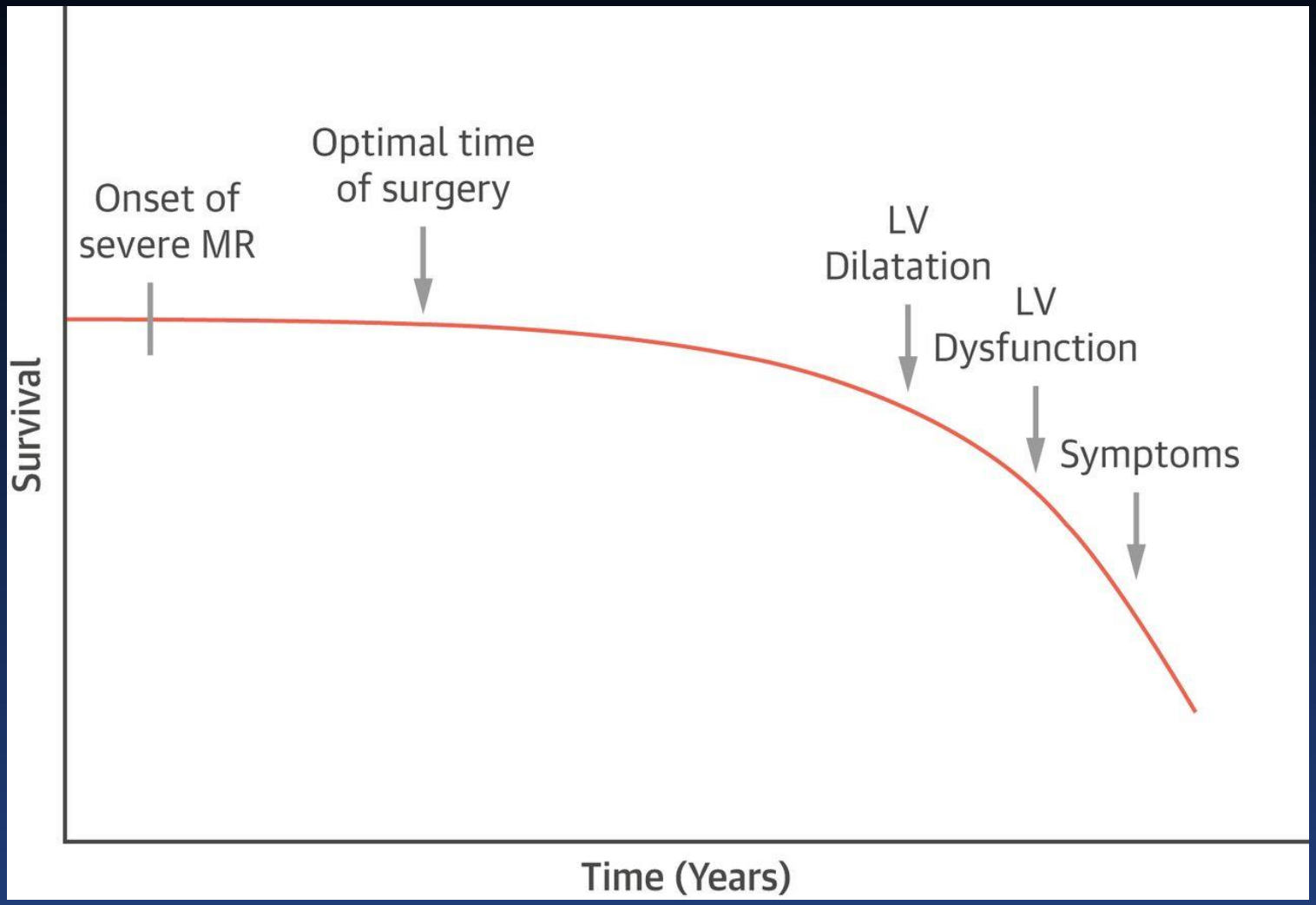
TREATMENT OF MITRAL REGURGITATION

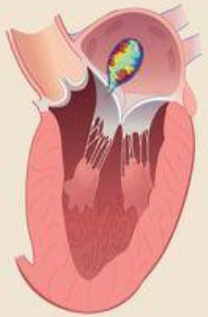
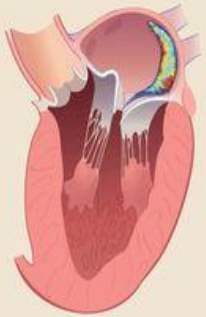
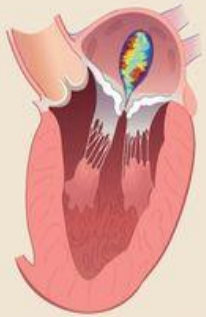
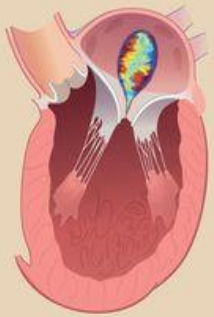
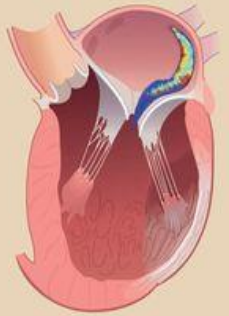
RAJA NAZIR FACC

NATURAL HISTORY OF MITRAL REGURGITATION



Abdallah El Sabbagh et al. JIMG 2018;11:628-643

CENTRAL ILLUSTRATION: Classification of the Etiology of MR

	Carpentier Type I	Carpentier Type II	Carpentier Type IIIa	Carpentier Type IIIb
	(normal leaflet motion and position)	(excess leaflet motion)	(restricted leaflet motion in systole and diastole)	(restricted leaflet motion in systole)
PRIMARY MR	 Leaflet Perforation Cleft	 Mitral Valve Prolapse	 Rheumatic Valve Disease Mitral Annular Calcification Drug Induced MR	
SECONDARY MR	 Atrial MR  Nonischemic Cardiomyopathy			 Ischemic Cardiomyopathy

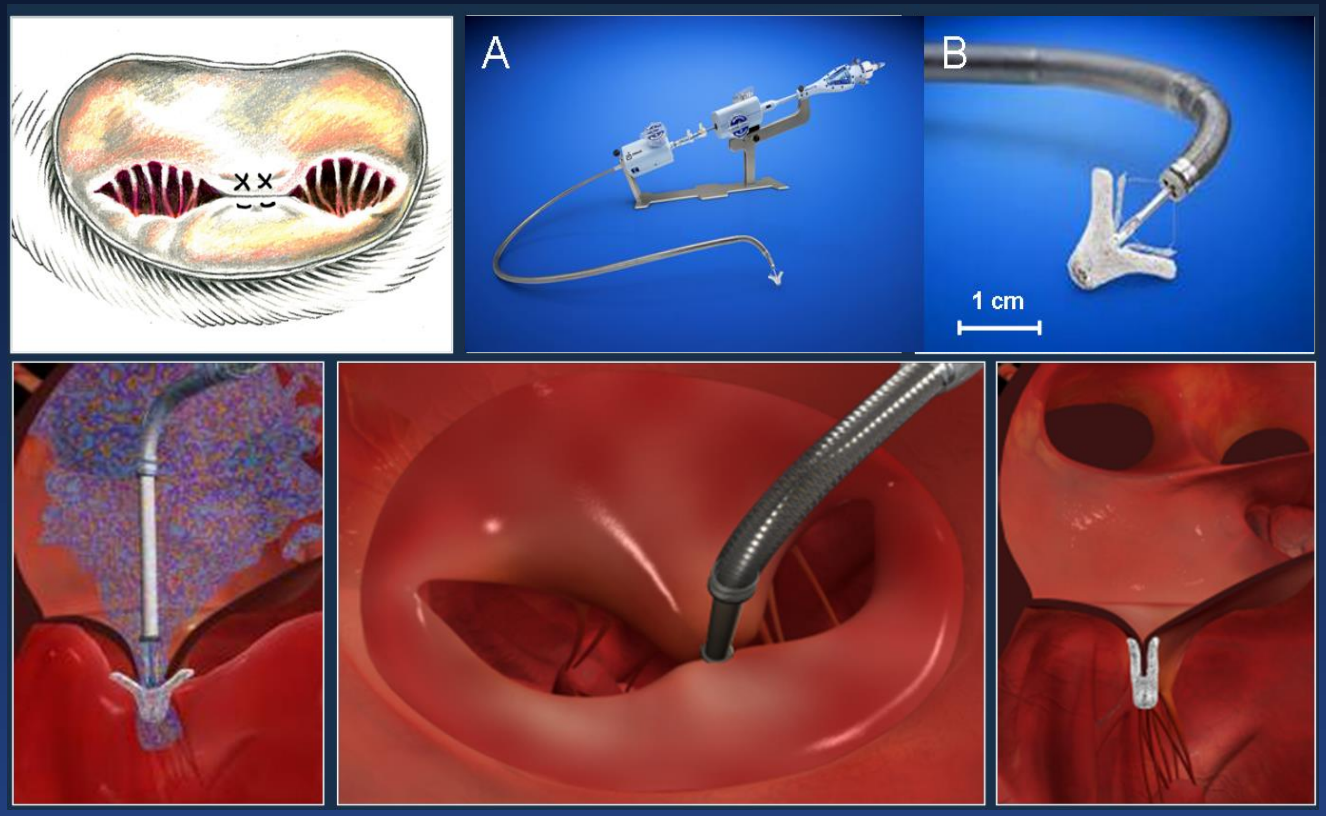
El Sabbagh, A. et al. J Am Coll Cardiol Img. 2018;11(4):628-43.

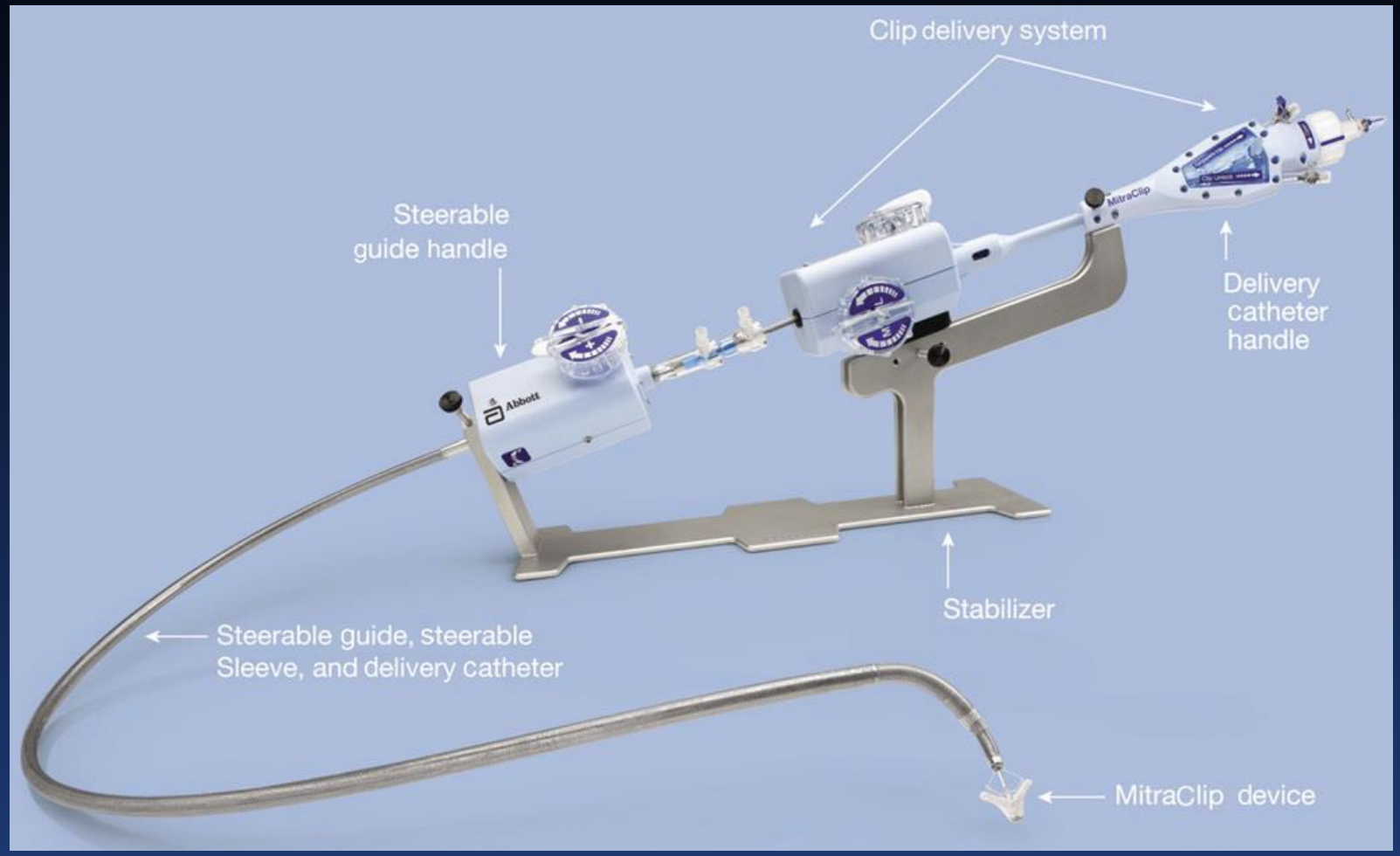
TREATMENT OPTIONS

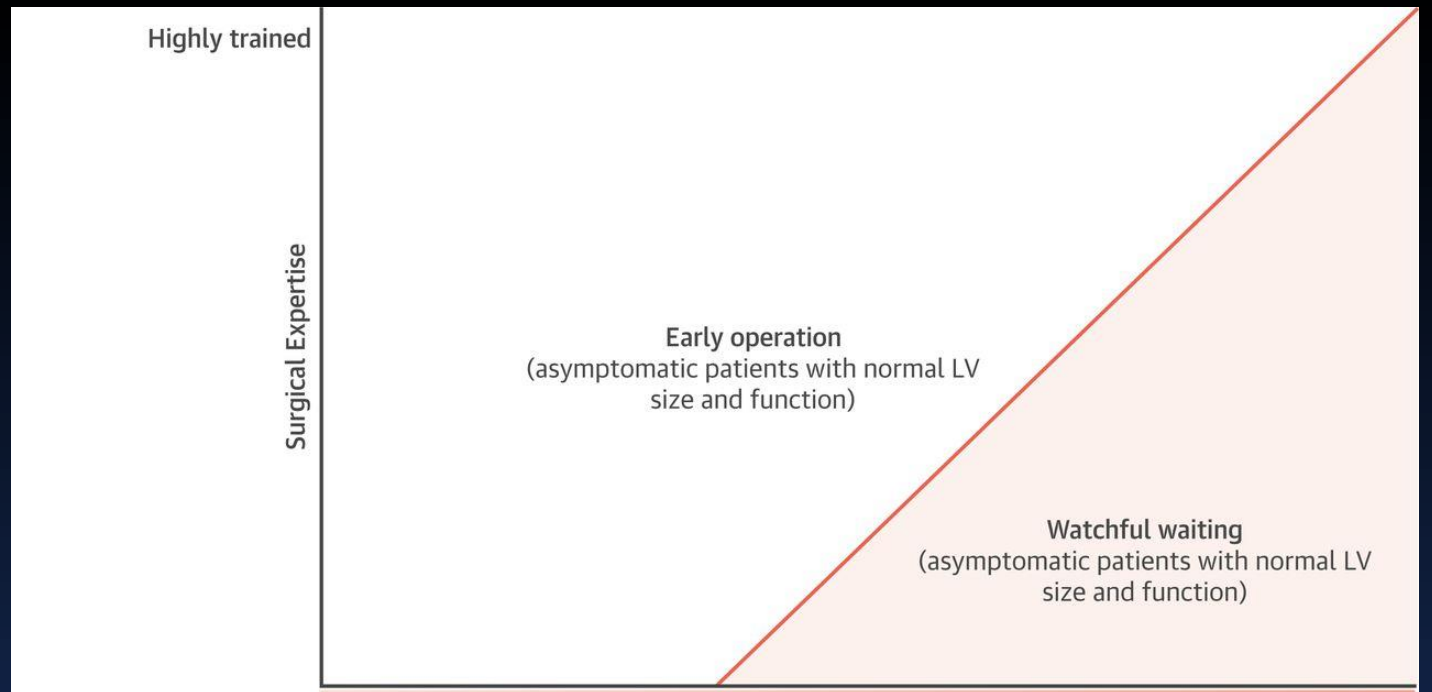
- SURGERY
  - REPAIR
  - REPLACEMENT
- PERCUTANEOUS INTERVENTIONS
  - MITRAL CLIP
  - AORTIC VALVE IN MITRAL POSITION
  - TREATMENTS IN PIPELINE

MitraClip Procedure

Percutaneous edge-to-edge repair of mitral valve leaflets in patients with primary or secondary mitral regurgitation.




Clip delivery system
Steerable
guide handle
Delivery
catheter
handle
Stabilizer
Steerable guide, steerable
Sleeve, and delivery catheter
MitraClip device



Primary MR			
Prolapse Segment	Posterior	Anterior	Bileaflet Severe Barlow
Calcification	None	Mild	Moderate
Annular dilatation	Mild	Moderate	Severe
Other		Perforation, Cleft	Rheumatic

Abdallah El Sabbagh et al. JIMG 2018;11:628-643

Primary mitral regurgitation

AMERICAN COLLEGE of CARDIOLOGY

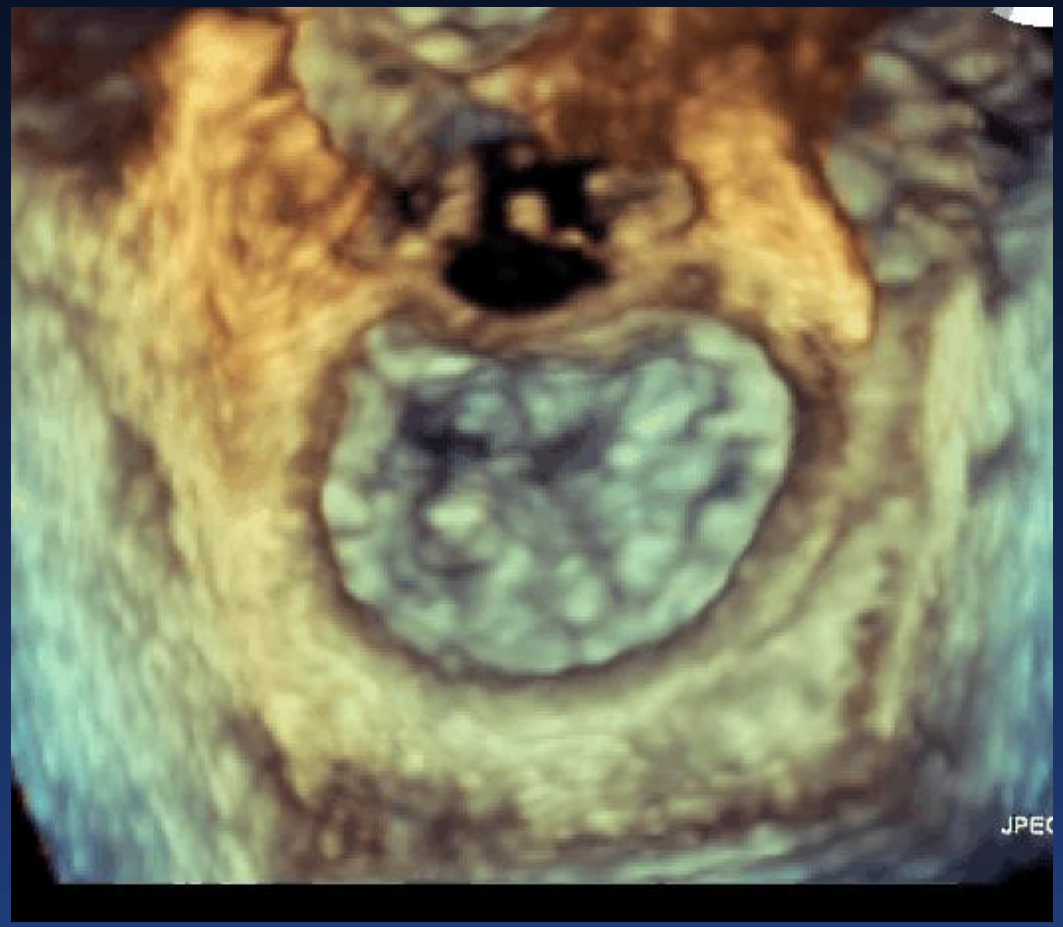
American Heart Association.

Class I

- MV surgery in symptomatic patients with severe MR and EF > 30%
- MV surgery in asymptomatic patients with severe MR and LV dysfunction (EF 30-60%) and/or LVESD >= 40 mm
- MV surgery in patients undergoing cardiac surgery for other reasons
- Repair is recommended in preference to MVR with only posterior leaflet pathology and recommended in patients with anterior or bileaflet pathology when high likelihood of success

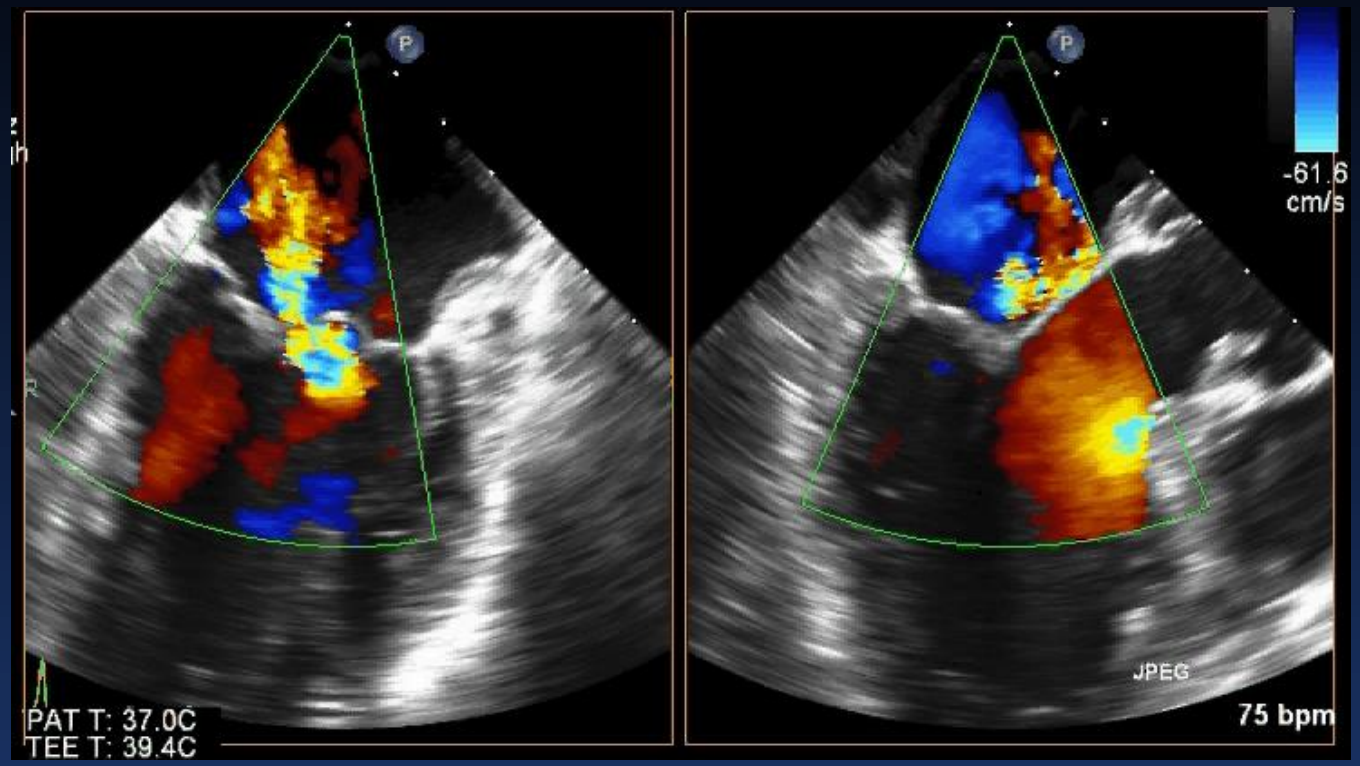
82 year old lady with shortness of breath. STS Score 11

CLIP OR SURGERY



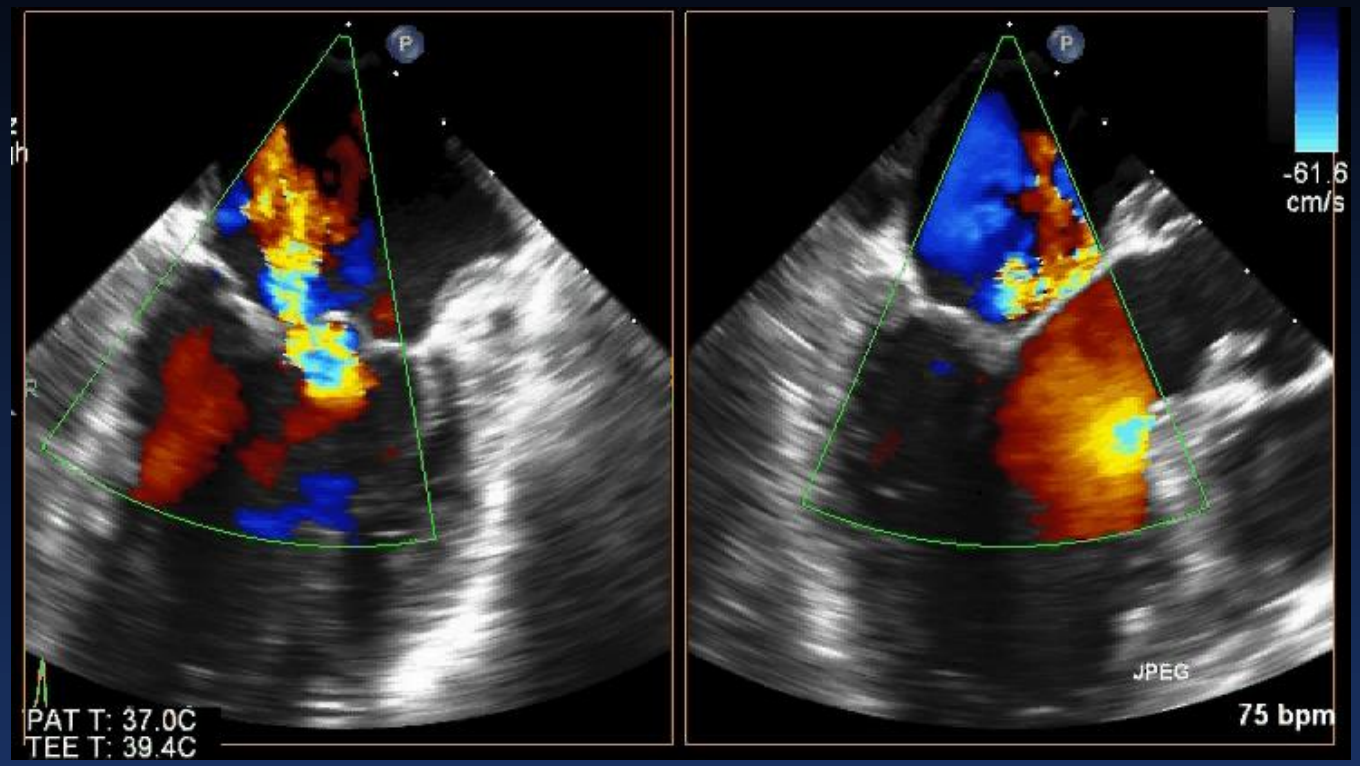
- **Localized prolapse/flail of P2**
- **Annulus not dilated**
- **Mitral valve area adequate**
- **Normal EF**
- **COPD**
- **CKD**

•*Baseline TEE*



- **Small flail gap and width**
- **No leaflet calcification**
- **Single jet**

•*Baseline TEE*



- **Small flail gap and width**
- **No leaflet calcification**
- **Single jet**

The NEW ENGLAND JOURNAL of MEDICINE

Percutaneous Repair or Surgery for Mitral Regurgitation

Ted Feldman, M.D., Elyse Foster, M.D., Donald G. 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*

CONCLUSIONS

Although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes. (Funded by Abbott Vascular; EVEREST II ClinicalTrials.gov number, NCT00209274.)

Feldman et al NEJM 2011

EVEREST II Randomized Clinical Trial

279 Patients enrolled at 37 sites

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

↓

Randomized 2:1

↙ ↘

Device Group
MitraClip System
n=184

Control Group
Surgical Repair
or Replacement
n=95

↓ ↓

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

EVEREST II RCT

Baseline Demographics & Co-morbidities

	Device (%) n=184	Control (%) n=95	p
Age (mean)	67.3 years	65.7 years	0.32
Male	62.5	66.3	0.60
Congestive heart failure	90.8	77.9	<0.01
Coronary artery disease	47.0	46.3	>0.99
Myocardial infarction	21.9	21.3	>0.99
Angina	31.9	22.2	0.12
Atrial fibrillation	33.7	39.3	0.42
Cerebrovascular disease	7.6	5.3	0.62
Peripheral vascular disease	6.5	11.6	0.17
Cardiomyopathy	17.9	14.7	0.61
Hypercholesterolemia	61.0	62.8	0.80
Hypertension	72.3	78.9	0.25
Moderate to severe renal disease	3.3	2.1	0.72
Diabetes	7.6	10.5	0.50
Previous cardiovascular surgery	22.3	18.9	0.54
MR Severity: 3+ to 4+	95.7	92.6	0.48
MR Etiology: Degenerative / Functional	73 / 27	73 / 27	0.81

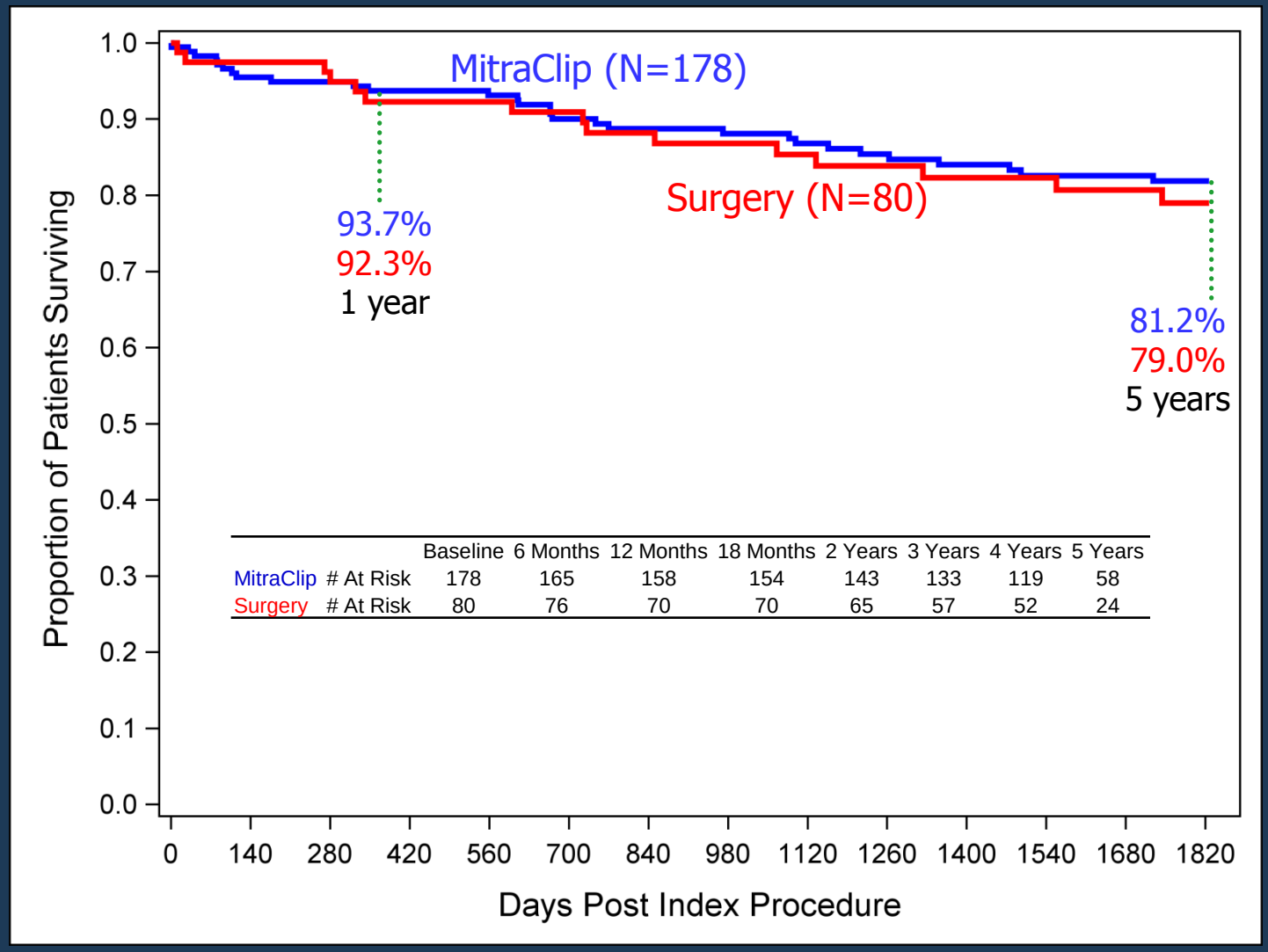
EVEREST II RCT

Met Primary Safety Endpoint

Intention to Treat Cohort 30 Day MAE, non-hierarchical	# Patients experiencing event	
	MitraClip Group (n=180)	Surgery Group (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%	48%
	p<0.0001	

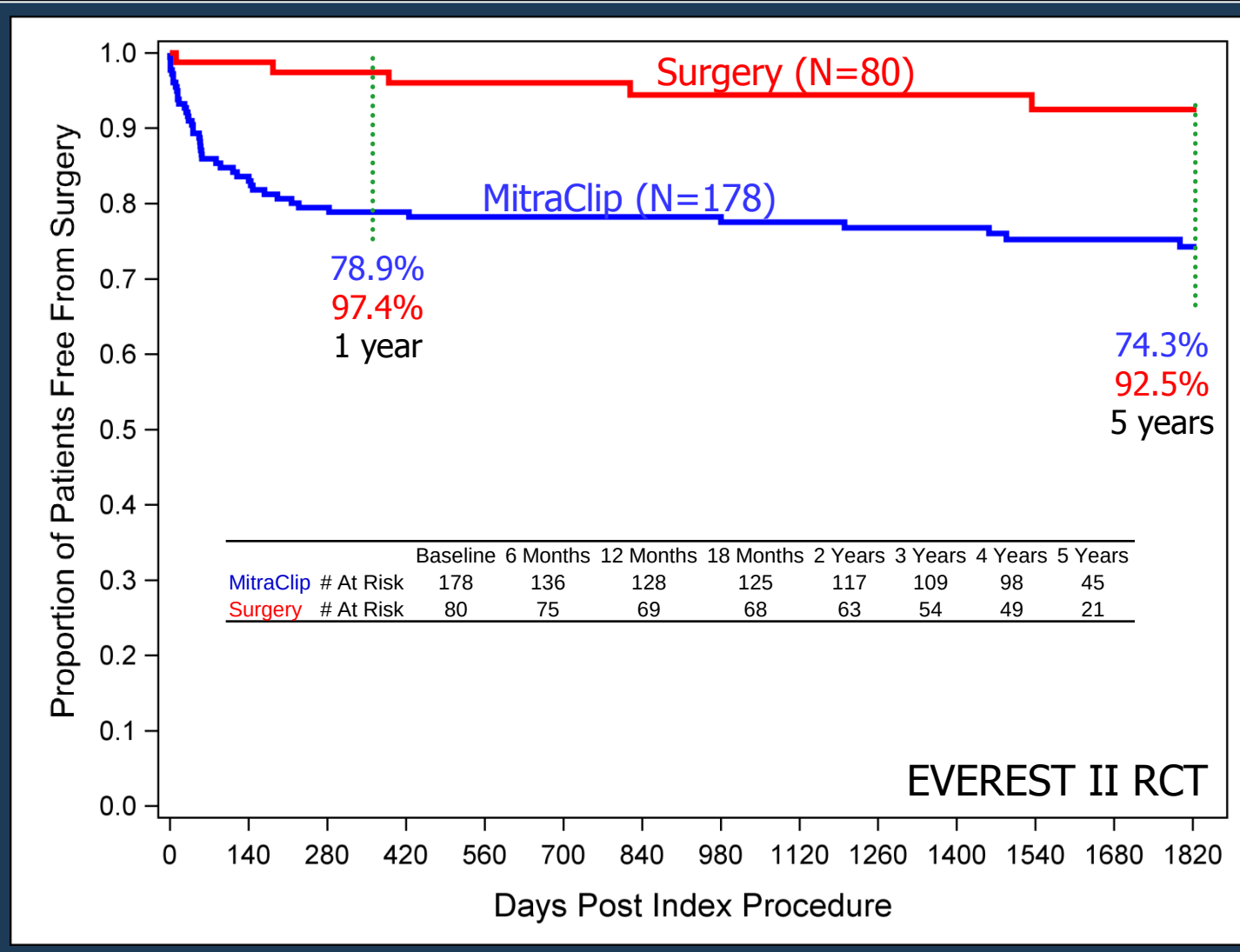
Kaplan-Meier Freedom From Mortality

EVEREST II RCT



		Baseline	6 Months	12 Months	18 Months	2 Years	3 Years	4 Years	5 Years
MitraClip	# At Risk	178	165	158	154	143	133	119	58
Surgery	# At Risk	80	76	70	70	65	57	52	24

Kaplan-Meier Freedom From MV Surgery in MitraClip Group or Re-operation in Surgery Group



		Baseline	6 Months	12 Months	18 Months	2 Years	3 Years	4 Years	5 Years
MitraClip	# At Risk	178	136	128	125	117	109	98	45
Surgery	# At Risk	80	75	69	68	63	54	49	21

Prohibitive Surgical Risk
DMR Cohort (n=127)

Age: 82 ±9 years

Prior MI: 24%

Prior stroke: 10%

Diabetes: 30%

COPD: 32%

Renal disease: 28%

Mean STS Risk

13.2%

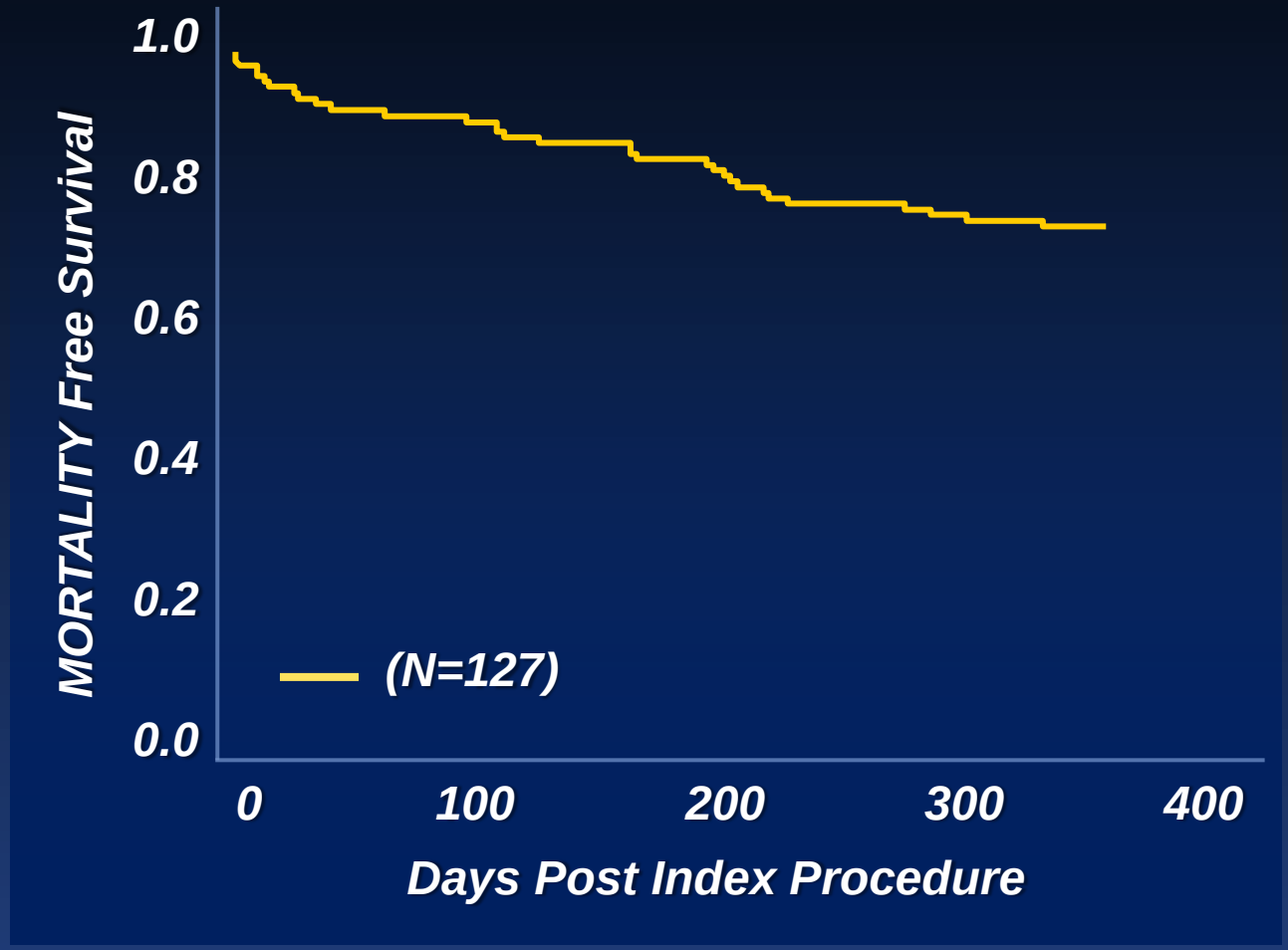
Lim et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair, JACC 2014;64:182-192.

Prohibitive Surgical Risk
DMR Cohort (n=127)

95% implant success

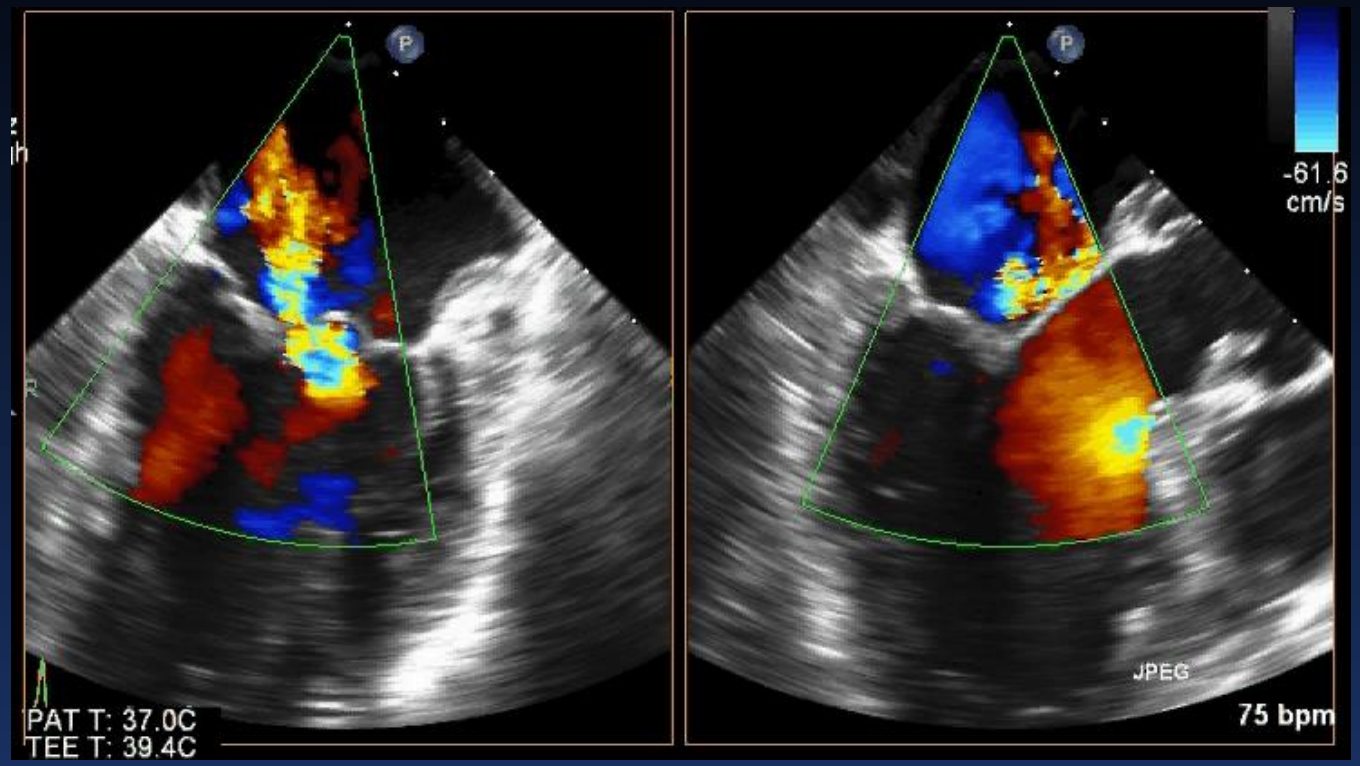
No procedural deaths

LOS = 2.9 days



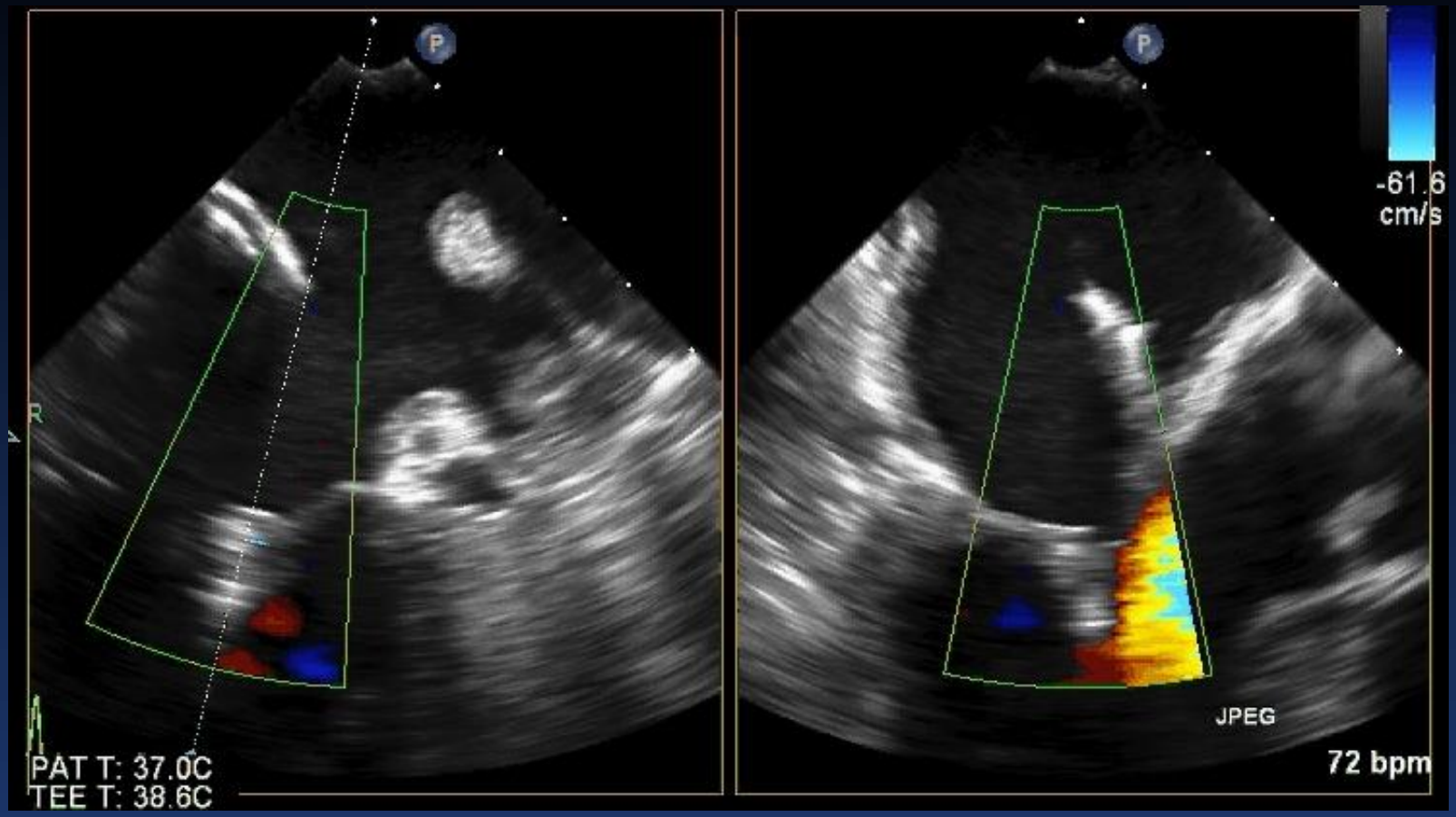
Lim et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair, JACC 2014;64:182-192.

•*Baseline TEE*

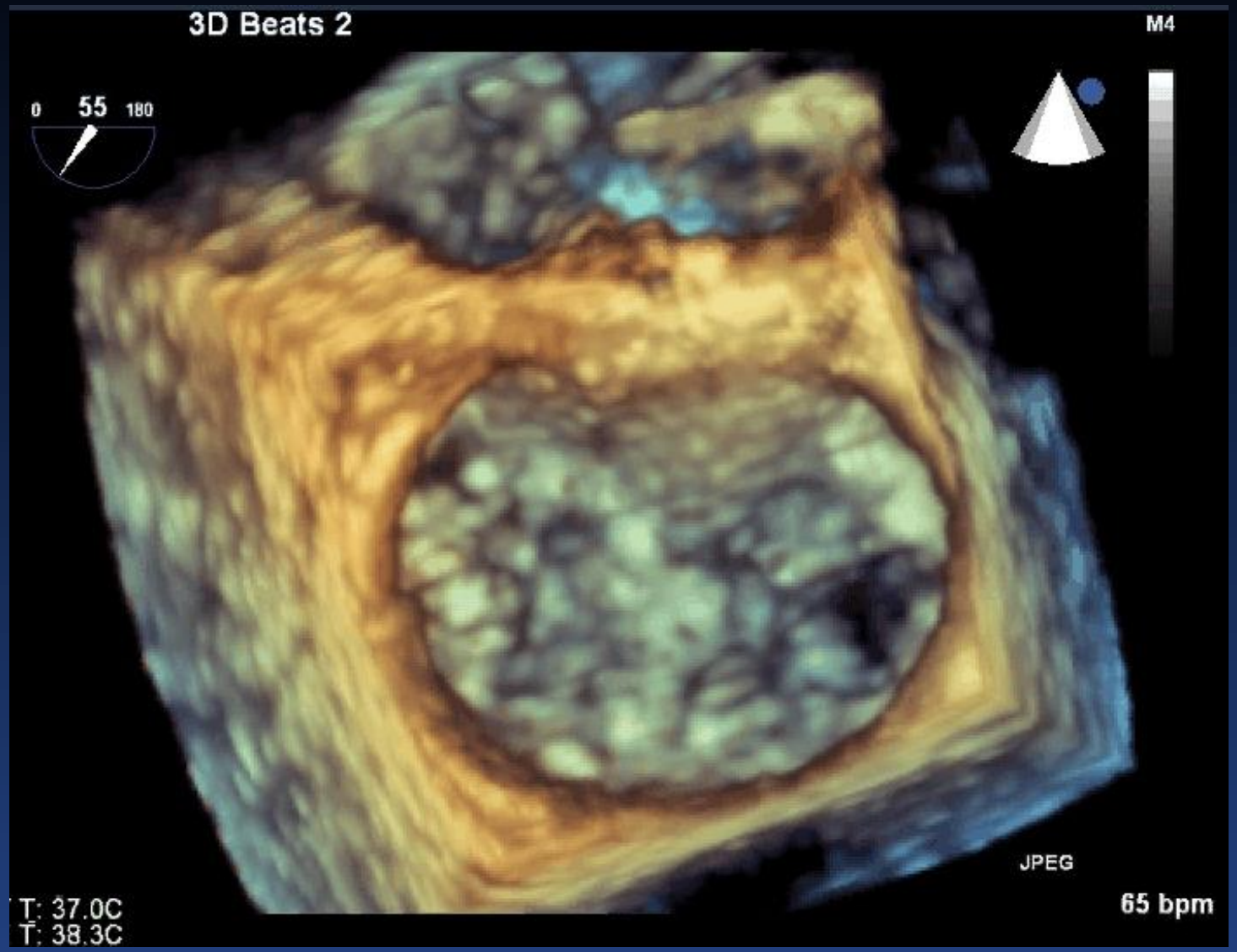


- **Small flail gap and width**
- **No leaflet calcification**
- **Single jet**

•One clip placed : Trace MR



•Post Mitral Clip deployment



SECONDARY MR

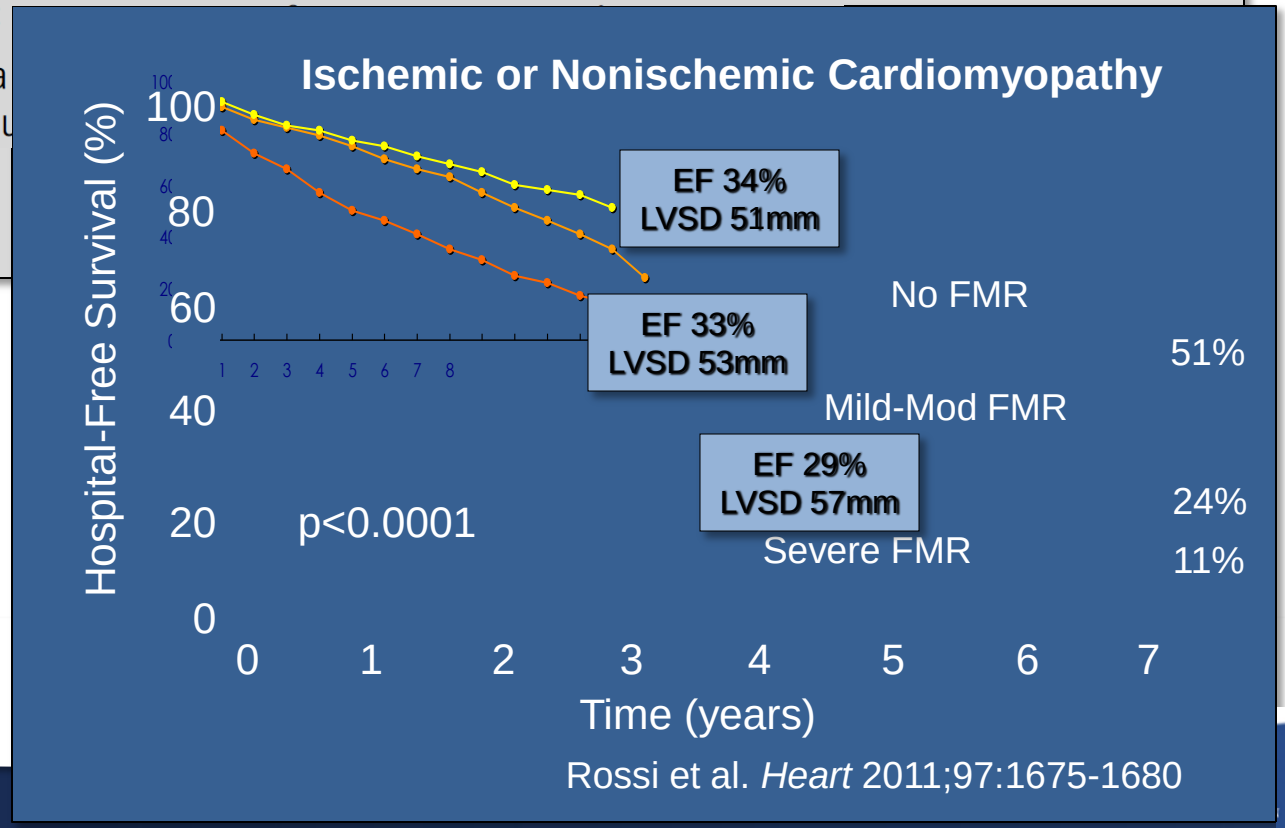
- Valve morphology normal
- Ventricular pathology causing MR
- Dilated ventricle
- Displacement of papillary muscles
- Annular dilatation
- LBBB/IVCD

ORIGINAL ARTICLE

Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy

Andrea Rossi,[1] Frank L Dini,[2]
Mariantonietta Cicoira,[1] Silvia
Stefano Ghio,[5] Maurice Enriqu

Heart 2011;**97**:1675–1680



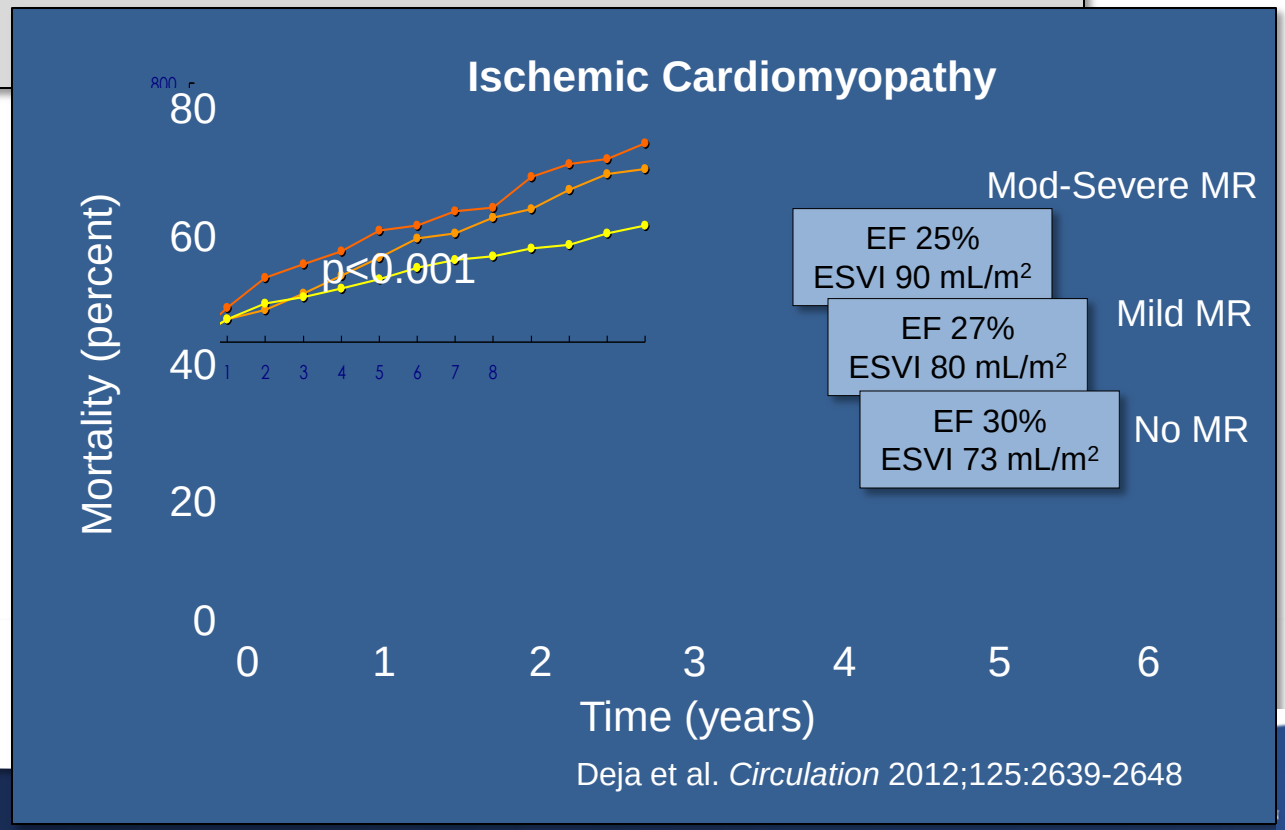
Valvular Heart Disease

Influence of Mitral Regurgitation Repair on Survival in the Surgical Treatment for Ischemic Heart Failure Trial

Marek A. Deja, Paul A. Grayburn, Benjamin Sun, Vivek Rao, Lilin She, Michal Krejca, Anil R. Jain, Yeow Leng Chua, Richard Daly, Michele Senni, Krzysztof Mokrzycki, Lorenzo Menicanti, Jae K. Oh, Robert Michler, Krzysztof Wróbel, Andre Lamy, Eric J. Velazquez, Kerry L. Lee and Robert H. Jones

STICH
FUNDED BY A GRANT FROM THE NATIONAL INSTITUTES OF HEALTH

Circulation. 2012;125:2639-2648



FUNCTIONAL MR

- MARKER FOR POOR PROGNOSIS or POOR LV
  - OR
- TARGET FOR THERAPY

- THERAPY THAT PRODUCES REVERSE REMODELLING WILL IMPROVE MR AND MORTALITY

Secondary mitral regurgitation

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association.

Class I

Guideline-directed medical therapy for heart failure, including CRT

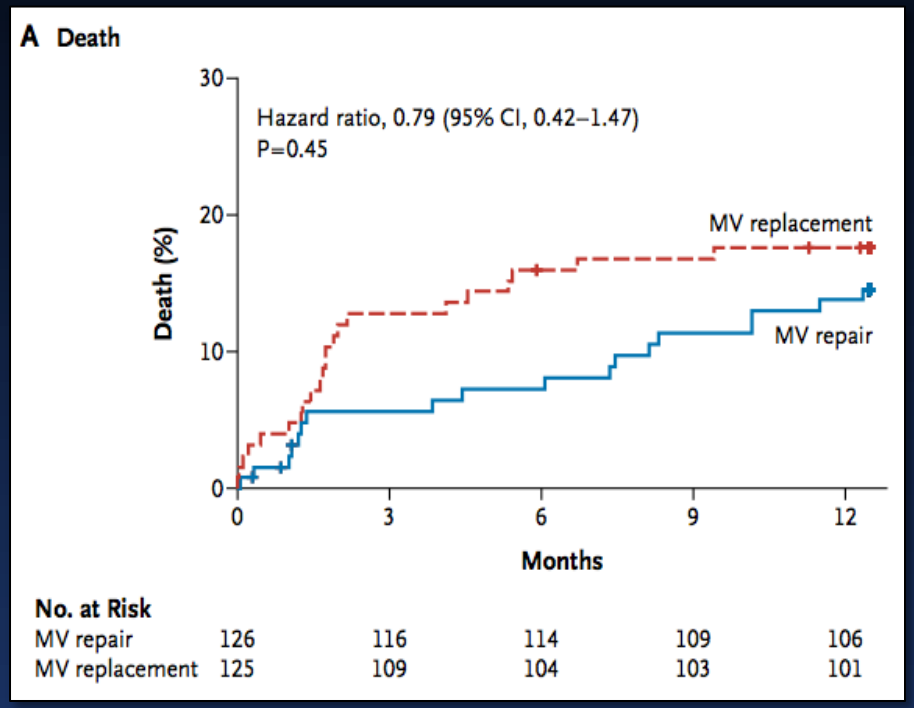
Class II

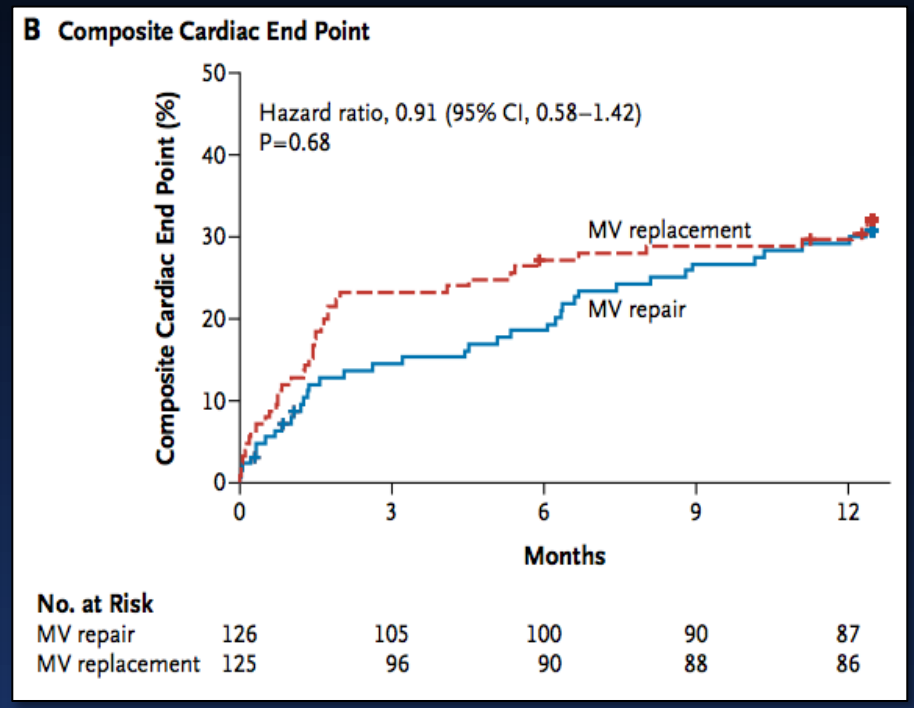
Mitral valve surgery is reasonable for patients with severe secondary MR (stage C and D) undergoing CABG or AVR

SURGERY FOR FUNCTIONAL MR

- After MI FIMR is present in 21% of patients, and 3-13% have at least moderate FIMR.
- For years, the ‘gold-standard’ treatment of FIMR is down-sized ring annuloplasty at the time of CABG
- However, this procedure has a failure rate of 20-30% in terms of recurrent FIMR after two to four years.
  - Is CABG + annuloplasty better than CABG alone ?
  - Does repair really have better outcome than replacement?
  - Does adding valvular repair or subvalvular LV reverse remodeling procedure shift that balance?

Cardiothoracic Surgericalt Trials Network
CSTN





The composite end point included death, stroke, subsequent mitral-valve (MV) surgery, hospitalization for heart failure, and an increase in the New York Heart Association class of 1 or more.

Secondary mitral regurgitation

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association.

Class IIa

It is reasonable to consider chordal sparing MVR over repair if operation is considered in patients with severe symptomatic ischemic MR despite GDMT

Class IIb

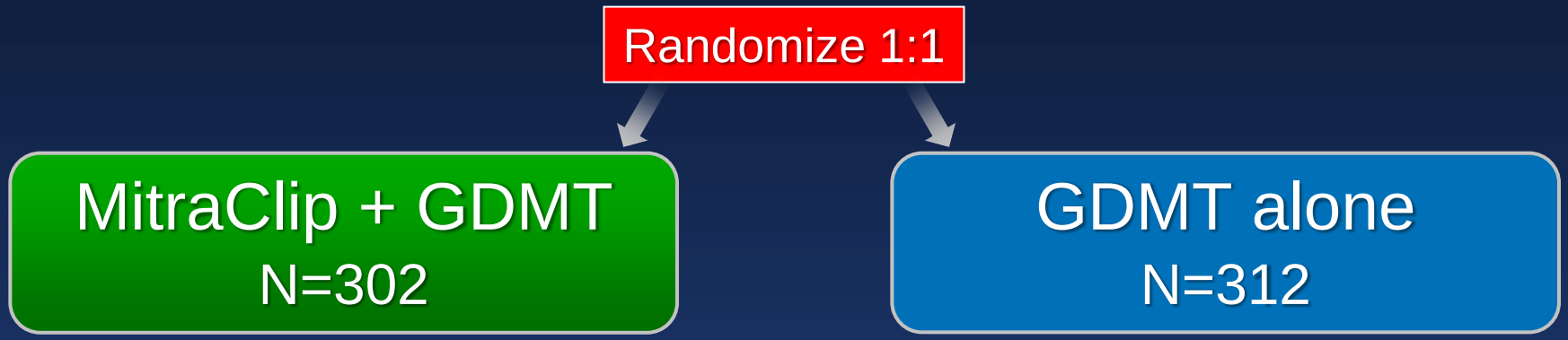
MV repair or replacement may be considered in patients with severe symptomatic secondary MR despite GDMT

WHAT ABOUT MITRAL CLIP

The COAPT Trial

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in 614 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT



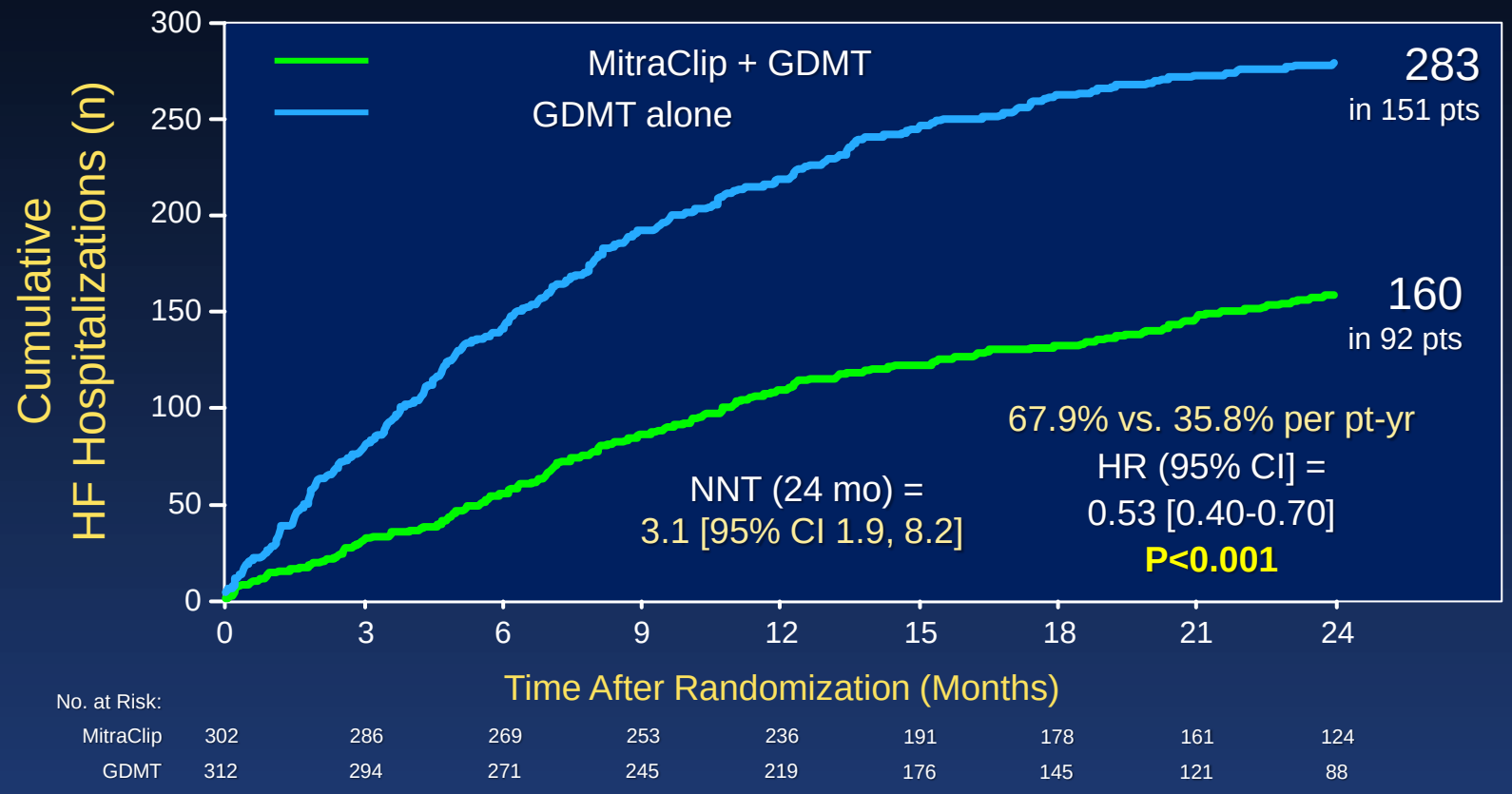
Primary endpoints:

Effectiveness: All HF hospitalizations through 24 mos, analyzed when last pt completes 12-mo FU

Safety: Freedom from device-related complications through 12 months

Primary Effectiveness Endpoint

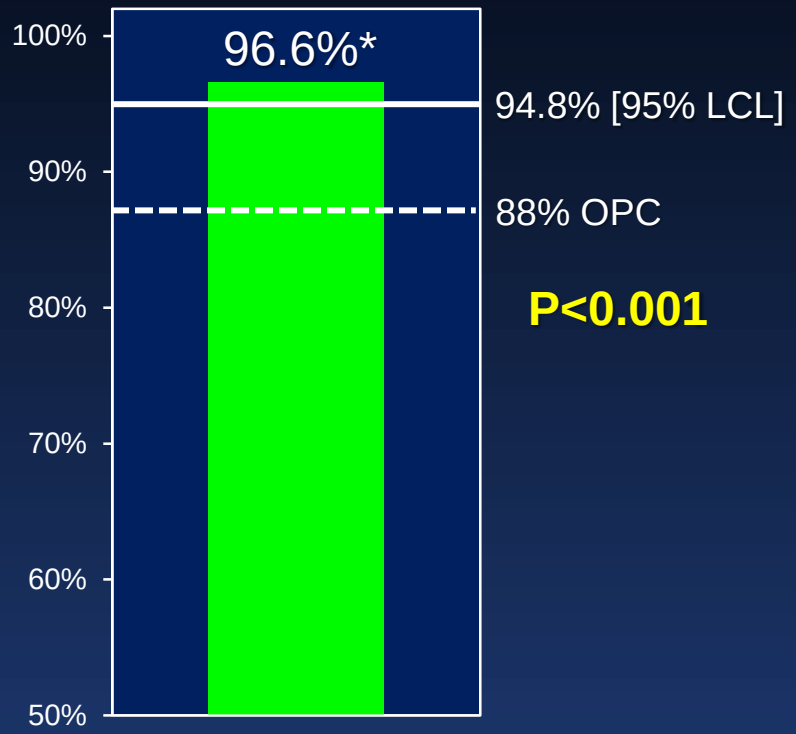
All Hospitalizations for HF within 24 months



No. at Risk:									
MitraClip	302	286	269	253	236	191	178	161	124
GDMT	312	294	271	245	219	176	145	121	88

Primary Safety Endpoint

Freedom from Device-related Complications within 12 months



MitraClip procedure attempted	N=293
Device-related complications	9 (3.4%)
- Single leaflet device attachment	2 (0.7%)
- Device embolization	1 (0.3%)
- Endocarditis requiring surgery	0 (0.0%)
- Mitral stenosis requiring surgery	0 (0.0%)
- Left ventricular assist device implant	3 (1.2%)
- Heart transplant	2 (0.8%)
- Any device-related complication requiring non-elective CV surgery	1 (0.3%)

*KM estimate; **Calculated from Z test with Greenwood's method of estimated variance against a pre-specified objective performance goal of 88%

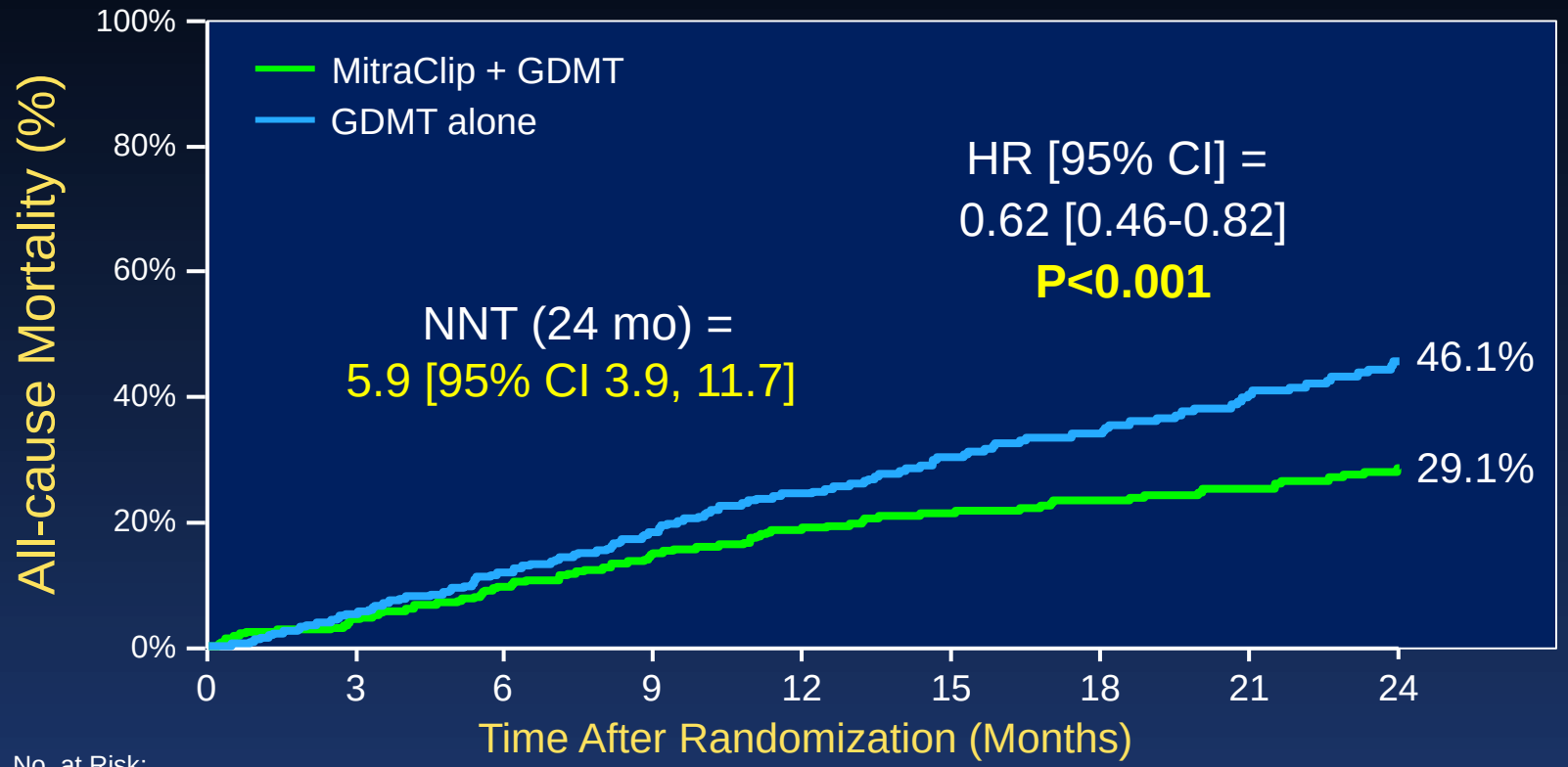
Powered Secondary Endpoints

- Tested in hierarchical order[1] -

	P-value
1. MR grade ≤2+ at 12 months	<0.001
2. All-cause mortality at 12 months[2]	<0.001
3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)	<0.001
4. Change in QOL (KCCQ) from baseline to 12 months	<0.001
5. Change in 6MWD from baseline to 12 months	<0.001
6. All-cause hospitalizations through 24 months	0.03
7. NYHA class I or II at 12 months	<0.001
8. Change in LVEDV from baseline to 12 months	0.003
9. All-cause mortality at 24 months	<0.001
10. Death, stroke, MI, or non-elective CV surgery for device-related compls at 30 days[3]	<0.001

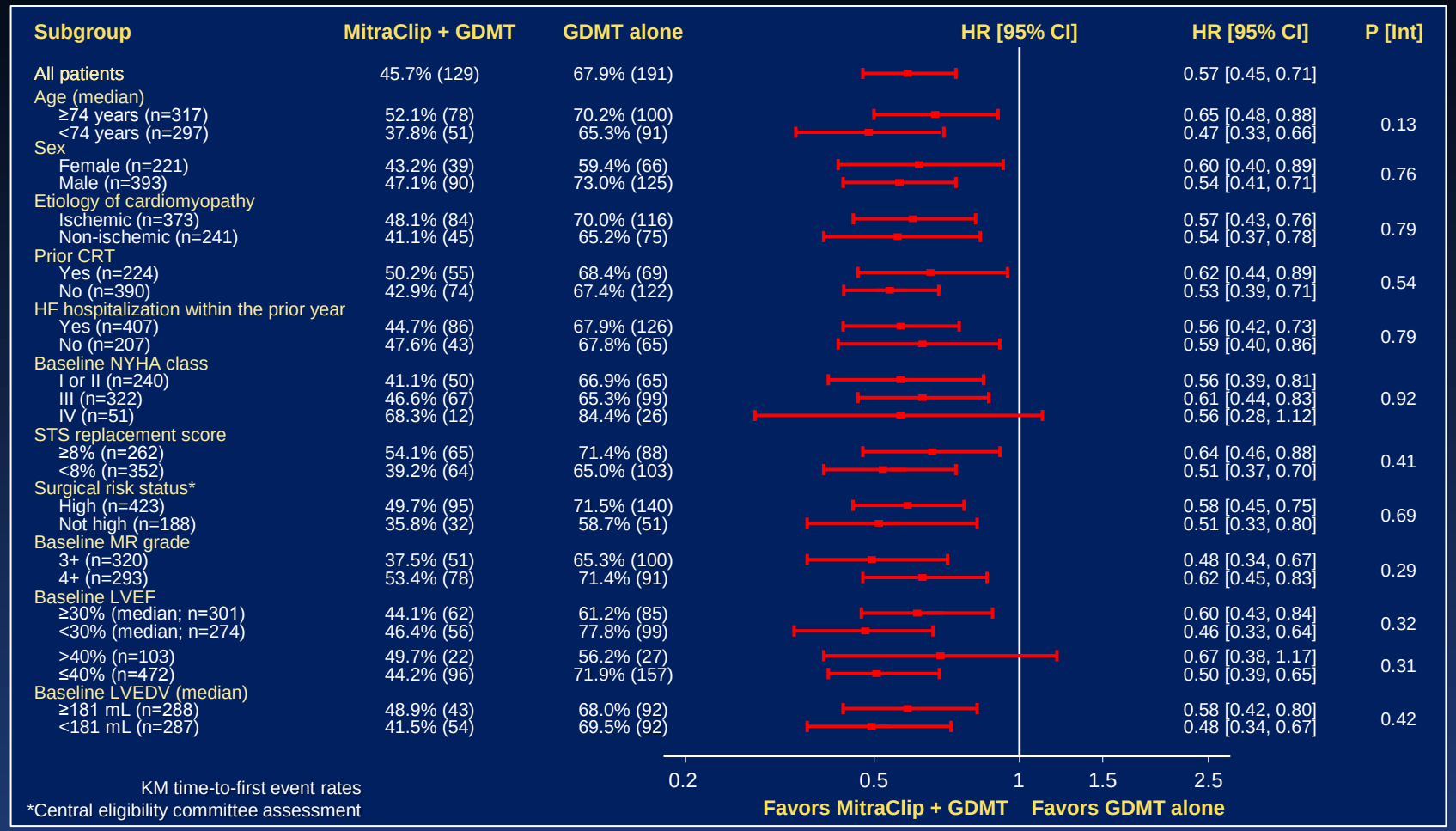
[1]All powered for superiority unless otherwise noted; [2]Powered for noninferiority of the device vs. the control group; [3]Powered for noninferiority against an objective performance goal

All-cause Mortality



No. at Risk:									
MitraClip + GDMT	302	286	269	253	236	191	178	161	124
GDMT alone	312	294	271	245	219	176	145	121	88

24-Month Death or HF Hospitalization



24-Month Event Rates (i)

	MitraClip + GDMT (n=302)	GDMT alone (n=312)	HR [95% CI]	P-value
Death, all-cause	29.1%	46.1%	0.62 [0.46, 0.82]	<0.001
- CV	23.5%	38.2%	0.59 [0.43, 0.81]	<0.001
- HF-related	12.0%	25.9%	0.43 [0.27, 0.67]	<0.001
- Non-HF-related	13.1%	16.6%	0.86 [0.54, 1.38]	0.53
- Non-CV	7.3%	12.7%	0.73 [0.40, 1.34]	0.31
Hospitalization, all-cause	69.6%	81.8%	0.77 [0.64, 0.93]	0.01
- CV	51.9%	66.5%	0.68 [0.54, 0.85]	<0.001
- HF-related	35.7%	56.7%	0.52 [0.40, 0.67]	<0.001
- Non-HF-related	29.4%	31.0%	0.98 [0.71, 1.36]	0.92
- Non-CV	48.2%	52.9%	0.91 [0.71, 1.17]	0.47
Death or HF hospitalization	45.7%	67.9%	0.57 [0.45, 0.71]	<0.001

Kaplan-Meier time-to-first event rates

24-Month Event Rates (ii)

	MitraClip + GDMT (n=302)	GDMT alone (n=312)	HR [95% CI]	P-value
MV intervention or surgery*	4.0%	9.0%	0.61 [0.27, 1.36]	0.23
- MitraClip	3.7%	6.6%	0.99 [0.38, 2.58]	0.99
- Mitral valve surgery	0.4%	2.5%	0.14 [0.02, 1.17]	0.07
PCI or CABG	2.8%	4.3%	0.62 [0.24, 1.60]	0.32
Stroke	4.4%	5.1%	0.96 [0.42, 2.22]	0.93
Myocardial infarction	4.7%	6.5%	0.82 [0.38, 1.78]	0.62
New CRT implant	2.9%	3.3%	0.85 [0.31, 2.34]	0.75
LVAD or heart transplant	4.4%	9.5%	0.37 [0.17, 0.81]	0.01
- LVAD	3.0%	7.1%	0.34 [0.13, 0.87]	0.02
- Heart transplant	1.4%	3.6%	0.35 [0.09, 1.32]	0.12

*Unplanned. Kaplan-Meier time-to-first event rates

MR Severity (Core Lab)

MR grade	≤1+	2+	3+	4+	P_{trend}	≤2+	P-value
Baseline			3+-4+				
MitraClip (n=302)	-	-	49.0%	51.0%	-	-	-
GDMT (n=311)	-	-	55.3%	44.7%		-	
30 days			7.4%				
MitraClip (n=273)	72.9%	19.8%	5.9%	1.5%	<0.001	92.7%	<0.001
GDMT (n=257)	8.2%	26.1%	37.4%	28.4%		34.2%	
6 months			6.3%				
MitraClip (n=240)	66.7%	27.1%	4.6%	1.7%	<0.001	93.8%	<0.001
GDMT (n=218)	9.2%	28.9%	42.2%	19.7%		38.1%	
12 months			5.3%				
MitraClip (n=210)	69.1%	25.7%	4.3%	1.0%	<0.001	94.8%	<0.001
GDMT (n=175)	11.4%	35.4%	34.3%	18.9%		46.9%	
24 months			0.9%				
MitraClip (n=114)	77.2%	21.9%	0%	0.9%	<0.001	99.1%	<0.001
GDMT (n=76)	15.8%	27.6%	40.8%	15.8%		43.4%	

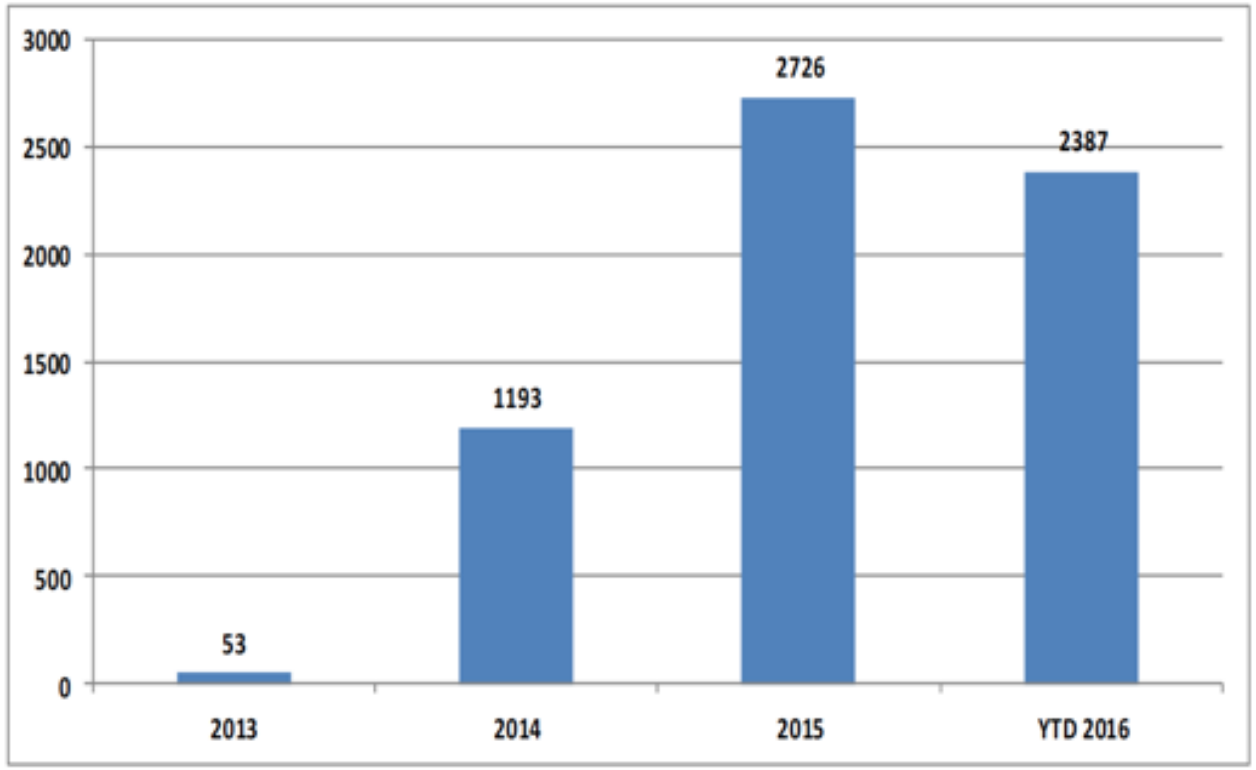
Why are the COAPT Results so Different from MITRA-FR?

Possible Reasons

	MITRA-FR (n=304)	COAPT (n=614)
Severe MR entry criteria	Severe FMR by EU guidelines: EROA >20 mm^2 or RV >30 mL/beat	Severe FMR by US guidelines: EROA >30 mm^2 or RV >45 mL/beat
EROA (mean ± SD)	31 ± 10 mm^2	41 ± 15 mm^2
LVEDV (mean ± SD)	135 ± 35 mL/m^2	101 ± 34 mL/m^2
GDMT at baseline and FU	Receiving HF meds at baseline – allowed variable adjustment in each group during follow-up per "real-world" practice	CEC confirmed pts were failing maximally-tolerated GDMT at baseline – few major changes during follow-up
Acute results: No clip / ≥3+ MR	9% / 9%	5% / 5%
Procedural complications*	14.6%	8.5%
12-mo MitraClip ≥3+ MR	17%	5%

*MITRA-FR defn: device implant failure, transfusion or vasc compl req surg, ASD, card shock, cardiac embolism/stroke, tamponade, urg card surg

Commercial Mitral Leaflet Procedures Submitted to the TVT Registry



Only commercial cases – does not include investigative cases (i.e. COAPT).

Source: STS/ACC TVT Registry Database as of Oct 17, 2016

STS National Database

Total Submitted MitraClip Cases = 6,359

NCDR

Leaflet Clip Procedure Details

Procedure Details (occurring during the procedure)	2014 *(n=1,023)*	2015 *(n=3,362)*
Other procedure performed concurrently	4.4%	4.5%
Conversion to open heart surgery	0.5%	0.8%
Mechanical assist required	1.9%	1.1%
Cardiopulmonary bypass required	0.1%	0.2%

Source: STS/ACC TVT Registry Data Mart 3,362 pt records from 2014-15, as of 4-24-16

Leaflet Clip Procedures Outcomes & Adverse Events at Discharge

Post Procedure Events (at discharge)	2014 *(n=1,023)*	2015 *(n=3,362)*
Myocardial Infarction	0%	0.1%
Acute Kidney Injury (stage 3)	1.2%	0.8%
Bleeding (major)	1.3%	1.3%
Bleeding (life threatening)	1.1%	1.1%
Major Vascular Complication	0.2%	0.3%

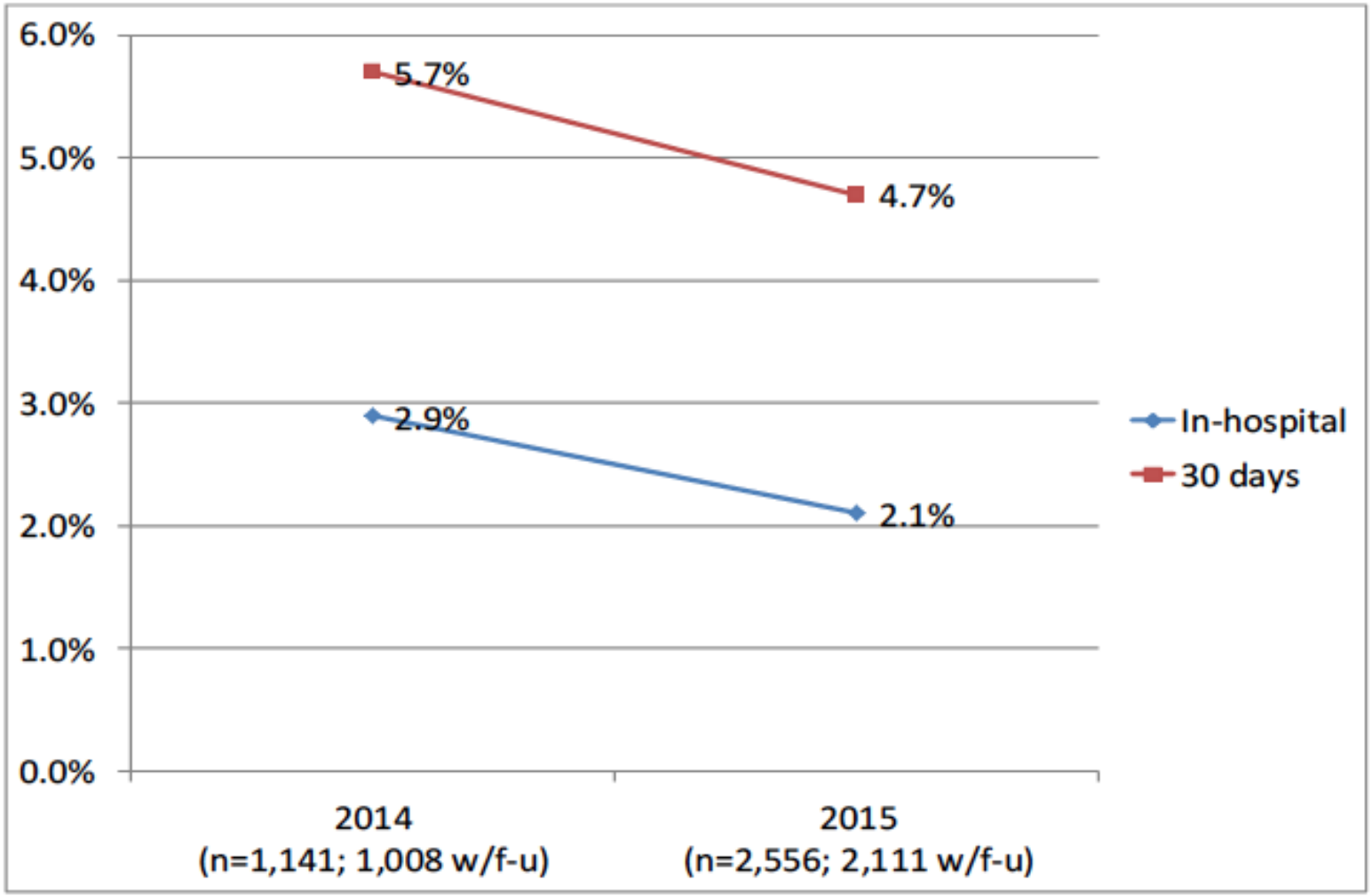
Source: STS/ACC TVT Registry Data Mart 3,362 pt records from 2014-15, as of 4-24-16

Leaflet Clip Procedures

At discharge	2014 *(n=1,023)*	2015 *(n=3,362)*
Mitral Regurgitation (<=2+)	92.0%	92.0%
MV Mean Gradient <=8 mmHg	92.3%	93.8%
Single Leaflet Device Attachment	1.2%	1.6%
MV Re-intervention	0.4%	0.9%
ASD requiring closure	1.6%	1.6%

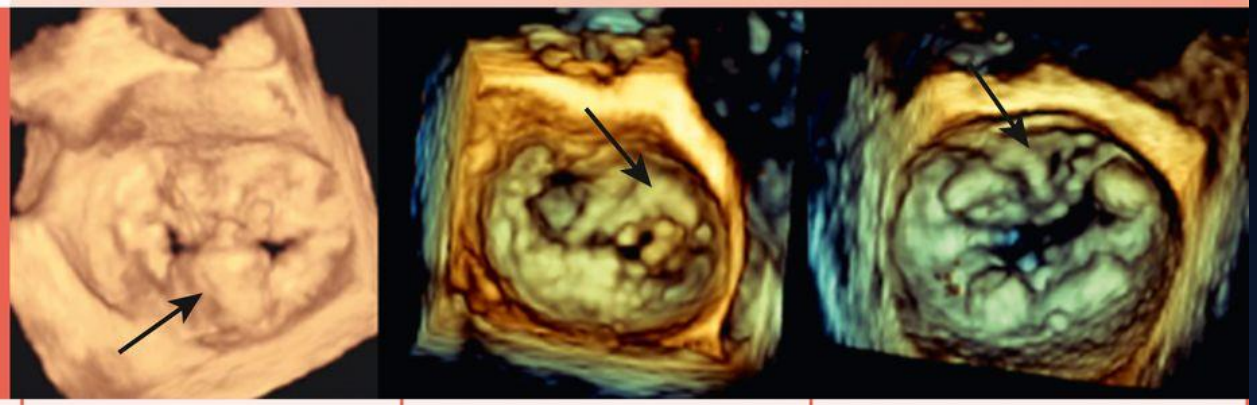
Source: STS/ACC TVT Registry Data Mart 3,362 pt records from 2014-15, as of 4-24-16

Mortality

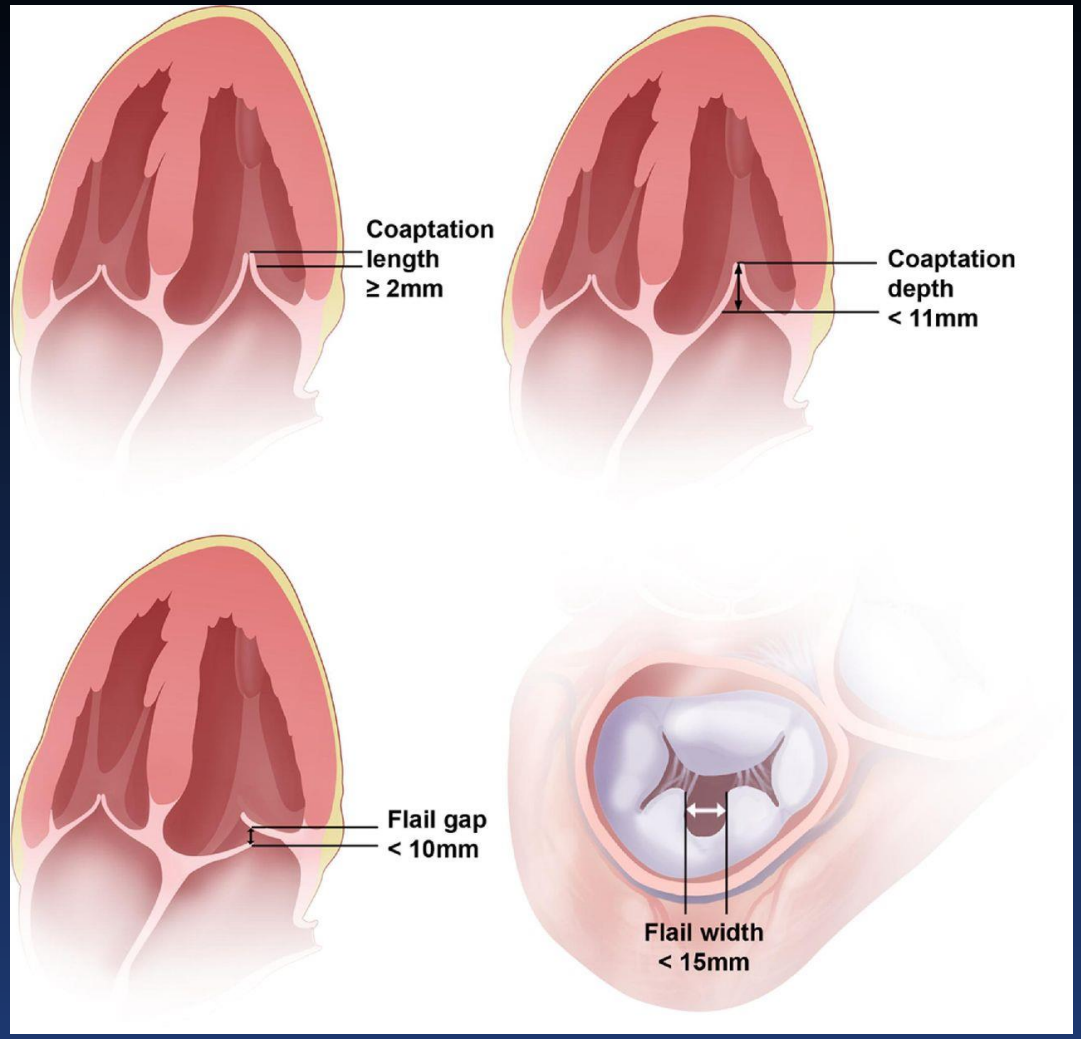


Source: STS/ACC TVT Registry Database 3,657 pt records from 2014-15, as of 10-12-16.

CONTRAINDICATION TO MITRAL CLIP

	Feasible		Unlikely
Transcatheter Mitral Valve Repair			
Segment	2	1 or 3	Severe Barlow
Calcification	None	Annular- sparing grasping zone	Grasping zone involved
MVA and MV Gradient	>4 cm^2 and <4 mm Hg	3.5-4 cm^2	<3.5 cm^2 and >5 mm Hg
Flail width	<15 mm	>15 mm	
Flail gap	<10 mm	>10 mm	

Abdallah El Sabbagh et al. JIMG 2018;11:628-643



Ted Feldman et al. JACC 2009;54:686-694

TRANSCUTANEOUS MITRAL VALVE REPLACEMT
TMVR

Transcatheter MV Implantation: Challenges

- **Fixation**
  - More complex structure
  - Asymmetric annulus
  - MAC
- **Delivery**
  - **Catheter size**
  - Approach (TA, TF, atrial)
- **Seal**
  - Paravalvular leak likely less well tolerated than with TAVR (hemolysis)
- **Function**
  - LVOT obstruction risk
  - Need to preserve the subvalvular apparatus
  - **Thrombus formation risk**

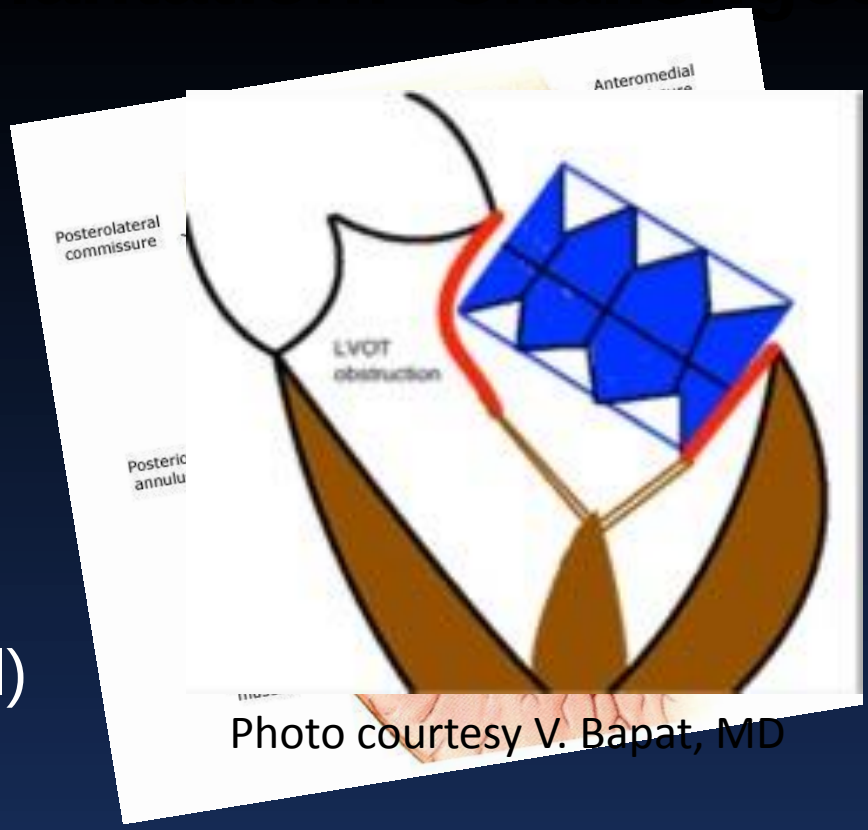
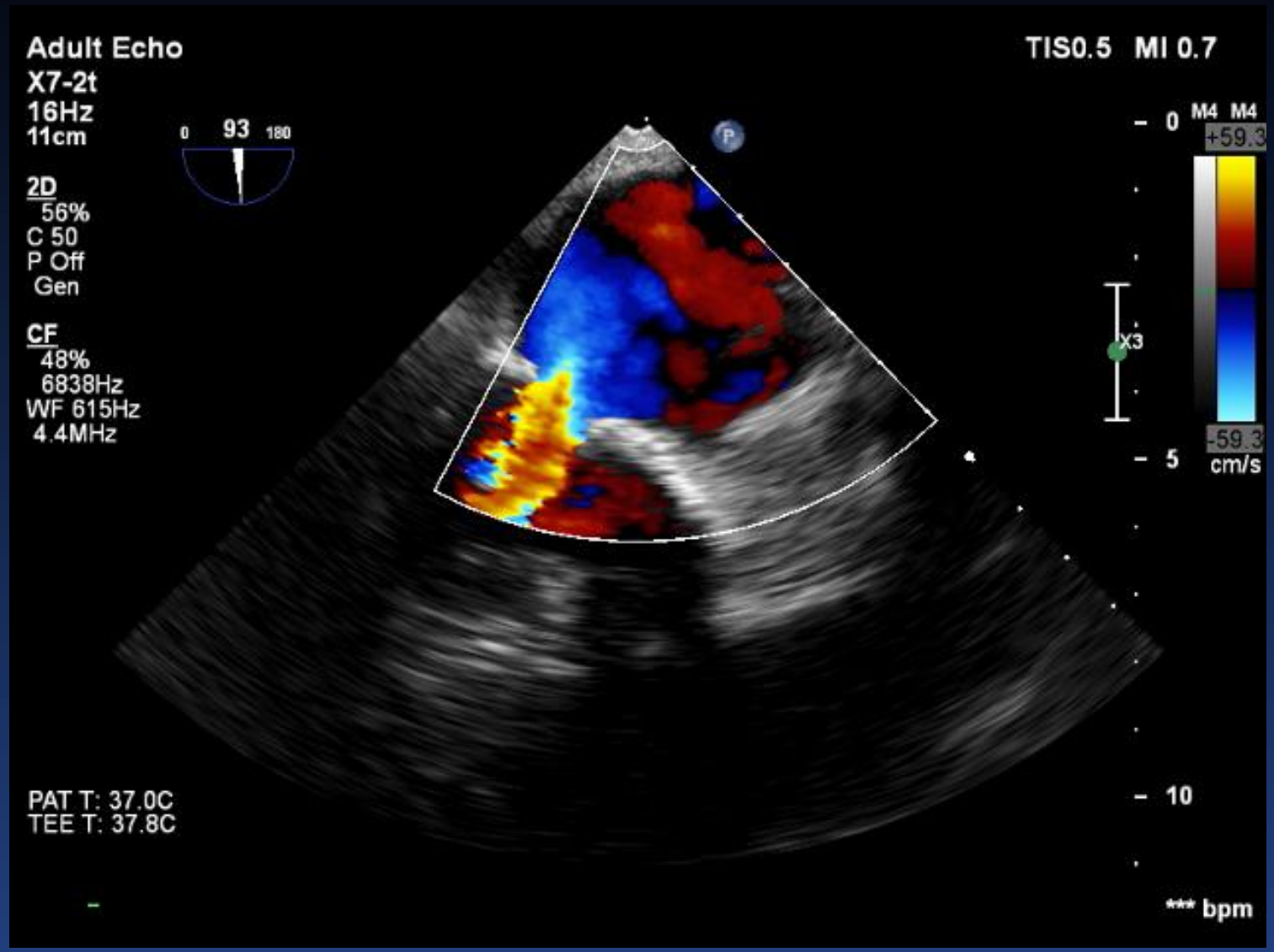
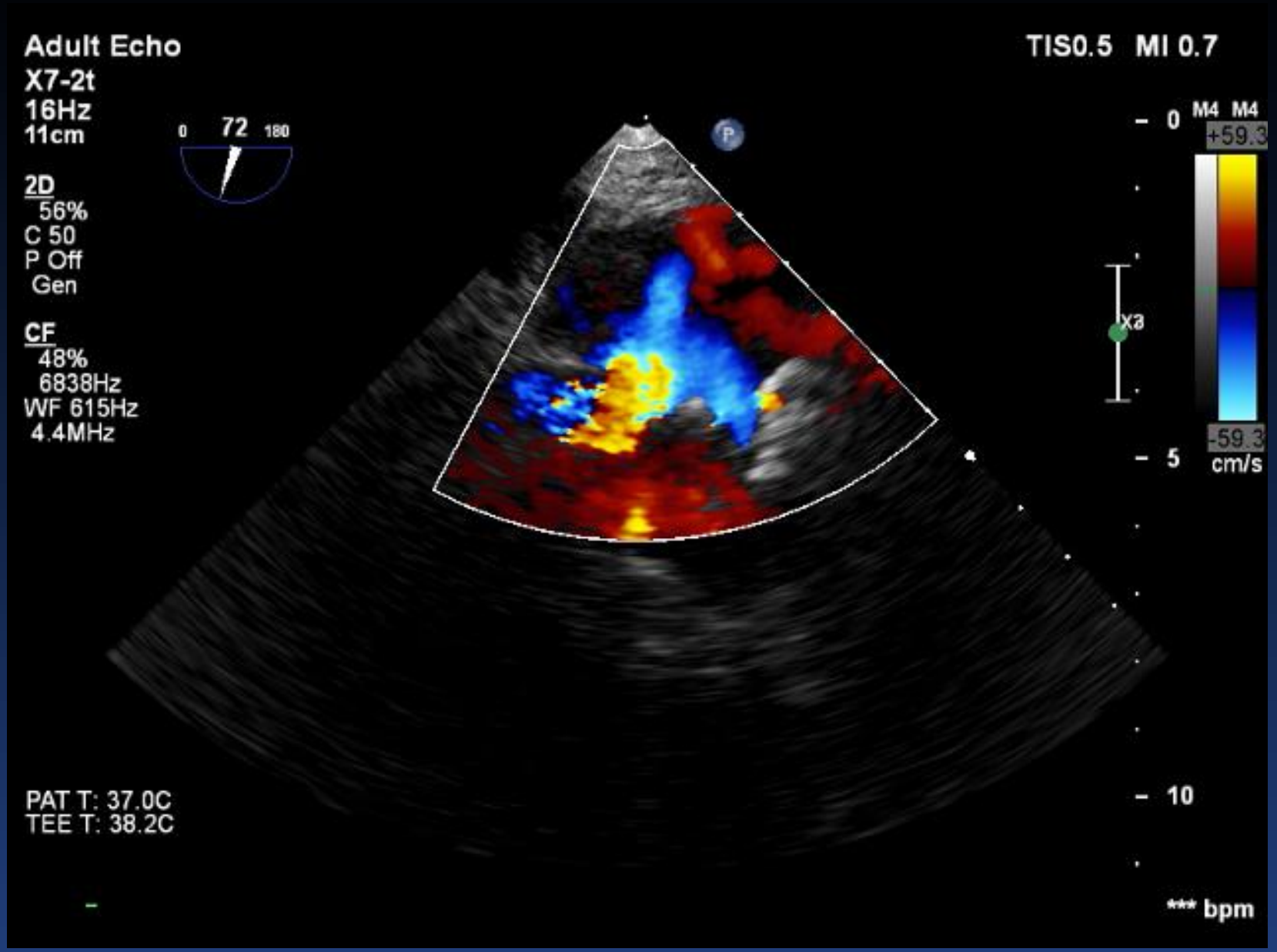
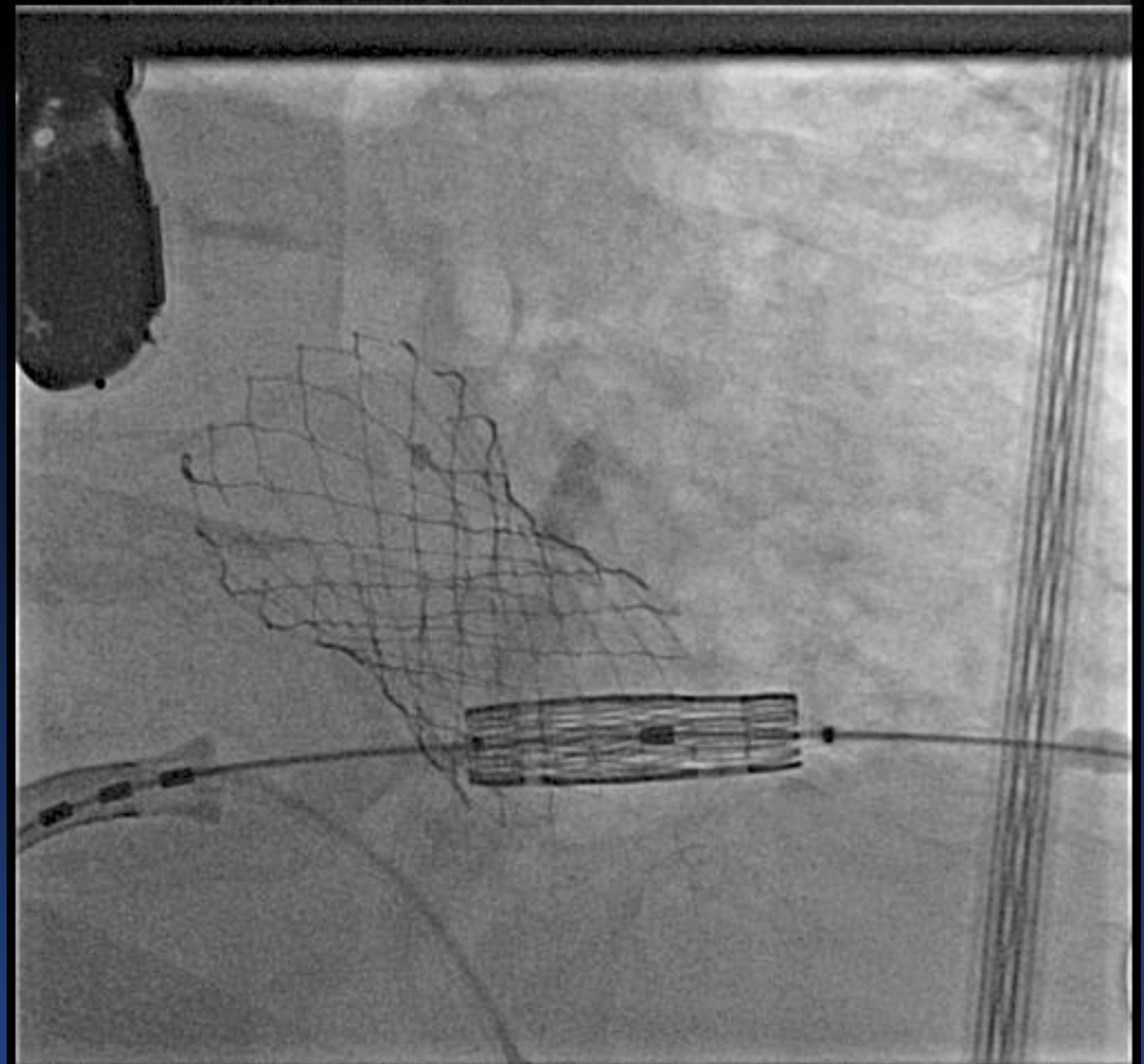


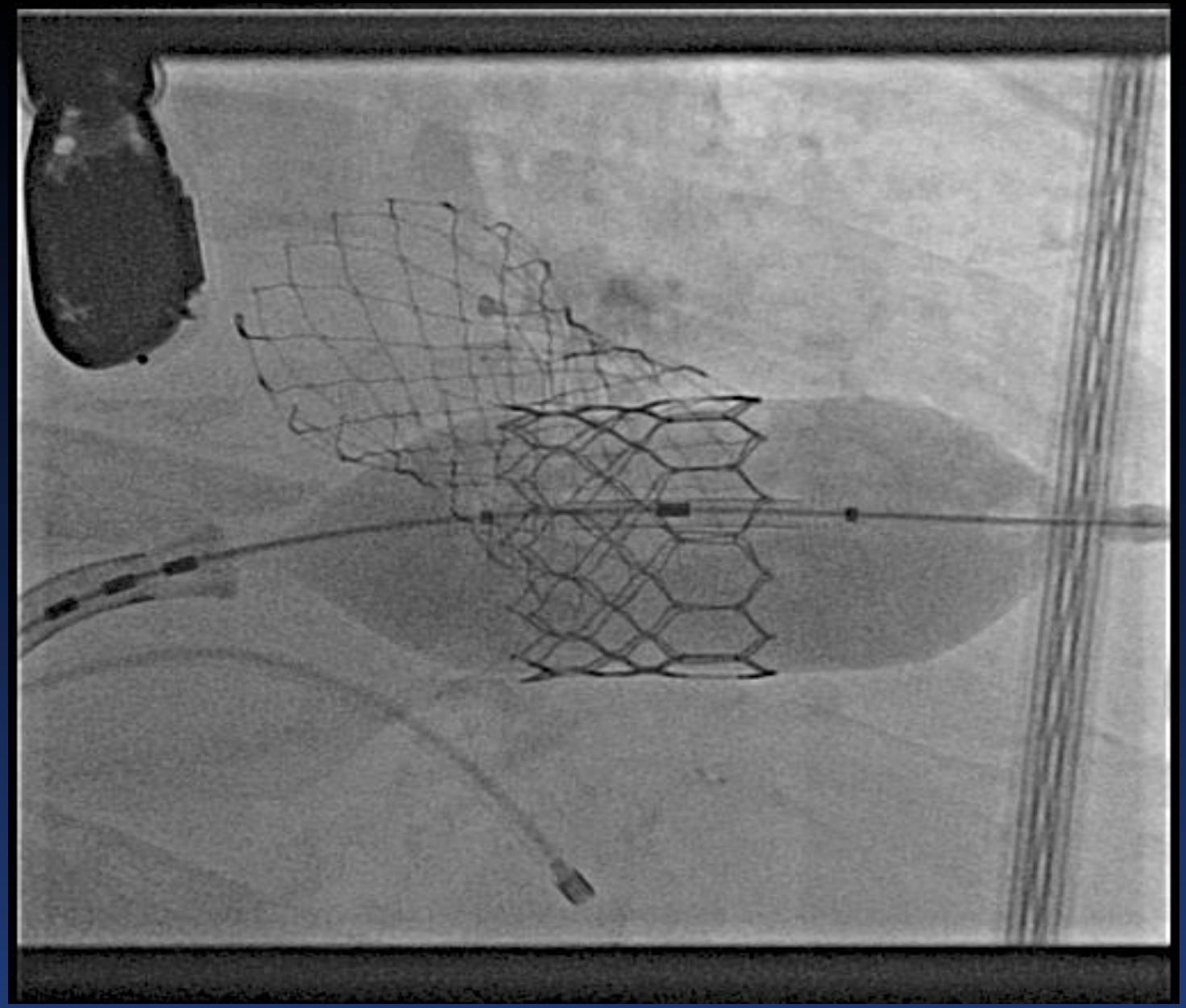
Photo courtesy V. Bapat, MD

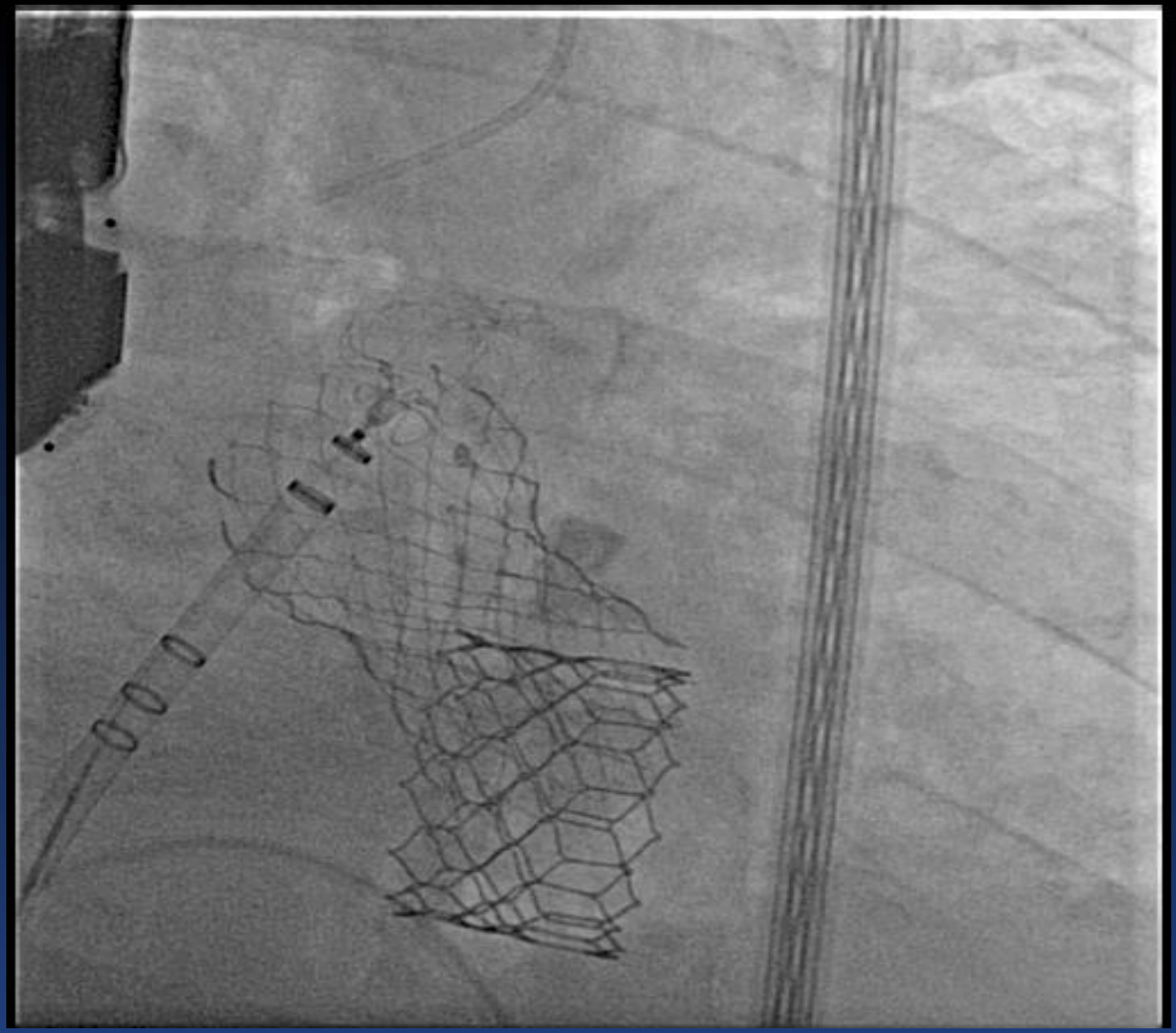
79 WITH SEVERE AS AND MR AND MILD MS PROHIBITIVE RISK FOR SURGERY

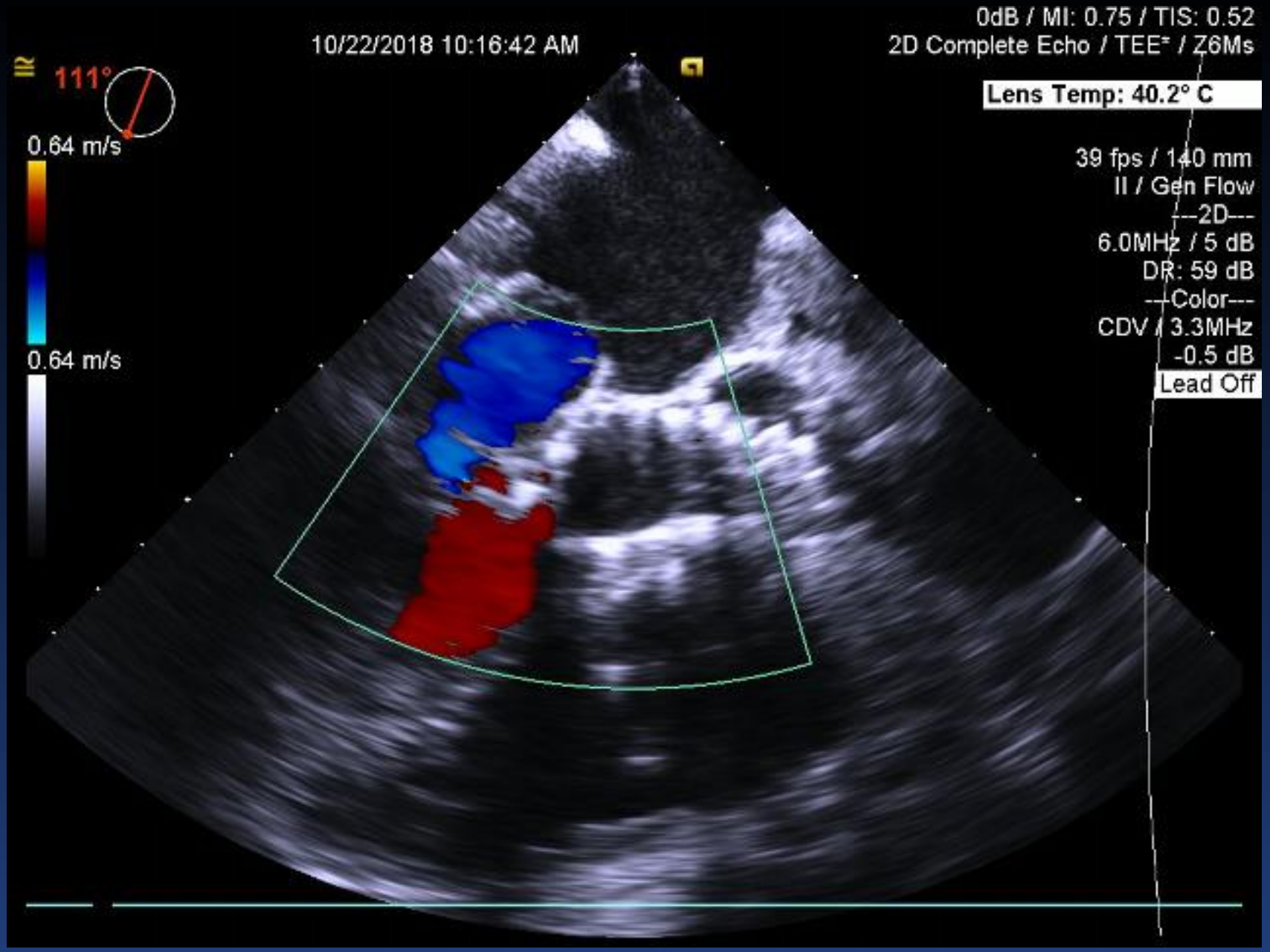



Adult Echo
X7-2t
16Hz
11cm
0 72 180
2D
56%
C 50
P Off
Gen
CF
48%
6838Hz
WF 615Hz
4.4MHz
TIS0.5 MI 0.7
M4 M4
+59.3
-59.3
cm/s
0
5
10
PAT T: 37.0C
TEE T: 38.2C
*** bpm





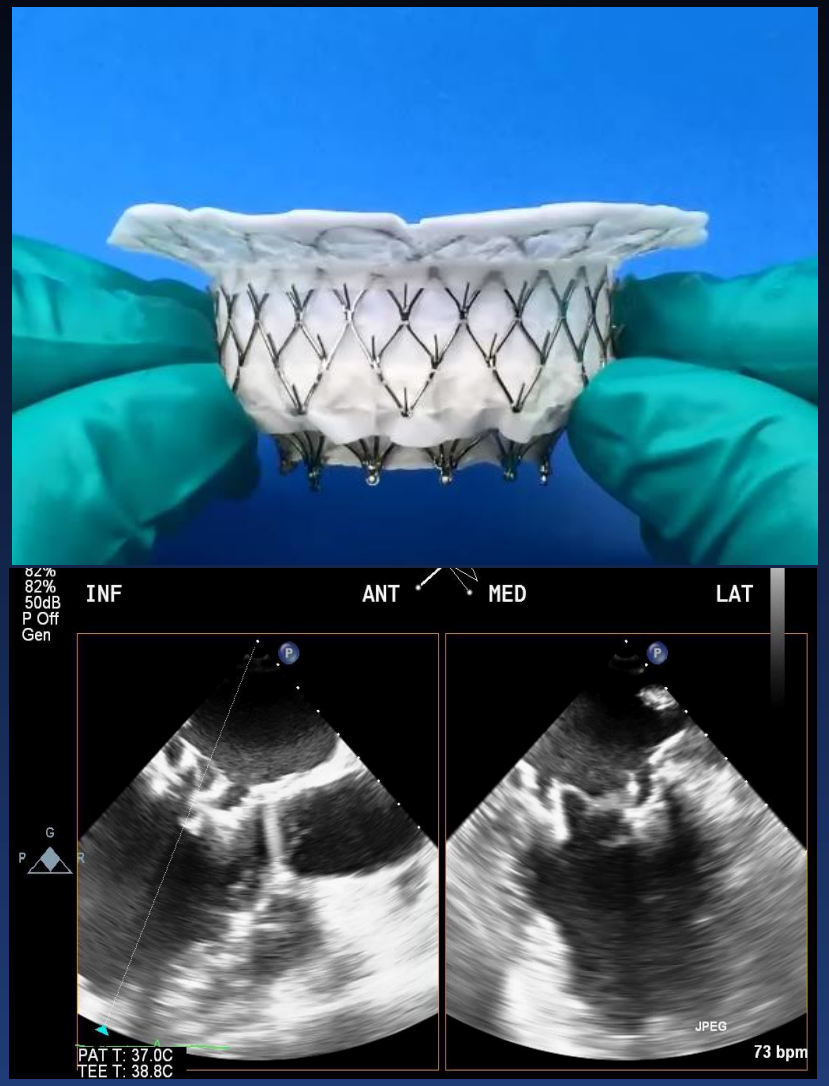



0dB / MI: 0.75 / TIS: 0.52
2D Complete Echo / TEE* / Z6Ms
10/22/2018 10:16:42 AM
111°
0.64 m/s
0.64 m/s
Lens Temp: 40.2° C
39 fps / 140 mm
II / Gen Flow
---2D---
6.0MHz / 5 dB
DR: 59 dB
---Color---
CDV / 3.3MHz
-0.5 dB
Lead Off

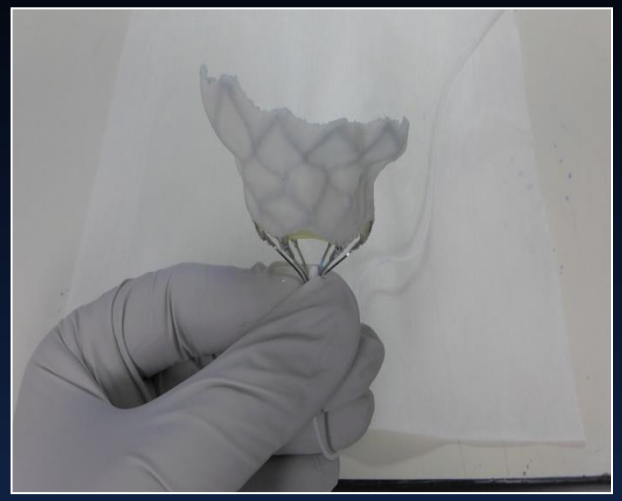
Medtronic Intrepid TMVR

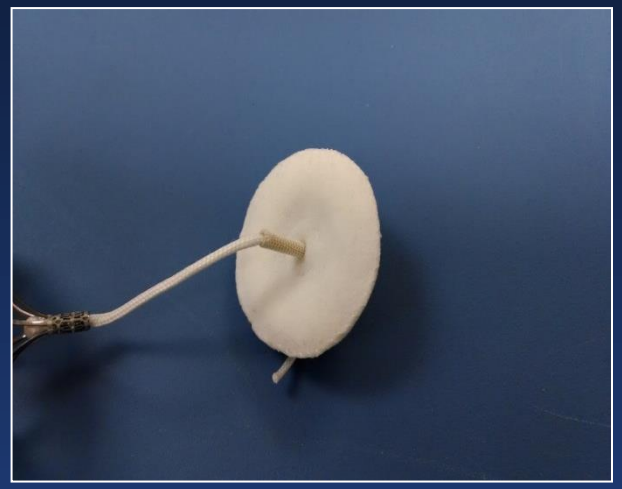
Differentiated, dual stent design

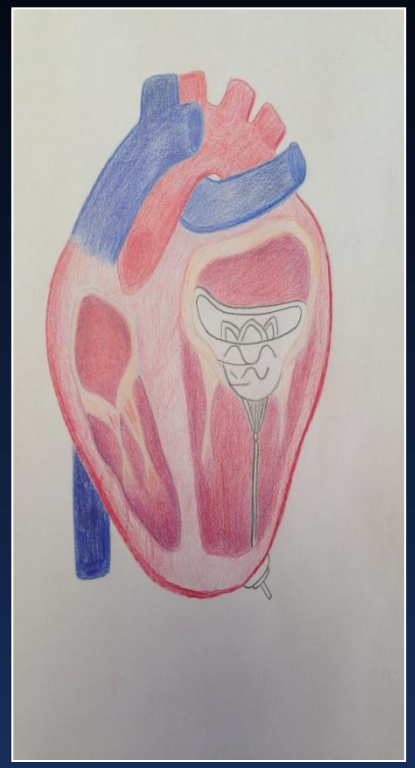
- Separates fixation & sealing from valve function
- Isolates valve from the dynamic anatomy
- Preserves native mitral apparatus
- **US Feasibility Trial Ongoing**

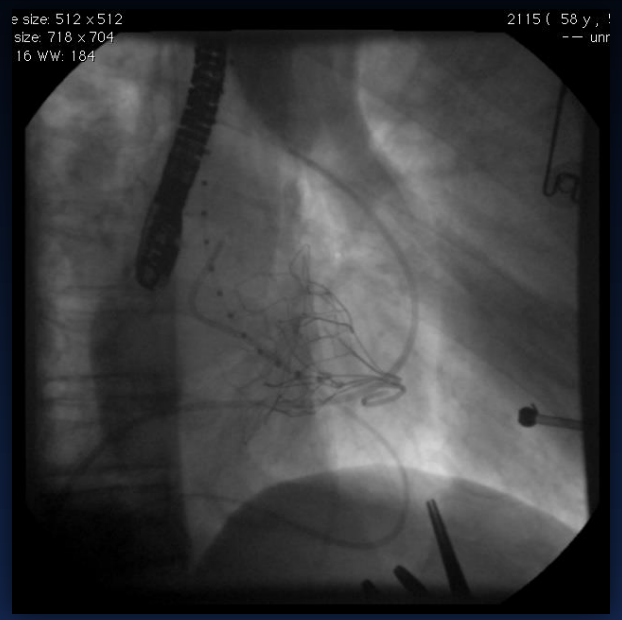


Abbott Tendyne TMVR









- Transapical deployment
- Apical anchor ensures stable deployment
- US feasibility trial ongoing

Images Courtesy of Dr. Neil Moat

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Early Experience With New Transcatheter Mitral Valve Replacement

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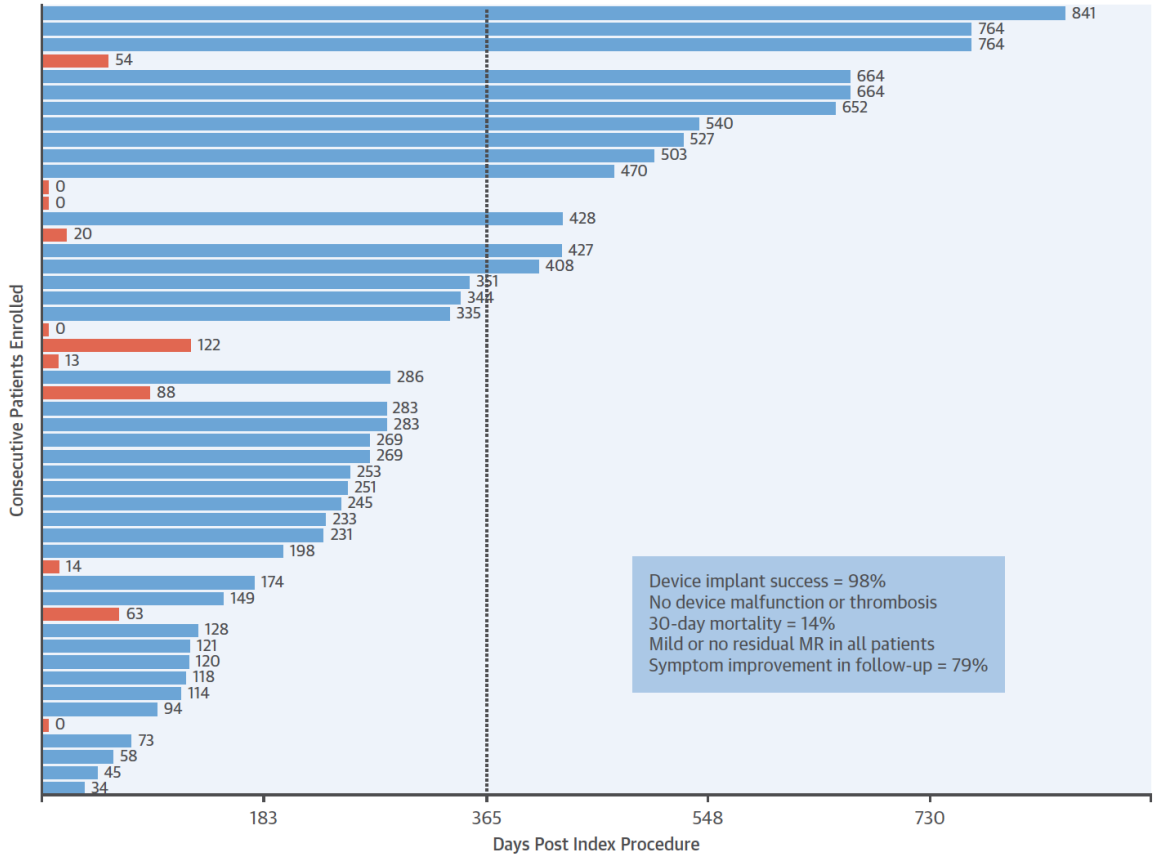
CENTRAL ILLUSTRATION Early Clinical Experience of TMVR with the New Valve Prosthesis



Bapat, V. et al. J Am Coll Cardiol. 2018;71(1):12-21.

Follow-up time for the 50 patients is illustrated with patients listed on the y-axis in descending order of treatment. X-axis indicates duration of follow-up. All deaths occurred before 365 days **(dotted line)**. **Blue** = surviving patients; **orange** = deceased patients; MR = mitral regurgitation; TMVR = transcatheter mitral valve replacement.

Mitral Heart Team