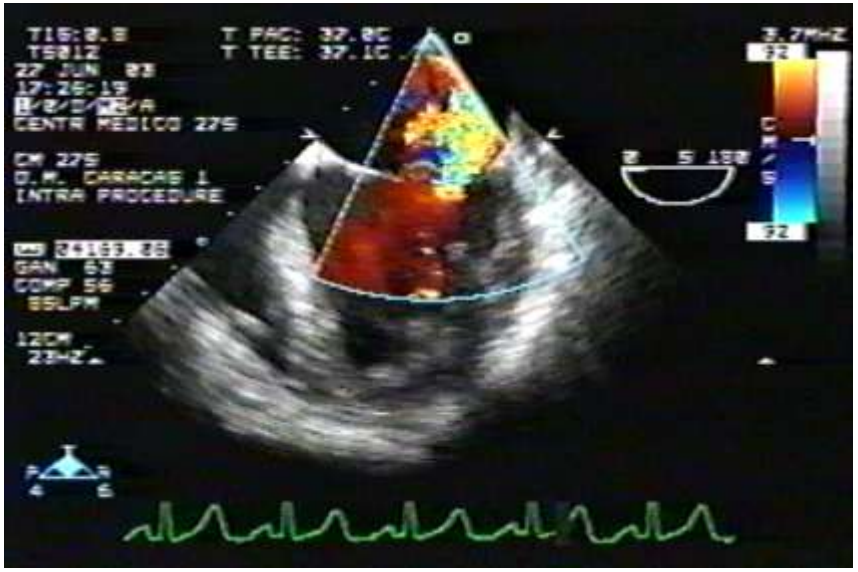


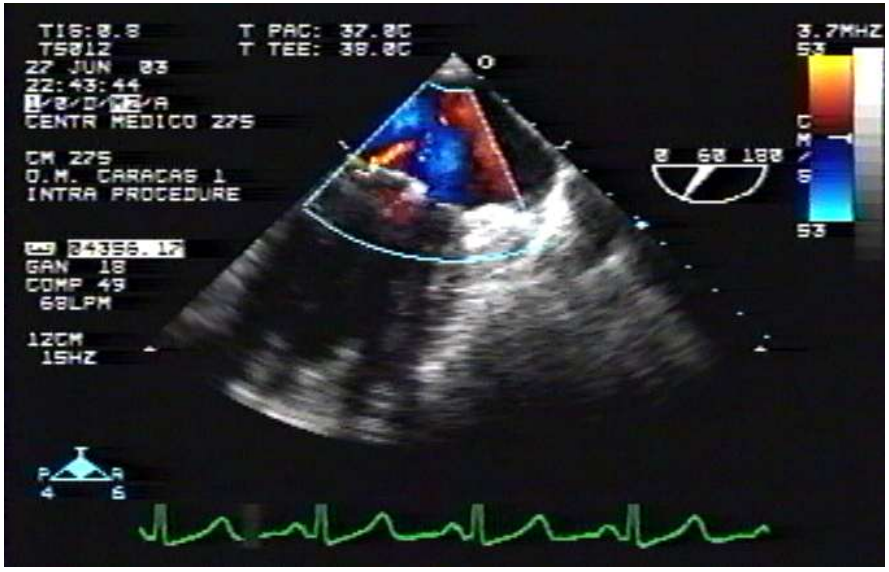
Clip Arms closed to 120 degrees

Clip Arms closed to 20 degrees

Evalve: Clip - Edge to Edge Mitral Valve





In-Hospital Outcomes

(N = 104)

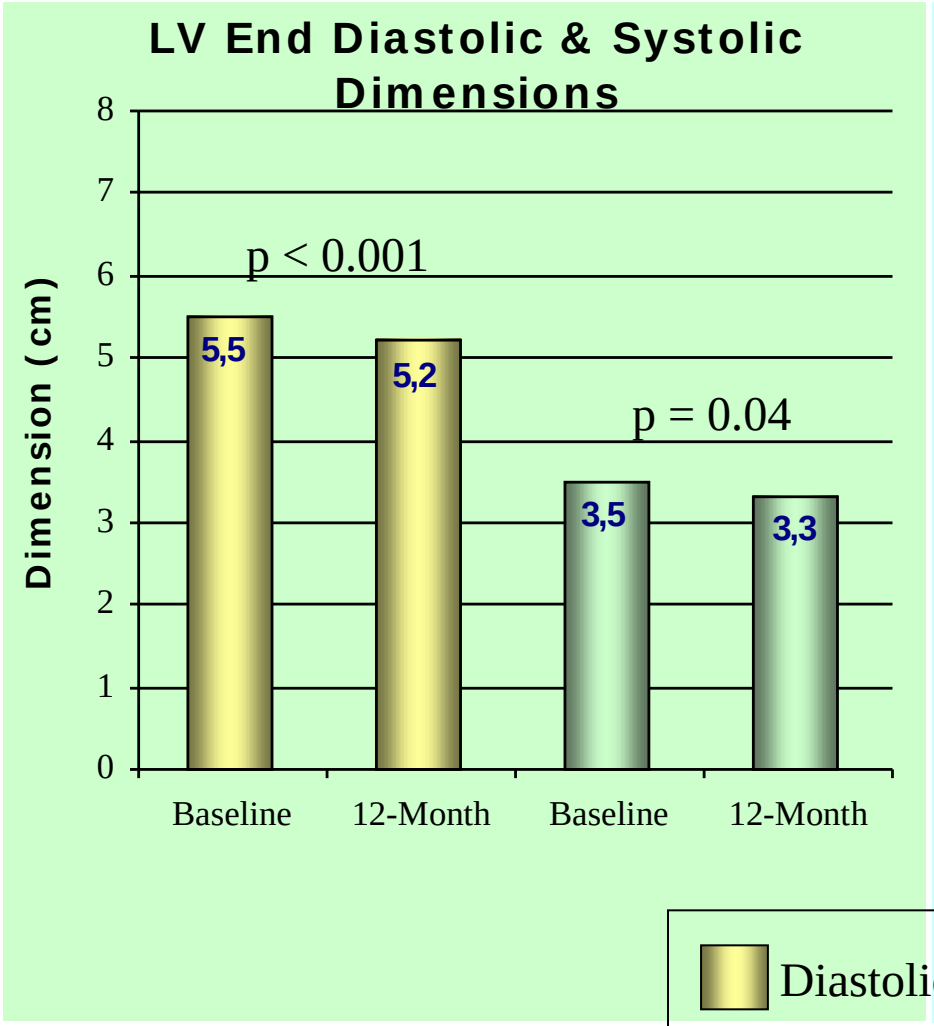
		2002 STS	
		Repair	Replacement
Death- Unrelated to Clip		1.5%	6.0%
Mechanical ventilation > 48 hours		5%	13%
Bleeding requiring transfusion		37%	56%
Transseptal complication requiring surgery		n/a	n/a
Effusion requiring pericardiocentesis		n/a	n/a
Renal failure or dialysis		3%	5%
Post-procedural hospital stay (median days)		5	7
ICU/CCU time (median days)		n/a	n/a
Discharged home (without home healthcare)		n/a	n/a

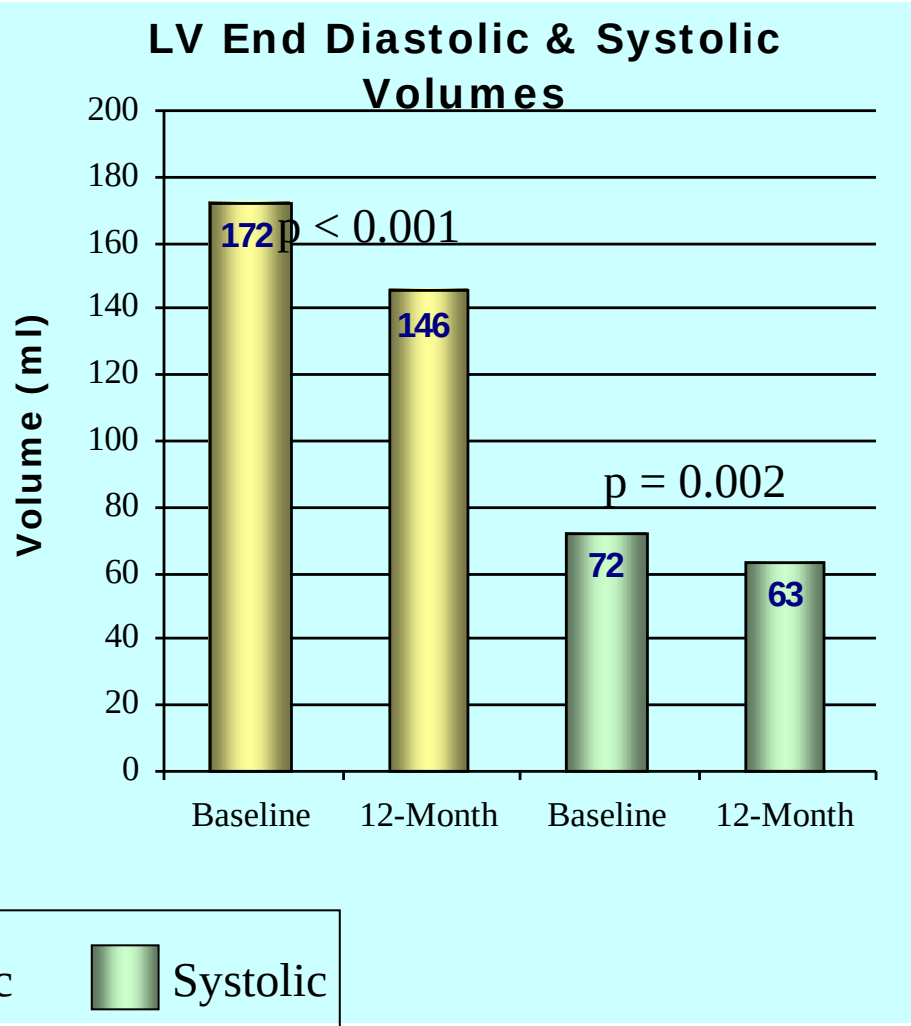
* Patient ventilated subsequently died

Reverse LV Remodeling

Matched Data, Acute Procedural Success Patients

n = 46



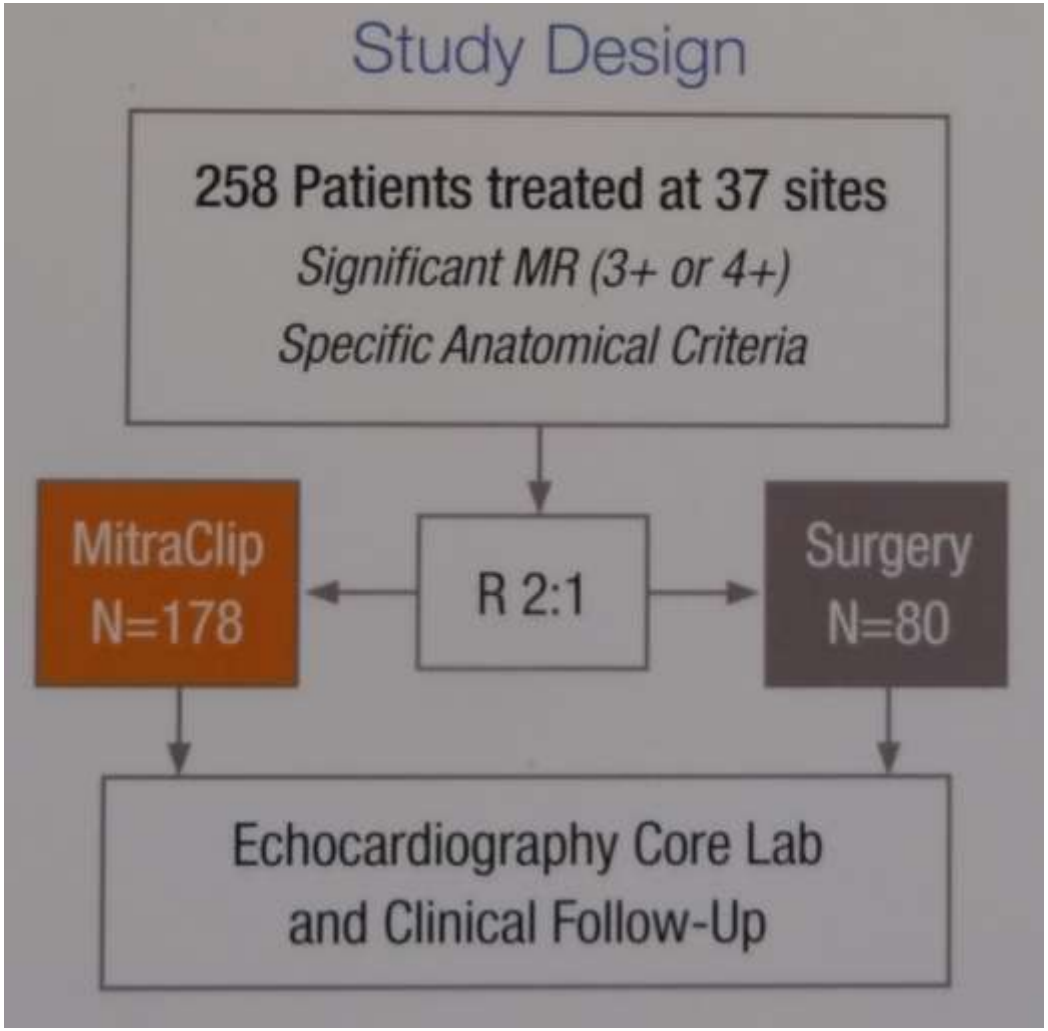


Diastolic Systolic

EVEREST II Randomized Controlled Trial (3-Year Data)

The EVEREST II Randomized Controlled Trial (RCT) is the first prospective and echo core lab adjudicated study comparing percutaneous mitral valve repair with the MitraClip device versus surgical mitral valve repair or replacement.

Study Design



Key Inclusion/Exclusion Criteria
EVEREST II RCT

Inclusion

- Candidate for MV Surgery
- Moderate to severe (3+) or severe (4+) MR
  - Symptomatic
    - >25% EF & LVESD ≤55mm
  - Asymptomatic with one or more of the following
    - LVEF 25-60%
    - LVESD ≥40mm
    - Pulmonary hypertension
    - Atrial fibrillation

ACC/AHA Guidelines
JACC 52:e1-e142, 2008

Exclusion

- AMI within 12 weeks
- Need for other cardiac surgery
- Renal insufficiency
  - Creatinine >2.5mg/dl
- Endocarditis
- Rheumatic heart disease
- MV anatomical exclusions
  - Mitral valve area <4.0cm^2
  - Leaflet flail width (≥15mm) and gap (≥10mm)
  - Leaflet tethering/coaptation depth (>11mm) and length (<2mm)

Study Design

EVEREST II Randomized Controlled Trial (RCT)

279 Patients enrolled at 37 sites

Significant MR (3+ or 4+)
Specific Anatomical Criteria

↓

Randomized 2:1

Percutaneous Group	Surgery Group
MitraClip System	Surgical Repair or Replacement
N=184	N=95

↓

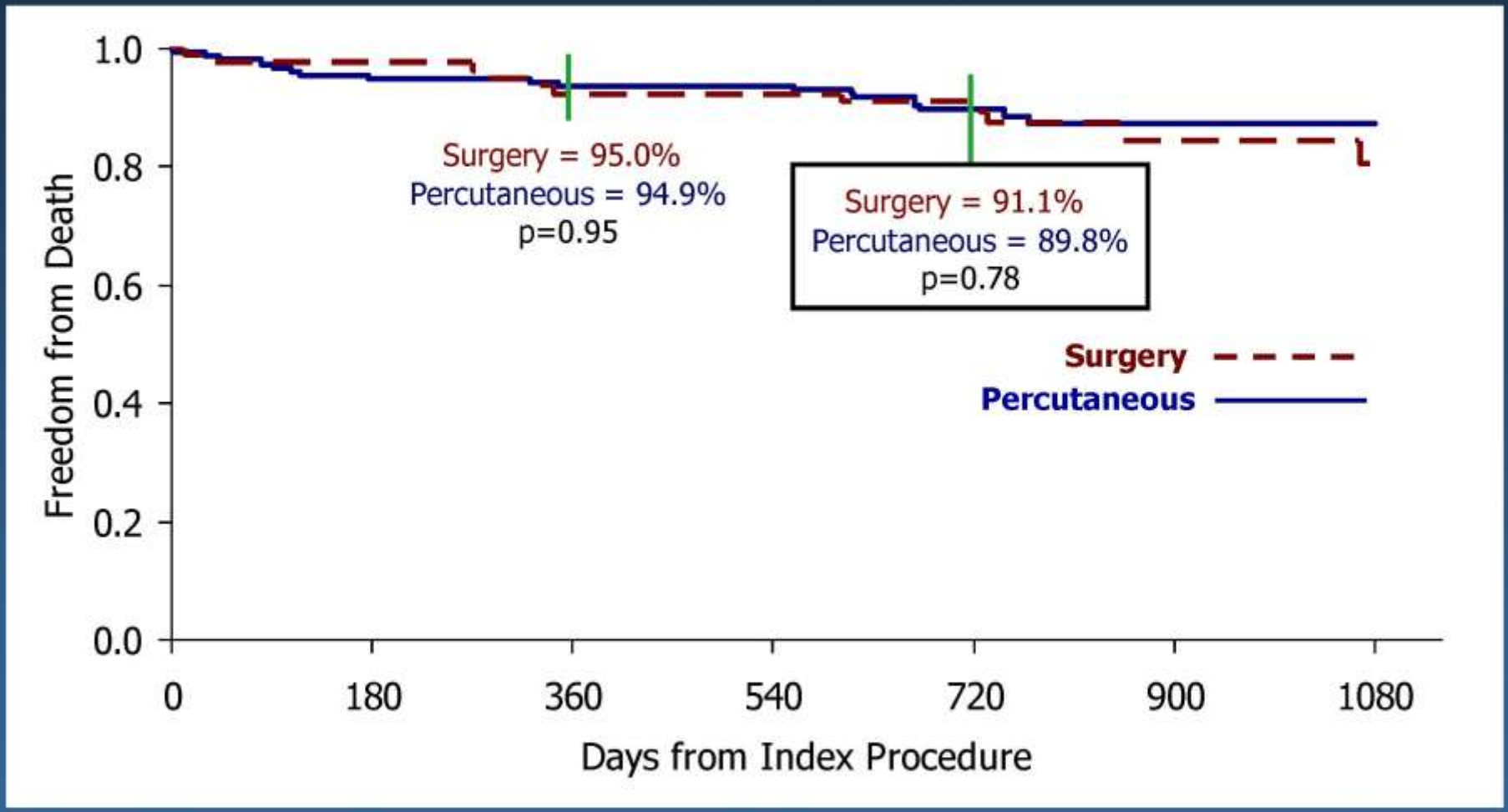
Echocardiography Core Lab and Clinical Follow-Up:
Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years

Safety Endpoint: 30 Day MAE
Intention to Treat

30 Day MAE	# (%) Patients experiencing event	
	Percutaneous (N=180)	Surgery (N=94)
Death	2 (1.1%)	2 (2.1%)
Major Stroke	2 (1.1%)	2 (2.1%)
Re-operation of Mitral Valve	0	1 (1.1%)
Urgent / Emergent CV Surgery	4 (2.2%)	4 (4.3%)
Myocardial Infarction	0	0
Renal Failure	1 (0.6%)	0
Deep Wound Infection	0	0
Ventilation > 48 hrs	0	4 (4.3%)
New Onset Permanent Atrial Fib	2 (1.1%)	0
Septicemia	0	0
GI Complication Requiring Surgery	2 (1.1%)	0
Transfusions ≥ 2 units	24 (13.3%)	42 (44.7%)
TOTAL % of Patients with MAE	**15.0%**	**47.9%**
	Difference (Percutaneous – Surgery) = -32.9%	
	p<0.001; (95% CI: -20.7%, -45.0%)	

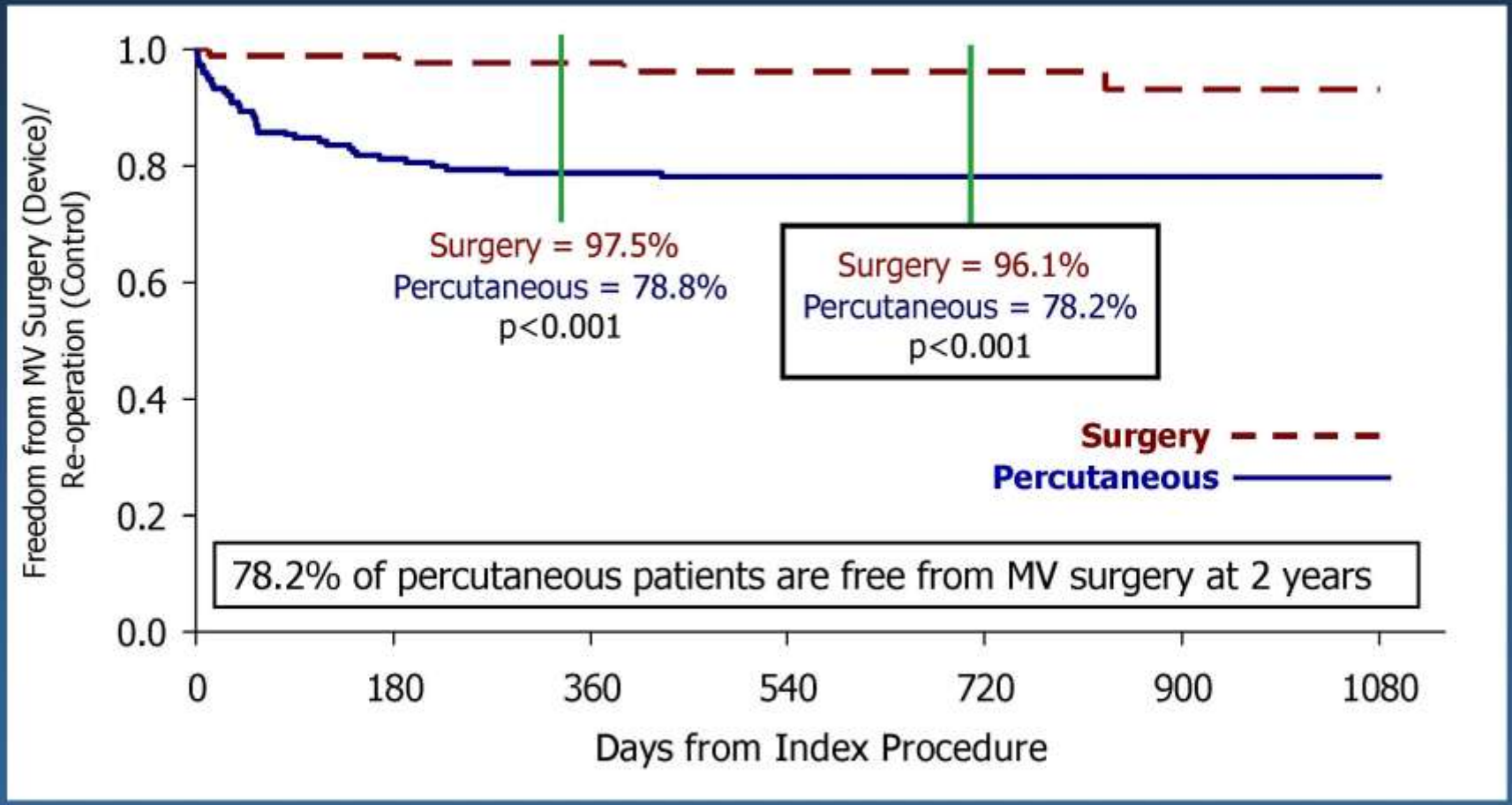
Kaplan-Meier Freedom from Death

Intention to Treat



At Risk:	0 Days	6m	1yr	1.5yr	2yr	3yr
Percutaneous	184	166	163	153	133	52
Surgery	95	78	74	71	63	25

Kaplan-Meier Freedom from MV Surgery (Percutaneous group) or Re-operation (Surgery group) Intention to Treat



At Risk:	0 Days	6m	1yr	1.5yr	2yr	3yr
Percutaneous	184	138	131	124	109	44
Surgery	95	77	72	69	61	24

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

Summary
EVEREST II RCT

- When percutaneous repair is compared to surgery
  - Percutaneous repair provides increased safety
  - Surgery provides more complete MR reduction
- 78% of percutaneous patients are free from surgery at 2 years
- Both percutaneous and surgical treatment reduced MR and demonstrated meaningful clinical benefits through 2 years
  - Significantly improved LV volumes and NYHA Functional Class
- No loss of device integrity through 2 years
- Follow-up is ongoing

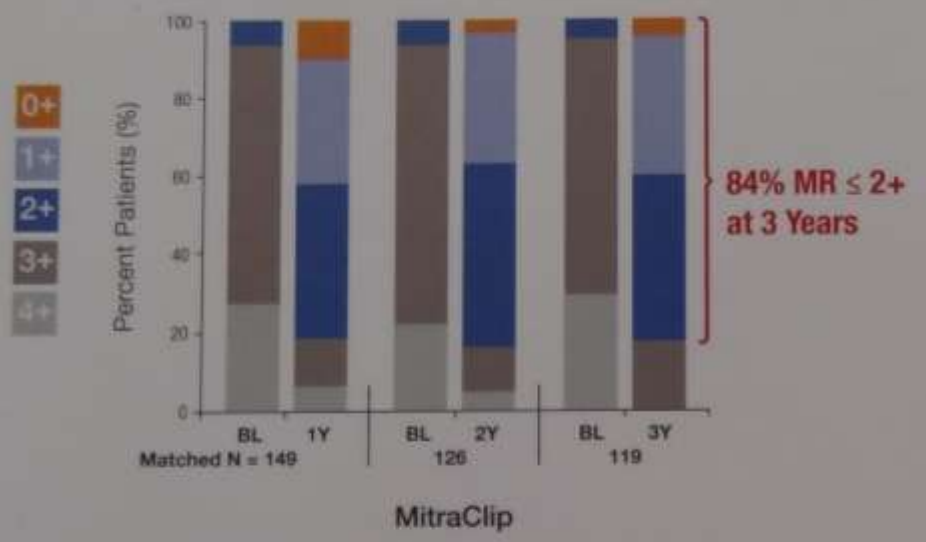
Conclusion
EVEREST II RCT

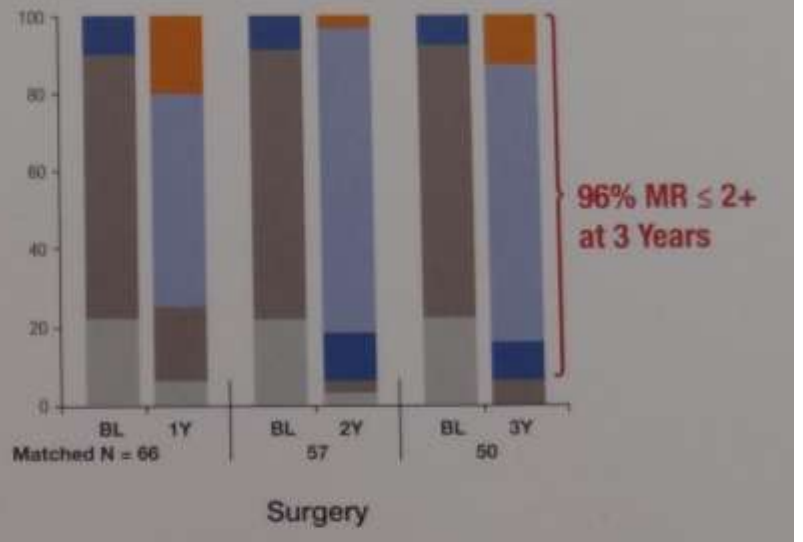
- The MitraClip procedure is a therapeutic option for select patients with significant mitral regurgitation
  - Favorable safety profile
  - Measurable clinical benefits
    - Improved LV volumes and NYHA Class
- Results are durable through 2 years

Low 30-Day MAEs Compared to Surgery

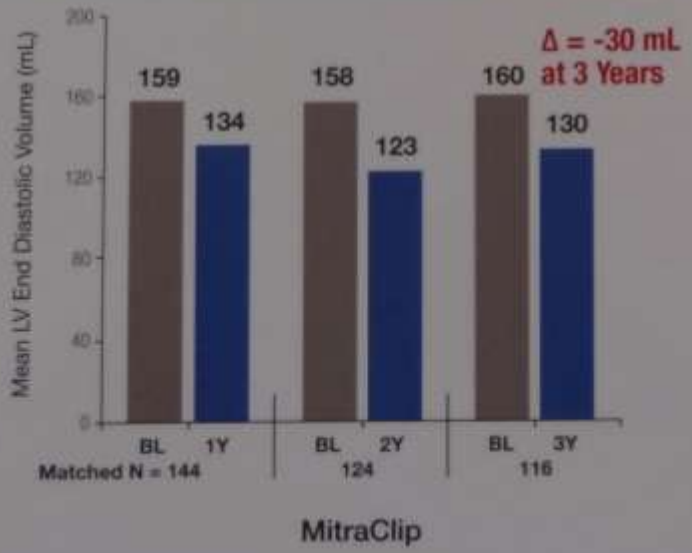
Major Adverse Events (MAE)	MitraClip (N=178)	Surgery (N=80)
Death	2 (1.1%)	2 (2.5%)
Stroke	1 (0.6%)	2 (2.5%)
Re-operation of Mitral Valve	0	1 (1.3%)
Urgent / Emergent CV Surgery	4 (2.2%)	4 (5.0%)
Myocardial Infarction	0	0
Renal Failure	1 (0.6%)	0
Deep Wound Infection	0	0
Ventilation > 48 Hrs	0	4 (5.0%)
New Onset Permanent Atrial Fib	2 (1.1%)	0
Septicemia	0	0
GI Complication Requiring Surgery	2 (1.1%)	0
MAE Major Bleeding Complication*	9 (5.1%)	37 (46.3%)
TOTAL % of Patients with MAE (95% CI: -20.7%, -45.0%)	**7.9%**	**50.0%**

Clinically Significant and Sustained Reduction of MR Grade from Baseline†

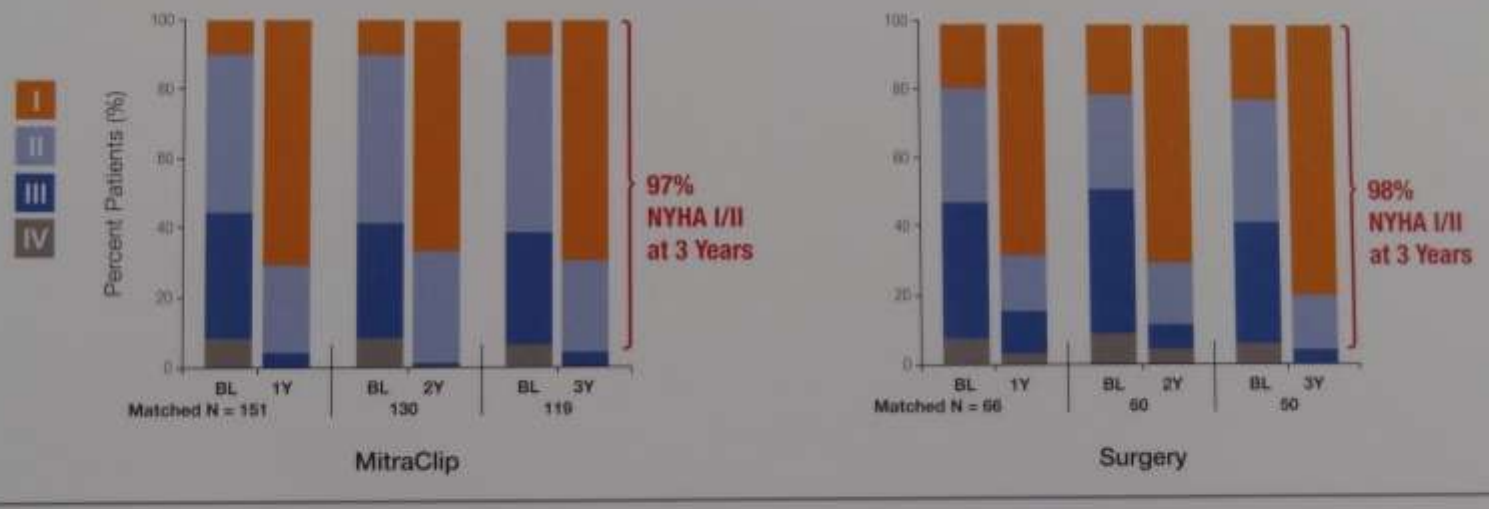




Reverse-Remodeling of Left Ventricle†



Significant NYHA Functional Class Improvement



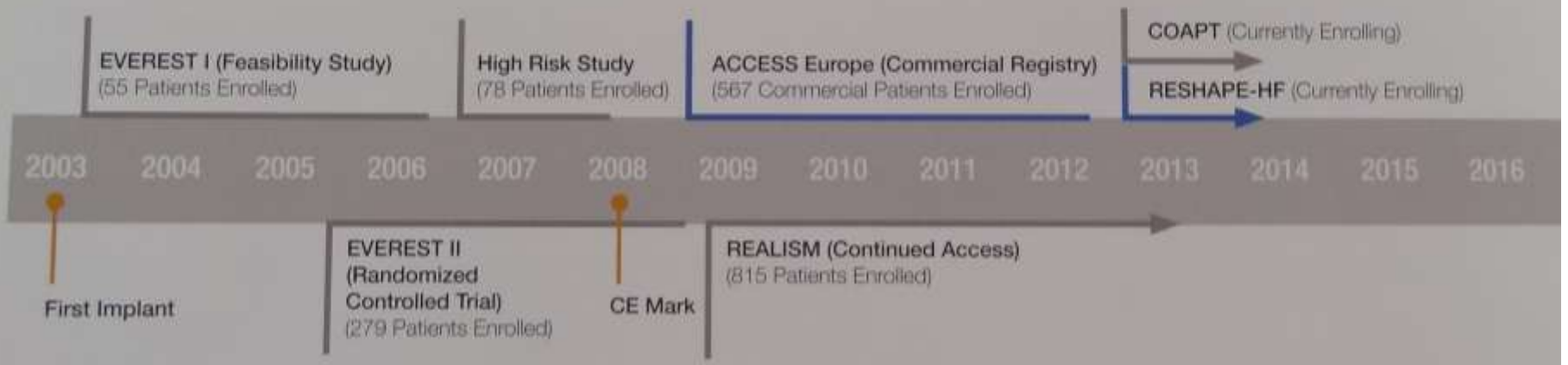
† $p<0.05$ for all changes from Baseline within groups

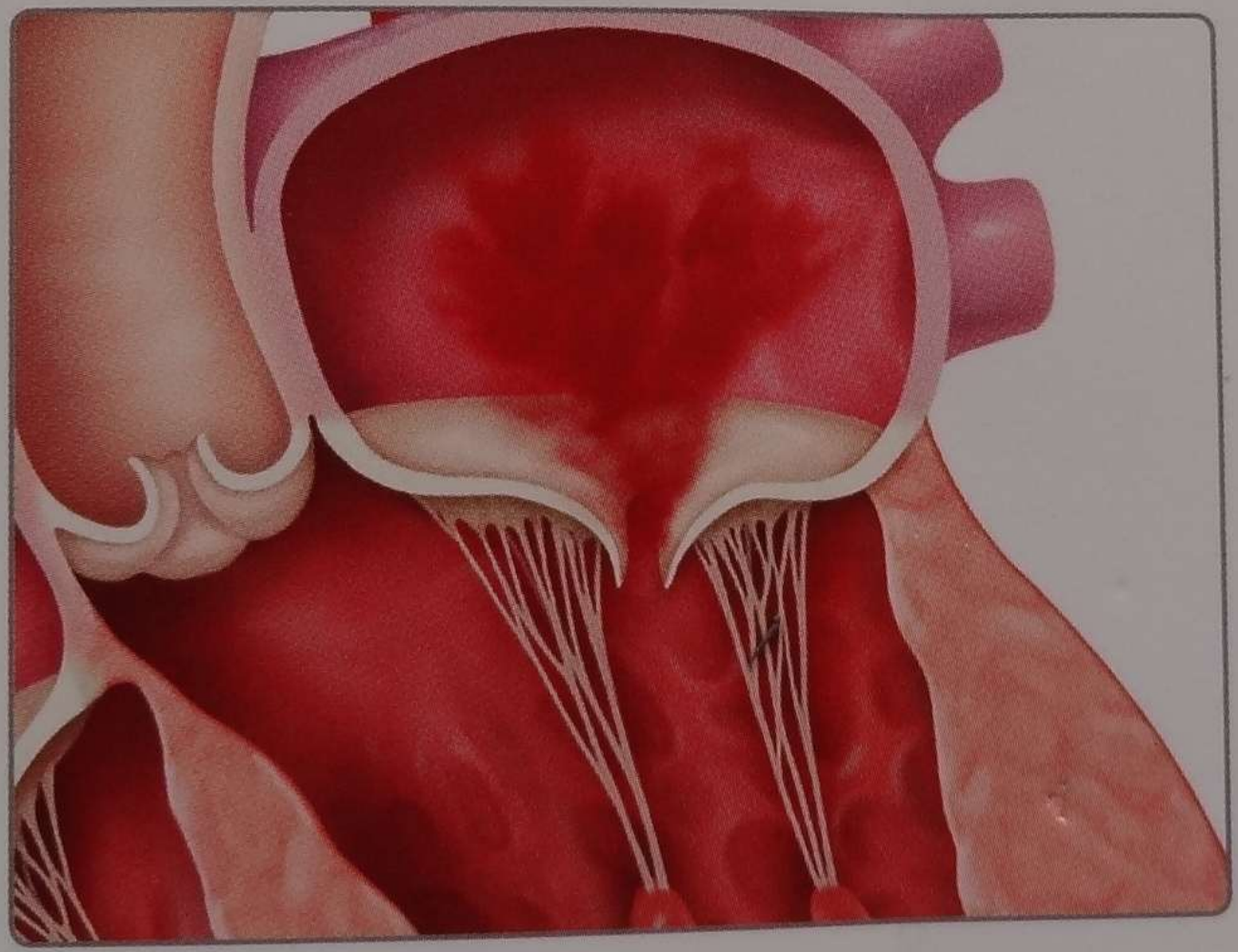
Source: Feldman T, Foster E, Qureshi M, et al. The EVEREST II Randomized Controlled Trial: Three Year Outcomes. Transcatheter Cardiovascular Therapeutics; October 22-26, 2012; Miami, FL.

"Results achieved
with the MitraClip are
durable through 3 years."

— Ted Feldman, M.D., et al. (TCT 2012)

Clinical Experience



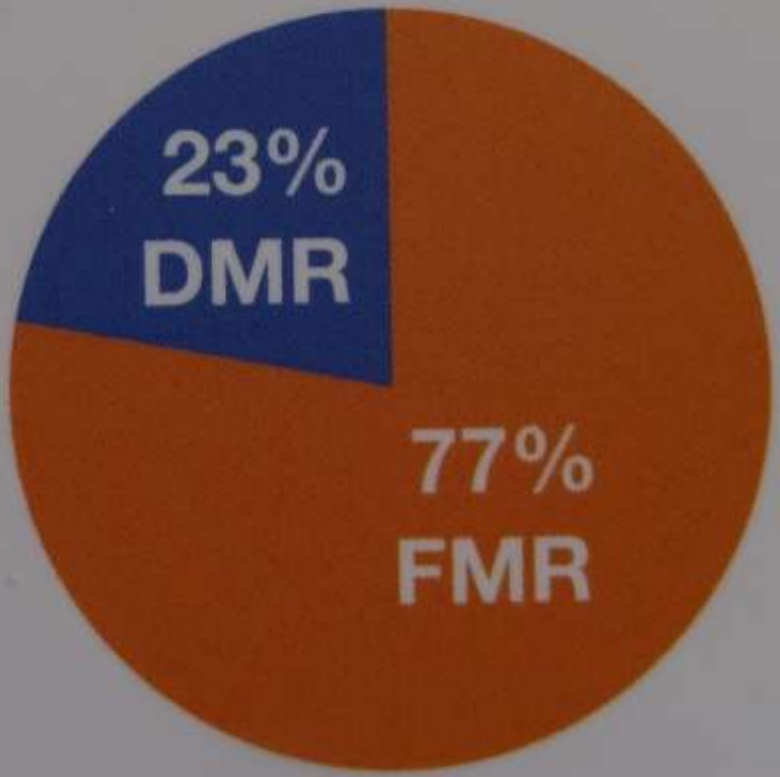


Functional MR

ACCESS-Europe: Real-world clinical experience (1-year data)

The ACCESS-Europe trial is a real-world study of patients treated with MitraClip therapy in a commercial setting. Fourteen centers across Europe have enrolled 567 patients as of October 2011.

Patient Type by Etiology



(N=567)

Baseline Demographics and Comorbidities

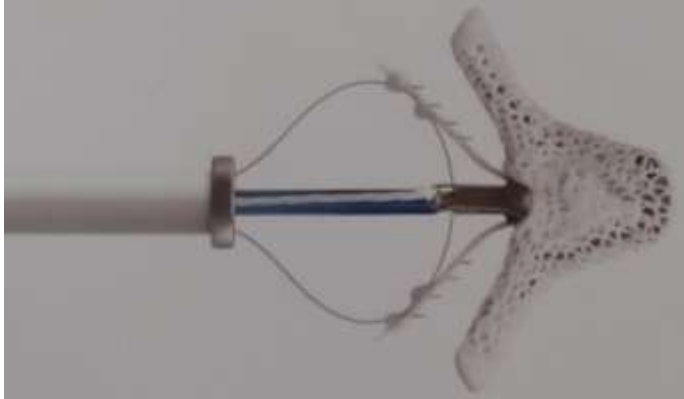
Demographics and Comorbidities	ACCESS-EU MitraClip Patients, N=567
Age (mean ± SD), years	74 ± 10
Logistic EuroSCORE, (%)	
Mean ± SD	23 ± 18
Logistic EuroSCORE ≥ 20, (%)	45
Male Gender, (%)	64
Mitral Regurgitation Grade ≥ 3+, (%)	98
NYHA Functional Class III or IV, (%)	85
Ejection Fraction < 40%, (%)	53

The majority of patients treated in the ACCESS-Europe trial have functional MR with extensive comorbidities.

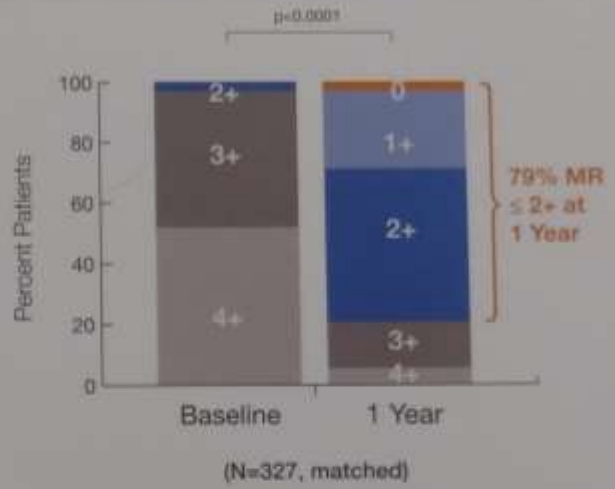
Site Reported Safety Events at 30 Days

30 Day Events*	ACCESS-EU MitraClip Patients Experiencing Events, N=567 # (%)
Death	19 (3.4)
Stroke	4 (0.7)
Myocardial Infarction	4 (0.7)
Renal Failure	27 (4.8)
Respiratory Failure	4 (0.7)
Need for Resuscitation	10 (1.8)
Cardiac Tamponade	6 (1.1)
Bleeding Complications	22 (3.9)

MitraClip therapy provides **significant clinical benefits,** including symptomatic and functional improvements in select patients with significant mitral regurgitation.



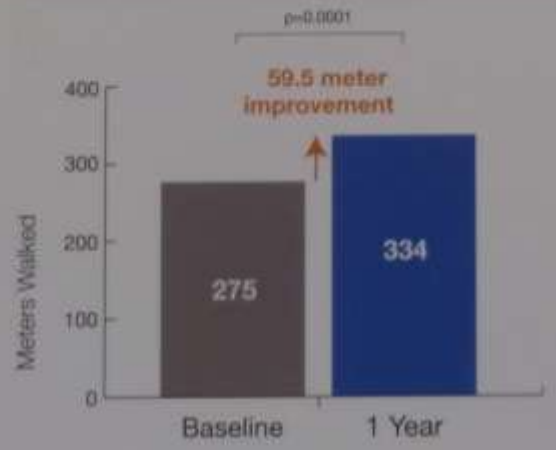
Mitral Regurgitation Grade Reduction



(N=327, matched)

As assessed by sites.

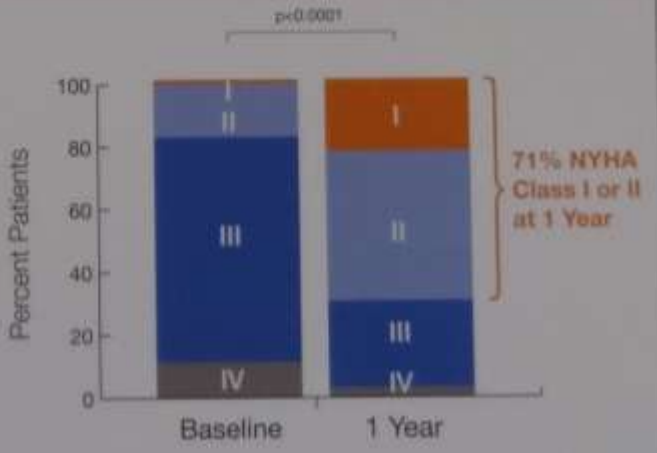
Functional Improvement in 6-Minute Walk Test



(N=216, matched)

Data presented as mean ± 95% confidence intervals (44.5, 74.6)

Significant NYHA Functional Class Improvement

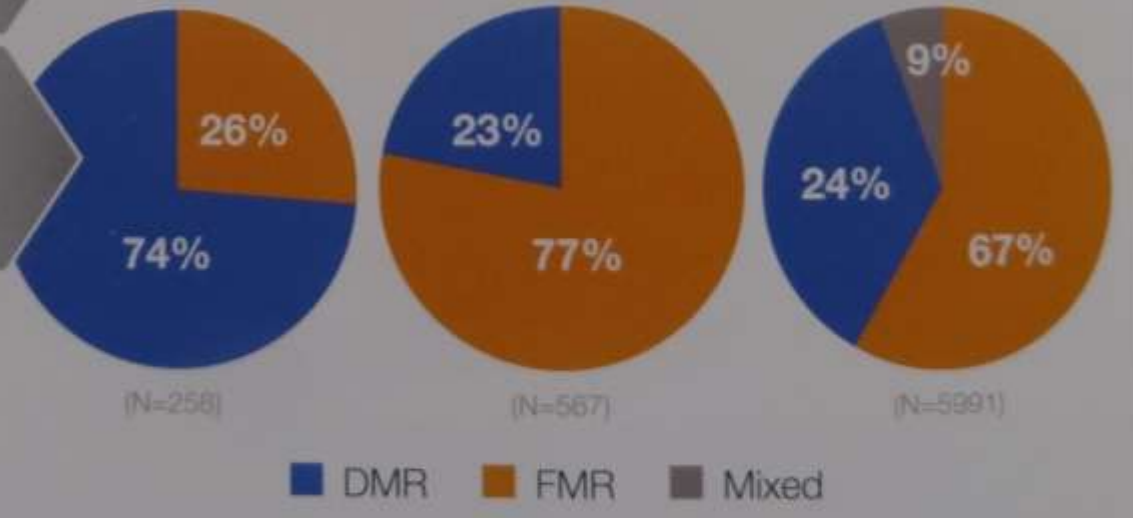


(N=343, matched)

MitraClip Implant Experience Evolving and Improving

	EVEREST II[6] (Randomized Controlled Trial)	ACCESS Europe[†, 12] (Commercial Registry)	Commercial[13] (Europe, Asia, Australia, Post-commercial Registries)
Device Time Implantation efficiency **increases** with experience	146 minutes*	117 minutes‡	95 minutes*
Implant Rate Patient screening and implantation experience **improve** implant rates	89%	99.6%	96%

Valve Etiology of Treated Patients
Unmet need in FMR has **driven** commercial adoption of MitraClip therapy



*Mean Device Time †ACCESS EU Analysis Cohort ‡Mean Procedure Time

Candidates for trans-catheter intervention

- Patients with degenerative MR who are at high risk from conventional surgery
- Patients with functional MR

  (ideally as part an RCT)

Issues and Problems

- CS approach to perc annuloplasty
  - CS not truly co-planar with annulus (just above)
  - Can pinch LCx artery (just below)
  - "Congested" intellectual property space
  - Unknowns
    - Long-term benefit of partial circumference ring
    - Risks of erosion, perforation, thrombosis
- Edge-to-edge repair
  - Large device with transseptal approach
  - Complex procedure
  - Valve morph and etiology may influence results
  - Unknowns
    - Importance of concomitant annuloplasty
    - Durability of repair and long-term leaflet stress


Discovery


United States