Major Game Changing Studies in Cardiology

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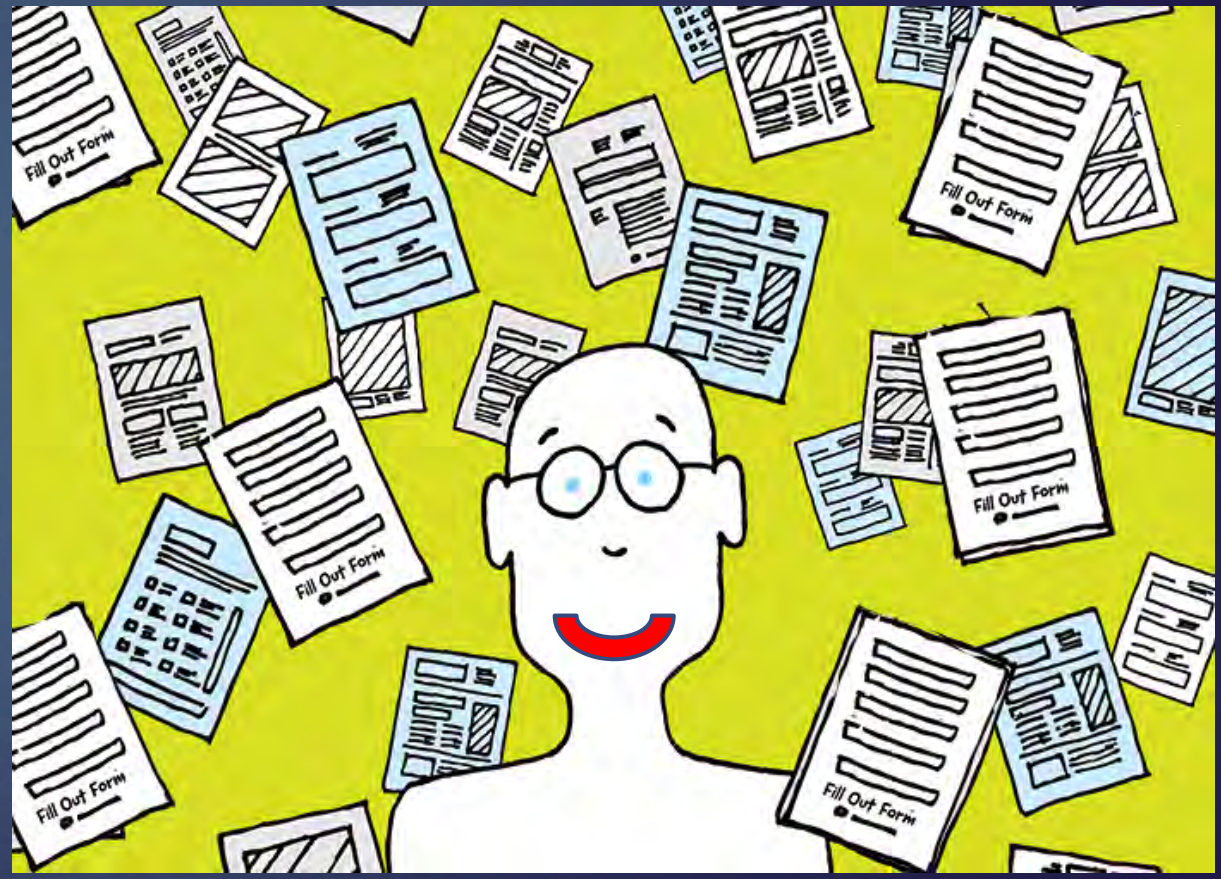
UNIVERSITY OF WASHINGTON

Disclosures

- No financial or industry disclosures

Our whirlwind tour of cardiology

- Coronary revascularization
- Antiplatelet therapy
- Atrial Fibrillation
- PFO Closure
- Valve Therapy



What we won't cover

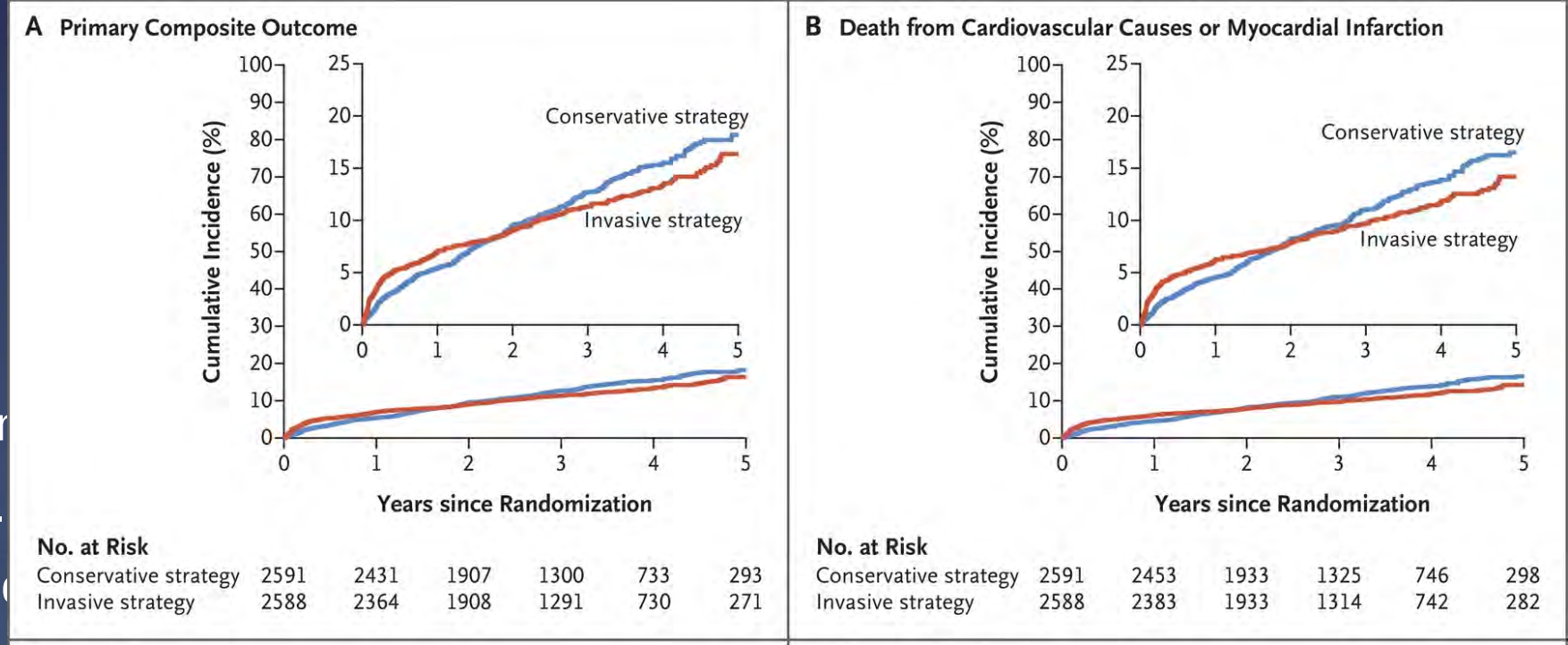
- Entresto (Valsartan-sacubitril)
  - Heart failure—Lowers Mortality/hospitalization
- PCSK9 inhibitors
  - Reduced MI/stroke/death
  - Patients intolerant to statins
  - Or not at goal on statins/ezetimibe

Stable Ischemic Coronary Artery Disease

ISCHEMIA…PRETTY MUCH WHAT WE THOUGHT

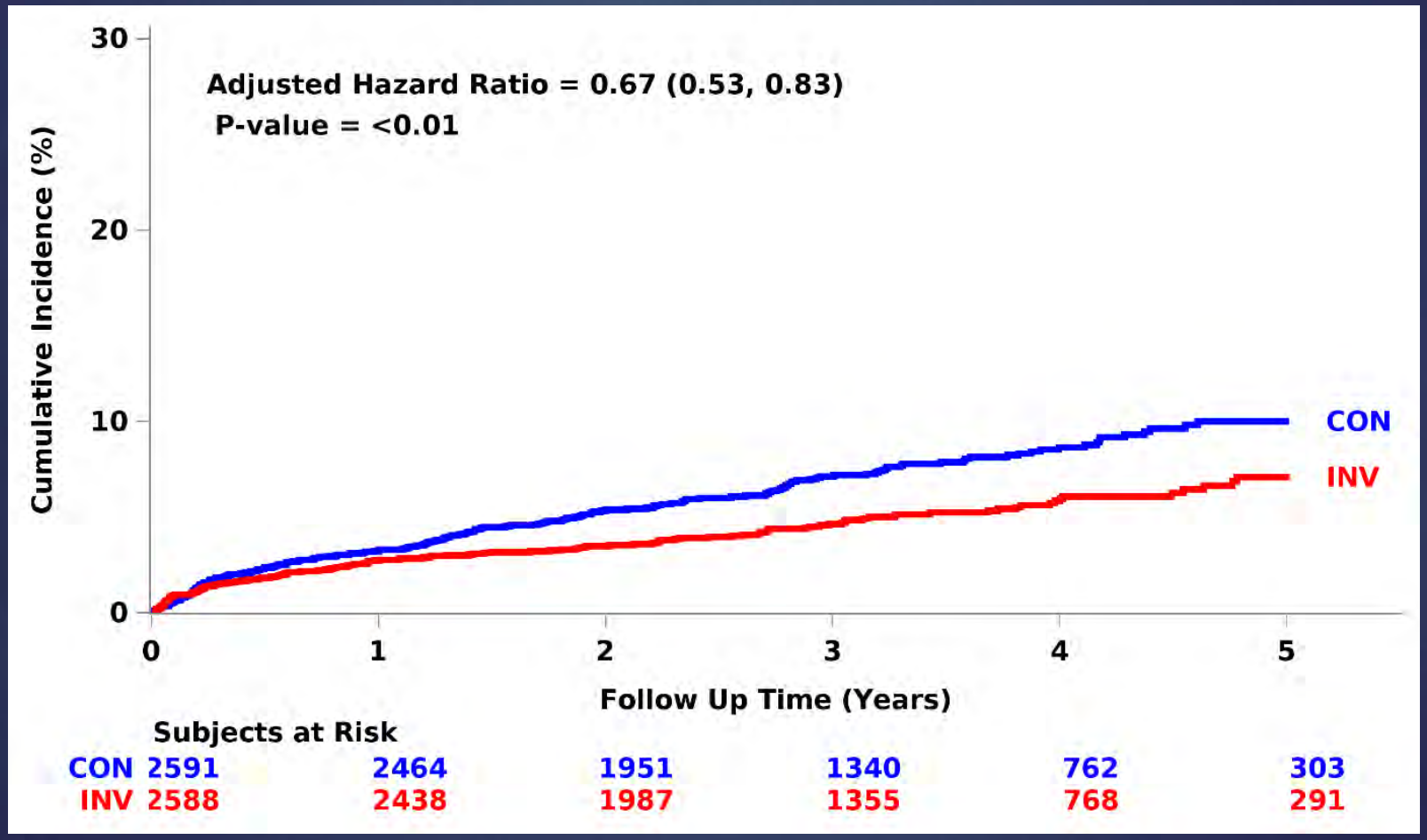
ISCHEMIA Tri

- 5139 patients with r
- Medical therapy v.
- Medical tx: 21% un
- Revasc: 79% under
- Improvement in qu



N Engl J Med 2020; 382:1395-1407

ISCHEMIA: Spontaneous MI



ISCHEMIA take home points

Chronic stable ischemic heart disease

- No mortality risk for medical therapy
  - 21% of patients will eventually need revascularization
  - Increased risk for a spontaneous MI
- Revascularization upfront
  - Periprocedural complications
  - No mortality benefit
  - Avoid a spontaneous MI

ISCHEMIA Take home point

Revascularize now or later?

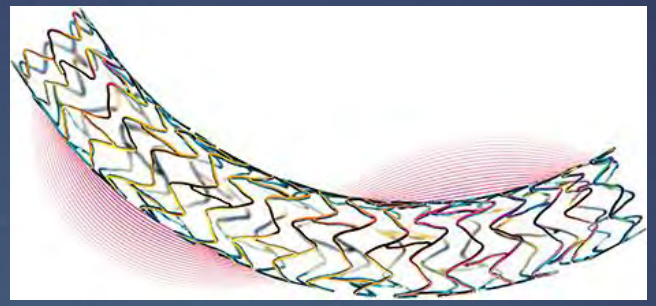
Patient preference-Quality of life

ANTIPLATELET THERAPY

LESS IS MORE

Dual antiplatelet therapy

- Remember these days?

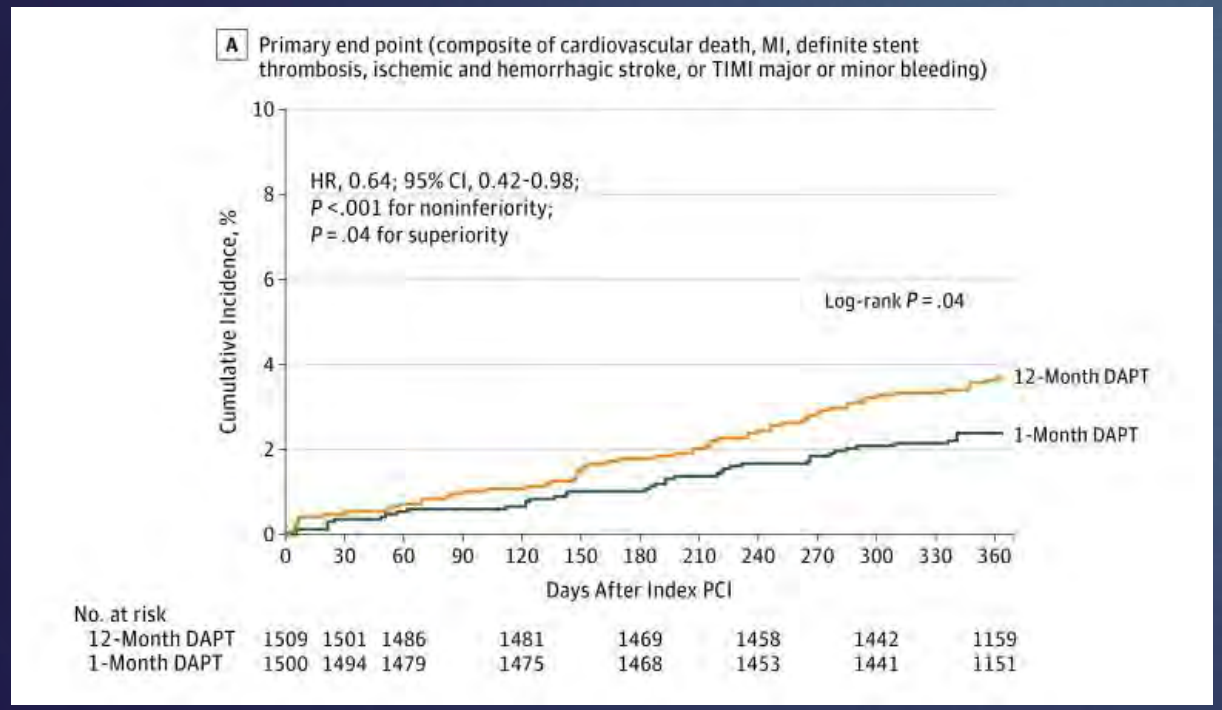


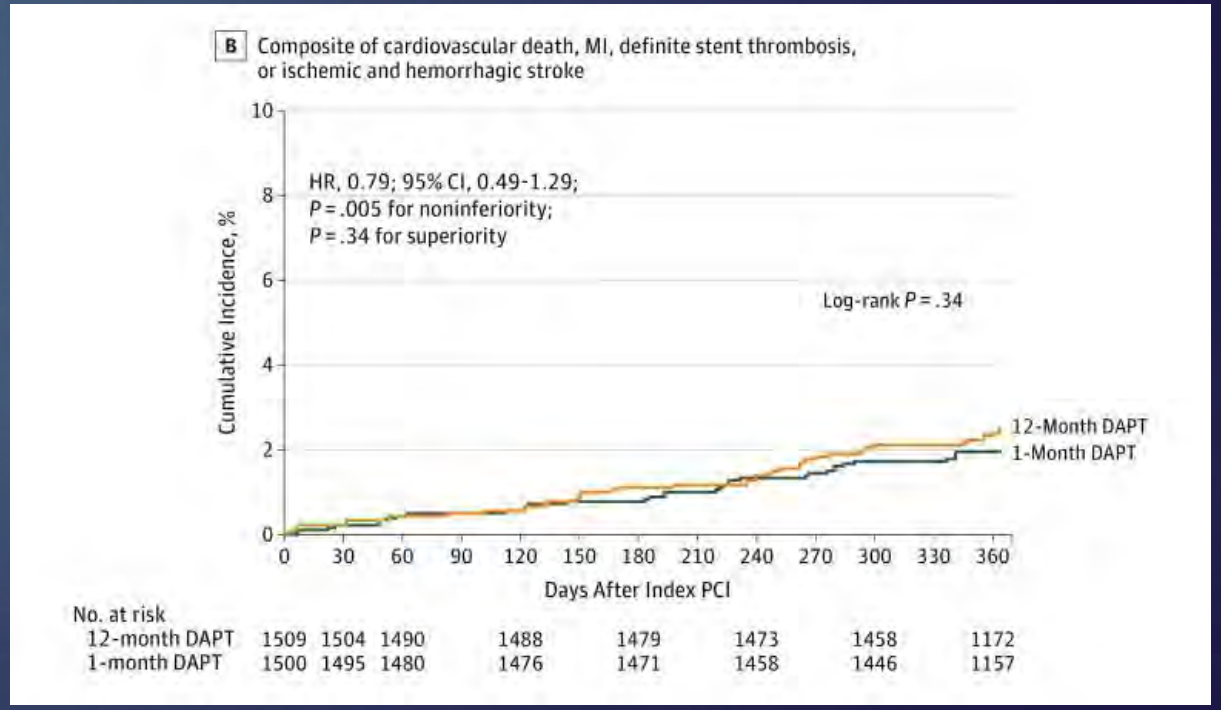
Late Stent Thrombosis

CoCr EES
EES implanted within PES
6 months antemortem

STOPDAPT-2

- Elective PCI
- 1 month of ASA+Clopidogrel, then Clopidogrel alone
- 12 months of ASA+Clopidogrel



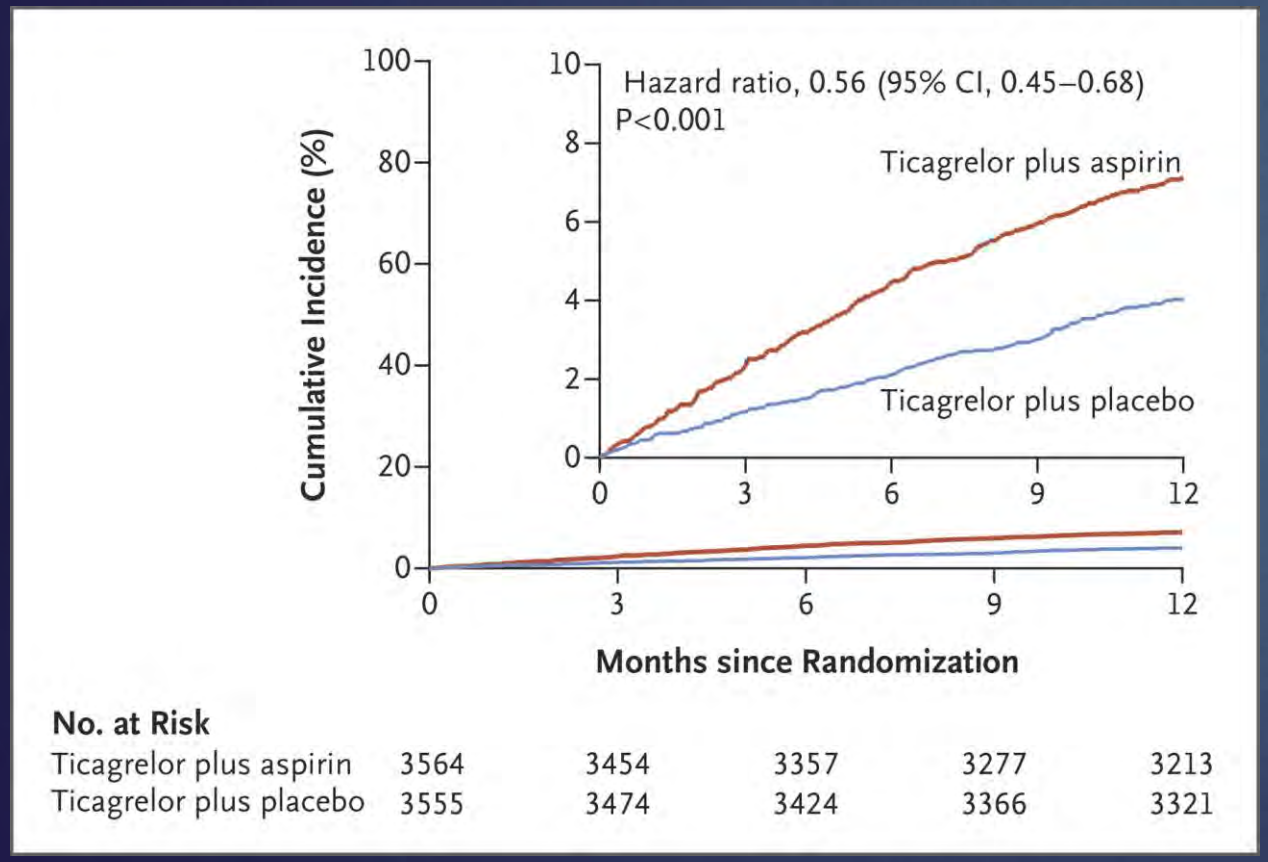


JAMA. 2019 Jun 25;321(24):2414-2427

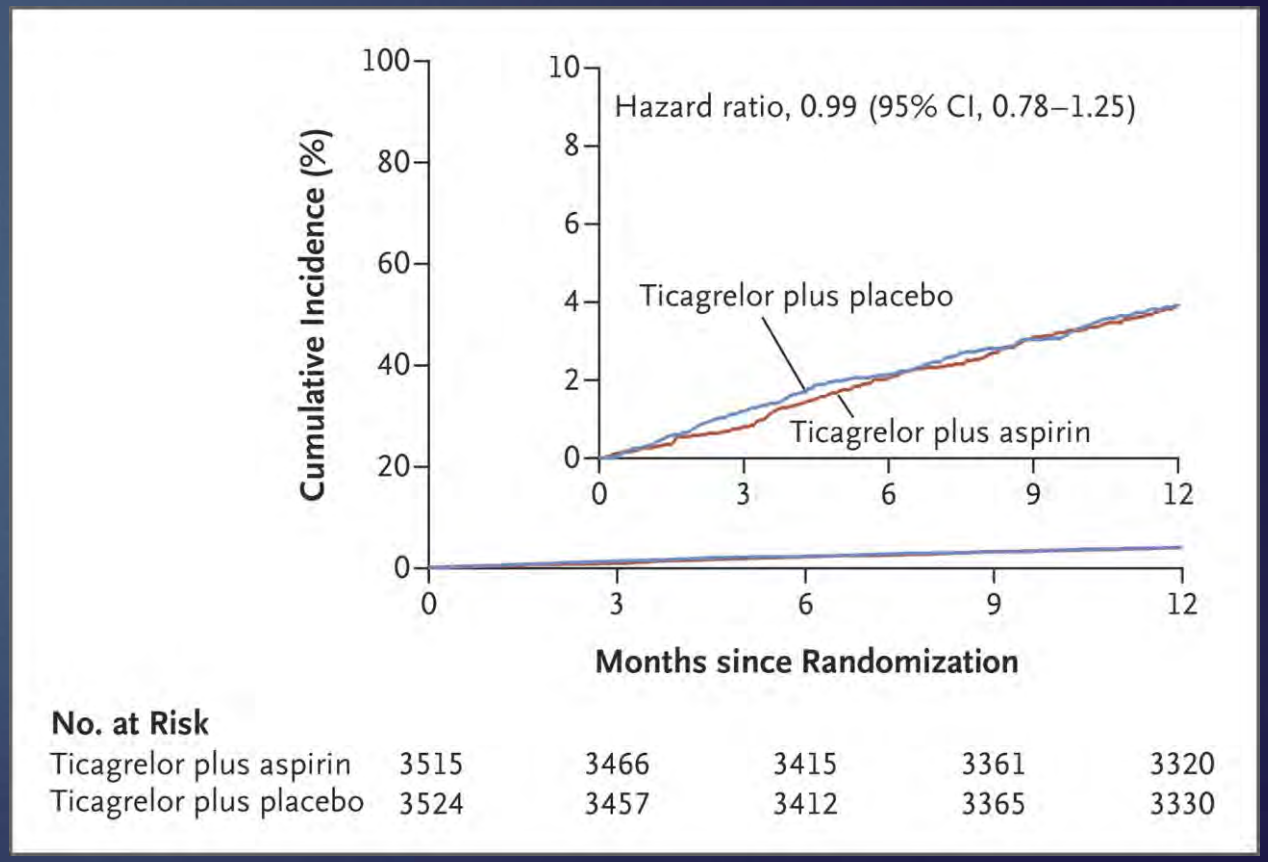
TWILIGHT

- 3 months of ASA+Ticagrelor v. 12 months DAPT

Death, MI Stroke, bleeding



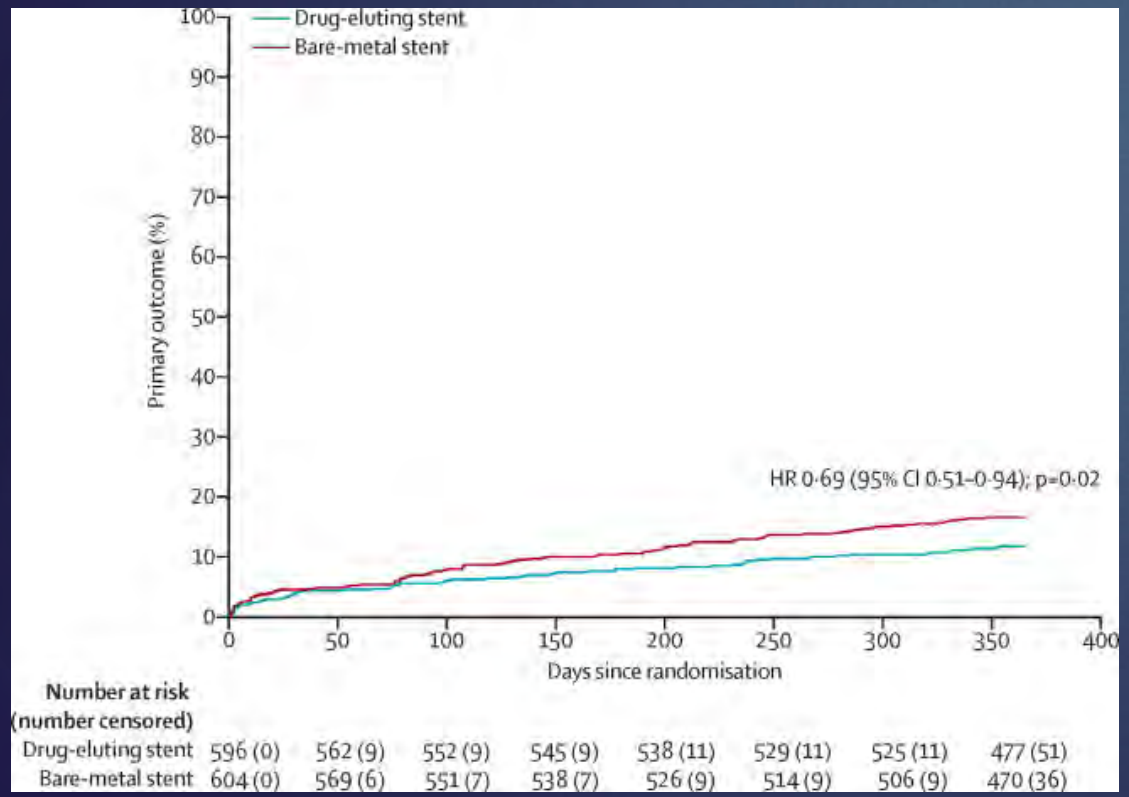
Death, MI Stroke

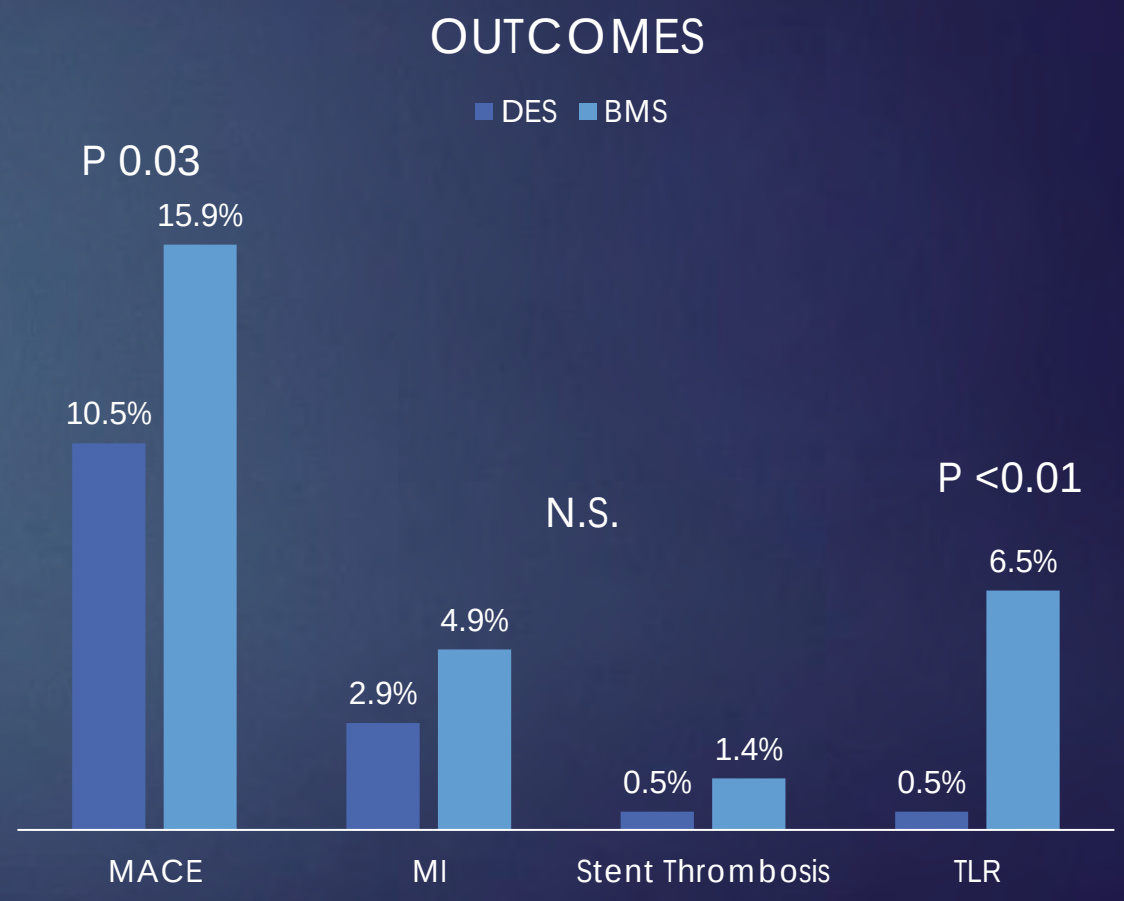


N Engl J Med 2019; 381:2032-2042

SENIOR

- Patients >75 undergoing PCI
- Bare metal stent vs. Drug eluting stent
- 1 month DAPT (6 months for MI) then ASA monotherapy





Varenne O. Lancet. 2018 Jan 6;391(10115):41-50.

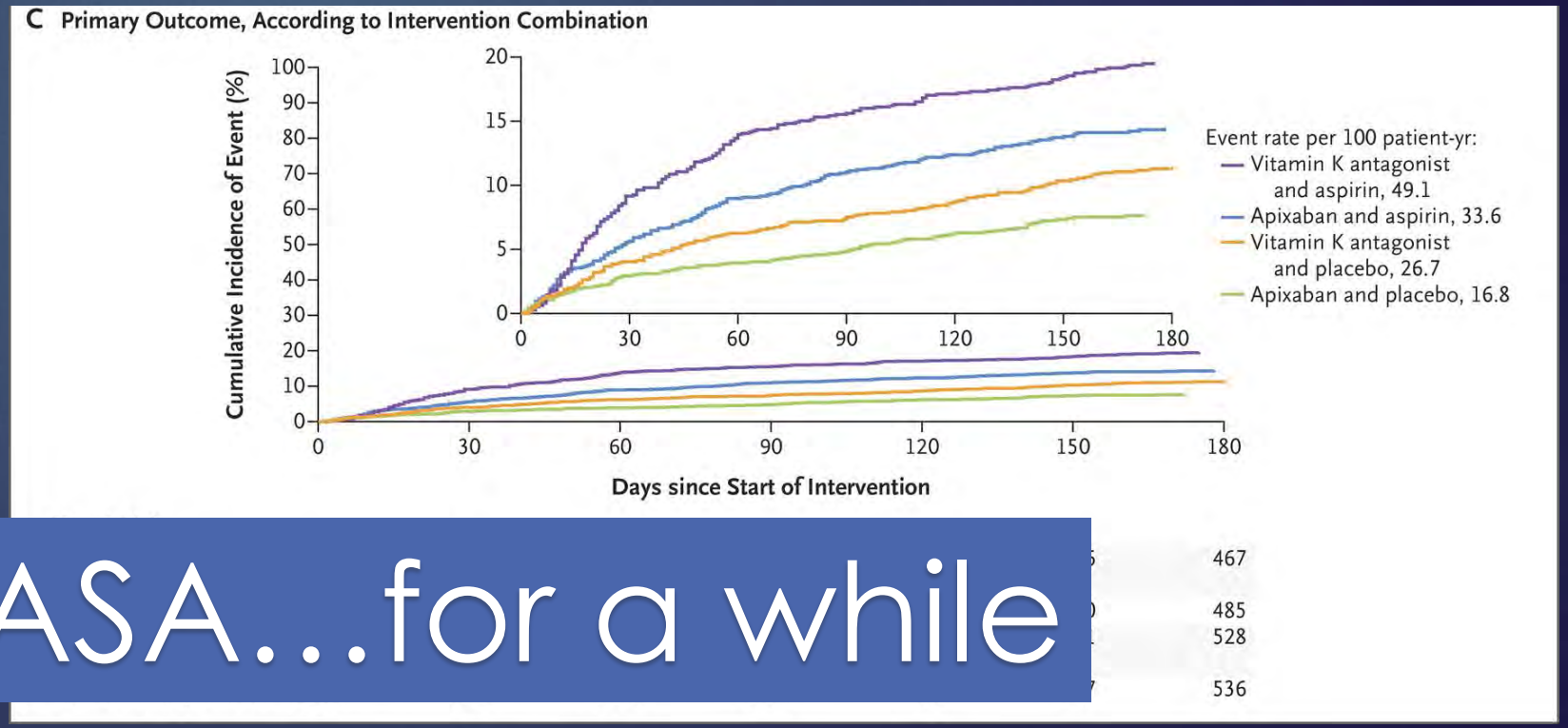
Post coronary stenting (PCI)

- STOPDAPT2
- TWIGHLIGHT,
- ONYX-ONE
- GLOBAL LEADERS
- SENIOR

- 6-12 months if you can do it
- 1-3 months for high risk bleeding patients
- No more bare metal stents

Anticoagulation and DAPT

- WOEST—VKA+P2Y12 better than triple therapy
- AUGUSTUS—Afib + PCI
  - P2Y12 + apixaban v. triple therapy



Drop the ASA…for a while

ATRIAL FIBRILLATION

A WHOLE NEW APPROACH

Atrial Fibrillation

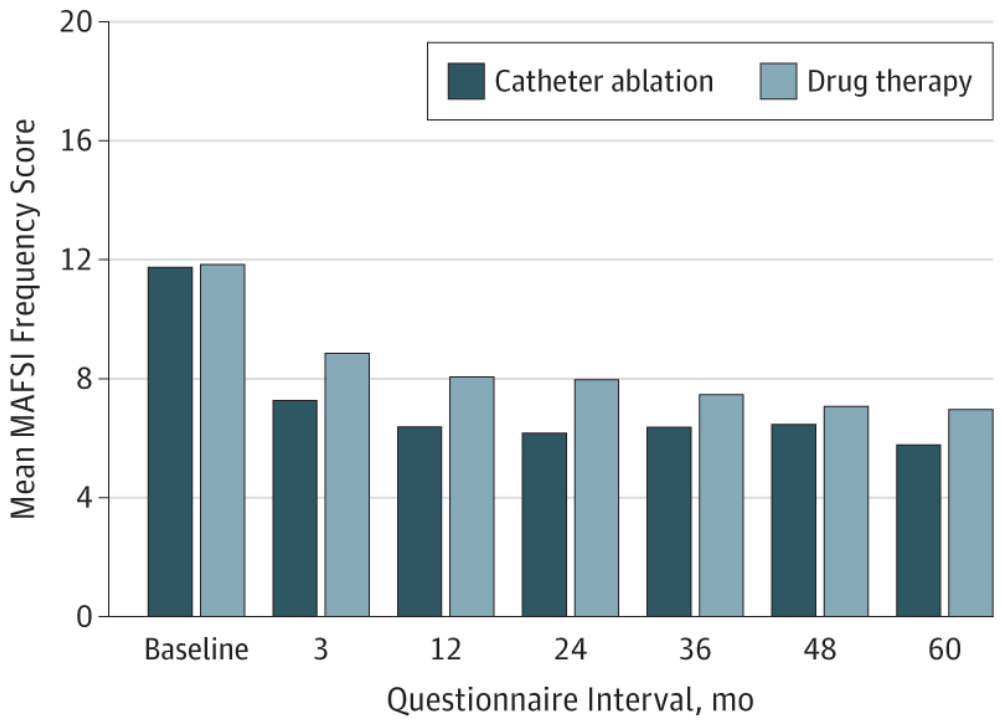
Rhythm Control = Rate Control

- AFFIRM
- RACE
- Not so fast….
  - CABANA
  - CASTLE-AF
  - EAST-AFNET 4

CABANA

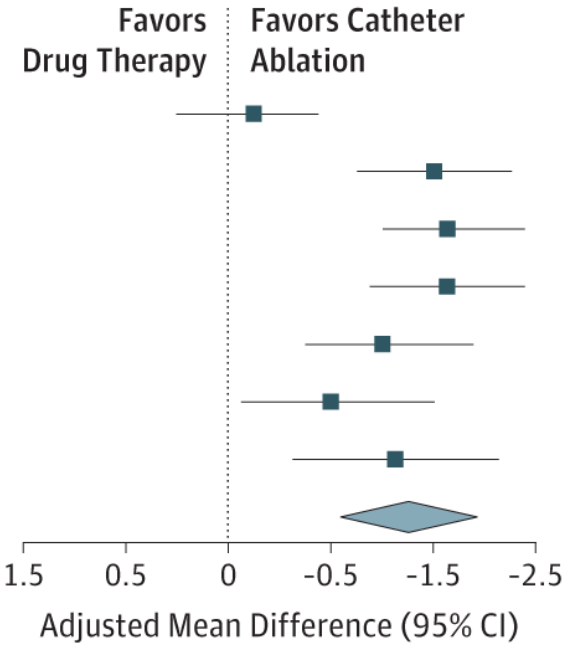
- 2204 patients with symptomatic atrial fibrillation

A Mean MAFSI frequency score



B Between-group MAFSI frequency score difference

Interval, mo	No. of Patients Ablation (n = 1108)	No. of Patients Drug Rx (n = 1096)	Adjusted Mean Difference (95% CI)
Baseline	1069	1061	-0.2 (-0.7 to 0.4)
3	897	894	-1.6 (-2.2 to -1.0)
12	828	831	-1.7 (-2.3 to -1.2)
24	759	724	-1.7 (-2.3 to -1.1)
36	571	559	-1.2 (-1.9 to -0.6)
48	424	419	-0.8 (-1.6 to -0.1)
60	279	295	-1.3 (-2.1 to -0.5)
All	3758	3722	-1.4 (-1.9 to -0.9)



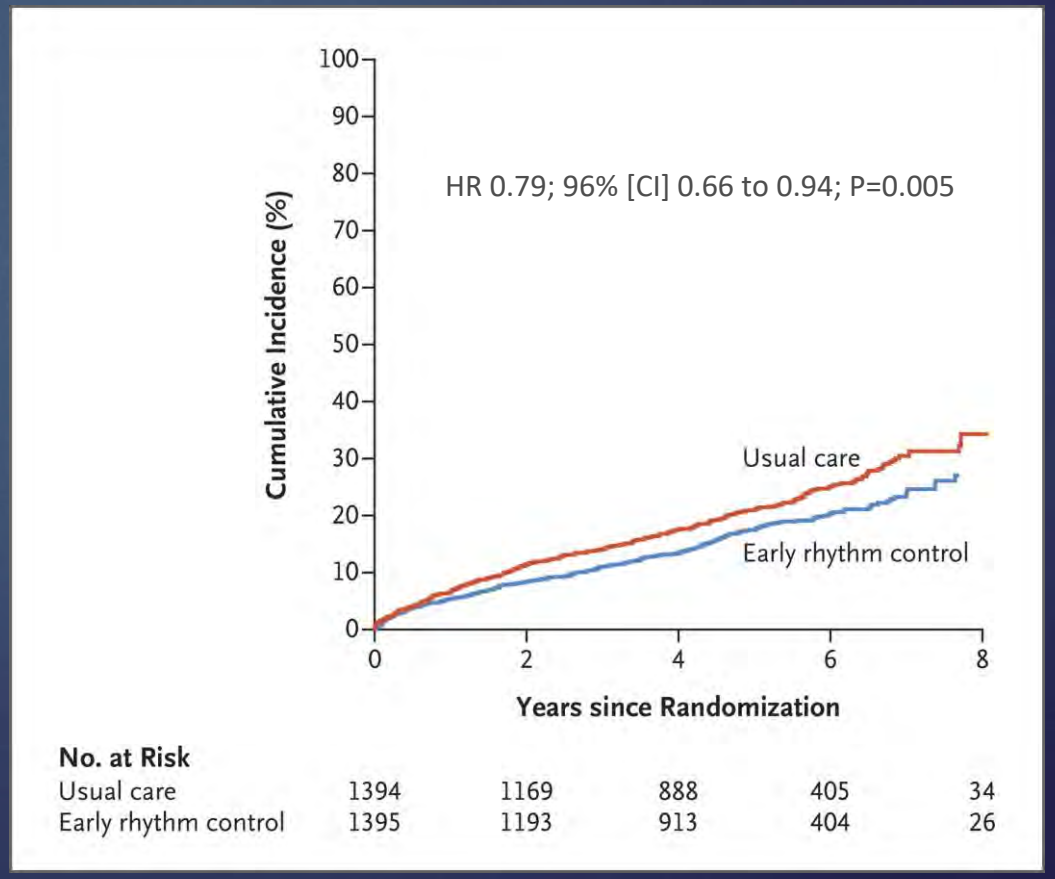
No. at risk

Drug therapy	1096	1036	1006	970	880	763	652	578	499	418	312
Catheter ablation	1108	1045	1021	996	915	793	700	614	535	432	309

JAMA. 2019;321(13):1261-1274.
JAMA. 2019;321(13):1275-1285.

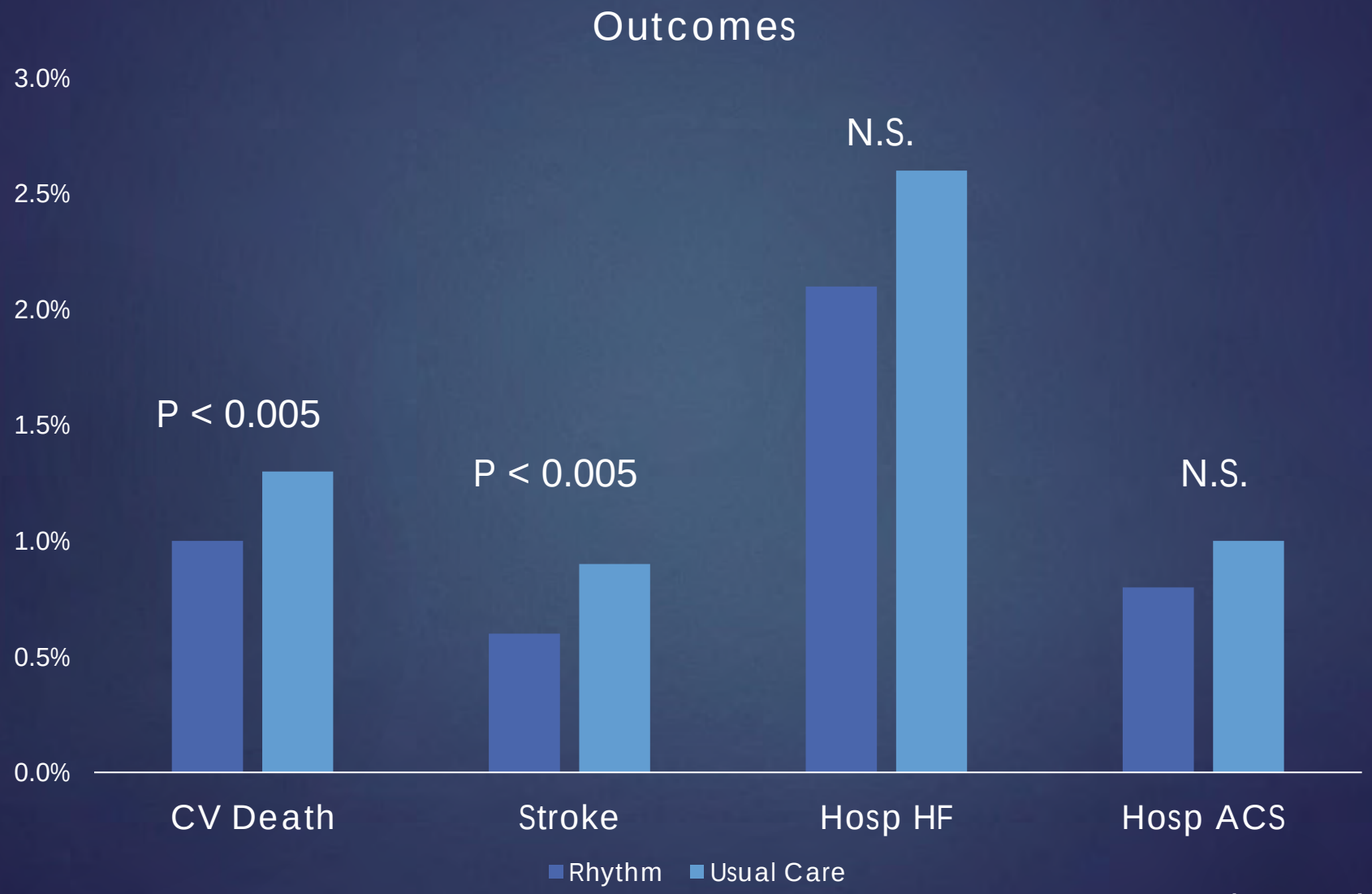
EAST-AFNET 4

- 2789 patients with new afib (<1 year)
- Rhythm control with meds +/- ablation v. rate control
  - Death, stroke, or adverse events related to rhythm-control therapy



N Engl J Med 2020; 383:1305-1316

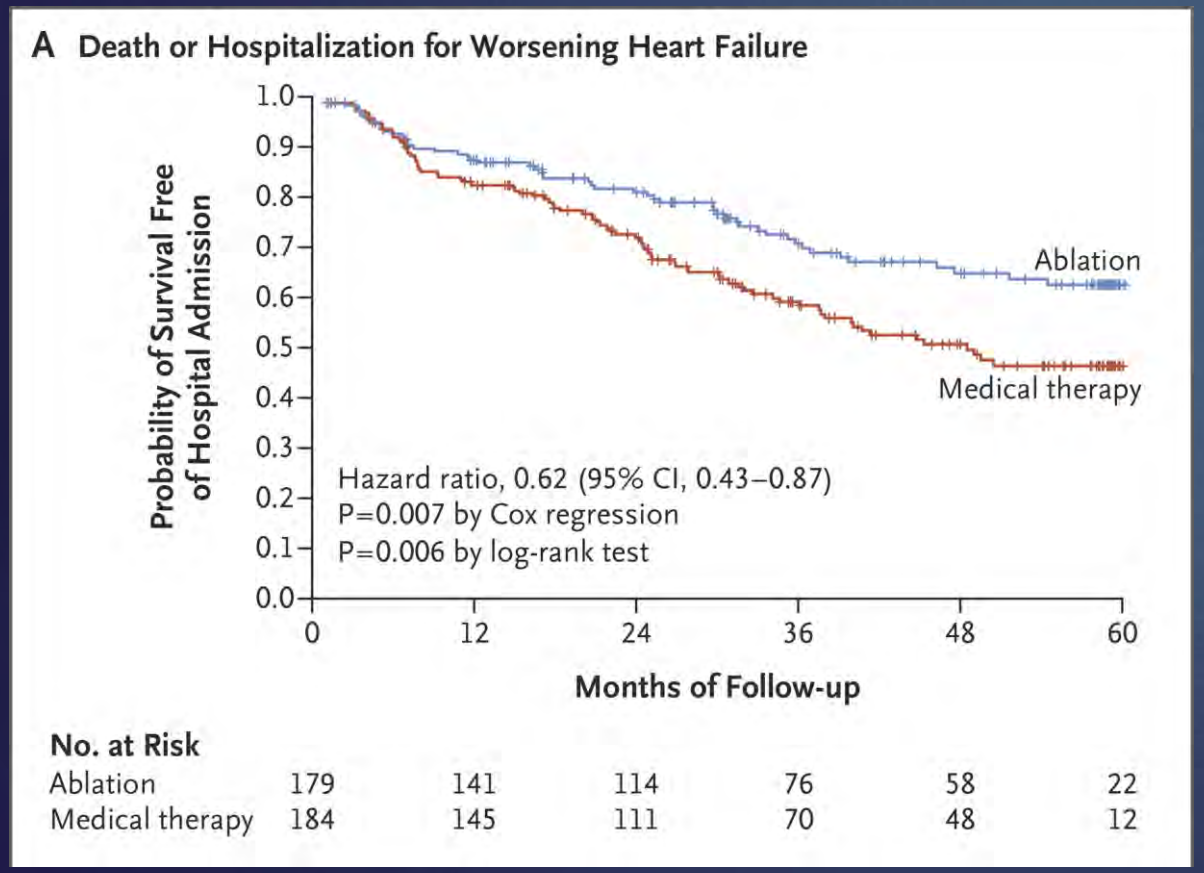
EAST-AFNET 4

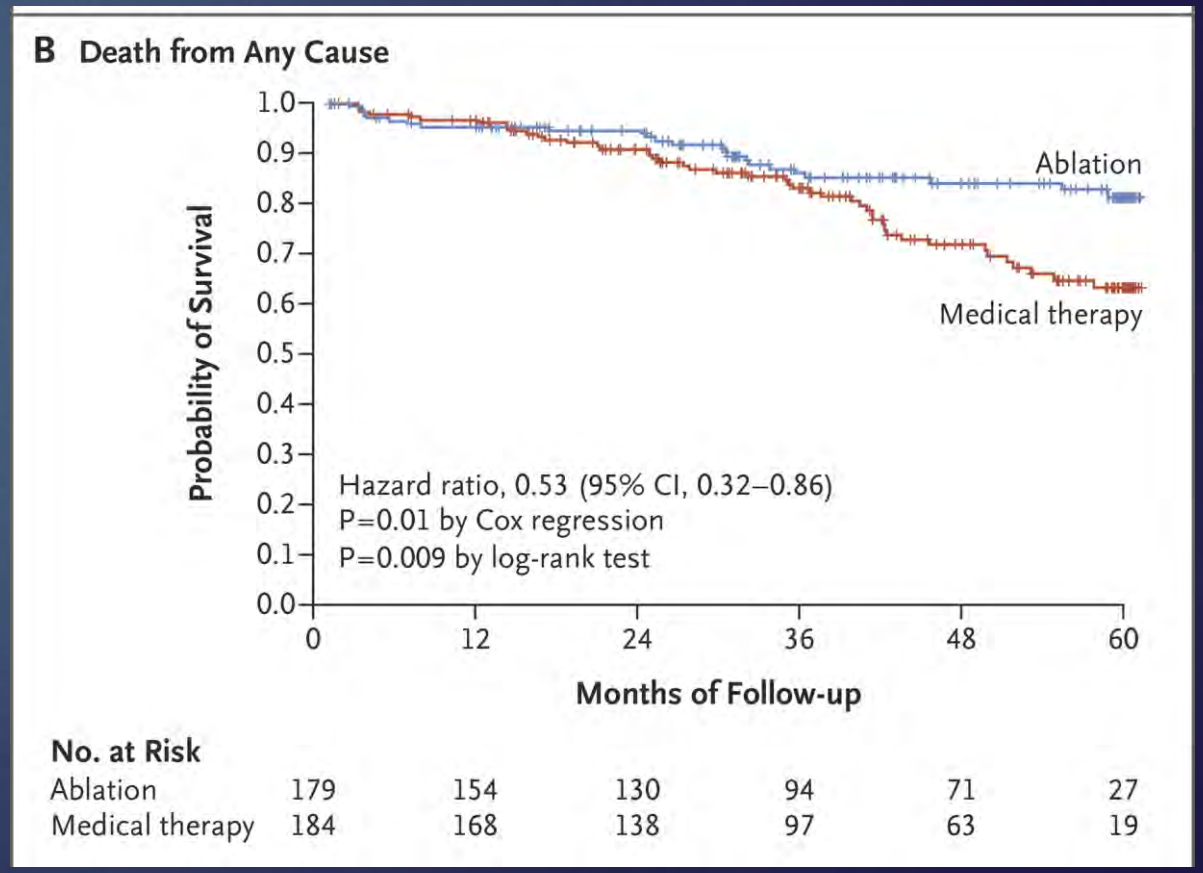


N Engl J Med 2020; 383:1305-1316

CASTLE-AF

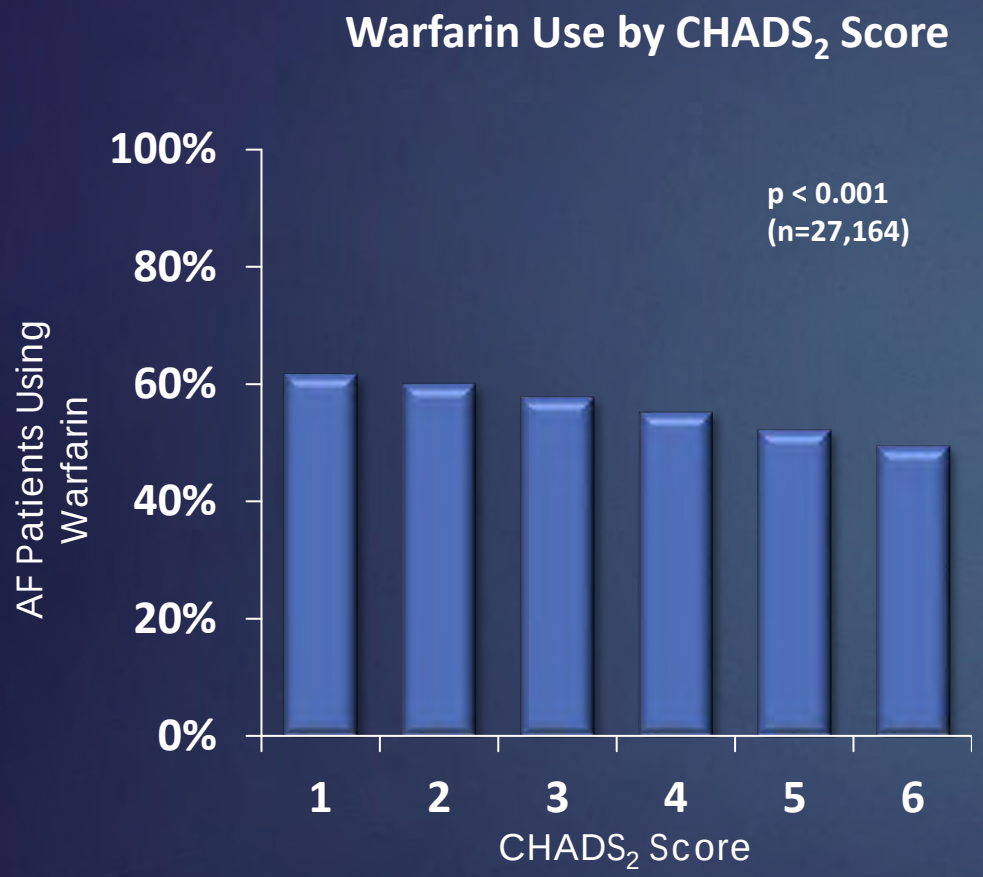
- 398 patients with EF < 35%, NYHA 2-4, and AFIB
- Catheter ablation v. medical therapy



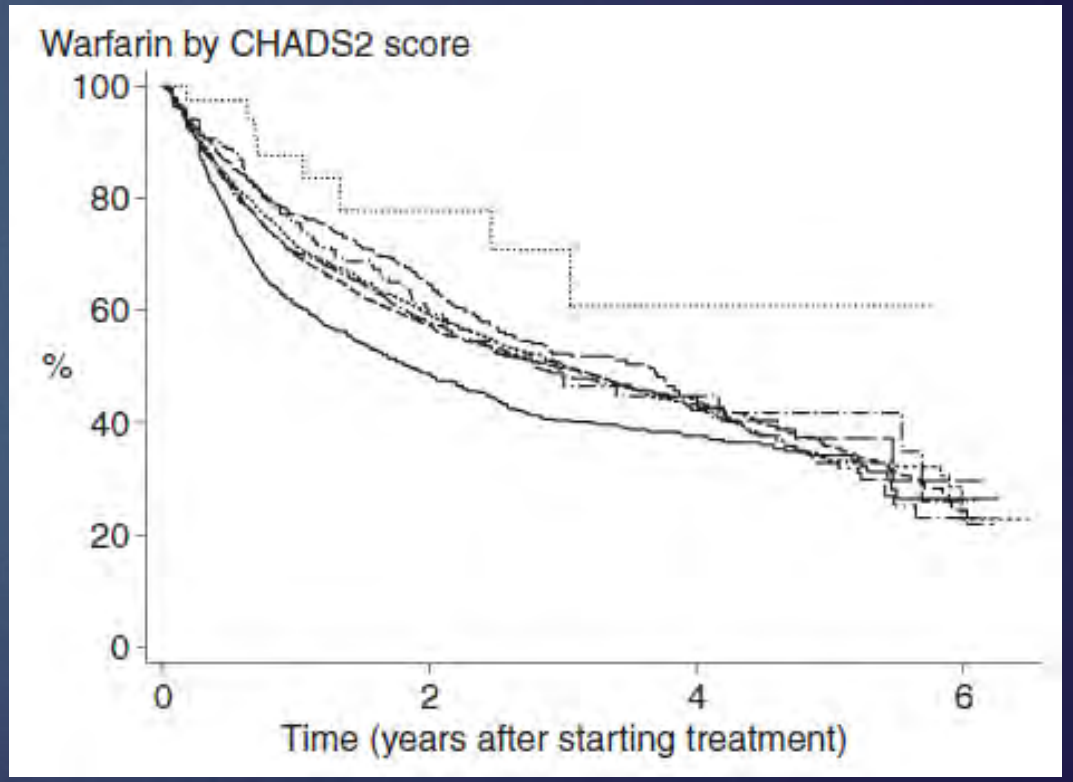


N Engl J Med 2018; 378:417-427

Anticoagulation—we are failing

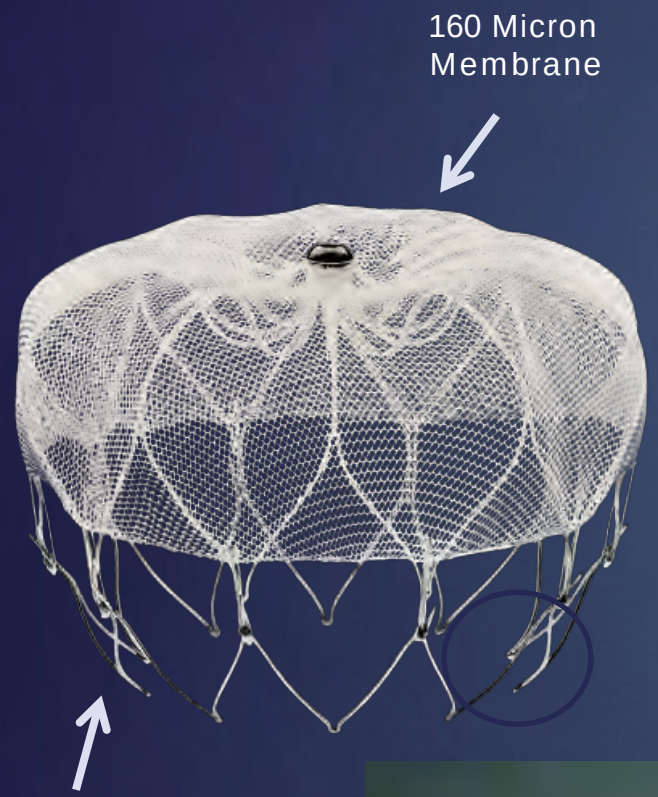


- Medicare claims data, 2006-2007[1]
  - Warfarin use less than 60% in high-risk patients

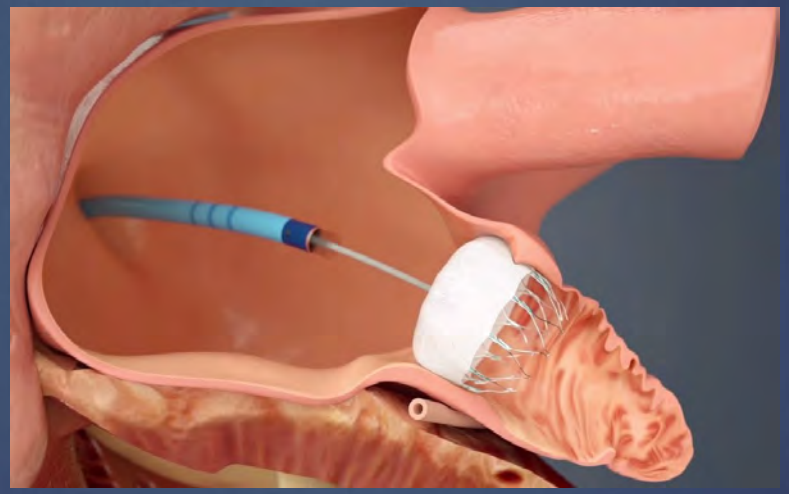


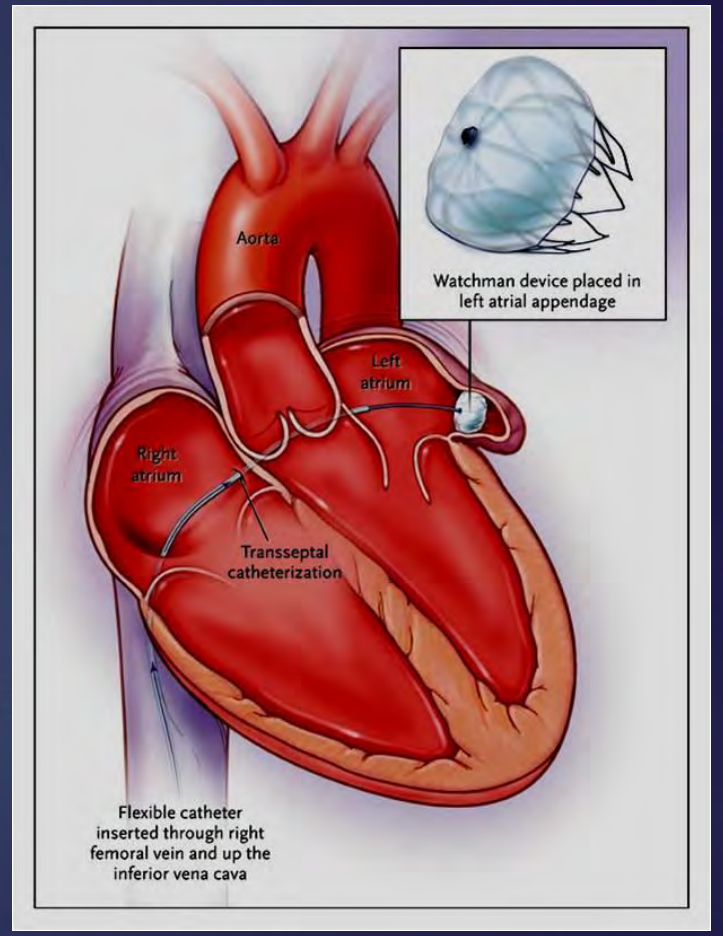
Piccini, et al.. Pharmacotherapy in Medicare beneficiaries with atrial fibrillation. Heart Rhythm. 2012;9:1403-1408
J Thromb and Haemostasis.

Watchman LAA closure device

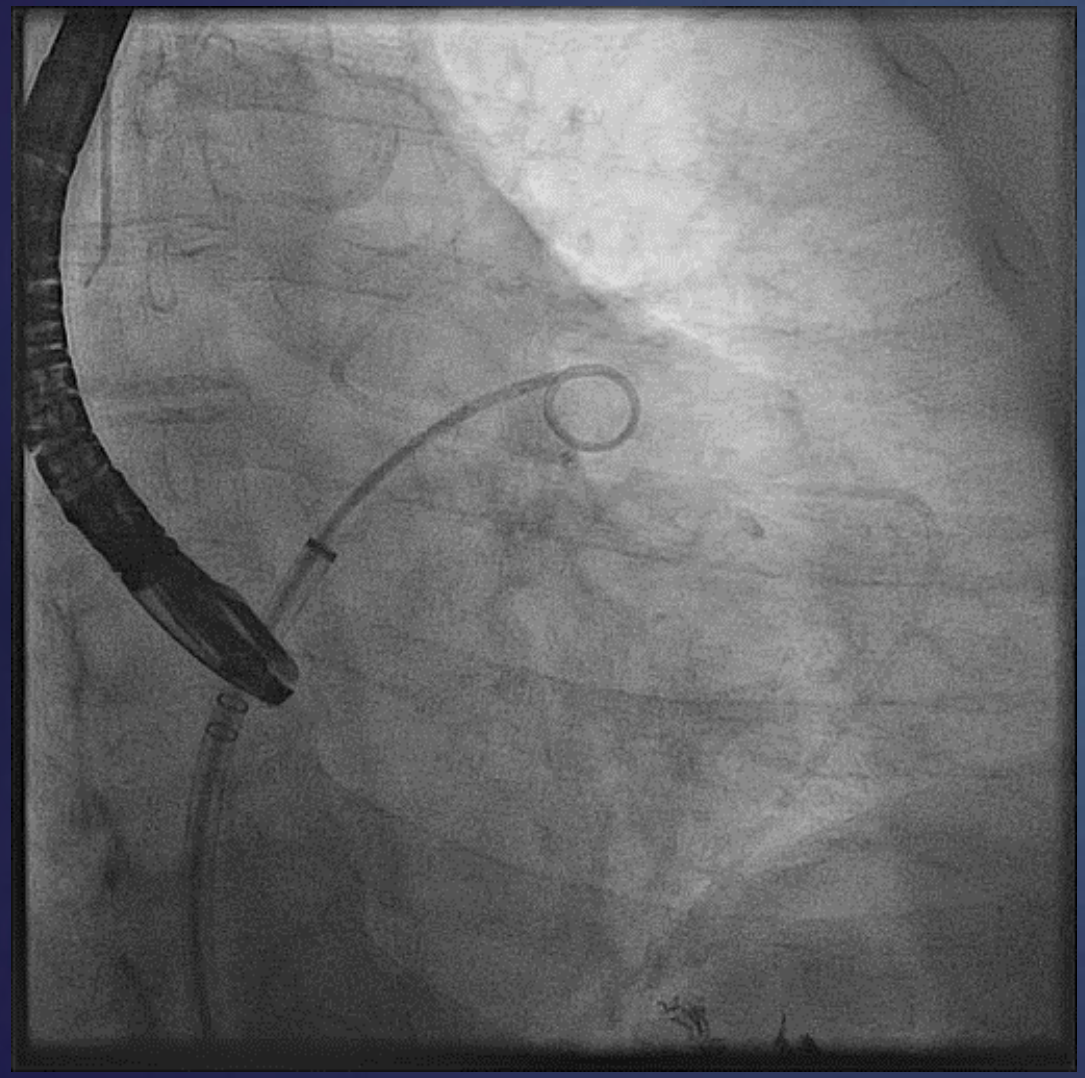


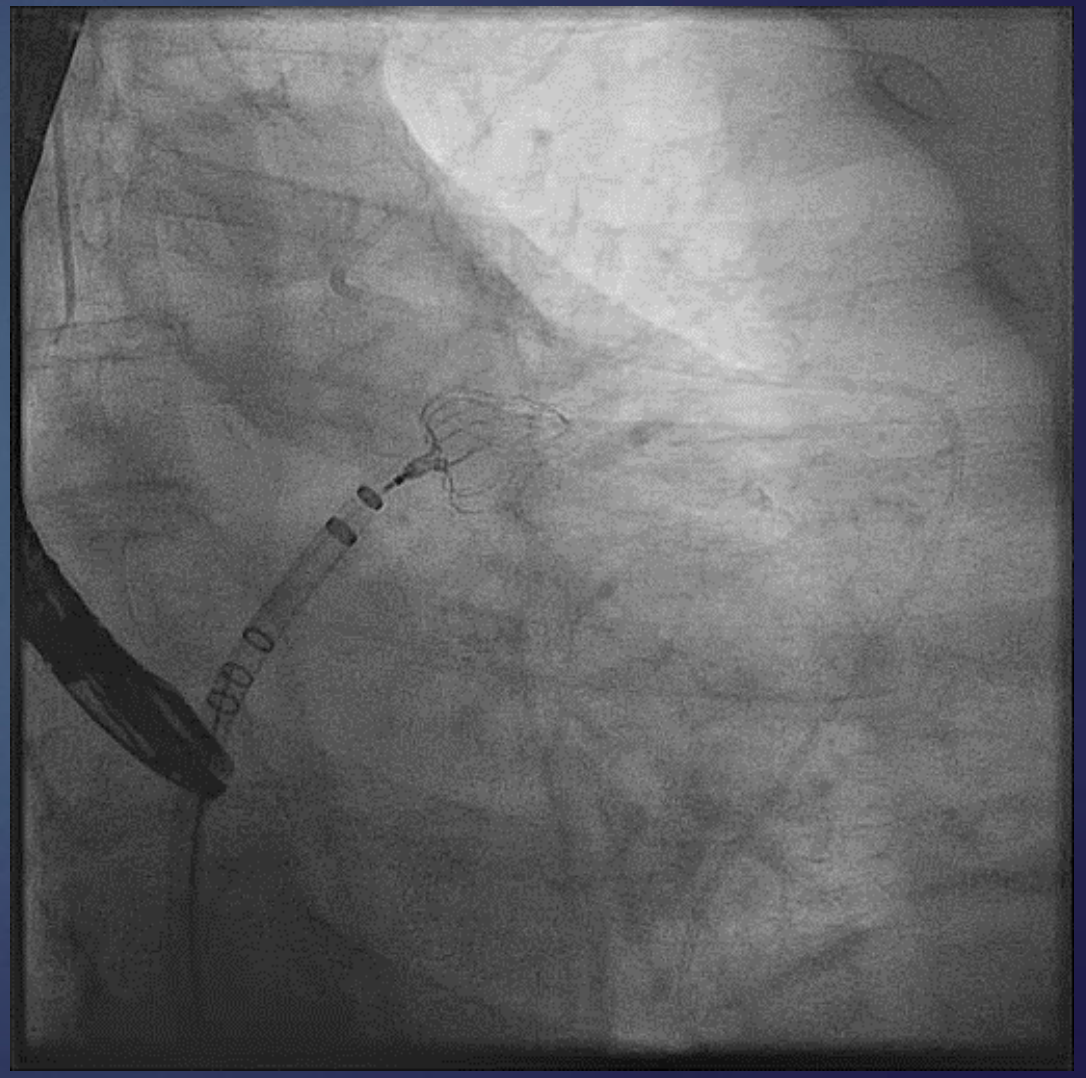
- Percutaneous femoral venous
  - Sizes: 21, 24, 27, 30, 33 mm diameter
- Transseptal puncture—inferior



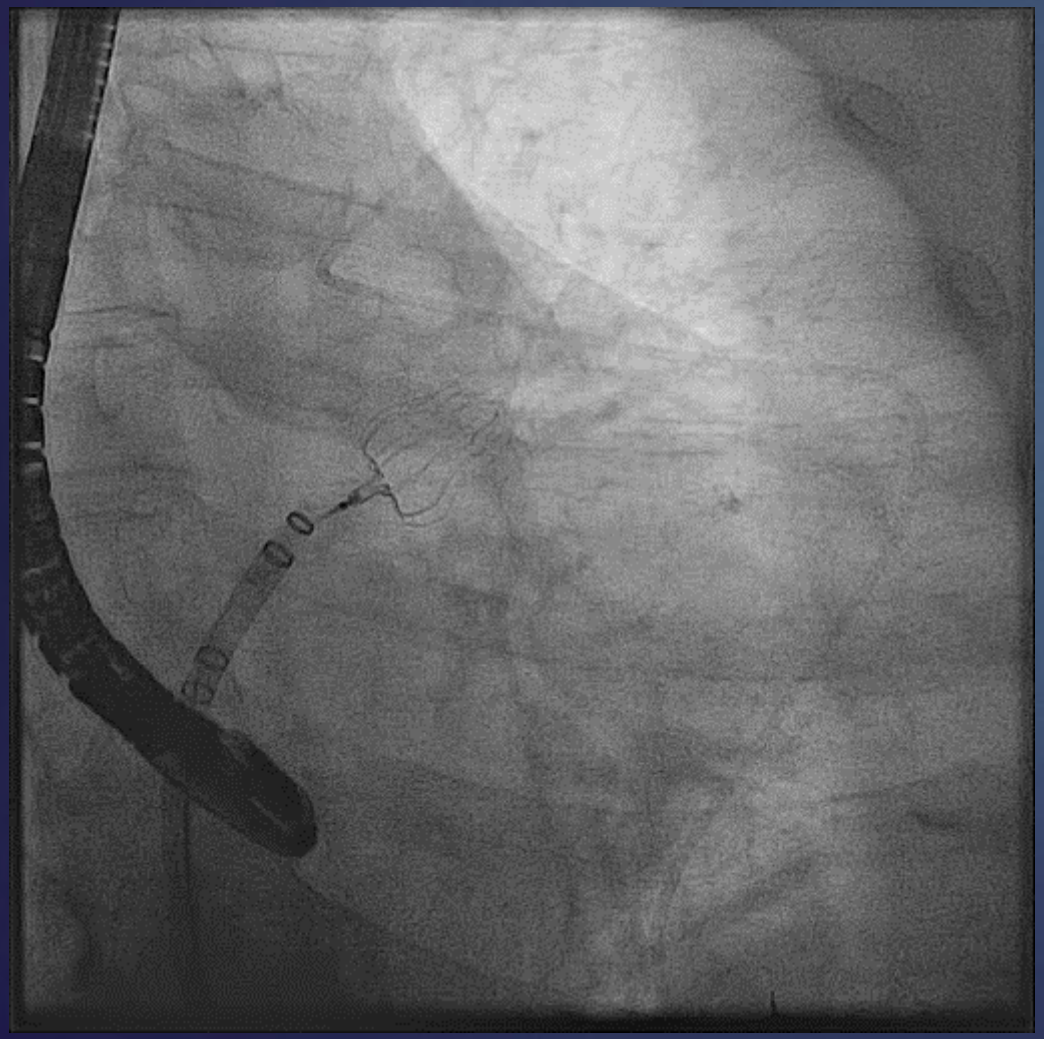


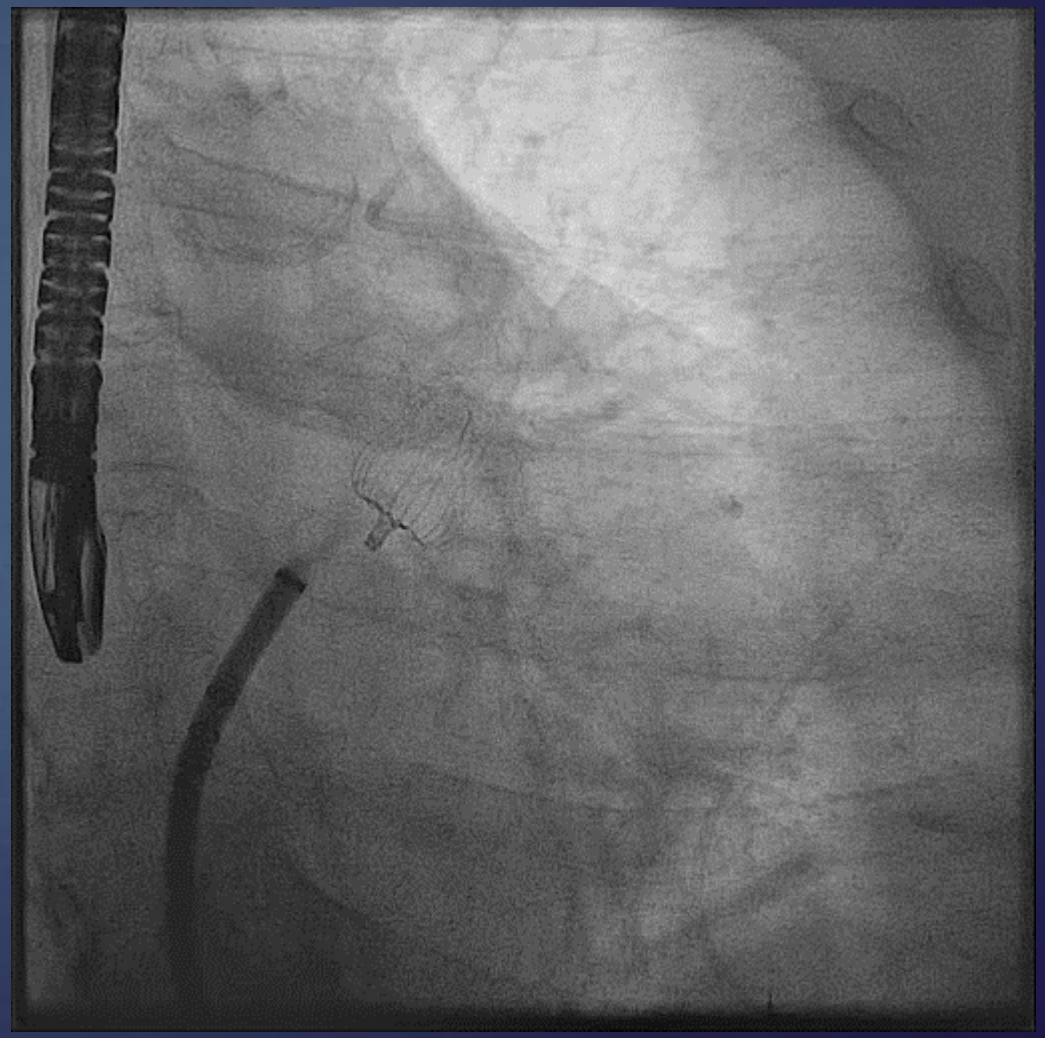
Left Atrial Appendage Closure





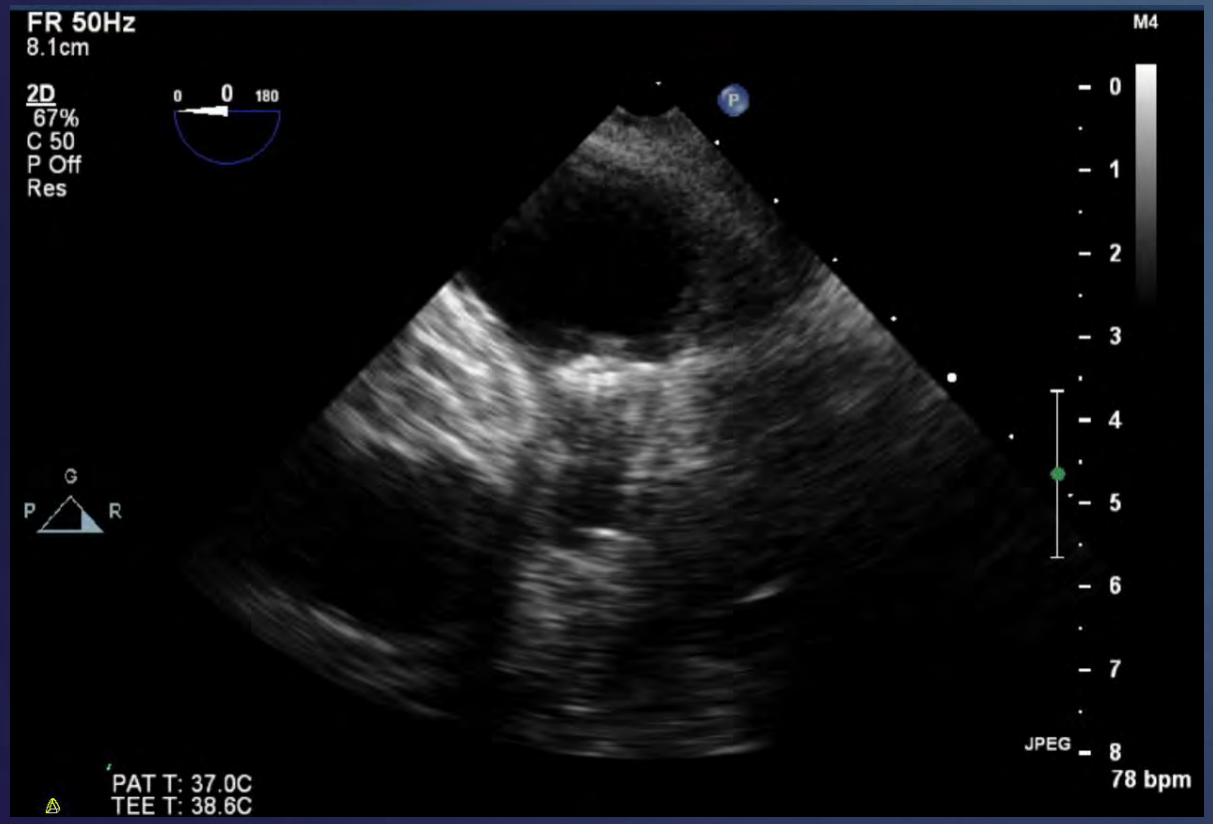
Left Atrial Appendage Closure

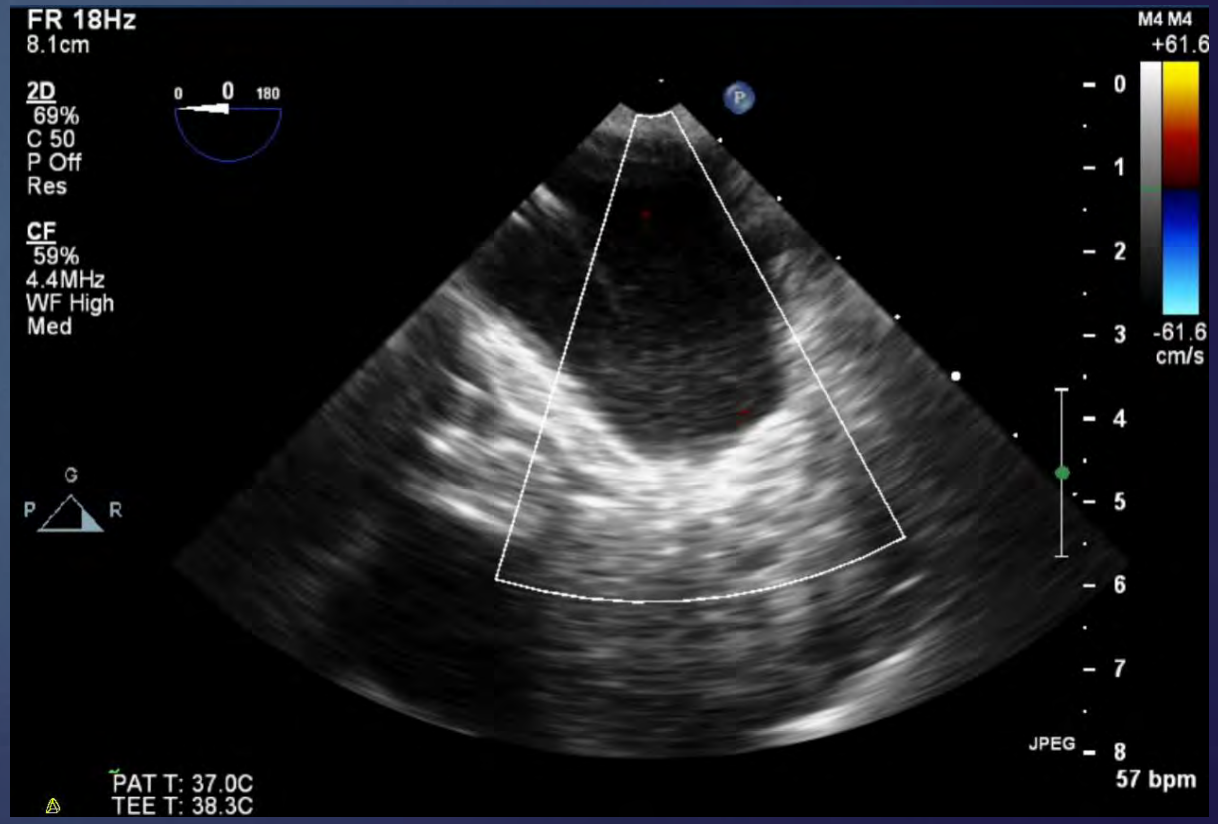




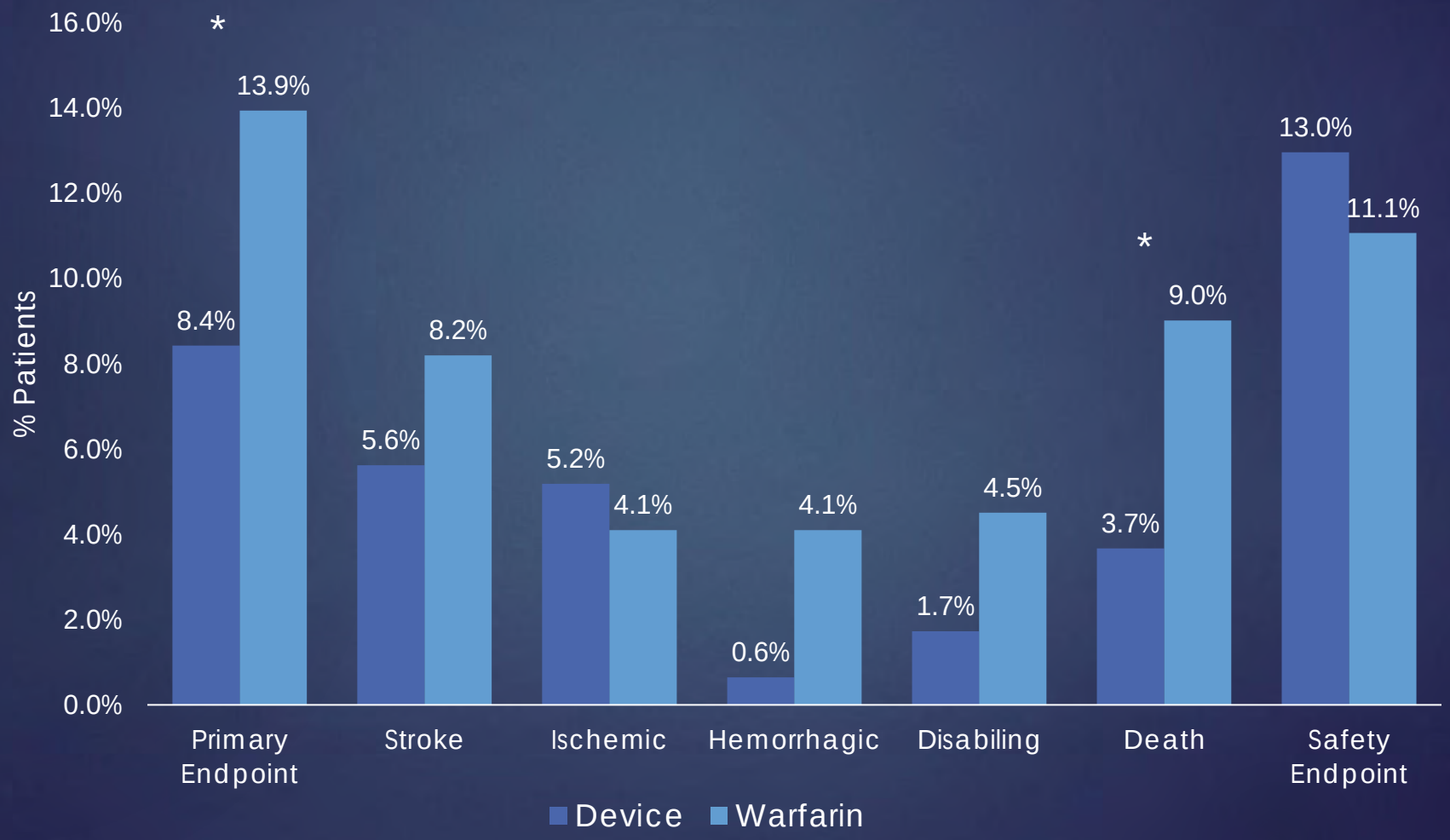
Left Atrial Appendage Closure

- PASS
  - Position
  - Anchoring
  - Size
  - Seal



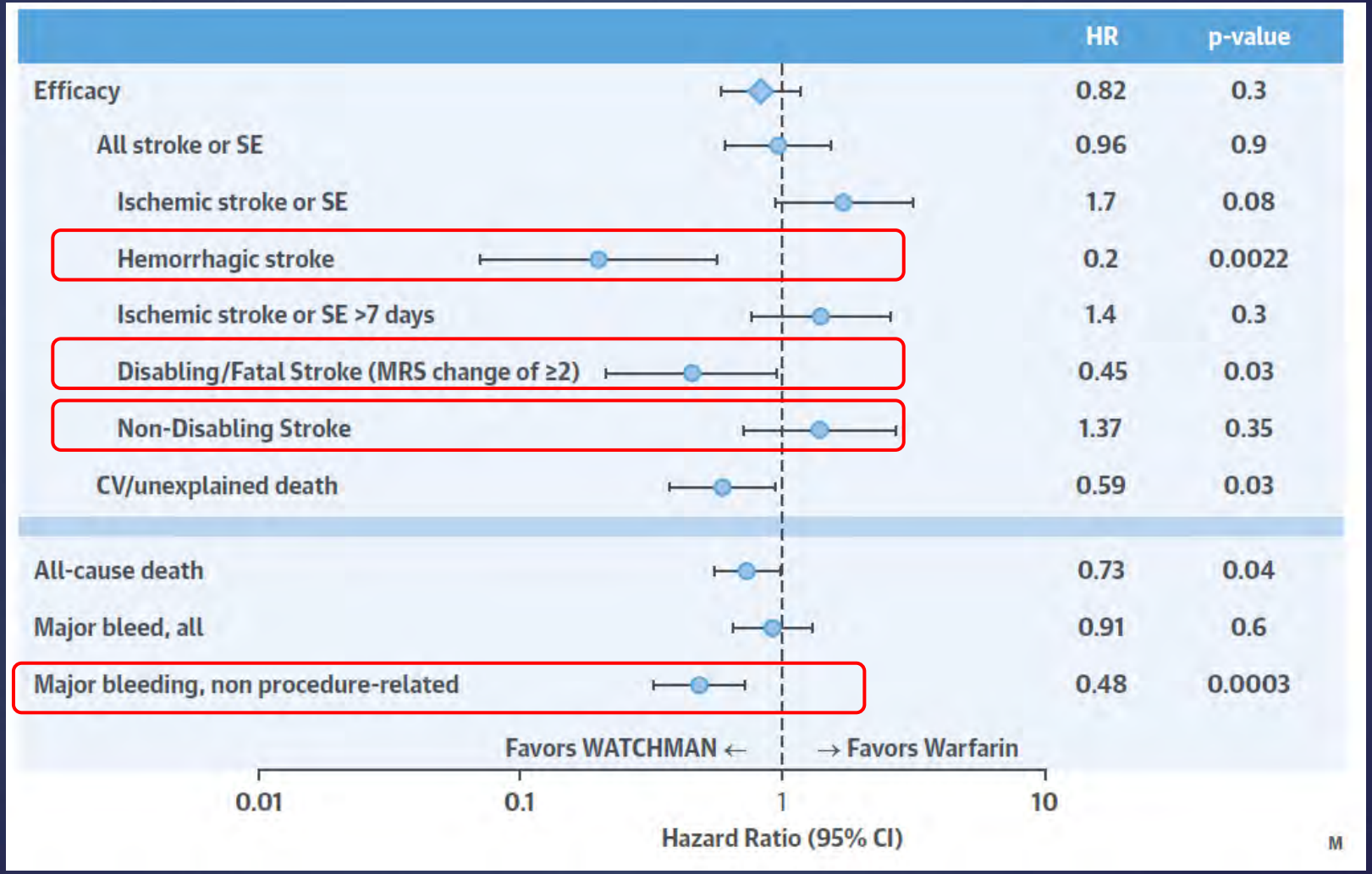


Left atrial appendage closure PROTECT AF: 4-year results



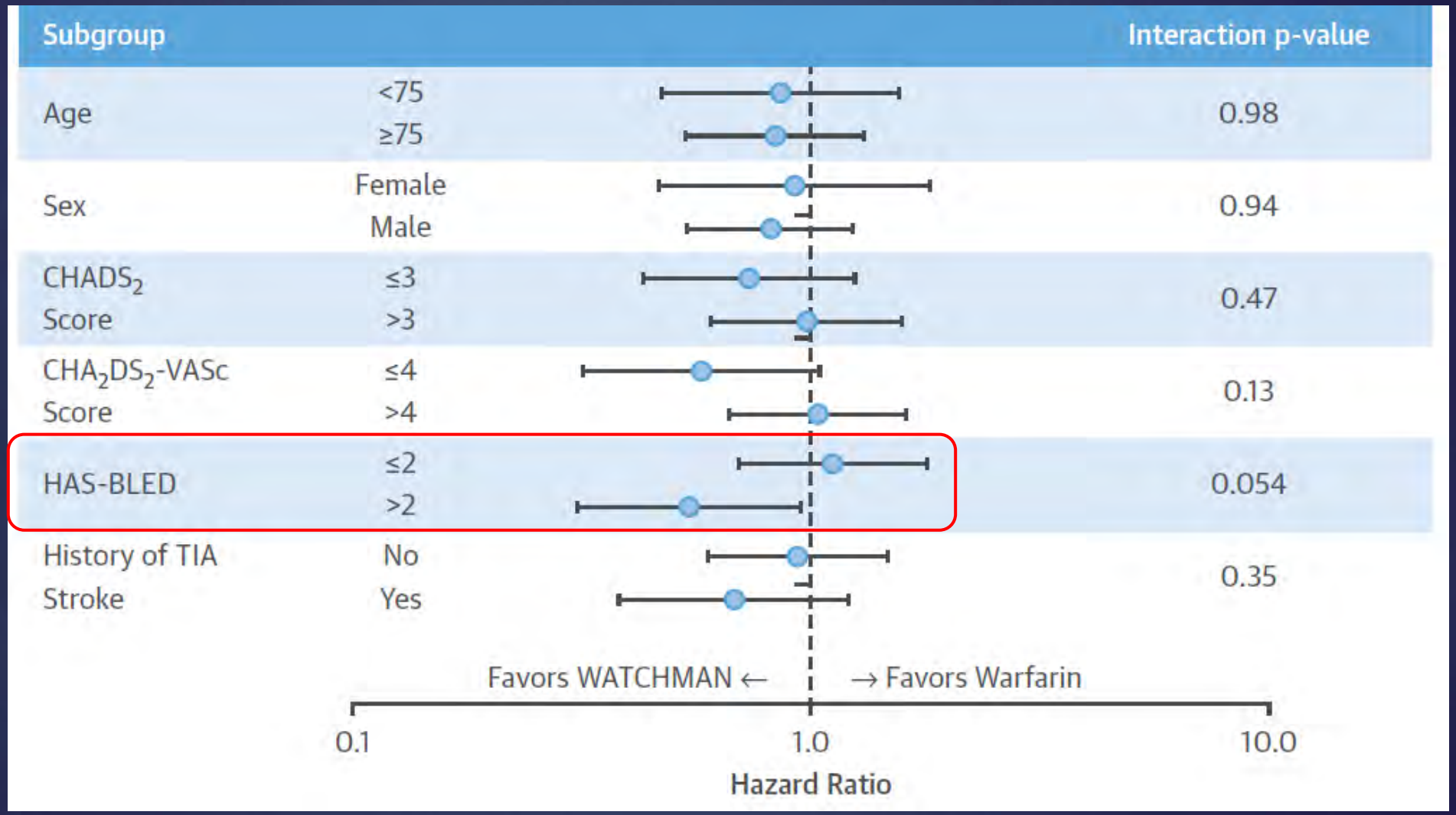
Reddy, VY et al. JAMA. 2014;312(19):1988-1998.

5 year outcomes meta-analysis PROTECT AF/PREVAIL

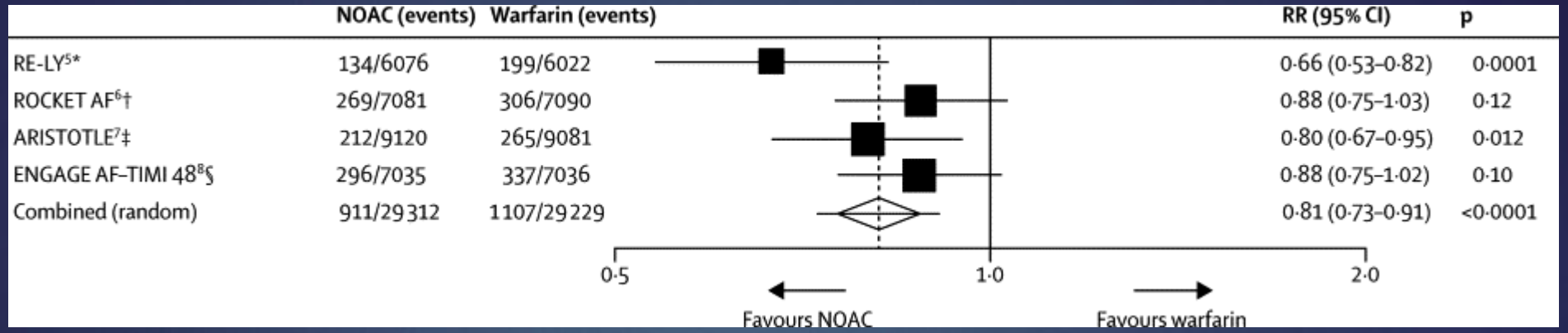


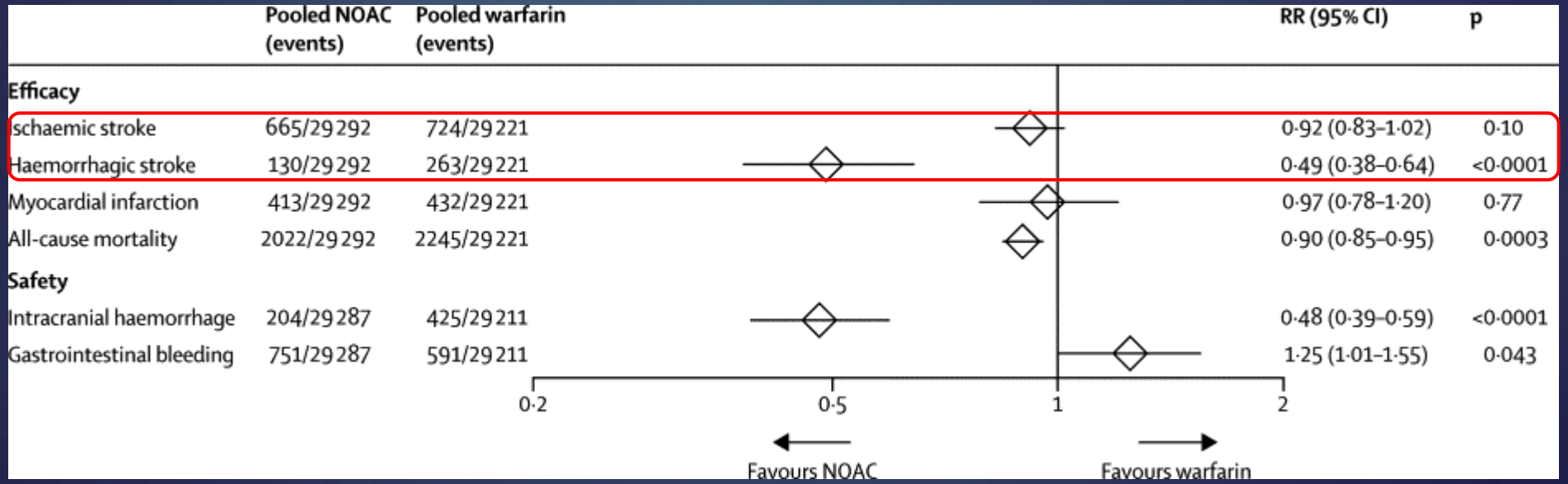
Reddy VY et al. J Am Coll Cardiol. 2017 Dec 18;70(24):2964-2975.

Patient characteristics



DOACs and Warfarin

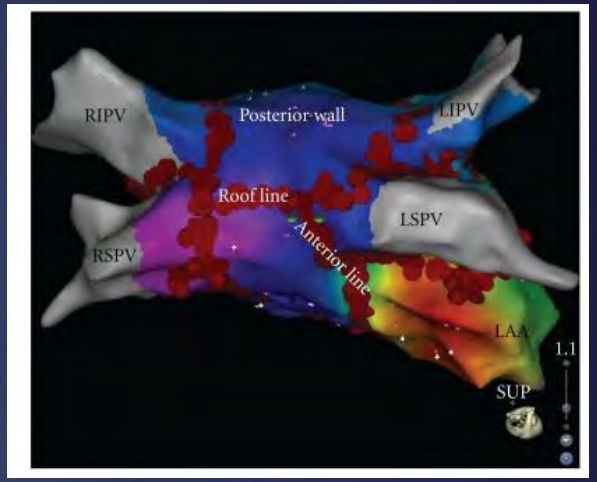


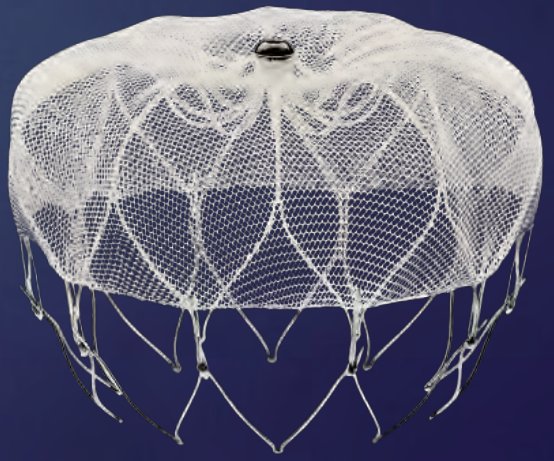


Ruff et al: Lancet 383: 955, 2014

Atrial fibrillation

- Rhythm control is a viable strategy
  - Heart failure/Low EF
  - Symptomatic
- Left atrial appendage closure
  - Not taking anticoagulant
  - Higher bleeding risk





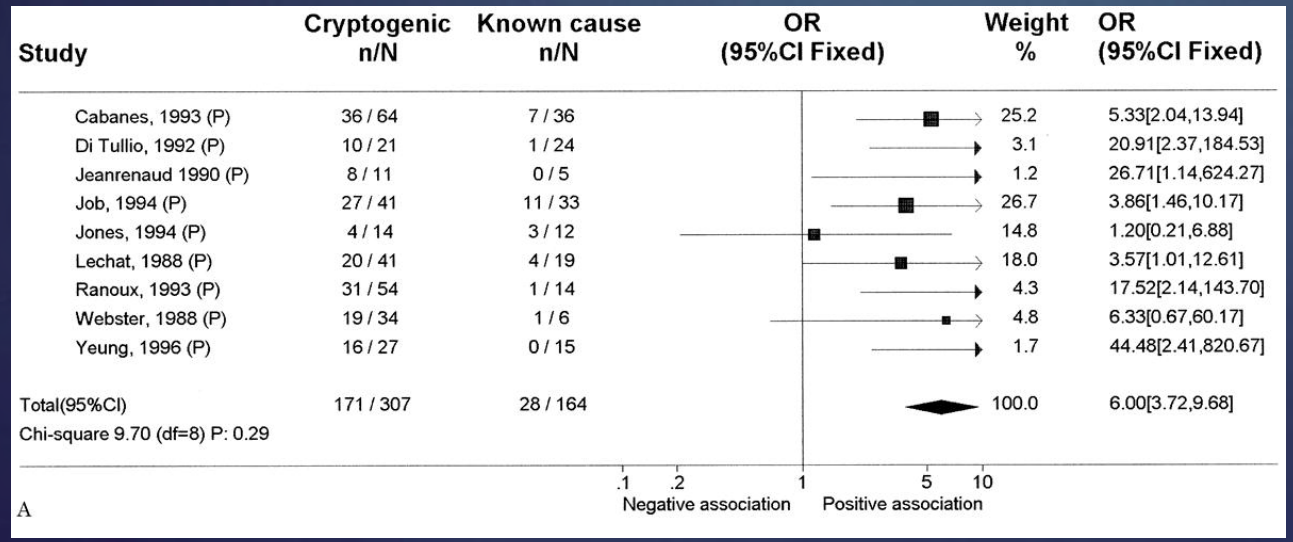
PFO Closure

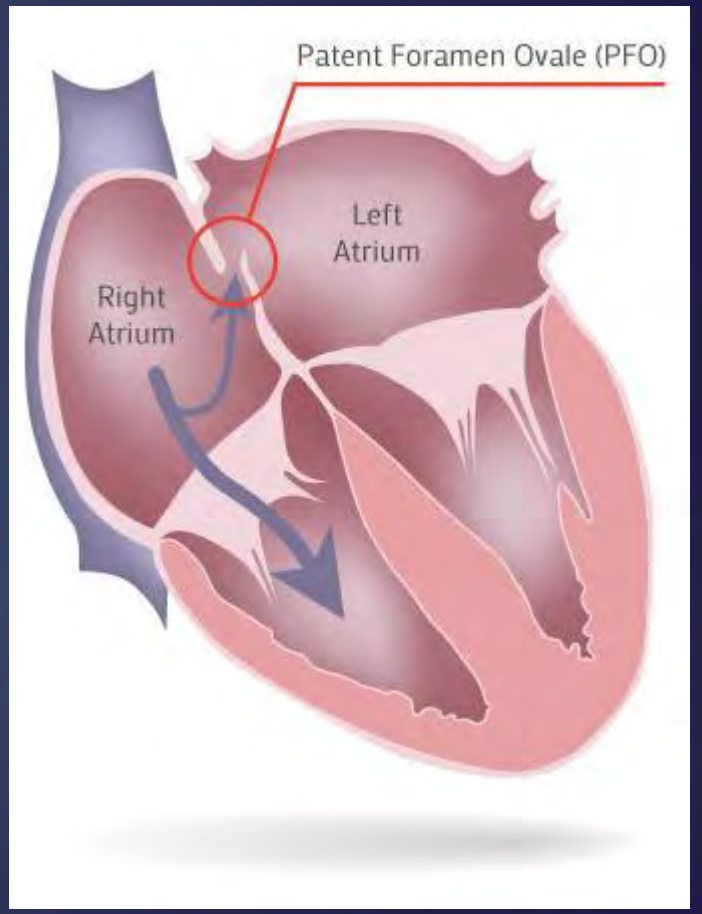
IT'S BACK!!! AND IT WORKS!

PFO and stroke association

- PFO present in about 25% of the general population
  - About 40-50% in patients with cryptogenic stroke
  - 70-80% in younger patients!
- Meta-analysis of case-control studies evaluating the association of stroke and PFO
  - 2020 control v. 2014 stroke patients
  - Any stroke OR 1.83 (1.24-2.66)

Age ≤ 55

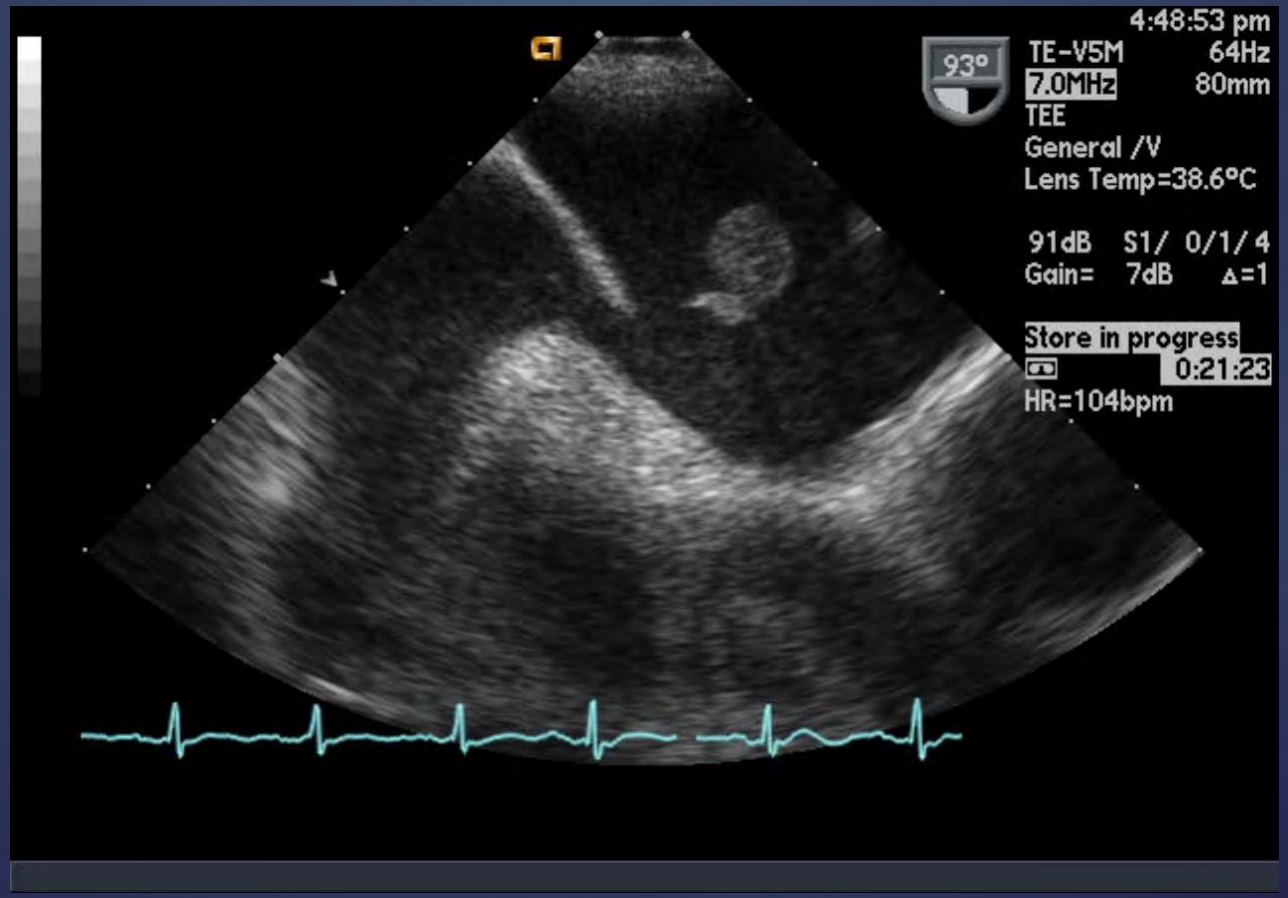




Overell JR. Neurology 2000. 55(8) 1172-1179.

Just a hypothesis?

- 60 yo man with embolic stroke



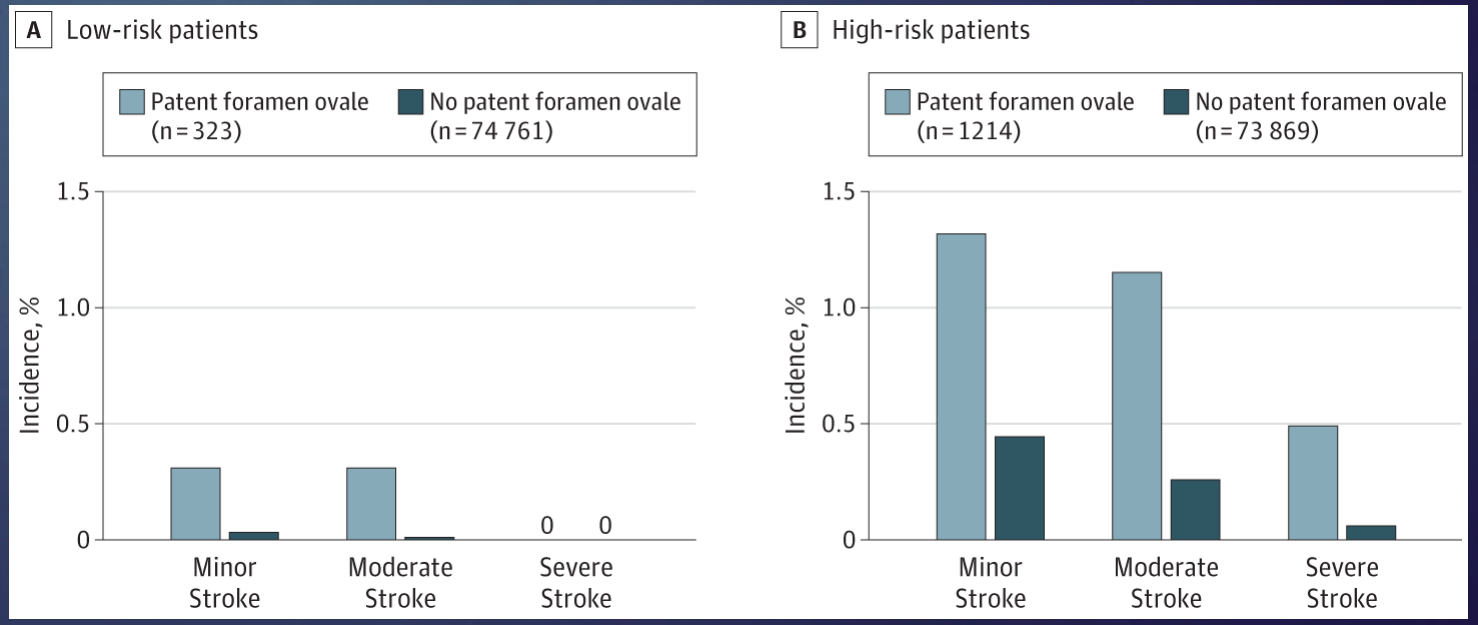
PFO and surgery

- 182,393 patients undergoing non-cardiac surgery
  - 1540 with PFOs

Strokes

- PFO 3.2%
- No-PFO 0.5% Adj OR 3.16 (CI 2.2 – 4.5)

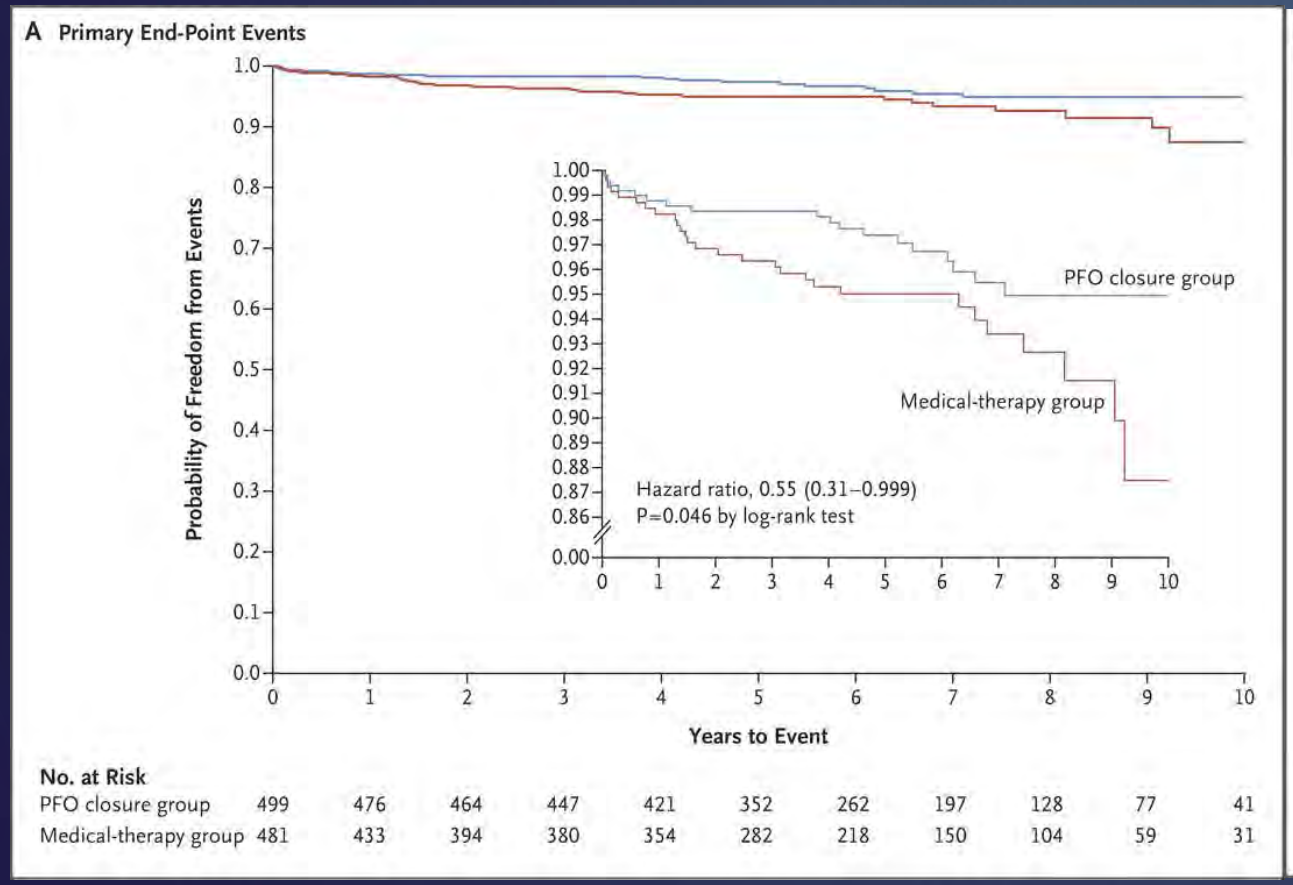
Embolic complications Adj OR 2.31 (CI 1.7 - 3.1)

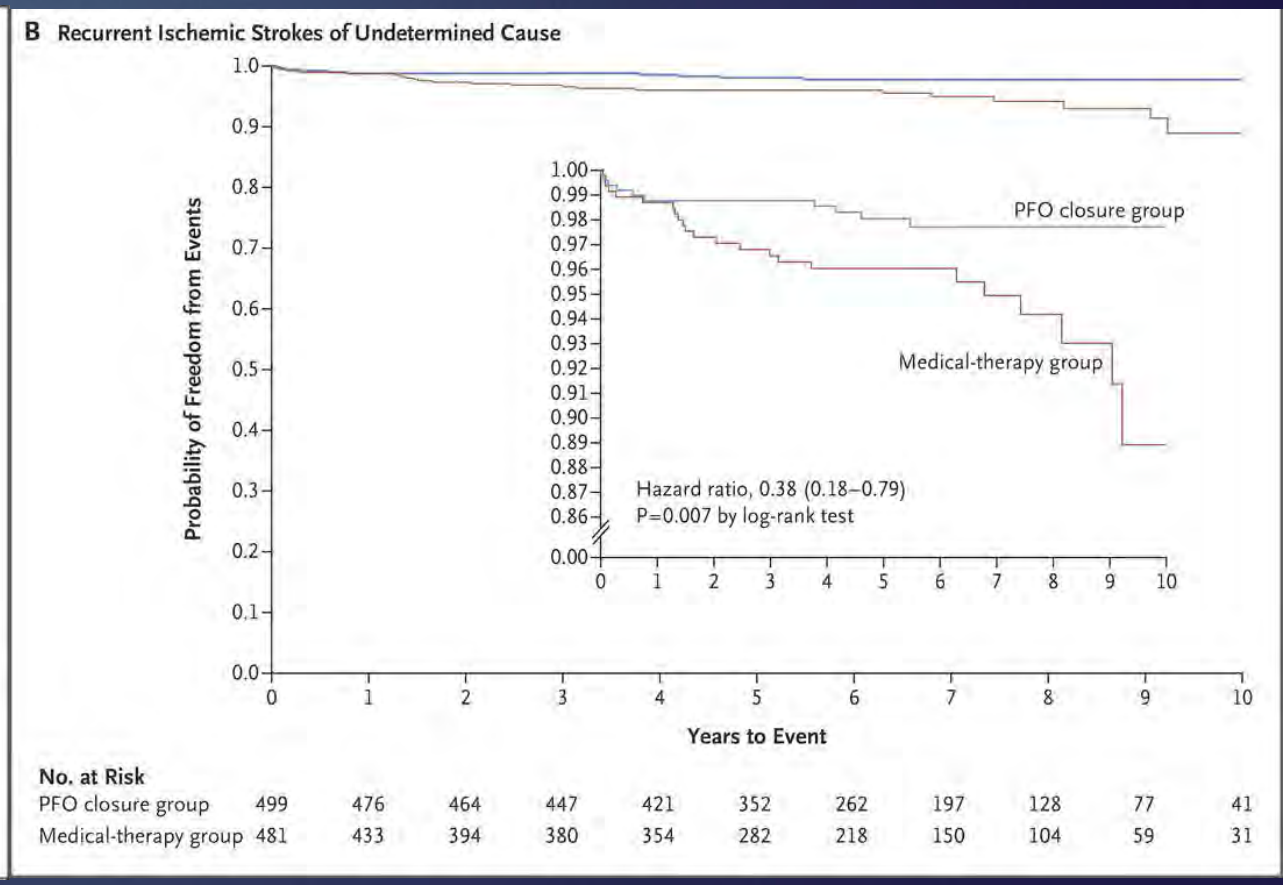


Ng PY et al. JAMA. 2018;319(5):452-462.

RESPECT trial: extended outcomes

- Strokes 3.6% v 5.8% (p 0.046)

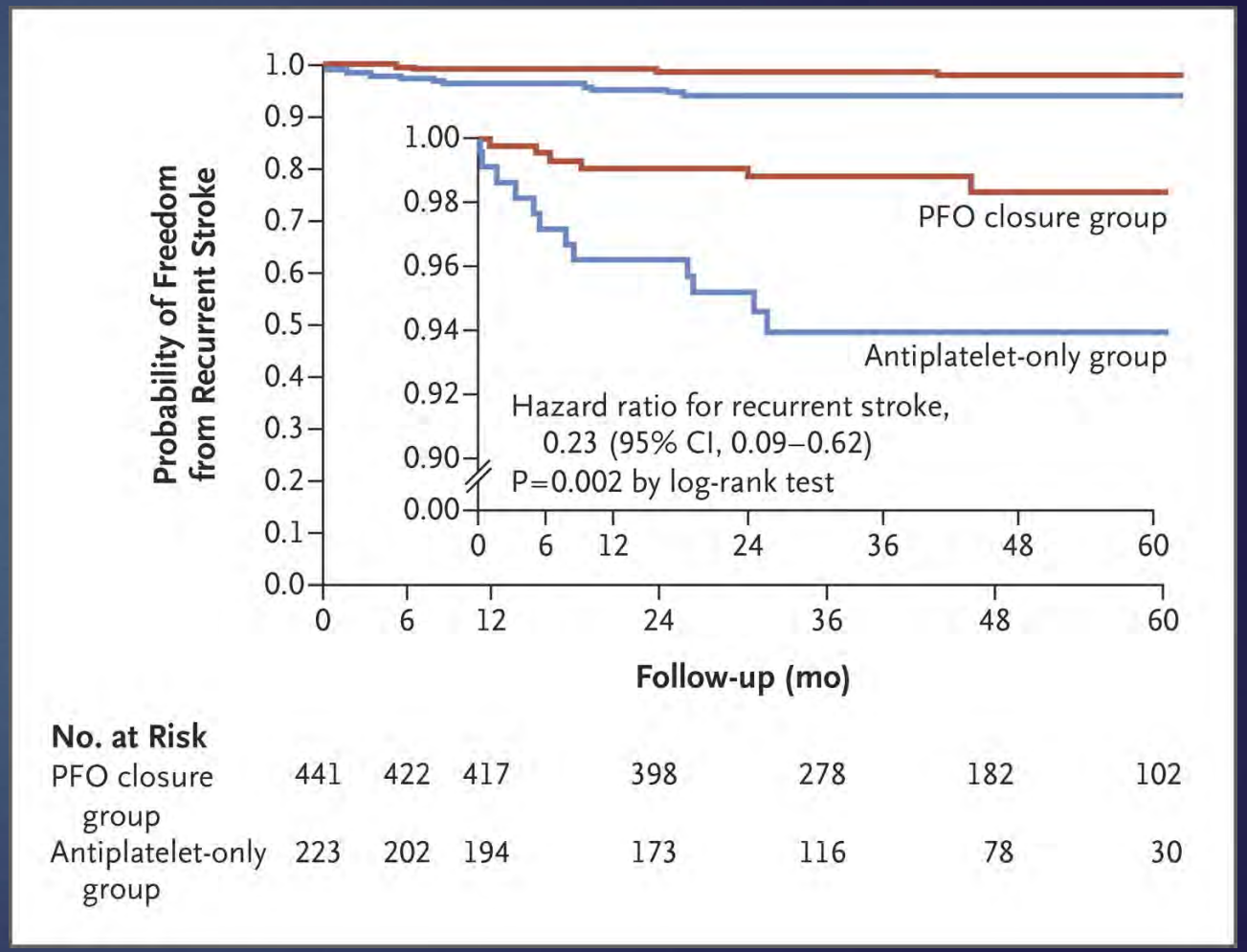




Saver JL. NEJM. 2017; 377:1022-1032

REDUCE

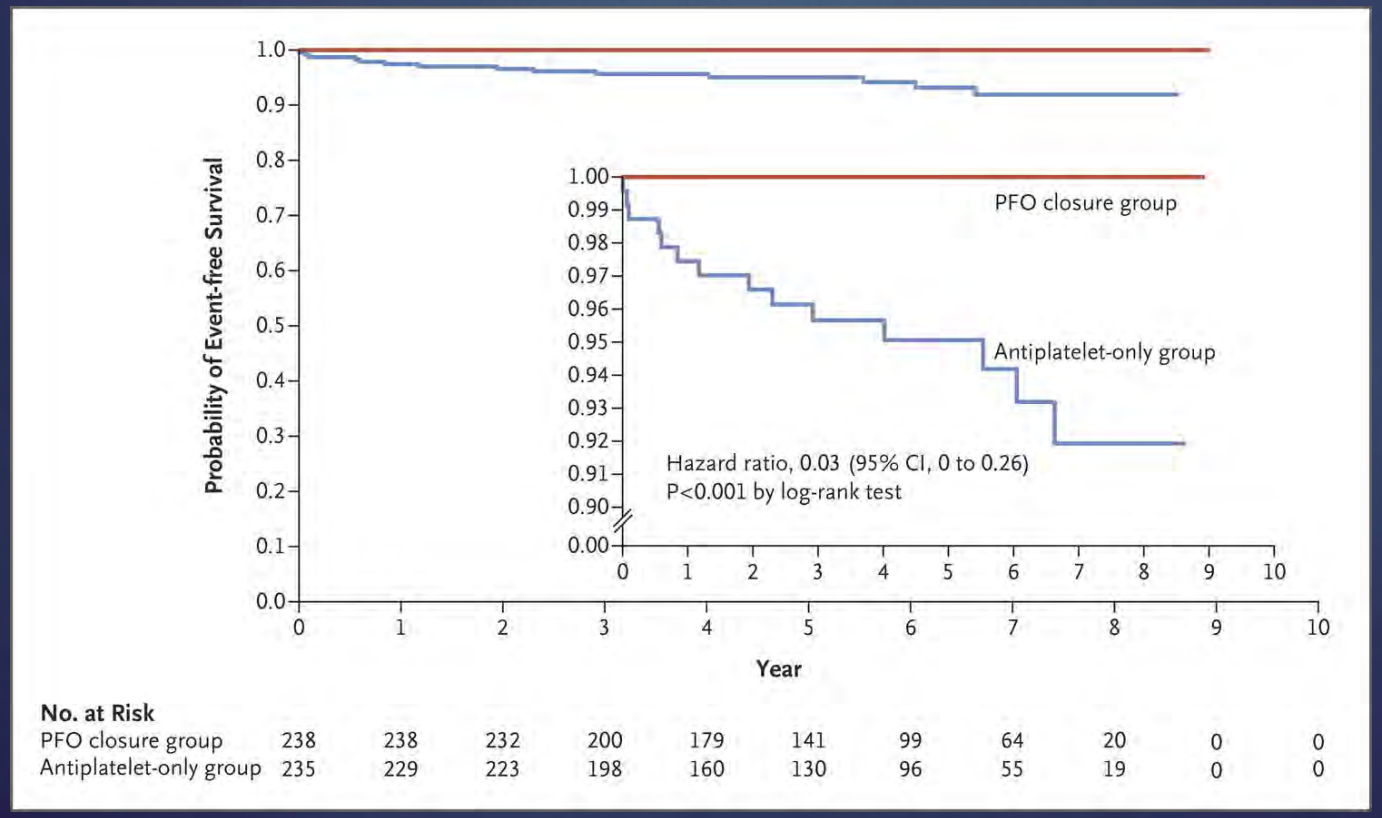
- 664 patients with cryptogenic stroke and PFO
- Randomized to 2:1 to Helex/Cardioform v. antiplatelet tx



Sondergaard L. NEJM. 377:1033-1042.

CLOSE trial

- 663 pts with cryptogenic stroke and PFO with ASA or large shunt
- PFO closure (open label) v. ASA v. anticoagulation
- Stroke 0% v. 6.2% v. 1.4%

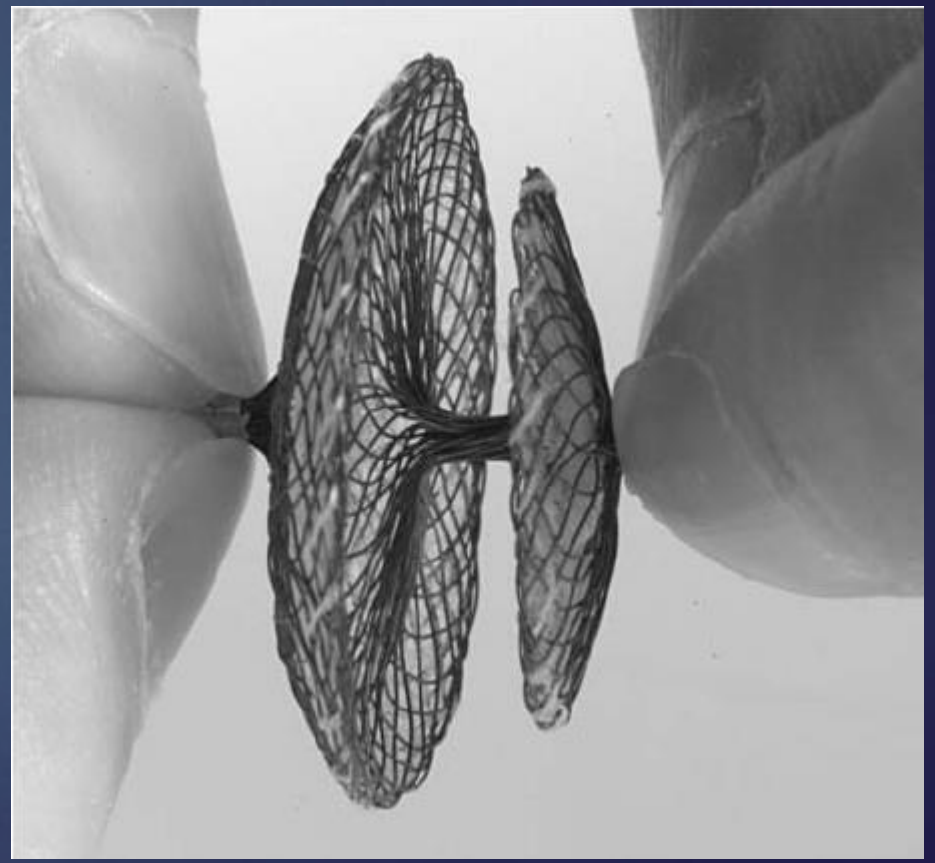


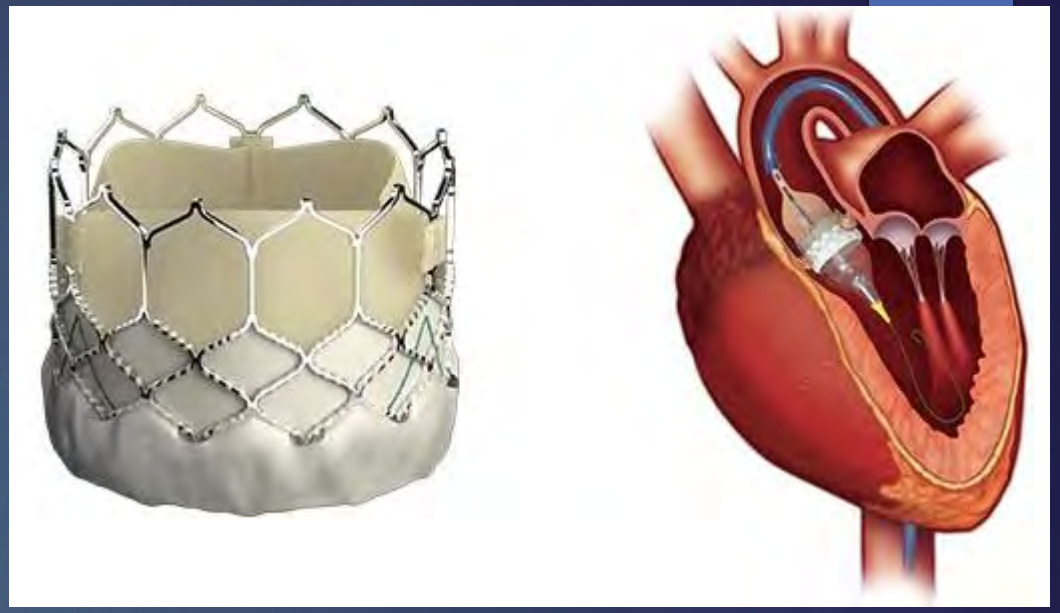
Mas JL. NEJM. 377:1011-1021.

PFO Closure

- Cryptogenic stroke and < 60
- Minimal risk factors

Just close it



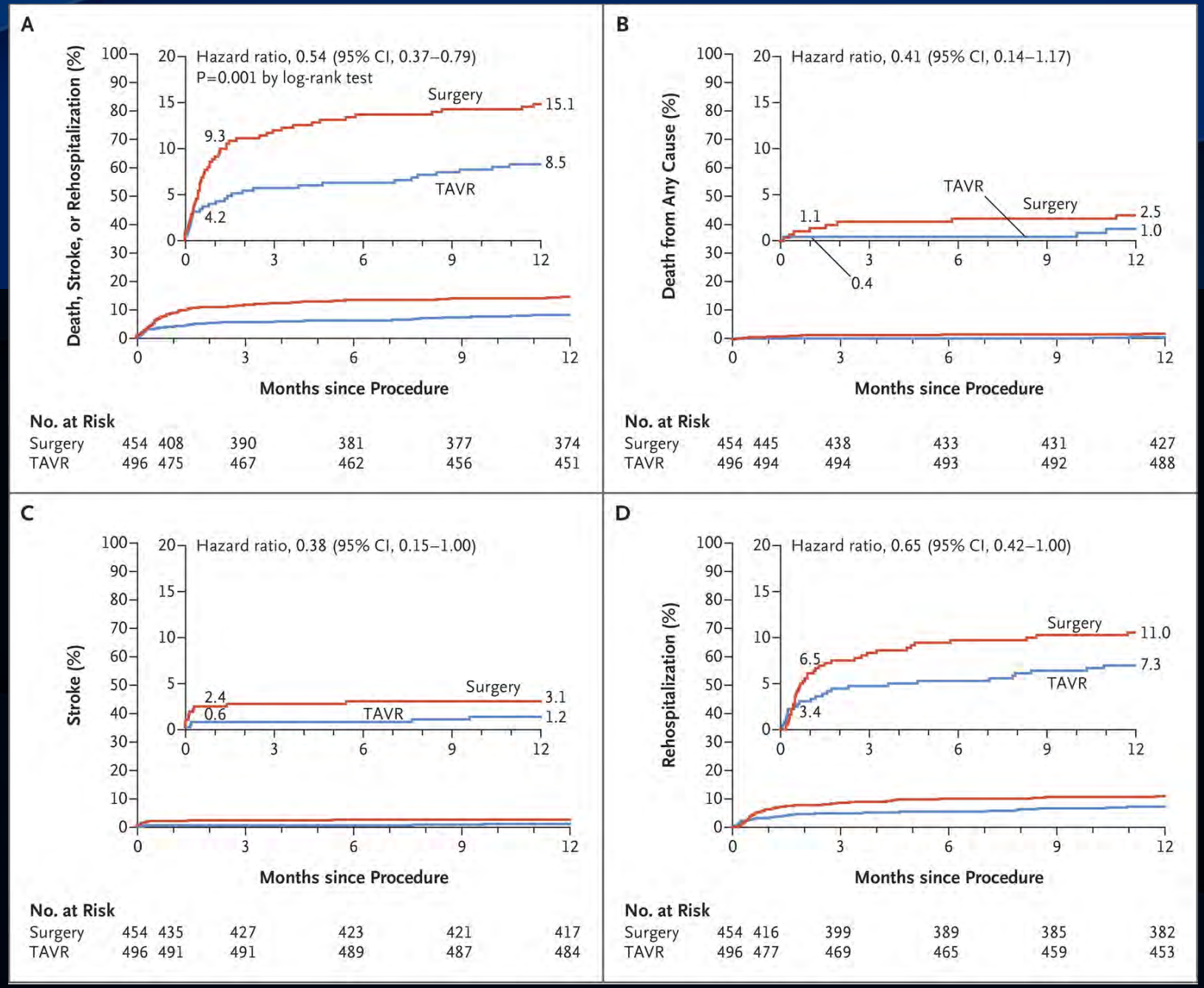


VALVE THERAPIES

TAVR ON STEROIDS….AND NOW MITRAL VALVES TOO?

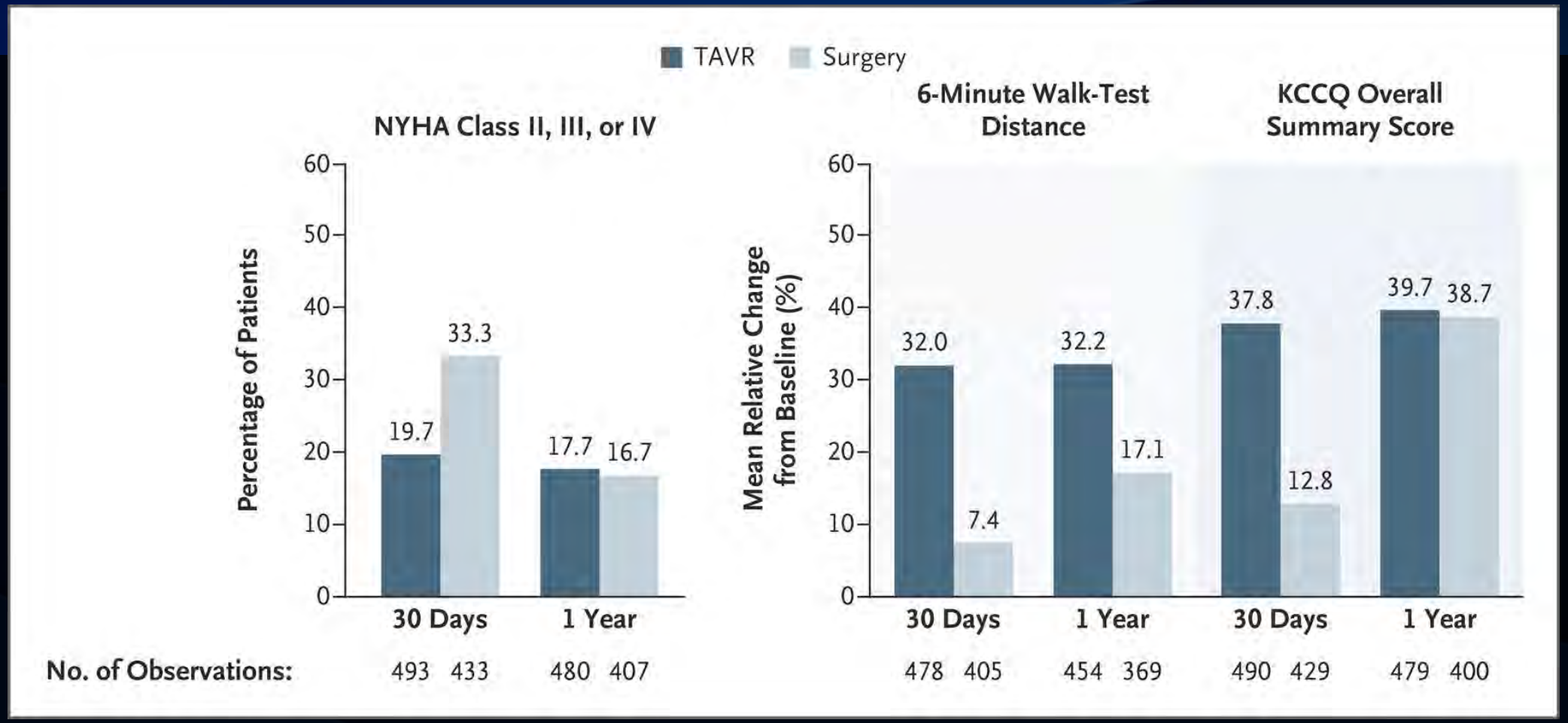
PARTNER 3

- 1000 Low risk patients
- TAVR v. SAVR



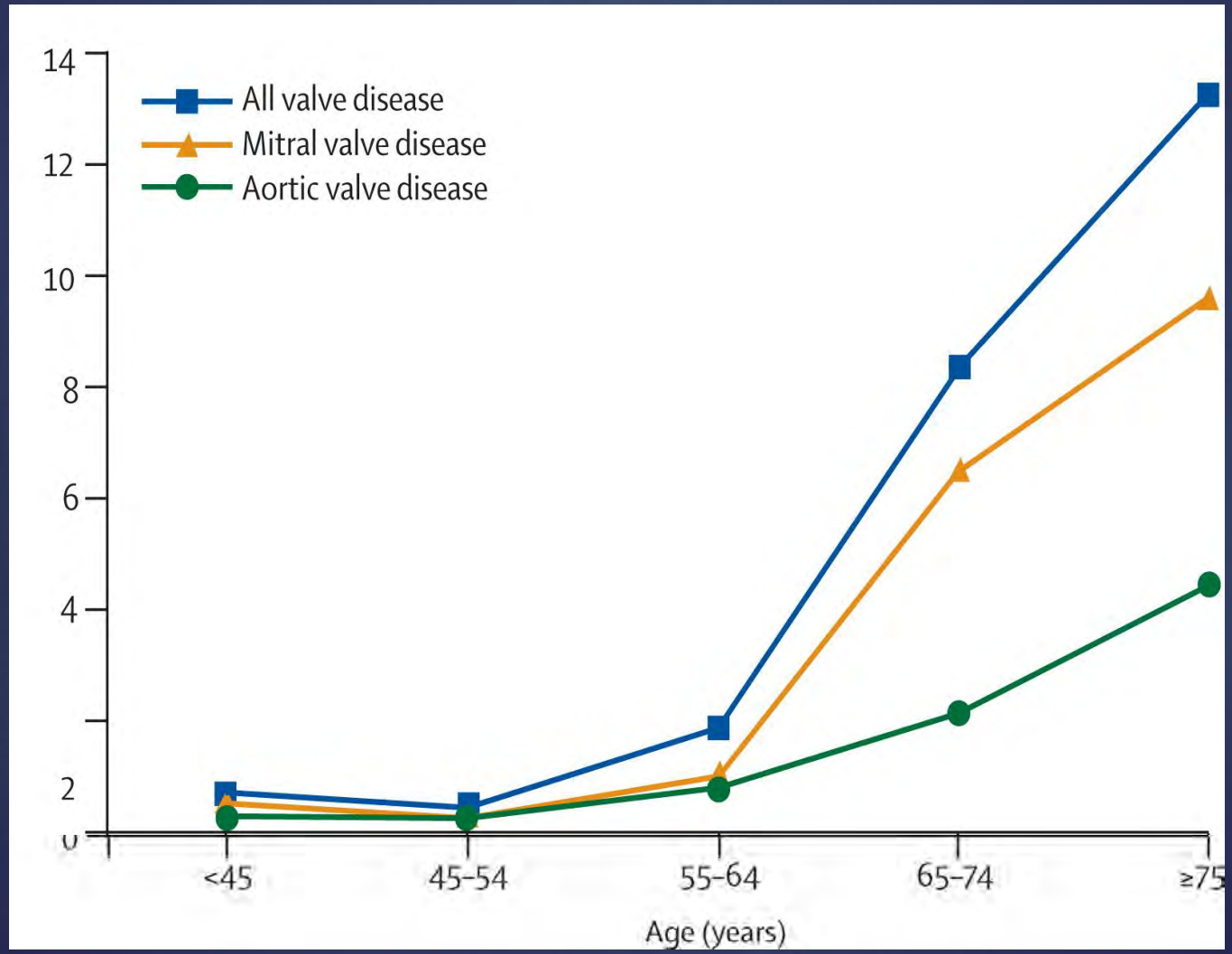
Mack MJ. NEJM. 2019

PARTNER 3



Mack MJ. NEJM. 2019

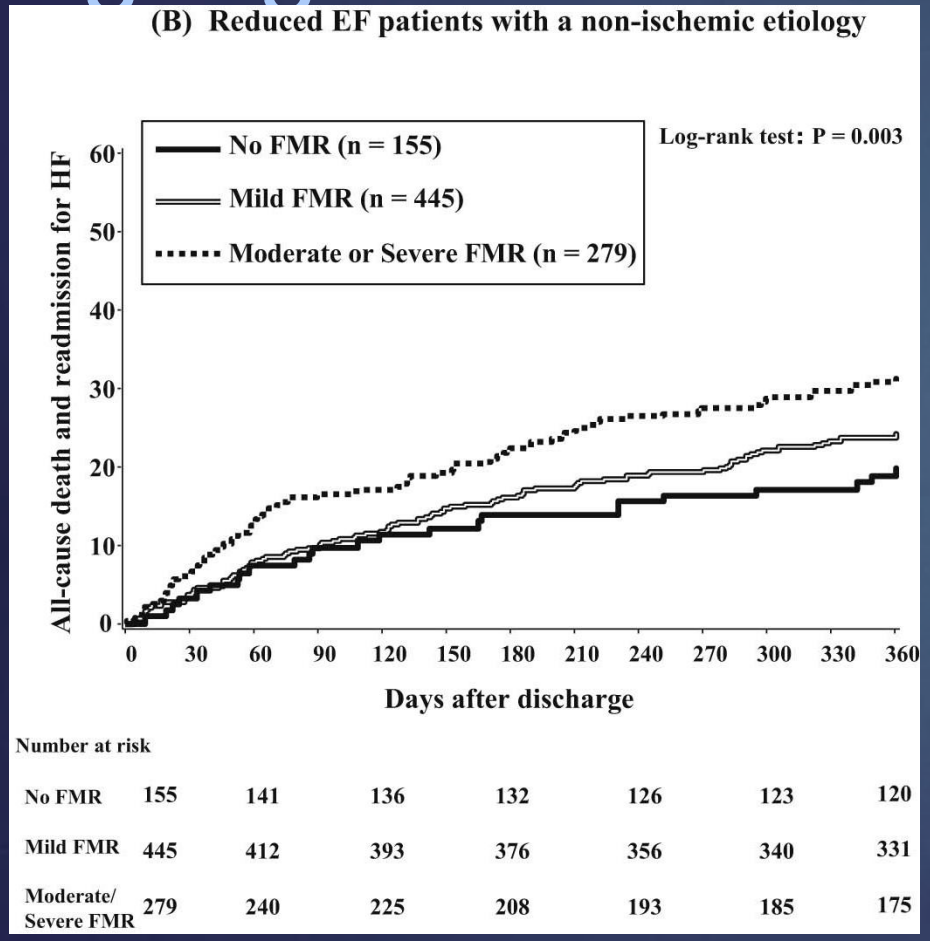
Epidemiology Valve Disease

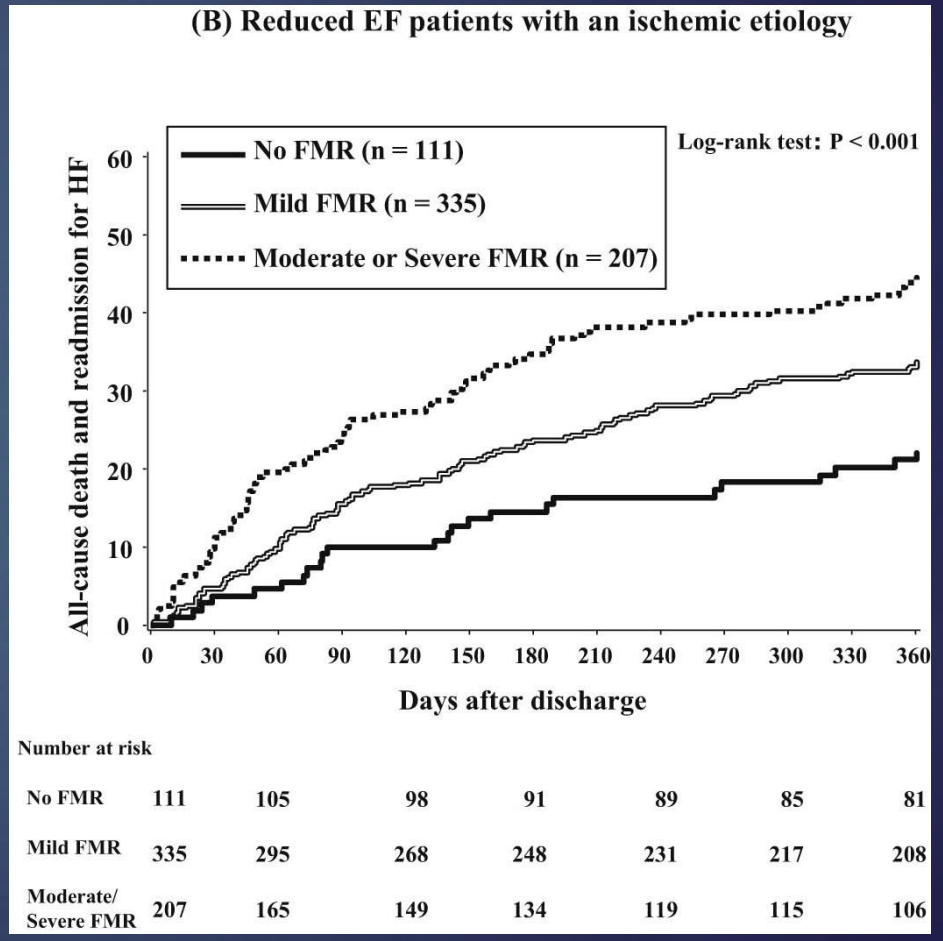


- 1.7% of US population

Nkomo VT. Et al. Lancet. 2006 Sep 16;368(9540):1005-11.

Epidemiology of Secondary Mitral Regurgitation





Kajimoto K. Ischemic or Nonischemic Functional Mitral Regurgitation and Outcomes in Patients With Acute Decompensated Heart Failure With Preserved or Reduced Ejection Fraction. Am J Cardiol. 2017.

Moderate-severe valve regurgitation (US)

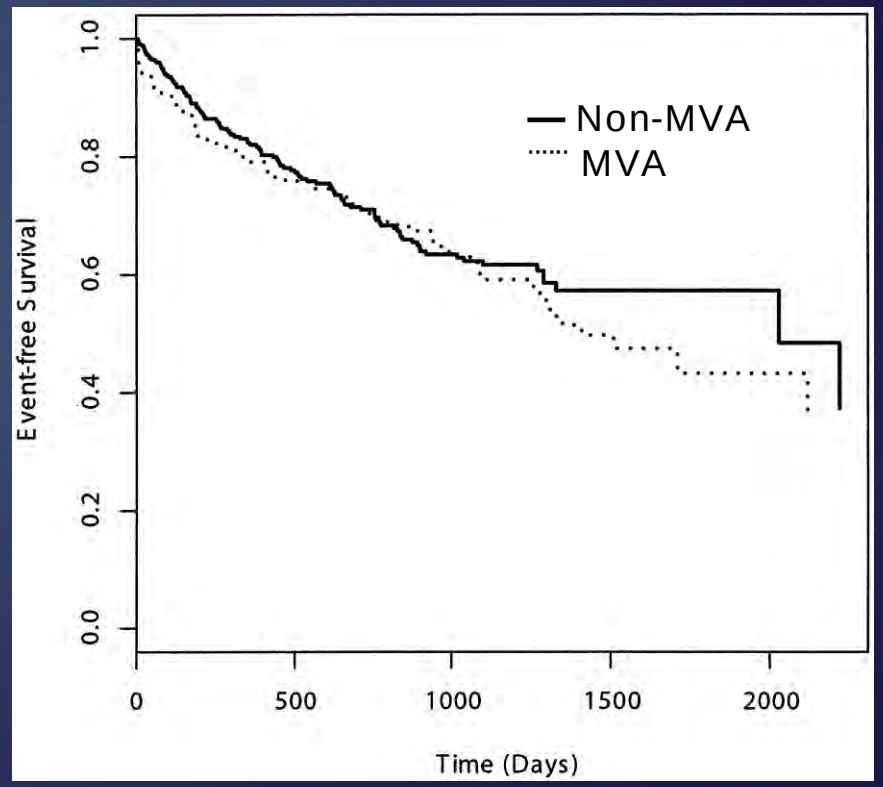
Stuge O. JTCVS. 2006.

Surgery for secondary MR

- Retrospective propensity matched comparison
- Patients with severe MR and LVEF <30%
- Those undergoing MV compared to those medically managed

AHA/ACC 2013 Guidelines

- Transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of <u>uncertain benefit</u> and should only be considered after careful candidate selection and with a background of GDMT (IIB)



Wu AH et al. J Am Coll Cardiol. 2005 Feb 1;45(3):381-7.

Secondary Mitral Regurgitation

LV dysfunction

Leaflet tethering

Papillary dysfunction

Annular dilation

Mitral regurgitation

Mortality

Primary Mitral Regurgitation

Secondary Mitral Regurgitation

LV dysfunction

Leaflet tethering

Papillary dysfunction

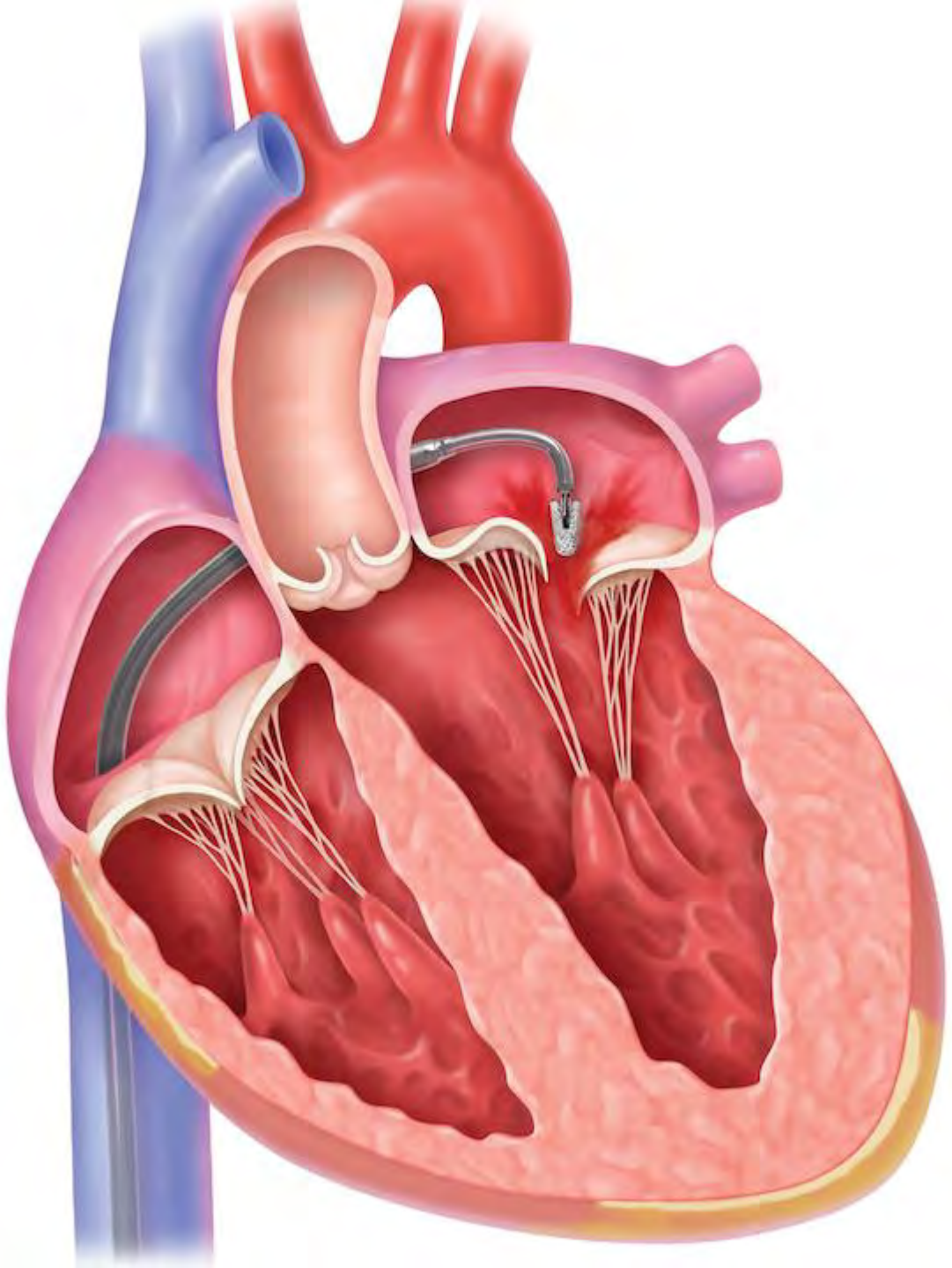
Annular dilation

Mitral regurgitation

LV Volume loading

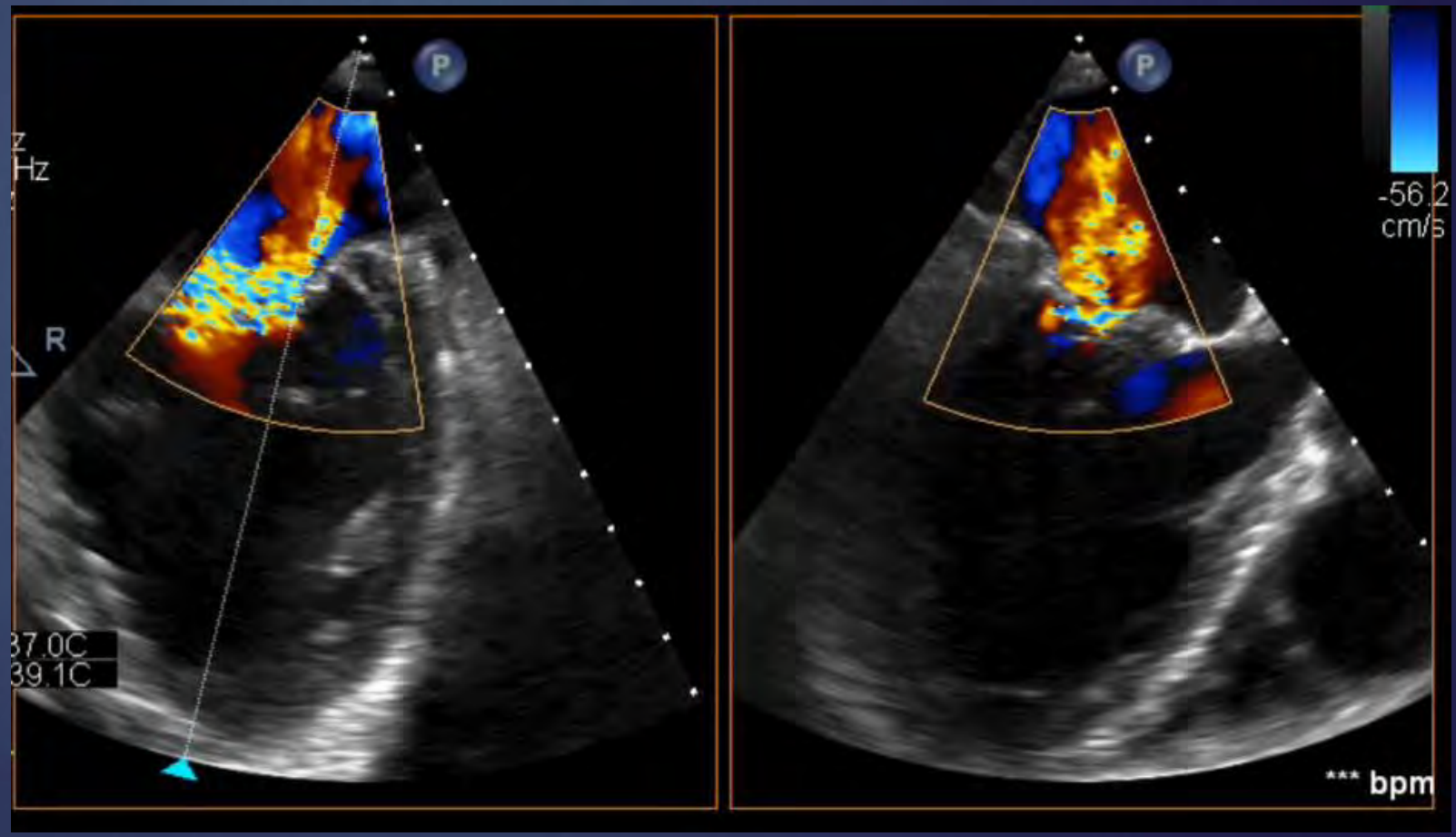
LV Dilation

MitraClip

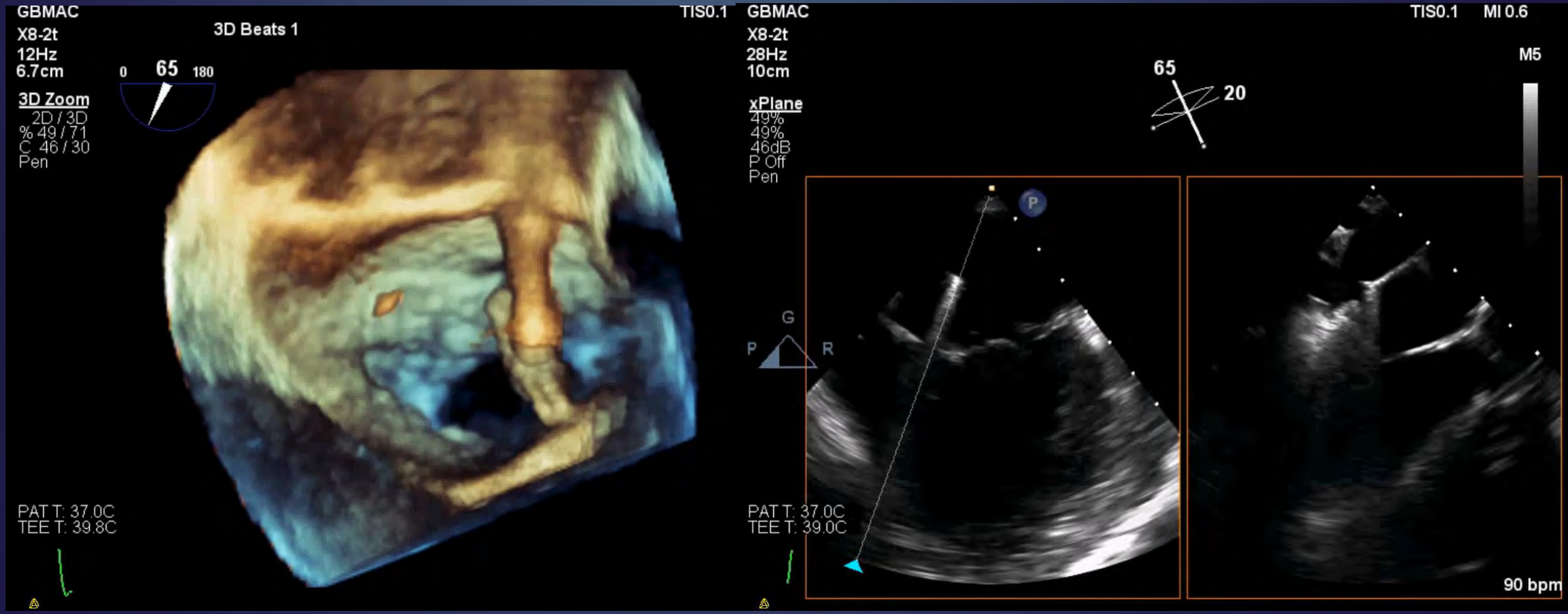


Heart failure and mitral regurgitation

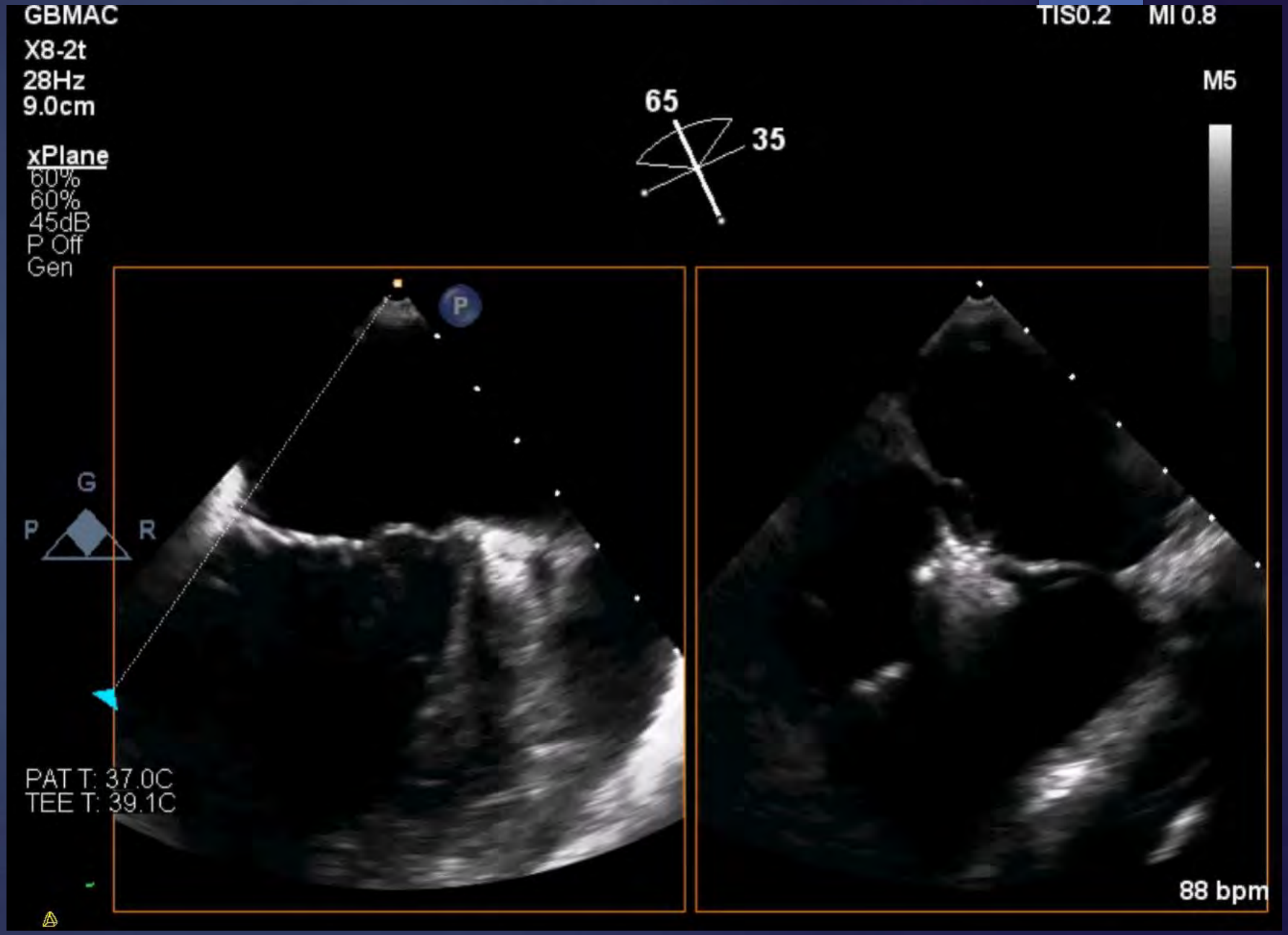
- 76 yo woman
- EF 20%-Biv pacer
  - LVEDV 148 mL (78)
- Moderate severe MR
  - EROA 0.35 cm2
- Multiple HF hospitalizations



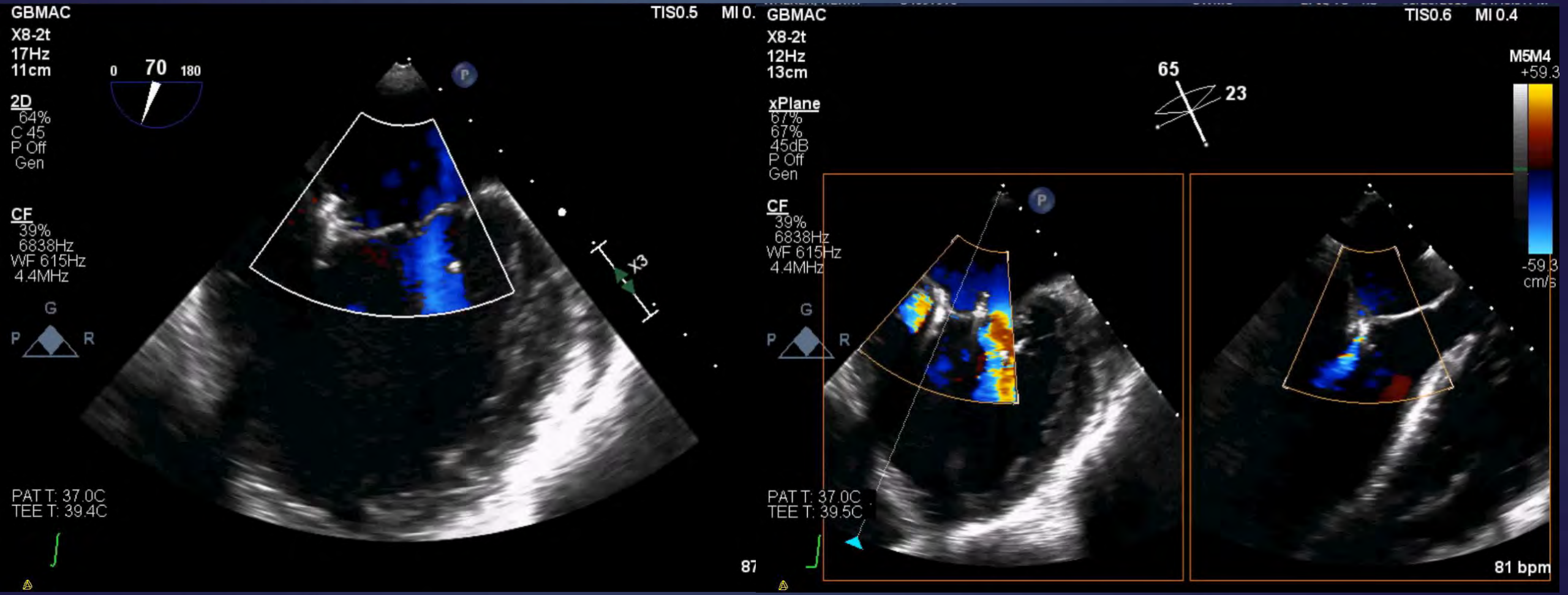
Clip rotation and approach



Grasping

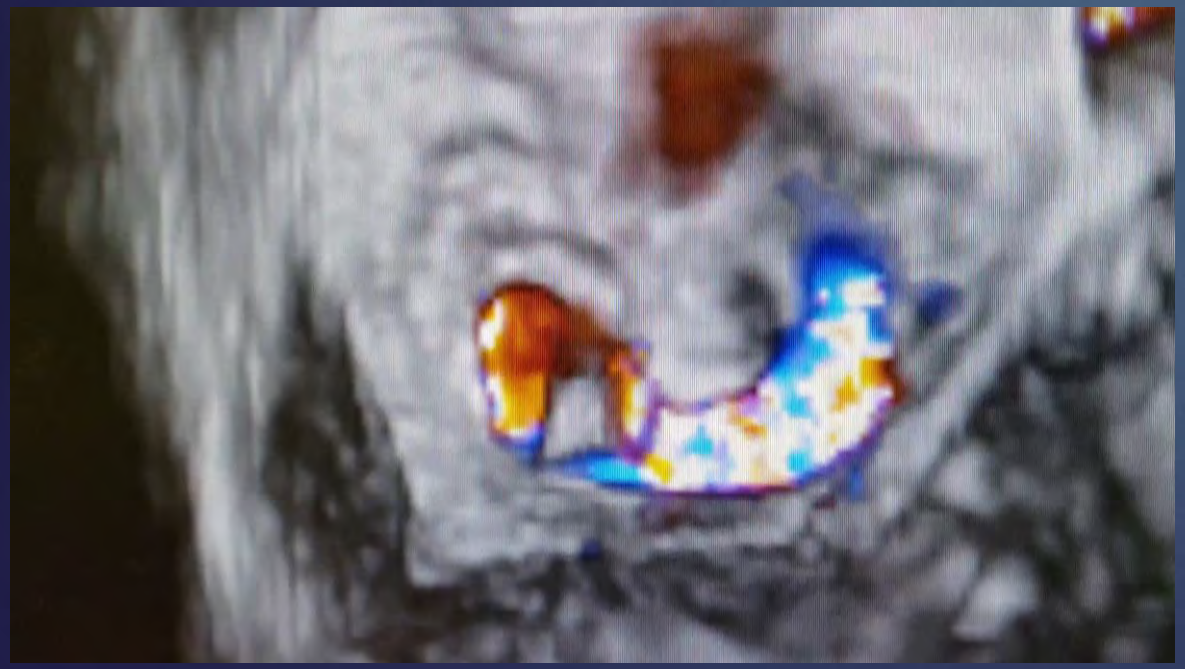

GBMAC
X8-2t
28Hz
9.0cm
xPlane
60%
60%
45dB
P Off
Gen
TIS0.2
MI 0.8
M5
65
35
P
G
P
R
PAT T: 37.0C
TEE T: 39.1C
88 bpm

Second clip laterally

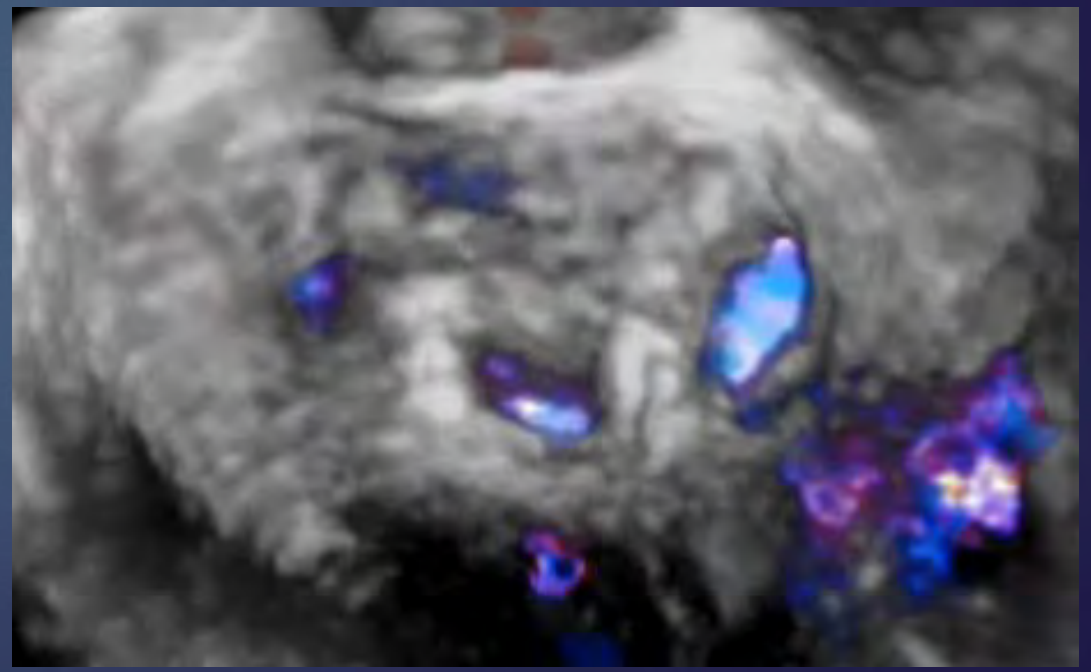


Heart failure and mitral regurgitation

- Remains out of the hospital
- TTE 2 months post-MitraClip: Mild MR
- EF increased to 29%
- LVEDV 148 → 126 mL



Baseline



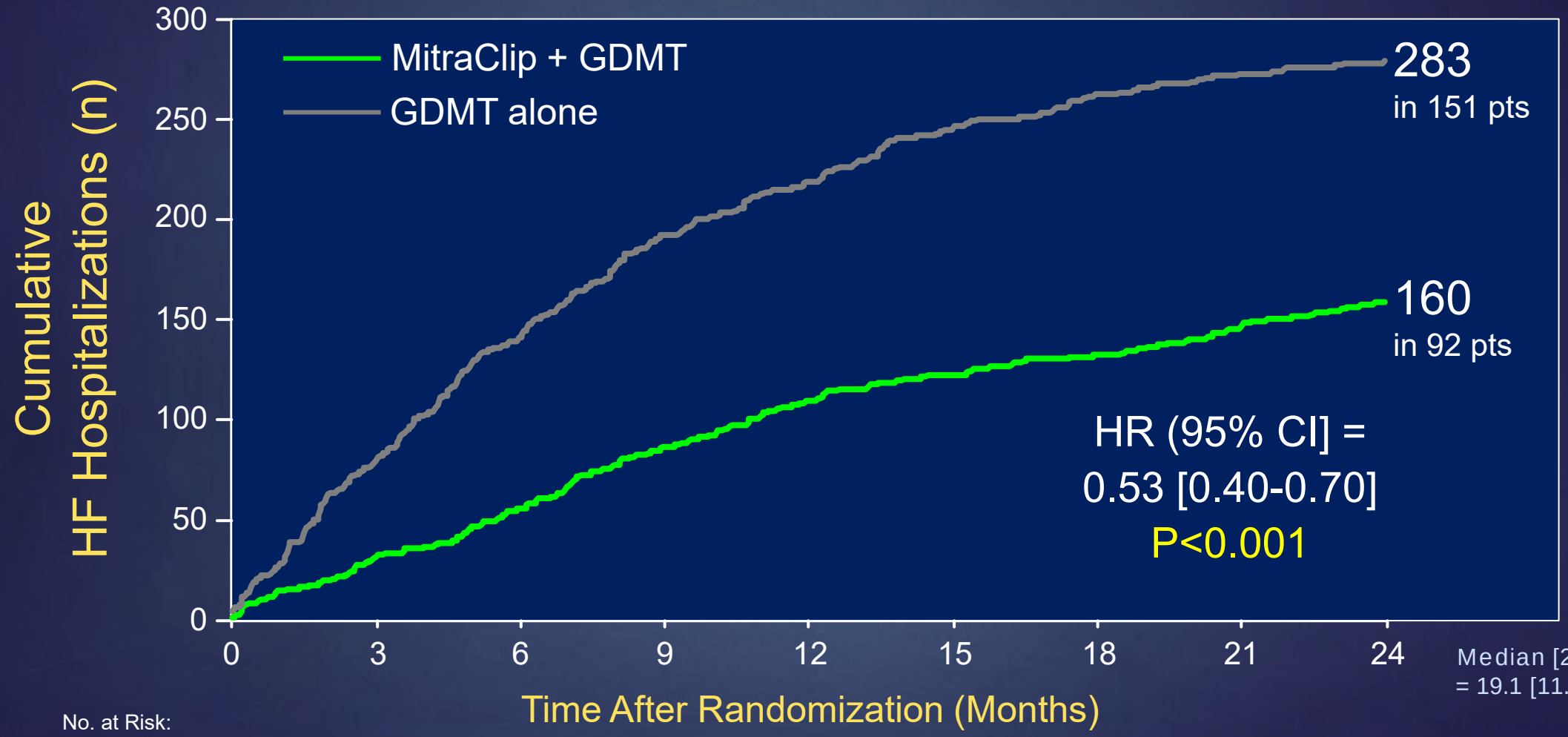
Post-MitraClip

COAPT

- 665 patients NYHA 2-4
- EF 20-50%
- Moderate to severe mitral regurgitation
- Medically optimized

Stone GW. NEJM. 2018; 379:2307-2318

Hospitalizations over 2 years



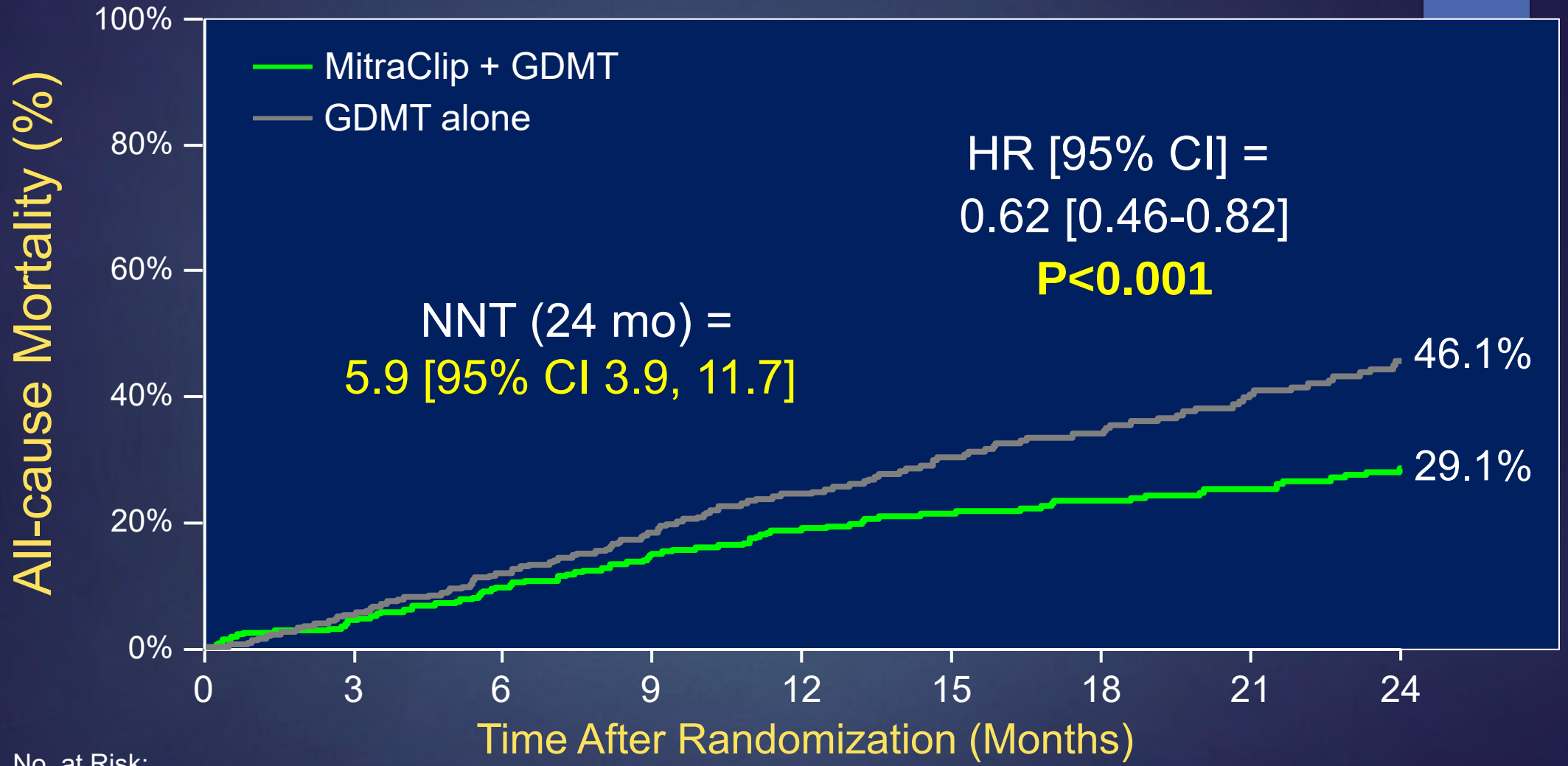
Median [25%, 75%] FU
= 19.1 [11.9, 24.0] mos

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. NEJM. 2018; 379:2307-2318

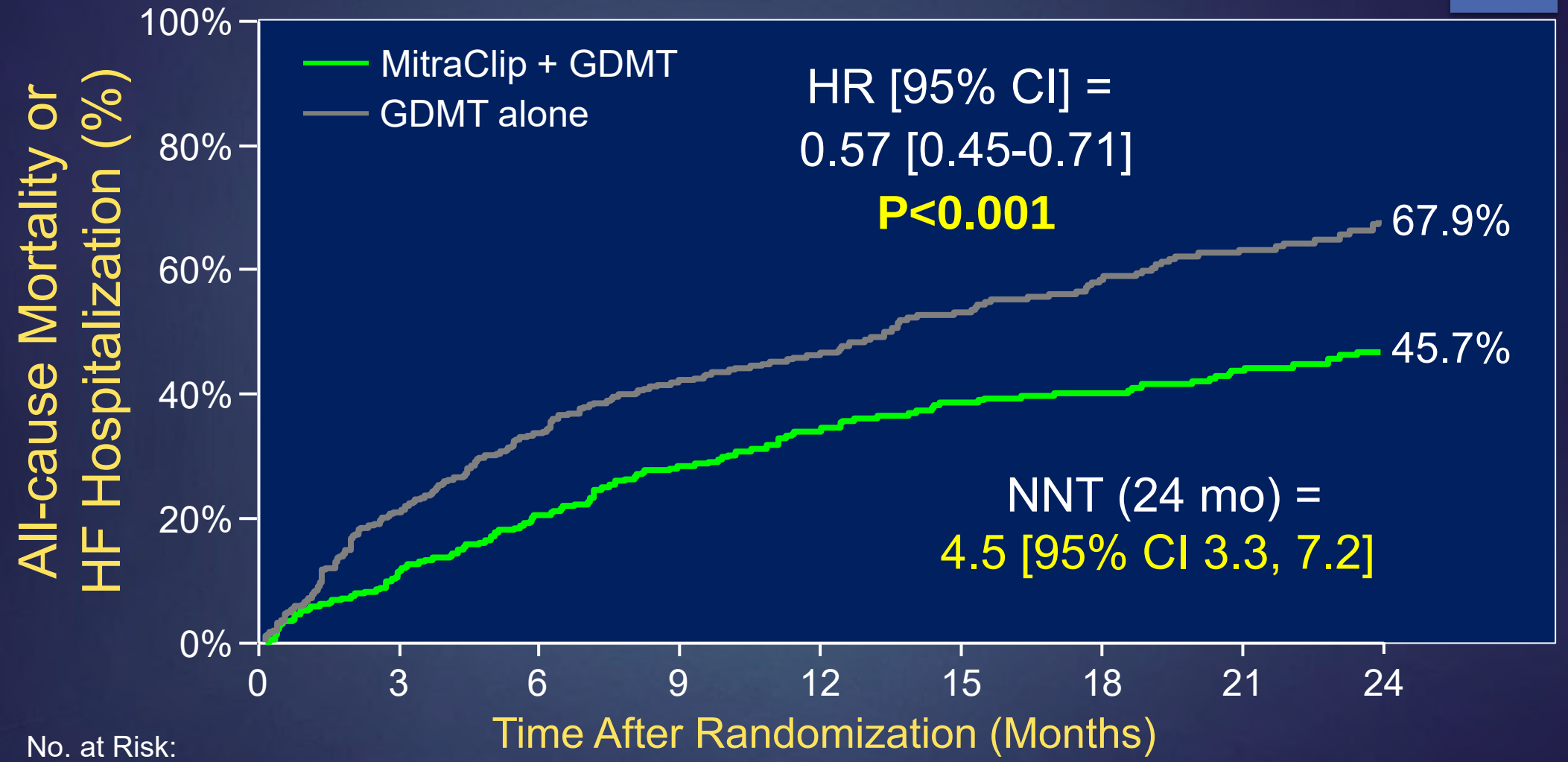
All-cause Mortality



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

Stone GW. NEJM. 2018; 379:2307-2318

Death or HF Hospitalization



No. at Risk:

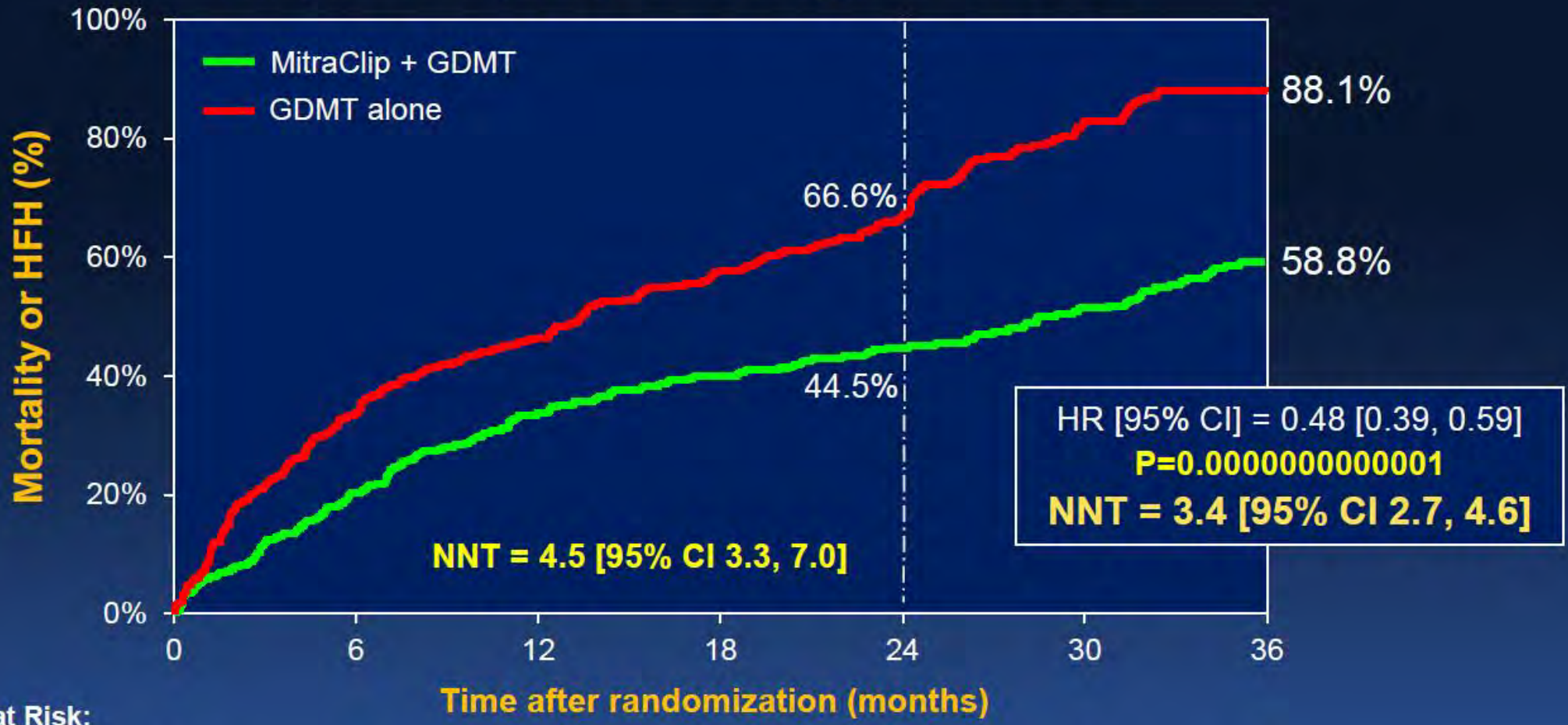
MitraClip + GDMT	302	264	238	215	194	154	145	126	97
GDMT alone	312	244	205	174	153	117	90	75	55

Stone GW. NEJM. 2018; 379:2307-2318

COAPT TRIAL

All-Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers

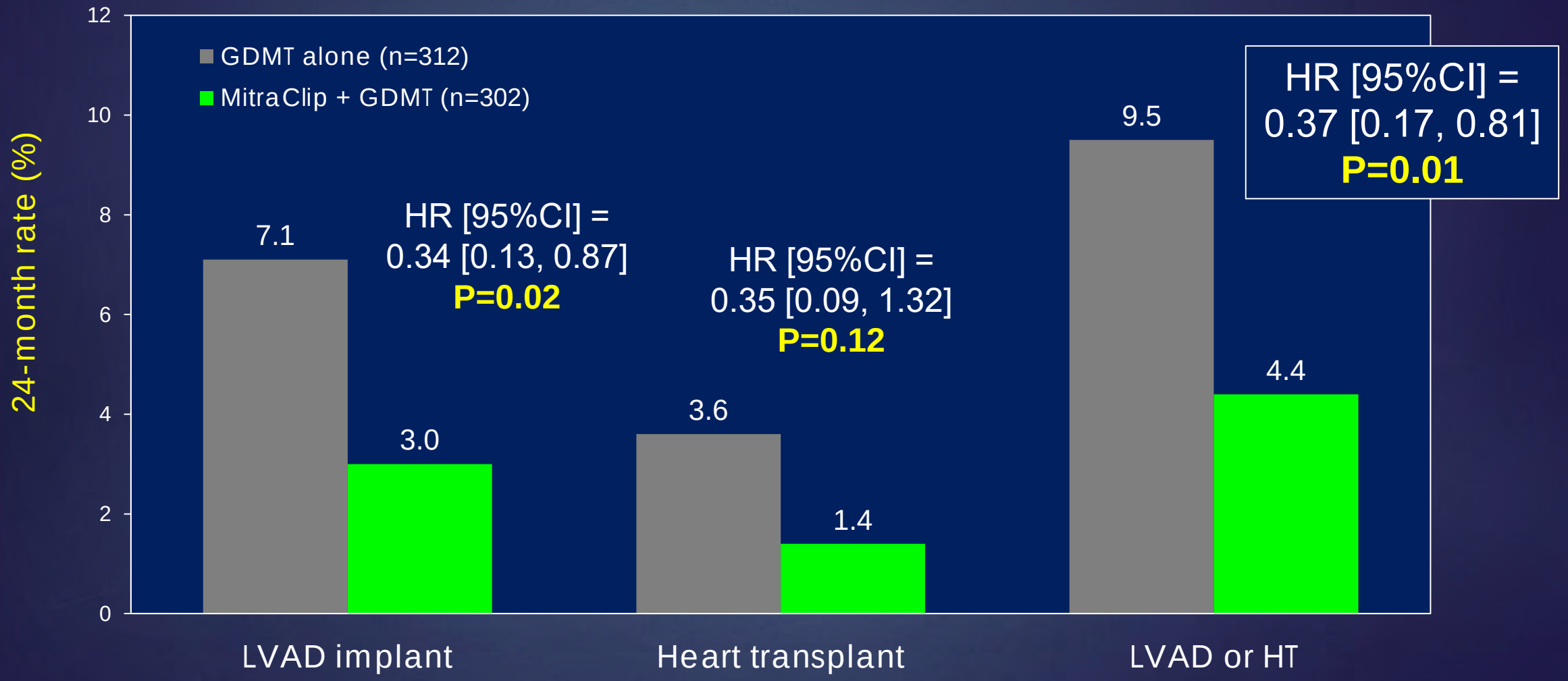


# at Risk:							
MitraClip + GDMT	302	238	196	176	148	101	66
GDMT alone	312	206	156	120	87	37	20

Event rates are Kaplan-Meier time-to-first event estimates

See Important Safety Information referenced within. ©2019 Abbott. All rights reserved. AP2948354-US Rev A

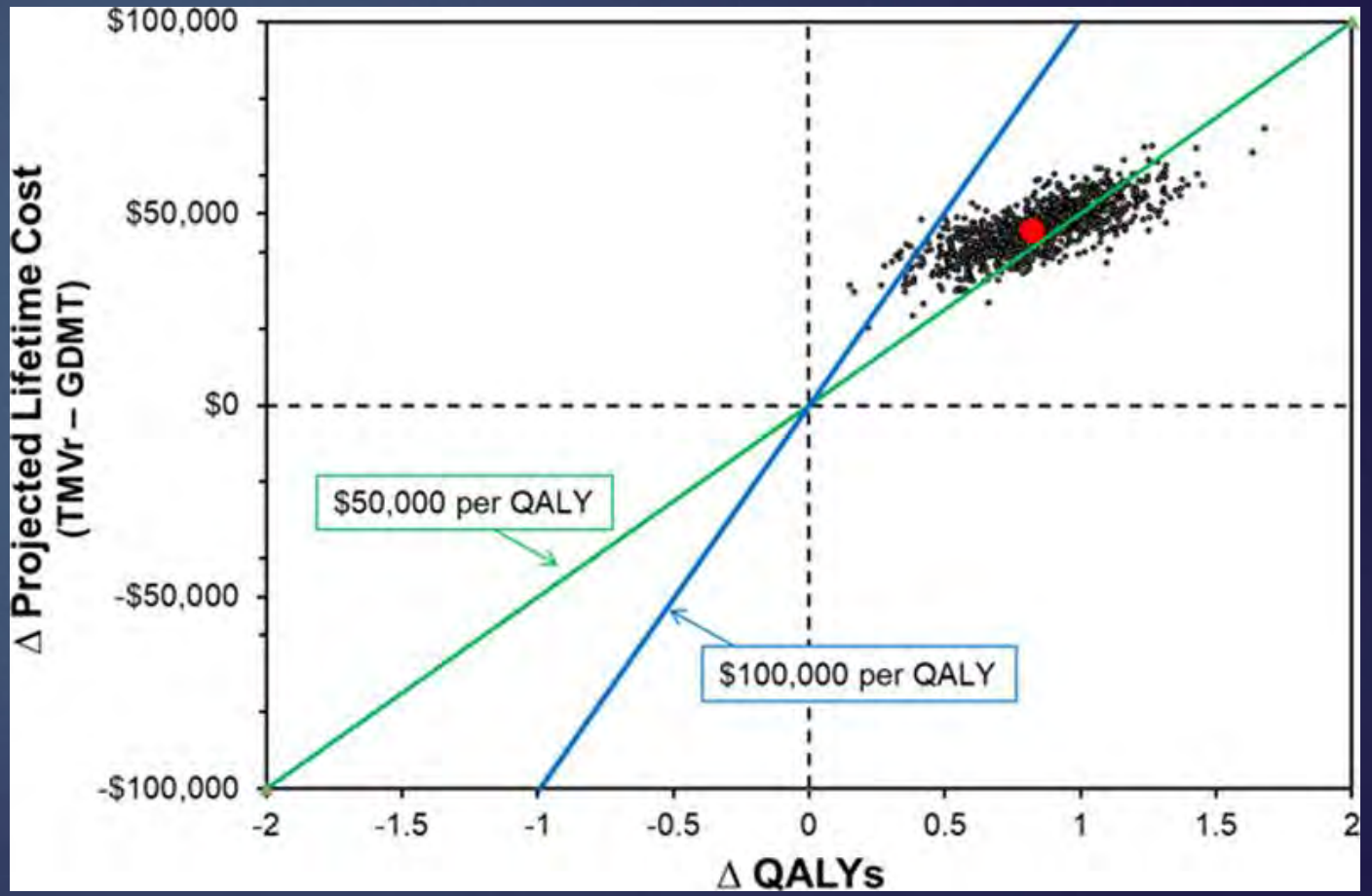
LVAD or Heart Transplant Within 24 Months



Stone GW. NEJM. 2018; 379:2307-2318

Cost-effectiveness

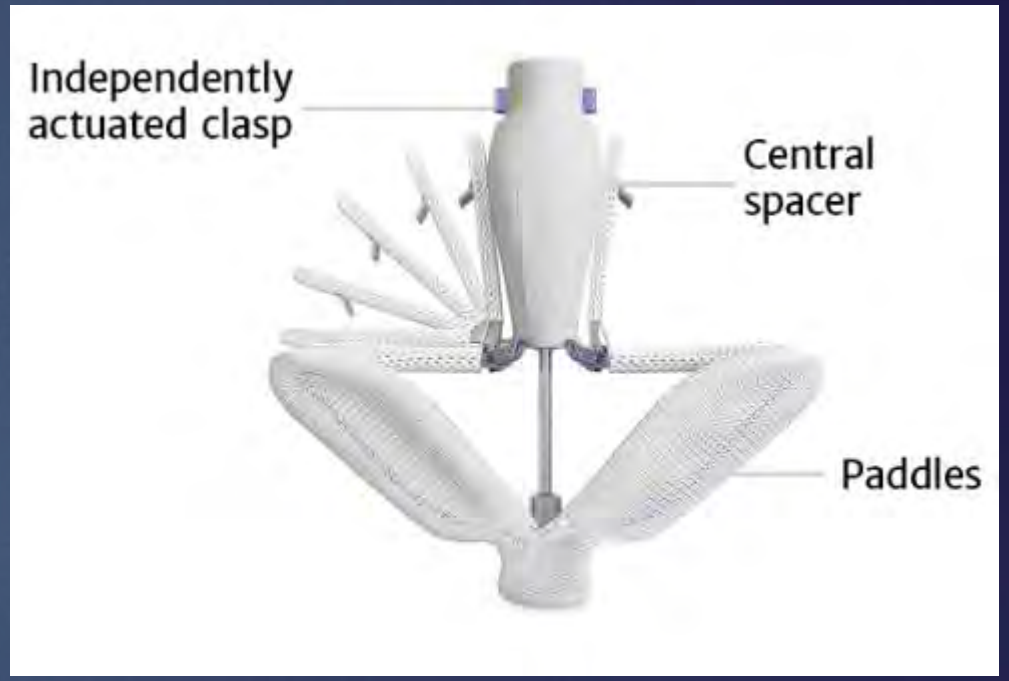
- ICER $55,600/ QALY
- ICR $40,361/ Life-year



Suzanne J. Baron. Circulation, 2019 Volume: 140, Issue: 23, Pages: 1881-1891.

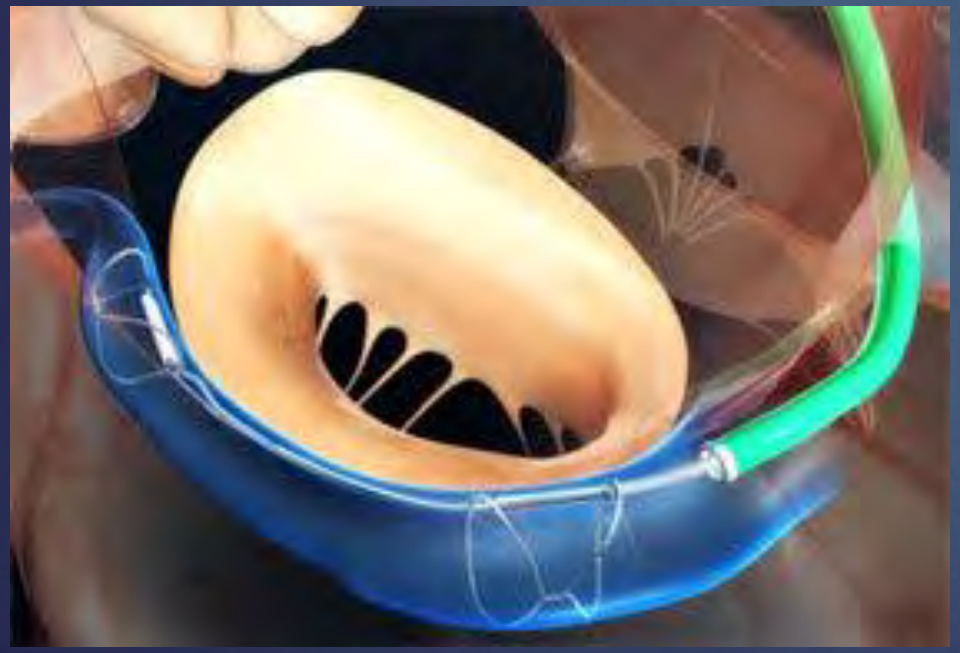
Edwards Pascal (CLASP II study)

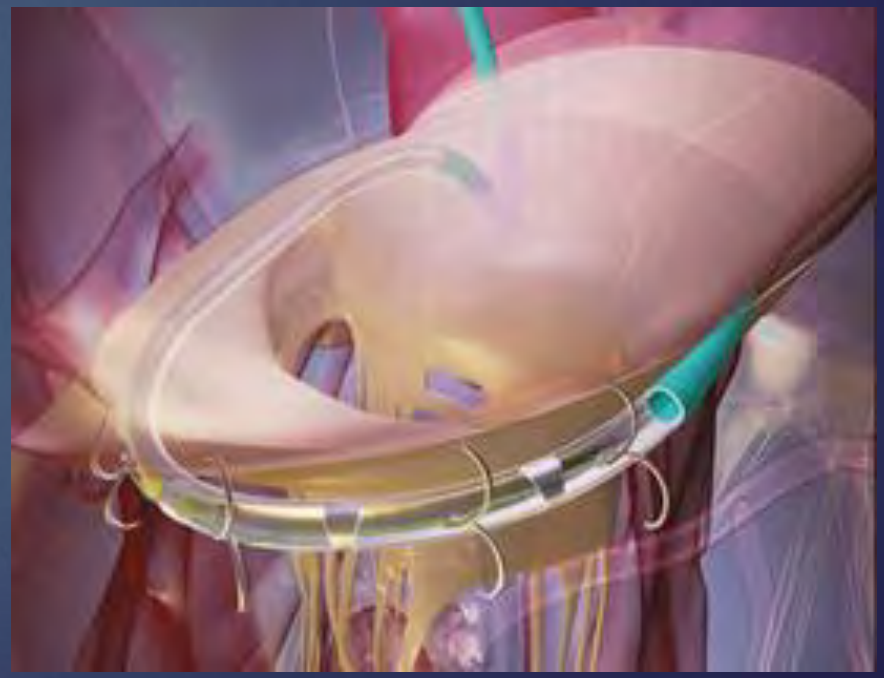
- 300 Patients with 3-4+ MR
  - Degenerative or Secondary
- Randomized to Mitraclip v. Pascal
- Prohibitive surgical risk



Percutaneous Annular Solutions

- Carillon (Cardiac Dimensions)
- AccuCinch (Ancora Heart)

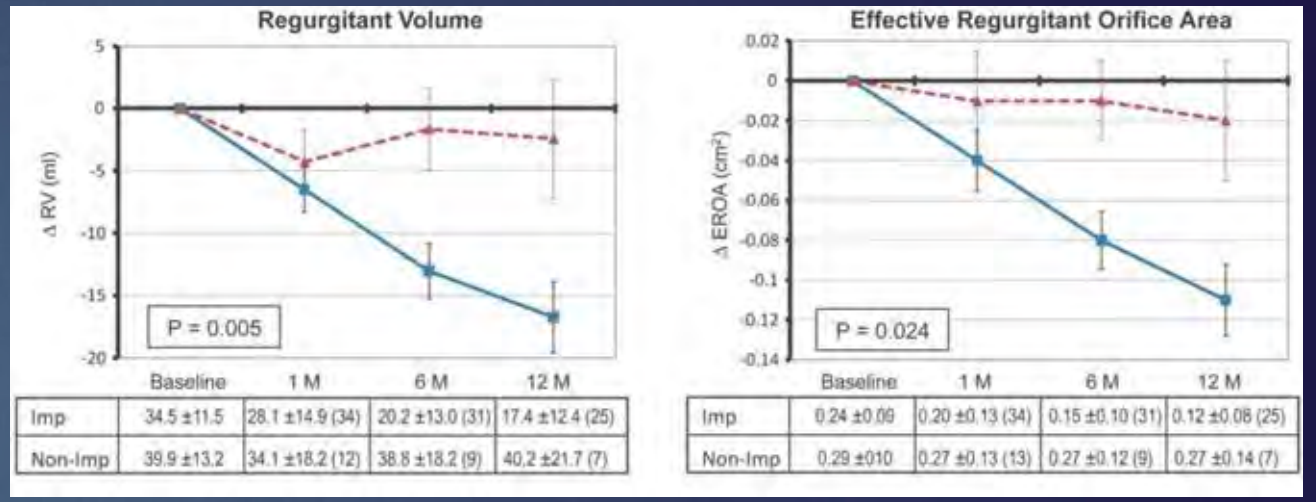




Carillon

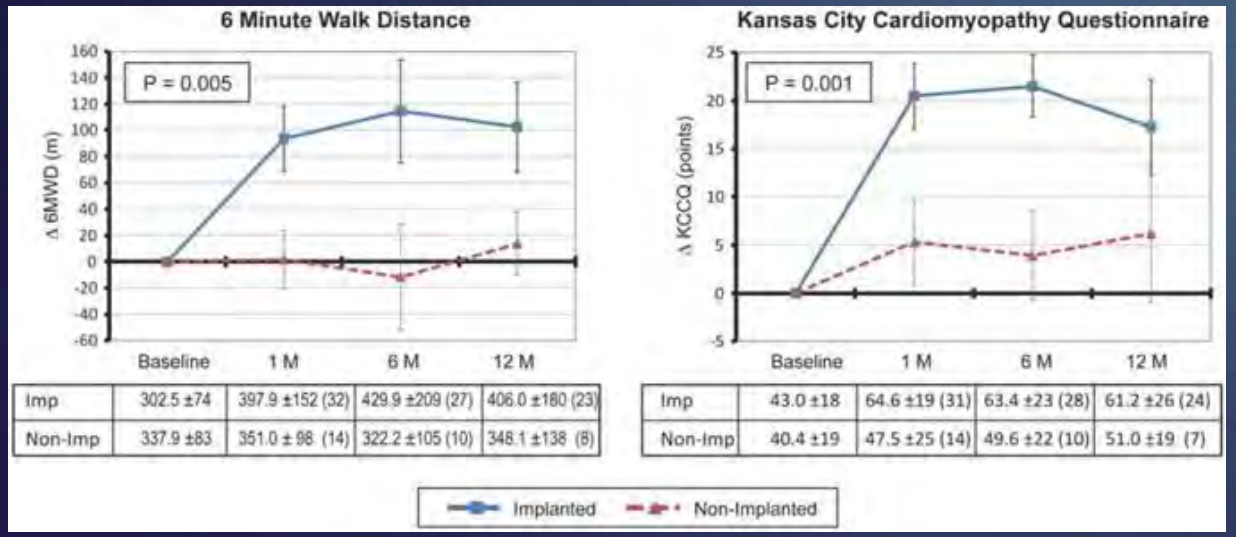
TITAN

- 36 patients with implant
- 17 patients with recaptured/non-deployed devices



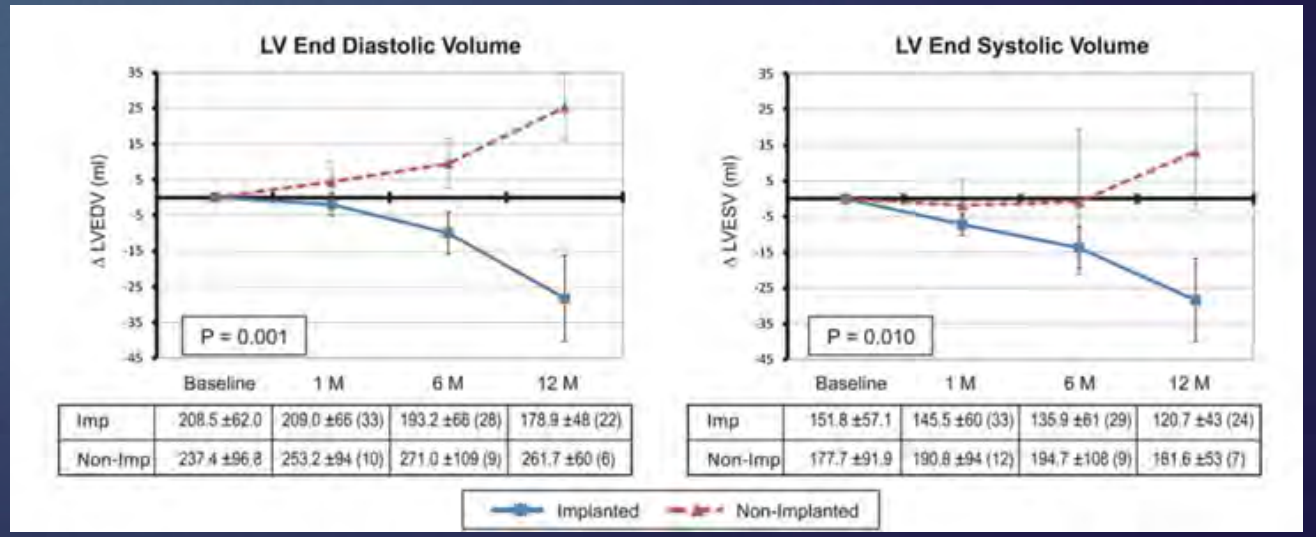
	Baseline	1 M	6 M	12 M
Imp	34.5 ±11.5	28.1 ±14.9 (34)	20.2 ±13.0 (31)	17.4 ±12.4 (25)
Non-Imp	39.9 ±13.2	34.1 ±18.2 (12)	38.8 ±18.2 (9)	40.2 ±21.7 (7)

	Baseline	1 M	6 M	12 M
Imp	0.24 ±0.09	0.20 ±0.13 (34)	0.15 ±0.10 (31)	0.12 ±0.08 (25)
Non-Imp	0.29 ±010	0.27 ±0.13 (13)	0.27 ±0.12 (9)	0.27 ±0.14 (7)



	Baseline	1 M	6 M	12 M
Imp	302.5 ±74	397.9 ±152 (32)	429.9 ±209 (27)	406.0 ±180 (23)
Non-Imp	337.9 ±83	351.0 ± 98 (14)	322.2 ±105 (10)	348.1 ±138 (8)

	Baseline	1 M	6 M	12 M
Imp	43.0 ±18	64.6 ±19 (31)	63.4 ±23 (28)	61.2 ±26 (24)
Non-Imp	40.4 ±19	47.5 ±25 (14)	49.6 ±22 (10)	51.0 ±19 (7)



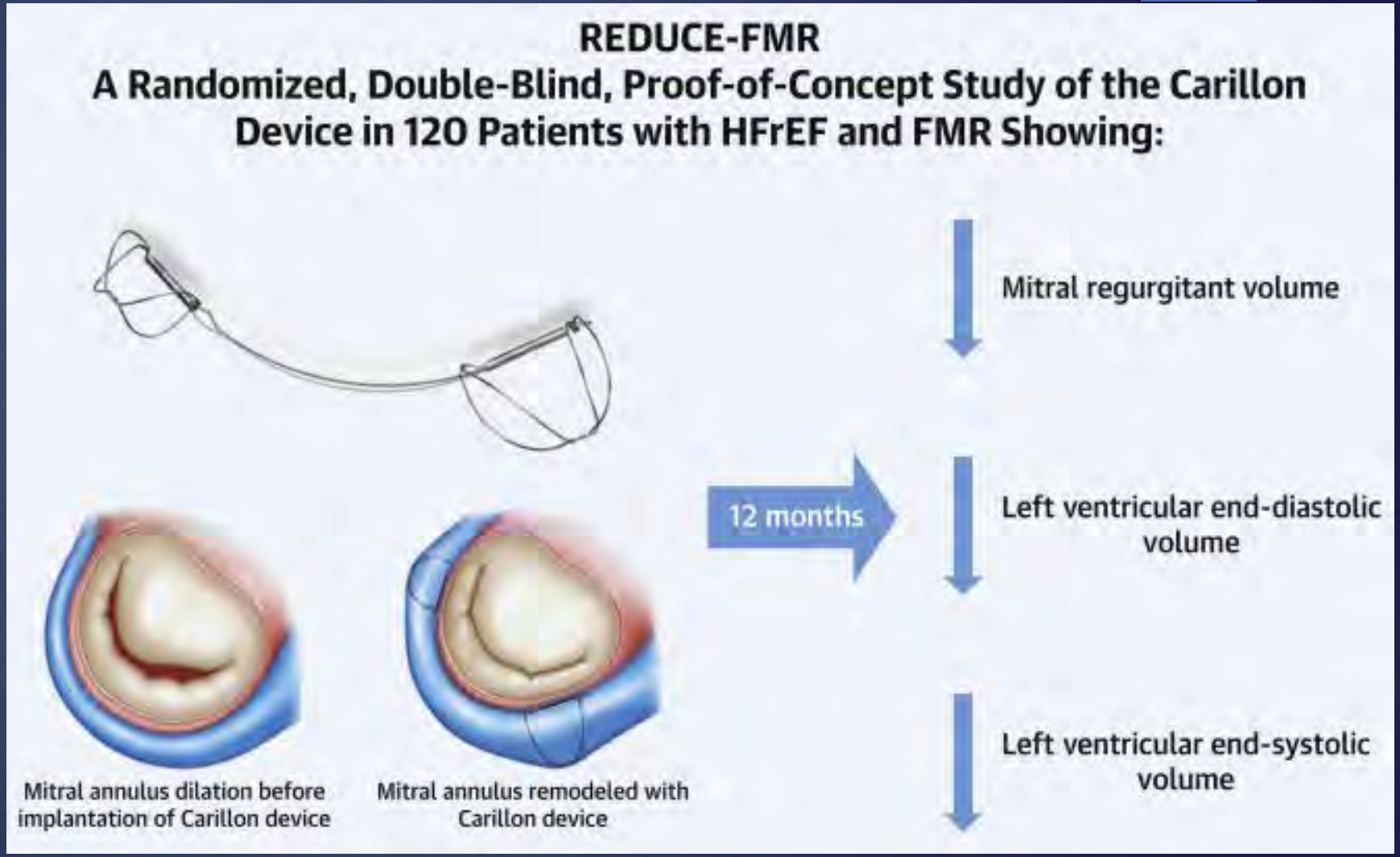
	Baseline	1 M	6 M	12 M
Imp	208.5 ±62.0	209.0 ±66 (33)	193.2 ±66 (28)	178.9 ±48 (22)
Non-Imp	237.4 ±96.8	253.2 ±94 (10)	271.0 ±109 (9)	261.7 ±60 (6)

	Baseline	1 M	6 M	12 M
Imp	151.8 ±57.1	145.5 ±60 (33)	135.9 ±61 (29)	120.7 ±43 (24)
Non-Imp	177.7 ±91.9	190.8 ±94 (12)	194.7 ±108 (9)	181.6 ±53 (7)

Tomasz S et al. Eur J Heart Failure. 2012. 14 98) 931-938.

REDUCE FMR

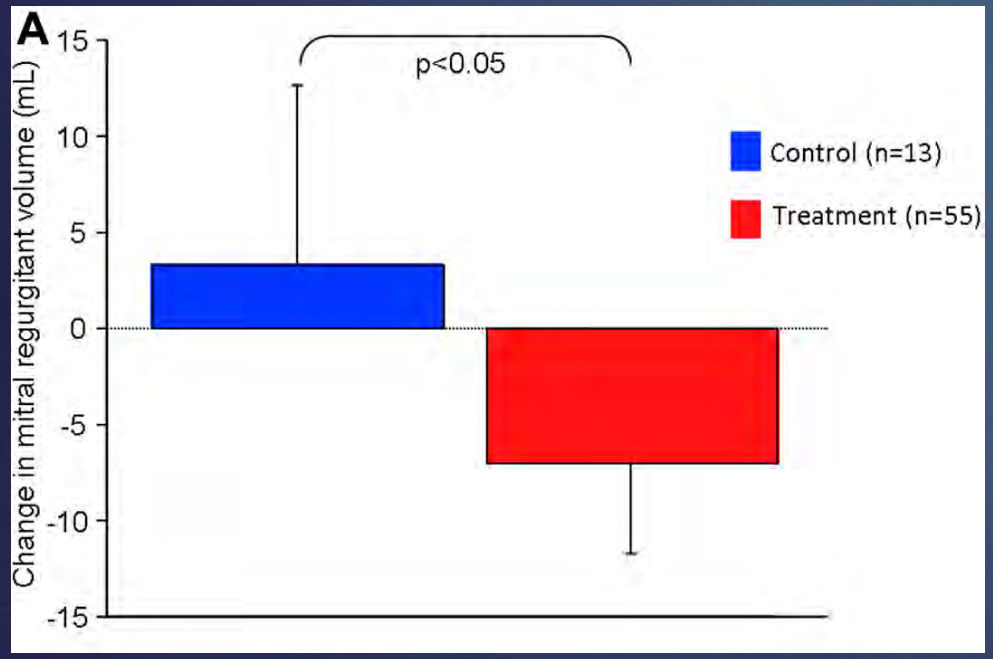
- MR 2-4+
- EF < 50%
- LVEDD > 55

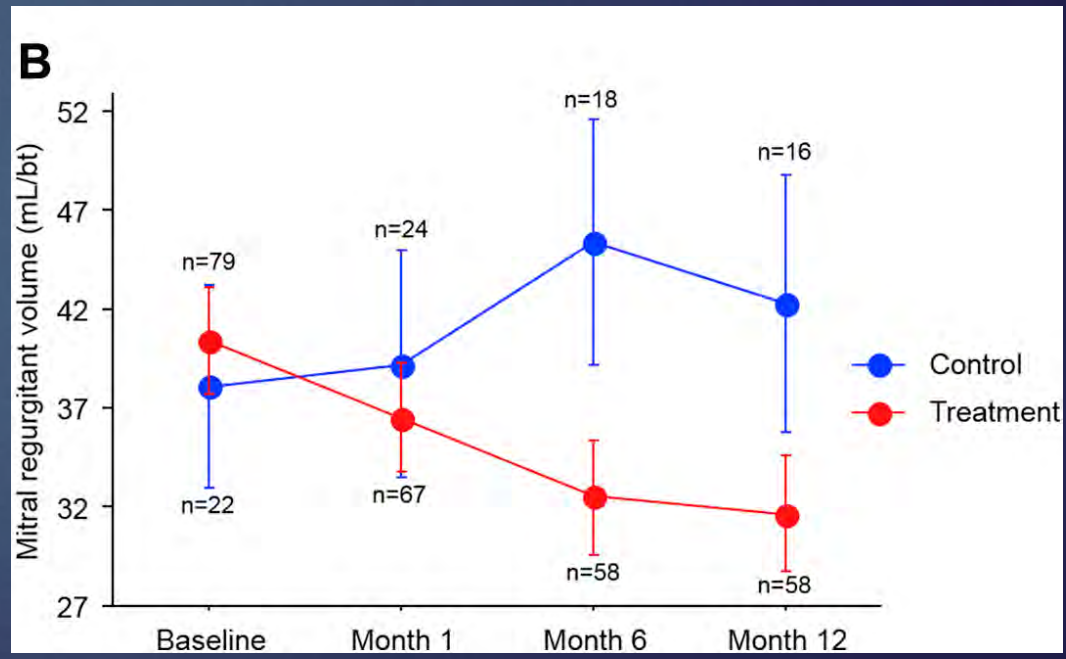


Witte KK. JACC Heart Fail. 2019.

REDUCE FMR

- 12 mo f/u

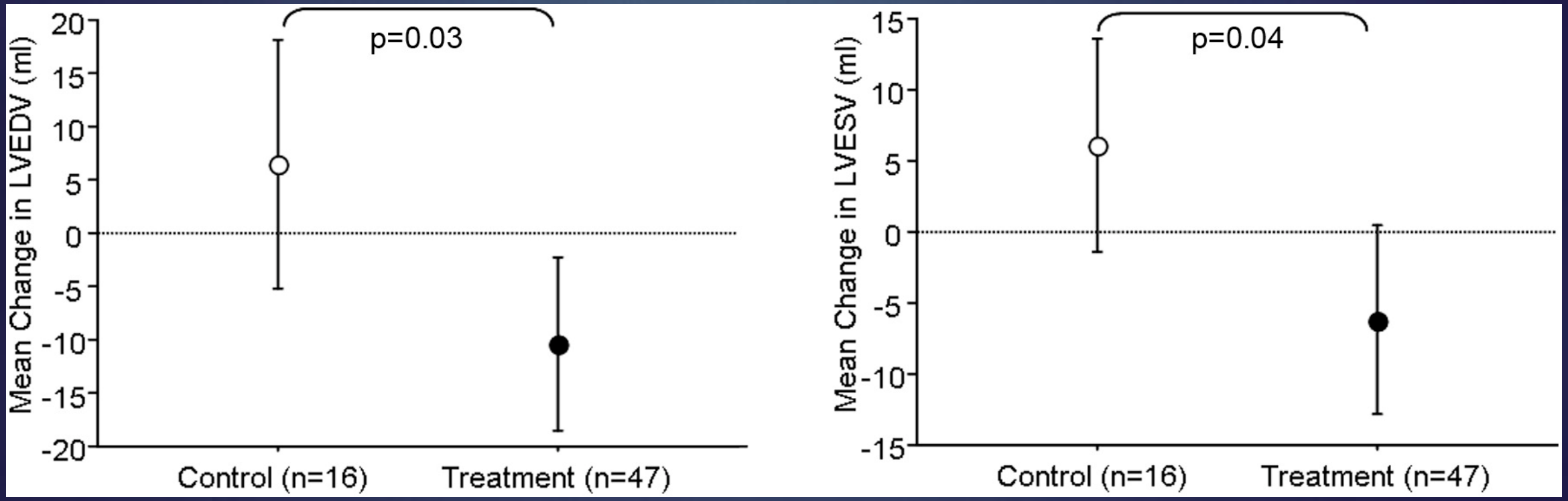




Witte KK. JACC Heart Fail. 2019.

REDUCE FMR

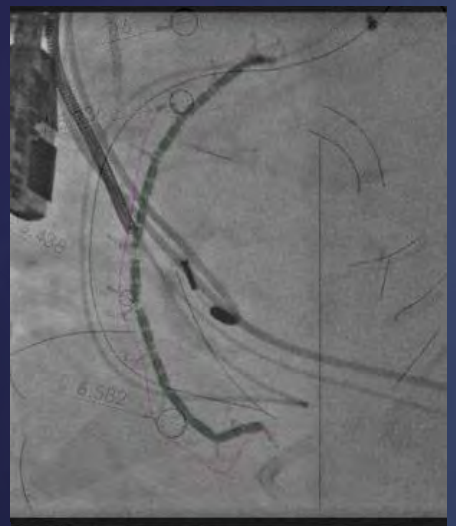
- 12 mo f/u

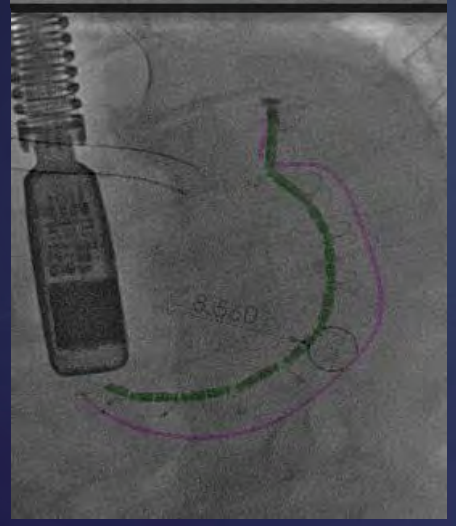


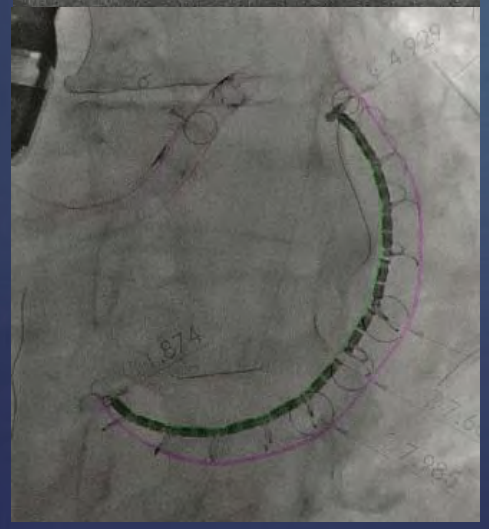
Witte KK. JACC Heart Fail. 2019.

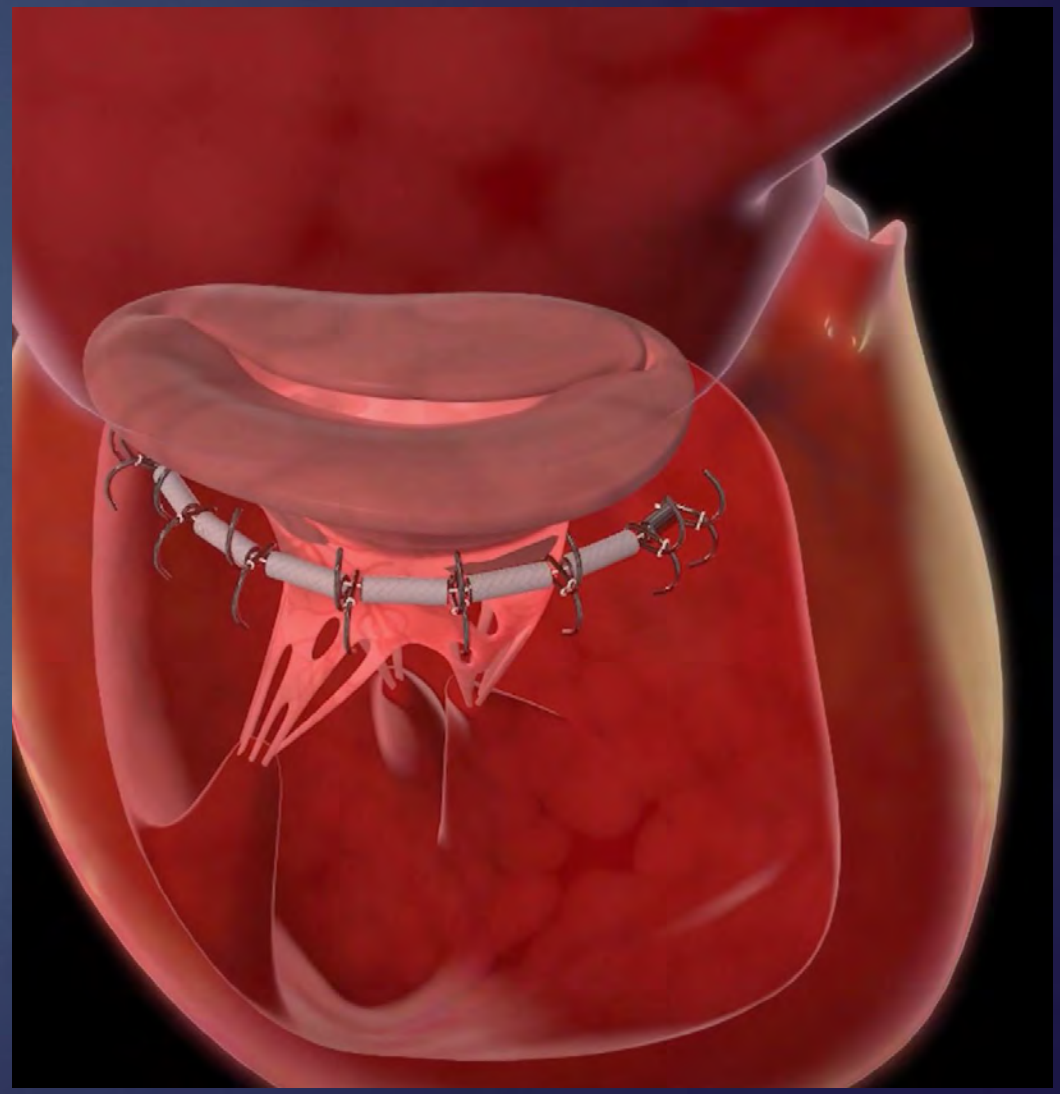
Ventricular solutions? AccuCinch

- Sub-valvular implant



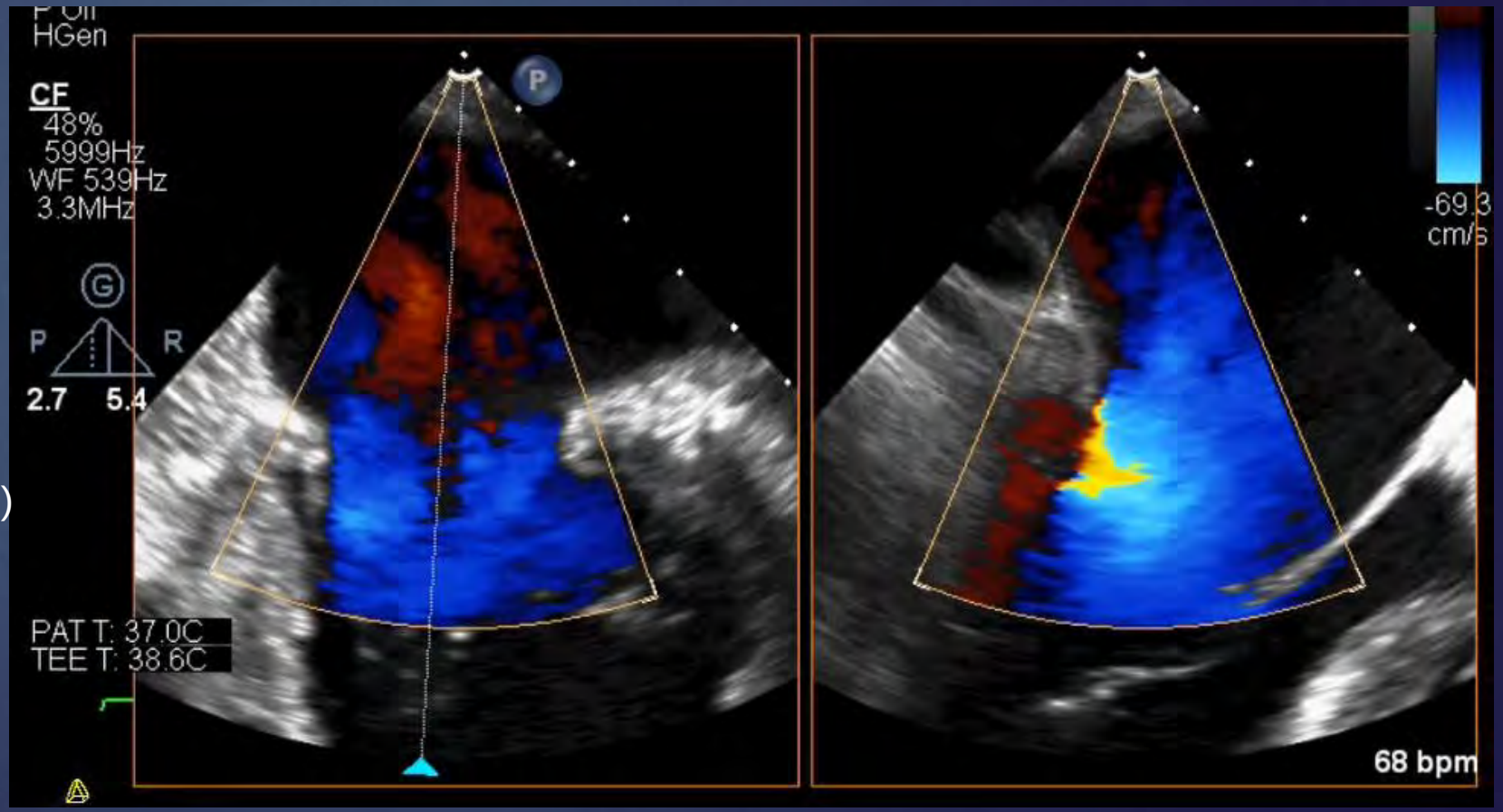






Mitral regurgitation

- 74 yo man
- HTN, Atrial fibrillation
- Non-ischemic dilated cardiomyopathy
  - NYHA Class III symptoms
  - EF 32%
    - LVEDV 272 mL (113 ml/m2)
  - Moderate MR
    - EROA 0.20 cm2



Accucinch

9 months later patient not rehospitalized, feels great

Decreased B-blocker, ACE-I

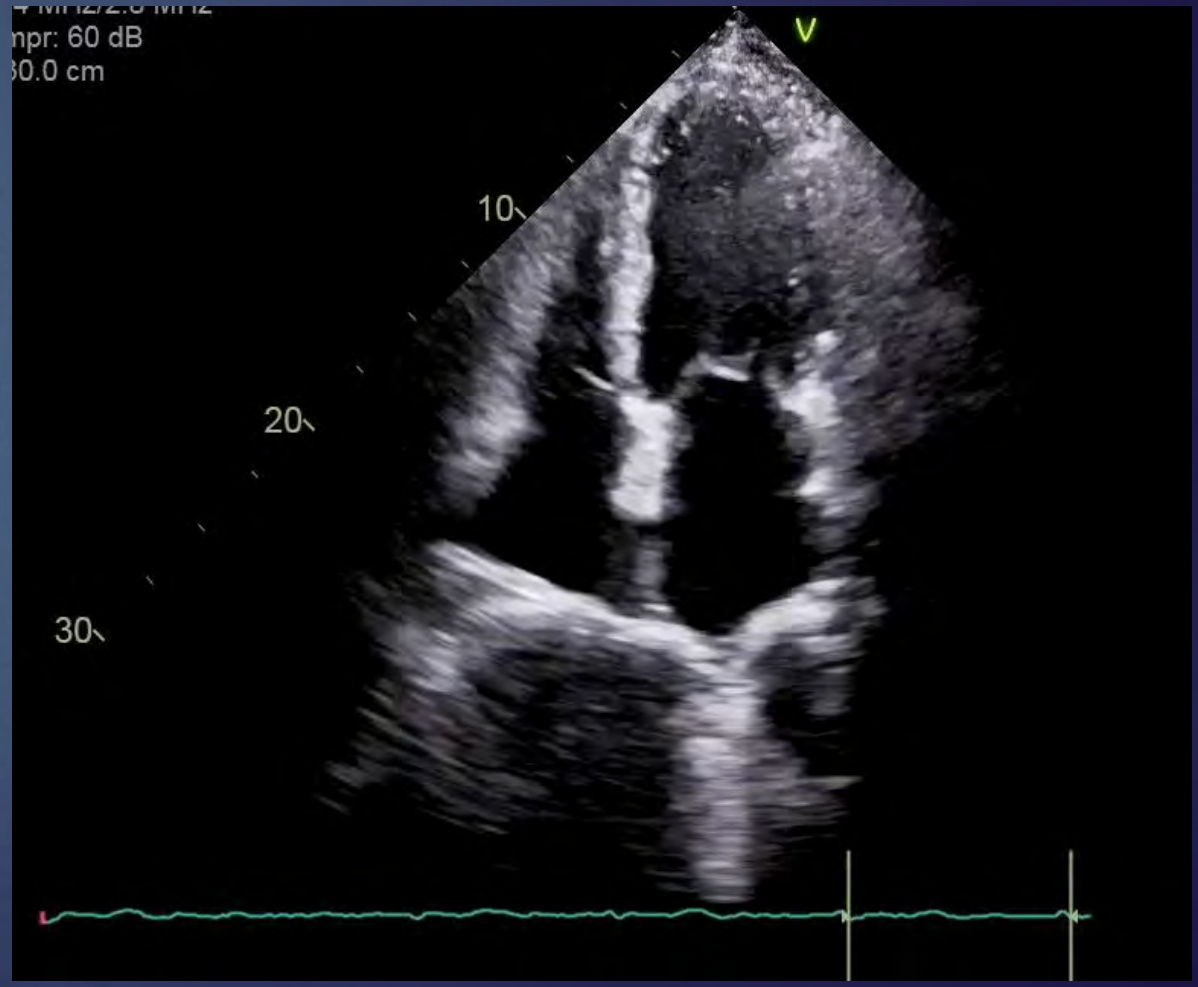
Baseline	Post-Accinch
NYHA Class 3	NYHA Class 1-2
LVEDV 272	LVEDV 168
LVEF 32%	LVEF 50%
MR Moderate-severe	MR Mild

TTE

505-003, @ 90 Day

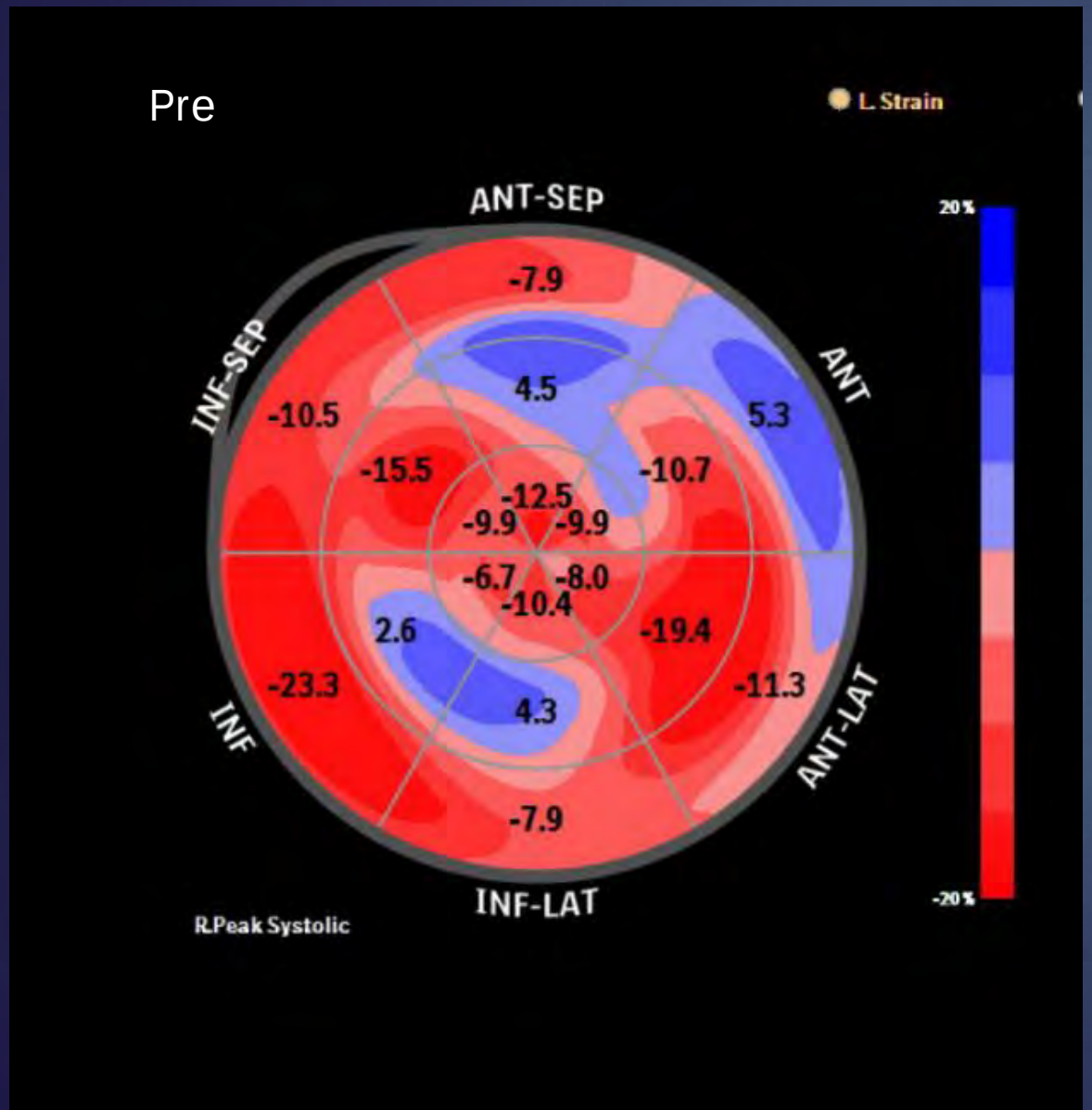
Apical 4-chamber (Baseline)

Apical 4-chamber (90-day)

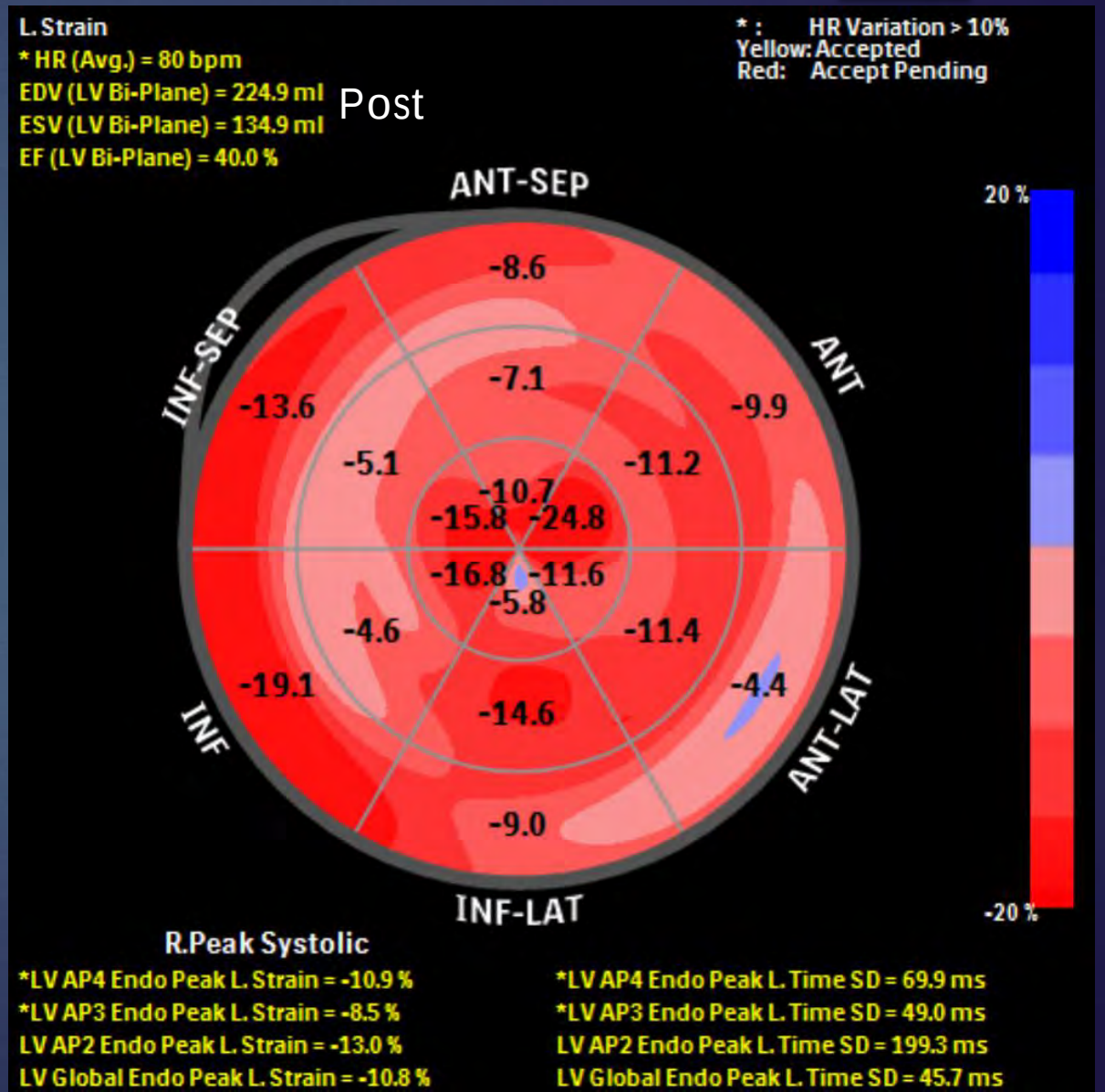


Strain imaging

Pre

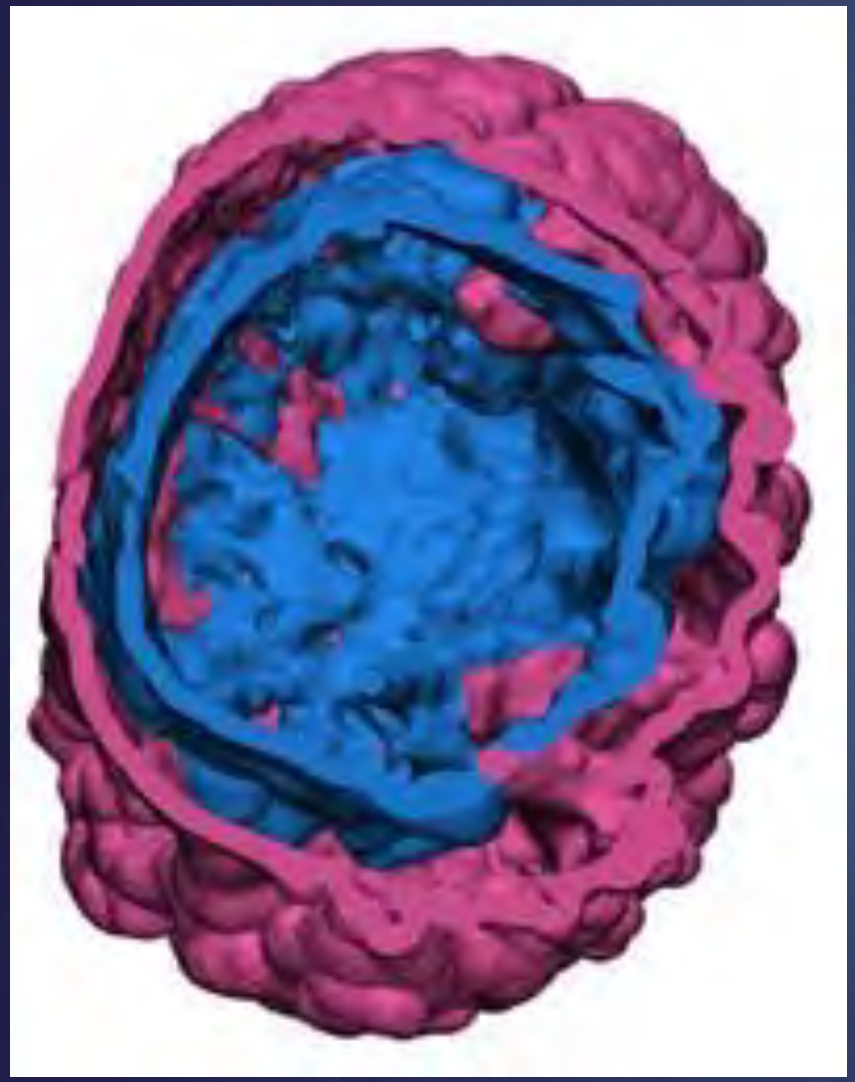


Post

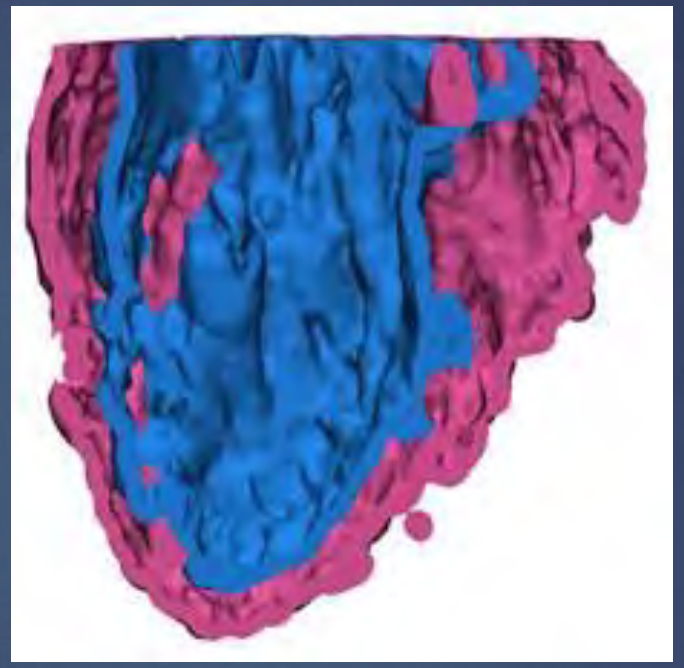


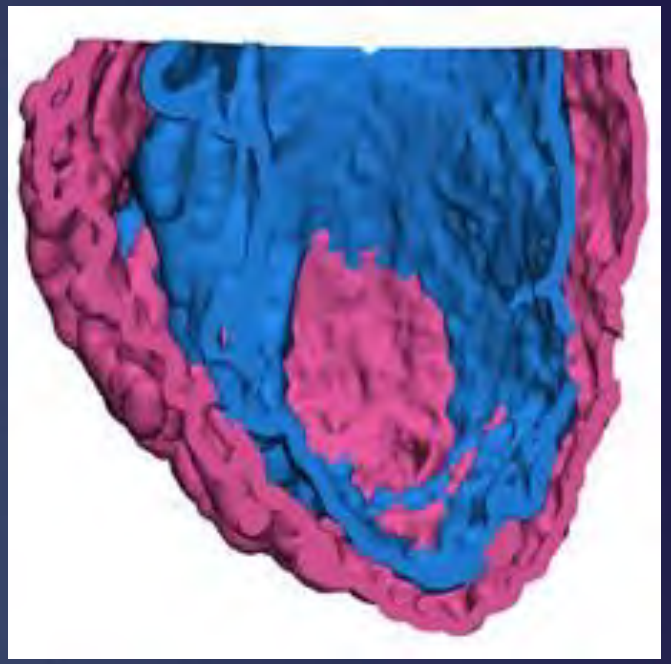
Change in LVESV

Pink—Baseline



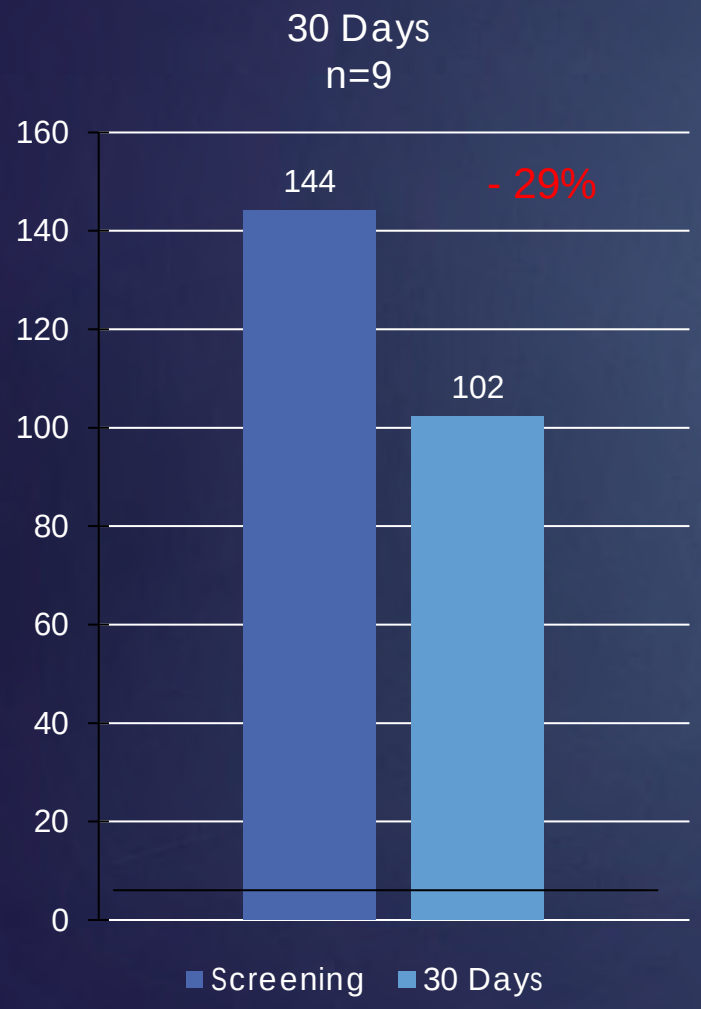
Blue—90 day post ACCUCINCH

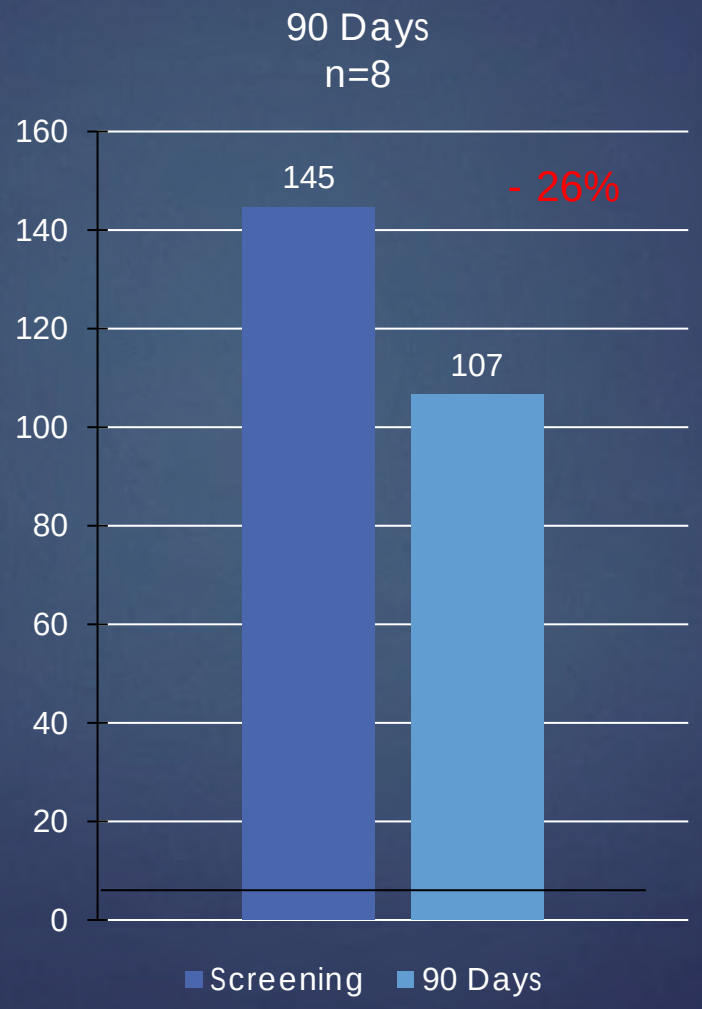


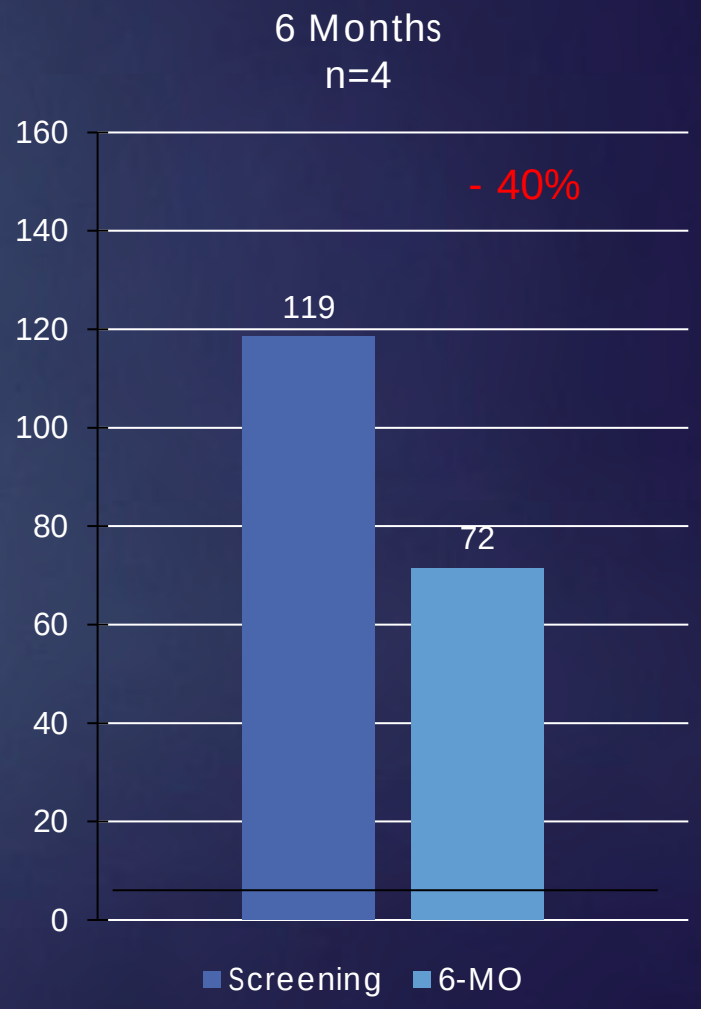


	Baseline mL	90 Day mL	Change mL	Change %
Systolic	**210**	**125**	-85 mL	-41%

ACCUCINCH: LVESV (mL)







Valve therapy takeaways

- TAVR is the treatment of choice of aortic stenosis
- MitraClip saves lives
- Much more to come

Cardiology Game Changers

- Coronary revascularization
  - ISCHEMIA
- Antiplatelet therapy
  - STOPDAPT2, TWILIGHT, AUGUSTUS
- Atrial Fibrillation
  - CABANA, EAST-AFNET4, CASTLE-AF
  - PROTECT-AF
- PFO Closure
  - RESPECT, REDUCE, CLOSE
- Valve Therapy
  - PARTNER, PIVOTAL, COAPT