MitraClip for Mitral Regurgitation & CHF

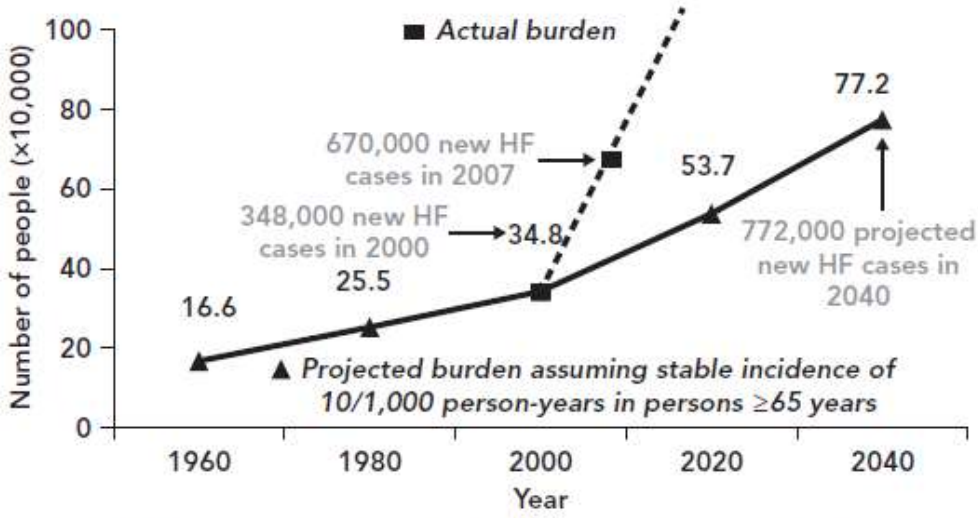
Oklahoma Heart Update in Cardiology
October 2019

Kamran Muhammad, MD FACC FSCAI

Outline & Key Points

- MR prevalence is age-dependent, affecting 9.3% of those aged >75 years
- Etiology:
  - Primary (valvular, degenerative)
  - **Secondary (ventricular, functional) and association with CHF**
- Excess mortality occurs from medical management and delays in intervention
- Surgery for secondary MR doesn't work
- Transcatheter Mitral Valve Repair with MitraClip for secondary MR in CHF is a powerful and effective treatment

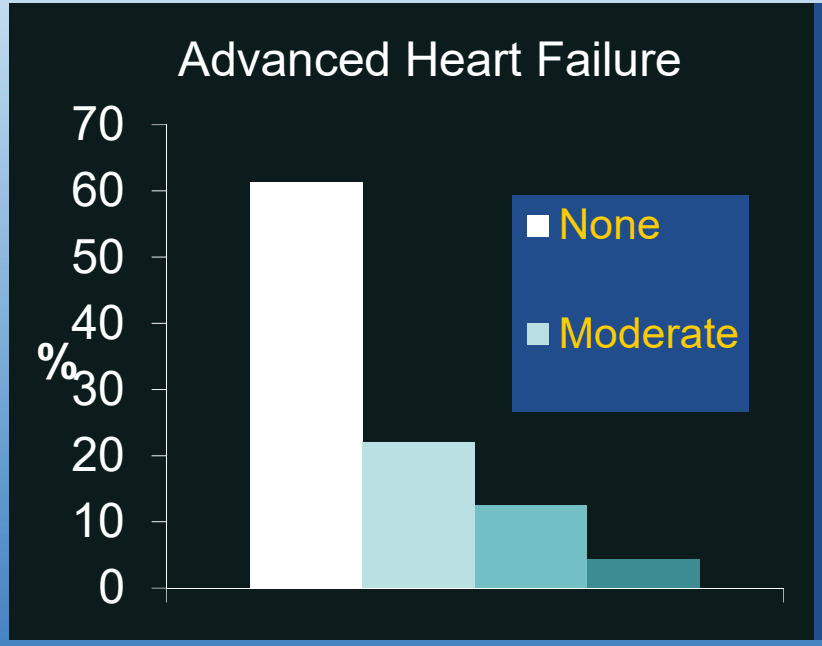
Burden of CHF: Leading Cause of Hospital Admission



The actual annual incidence of heart failure (HF) reported in the US (squares and dotted line) exceeded the projected annual incidence (triangles and solid line) calculated based on a stable incidence of 10 per 1,000 person-years in persons aged ≥65 years. Source: Lam et al., 2011.[69] Reproduced with permission, © 2011 John Wiley & Sons.

MR and Heart Failure

Prevalence in CHF

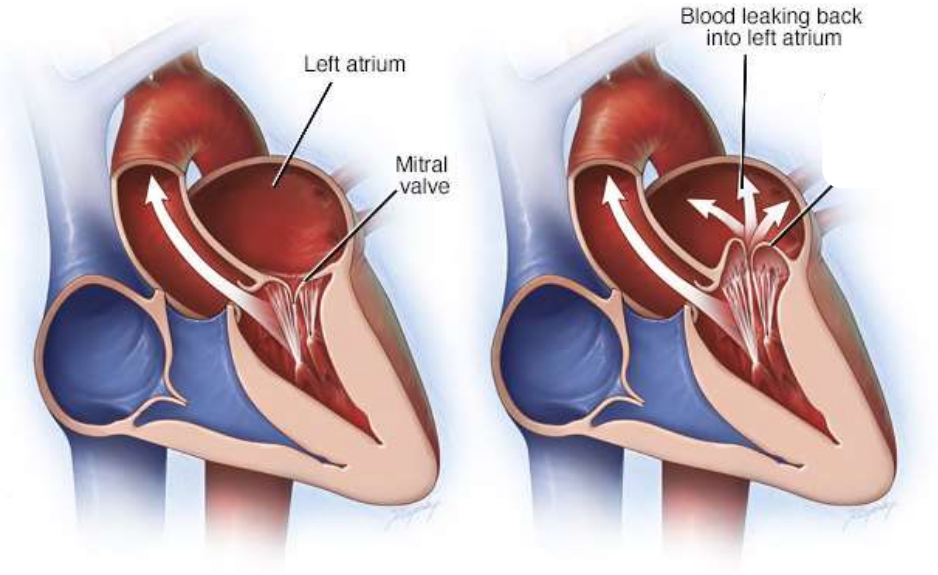


Moderate or severe MR present in ~40%

~5 million people with heart failure in U.S.

Patel JB, et al. J Card Fail 2004;10:285-291; Go AS, et al. Circulation 2013;127:e6.

Mitral Regurgitation (MR)



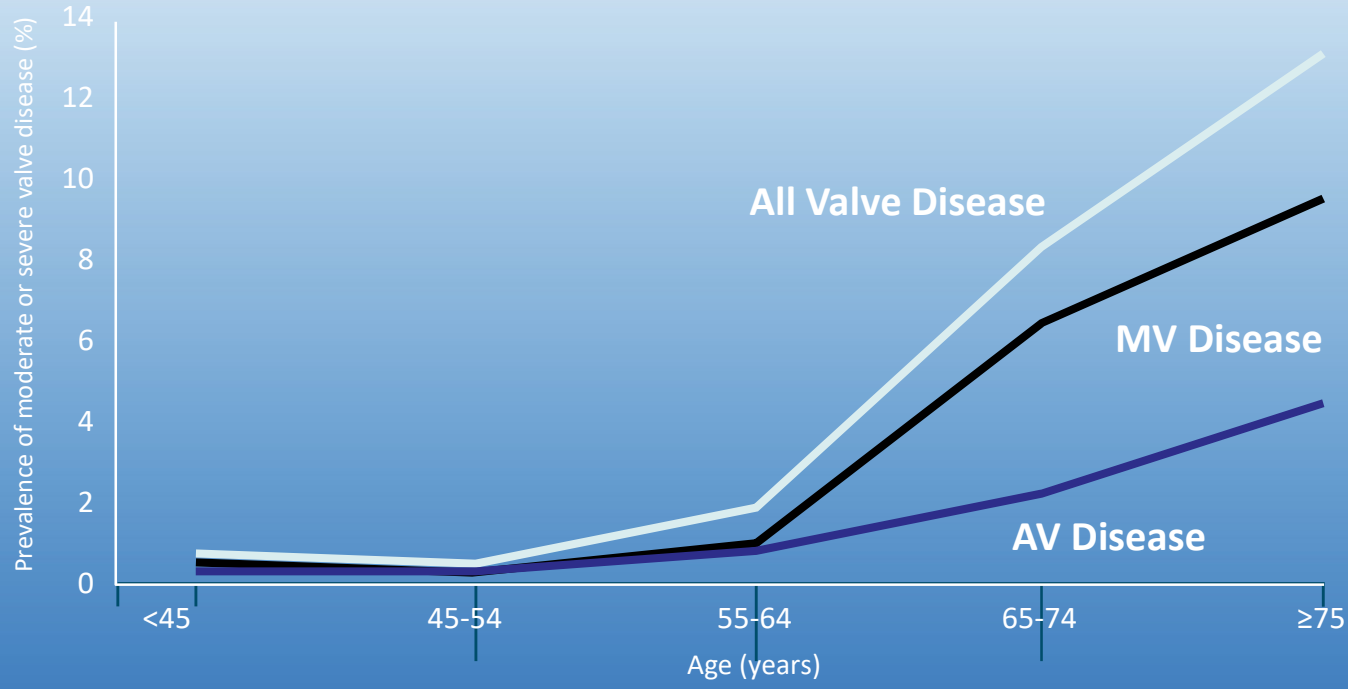
MR occurs when the mitral valve fails to close completely, causing blood flow to flow backward

Symptoms may include:

- Shortness of breath
- Swollen feet or ankles
- Fatigue
- Lightheadedness
- Cough

Prevalence of Mitral Valve Disease

MITRAL VALVE DISEASE IS 2-3X AORTIC VALVE DISEASE



Nkomo, et al. Lancet. 2006; 368: 1007

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Mitral Regurgitation is Classified into 2 Types

MR occurs when the mitral valve fails to close completely, causing blood flow to move backward into the left atrium[1]

PRIMARY VALVE ABNORMALITY

- Leaflets
- Subvalvular apparatus
- Chordae and papillary muscles

SECONDARY - LEFT VENTRICLE DILATION

- Leaflet tethering
- Mitral annular dilation
- Incomplete coaptation of the mitral valve

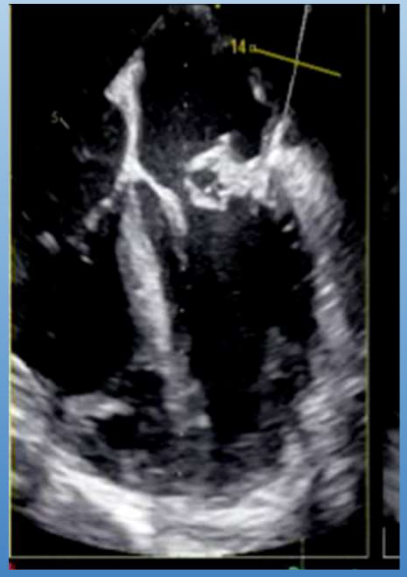
Prognostic Determinants

- Severity
- Left Ventricular Function
- Symptoms

Classification of MR

Primary

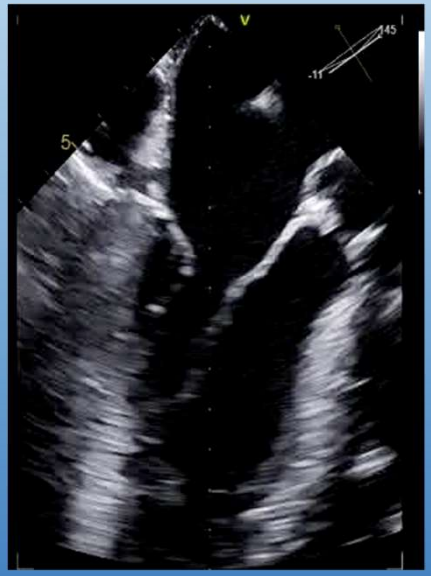
"The Valve"



Usually myxomatous

Secondary

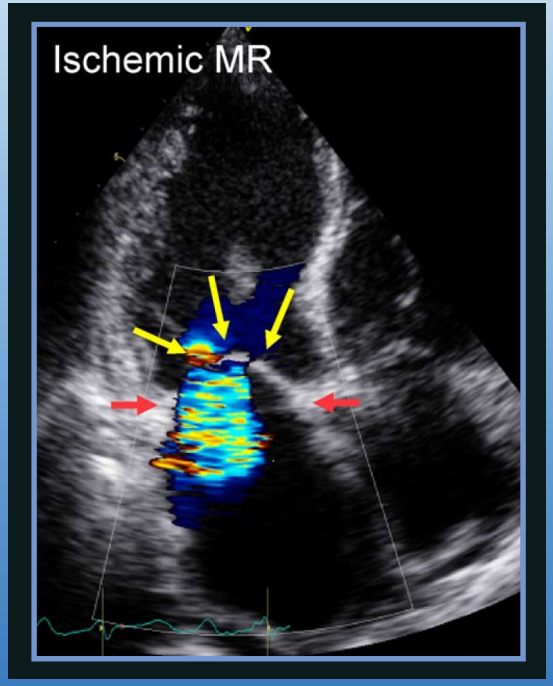
"The Ventricle"



Ischemic or not

Secondary Mitral Regurgitation

A Ventricular Problem

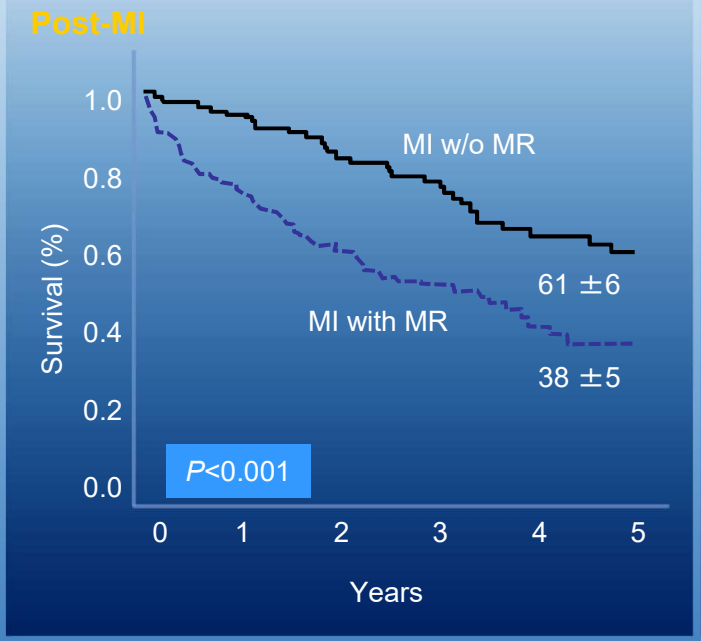


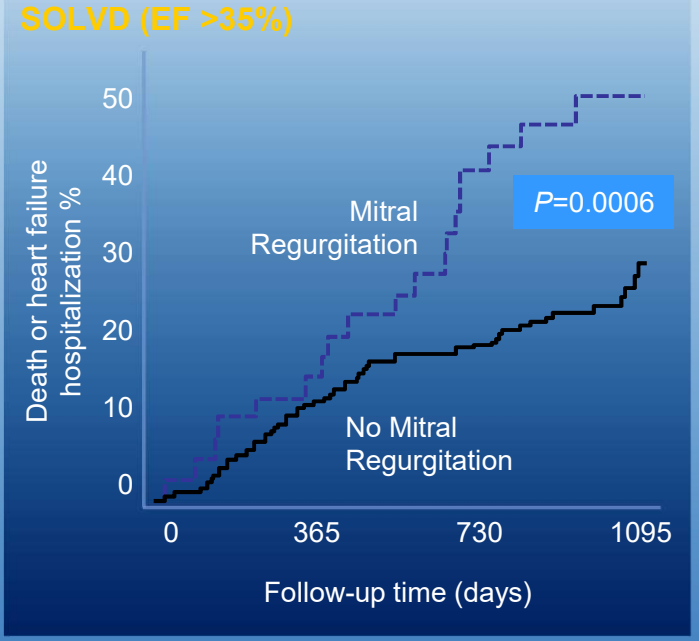
- Regional or Global Dysfunction
- Papillary muscle displacement
- Annular flattening
- Leaflet tethering

Trichon BH, et al. Am J Cardiol 2003;91:538-43

Secondary Mitral Regurgitation

A Harbinger of Poor Outcome





Two-fold Increase Risk of Death

Grigioni F, et al. Circulation 2001;103:1759-64;
Basket JF, et al. Can J Cardiol 2007;23:797-800

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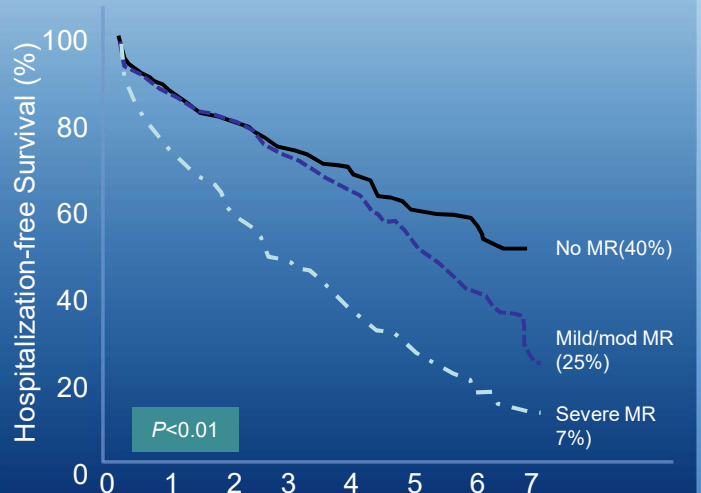
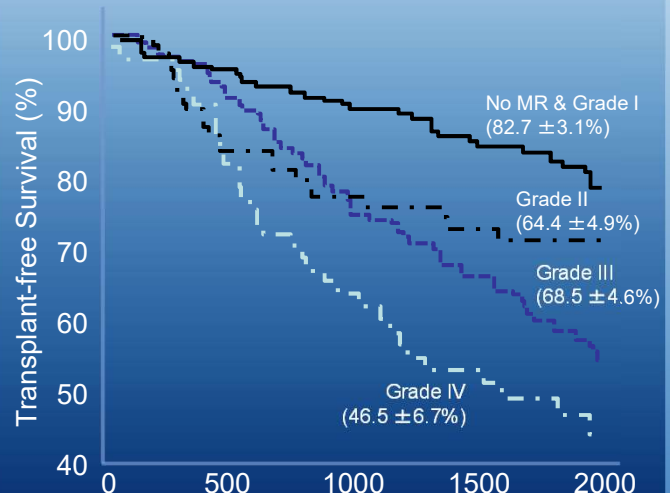
Secondary Mitral Regurgitation

Increased Severity = Increased Morbidity

Hospitalization-free survival decreased with increased MR severity[1]



Transplant-free survival decreased with increased MR severity[2]



1. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure: a quantitative analysis of 1256 patients with ischemic and non-ischaemic dilat cardiomyopathy. *Heart.* 2011;97(20):1675-1680.
2. Bursi F, Barbieri A, Grigioni F, et al. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: a long-term outcome study. *Eur J Heart Fail.* 2010;12(4):382-388.

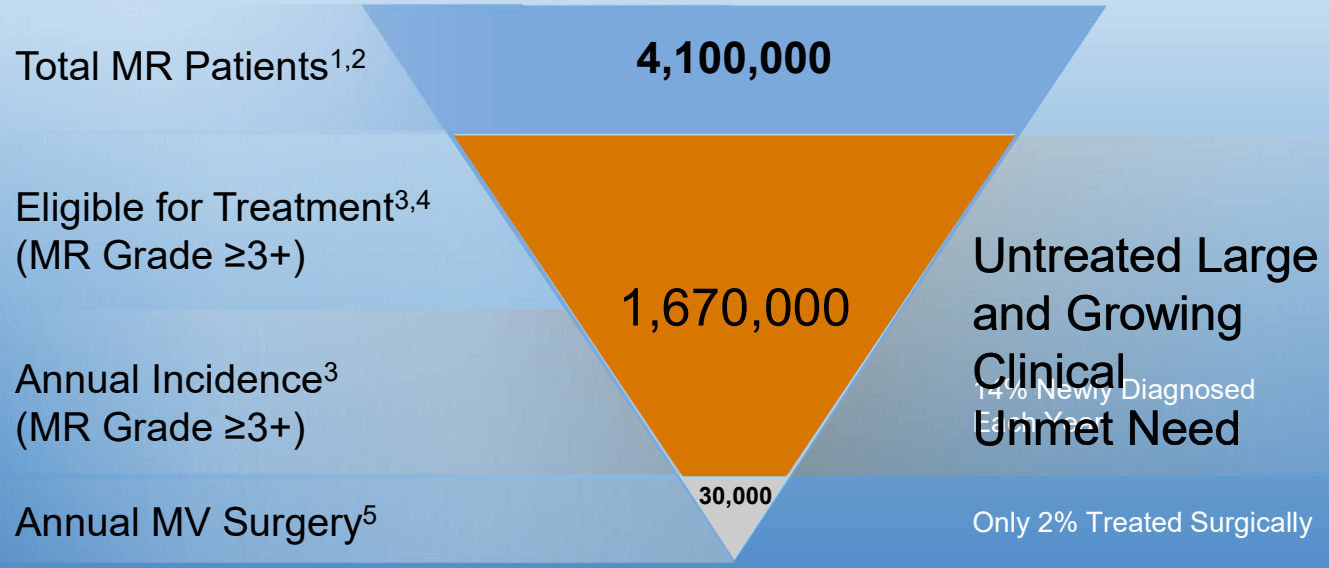
MITRAL REGURGITATION

Untreated severe MR is associated with increased morbidity and mortality

What about therapy?

A Largely Untreated Patient Population

Mitral Regurgitation 2009 U.S. Prevalence



1. US Census Bureau. Statistical Abstract of the US: 2006, Table 12.
2. Nkomo et al. Burden of Valvular Heart Diseases: A Population-based Study, Lancet, 2006; 368: 1005-11.
3. Patel et al. Mitral Regurgitation in Patients with Advanced Systolic Heart Failure, J of Cardiac Failure, 2004.
4. ACC/AHA 2008 Guidelines for the Management of Patients with Valvular Heart Disease, Circulation: 2008
5. Gammie, J et al, Trends in Mitral Valve Surgery in the United States: Results from the STS Adult Cardiac Database, Annals of Thoracic Surgery 2010.

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Pathophysiology of MR

[1] Cioffi G, et al. Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure. European Journal of Heart Failure 2005 Dec;7(7):1112-7

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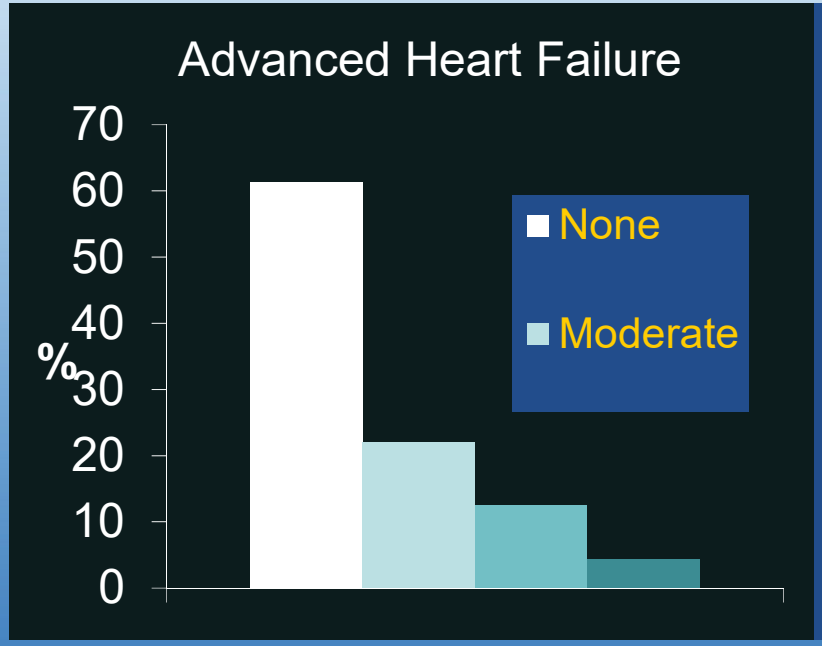
MR and Heart Failure

Prevalence in CHF



Moderate or severe MR present in ~40%

~5 million people with heart failure in U.S.

Patel JB, et al. J Card Fail 2004;10:285-291; Go AS, et al. Circulation 2013;127:e6.

Current Therapy Considerations

Less Invasive

Increased MR Reduction

General Principles of Therapy

Secondary MR

Medical therapy first

Consider CRT

Surgery only in highly selected patients with HF

Surgical Intervention

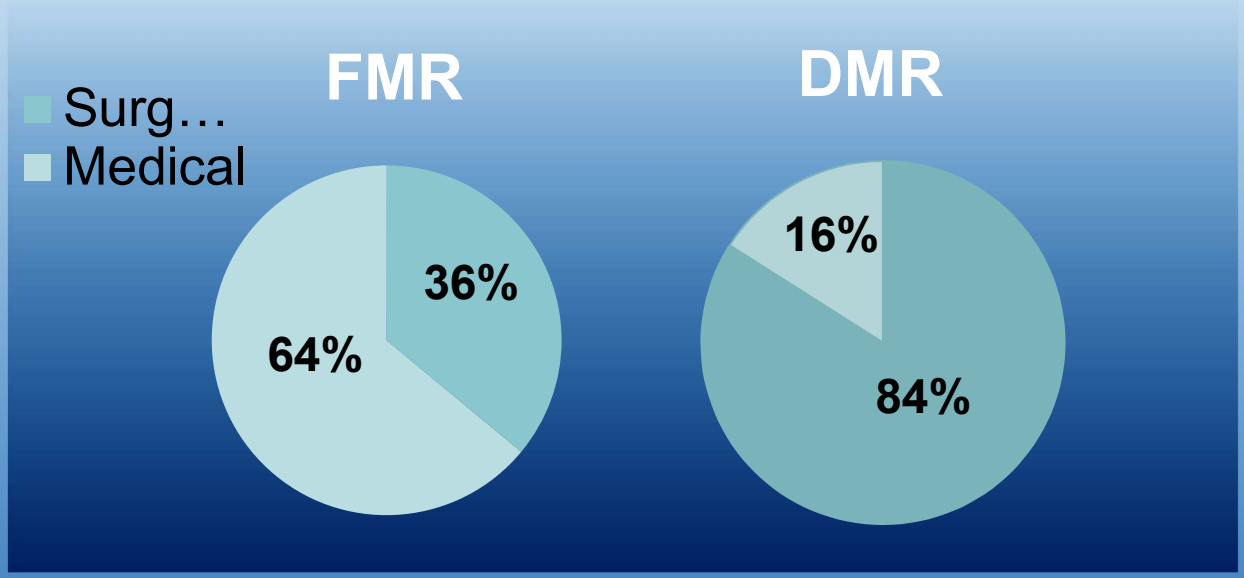
ACC/AHA Guidelines – Secondary MR

Surgery may be considered for severe symptoms despite optimal GDMT for HF (IIb)

Also for other CV surgery if severe (IIa) or moderate (IIb)

Medical Management

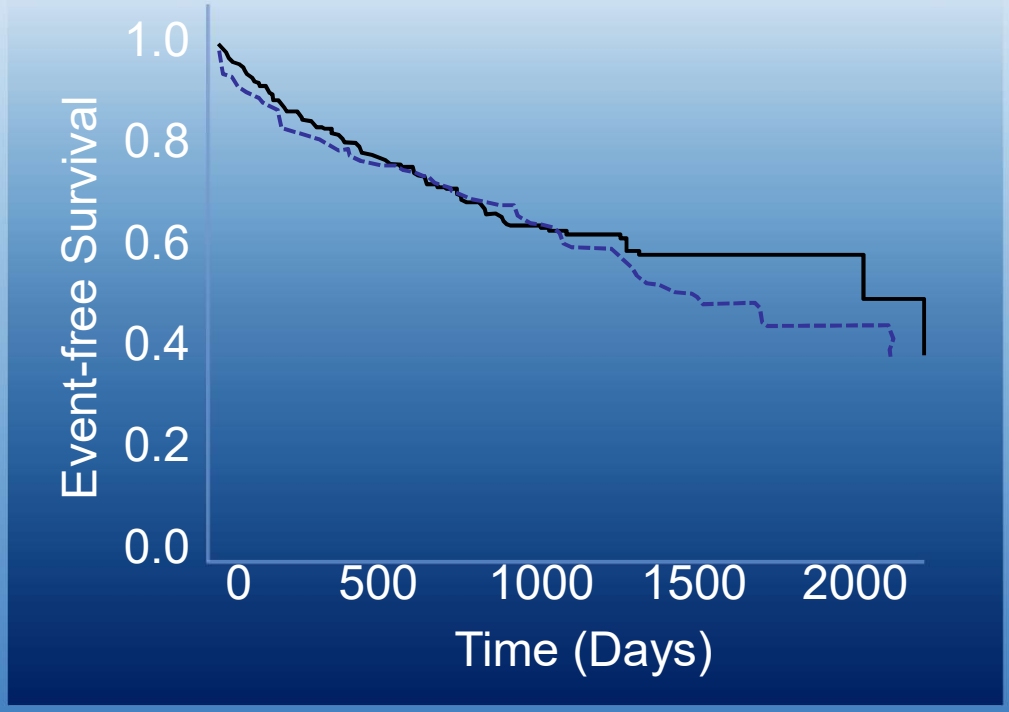
1,095 pts with severe MR and CHF



5-yr mortality for medically managed = 50%

Goel SS, et al. J Am Coll Cardiol 2014;63:185-90

Surgery for Secondary MR



No Mortality Benefit

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Treatment Options for HF Patients with Secondary Mitral Regurgitation

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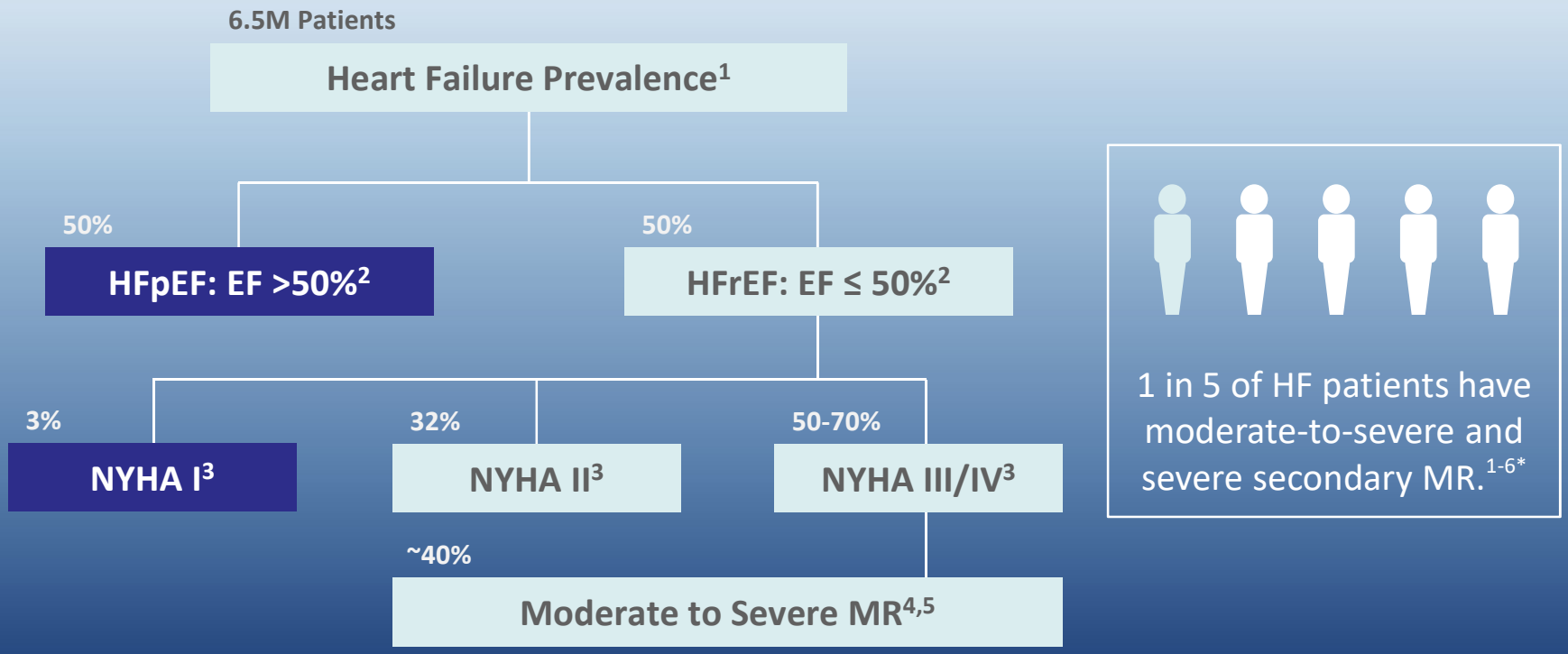
Prevalence of SMR is 2-3x Larger than PMR



* Heart Failure patients with reduced EF and with moderate to severe and severe secondary MR

1. AHA Heart Disease and Stroke Statistics Update, Circulation 2017
2. Yancy CW et al, JACC 2013
3. Pecini et al EHJ 2011
4. Asgar et al, JACC 2015
5. Nieminen et al, EHJ 2006
6. Patel et al, Journal of Cardiac Failure 2004.

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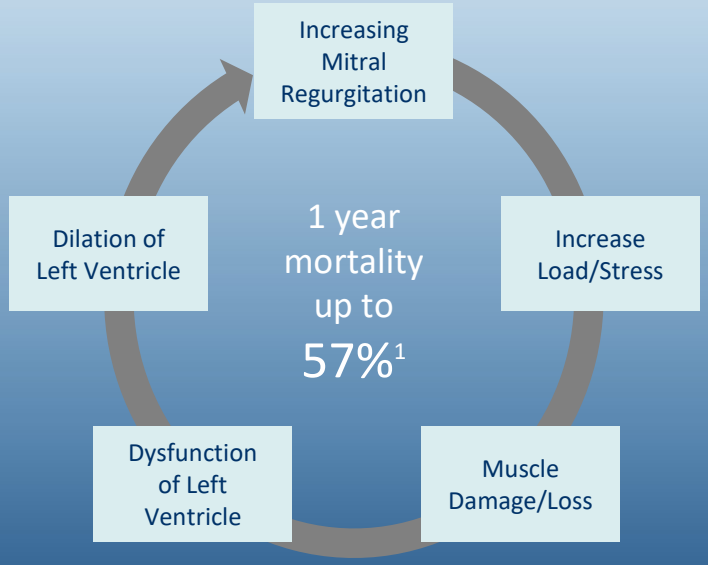
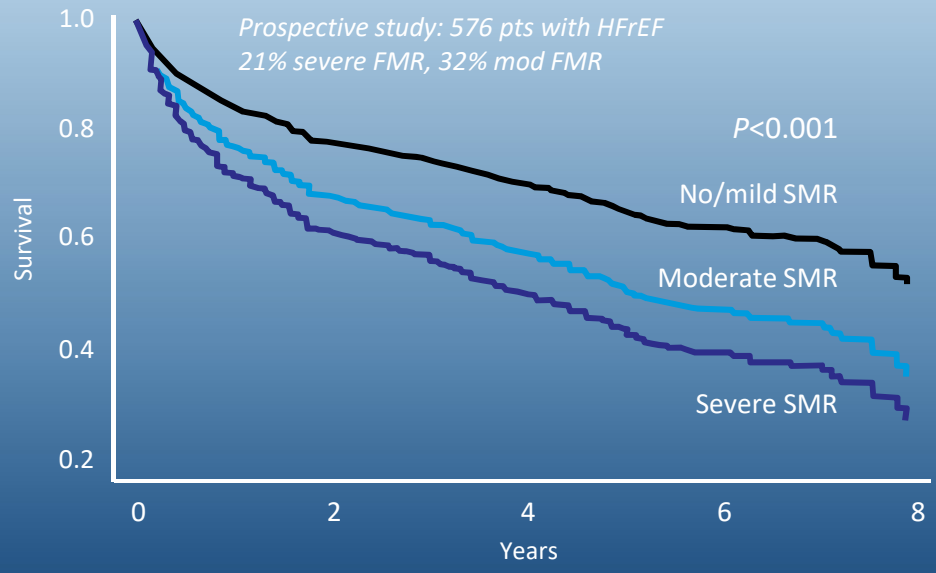
Secondary MR is a Predictor of Mortality



SEVERE SECONDARY MR IS AN INDEPENDENT PREDICTOR OF MORTALITY[2]



1.Cioffi G, et al. European Journal of Heart Failure 2005 Dec;7(7):1112-7
2.Goliasch G et al. EHJ 2018;39:39-46. Graph courtesy of Dr. G Stone

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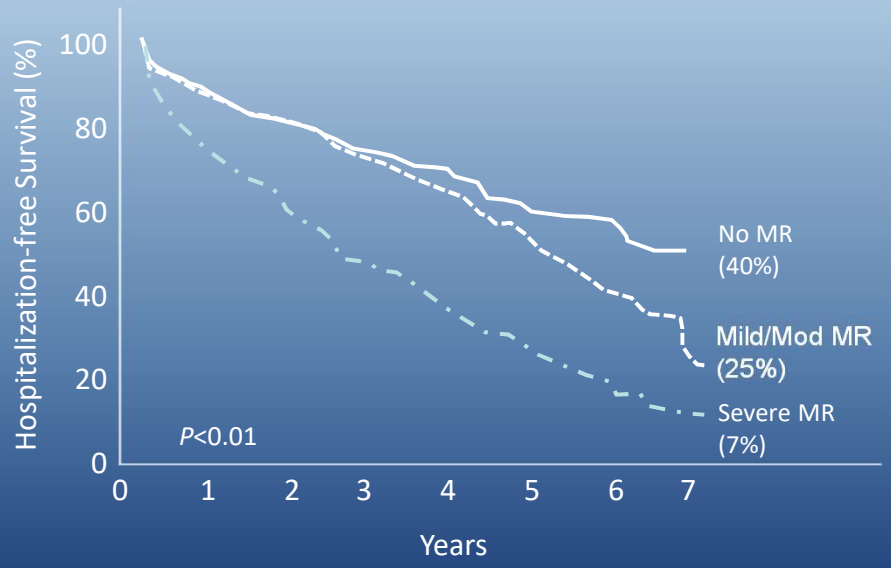
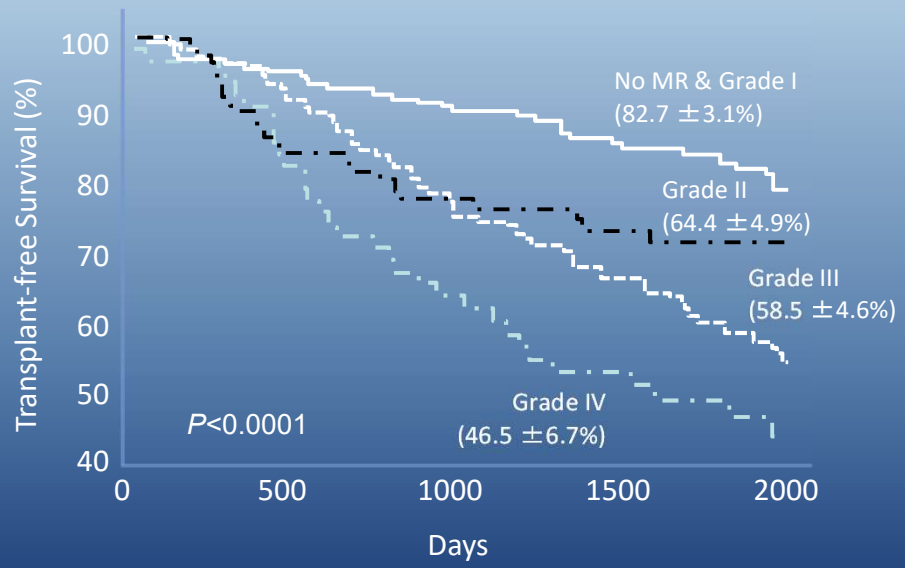
Secondary MR Worsens Heart Failure Outcomes

HOSPITALIZATION-FREE SURVIVAL DECREASED WITH INCREASED MR SEVERITY[1]



TRANSPLANT-FREE SURVIVAL DECREASED WITH INCREASED MR SEVERITY[2]



1.Rossi A, et al. Heart 2011; 97:1675-1680
2.Bursi F, et al. Eur J Heart Fail 2010; 12:382-388

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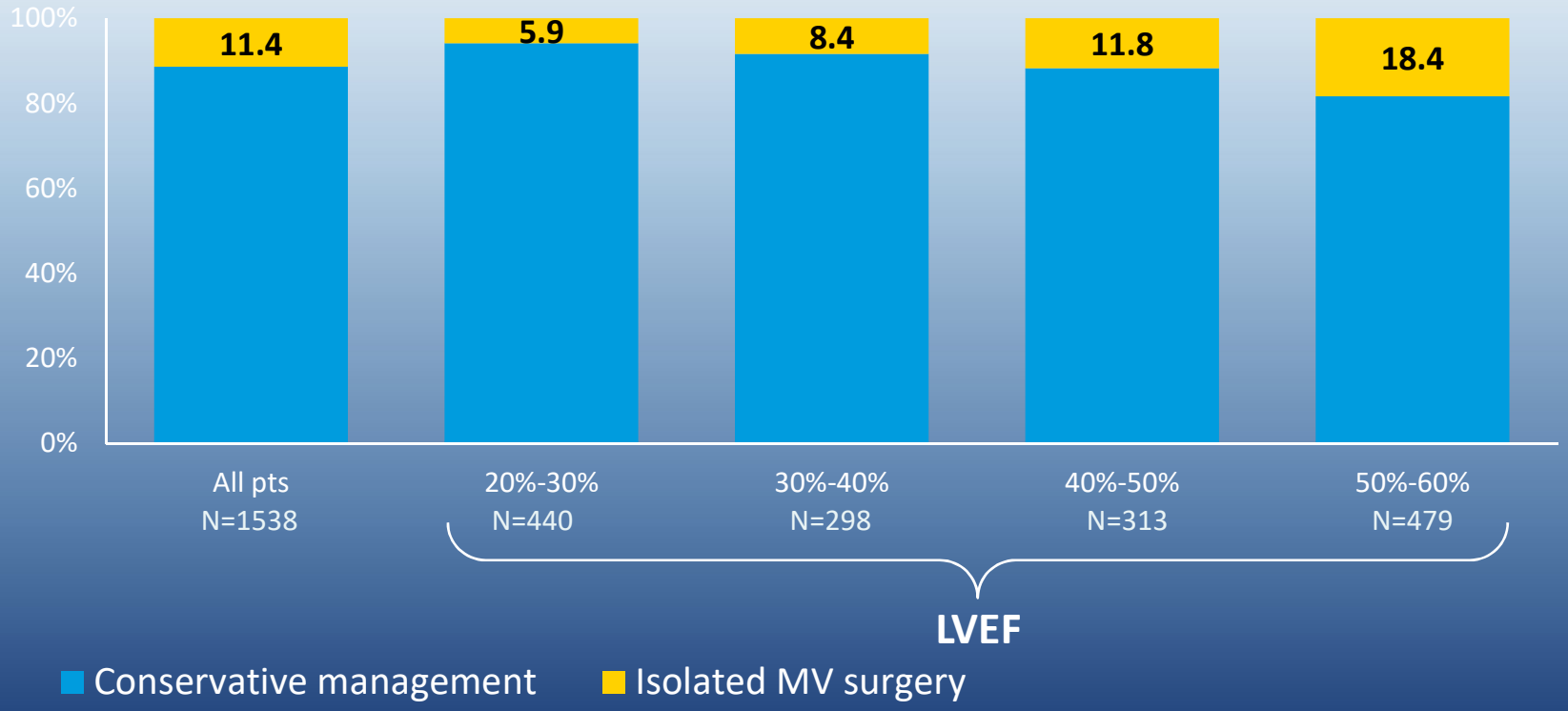
How Are Patients With Isolated Secondary MR Treated Today?



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GUIDELINE DIRECTED MEDICAL THERAPY (GDMT) IN THE HEART FAILURE PATIENT WITH REDUCED EJECTION FRACTION

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GMDT is Well Defined for HFrEF Patients

ACC/AHA 2014 VALVE GUIDELINES

MEDICAL THERAPY FOR SECONDARY MITRAL REGURGITATION

Pts with chronic secondary MR (stages B to D) and HF with reduced LVEF should receive standard GDMT therapy for HF, including ACE inhibitors, ARBs, beta blockers, and/or aldosterone antagonists as indicated.

Nishimura et al. JACC 2014; 63:e57-185, JACC 2017 70:252-289 (unchanged in 2017 updates)
Yancy et al. JACC 2018 Jan 16;71(2):201-230. doi: 10.1016/j.jacc.**2017**.11.025.

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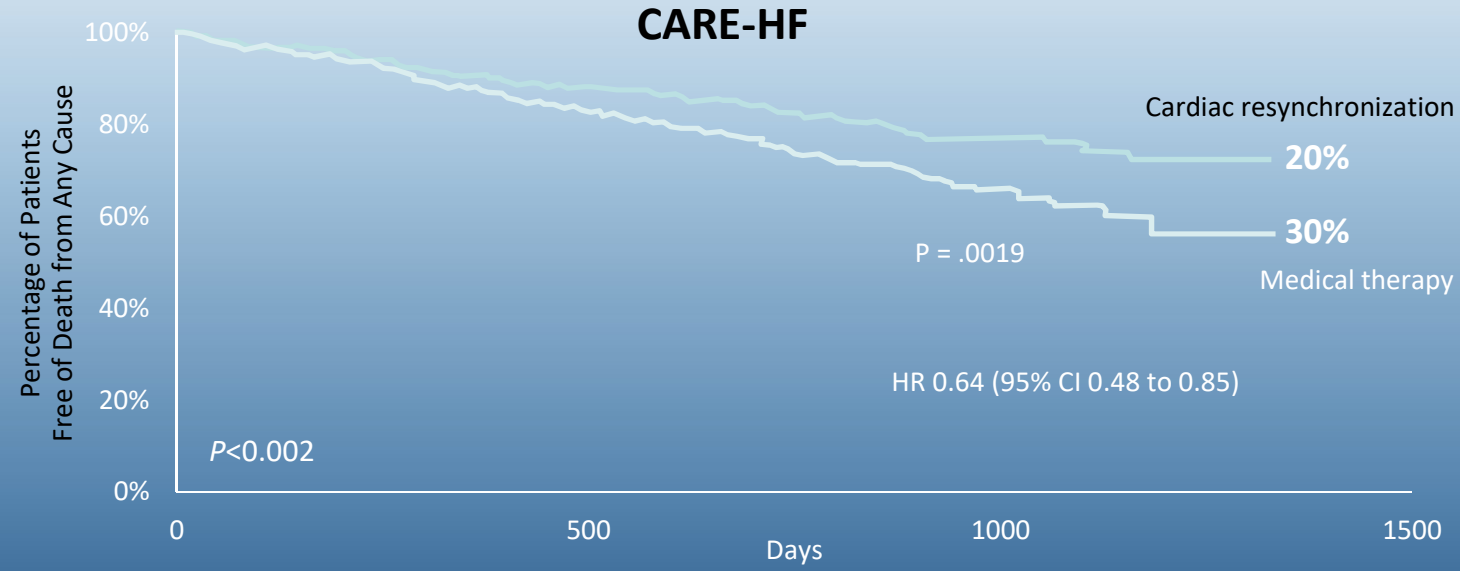
Cardiac Resynchronization Thearapy Improves Survival in HFrEF



No. at Risk:

Cardiac resynchronization	409	376	351	213	89	8
Medical therapy	404	365	321	192	71	5

Cleland GF et al. NEJM. 2005; 352:1539-1549

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GMDT is Well Defined for HFrEF Patients

ACC/AHA 2014 VALVE GUIDELINES

CRT FOR SECONDARY MITRAL REGURGITATION

Cardiac resynchronization therapy with biventricular pacing is recommended for symptomatic pts with chronic severe secondary MR (stages B to D) who meet the indications for device therapy.

Nishimura et al. JACC 2014; 63:e57-185, JACC 2017 70:252-289 (unchanged in 2017 updates)
Yancy et al. JACC 2018 Jan 16;71(2):201-230. doi: 10.1016/j.jacc.**2017**.11.025.

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2017 AHA/ACC Valve Guidelines

CLASS OF RECOMMENDATION	LEVEL OF EVIDENCE
IIb	B

Mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for heart failure

Class IIb = weak recommendation; benefit ≥ risk; may be reasonable; effectiveness is uncertain

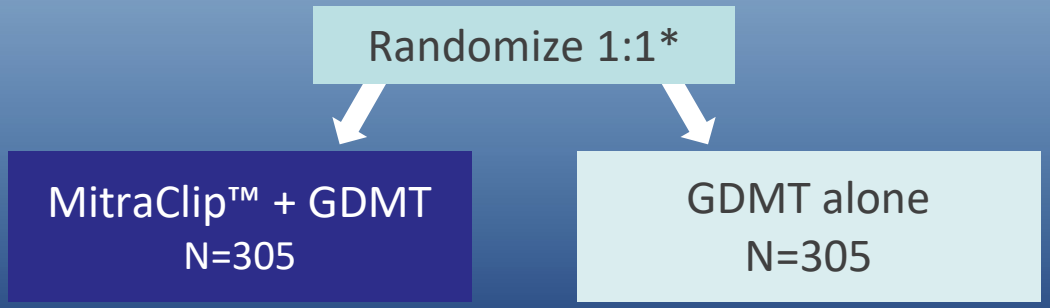
Nishimura RA et al. J Am Coll Cardiol 2017;70:252–89

NEW CLINICAL EVIDENCE

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 ~610 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT



*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

Stone GW et al. NEJM 2018

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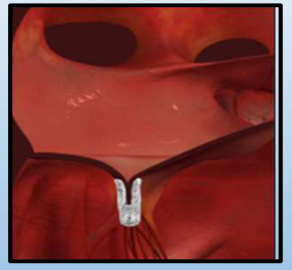
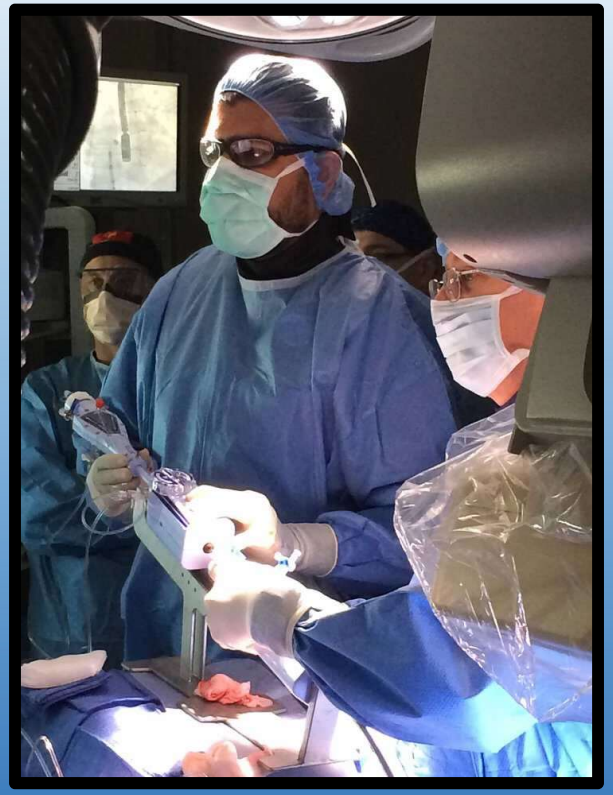
Transcatheter Mitral Valve Repair - MitraClip



- Minimally invasive catheter-based therapy
- Performed using venous access and real-time imaging (transesophageal echocardiography and fluoroscopy)
- Grasps the mitral valve leaflets, resulting in fixed coaptation of the mitral leaflets



MitraClip® System

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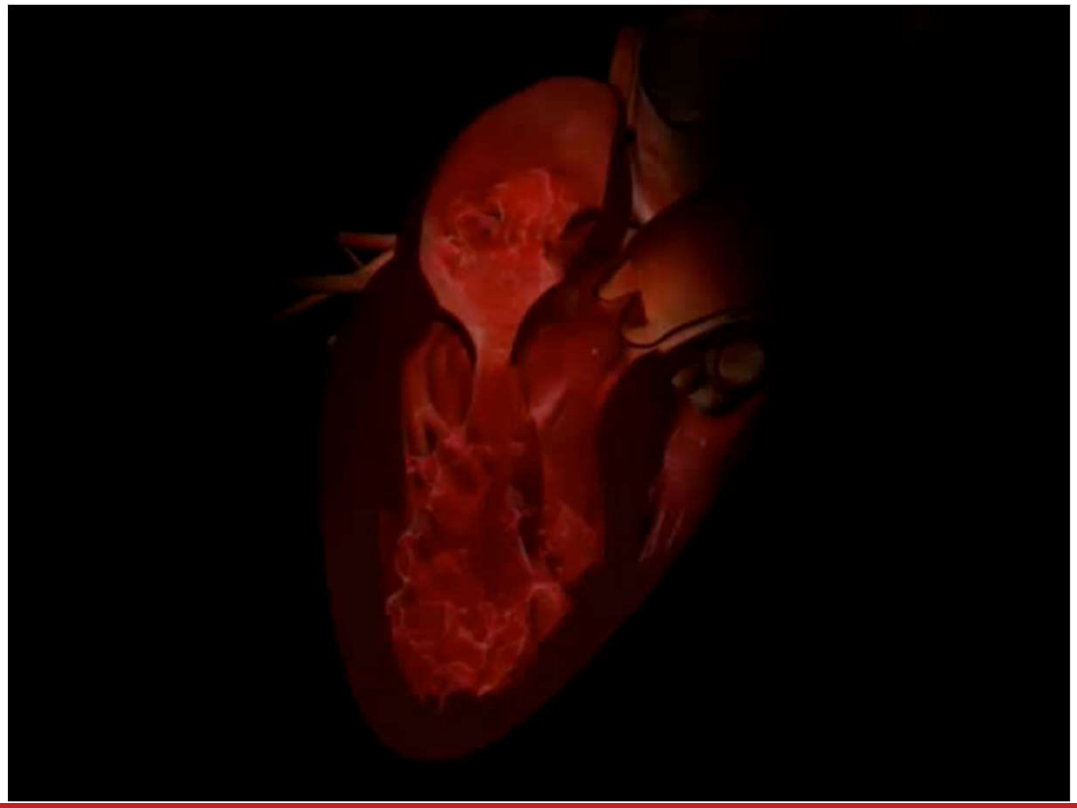
MitraClip® Indications

- The MitraClip Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to:
  - Primary degenerative mitral regurgitation in patients who have been deemed high risk for mitral valve surgery by a heart team – FDA approved October 2013.
  - Secondary functional mitral regurgitation when used with maximally tolerated guideline-directed medical therapy (GDMT) – FDA approved March 13, 2019.

MitraClip® System



MitraClip® Experience

- EVEREST I Feasibility (n=55)
- EVEREST II Pivotal
  - Pre-Randomization (n=60)
  - HR Registry (n= 78)
  - Randomized (2:1 Clip to Surgery) (n= 279)
- REALISM Registry

  Continued Access (n=965)
- COAPT Trial (n=614)
- Worldwide Commercial Use:

  >100,000 patients

Purpose

- COAPT is a landmark trial to further study the MitraClip device in symptomatic FMR patients with heart failure
- The study will generate important clinical and economic data to support reimbursement and evidence to support the development of treatment guidelines
- COAPT is the first randomized controlled clinical trial to compare non-surgical (medical) standard of care treatment to a percutaneous intervention to reduce MR

Primary Endpoints

- **PRIMARY EFFECTIVENESS ENDPOINT: ALL HF HOSPITALIZATIONS THROUGH 24 MONTHS***
- **Primary safety endpoint: Freedom at 12 months from device-related complications:**
  - Single leaflet device attachment
  - Device embolization
  - Endocarditis requiring surgery
  - Echo core laboratory-confirmed mitral stenosis requiring surgery
  - Left ventricular assist device implant
  - Heart transplant
  - Any device-related complication requiring non-elective cardiovascular surgery

*Analyzed when the last subject completes 12 months of follow-up; **Objective performance goal. Stone GW et al. NEJM 2018

Baseline Characteristics (i)

	MITRACLIP™ + GDMT (N=302)	GDMT ALONE (N=312)		MITRACLIP + GDMT (N=302)	GDMT ALONE (N=312)
Age (years)	71.7 ± 11.8	72.8 ± 10.5	BMI (kg/m^2)	27.0 ± 5.8	27.1 ± 5.9
Male	66.6%	61.5%	CrCl (ml/min)	50.9 ± 28.5	47.8 ± 25.0
Diabetes	35.1%	39.4%	- ≤60 ml/min	71.6%	75.2%
Hypertension	80.5%	80.4%	Anemia (WHO)	59.8%	62.7%
Hyperchol.	55.0%	52.2%	**BNP (pg/mL)**	**1015 ± 1086**	**1017 ± 1219**
Prior MI	51.7%	51.3%	**NT-proBNP (pg/mL)**	**5174 ± 6567**	**5944 ± 8438**
Prior PCI	43.0%	49.0%	STS replacement sco	7.8 ± 5.5	8.5 ± 6.2
Prior CABG	40.1%	40.4%	• ≥8	41.7%	43.6%
Prior stroke or TIA	18.5%	15.7%	Surgical risk (central eligibility committee)		
PVD	17.2%	18.3%	• High*	68.6%	69.9%
COPD	23.5%	23.1%	• Not-high	31.4%	30.1%
H/o atrial fibr	57.3%	53.2%			

- STS repl score ≥8% or one or more factors present predicting extremely high surgical risk. Stone GW et al. NEJM 2018

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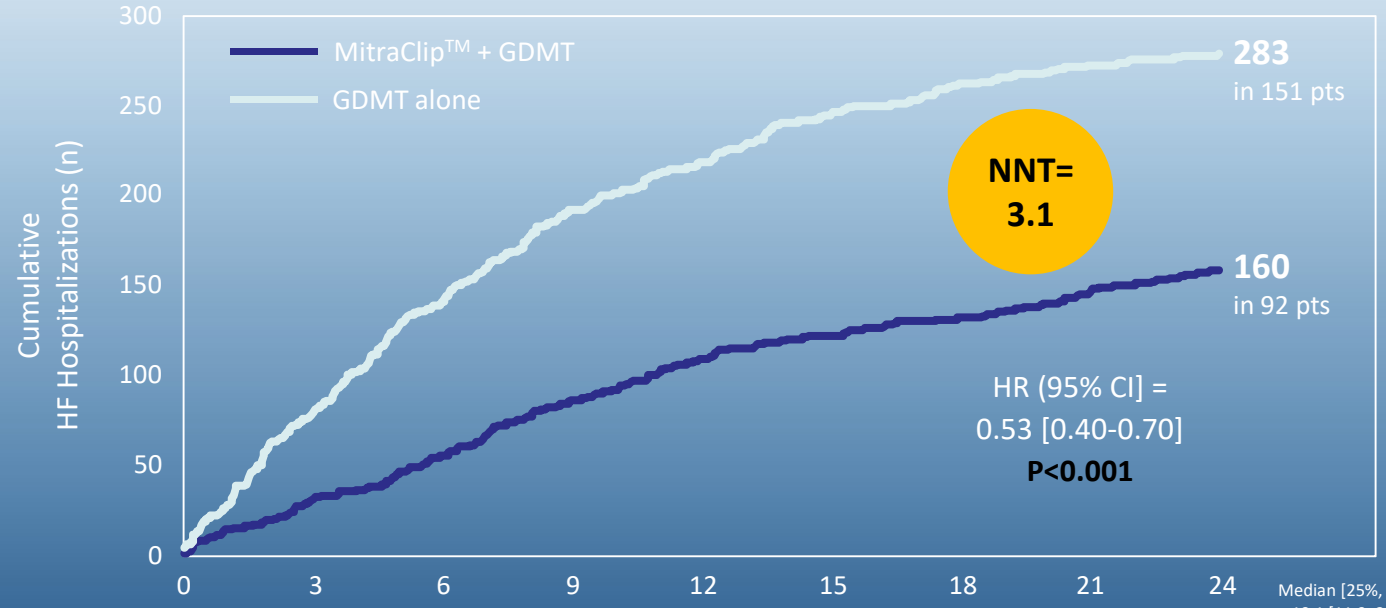
Baseline Characteristics (ii)

HF PARAMETERS	MITRACLIP™ + GDMT (N=302)	GDMT ALONE (N=312)	ECHO CORE LAB	MITRACLIP + GDMT (N=302)	GDMT ALONE (N=312)
Etiology of HF			**MR severity**		
• Ischemic	60.9%	60.6%	**• Mod-to-sev (3+)**	**49.0%**	**55.3%**
• Non-ischemic	39.1%	39.4%	**• Severe (4+)**	**51.0%**	**44.7%**
NYHA class			**EROA, cm^2**	**0.41 ± 0.15**	**0.40 ± 0.15**
• I	0.3%	0%	LVESD, cm	5.3 ± 0.9	5.3 ± 0.9
• II	42.7%	35.4%	LVEDD, cm	6.2 ± 0.7	6.2 ± 0.8
• III	51.0%	54.0%	LVESV, mL	135.5 ± 56.1	134.3 ± 60.3
• IV	6.0%	10.6%	**LVEDV, mL**	**194.4 ± 69.2**	**191.0 ± 72.9**
HF hosp within 1 yr	58.3%	56.1%	LVEF, %	31.3 ± 9.1	31.3 ± 9.6
Prior CRT	38.1%	34.9%	• ≤40%	82.2%	82.0%
Prior defibrillator	30.1%	32.4%	RVSP, mmHg	44.0 ± 13.4	44.6 ± 14.0

Stone GW et al. NEJM 2018

Primary Effectiveness Endpoint

All hospitalizations for HF within 24 months



Median [25%, 75%] FU = 19.1 [11.9, 24.0] mos

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

Stone GW et al. NEJM 2018

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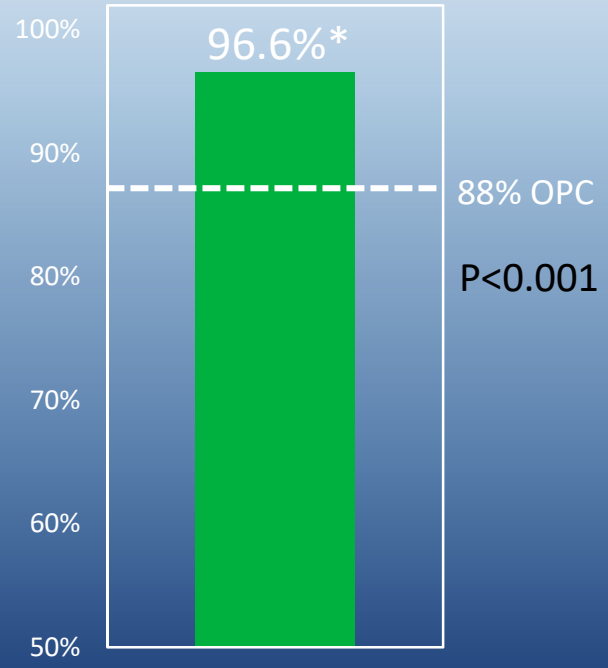
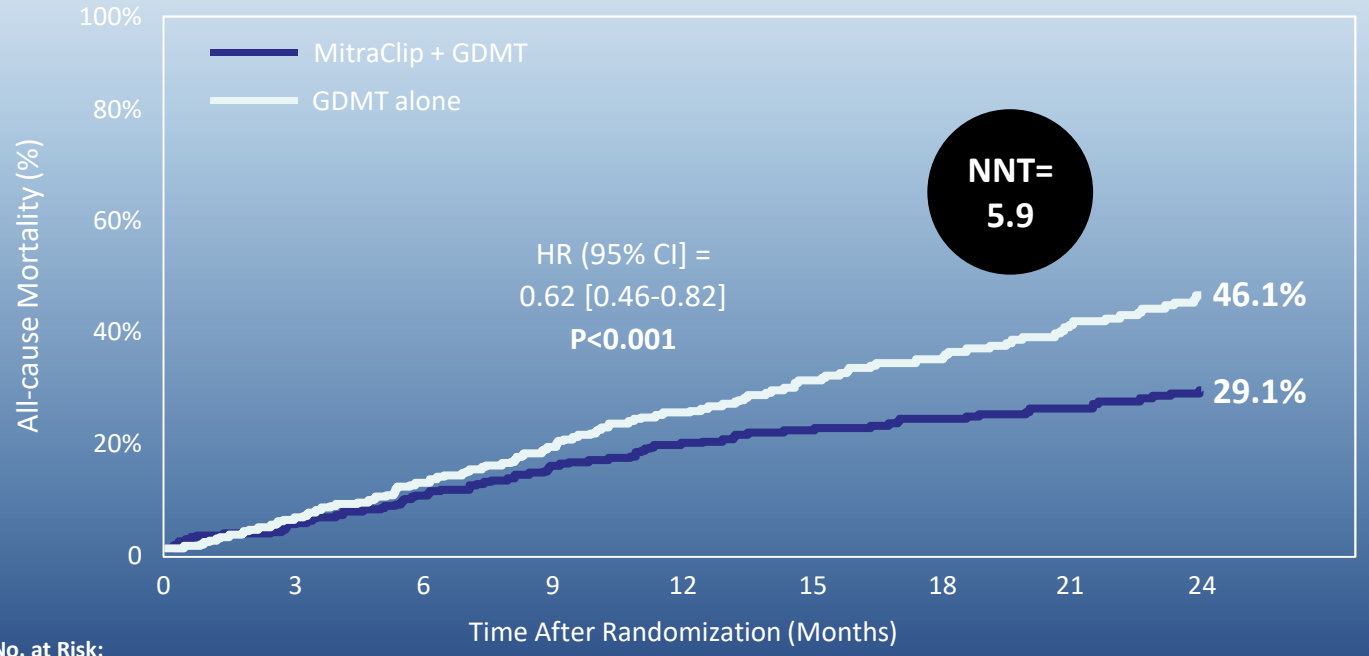
Primary Safety Endpoint

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%)

MitraClip™ + GMDT Improves Survival vs. GDMT Alone



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

Stone GW et al. NEJM 2018

Oklahoma Heart Institute

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
2. performance goal

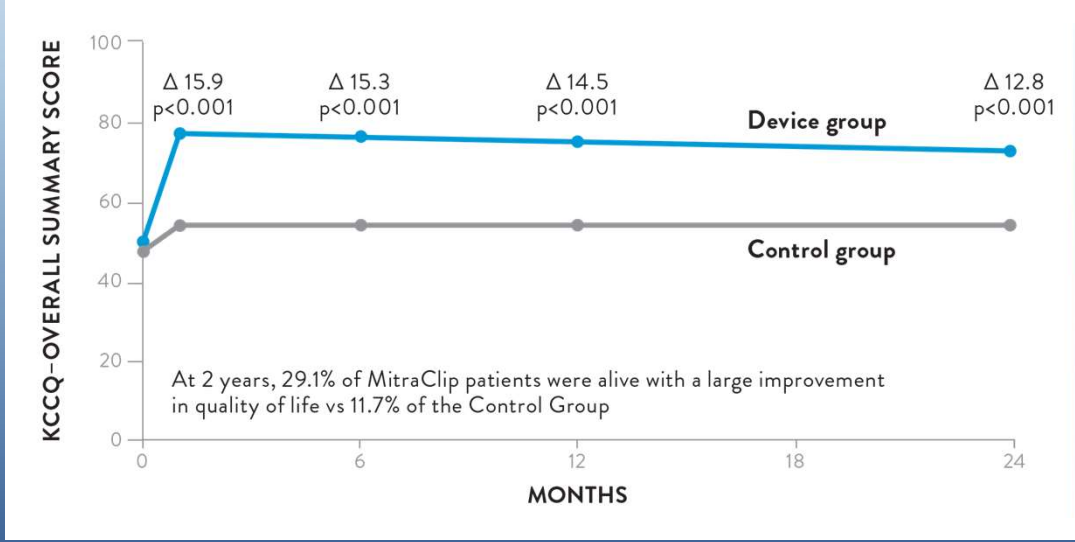
Stone GW et al. NEJM 2018

Improvement in Quality of Life with MitraClip™ + GDMT

Primary outcome: KCCQ-OS

2.5x

MORE LIKELY TO EXPERIENCE A LARGE IMPROVEMENT IN QUALITY OF LIFE WITH MITRACLIP



Note: KCCQ Minimum for Clinically Important Difference (MCID)= 5 points; Large Improvement Defined as ≥20 Points in KCCQ from Baseline; Quality of Life is Assessed Only in Surviving Patients

Arnold SV et al. TCT 2018

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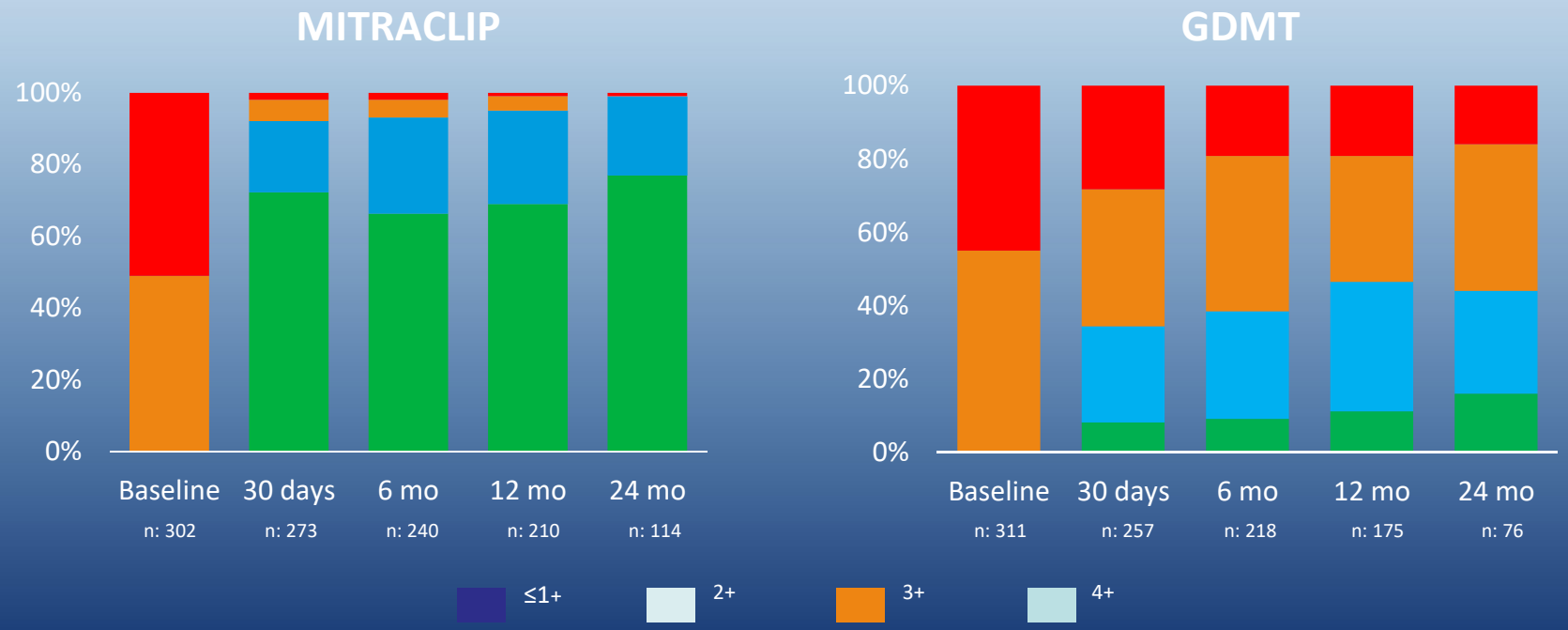
MitraClip™ Reduces Secondary MR

99.1% of MitraClip patients had MR ≤2+ at 24 months



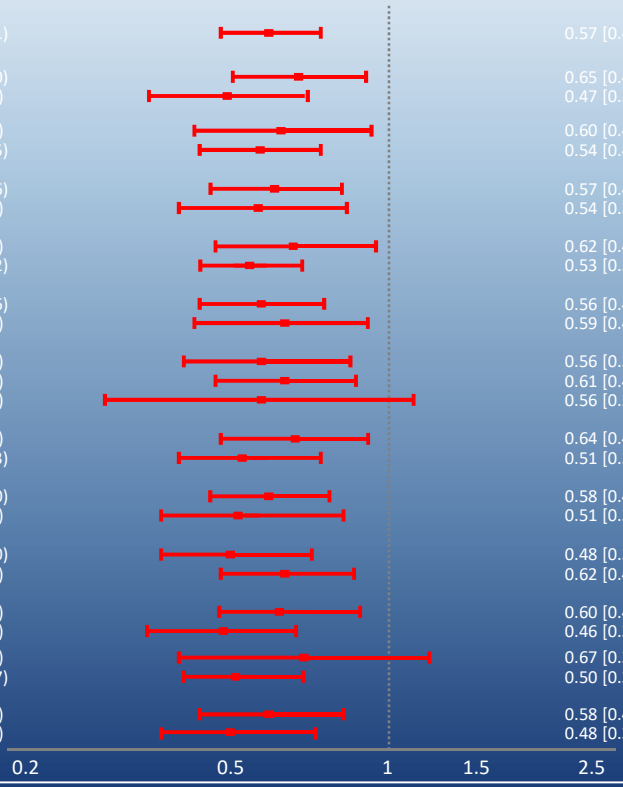
Note: Unpaired data

Stone GW et al. NEJM 2018

Oklahoma Heart Institute

24-Month Death or HF Hospitalization by Sub-Group

Subgroup	MitraClip™ + GDMT	GDMT alone	HR [95% CI]	P [Int]
All patients	45.7% (129)	67.9% (191)	0.57 [0.45, 0.71]	
AGE (median)				
≥74 years (n=317)	52.1% (78)	70.2% (100)	0.65 [0.48, 0.88]	0.13
<74 years (n=297)	37.8% (51)	65.3% (91)	0.47 [0.33, 0.66]	
SEX				
Female (n=221)	43.2% (39)	59.4% (66)	0.60 [0.40, 0.89]	0.76
Male (n=393)	47.1% (90)	73.0% (125)	0.54 [0.41, 0.71]	
Etiology of cardiomyopathy				
Ischemic (n=373)	48.1% (84)	70.0% (116)	0.57 [0.43, 0.76]	0.79
Non-ischemic (n=241)	41.1% (45)	65.2% (75)	0.54 [0.37, 0.78]	
Prior CRT				
Yes (n=224)	50.2% (55)	68.4% (69)	0.62 [0.44, 0.89]	0.54
No (n=390)	42.9% (74)	67.4% (122)	0.53 [0.39, 0.71]	
HF hospitalization within the prior year				
Yes (n=407)	44.7% (86)	67.9% (126)	0.56 [0.42, 0.73]	0.79
No (n=207)	47.6% (43)	67.8% (65)	0.59 [0.40, 0.86]	
Baseline NYHA class				
I or II (n=240)	41.1% (50)	66.9% (65)	0.56 [0.39, 0.81]	
III (n=322)	46.6% (67)	65.3% (99)	0.61 [0.44, 0.83]	0.92
IV (n=51)	68.3% (12)	84.4% (26)	0.56 [0.28, 1.12]	
STS replacement score				
≥8% (n=262)	54.1% (65)	71.4% (88)	0.64 [0.46, 0.88]	0.41
<8% (n=352)	39.2% (64)	65.0% (103)	0.51 [0.37, 0.70]	
Surgical risk status*				
High (n=423)	49.7% (95)	71.5% (140)	0.58 [0.45, 0.75]	0.69
Not high (n=188)	35.8% (32)	58.7% (51)	0.51 [0.33, 0.80]	
Baseline MR grade				
3+ (n=320)	37.5% (51)	65.3% (100)	0.48 [0.34, 0.67]	0.29
4+ (n=293)	53.4% (78)	71.4% (91)	0.62 [0.45, 0.83]	
Baseline LVEF				
≥30% (median; n=301)	44.1% (62)	61.2% (85)	0.60 [0.43, 0.84]	0.32
<30% (median; n=274)	46.4% (56)	77.8% (99)	0.46 [0.33, 0.64]	
>40% (n=103)	49.7% (22)	56.2% (27)	0.67 [0.38, 1.17]	0.31
≤40% (n=472)	44.2% (96)	71.9% (157)	0.50 [0.39, 0.65]	
Baseline LVEDV (median)				
≥181 mL (n=288)	48.9% (43)	68.0% (92)	0.58 [0.42, 0.80]	0.42
<181 mL (n=287)	41.5% (54)	69.5% (92)	0.48 [0.34, 0.67]	



Favors MitraClip + GDMT | Favors GDMT alone

KM time-to-first event rates; *Central eligibility committee assessment; Stone GW et al. NEJM 2018

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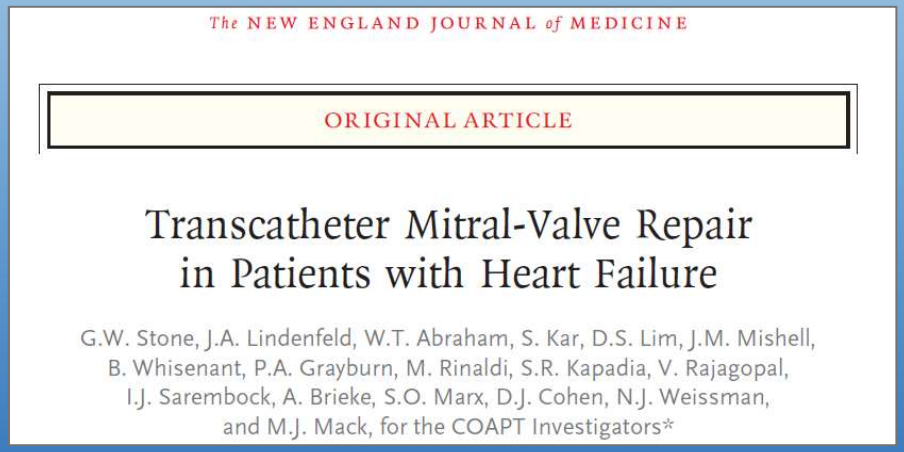
Indication for SMR Approved March 13, 2019

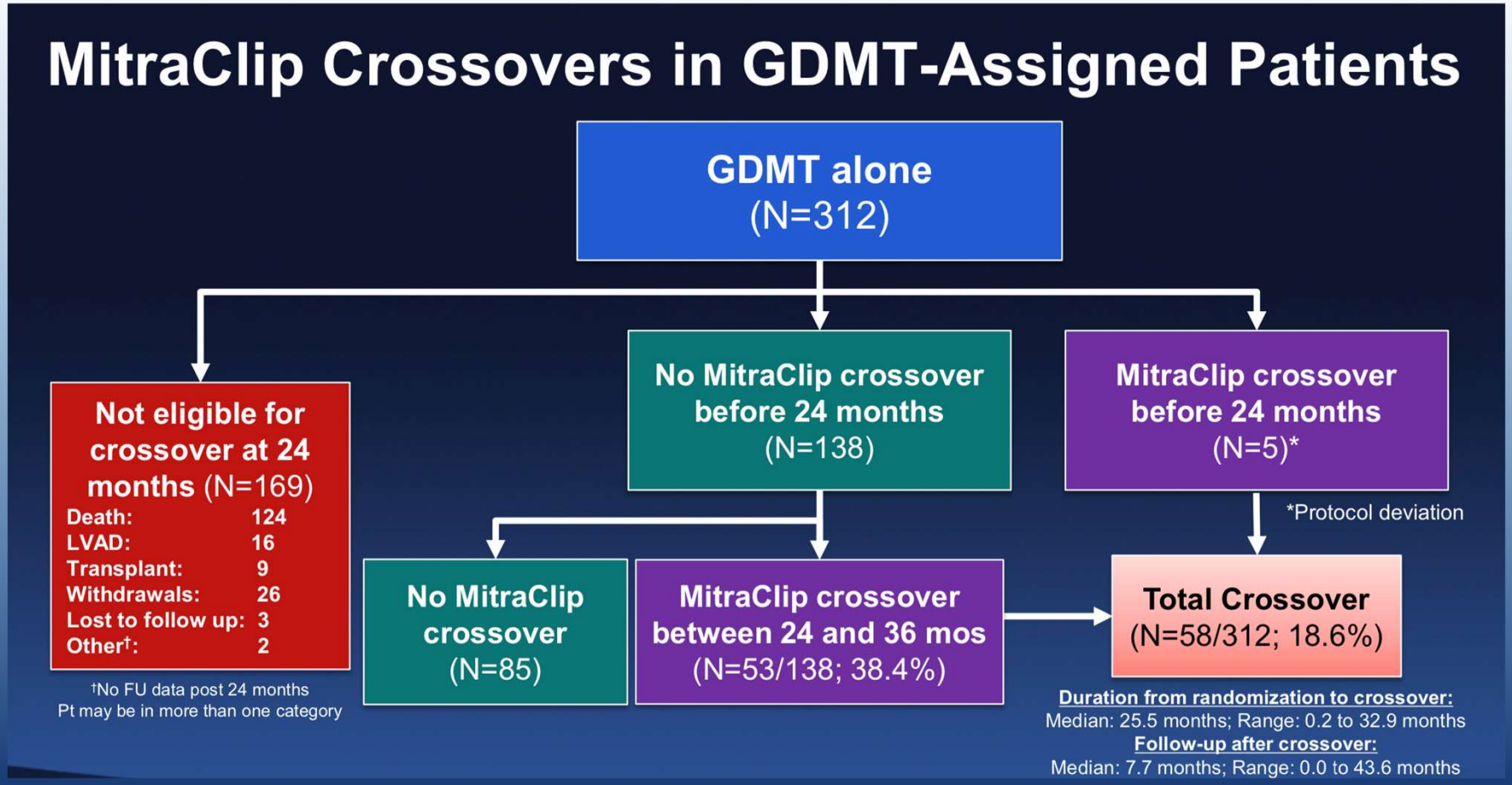
The MitraClip™ System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of **symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation**



COAPT: 3-Year Outcomes

- In the COAPT trial, treatment of symptomatic patients with heart failure (HF) and severe secondary MR with the MitraClip improved survival at 2 years, reduced HF hospitalizations (HFH), and improved quality of life compared to maximally-tolerated guideline-directed medical therapy (GDMT) alone
- Per protocol, subjects randomized to GDMT were not allowed to crossover to the MitraClip prior to 24 months, but were permitted to do so **after 24 months**

MitraClip Crossovers in GDMT-Assigned Patients

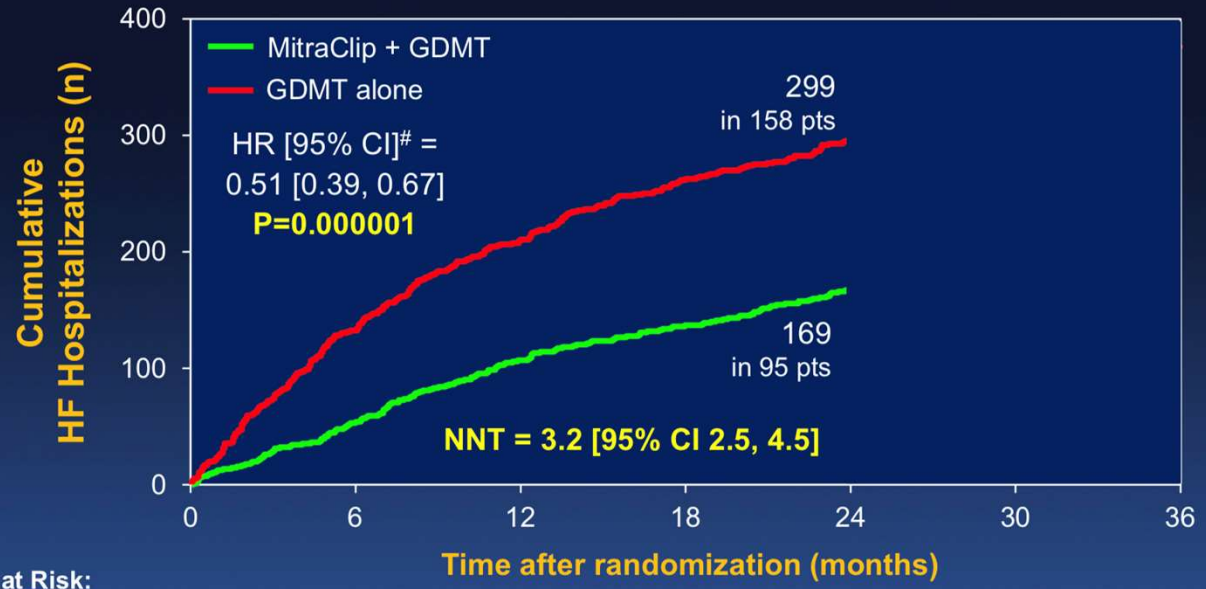


COAPT TRIAL

Primary Effectiveness Endpoint

All Hospitalizations for HF within 36 months

All patients, ITT, including crossovers



# at Risk:					
MitraClip + GDMT	302	269	238	219	189
GDMT alone	312	272	223	185	144

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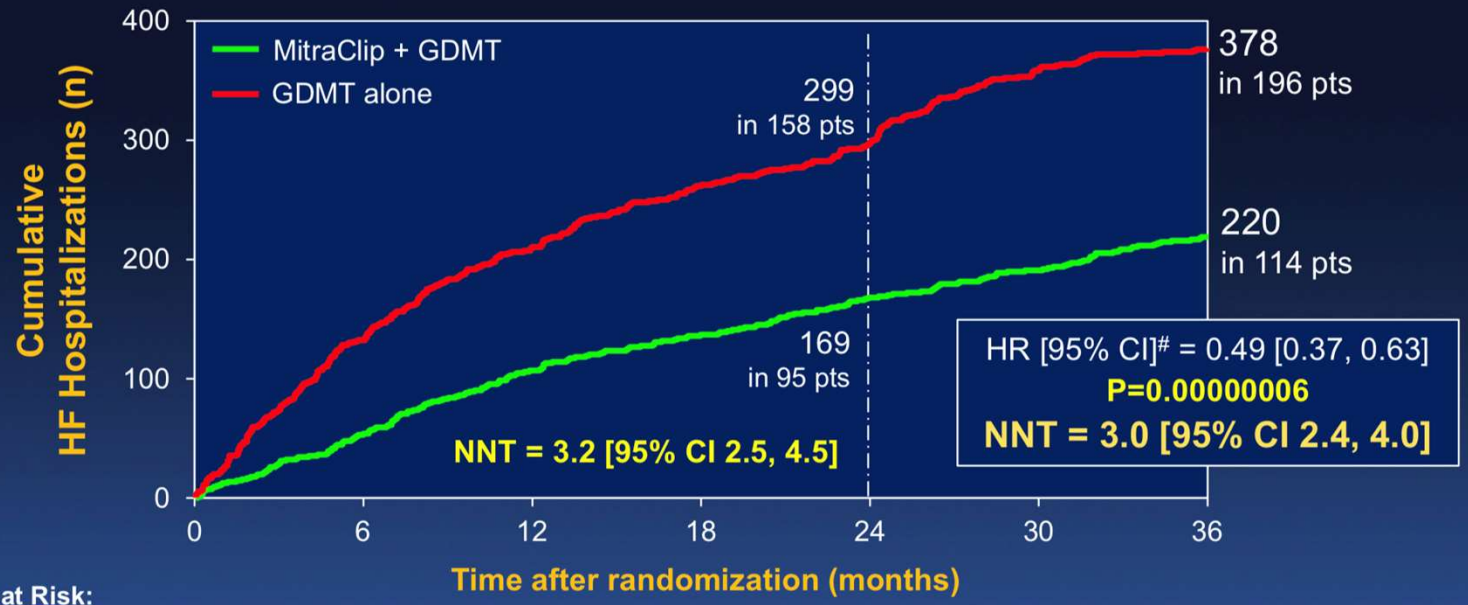
COAPT TRIAL

Primary Effectiveness Endpoint

All Hospitalizations for HF within 36 months

All patients, ITT, including crossovers



# at Risk:							
MitraClip + GDMT	302	269	238	219	189	128	93
GDMT alone	312	272	223	185	144	89	68

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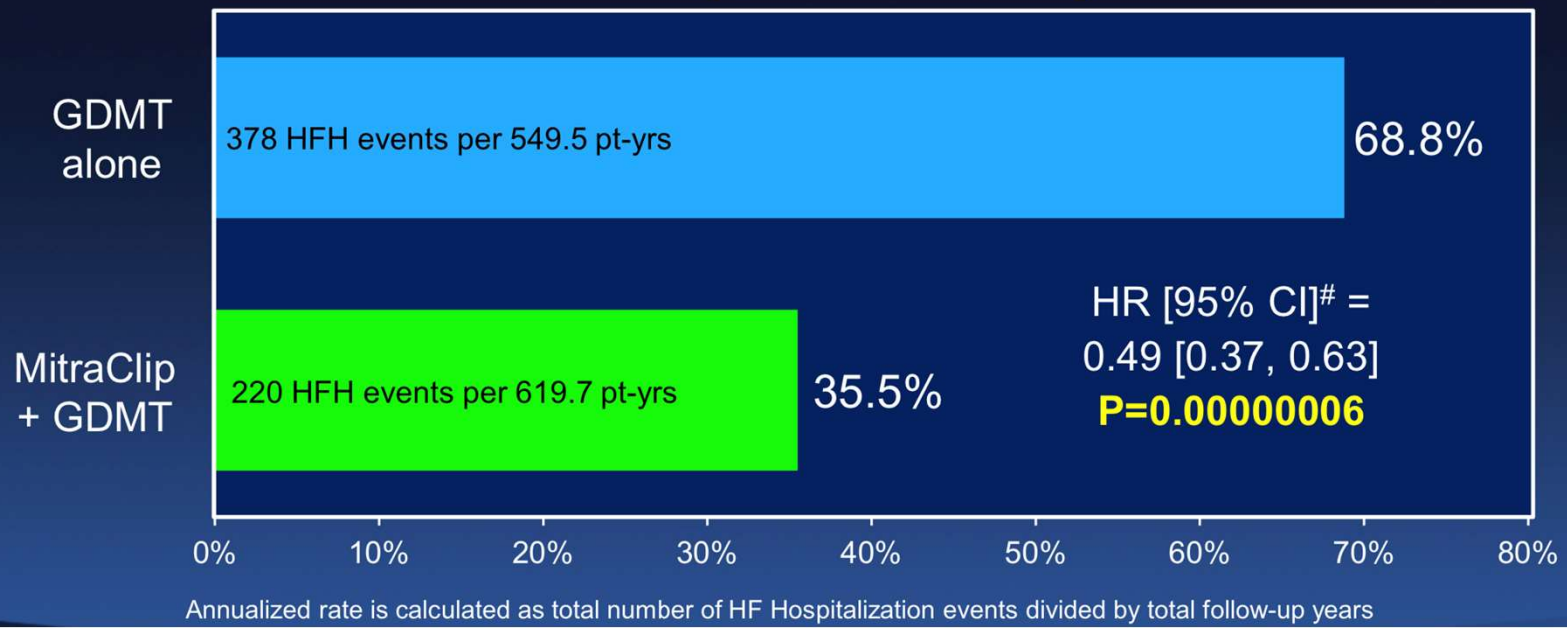
COAPT TRIAL

Primary Effectiveness Endpoint

Annualized Rates of HF Hospitalizations within 36 months

All patients, ITT, including crossovers

NNT= 3.0 [95% CI 2.4, 4.0]



Annualized rate is calculated as total number of HF Hospitalization events divided by total follow-up years

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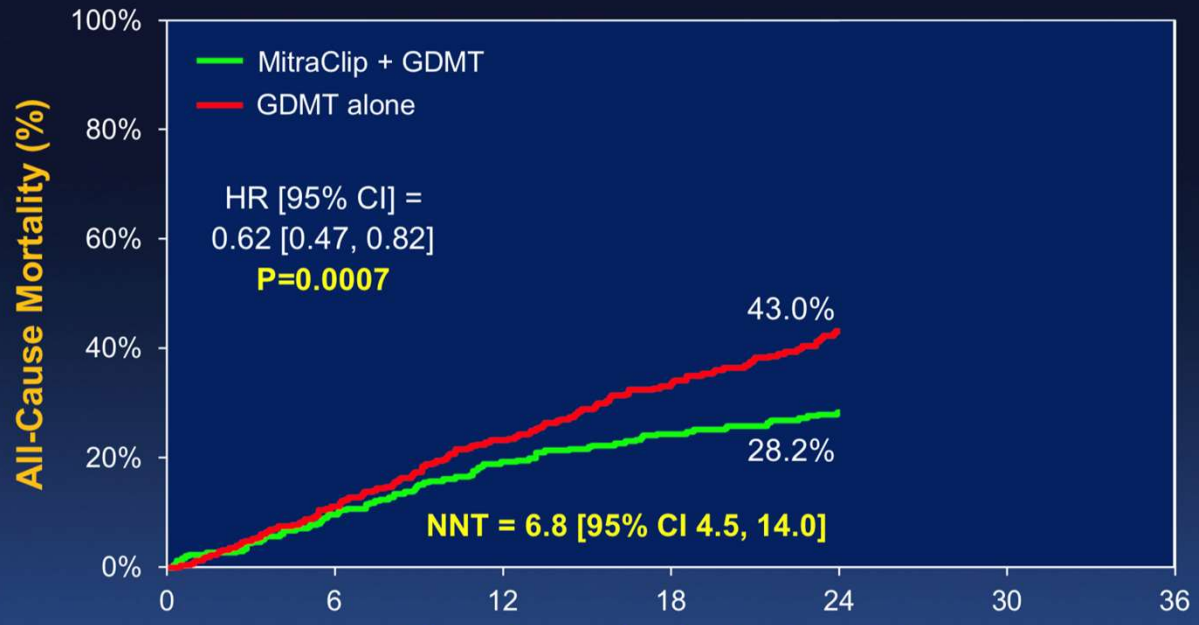
COAPT TRIAL

All-Cause Mortality

All patients, ITT, including crossovers



# at Risk:					
MitraClip + GDMT	302	269	238	219	189
GDMT alone	312	272	223	186	145

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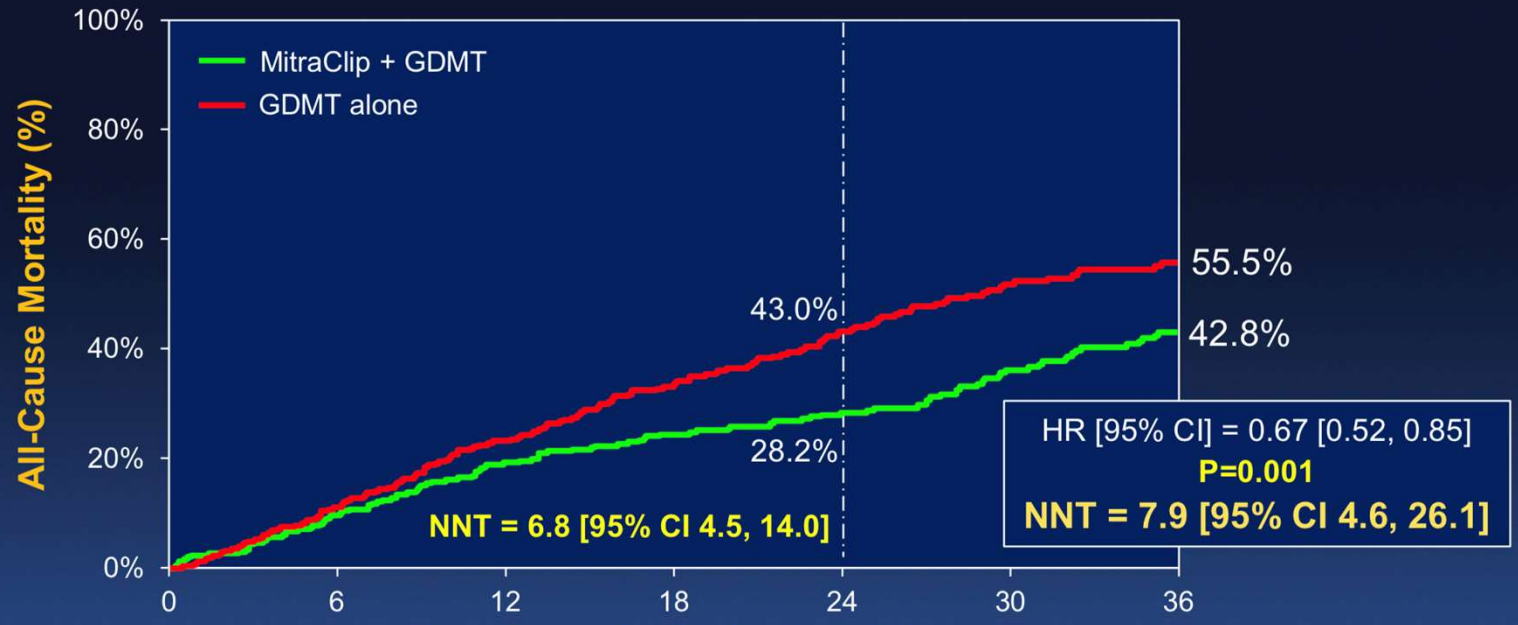
COAPT TRIAL

All-Cause Mortality

All patients, ITT, including crossovers



# at Risk:							
MitraClip + GDMT	302	269	238	219	189	128	93
GDMT alone	312	272	223	186	145	91	70

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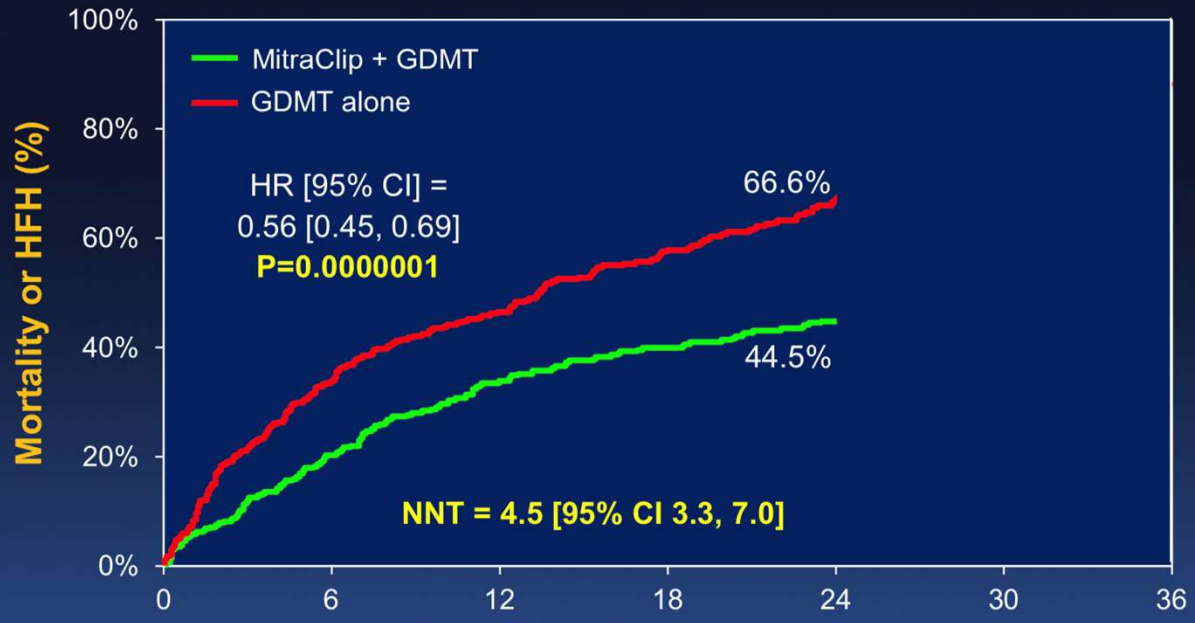
COAPT TRIAL

All-Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers



# at Risk:					
MitraClip + GDMT	302	238	196	176	148
GDMT alone	312	206	156	120	87

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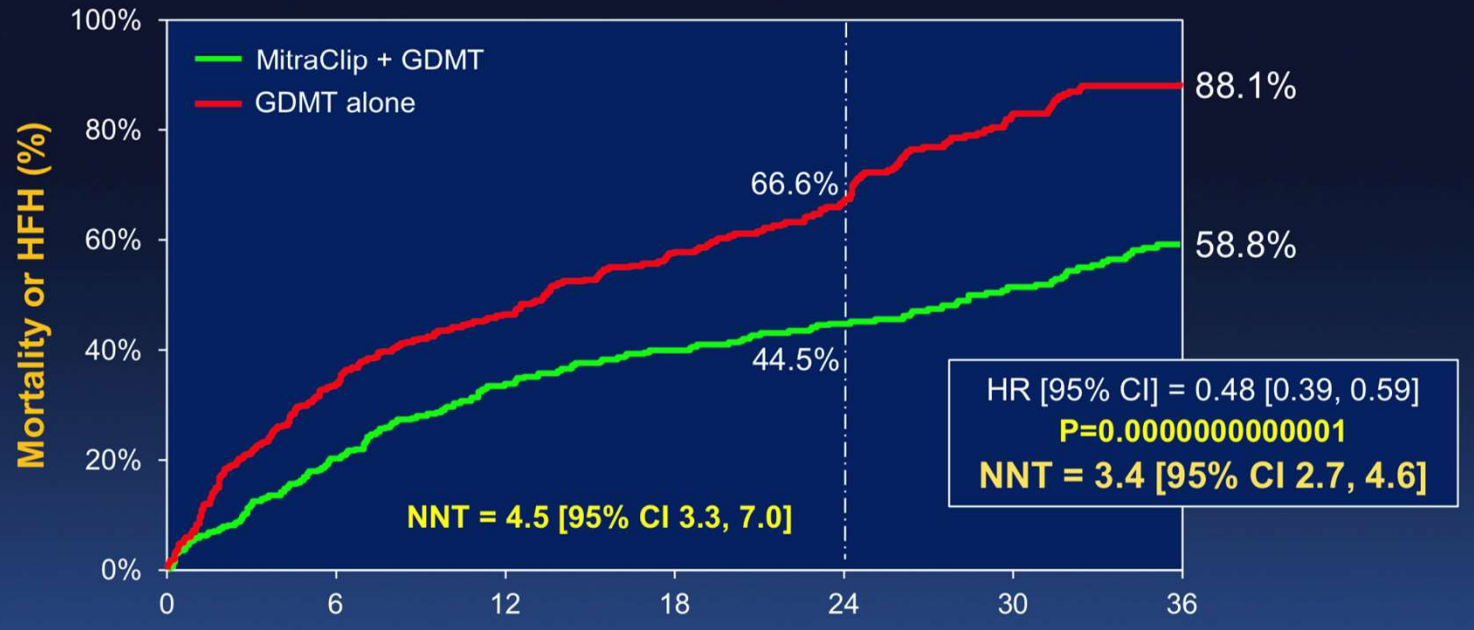
COAPT TRIAL

All-Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers



# at Risk:							
MitraClip + GDMT	302	238	196	176	148	101	66
GDMT alone	312	206	156	120	87	37	20

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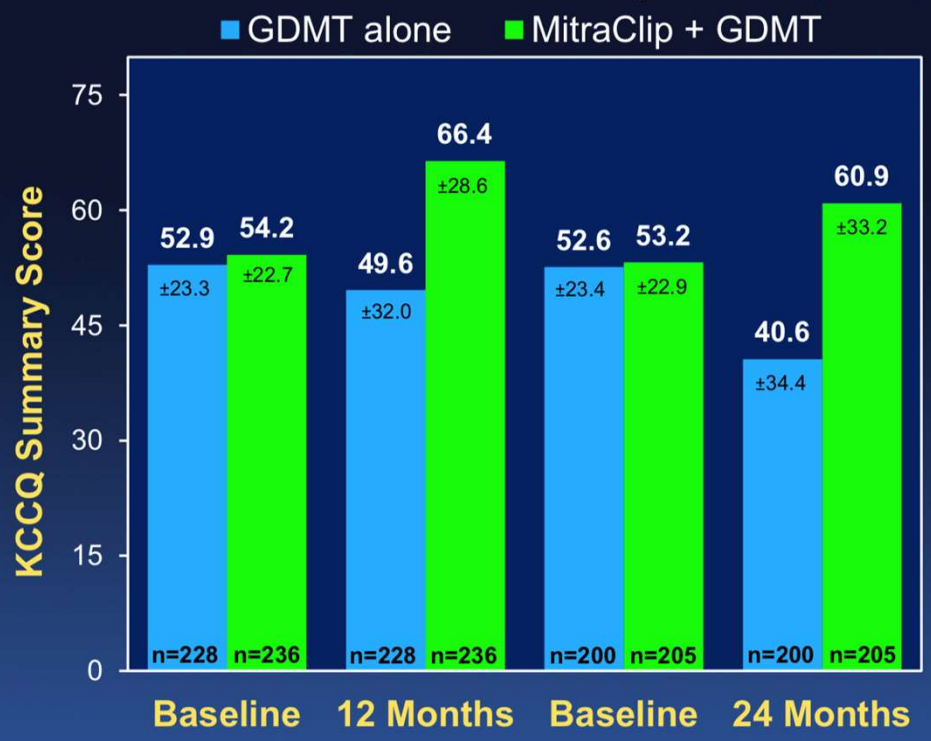
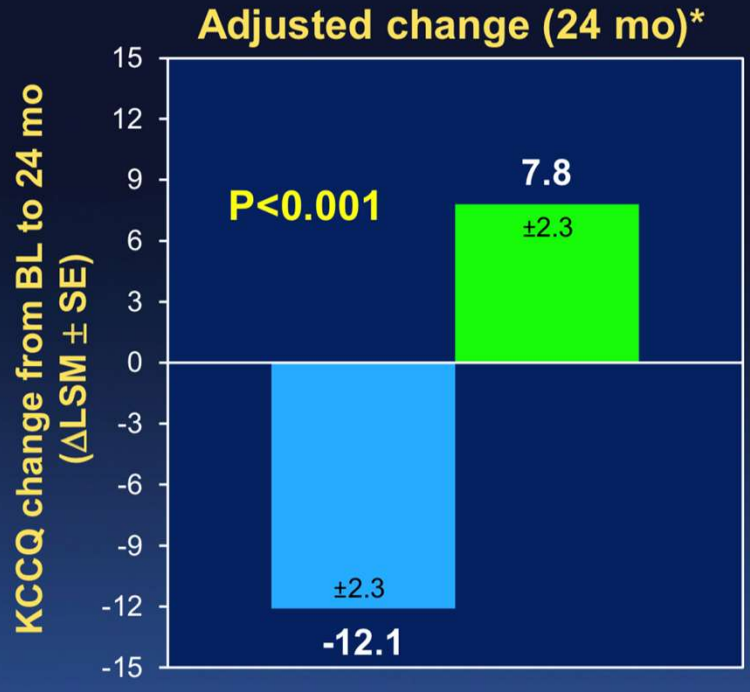
COAPT TRIAL

KCCQ Summary Score

All patients, ITT, 24 months





Pts with adjudicated HF death are assigned KCCQ score of 0 at 24 months. *ANCOVA model with baseline KCCQ and treatment effect as covariates

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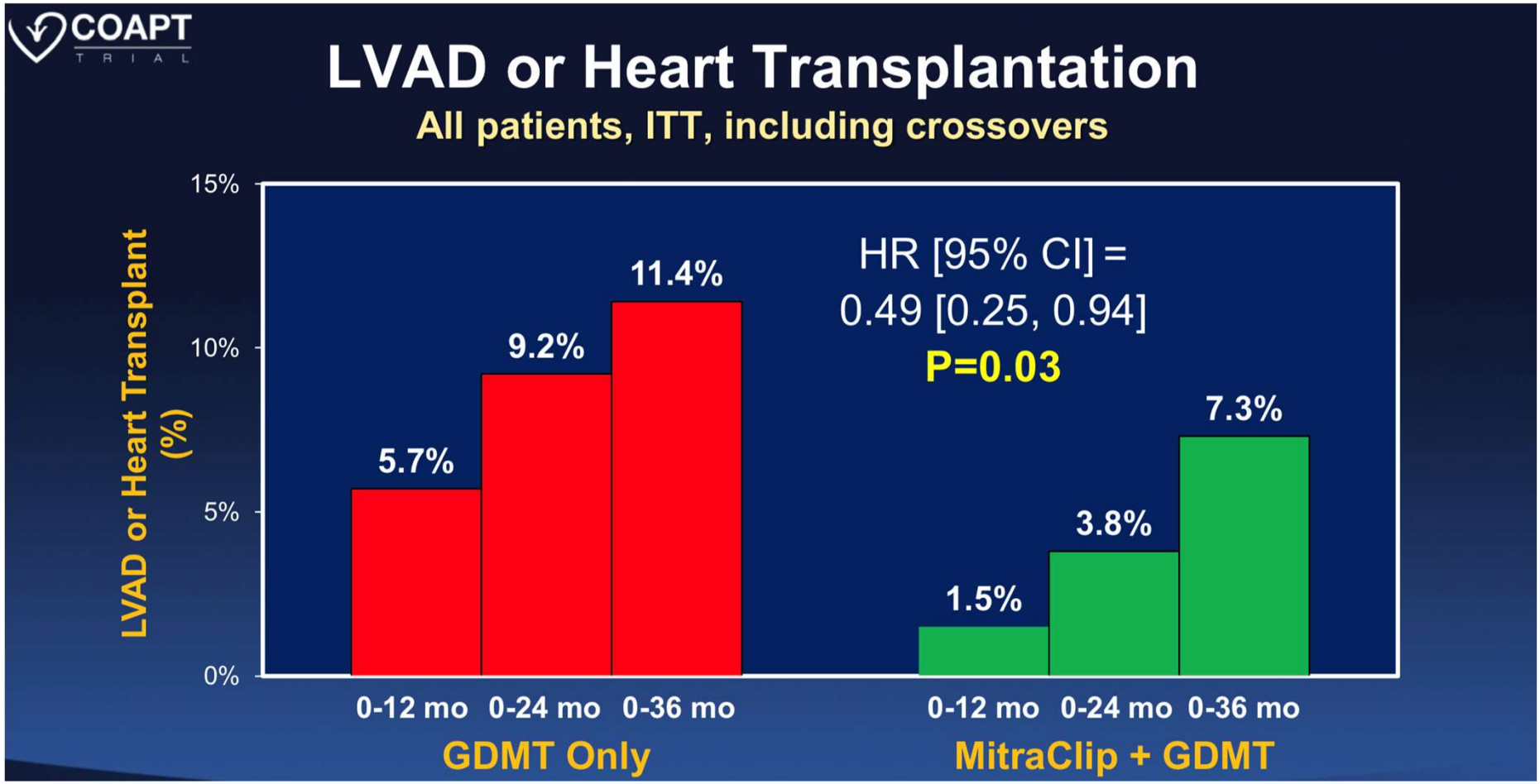
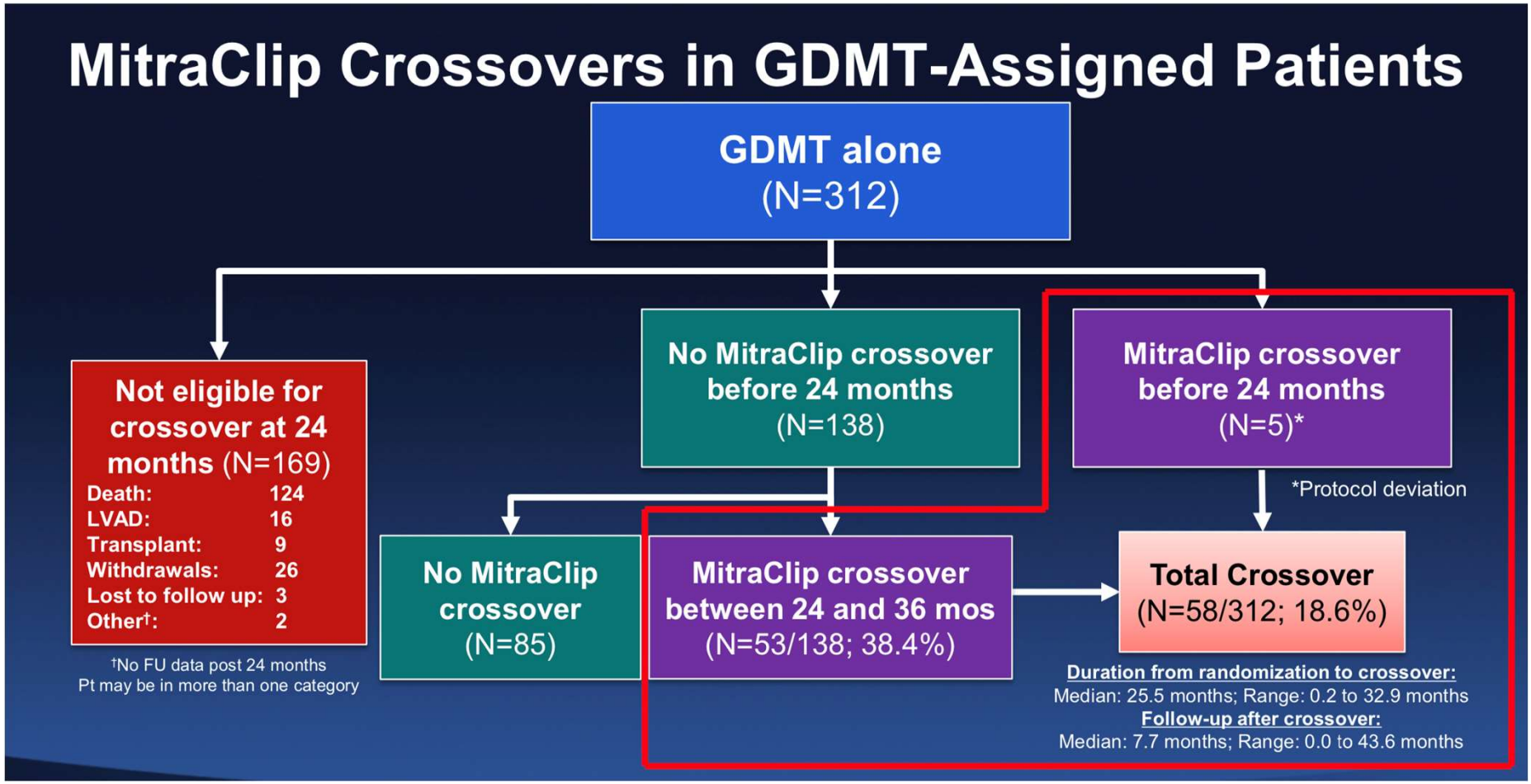

COAPT
TRIAL
LVAD or Heart Transplantation
All patients, ITT, including crossovers
LVAD or Heart Transplant (%)
15%
10%
5%
0%
5.7%
9.2%
11.4%
HR [95% CI] =
0.49 [0.25, 0.94]
P=0.03
1.5%
3.8%
7.3%
0-12 mo
0-24 mo
0-36 mo
GDMT Only
0-12 mo
0-24 mo
0-36 mo
MitraClip + GDMT

MitraClip Crossovers in GDMT-Assigned Patients



COAPT TRIAL

First Heart Failure Hospitalization

GDMT pts censored at time of crossover; Crossovers landmarked at MitraClip procedure

# at Risk:							
MitraClip + GDMT	302	238	196	176	148	101	66
GDMT only, crossovers censored	312	205	155	119	85	33	19
GDMT crossovers to MitraClip	58	30	22				

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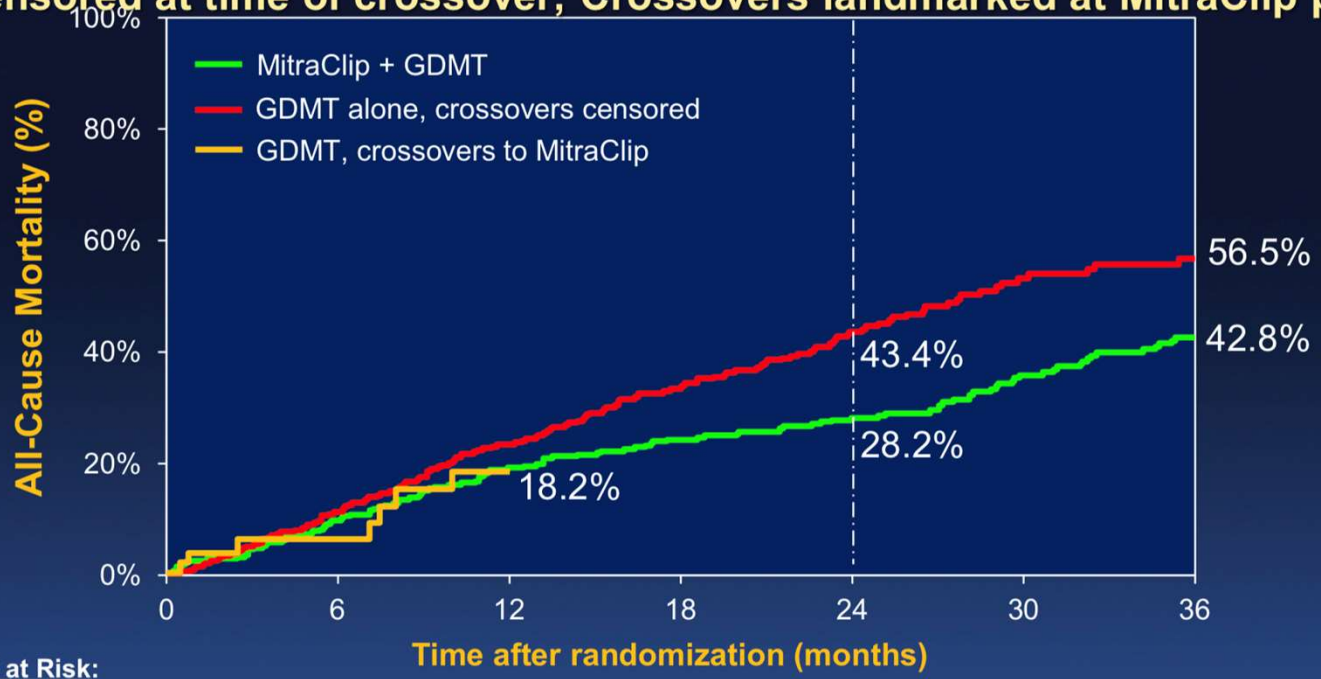
COAPT TRIAL

All-Cause Mortality

GDMT pts censored at time of crossover; Crossovers landmarked at MitraClip procedure



# at Risk:							
MitraClip + GDMT	302	269	238	219	189	128	93
GDMT only, crossovers censored	312	271	222	183	134	60	41
GDMT crossovers to MitraClip	58	33	24				

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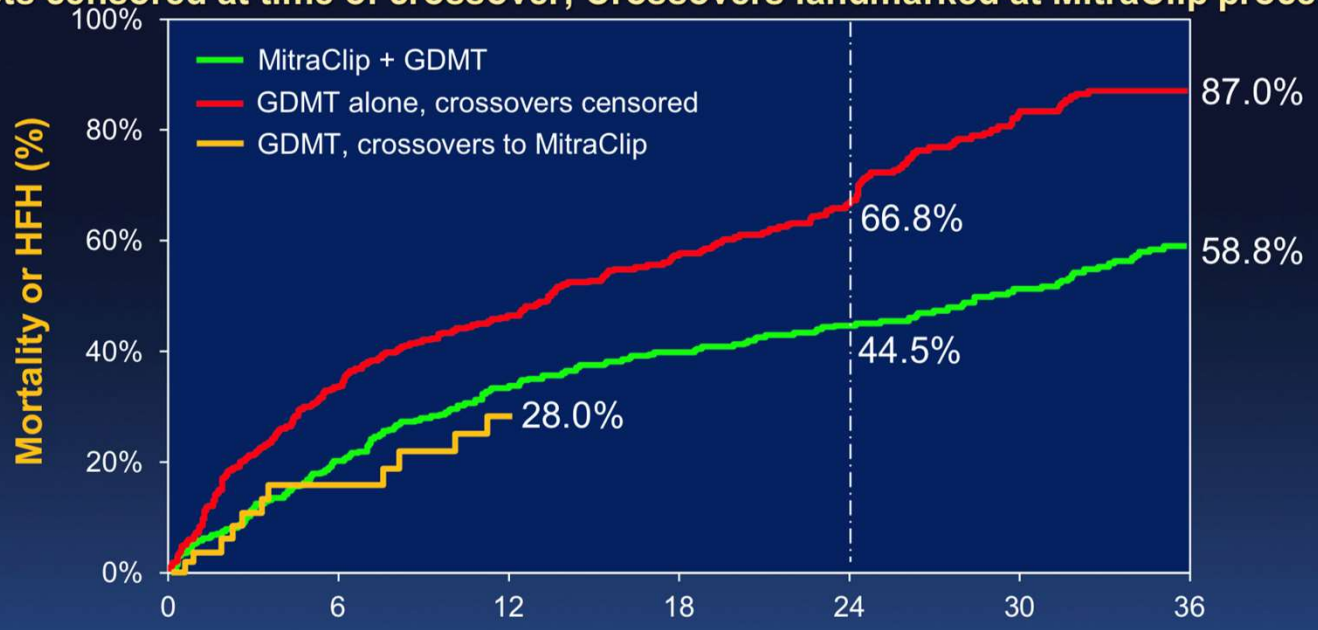
COAPT TRIAL

All-Cause Mortality or HF Hospitalization

GDMT pts censored at time of crossover; Crossovers landmarked at MitraClip procedure



# at Risk:							
MitraClip + GDMT	302	238	196	176	148	101	66
GDMT only, crossovers censored	312	205	155	119	85	33	19
GDMT crossovers to MitraClip	58	30	22				

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COAPT TRIAL

Conclusions

In pts with HF and 3+/4+ secondary MR who remained symptomatic despite maximally-tolerated GDMT:

- At 36 months transcatheter mitral leaflet approximation with the MitraClip was safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, QOL and functional capacity compared to GDMT alone
- GDMT only-assigned pts who crossed-over and received a MitraClip experienced fewer HF hospitalizations and deaths or HFHs within 12 months than those who did not crossover, with rates comparable to pts originally assigned to the MitraClip

Current Heart Failure Guidelines: GDMT and CRT

NO TREATMENT OPTIONS FOR PATIENTS WHO REMAIN SYMPTOMATIC DESPITE BEING ON *MAXIMALLY TOLERATED* GDMT

COR	LOE	
I	A	Patients with chronic secondary MR (stages B to D) and HF with reduced LVEF should receive **standard GDMT therapy for HF**, including ACE inhibitors, ARBs, beta blockers, and/or aldosterone antagonists as indicated
I	A	**Cardiac resynchronization therapy** with biventricular pacing is recommended for symptomatic patients with chronic severe secondary MR (stages B to D) who meet the indications for device therapy
IIa	C	**Mitral valve surgery** is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.
IIb	B	[**Surgical] mitral valve repair or replacement** may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for heart failure
IIb	C	**MV repair** may be considered for patients with chronic moderate secondary MR (stage B) who are undergoing other cardiac **surgery**

Only Mitral Valve Device Shown to Improve Survival

OF HEART FAILURE PATIENTS* WITH SECONDARY MR

In patients with advanced heart failure and moderate-to-severe or severe secondary MR who remain symptomatic despite maximally-tolerated GDMT

MitraClip™

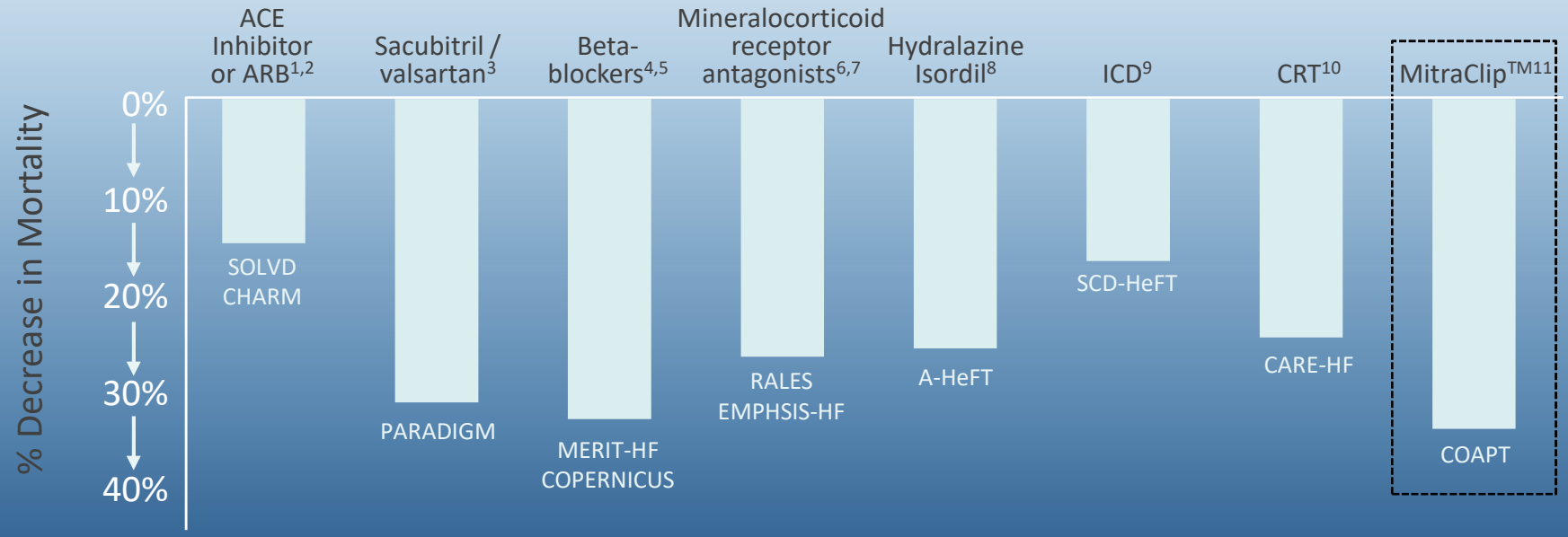
- Improves survival
- Reduces MR
- Reduces HF hospitalizations
- Improves quality of life
- Is safe

*MitraClip patients who were on maximally tolerated GDMT vs. GDMT alone.
Note: Graphics not indicative of market size.

COAPT™ TRIAL

Oklahoma Heart Institute

Mortality Benefits Observed Across Key Therapies for Treatment of Select HFrEF Patients



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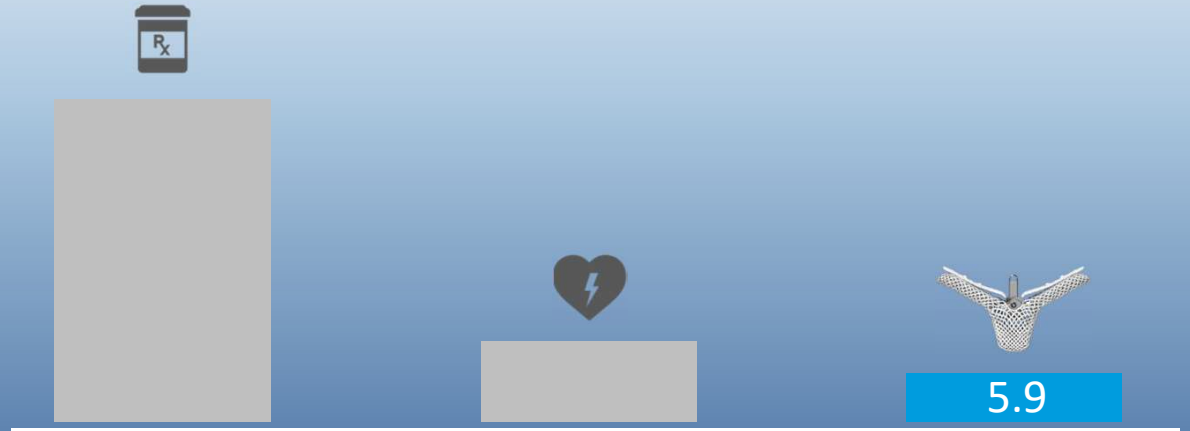
COAPT™ Sets a New Standard with NNT of 5.9

Number Needed to Treat (NNT) to prevent one death from any cause



Trial Name	PARADIGM-HF[1]	CARE-HF[2]	COAPT[3]
Mean Follow-up	27 Months	29.4 Months	19.1 Months
Drug/Device Name	GDMT	CRT + GDMT	MitraClip + Definitive GDMT Confirmed

Oklahoma Heart Institute

Conclusions

Mitral Regurgitation in the heart failure patient has been associated with worsening outcomes in multiple studies

GDMT has been shown to be effective in reducing HF hospitalizations and improving mortality

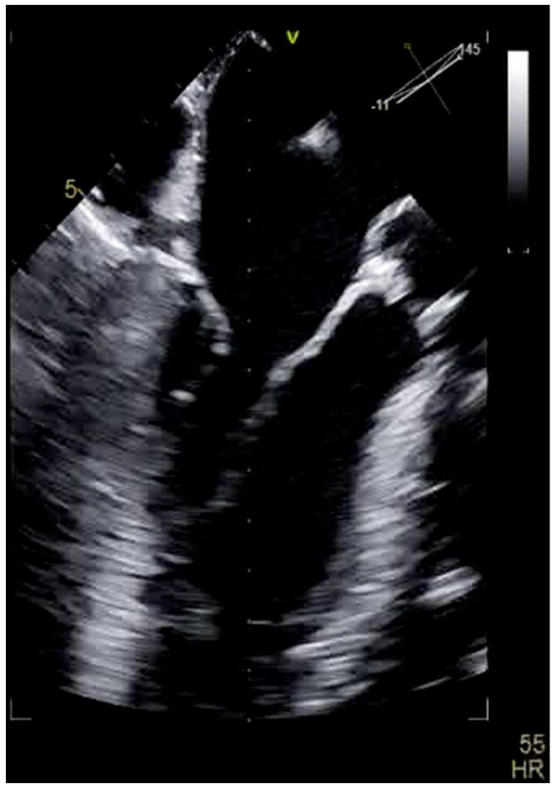
The COAPT™ trial, randomizing MitraClip + GDMT vs. GDMT alone, is a landmark clinical trial demonstrating a reduction in mitral regurgitation, reduction in HF hospitalizations (NNT= 3.1) and improvement in mortality (NNT=5.9) in HFrEF patients

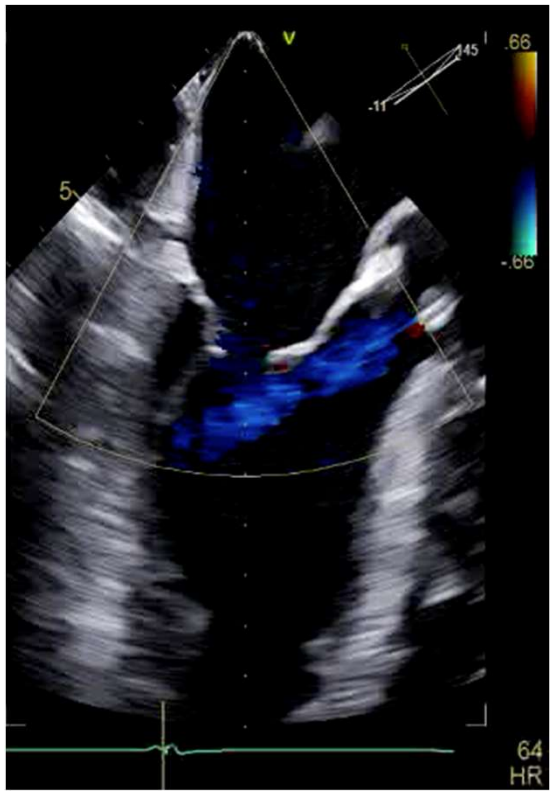
Early identification and referral to a multi-disciplinary team specializing in heart failure and mitral valve transcatheter repair, with MitraClip™, is an important next step to improve the prognosis of these patients

Case Review

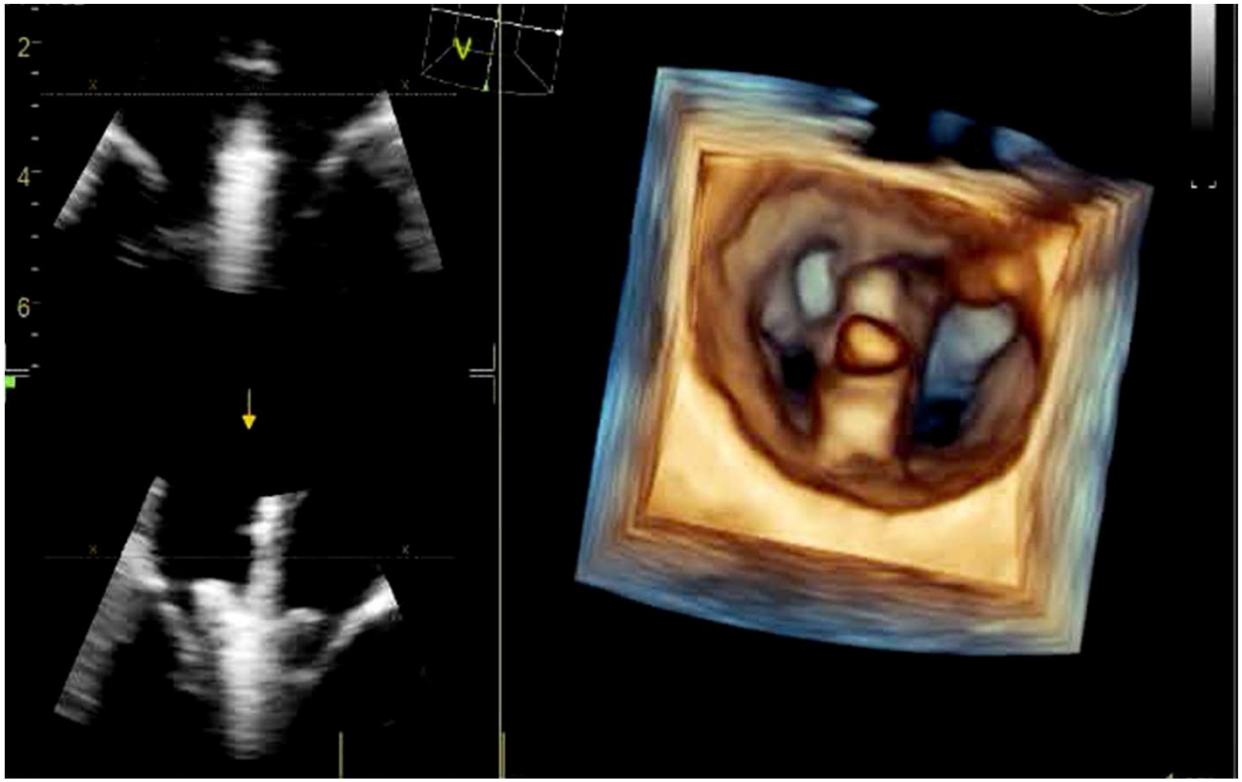
- 81 y/o male with progressive SOB, orthopnea and LE edema. He had to quit working at Home Depot
- CAD s/p CABG and previous stent placement
- **Ischemic CM (LVEF 35%) with NYHA class III CHF symptoms**
- Severe 4+ secondary/functional MR
- Extreme Risk: STS Risk for MVR 14.9%, Repair 10.7%

Severe 4+ Functional MR

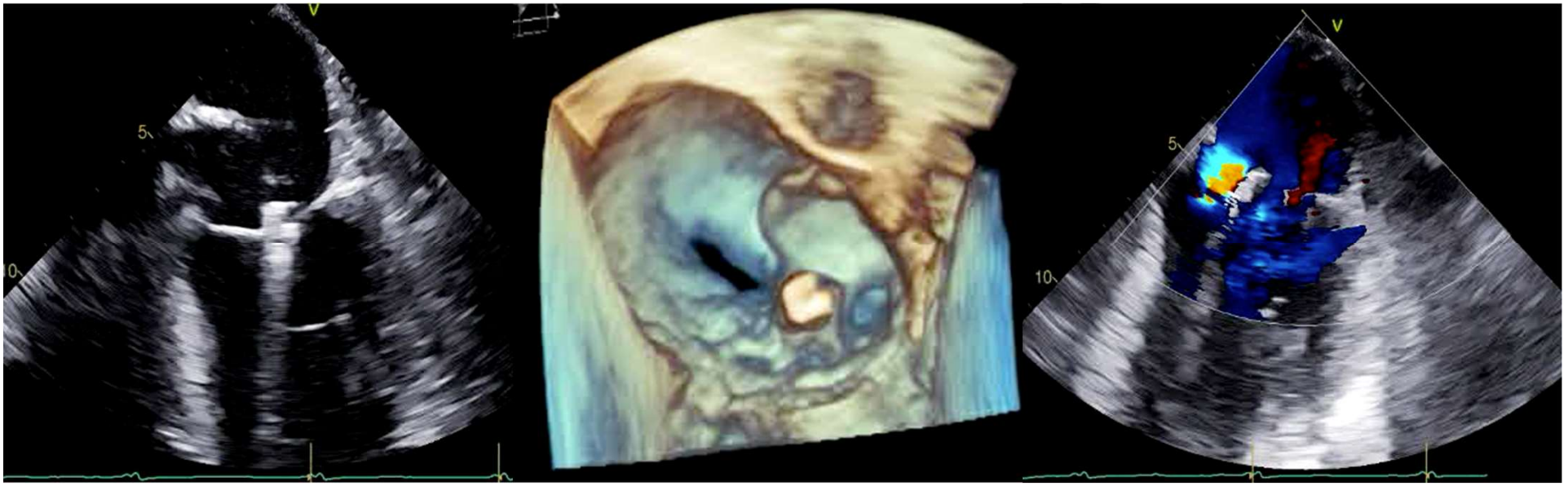




Clip 1 Alignment

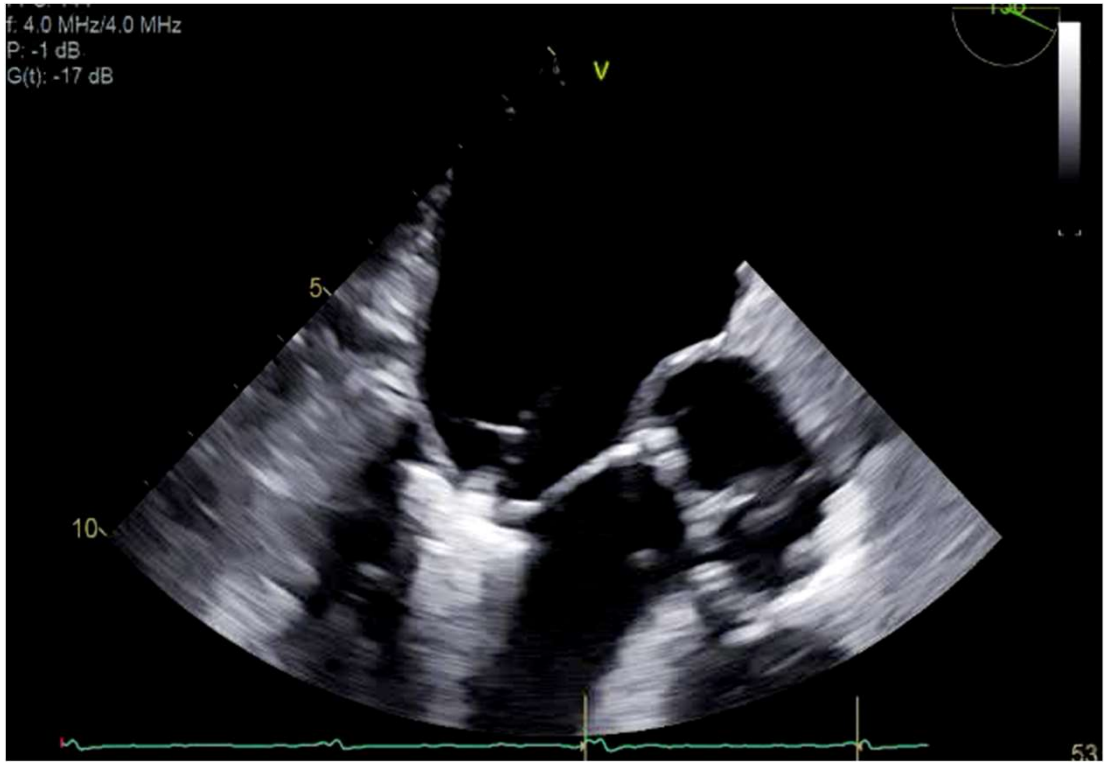


Clip 1 Placement

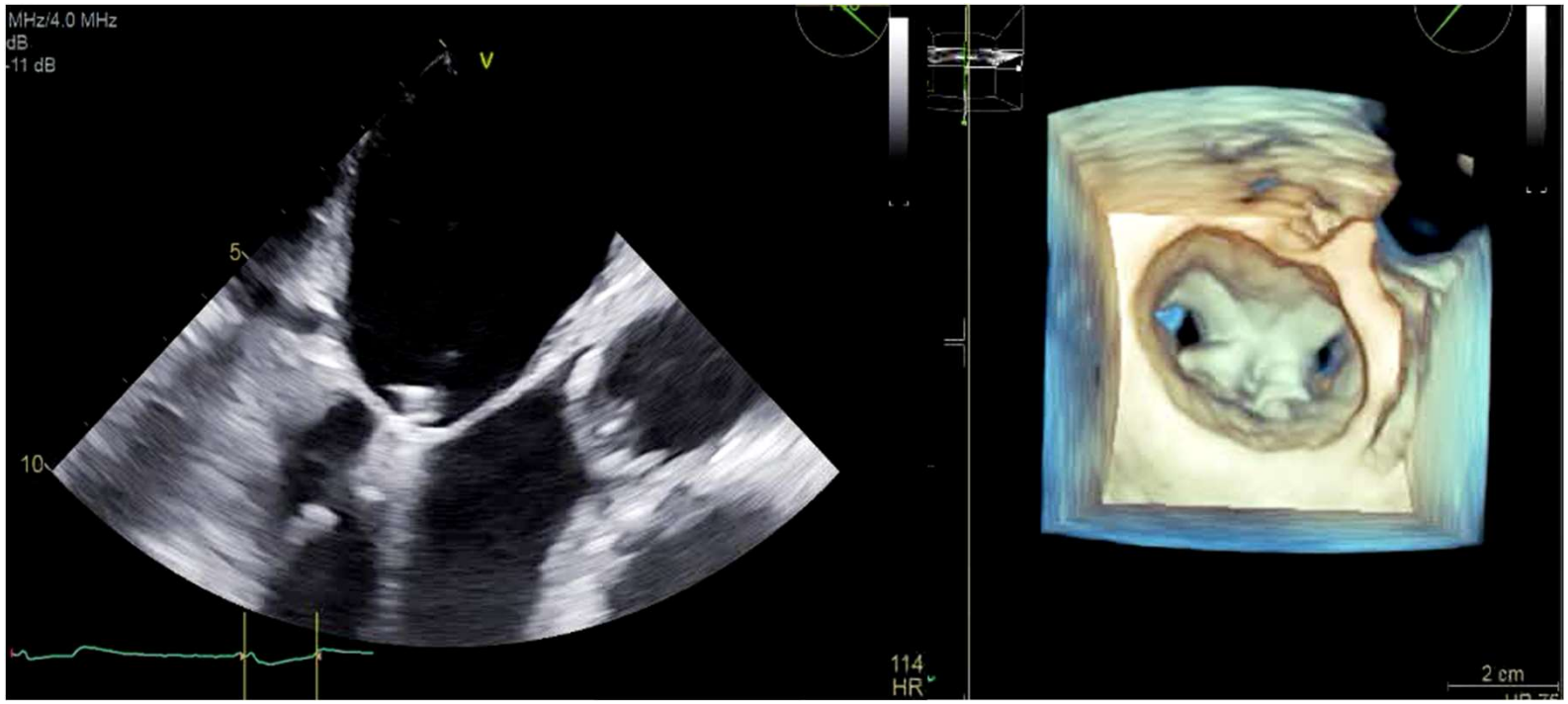


Residual Moderate 2+ Mitral Regurgitation After 1 Clip

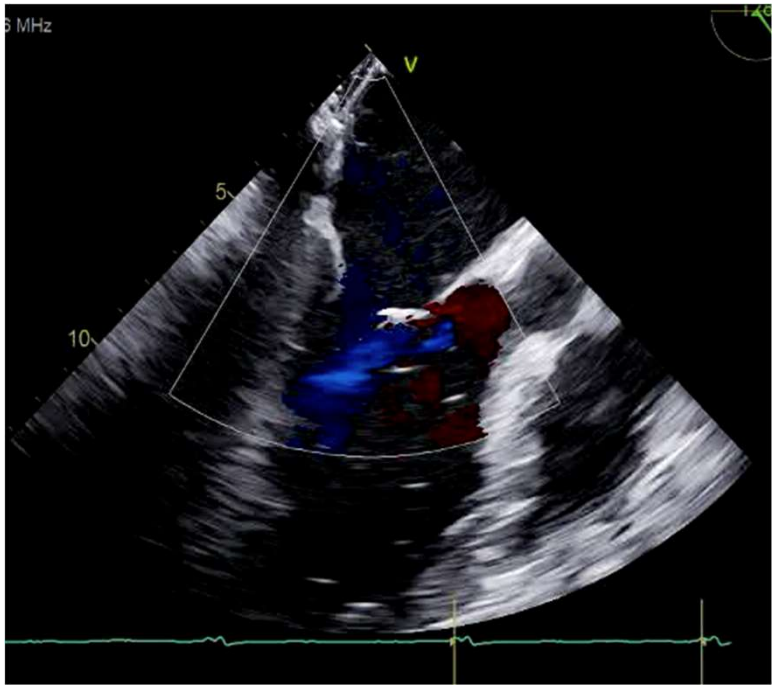
Placement Clip 2



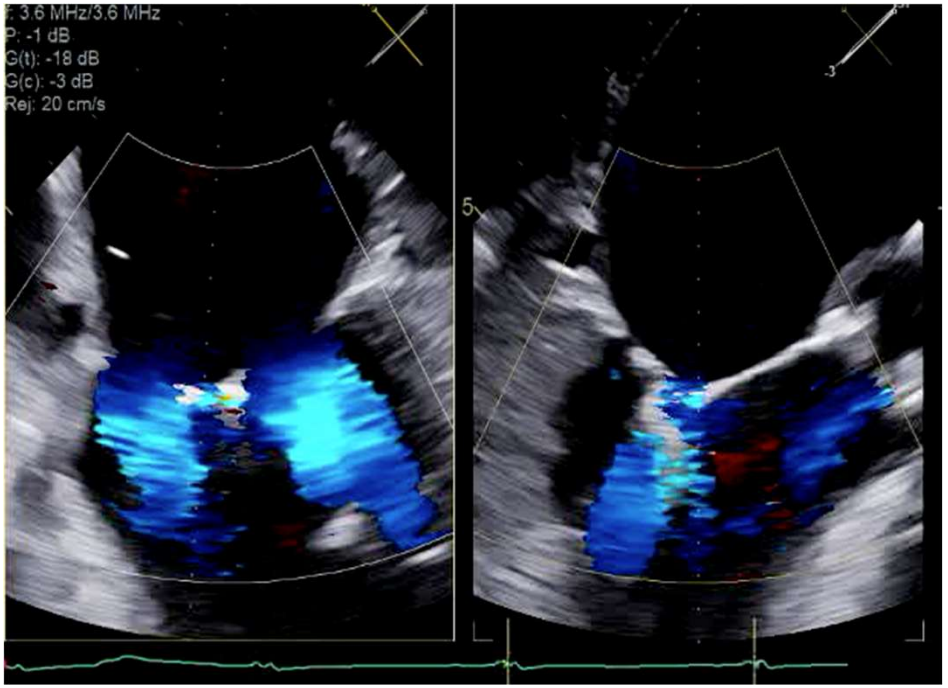
Implantation of 2 MitraClips



Successful Implantation of 2 MitraClips



Baseline Severe 4+ MR



Improved to Mild 1+ MR

Follow Up – 10/3/19 Office Visit

- Patient now with NYHA Class I CHF – reports he feels 10x better following MitraClip
- Continued mild 1+ MR by Echocardiogram
- Routine work out program 3x per week
- Pt now working at Macy's

SUMMIT Trial

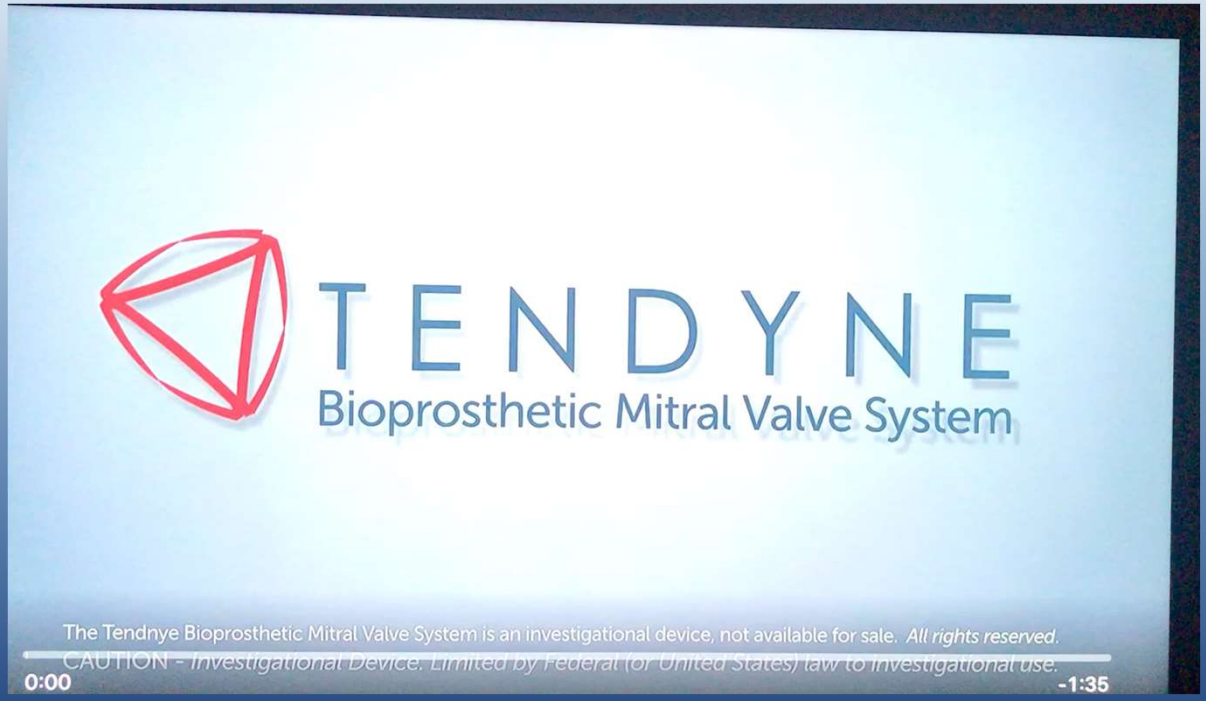
SUMMIT
TENDYNE TRIAL

Tendyne Mitral Valve System

Clinical Trial to Evaluate the **S**afety and Effectiveness of **U**sing the Tendyne **M**itral Valve System for the Treatment of Symptomatic **Mit**ral Regurgitation (SUMMIT)

Oklahoma Heart Institute

SUMMIT Video



THANK YOU !

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