The Future of Transcatheter Mitral Valve Repair and Replacement

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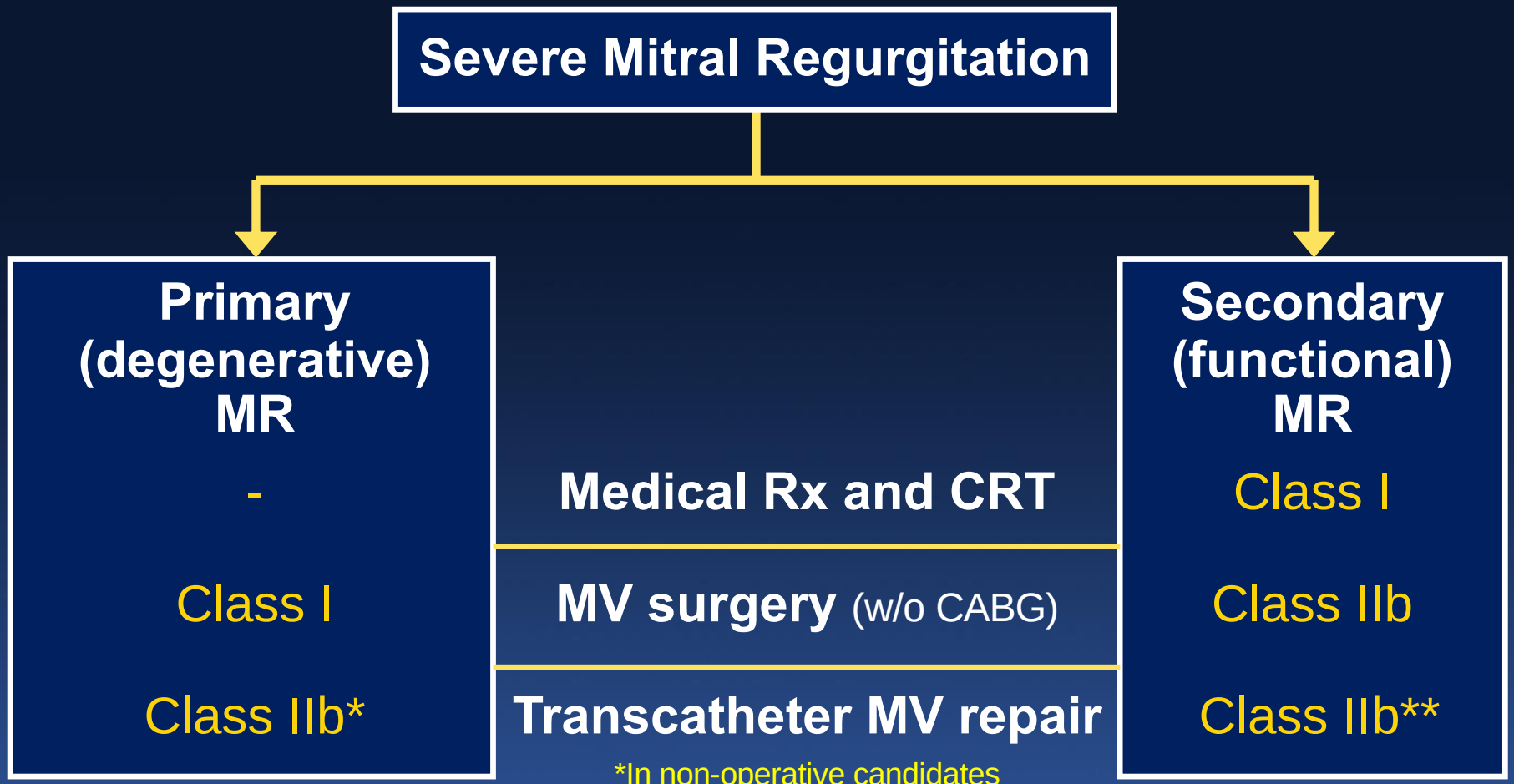
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Consultant or equity	• Neovasc, Ancora, Valfix, Gore
• Institutional conflict	• Columbia University, receives royalties for sale of the MitraClip

Updated US and EU Valve and HF Guidelines

Treatment of Chronic Symptomatic MR



*In non-operative candidates

**In the US and EU HF guidelines and the EU Valve guidelines but not the US Valve guidelines

EVEREST II Randomized Clinical Trial

279 patients enrolled at 37 sites

Severe MR (3+ or 4+)

73% DMR, 27% FMR

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
Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years

EVEREST II: 279 pts with 3+/4+ MR randomized 2:1 to MitraClip vs. Surgical Repair

Primary Endpoints (per protocol cohort)

Safety†

Major Adverse Events

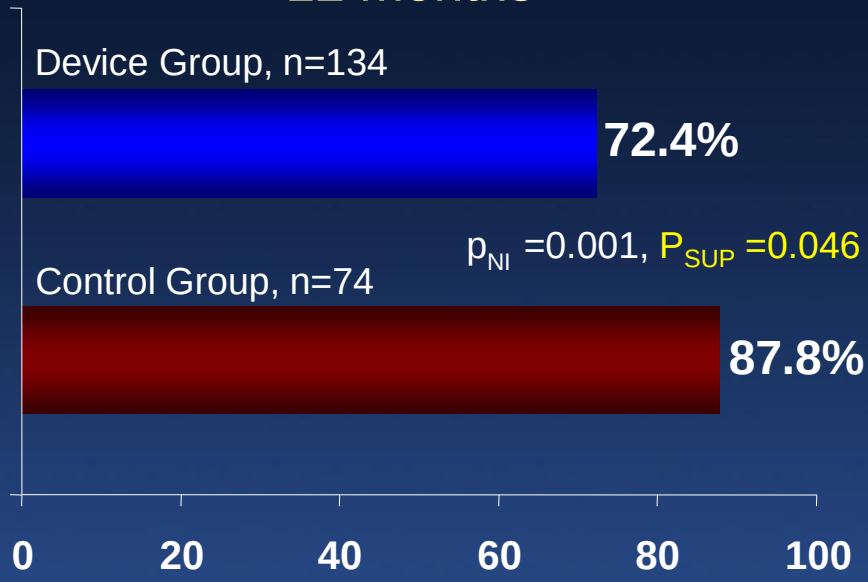
30 days

† Death, major stroke, reoperation of MV, urgent/emergent CV surgery, MI, renal failure, deep wound infection, sepsis, ventilation >48 hrs, new permanent AF, GI complication requiring surgery, transfusion ≥2U

Effectiveness‡

Clinical Success Rate*

12 months

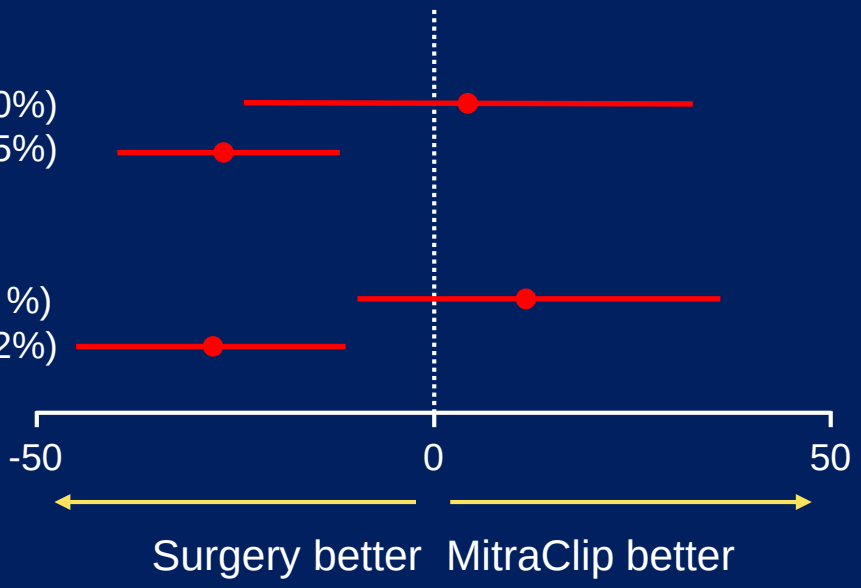


‡ Freedom from death, MV surgery or reoperation for MV dysfunction, or MR >2+ at 12 months

EVEREST II: Primary EP at 1 and 5 Years - DMR (73%) vs. FMR (27%) -

(Freedom from Death, MV Surgery, or 3+ or 4+ MR): ITT

Etiology	MitraClip	Surgery	*P* value for Interaction
1 year			
Functional	26/48 (54.2%)	12/24 (50.0%)	0.02
Degenerative	74/133 (55.6%)	53/65 (81.5%)	
5 years			
Functional	17/42 (40.5%)	4/14 (28.6 %)	0.02
Degenerative	51/112 (45.5%)	32/42 (76.2%)	



Feldman T et al. *NEJM* 2011;364:1395-406
Feldman T et al. *JACC* 2015;66:2844–54

FDA MitraClip Approval

October 24th, 2013

The MitraClip is approved for treatment of patients with 3+-4+ primary (degenerative) MR who are at "prohibitive risk" for mitral valve surgery and are likely to benefit from MR reduction

MitraClip Therapy

STS/ACC TVT Registry

145 US hospitals, Nov 2013 – Sept 2015

2,952 patients

Median age: 82 years

STS-PROM (MVR): 9.2%

Etiology: DMR 85.9%

Mixed 8.8%, FMR 8.6%

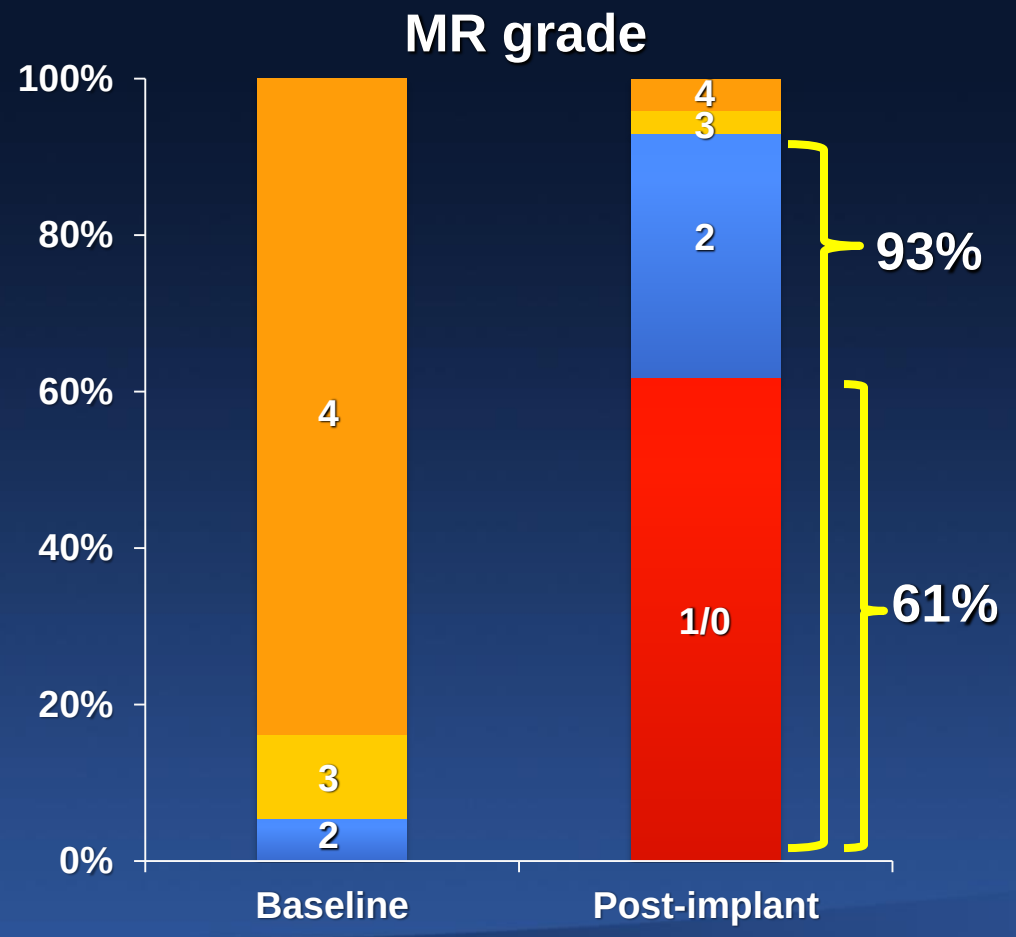
Median LVEF: 55%

MAC: 36.7%

TR: Severe 16.0%, moderate 34.9%

Procedure success: 91.8%

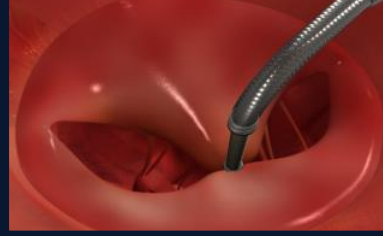
In-hosp death: 2.7%

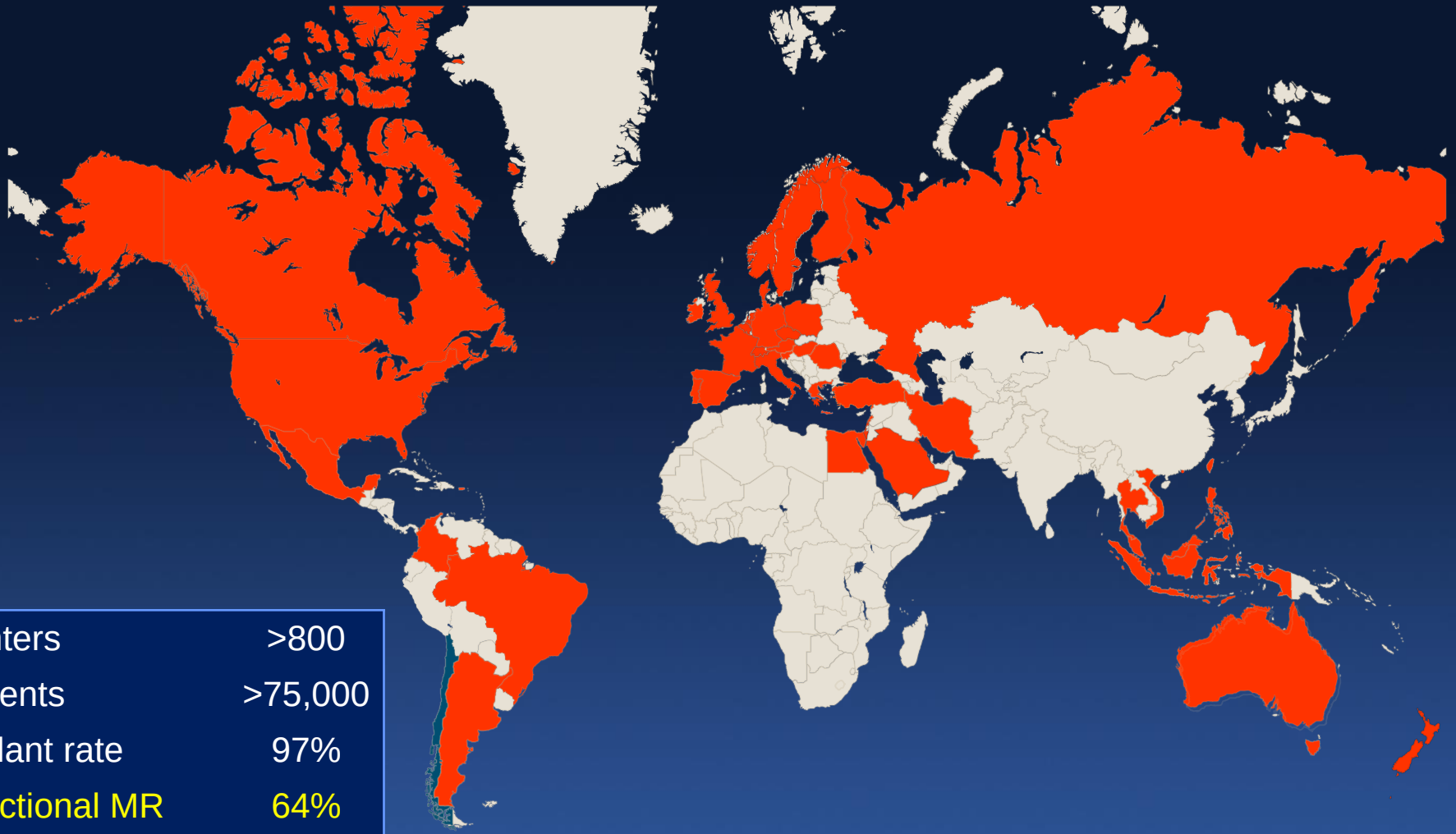


Sorajja P et al. J Am Coll Cardiol 2017;70:2315–27

MitraClip Therapy

Global Use, November 2018





Centers	>800
Patients	>75,000
Implant rate	97%
Functional MR	64%
Degenerative MR	22%
Mixed	14%

Data source: Abbott Vascular

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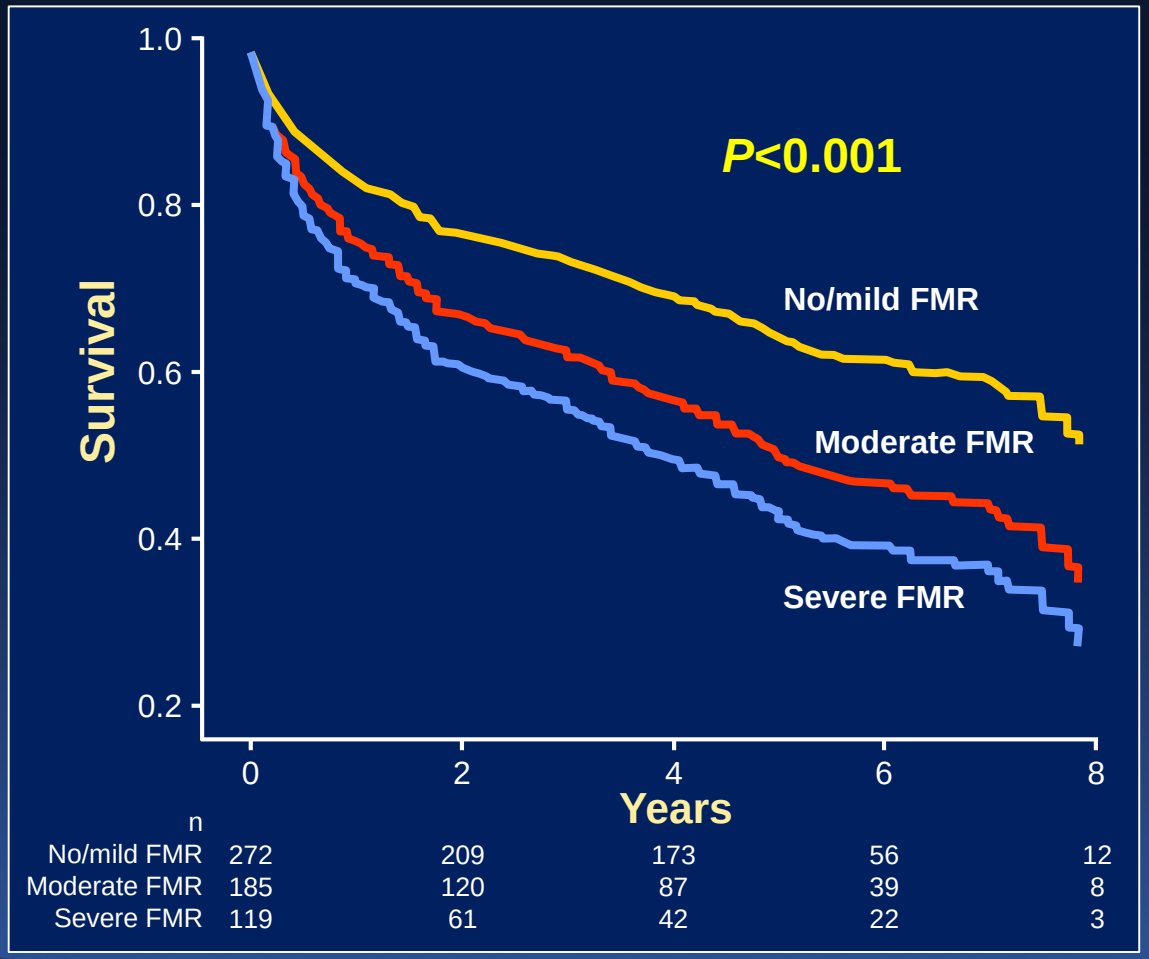
Prognostic Utility of FMR

Prospective study of 576 pts with HFrEF; 47% died during median 5-year FU; severe FMR in 21%, mod FMR in 32%



Severe FMR was an independent predictor of long-term mortality after MV adjustment for clinical variables HR [95%CI] = 1.61 [1.22, 2.12], *P*=0.001, and after MV adjustment for clinical, echo, biomarker and medication variables HR [95%CI] = 1.38 [1.03, 1.84], *P*=0.03

The MITRA-FR Trial

304 pts with SMR due to LV dysfunction with LVEF 15-40%, NYHA II-IV, HF hospitalization within the prior 12 months

MR defined by EU “severe” criteria as EROA >20 mm² or RVol >30 mL/beat. Both groups with “real-world” HF meds (not maximally-tolerated GDMT)

Randomize 1:1
at 37 French centers

MitraClip + MT
N=152

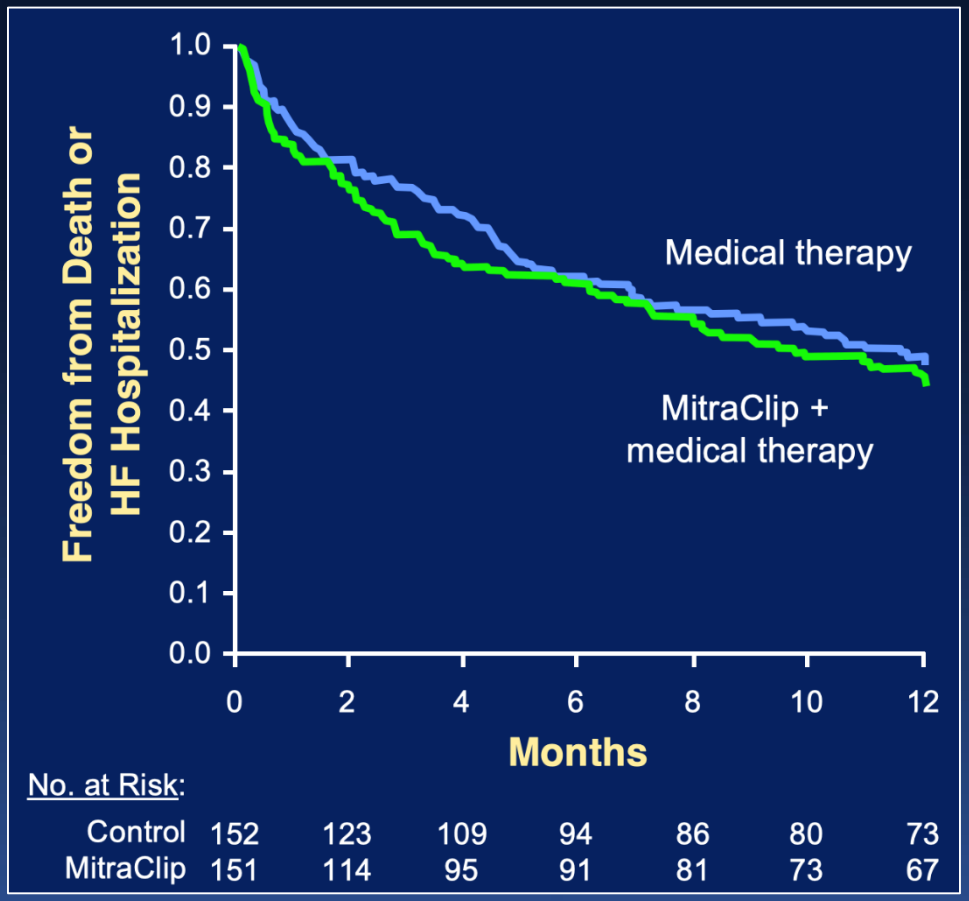
MT alone
N=152

Primary endpoint

Freedom from death or HF hospitalizations through 12 months

MITRA-FR: 12-Month Outcomes

Primary endpoint: Freedom from death or HF hospitalizations



	MitraClip + MT	MT alone	OR [95% CI] or HR [95% CI]*	*P*
1° EP: Death or HF hosp	54.6%	51.3%	1.16 [0.73–1.84]	0.53
Death	24.3%	22.4%	1.11 [0.69–1.77]*	0.65
CV death	21.7%	20.4%	1.09 [0.67–1.78]*	0.74
HF hosp	48.7%	47.4%	1.13 [0.81–1.56]*	0.59
MACE*	56.6%	51.3%	1.22 [0.89–1.66]*	–

* MACE = Death, MI, CVA, HF hosp

COAPT TRIAL

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 (US ASE critertia) who remained symptomatic despite maximally-tolerated GDMT and CRT if appropriate

Primary endpoint

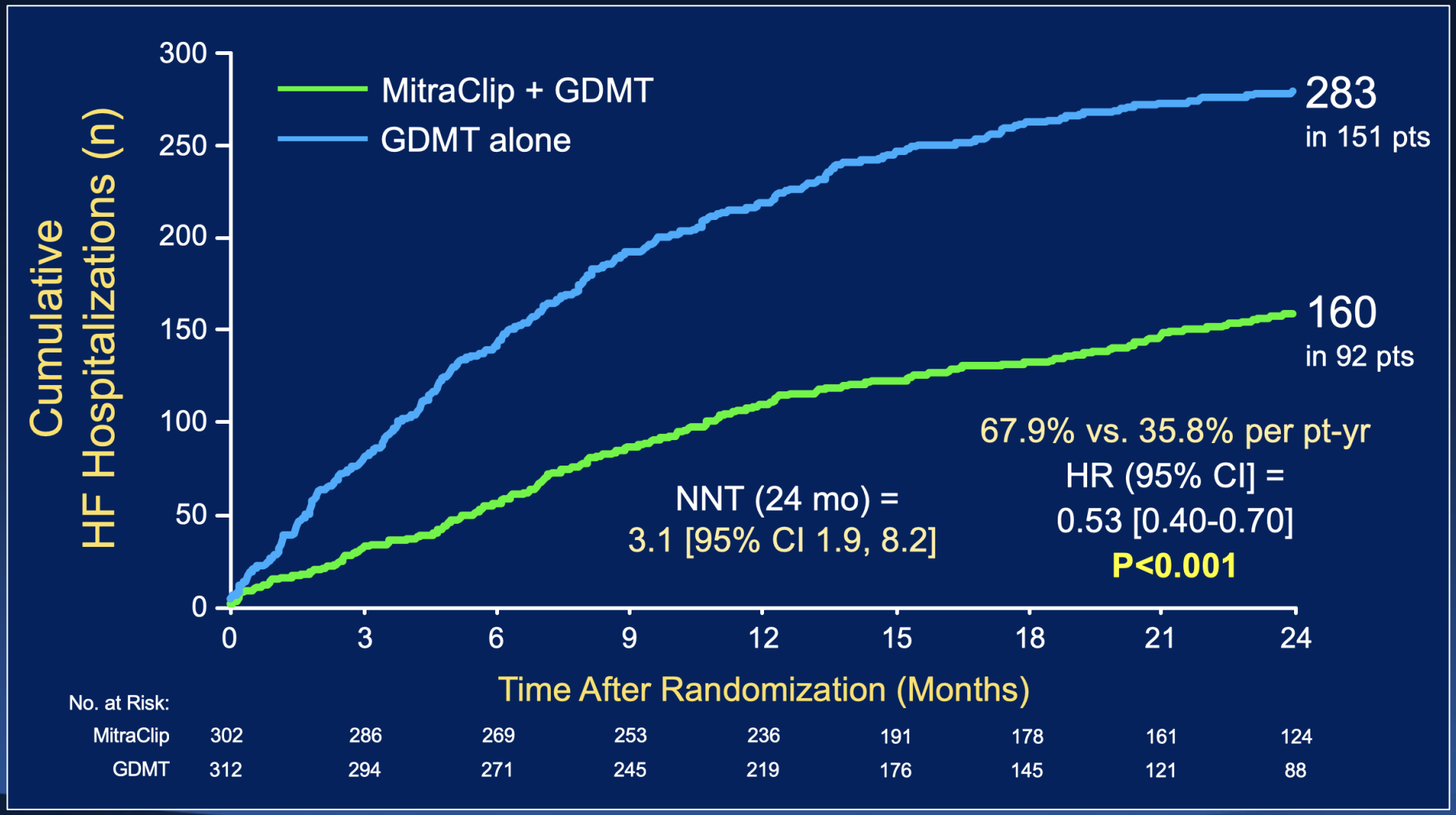
All HF hospitalizations through 24 months

Stone GW et al. N Engl J Med. 2018;379:2307-18

COAPT TRIAL

All HF Hospitalizations

Primary Effectiveness



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Stone GW et al. N Engl J Med. 2018;379:2307-18

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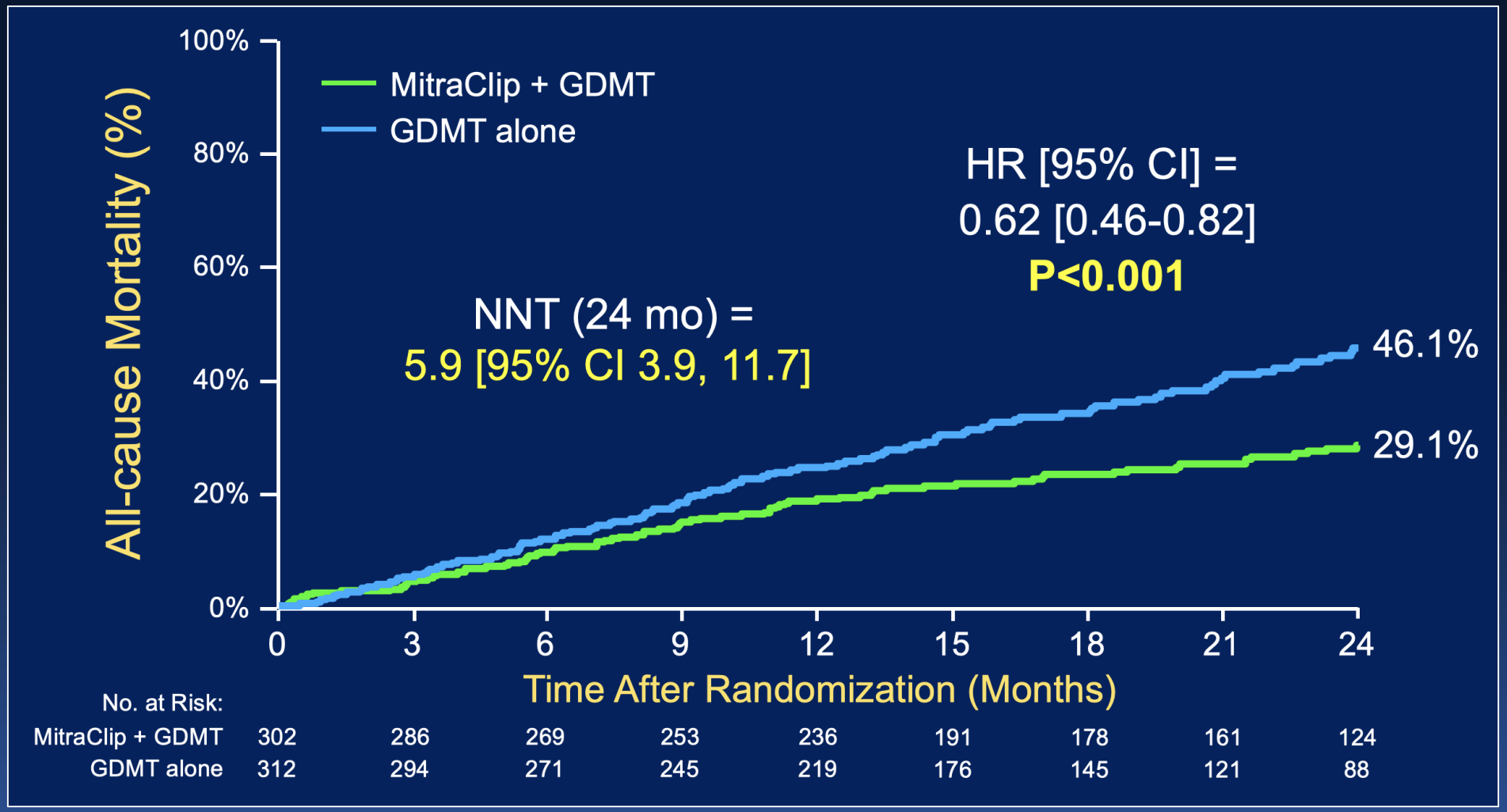
COAPT TRIAL

All-cause Mortality



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 or PSVFR or other
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	83%	95%

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

March 14th, 2019

FDA approves MitraClip for treatment of select patients with severe secondary MR who remain symptomatic despite GDMT

Transcatheter MV Repair: Device Landscape 2019

Edge-to-edge
- Abbott MitraClip***
- Edwards Pascal*
- MitraFlex

Direct and indirect annuloplasty
- CDI Carillon**
- Mitralign TAMR**
- Edwards Cardioband**
- Ancora Heart Accucinch*
- Millipede IRIS*
- MVRx Arto*
- Mardil VenTouch*
- Mitraspan TASRA*
- Valcare Amend*
- Micardia enCor*
- MitraLoop Cerclage*
- Cardiac Implants RDS*
- QuantumCor (RF)
- Valfix

MV replacement
- Edwards CardiAQ*
- Edwards Sapien M3*
- Neovasc Tiara*
- Abbott Tendyne*
- Medtronic Intrepid*
- HighLife*
- Caisson*
- NCSI NaviGate*
- MValve*
- CardioValve*
- Cephea*
- St. Jude
- Micro Interventional
- ValveXchange
- MitrAssist
- Braile Quattuor
- Direct Flow
- Sinomed Accufit
- Valcare Corona
- Epigen

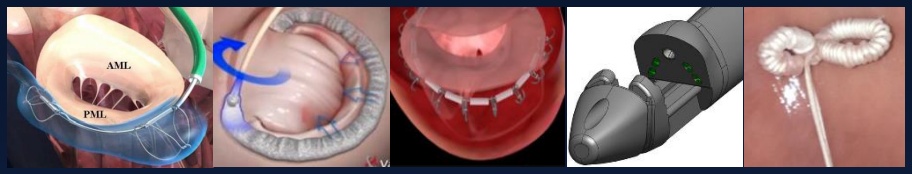
MV replacement (cont)
- MitralHeal
- HT Consultant Saturn
- Lutter valve
- Transcatheter Technologies
- Tresillo
- Venus
- Verso
- Transmural Systems
- Saturn (InnovaHeart)
- 4C Altara

Other approaches
- NeoChord DS 1000**
- Harpoon neochords*
- Babic chords*
- Pipeline Medical (Gore)
- Middle Peak Medical*
- St. Jude leaflet plication*
- Cardiosolutions Mitra-Spacer*
- Mitralix*
- Mitraltech Vchordal
- Coramaze Mitramaze

*In patients *CE mark *FDA approved

Implications of COAPT for New Devices to Treat Secondary MR in Heart Failure

For MV repair technologies



- Will they be as safe as the MitraClip?
- Will they be as effective as the MitraClip?
- Will they be as durable as the MitraClip?
- Will they be able to treat the same or different pts? E.g. MAC, wide/multiple jets, extreme tethering, small annulus
- Will they be able to treat MitraClip failures or recurrences (or will the MitraClip be able to treat their failures or recurrences)?

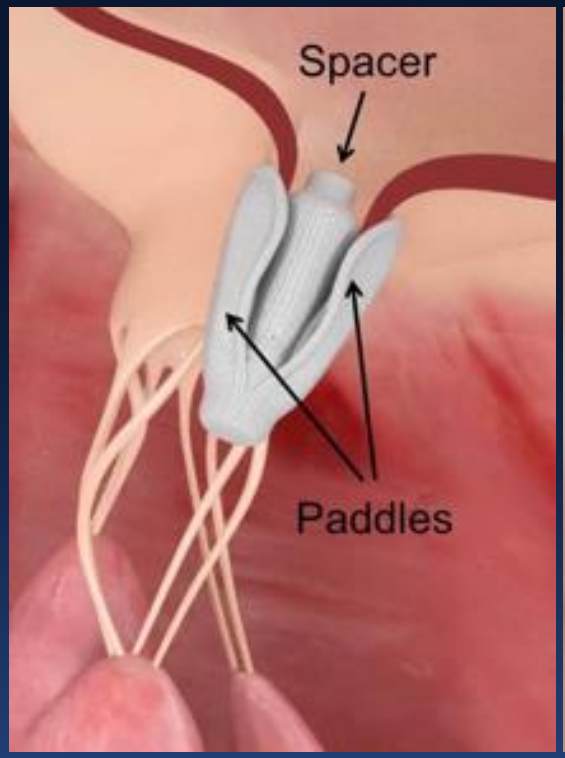
For MV replacement technologies

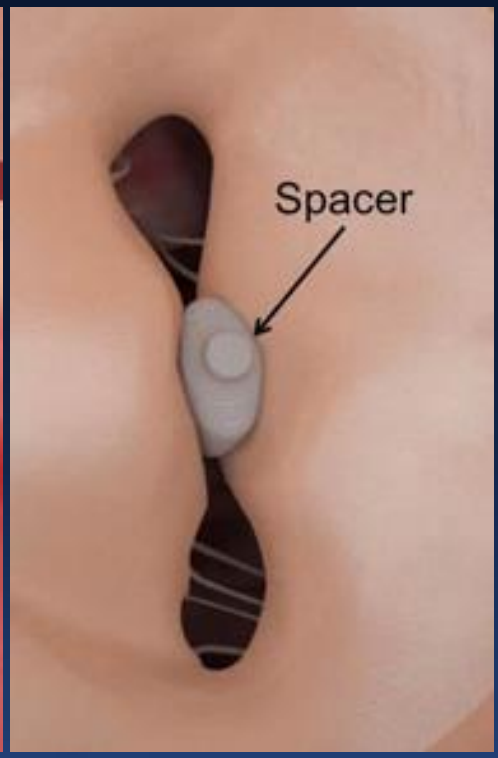
- Given the likelihood of greater procedural complications and the need to anticoagulate, they must be shown to be more effective than the MitraClip, or able to treat MitraClip ineligible pts

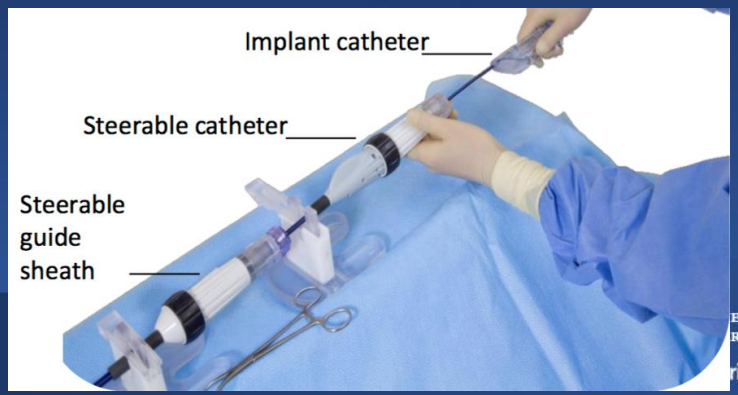
PASCAL

PAddles, Spacer, Clasps, ALfieri

- Spacer placed between both MV leaflets
- Independent leaflet clasping
- Longer and wider paddles for better leaflet capture
- Minimal dependence on septal puncture height
- Simple “Commander-like” delivery system
- Transfemoral/transseptal approach



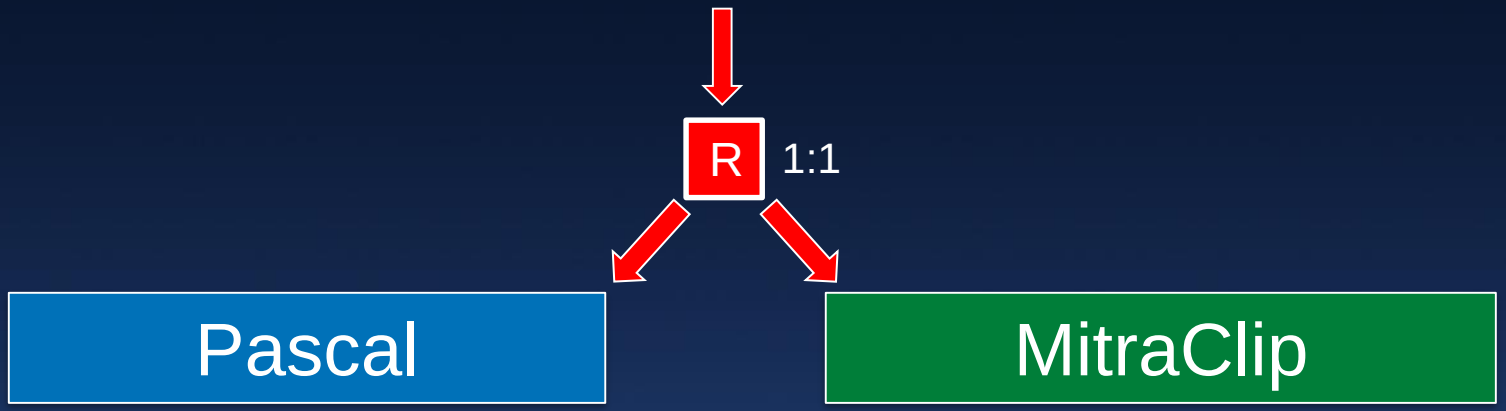




CLASP IID

Edwards PASCAL TrAnScatheter Mitral Valve RePair System Pivotal Clinical Trial

675 pts with 3+ or 4+ degenerative MR at prohibitive risk for mitral valve surgery by local heart team assessment

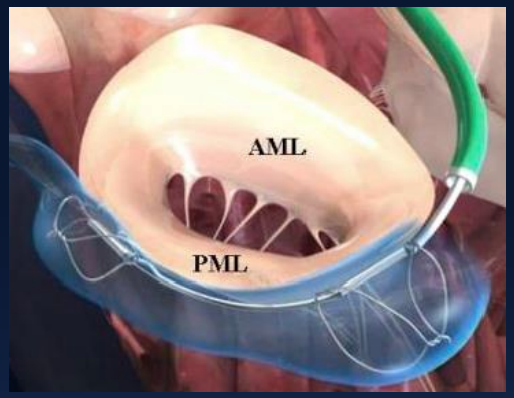


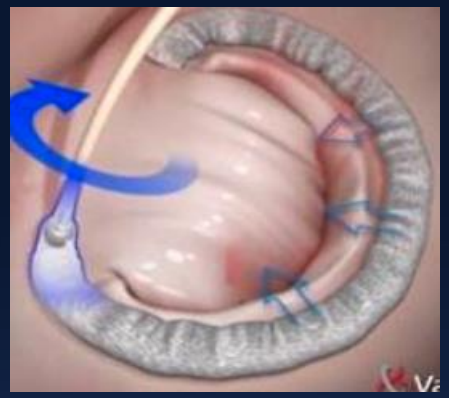
5-year FU

Primary safety endpoint: Major adverse events at 30 days (powered for noninferiority)

Primary effectiveness endpoint: MR severity at 6 months (powered for noninferiority)

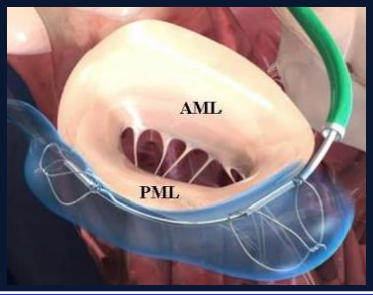
Novel MV Repair Devices with Ongoing US Pivotal Randomized Trials

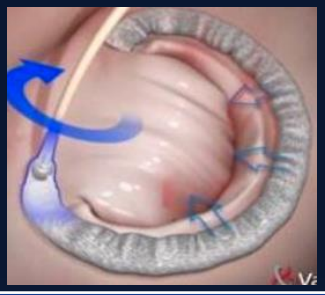




	Cardiac Dimensions Carillon	Edwards Cardioband	NeoChord DS1000
Mechanism and study population	Coronary sinus mediated posterior annulus cinching for FMR	LA semi-rigid posterior partial annuloplasty band with anchor cinching for FMR	Transapical PTFE neochords for DMR

Novel MV Repair Devices with Ongoing US Pivotal Randomized Trials

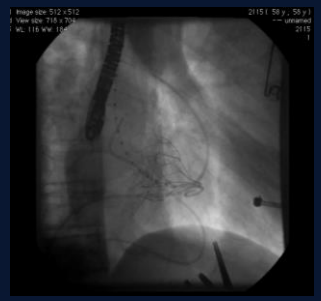
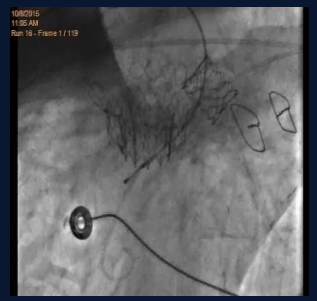




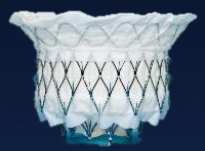
	Cardiac Dimensions Carillon	Edwards Cardioband	NeoChord DS1000
Trial acronym	CARILLON NCT03142152	ACTIVE NCT03016975	RECHORD NCT02803957
N rand	N=400; FMR 2:1 vs. GDMT	N=375; FMR 2:1 vs. GDMT	N=585; DMR 1:1 vs. MV surgery
Primary endpoints	1-year efficacy: Requires superiority of both a) hierarchical composite endpoint of death, HF hospitalize-tion, and improvement in 6MWD; b) change in regurgitant vol 1-year safety: Device-related major adverse events (PG)	1-year efficacy: Prevalence of MR ≤2+ and superiority in the hierarchical composite endpoint of CV death, HF hospitalization, and improvement in 6MWD and KCCQ (Win ratio)	Safety at 30 days: Major Adverse Events (superiority) Efficacy at 1 year: Grade II, III or IV MR, MV replacement or MV reintervention (noninferiority)

12 Transcatheter MVR Systems in Human Use

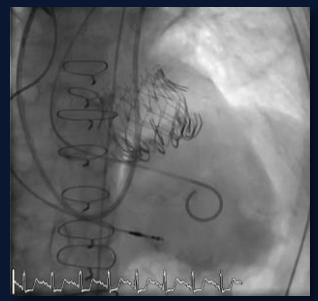
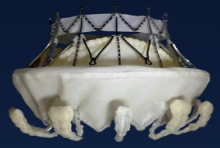
Pivotal US trials

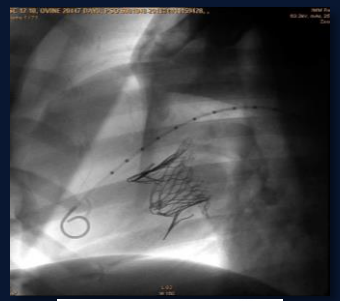

Abbott Tendyne



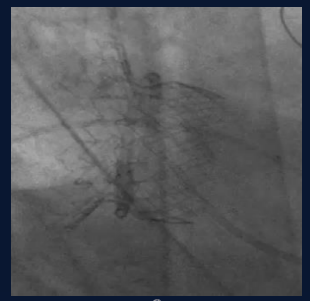
Medtronic Intrepid

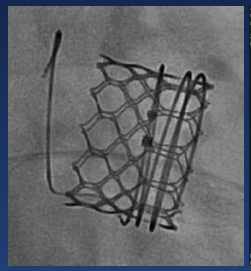
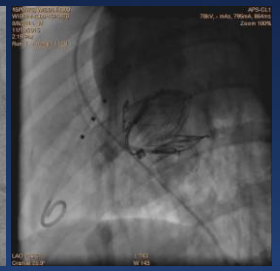
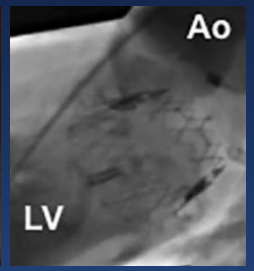
Edwards CardiAQ

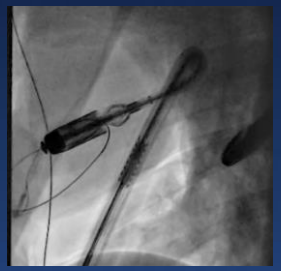
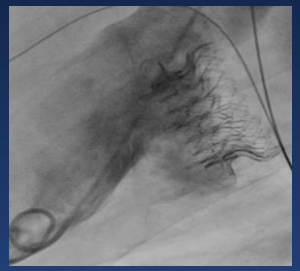
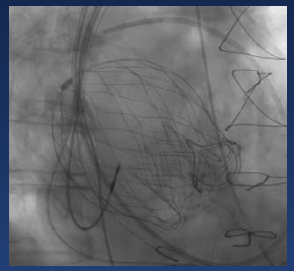
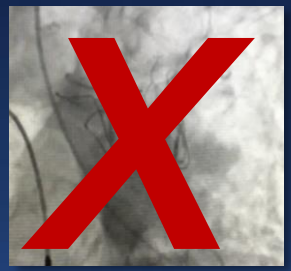



Neovasc Tiara




HighLife

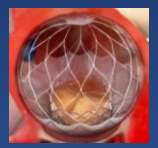
Edwards Sapien M3

Caisson

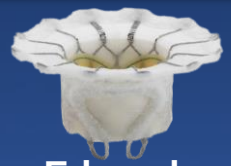
NaviGate

Cardiovalve

Abbott Cephea



4C AltaValve



Edwards Fortis

TMV Repair and Replacement: 2019 Status Update (i)

- More than 60 transcatheter devices have been developed to address the multi-dimensional disease state of MR
- One device (MitraClip) is firmly established and is in widespread use in the US and EU; 4 others have CE mark in EU; most have been used in small numbers of patients or are still in pre-clinical testing; and more than a handful have failed

TMV Repair and Replacement: 2019 Status Update (ii)

- The COAPT trial has demonstrated that the MitraClip improves prognosis in selected pts with HF and secondary MR who remain symptomatic despite maximally-tolerated GDMT – a paradigm shift for HF Rx
- Annuloplasty devices, neochords, TMVR and other novel approaches offer great potential to expand treatment options for pts with severe primary and secondary MR - studies are ongoing!