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The 21st Century Approach to Mitral Regurgitation: Transcatheter Mitral Valve Repair

Adnan K. Chhatriwalla MD, FACC
Saint Luke's Mid America Heart Institute
University of Missouri - Kansas City

Disclosures

- Travel reimbursement from Abbott Vascular, Edwards Lifesciences, Medtronic Inc and St Jude Medical

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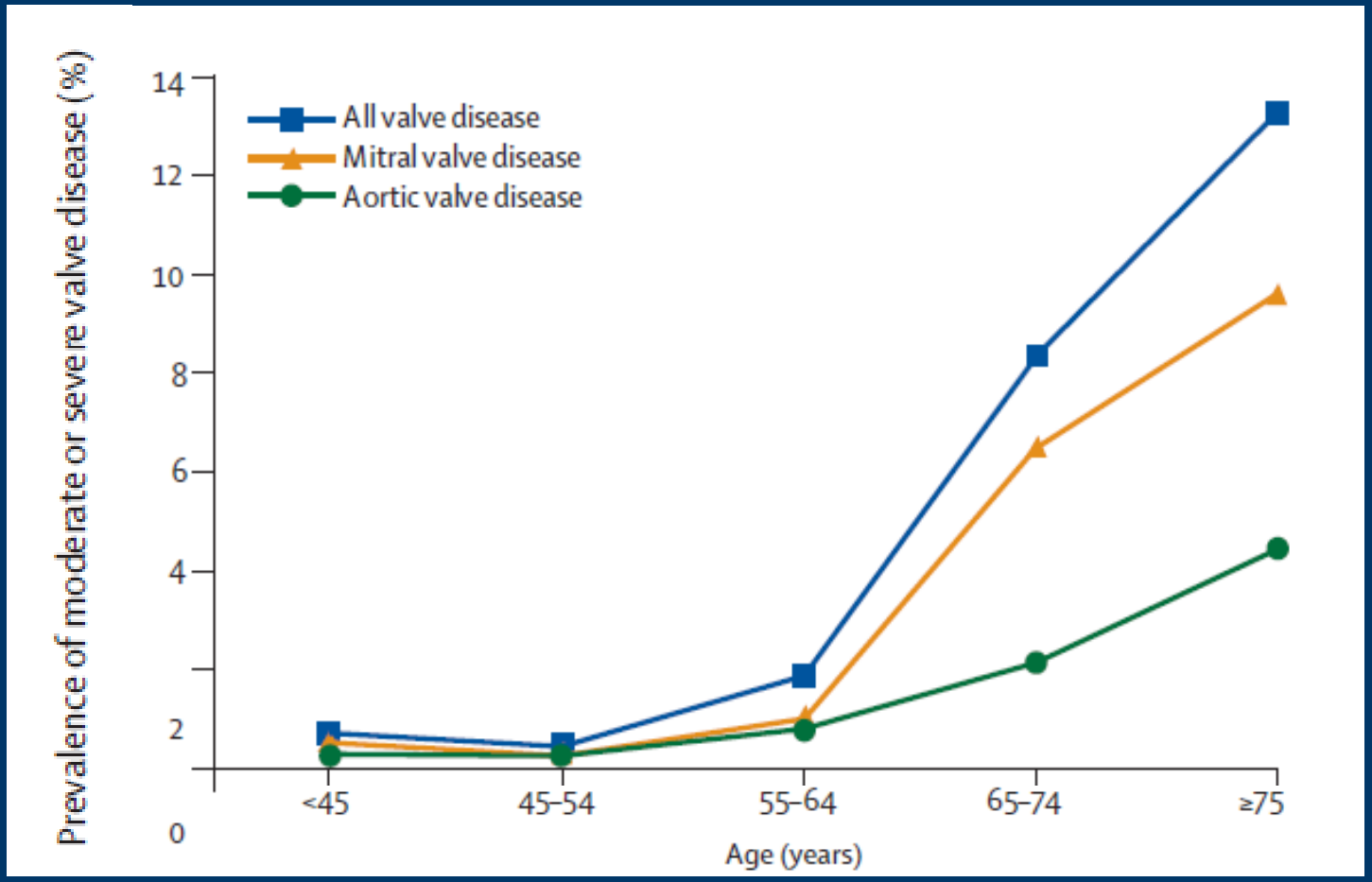
Prevalence of Mitral Valve Disease



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Nkomo et al. *Lancet* 2006; 368: 1005-11

Prevalence of Mitral Valve Disease

Participants N = 11, 911	Age 18-64 N = 6,287	Age 65-74 N = 3,579	Age ≥ 75 N = 1,745	Frequency adjusted to 2000 US adult population
Mitral Regurgitation (n = 449)	36 (0.58%)	250 (6.4%)	163 (9.3%)	1.7% 95% CI [1.5-1.9]
Mitral Stenosis (n = 15)	4 (0.06%)	7 (0.2%)	4 (0.2%)	0.1% 95% CI [0.02-0.2]

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Nkomo et al. *Lancet* 2006; 368: 1005-11

Mechanism of Mitral Regurgitation

- **Organic**: Valve components are abnormal
  - Prolapse
  - Ruptured chordae/flail leaflet
  - Rheumatic disease
  - Congenital abnormality
  - Endocarditis
- **Functional**: valve components are normal
  - LV dilation and remodeling leads to …
    - Annular enlargement
    - Papillary muscle displacement

Chronic Severe MR: Indications for Surgery

- **Class I**
  - Symptomatic (NYHA II-IV) in the absence of LV dysfunction (e.g. LVEF > 30%) and/or ESDd ≥ 55mm)
  - Asymptomatic with LVEF 30-60% and/or ESDd ≥ 40mm
- **Class IIa**
  - Asymptomatic with preserved LV function (e.g. LVEF > 60% and ESDd ≤ 40mm) +/- the presence of new onset AF or pulmonary hypertension
  - Symptomatic (NYHA III-IV) with evidence of LV dysfunction in setting of organic mitral disease
- **Class IIb**
  - Symptomatic (NYHA II-IV) despite optimal therapy with evidence of LV dysfunction in the setting of functional mitral regurgitation

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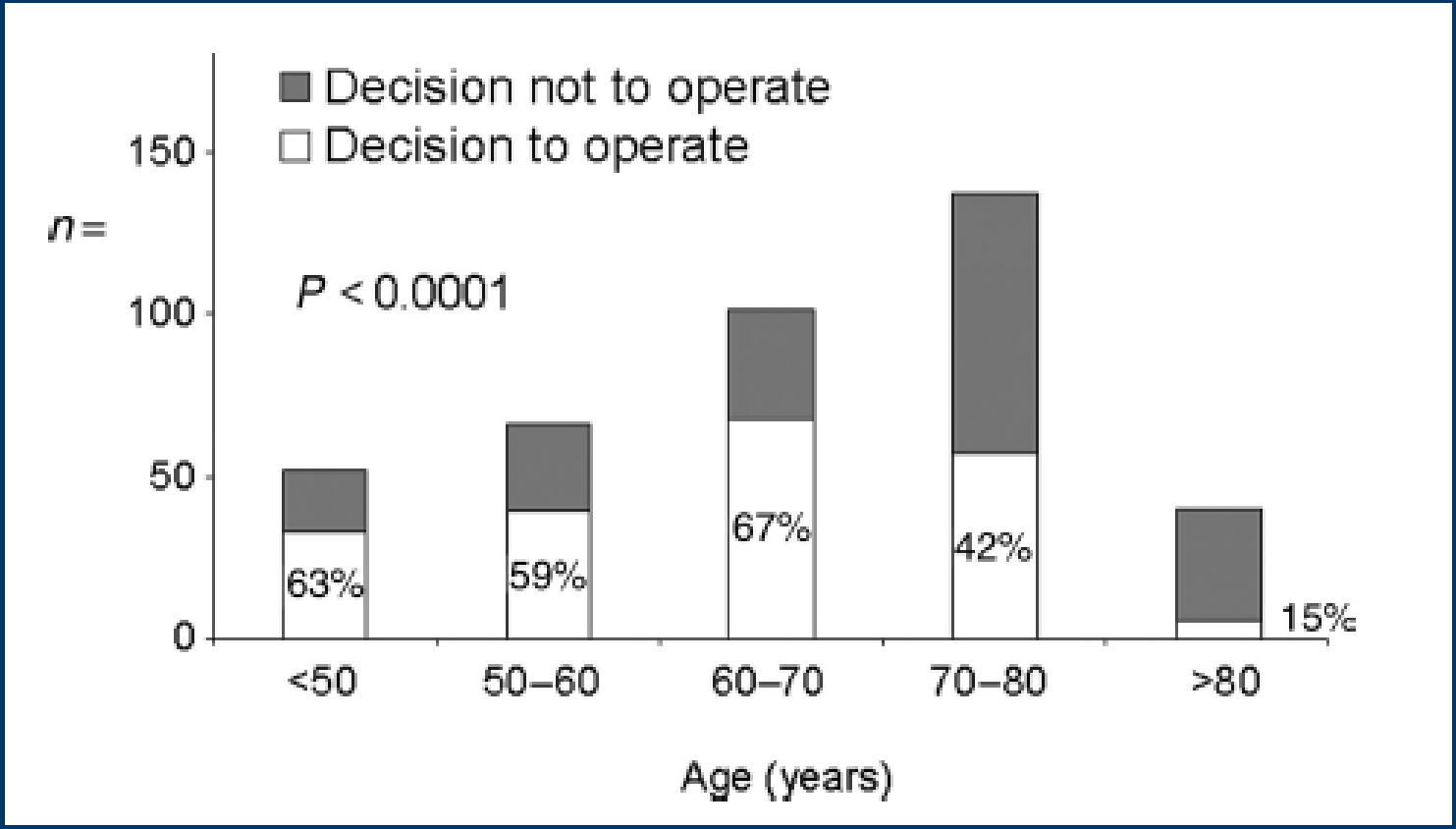
Bonow et al. *Circulation* 2008; 118: e523-e661.

Surgery is Underutilized in Symptomatic Patients



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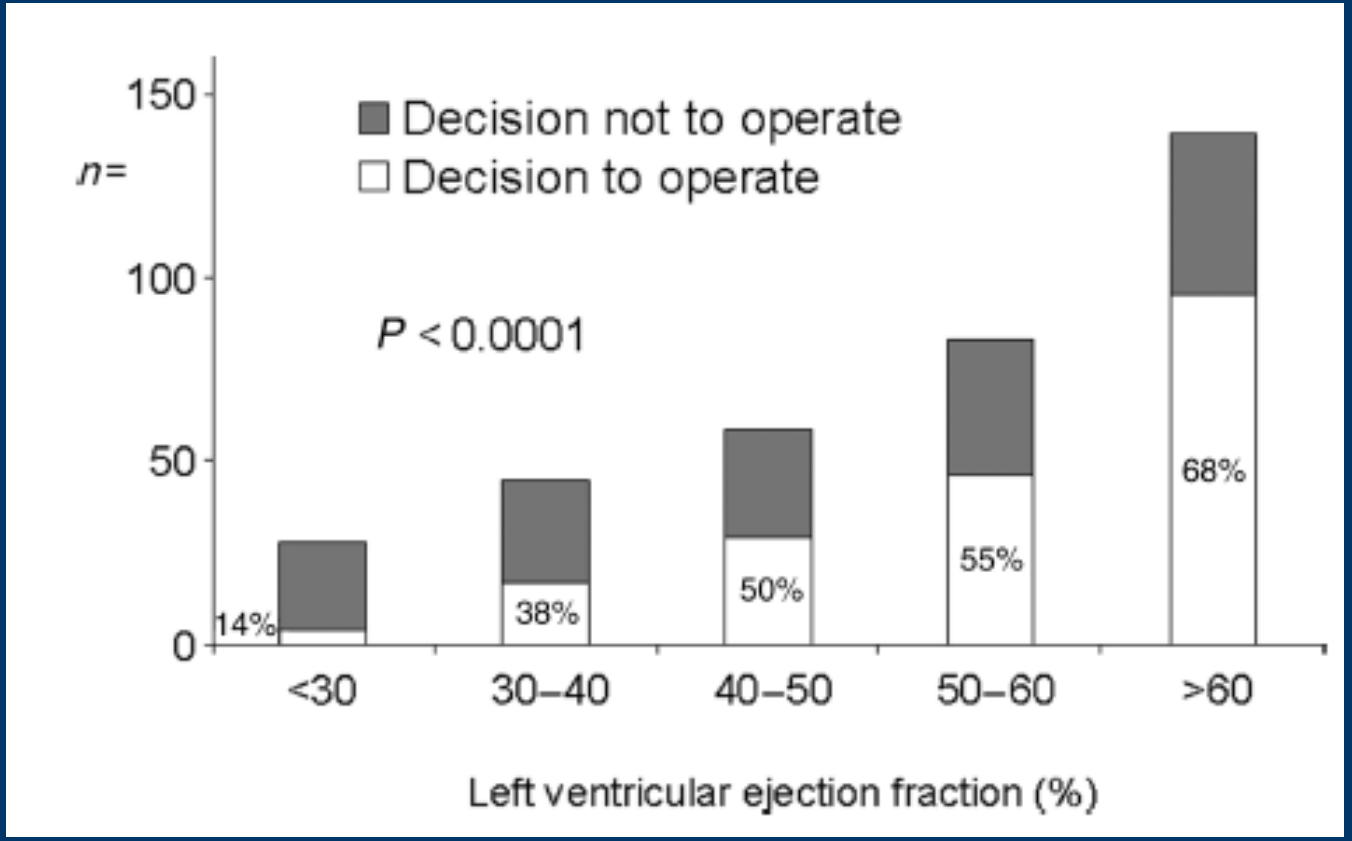
Mirabel et al. *Eur Heart J* 2007; 28: 1358-1365.

Surgery is Underutilized in Symptomatic Patients



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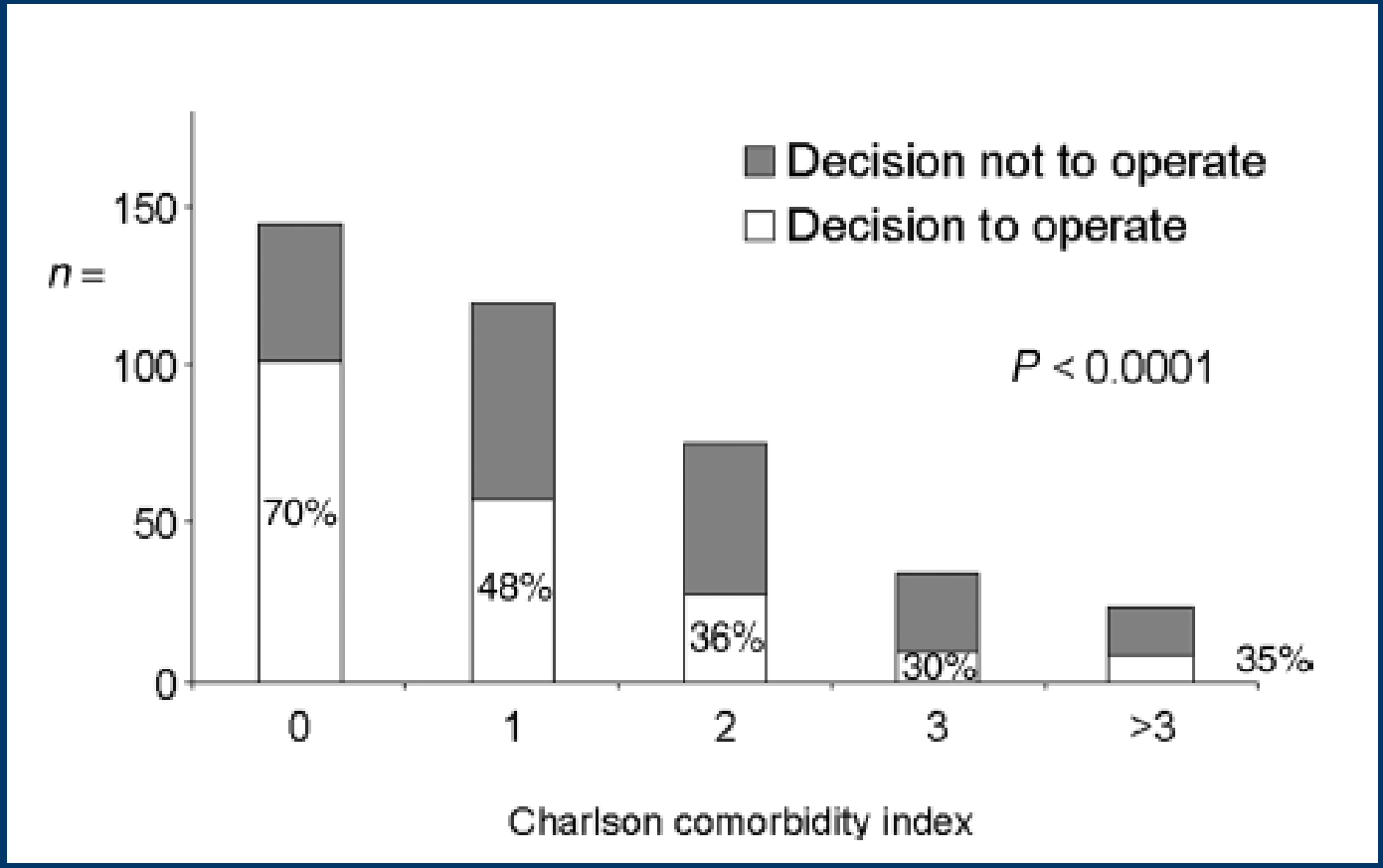
Mirabel et al. *Eur Heart J* 2007; 28: 1358-1365.

Surgery is Underutilized in Symptomatic Patients



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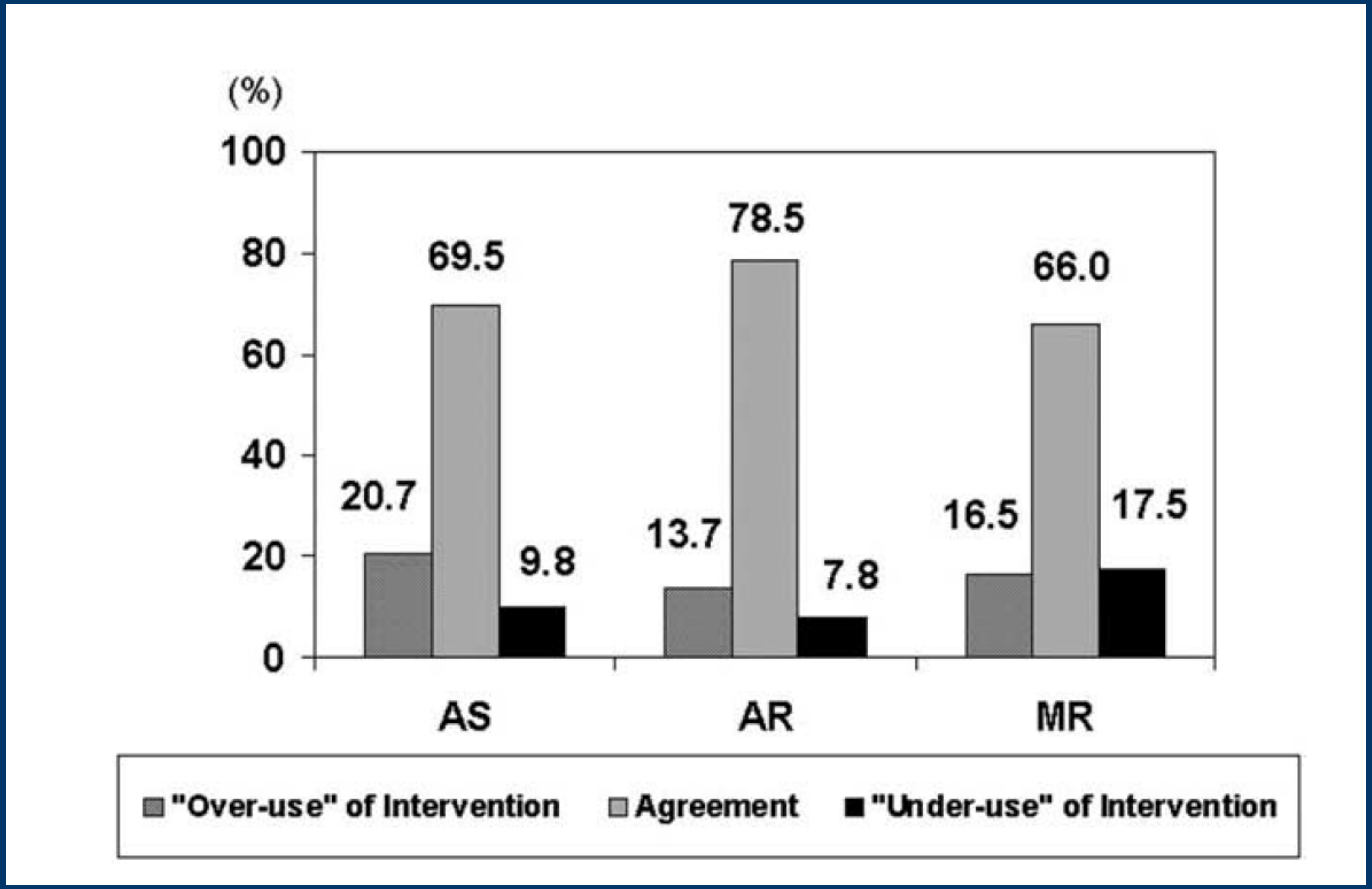
Mirabel et al. *Eur Heart J* 2007; 28: 1358-1365.

Surgery is Underutilized in Asymptomatic Patients



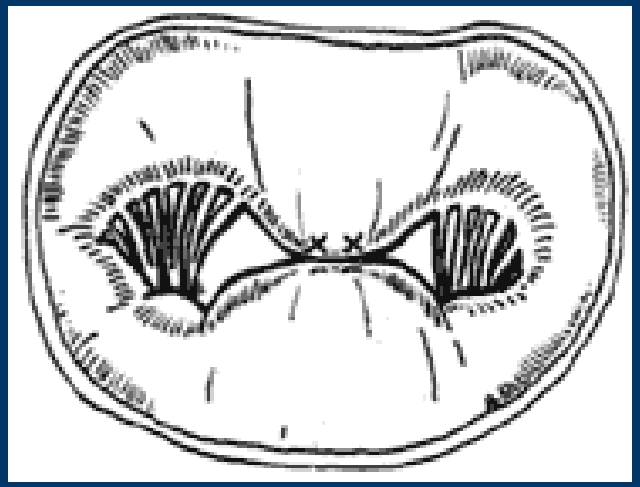
Iung et al. *Eur Heart J* 2003; 24: 1231-1243.

Need for Alternative Therapies

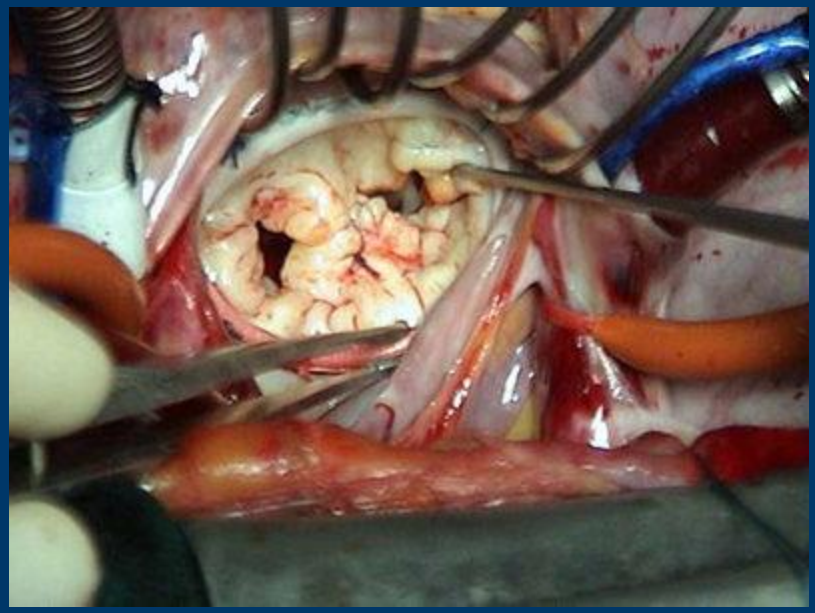
- Evolving technologies are all based upon surgical techniques
  - Edge-to-Edge Repair (Alfieri technique)
  - Annuloplasty
    - Indirect
    - Direct
  - Chordal Replacement
  - Percutaneous Mitral Valve Implant

Edge-to-Edge Repair: Alfieri Technique

- Described in 1992
  - Suture part of anterior and posterior leaflet edges together
  - Usually applied to A2-P2 central segment



- Usually used in conjunction with mitral annuloplasty



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Edge-to-Edge Repair

- Pathophysiologic effects of Edge-to Edge repair
  - Facilitates proper leaflet coaptation
  - Creates tissue bridge
  - Restrains LV wall

- Can lead to decrease in mitral valve area so should be avoided in patients with . . .
  - Rheumatic MR
  - Severe annular calcification with thickened leaflets
  - Ring size less than 30 mm

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The Mitraclip System

MitraClip System

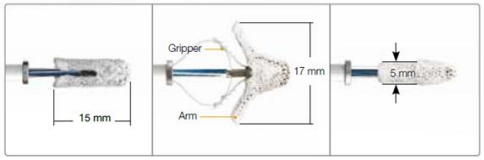
The MitraClip System performs **percutaneous mitral valve repair** by creating a vertical line of coaptation, forming a double-orifice valve.

- Beating heart procedure—no cardiopulmonary bypass
- Allows for real-time positioning and repositioning to optimize MR reduction
- Designed to preserve surgical options
- Femoral venous access
- Limited hospital length of stay

The Clip Delivery System and Steerable Guide Catheter are designed to fit co-axially to accurately position and reposition multiple implants with the use of one guide.

Steerable Guide Catheter

Clip Delivery System



MitraClip Device (Implant)

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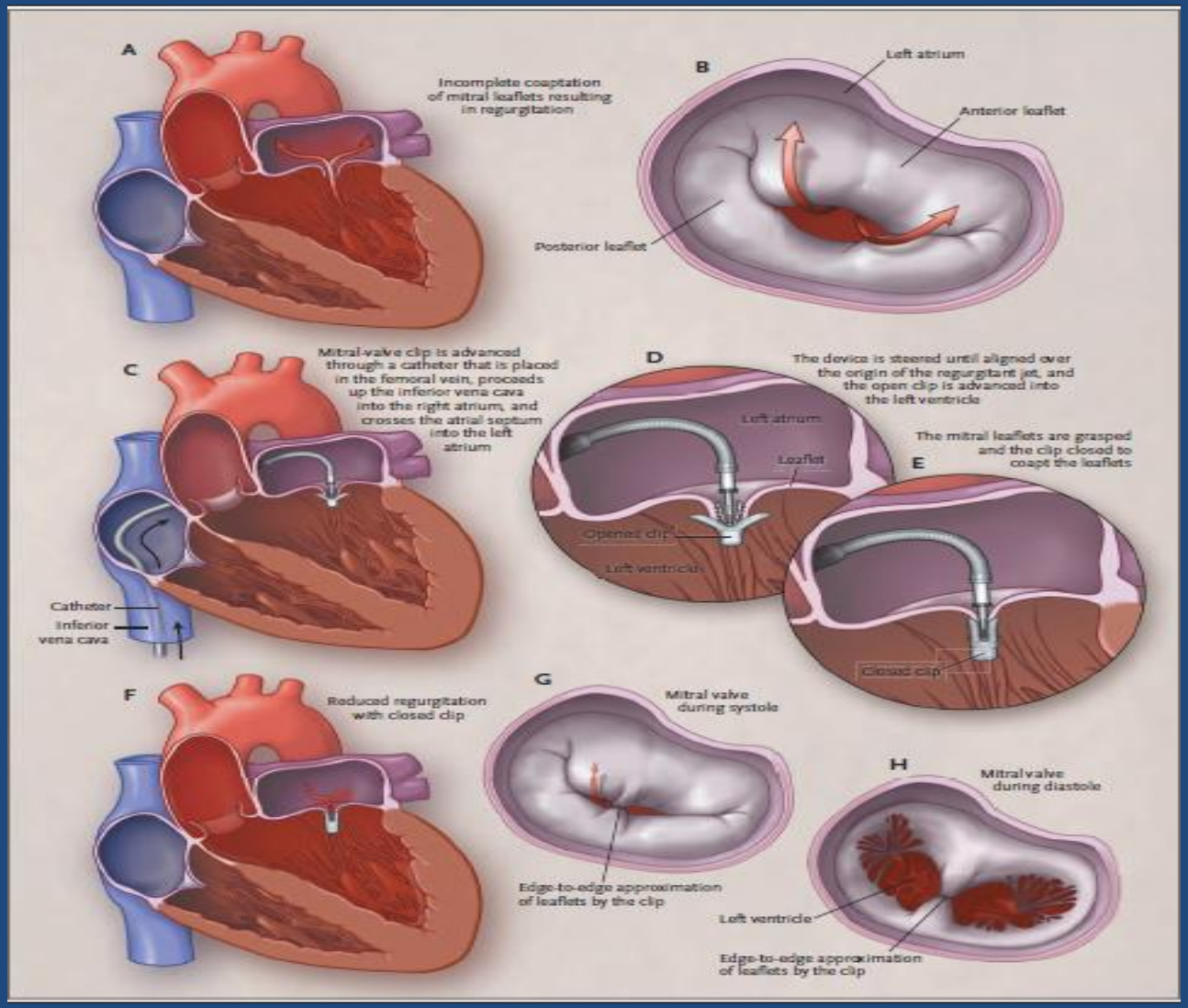
The MitraClip System



EVEREST II Randomized Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 14, 2011 VOL. 364 NO. 15

Percutaneous Repair or Surgery for Mitral Regurgitation

Ted Feldman, M.D., Elyse Foster, M.D., Donald D. Glower, M.D., Saibal Kar, M.D., Michael J. Rinaldi, M.D., Peter S. Fail, M.D., Richard W. Smalling, M.D., Ph.D., Robert Siegel, M.D., Geoffrey A. Rose, M.D., Eric Engeron, M.D., Catalin Loghin, M.D., Alfredo Trento, M.D., Eric R. Skipper, M.D., Tommy Fudge, M.D., George V. Letsou, M.D., Joseph M. Massaro, Ph.D., and Laura Mauri, M.D., for the EVEREST II Investigators*

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EVEREST II Study Design

- Design:
  - RCT comparing mitraclip vs. surgery in a 2:1 randomization fashion
- Primary Efficacy Endpoint
  - Composite of freedom from death, from mitral valve surgery and from grade 3+ or 4+ MR at 12 months
- Primary Safety Endpoint
  - Rate of major adverse events at 30 days
    - Includes death, MI, reoperation for failed MV repair, CT surgery for complications, stroke, renal failure, wound infection, mechanical ventilation > 48 hrs, GI complication requiring surgery, new-onset AF, septicemia or transfusion of > 2U PRBC

EVEREST II Study Design

- **Inclusion Criteria**
  - 3+ or 4+ chronic MR AND
    - Symptomatic with EF > 25% and LVSDd < 55mm

      OR
    - Asymptomatic with . . .
      - EF 25%-60% *or*
      - LVSDd > 40 mm *AND*
      - Atrial Fibrillation *or*
      - PASP > 50 at rest or > 60 with exercise
- **Exclusion Criteria**
  - Anatomical criteria making percutaneous closure untenable
  - Recent MI
  - Prior mitral valve surgery or valvuloplasty
  - Not candidate for surgery

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EVEREST II: Baseline Characteristics

Characteristic	MitraClip (N=184)	Surgery (N=95)	p-value
Age (years)	67.3 ± 12.8	65.7 ± 12.9	0.32
Male sex	115 (62%)	63 (66%)	0.60
Prior CHF	*167 (91%)*	*74 (78%)*	*0.005*
Prior MI	40 (22%)	20 (21%)	0.99
AF	59 (34%)	35 (39%)	0.42
Diabetes	14 (8%)	10 (11%)	0.50
COPD	27 (15%)	14 (15%)	0.99
Prior CABG	38 (21%)	18 (19%)	0.87

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EVEREST II: Baseline Characteristics

Characteristic	MitraClip (N=184)	Surgery (N=95)	p-value
LVEF	60.0 ± 10.1	60.6 ± 11.0	0.65
NYHA Class			0.16
I	17 (9%)	19 (20%)	
II	73 (40%)	21 (33%)	
III	82 (45%)	41 (43%)	
IV	12 (7%)	4 (4%)	
Severity of MR			0.38
1-2+	8 (4%)	7 (7%)	
3+	130 (71%)	67 (71%)	
4+	46 (25%)	21 (22%)	
Cause of MR			0.81
Functional	49 (26%)	26 (27%)	
Degenerative	135 (74%)	69 (73%)	

EVEREST II: Efficacy Results

Event	MitraClip	Surgery	p-value
Composite Efficacy Endpoint	***100 (55%)***	***65 (73%)***	***0.007***
Death	11 (6%)	5 (6%)	1.00
Surgery for MV dysfunction	*37 (20%)*	*2 (2%)*	*< 0.001*
Grade 3+ or 4+ MR	38 (21%)	18 (20%)	1.00

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EVEREST II: Safety Results

Event	MitraClip	Surgery	p-value
Any Major Adverse Event	*27 (15%)*	*45 (48%)*	*< 0.001*
- *Excluding transfusion*	*9 (5%)*	*9 (10%)*	*0.23*
Transfusion ≥ 2U PRBC	24 (13%)	42 (45%)	< 0.001
Urgent CT surgery	4 (2%)	4 (4%)	0.57
Renal failure	1 (< 1%)	0	1.00
Stroke	2 (1%)	2 (2%)	0.89
Mechanical ventilation ≥ 48 hrs	0 (0%)	4 (4%)	0.02

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EVEREST II: Secondary Endpoints

Characteristic	MitraClip (N=184)	Surgery (N=95)	p-value
Change in LVEF	-2.8 ± 7.2 *	-6.8 ± 10.1 *	0.005
Change in EDV	-25.3 ± 28.3 *	-40.2 ± 35.9 *	0.004
Change in QOL score			
12 mo. (physical)	4.4 ± 9.8 *	4.4 ± 10.4 *	0.98
12 mo. (mental)	5.7 ± 9.6 *	3.8 ± 10.3 *	0.24
Severity of MR			< 0.001
0-1+	66 (43%)	52 (76%)	
2+	59 (39%)	14 (20%)	
3+	21 (14%)	3 (4%)	
4+	7 (5%)	0 (0%)	

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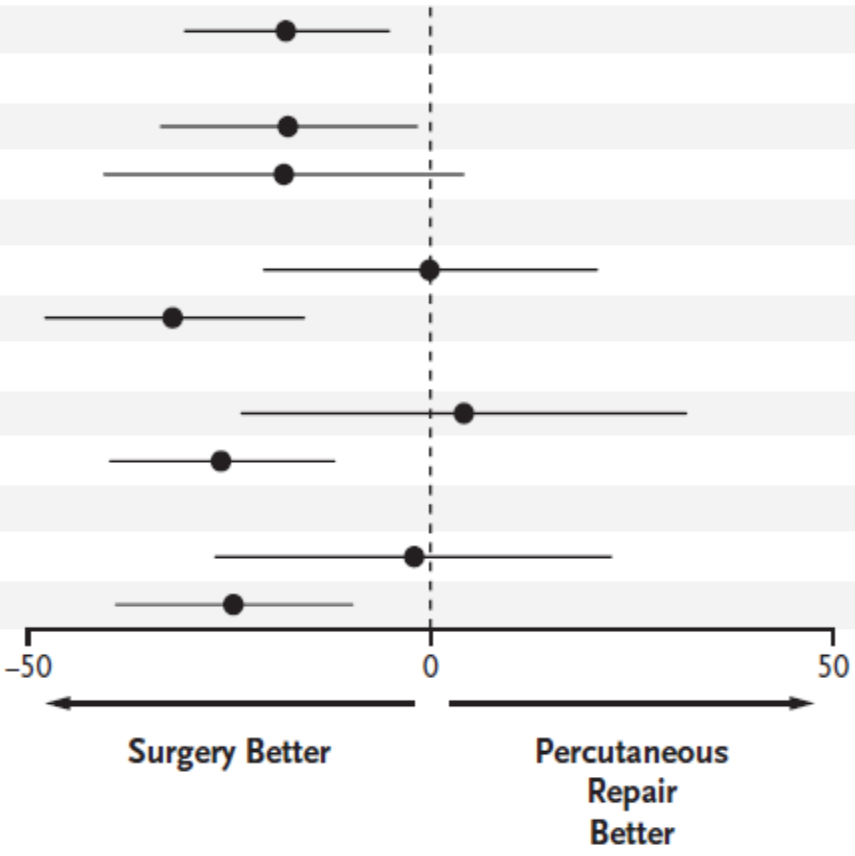
* - p value < 0.01 from baseline

EVEREST II: Subgroup Analyses

Subgroup	Percutaneous Repair	Surgery	P Value for Interaction
	no. of events/total no. (%)		
All patients	100/181 (55)	65/89 (73)	
Sex			0.97
Male	63/114 (55)	43/59 (73)	
Female	37/67 (55)	22/30 (73)	
Age			0.009
≥70 yr	52/86 (60)	23/38 (61)	
<70 yr	48/95 (51)	42/51 (82)	
MR			
Functional	26/48 (54)	12/24 (50)	0.02
Degenerative	74/133 (56)	53/65 (82)	
LVEF			0.06
<60%	35/68 (51)	15/28 (54)	
≥60%	64/111 (58)	50/61 (82)	



EVEREST II RCT: Summary

- Surgery was found to be superior to MitraClip in terms of primary efficacy endpoint
  - Driven by need for MV surgery in MitraClip group
- MitraClip was found to be superior to Surgery in terms of primary safety endpoint
  - Driven entirely by need for transfusions with surgery
- MitraClip patients did experience durable improvements
  - Quality of Life measurements
  - LV ejection fraction
  - LVEDV and dimensions
  - Severity of MR

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EVEREST II High Risk Registry

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Acute and 12-Month Results With Catheter-Based Mitral Valve Leaflet Repair

The EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study

Patrick L. Whitlow, MD,* Ted Feldman, MD,† Wes R. Pedersen, MD,‡ D. Scott Lim, MD,§ Robert Kipperman, MD,‖ Richard Smalling, MD, PHD,¶ Tanvir Bajwa, MD,# Howard C. Herrmann, MD,** John Lasala, MD, PHD,†† James T. Maddux, MD,‡‡ Murat Tuzcu, MD,* Samir Kapadia, MD,* Alfredo Trento, MD,§§ Robert J. Siegel, MD,§§ Elyse Foster, MD,‖‖ Donald Glower, MD,¶¶ Laura Mauri, MD,## Saibal Kar, MD,§§ on behalf of the EVEREST II Investigators

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EVEREST II High Risk Registry

- **Study Design**: Multicenter, single arm study

- **Key Inclusion Criteria**
  - Symptomatic 3+ or 4+ MR
  - Predicted surgical risk ≥ 12% by STS score or surgeon evaluation

- **Comparator Group**
  - Retrospectively matched group of patients treated with maximum medical therapy

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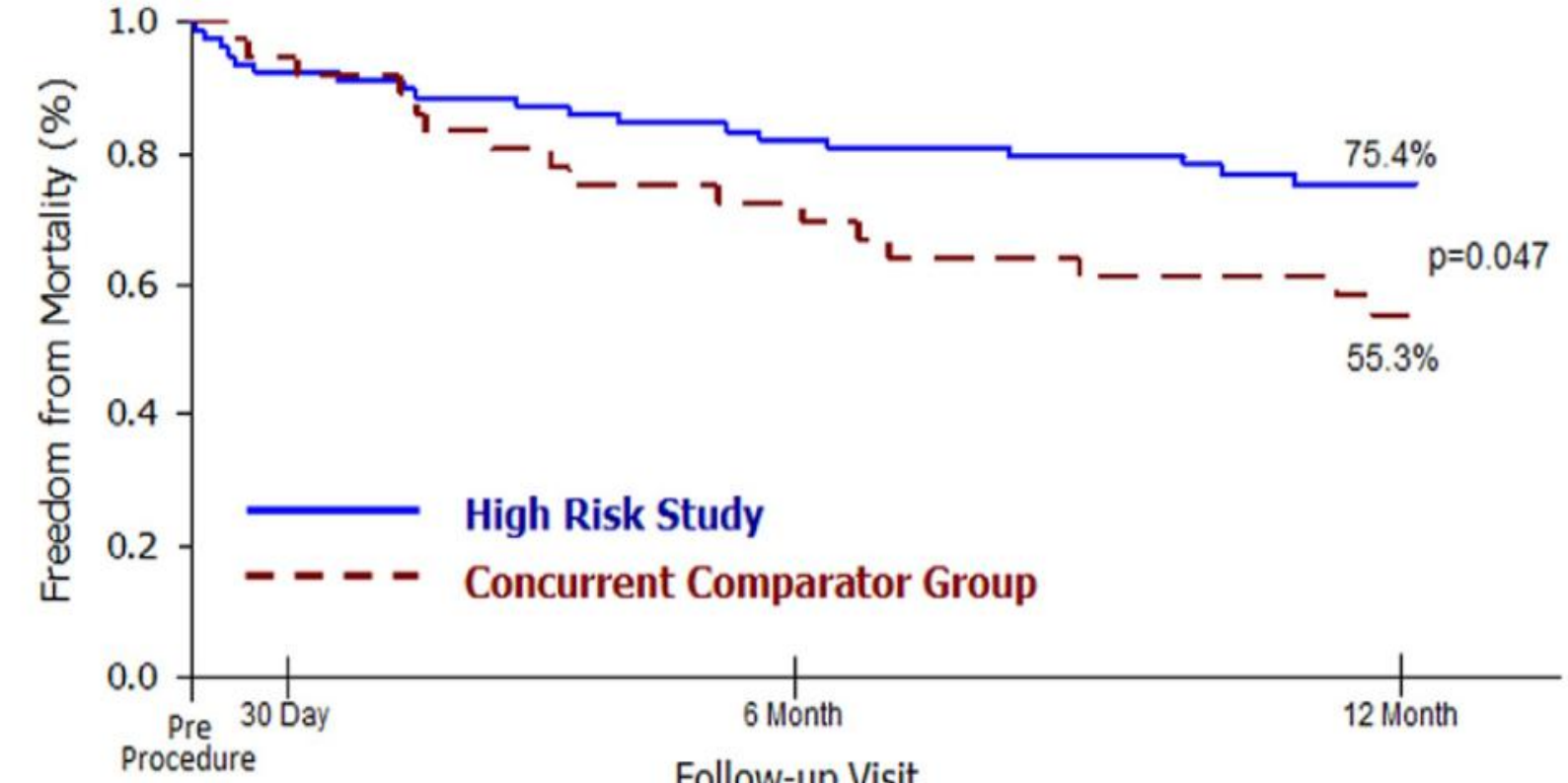
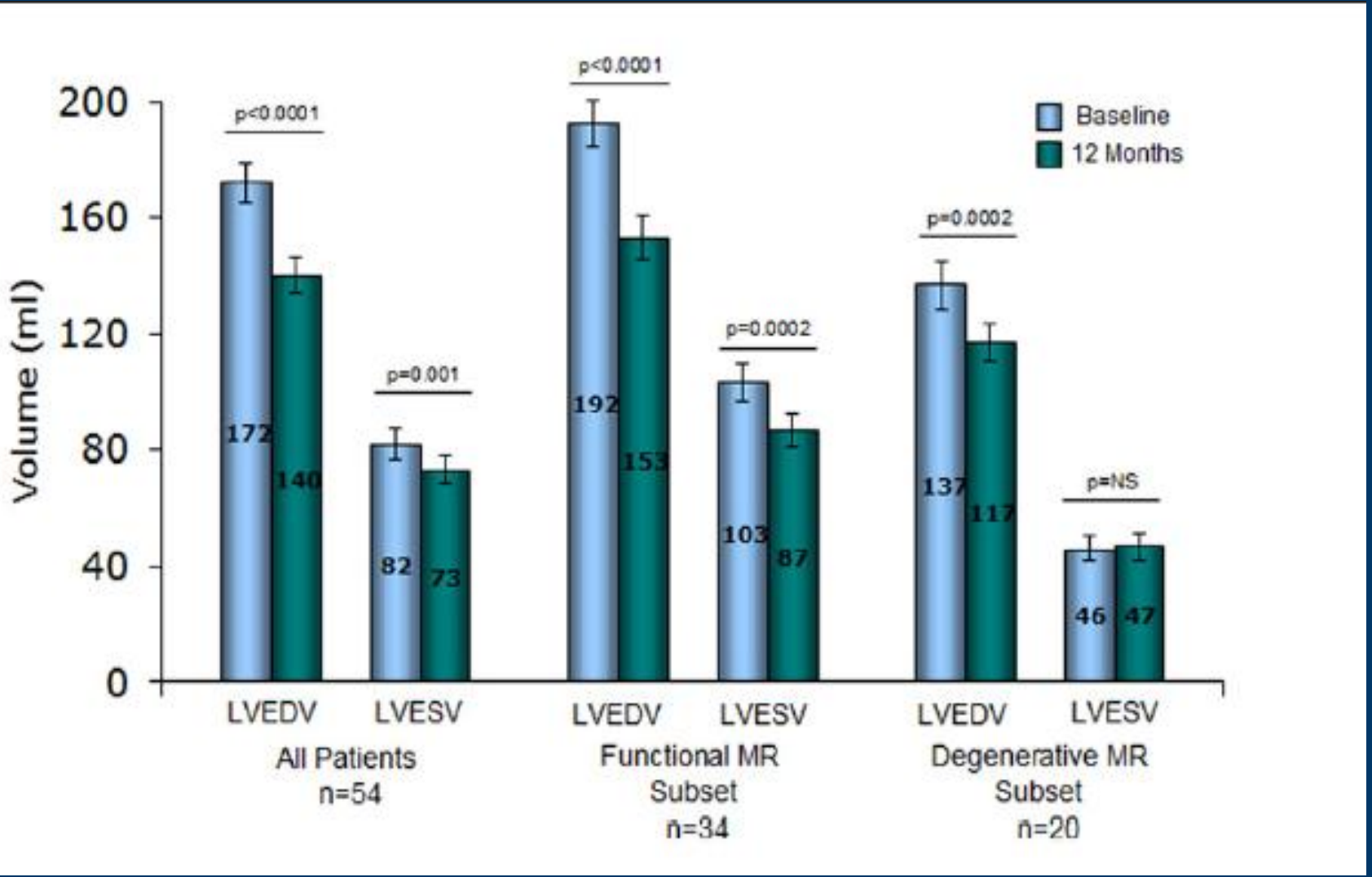
EVEREST II HRR: Baseline Characteristics

Characteristic	MitraClip (N=78)	Medical Rx (N=38)	p-value
Age (years)	76.7 ± 9.8	77.2 ± 13.0	0.85
Male sex	62%	50%	0.84
Prior CHF	*100%*	*83.3%*	*0.0007*
COPD	34.6%	33.3%	0.95
NYHA Class III or IV	89.7%	83.9%	0.20
LVEF	54.4 ± 13.7	55.2± 18.1	0.82
MR Etiology Functional Degenerative	 59.0 41.0	 63.9 36.1	0.49
STS Score	14.2 ± 8.2	14.9 ± 8.5	0.68

EVEREST II HRR: Mortality



EVEREST II HRR: LV Volumes



EVEREST II HRR: Other Outcomes

Outcome at 12 months	MitraClip	p-value
Death		N/A
30 days	6/78 (7.7%)	
12 months	19/78 (24.4%)	
Stroke	2/78 (2.6%)	N/A
NYHA Class		
I/II	40/54 (74.1%)	< 0.0001
III/IV	14/54 (25.9%)	< 0.0001
MR grade ≤ 2+	42/54 (77.8%)	< 0.0001
Quality of Life (n=47)		
Physical	31.6 (BL) → 36.5 (12 mo)	0.01
Mental	44.2 (BL) → 49.2 (12 mo)	0.06

EVEREST II High Risk Registry: Summary

- **Patients with moderate to severe MR at high risk for MV surgery could be successfully treated with MitraClip**
  - Procedural mortality rate at 30 days less than predicted for surgery and similar to comparator control group
  - Durable improvements in NYHA functional class, decrease in severity in MR and improvement in LV volumes
- **Limitations**
  - Comparator group recruited retrospectively
  - Limited number of patients
  - Heterogeneous group with regards to determination of “high risk”

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Current Status of the MitraClip

- October 24, 2013: FDA approved the MitraClip for the following commercial indication:
  - "*The MitraClip is intended to treat patients with significant symptomatic* ***degenerative*** *mitral regurgitation with MR ≥ 3+ who have too high a risk for surgery*"

- COAPT trial to evaluate the role of MitraClip in treating functional MR is ongoing

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COAPT Trial

- **Design:** Prospective, multicenter, RCT
- **Objective:**
  - examine safety and efficacy of MitraClip device used in addition to standard care for *functional* MR and CHF compared to standard care alone
- **Primary Endpoints**
  - *Efficacy*: recurrent HF hospitalizations at 12 months
  - *Safety*: composite of mortality, stroke, LVAD, heart transplant or worsening kidney function at 12 months

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Case History: BC

- 89 y/o female, known severe mitral regurgitation
- *Chief Complaint*: increasing fatigue, dyspnea on exertion, weakness
- *Hx:* HTN, CKD, Hx Breast Cancer 2003 s/p lumpectomy, squamous cell 2007, right nephrectomy 1970, severe MR, osteoporosis
- *STS score MV Repair* – 5%
- *STS score MV Replacement* – 8.3%
- Surgical evaluation with Dr Borkon: High surgical risk

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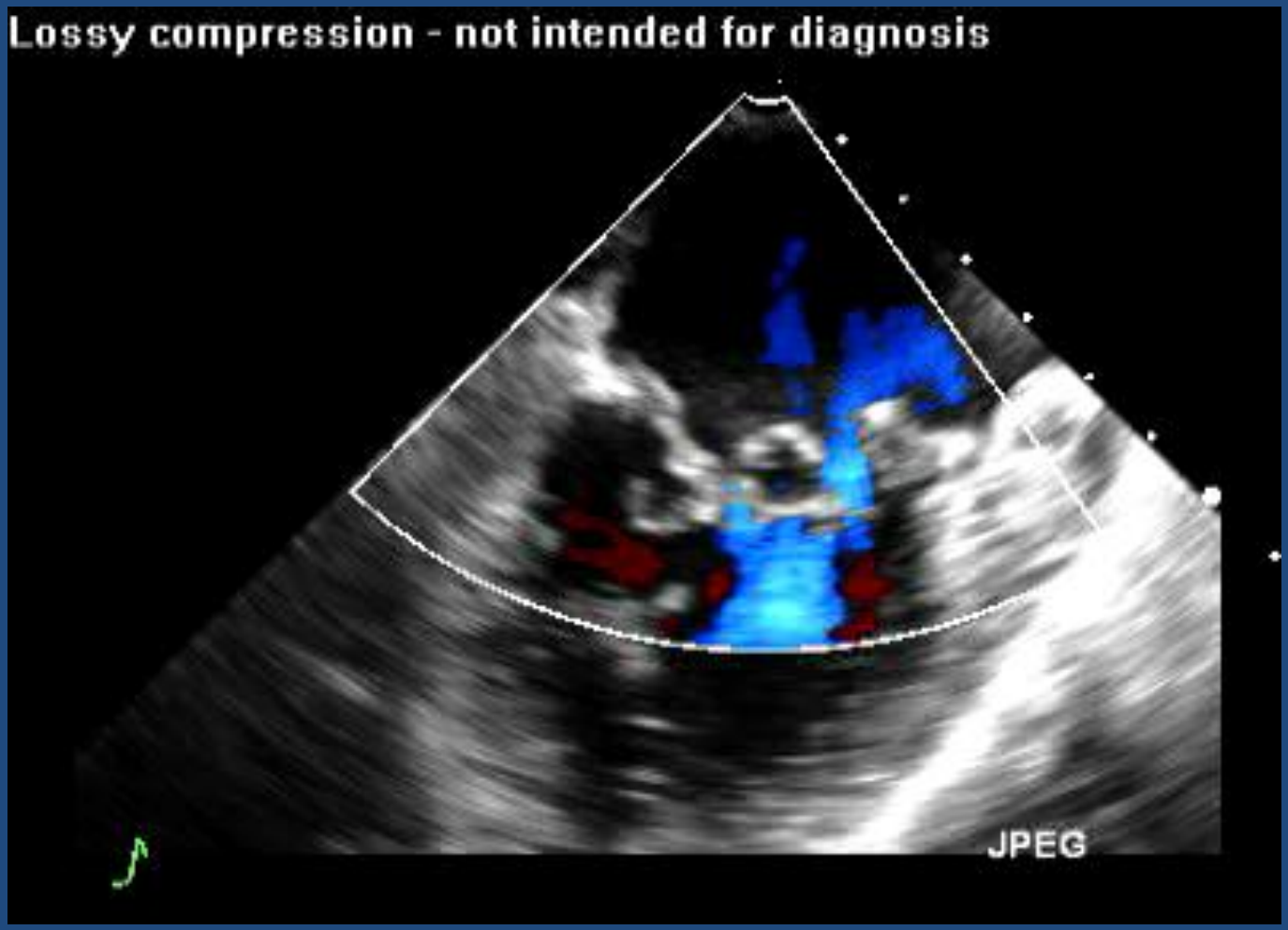
BC: TEE

- CONCLUSIONS

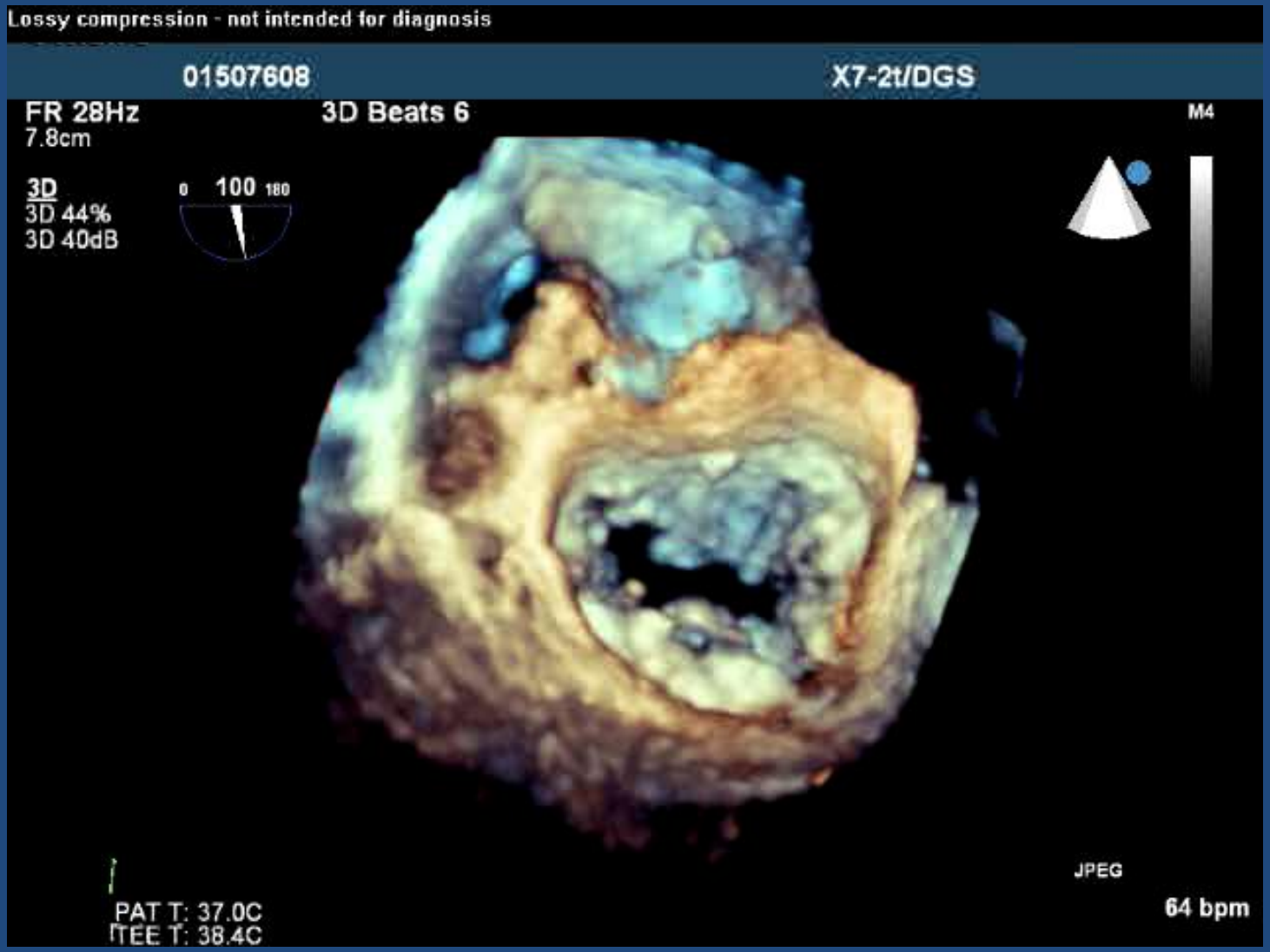
  1. Normal left ventricular systolic function, with an estimated ejection fraction of 60%.

  2. Diffusely myxomatous mitral valve with bileaflet prolapse. Moderate to severe mitral regurgitation. There is more prominent prolapse involving P1 and P2 scallops. Regurgitant volume is 26 cm^3. Regurgitant fraction is 50%.

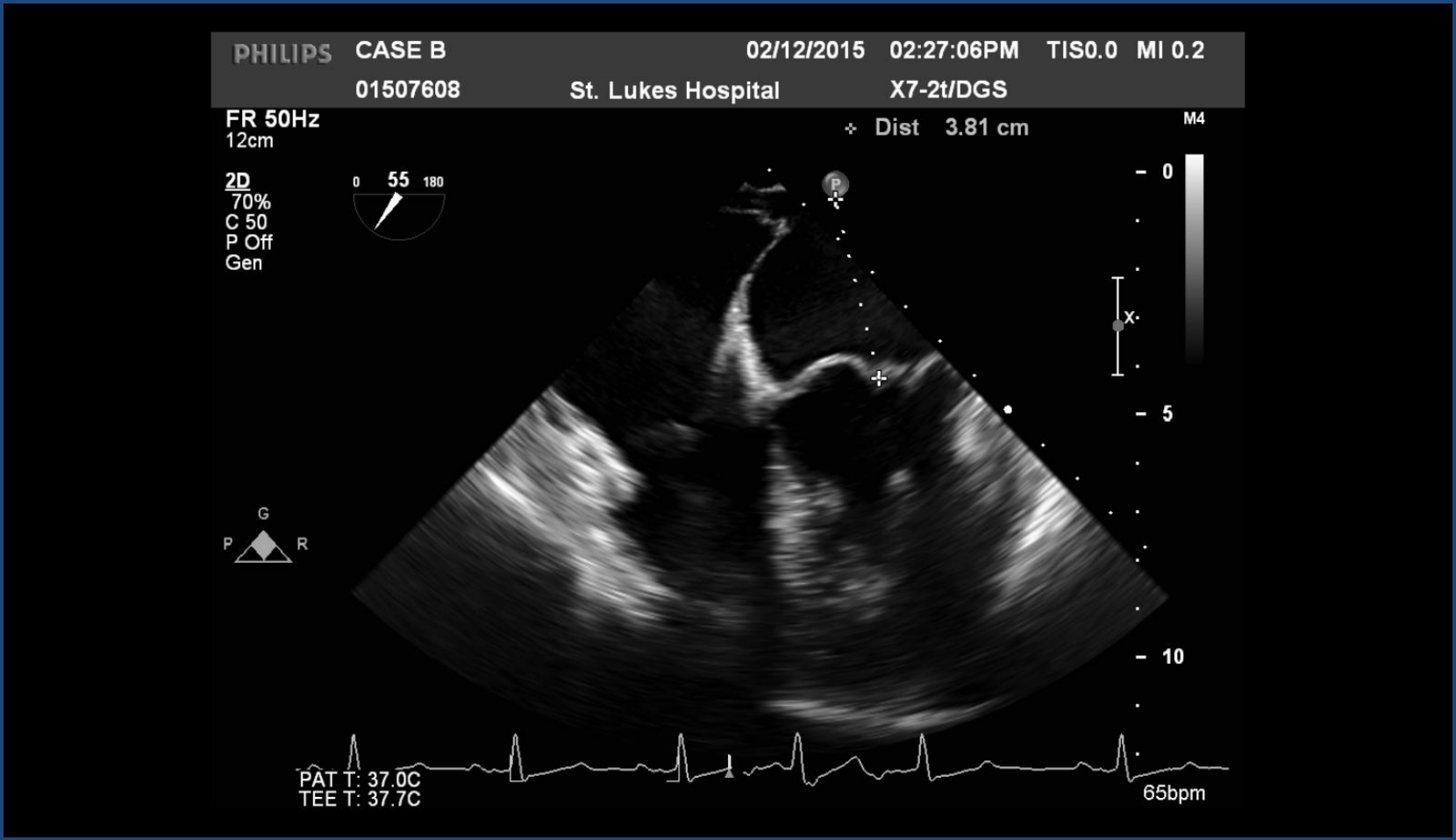
BC Pre-procedure TEE



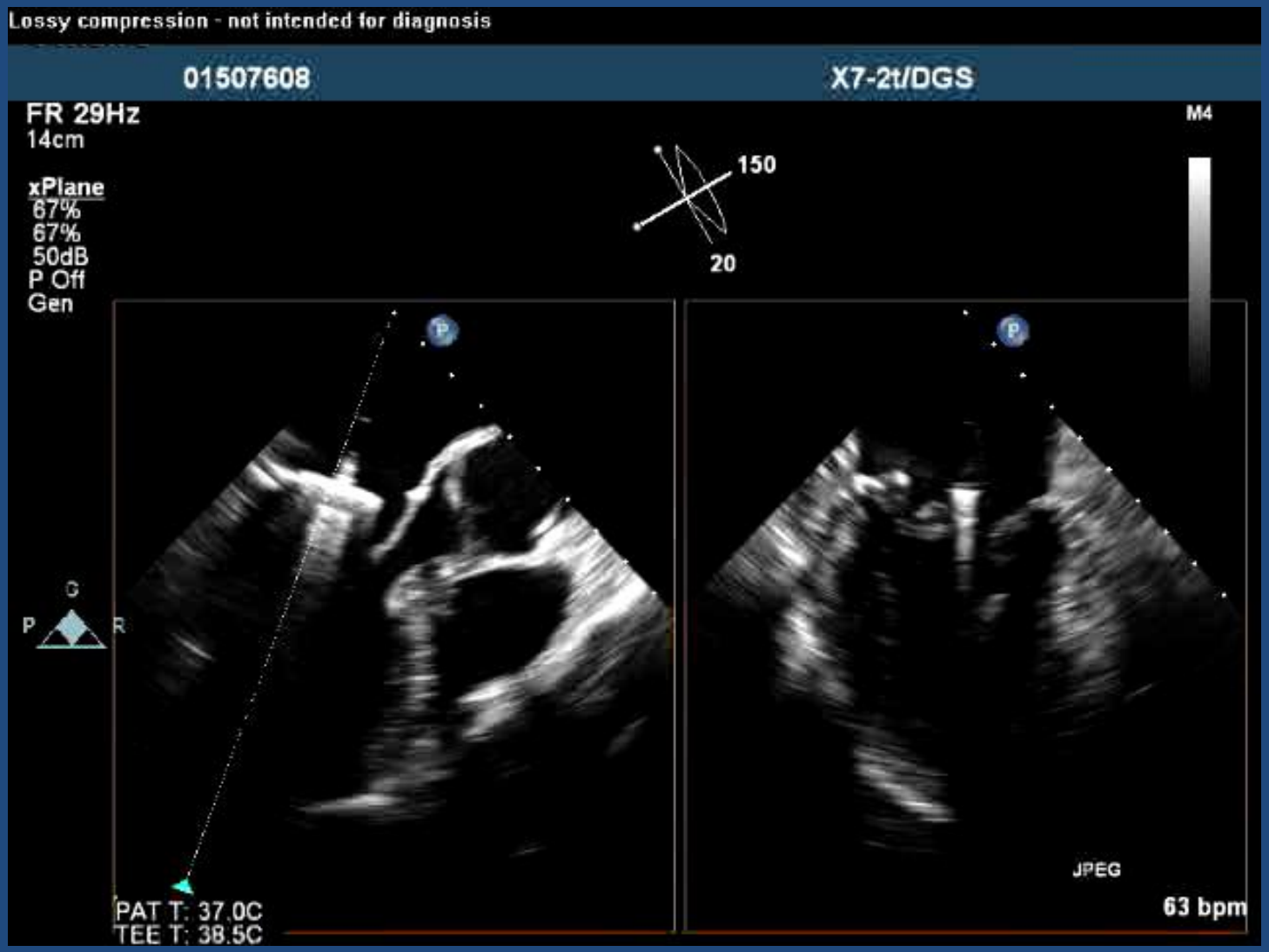
BC Pre-procedure TEE



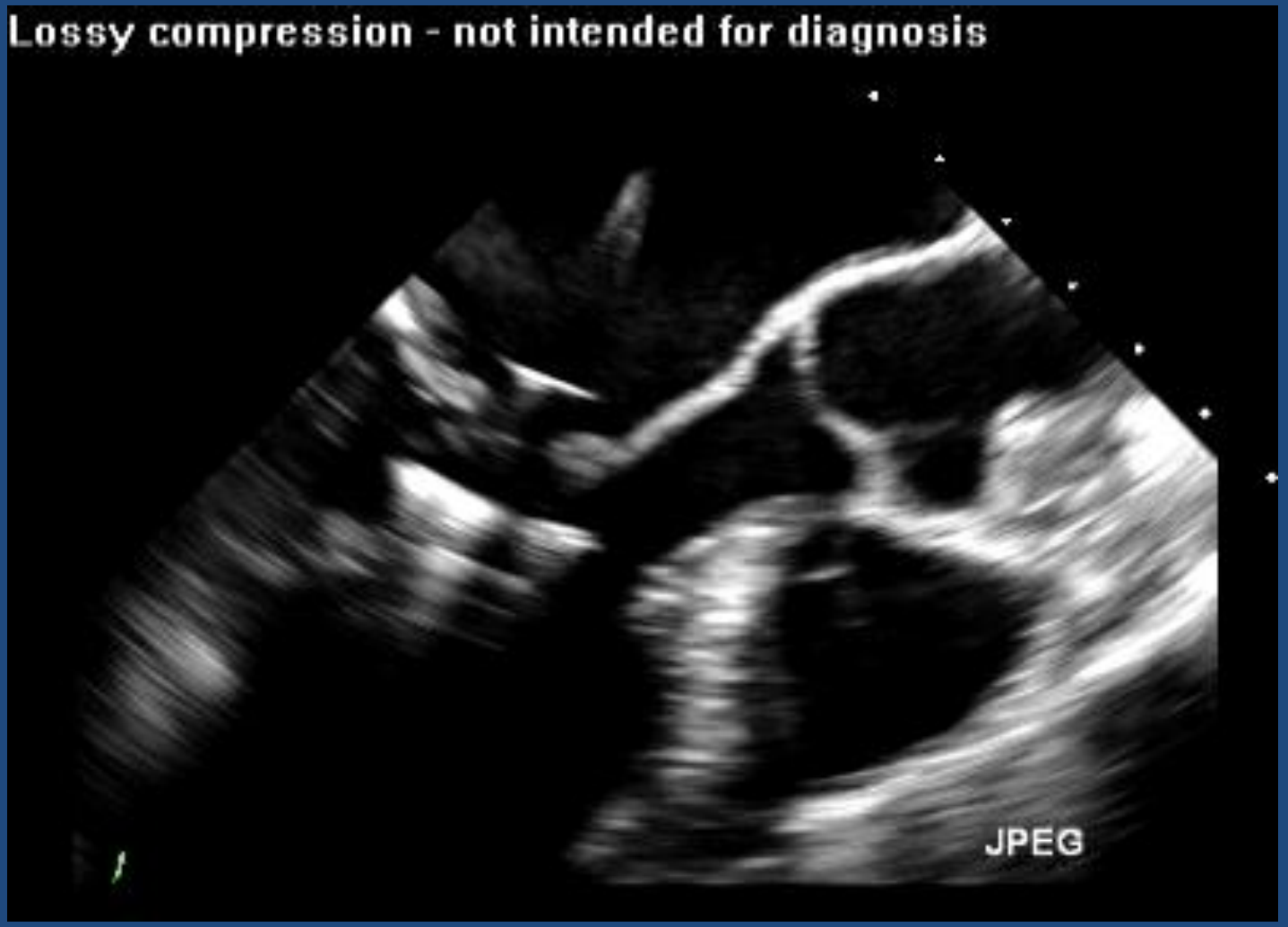
Crossing the Septum



Clip Alignment

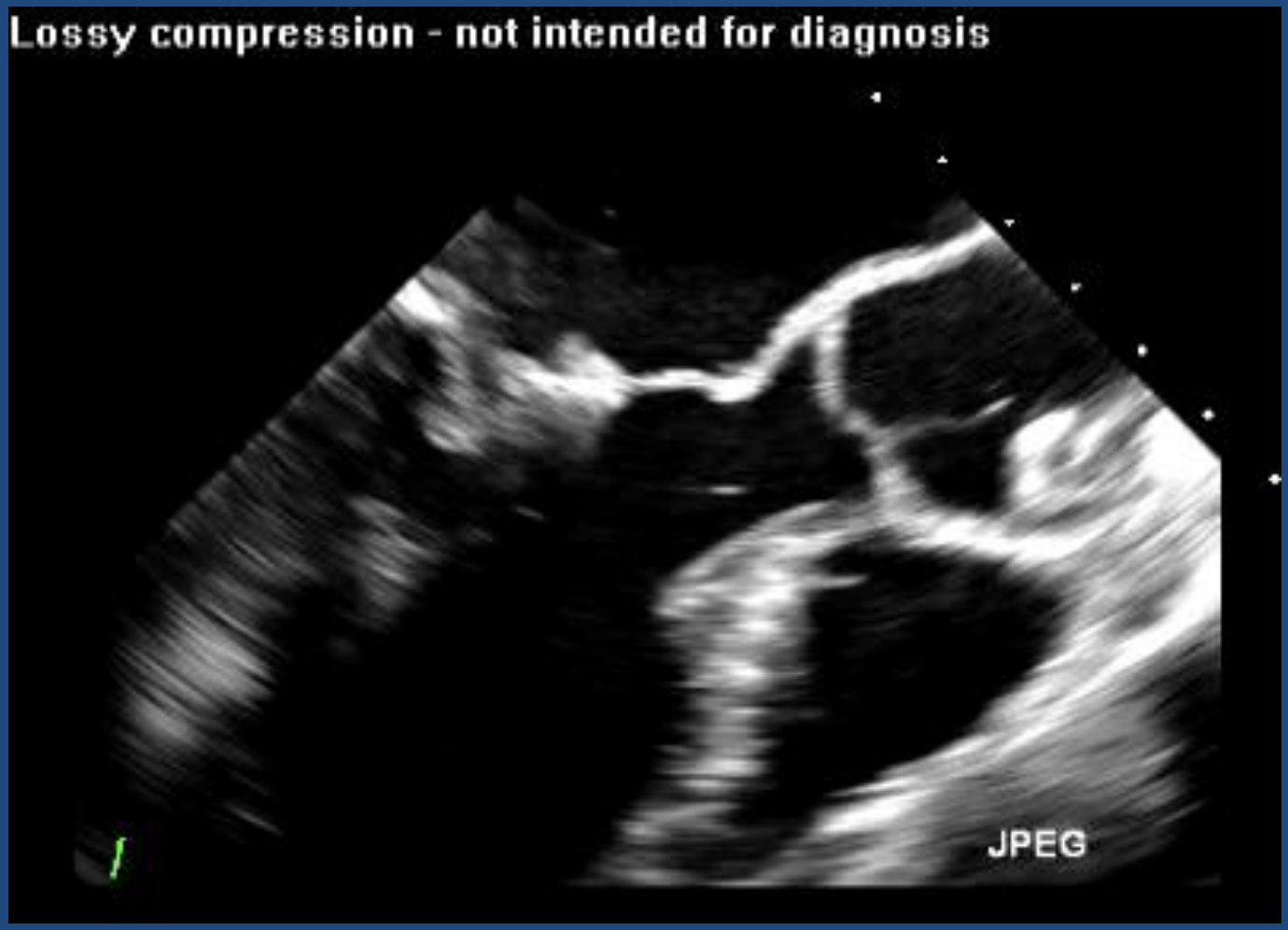


Clip in LV

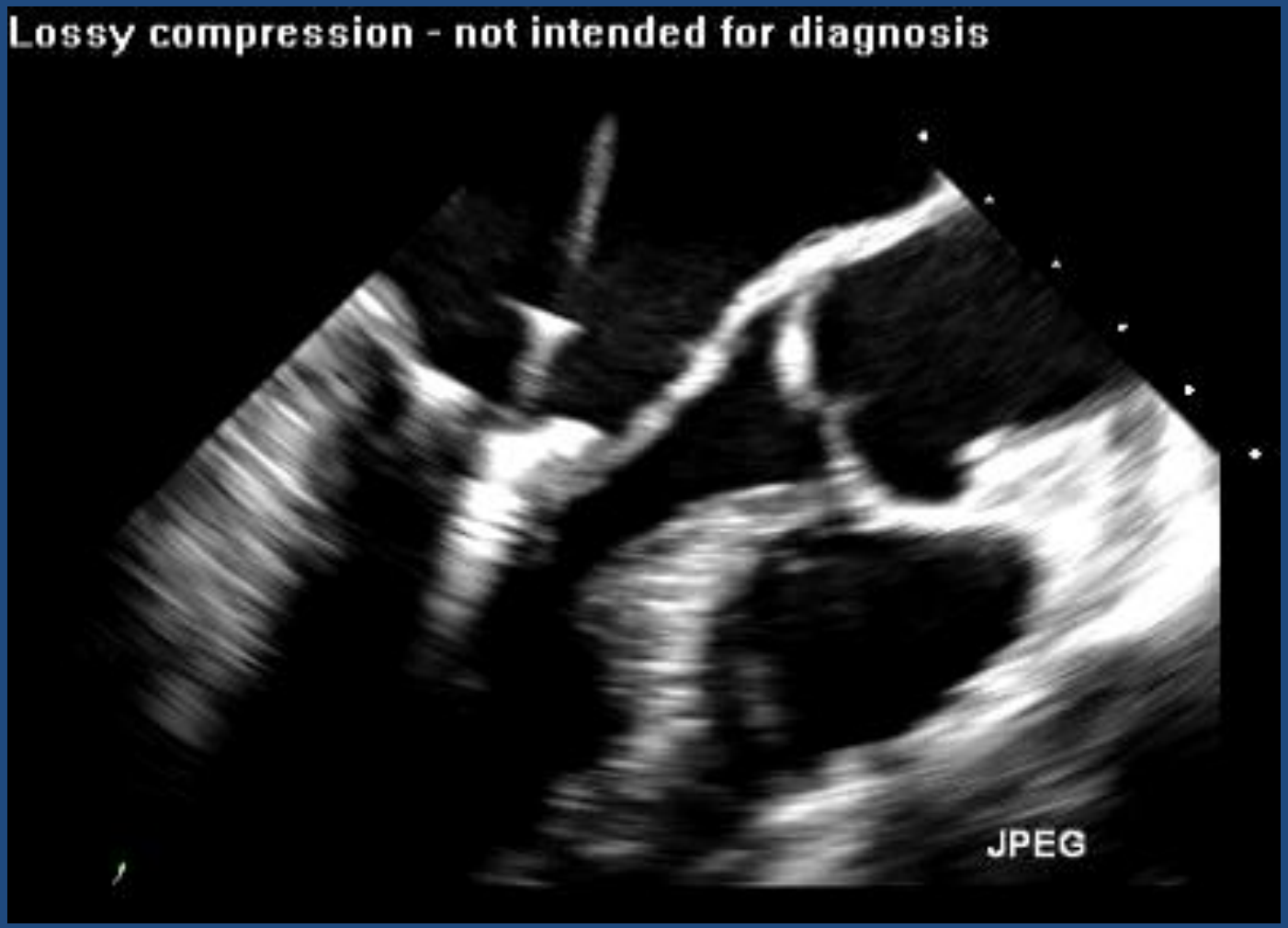


Clip in LV

Failed Grasp

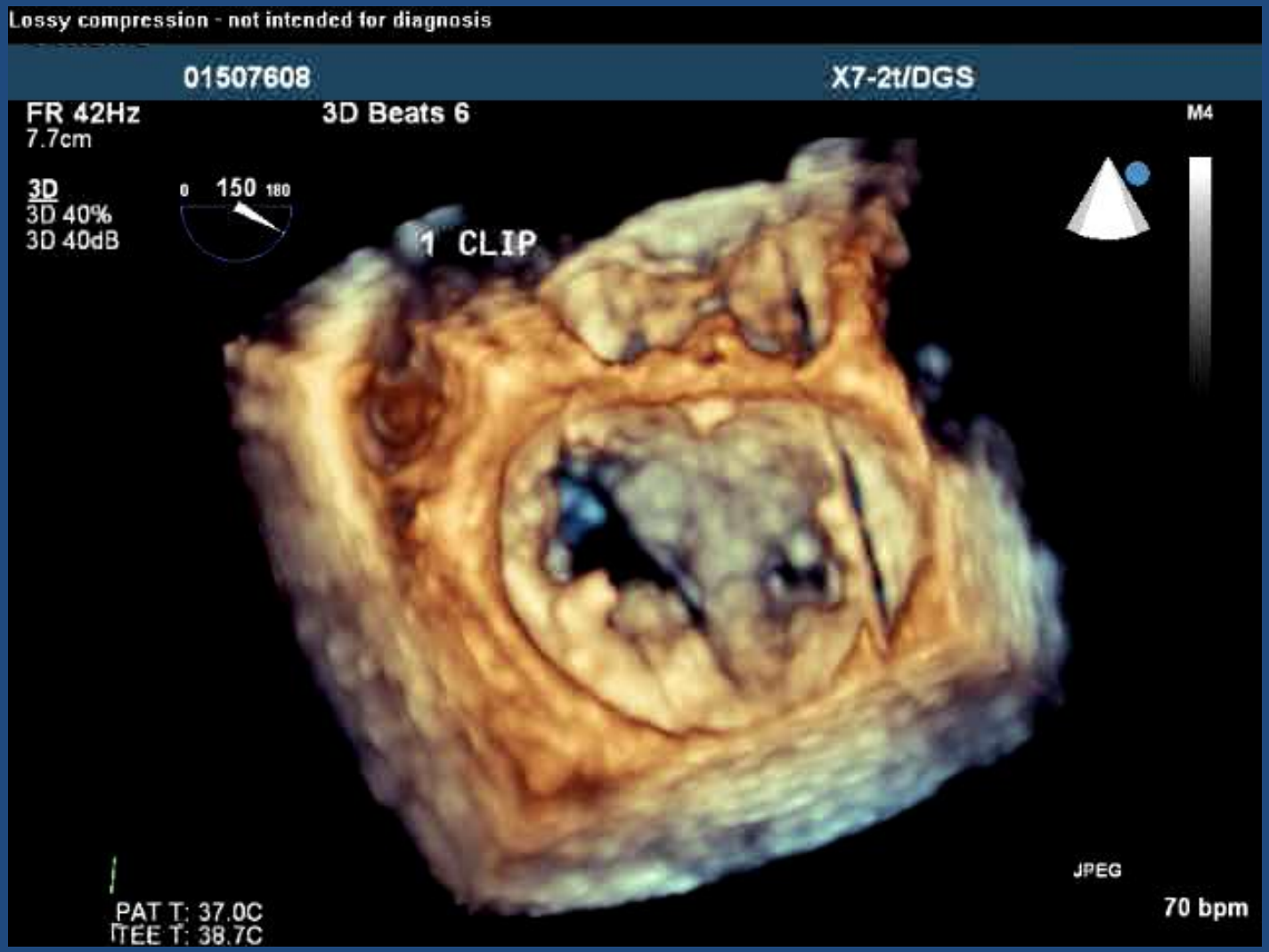


Successful Grasp



Successful Grasp

3D Imaging


Lossy compression - not intended for diagnosis
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FR 42Hz
7.7cm
3D Beats 6
M4
3D
3D 40%
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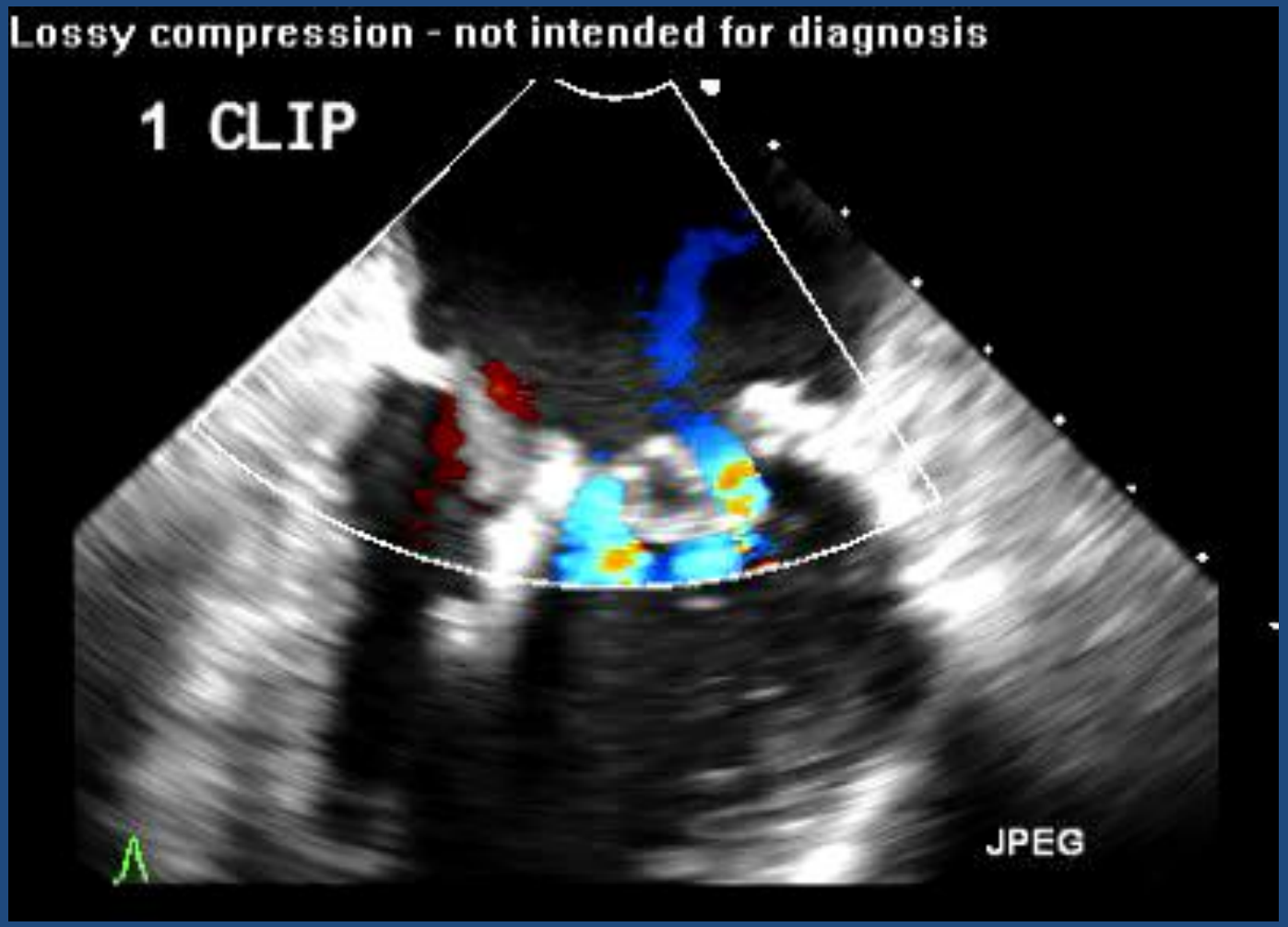
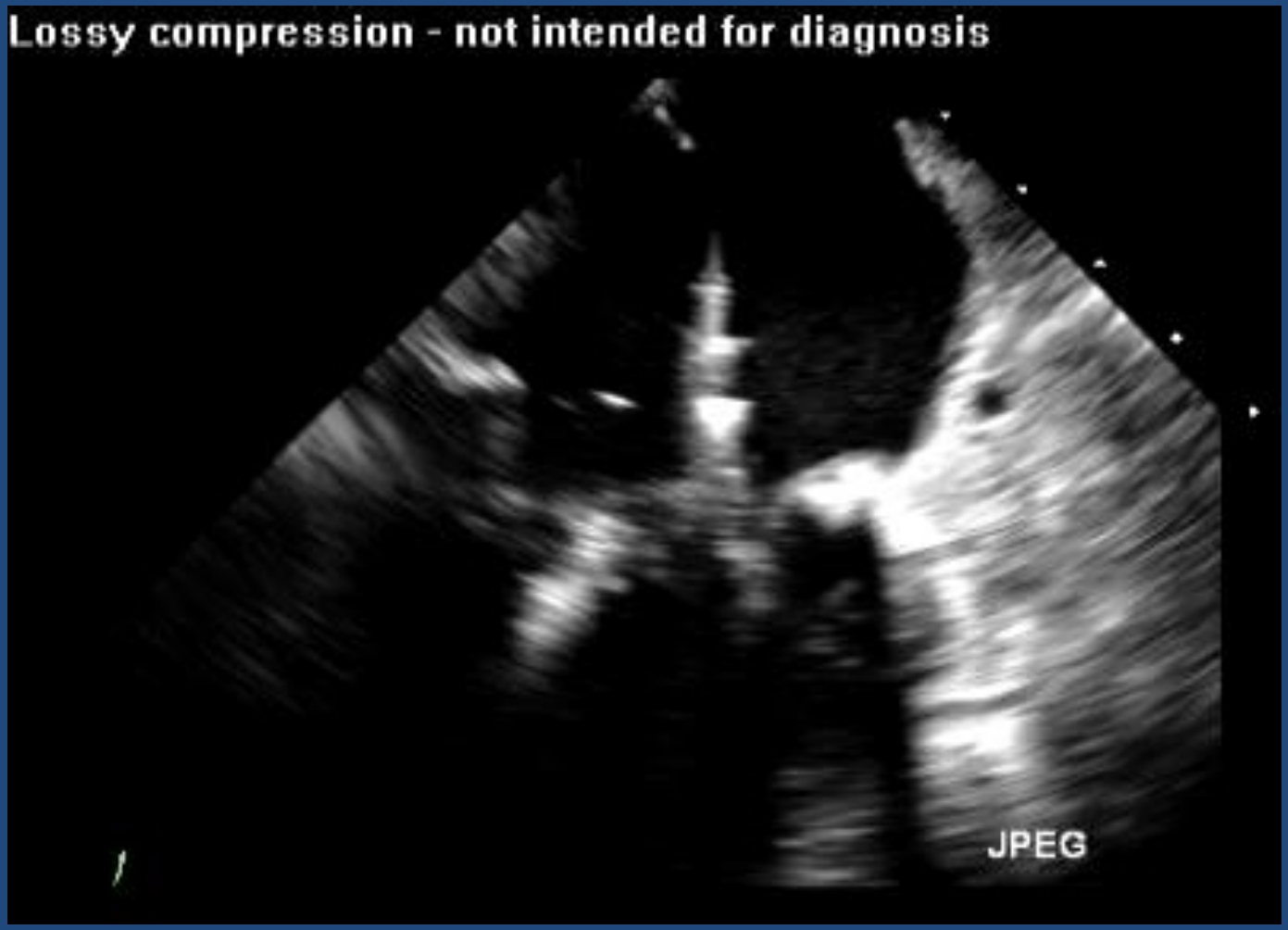
1 CLIP
JPEG
PAT T: 37.0C
TEE T: 38.7C
70 bpm

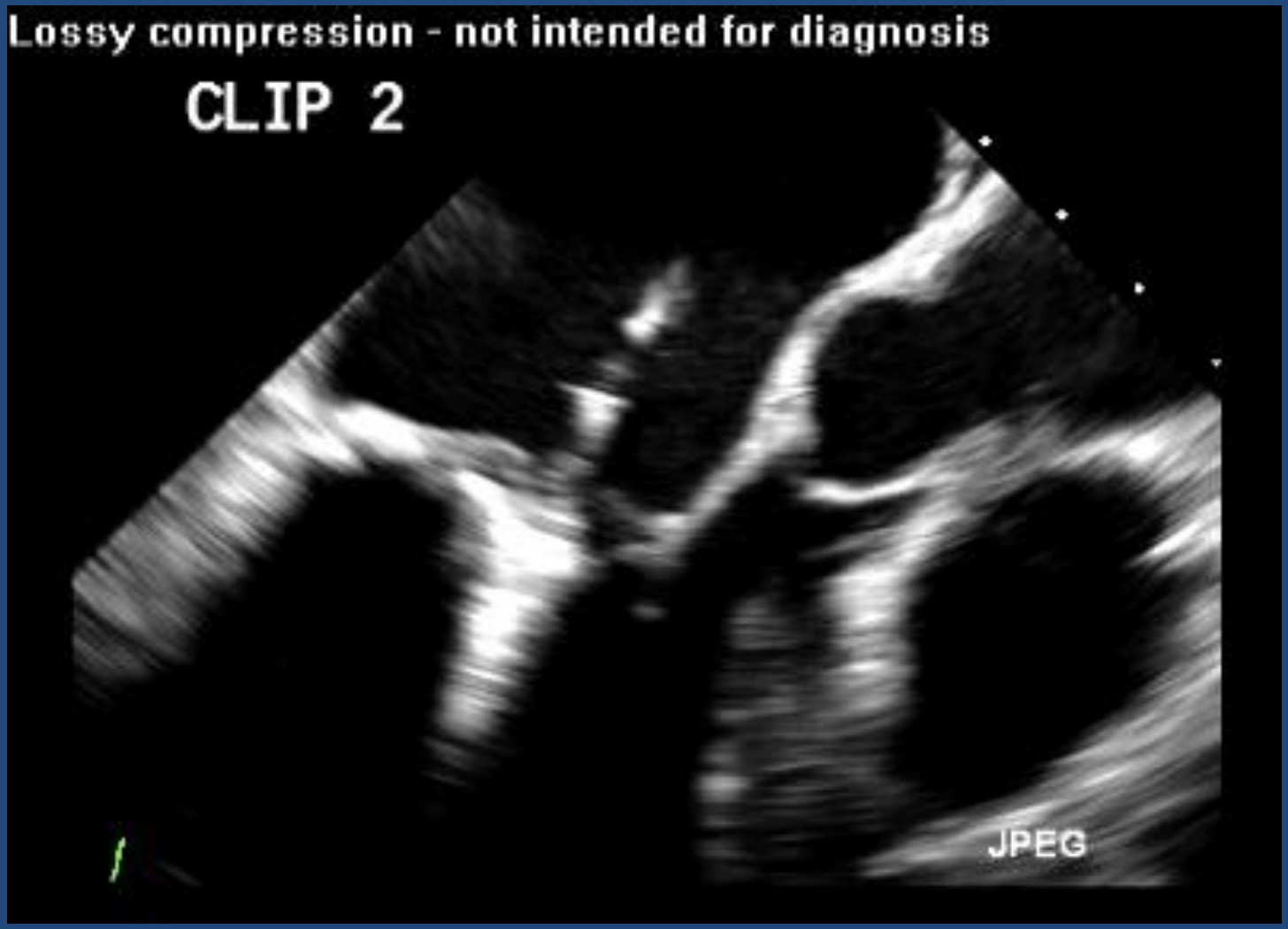
Residual MR



Advancing 2nd Clip

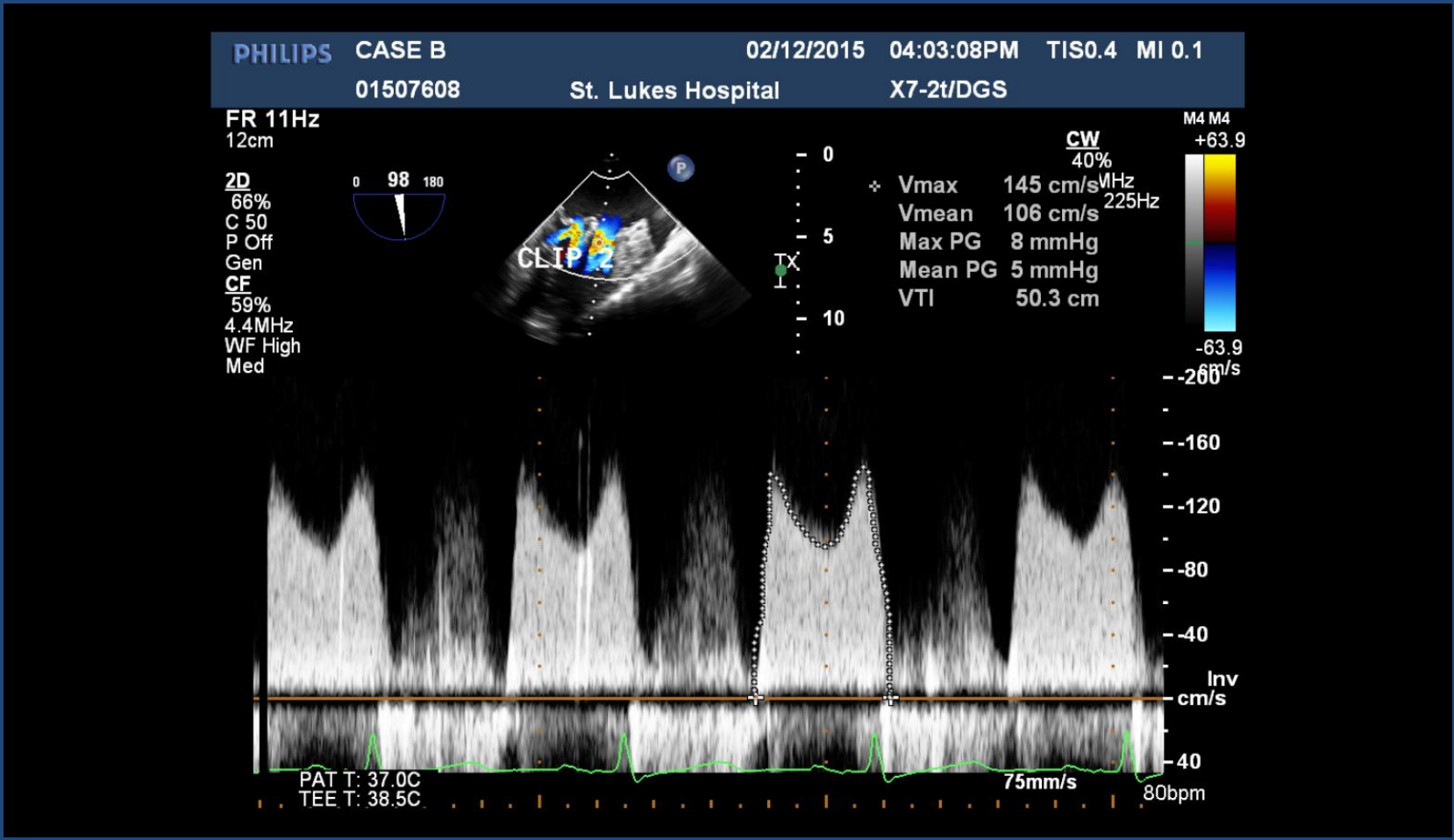


2nd Grasp

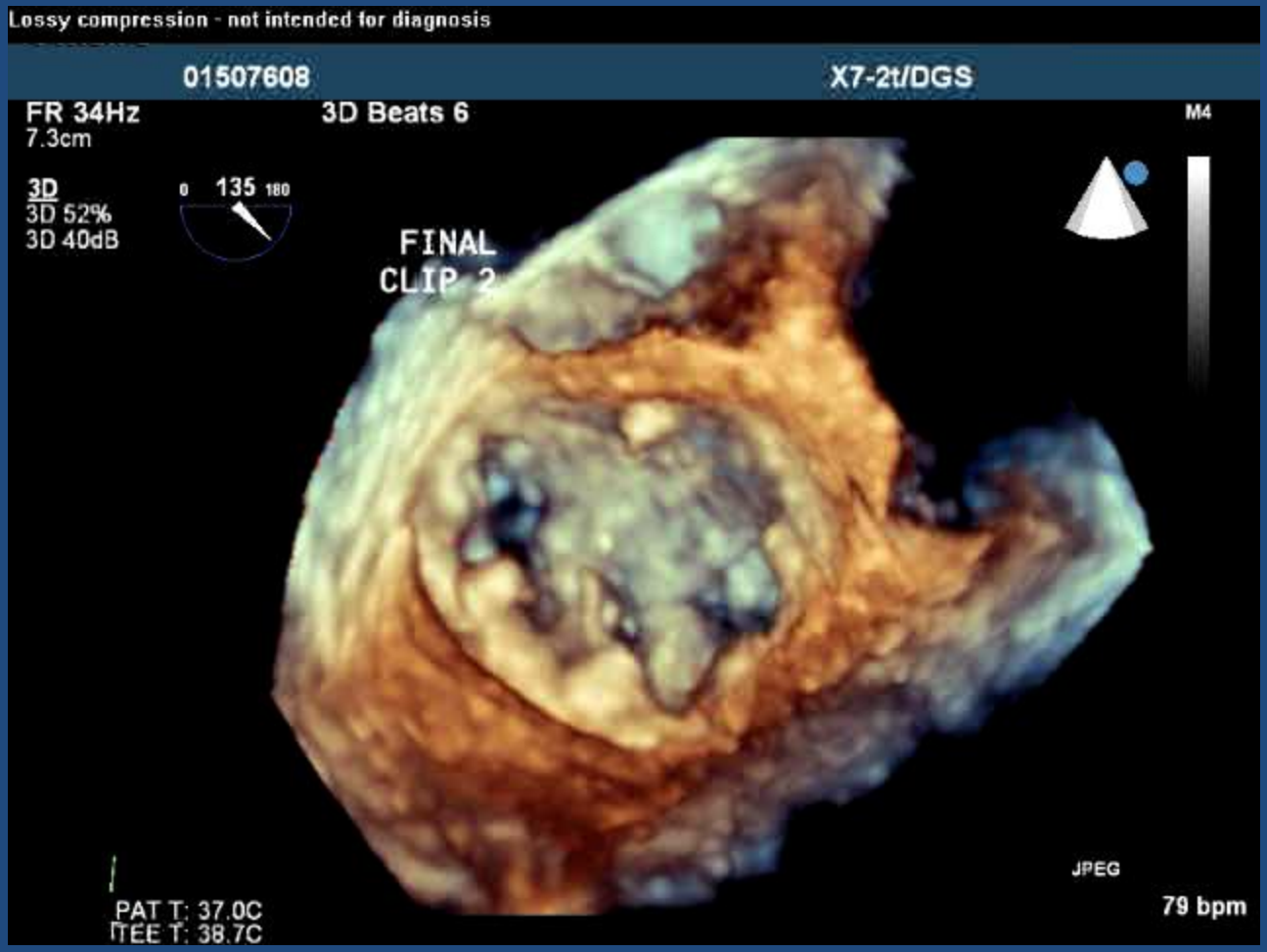


2nd Grasp

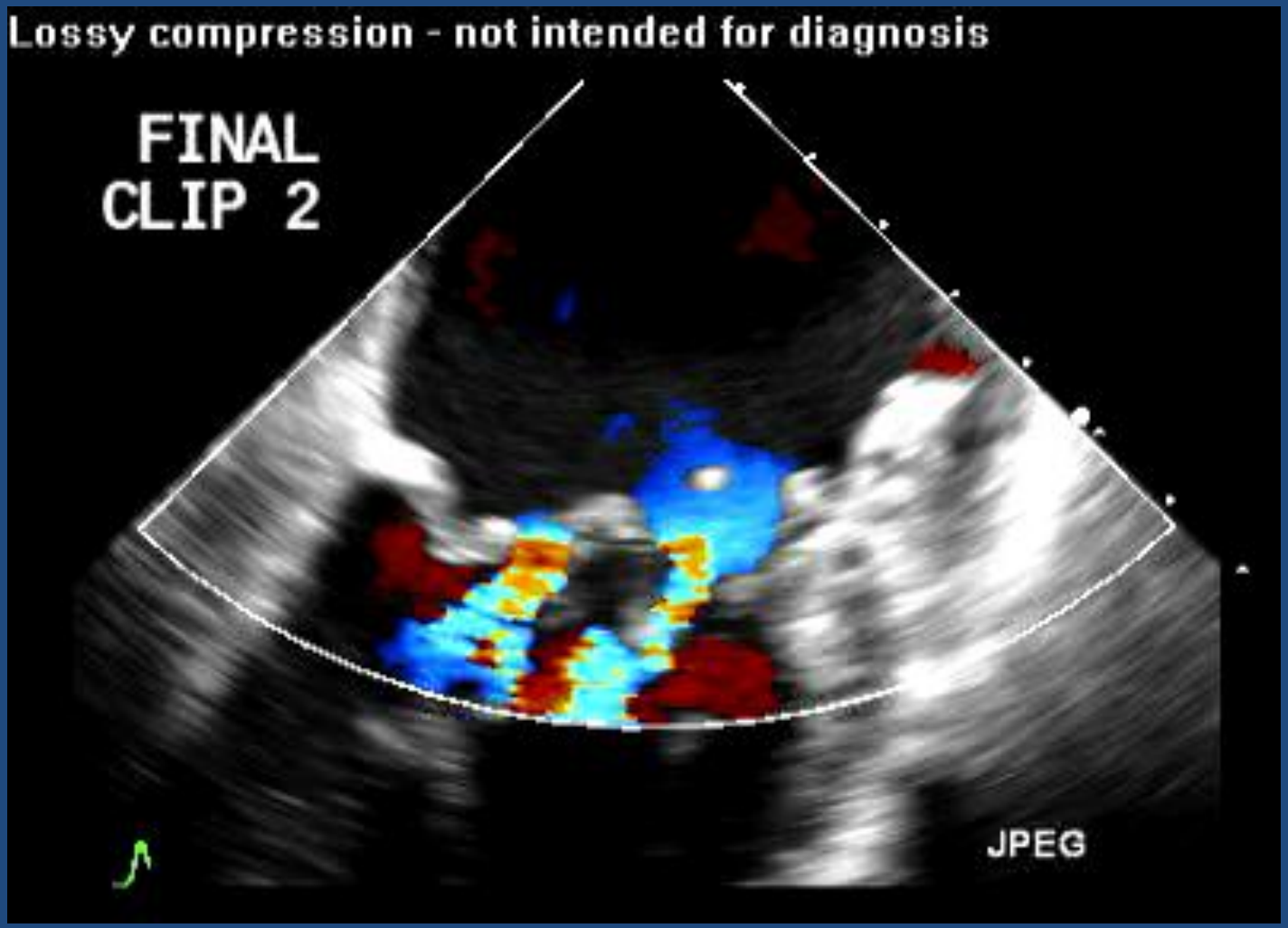
Mitral Valve Gradient



3D imaging – 2 clips



Final Result



Home the Next Day!

Evolving Technologies for Mitral Valve Disease

- Based on Surgical Techniques
  - Annuloplasty
    - Direct
    - Indirect
  - Chordal Replacement
  - Mitral Valve Replacement

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Annuloplasty: Surgical Theory

- **Principles**
  - All valves with significant chronic MR have some degree of annular dilation
  - Re-establishing physiologic configuration of mitral annulus will improve leaflet coaptation
- **Percutaneous Approaches**
  - *Indirect* **:** Implant device within coronary sinus with aim of "pushing" posterior annulus anteriorly
  - *Direct* **:** Device reshapes and cinches mitral annulus directly without involving coronary sinus

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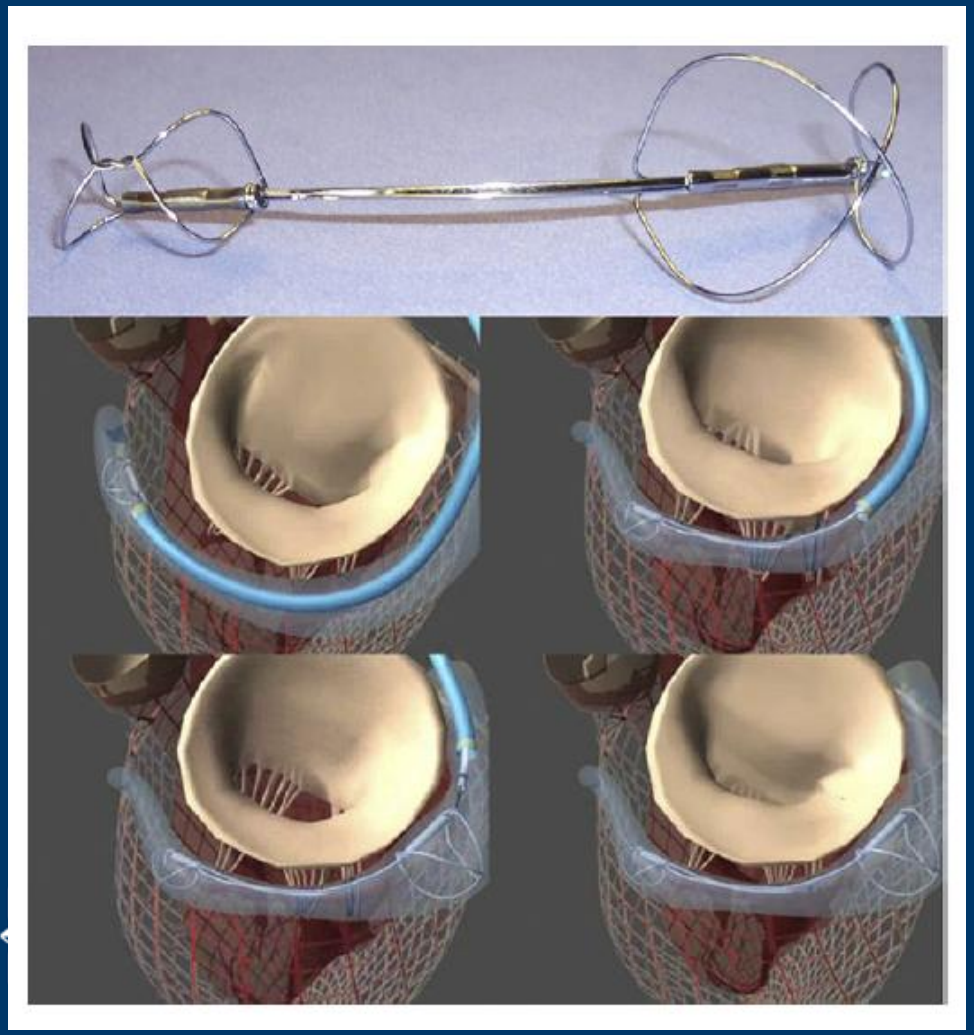
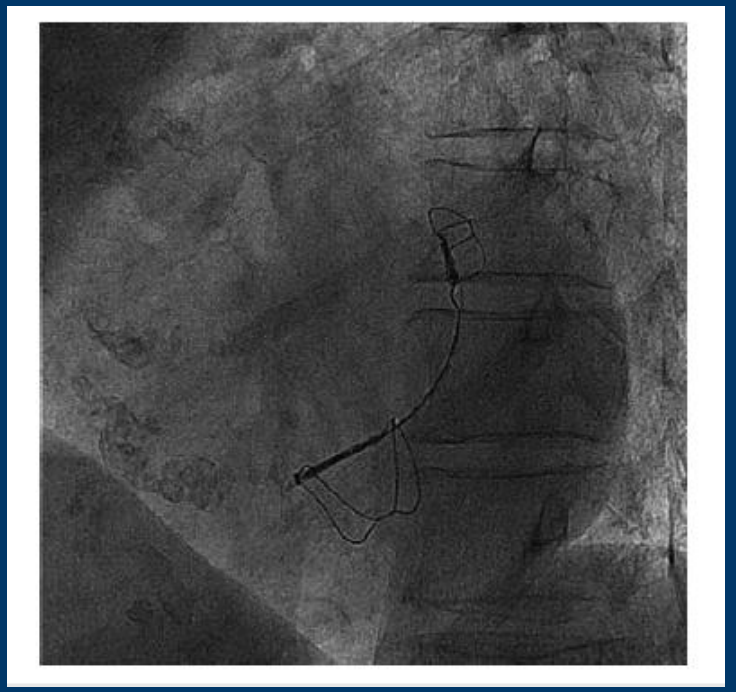
Indirect Percutaneous Mitral Annuloplasty
The Carillon XE Device





The Carillon XE Device

AMADEUS Trial [1]

- **First-In-Man Trial**
- **48 patients with . . .**
  - Symptomatic moderate-severe functional MR
  - EF < 40%
- **Results**
  - 20-30% reduction in MR
  - Improvement in HF symptoms
  - Low rates of adverse events

TITAN Trial [2]

- **Phase II single arm study**
- **53 patients with . .**
  - At least moderate (2+) functional MR
  - NYHA Class II-IV
  - EF < 40%
- **Of the 53 patients,**
  - 36 had successful implant
  - 17 had device recaptured

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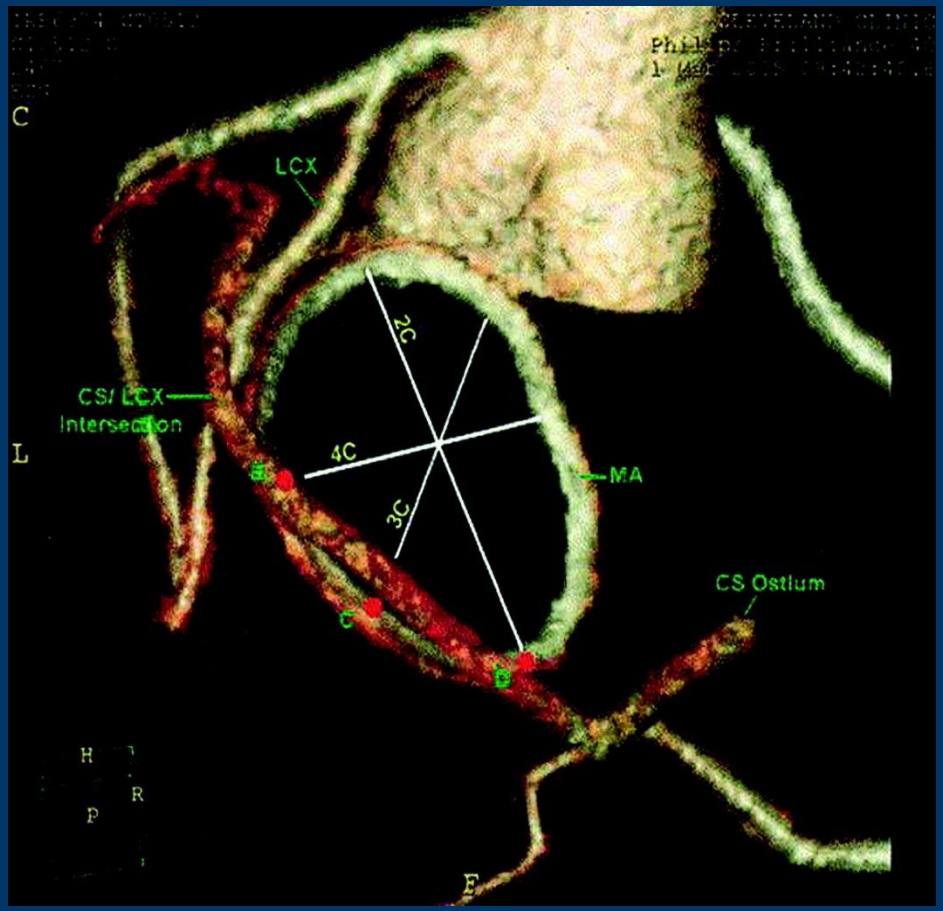
1. Scfhofer et al. *Circulation* 2009; 120: 326-333.
2. Siminiak et al. *Eur J Heart Failure* 2012; 14: 931-8.

Indirect Mitral Valve Annuloplasty: Limitations

- Coronary compression
- Anatomical limitations of the relationship of the coronary sinus to the mitral annulus
- Variability in coronary sinus anatomy
- May preclude future CRT



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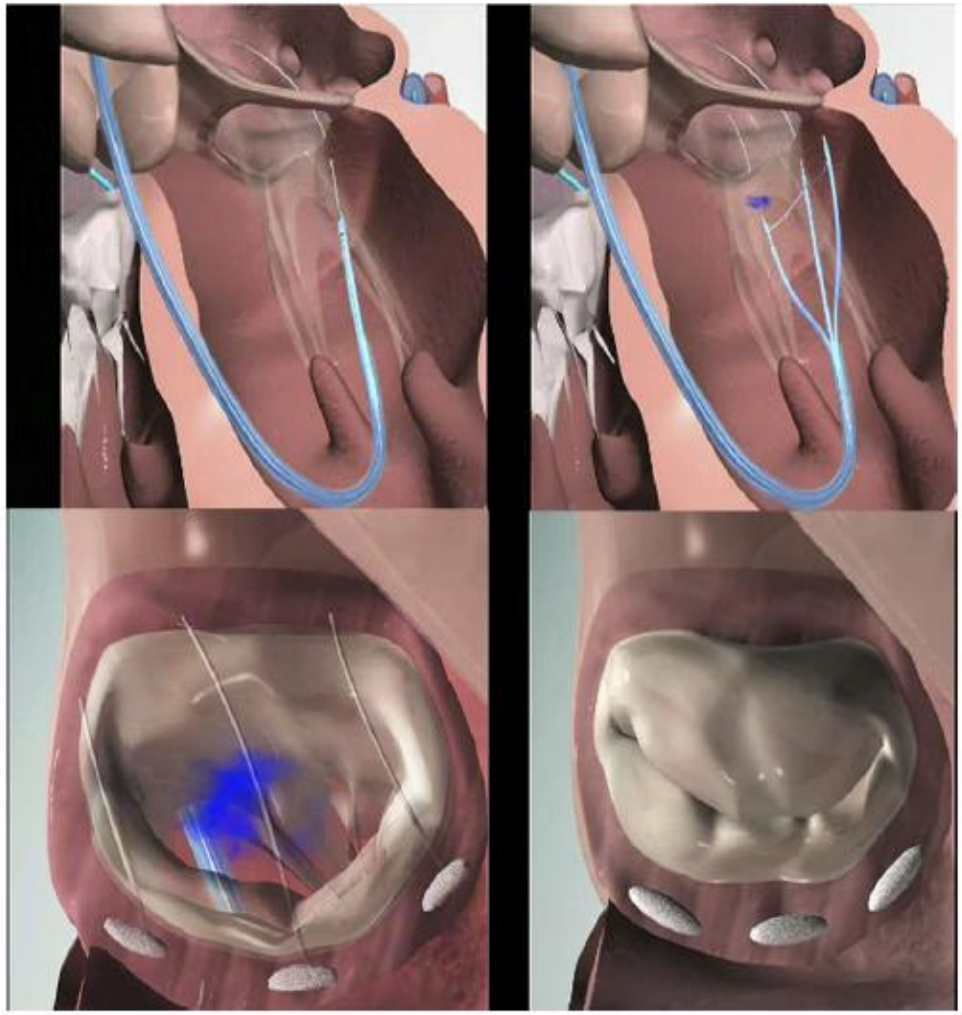
Direct Percutaneous Mitral Annuloplasty: Mechanical Cinching Approach

- **Principle**
  - Sutures implanted onto/near annulus and used to directly cinch the posterior annulus
- **Devices**
  - Mitralign
  - Accucinch
- **Limitations**
  - Only cinches posterior annulus



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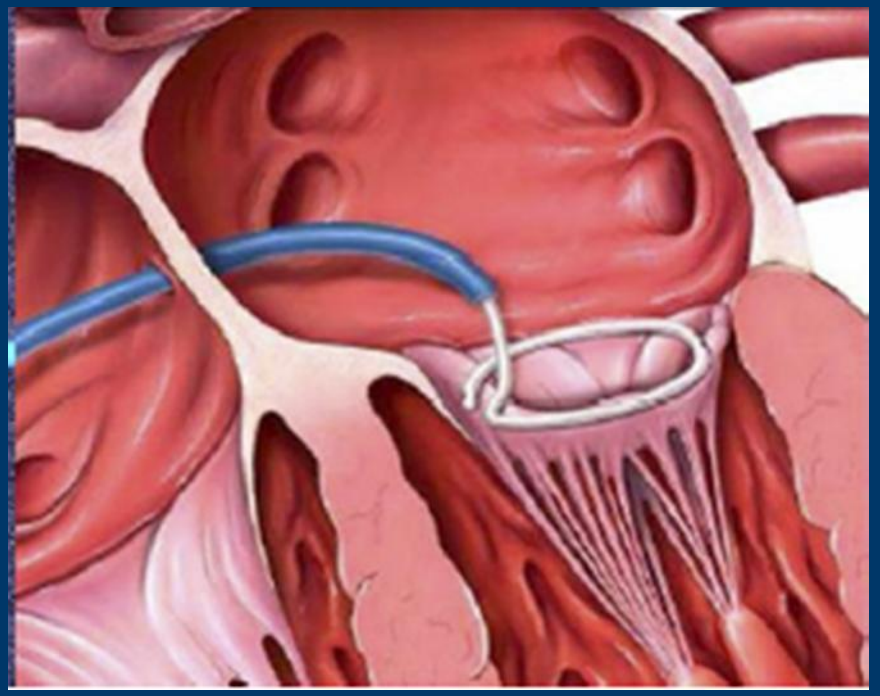
Direct Percutaneous Mitral Annuloplasty: Energy-Mediated Cinching Approach

- **Principle**
  - Heat energy is applied to annulus causing scarring and shrinking
- **Devices**
  - QuantumCor
  - ReCor
- **Limitations**
  - Imprecise scarring can lead to MS or residual MR
  - Possible damage to neighboring structures, e.g., leaflets, aortic valve, coronary sinus or circumflex artery



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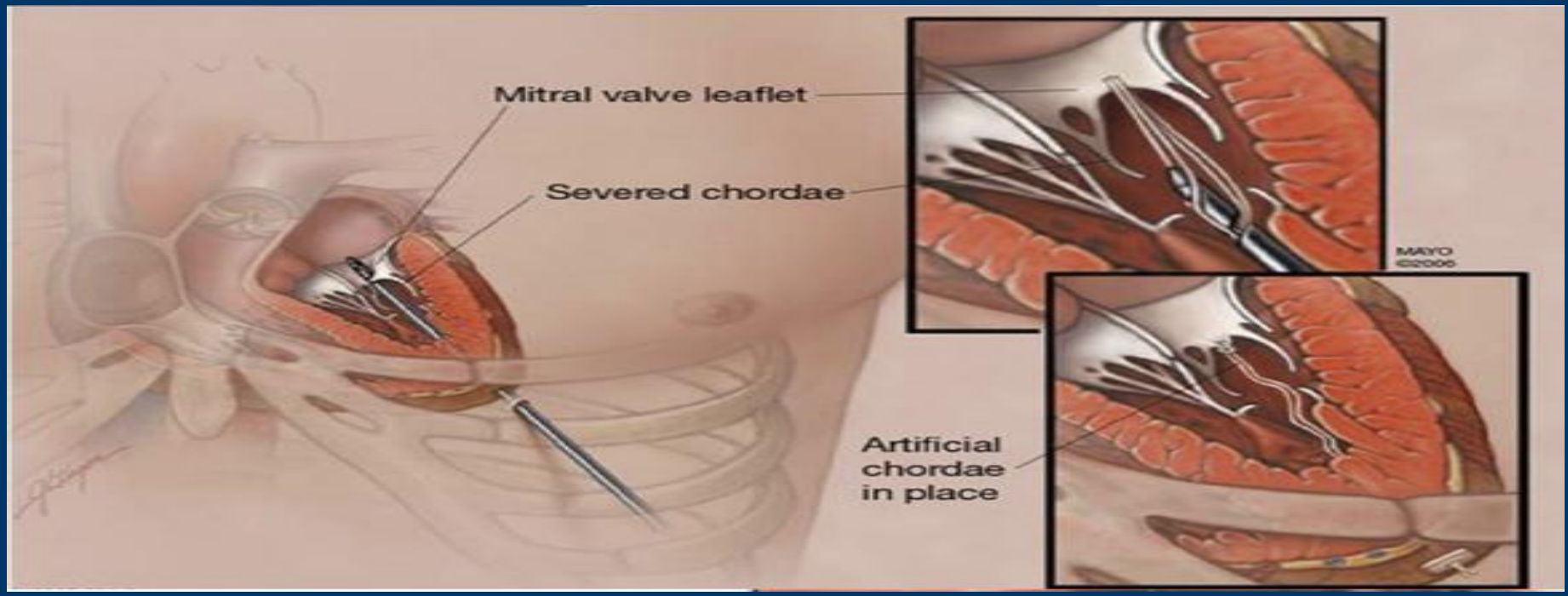
Surgical Chordal Replacement

- Initially used as adjuncts in surgical treatment for anterior or posterior leaflet prolapse
- Sometimes used on either/both anterior and posterior leaflets with limited leaflet resection . . .
  - Preserve tissue
  - Increase leaflet coaptation surface area
  - Replace thickened rheumatic chords
- Long-term durability of aggressive chordal replacement has not been established

Chordal Reconstruction: Percutaneous Techniques

- **Principles**
  - Synthetic chord is implanted and anchored between LV myocardium and leaflet via transapical puncture
  - Mainly for degenerative MR



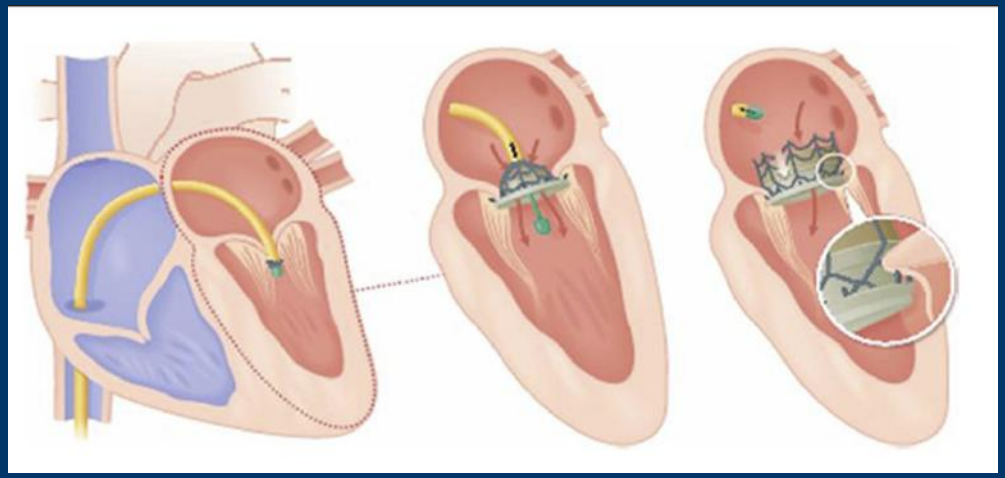
Chordal Reconstruction: Percutaneous Technology

- **Current Status of Devices**
  - *NeoChord*: received CE mark in early 2013; TACT registry enrolling in Europe
  - *MitraFlex*: pre-clinical stages
  - *Babic*: pre-clinical stages

- **Limitations**
  - Requires precise adjustment of chordal length
  - May pre-dispose to LV thrombus

Transcatheter Mitral Valve Replacement

- **Currently in various stages of testing**
  - CardiAQ
  - Endovalve-Herrmann
  - Lutter
- **Involves variety of approaches**
  - Trans-septal
  - Trans-apical
  - Mini-thoractomy
- **Challenges**
  - Risk of paravalvular leaks
  - Possible LVOT obstruction



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Finding the Right Patient

Who Might Benefit from TMVR?

- Patients with:
  - Moderate to severe mitral regurgitation
  - Symptoms
  - Appropriate anatomy
  - At high or prohibitive risk for surgery
- Agreement from the Heart Team that the patient is likely to benefit

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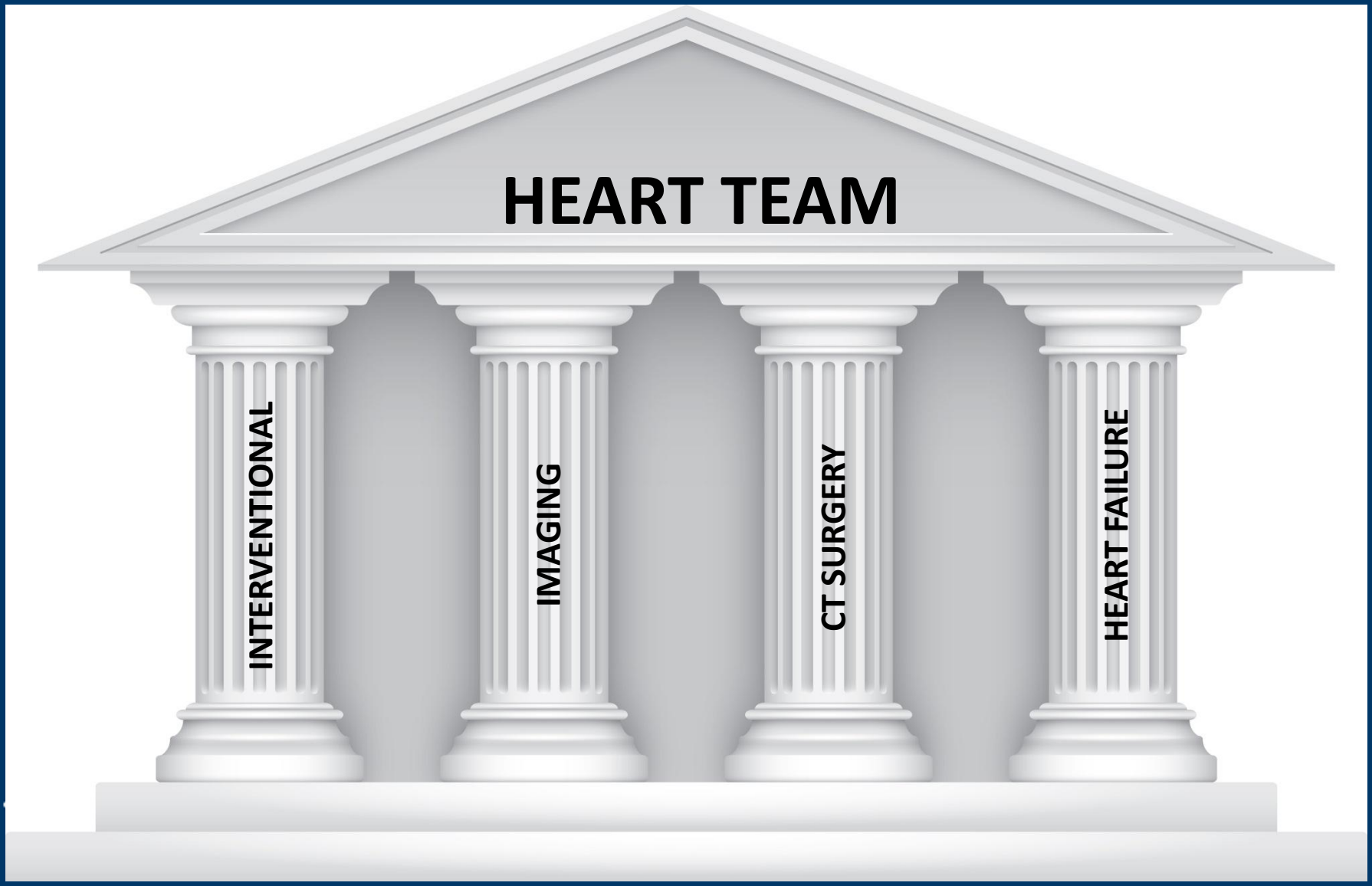
The Importance of the Heart Team



Who Might Not be a Candidate for TMVR?

- Patients with:
  - Mixed valve disease
  - Complex CAD that would benefit from surgery
  - Inappropriate anatomy
  - Life expectancy limited by other medical problems

- Patients who are not interested in undergoing a major cardiovascular procedure

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Conclusions

- Evolving percutaneous technologies to treat MR are derived from surgical techniques
- Most devices remain in development, however Mitraclip has gained FDA approval for treatment of patients with degenerative MR who are not candidates for surgery
- Challenges of mitral valve anatomy may make developing a one-size-fits-all strategy difficult

Thank You

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