AP Valve
Seoul, August 9th, 2019

Transcatheter Mitral Valve Repair: Current Status and Future Perspectives

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Disclosure Eberhard Grube, MD

Physician Name	Company/Relationship
Speaker Bureau/Advisory Board:	Medtronic: C, SB, AB, OF LivaNova: C, SB, AB Highlife: AB, SB Boston Scientific: C, SB, AB Jena Valve: C,SB, AB CardioMech: C, SB, AB Mitral Technology: C, SB, AB
Equity Interest:	InSeal Medical: E, AB, MTEx: E, AB, SB Cardiovalve: E, SB, Claret: E, AB Shockwave: E, AB Valve Medical: E, AB Millipede E, AB, SB Pie-Cardia: E, AB, SB Imperative Medical: E, AB Ancora: E, AB, SB

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"Aaaaahhh – Mitral!"

"The next TAVI!"

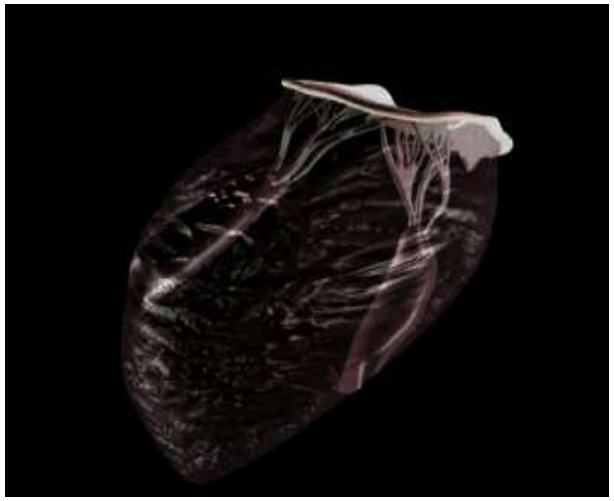
Well that is (unfortunately) not the Case

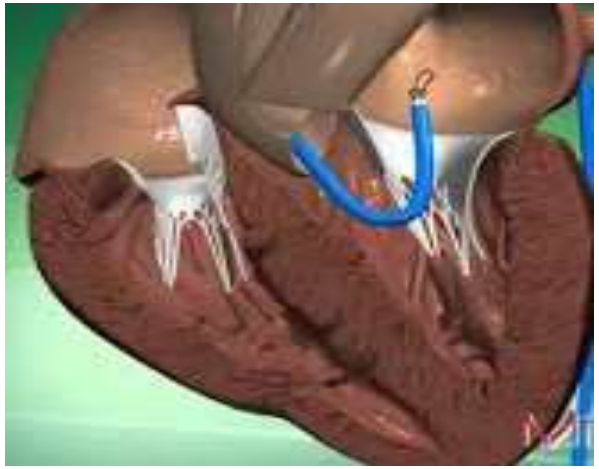
Aortic Valve

Mitral Valve

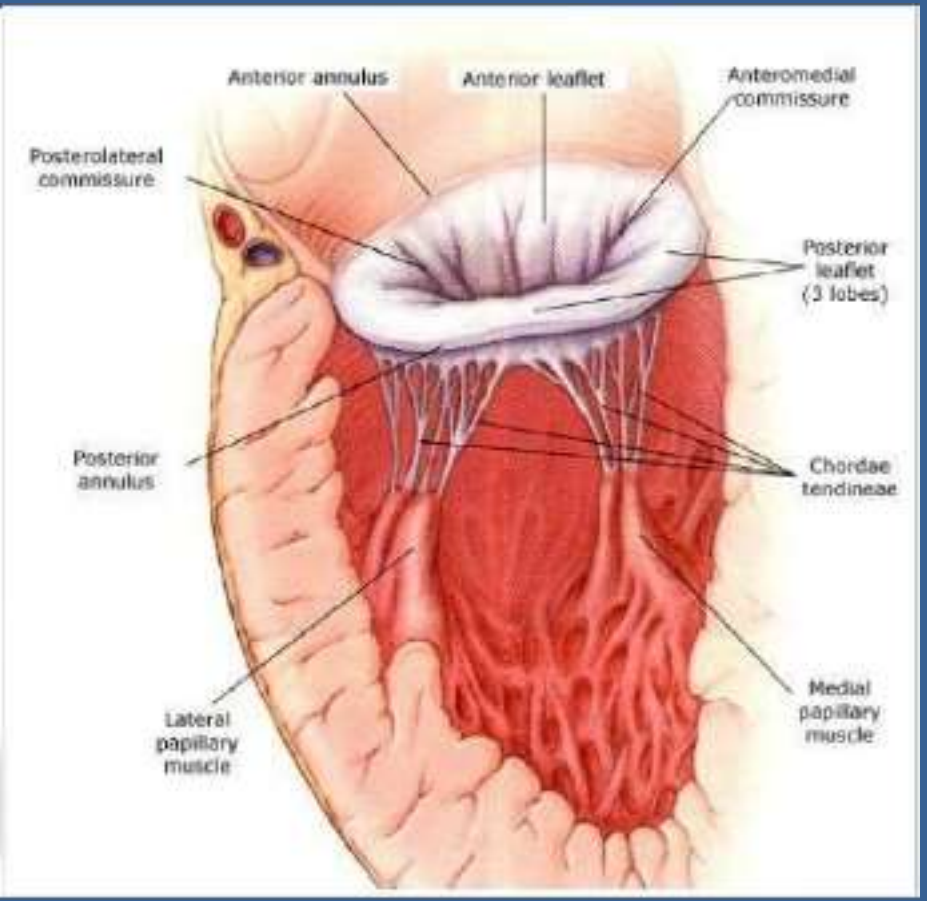
The Mitral Valve is very Special

- High Variability und Instability of the Anatomy
- Complex Apparatus /Annulus, Leaflets, Chordae, Papillary Muscles, LV etc...
- Access:
  - Trans-apical
  - Trans-atrial
  - Trans septal
- Two Pathologies:
  - Primary and Secondary Mitral Insufficiency





Mitral Valve

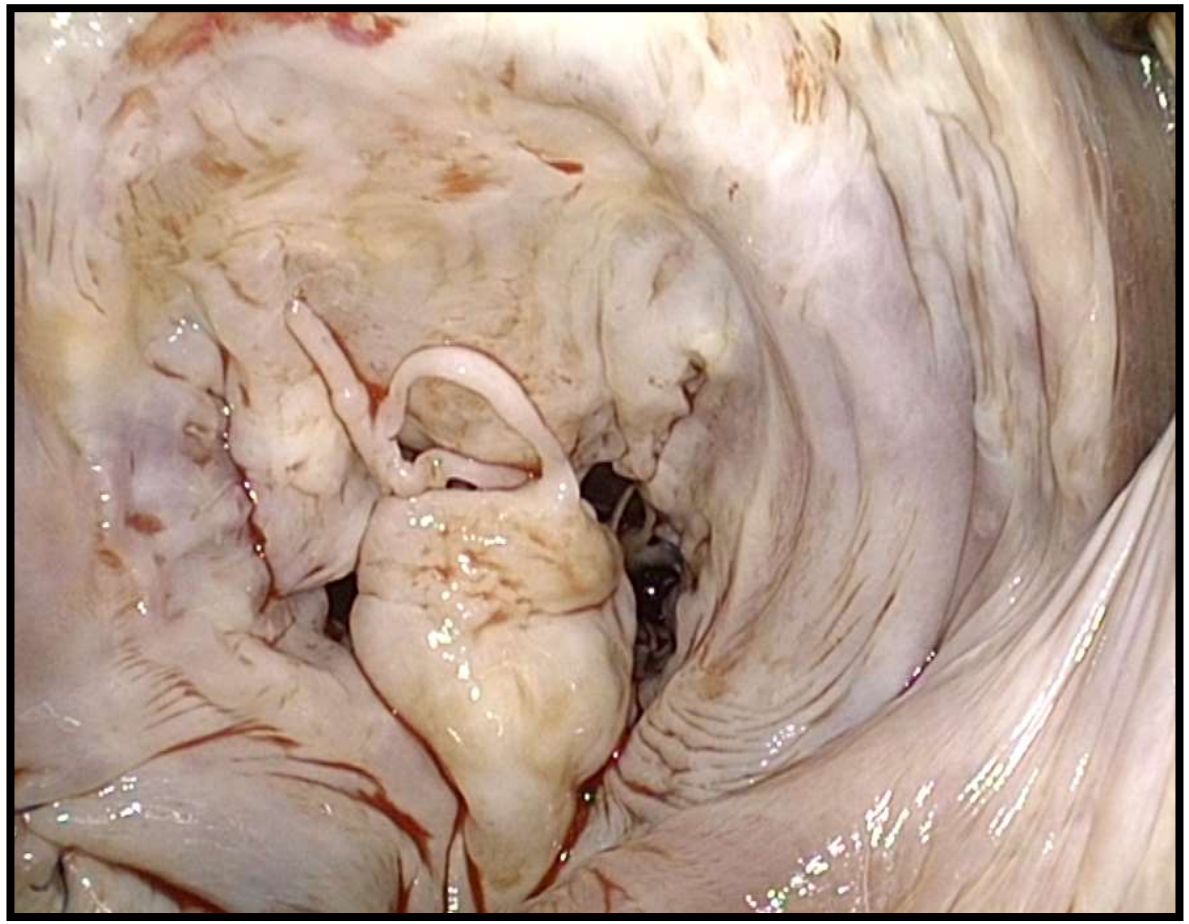


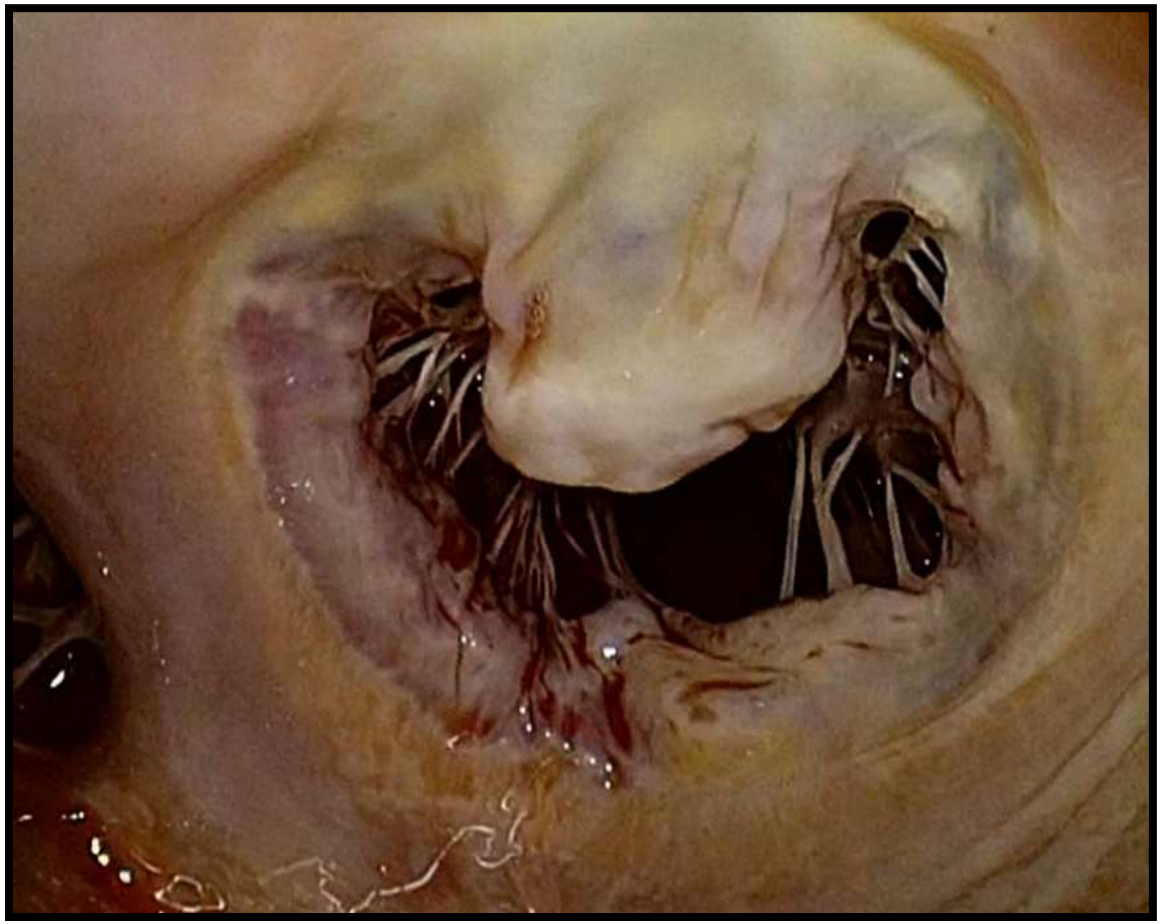
Two Types of Mitral Disease

Degenerative MR: Prolapse/Flail

Functional MR: Ventricular Problem

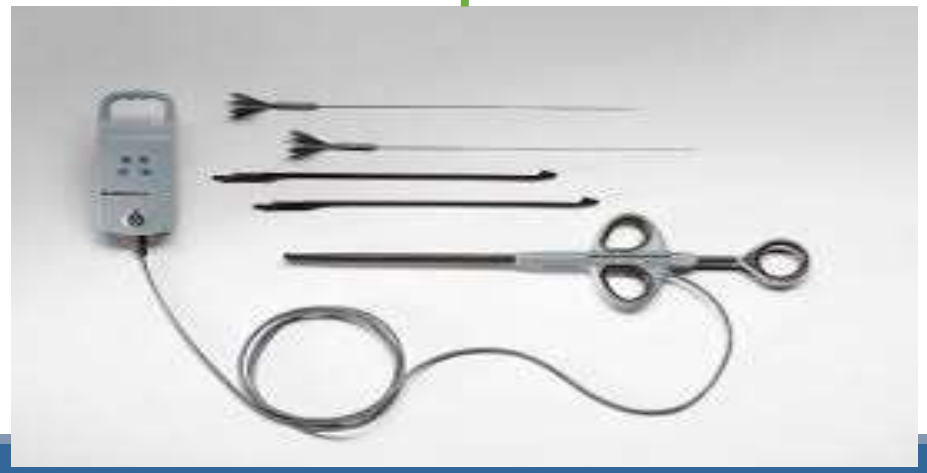
Degenerative MR *is not* Functional MR





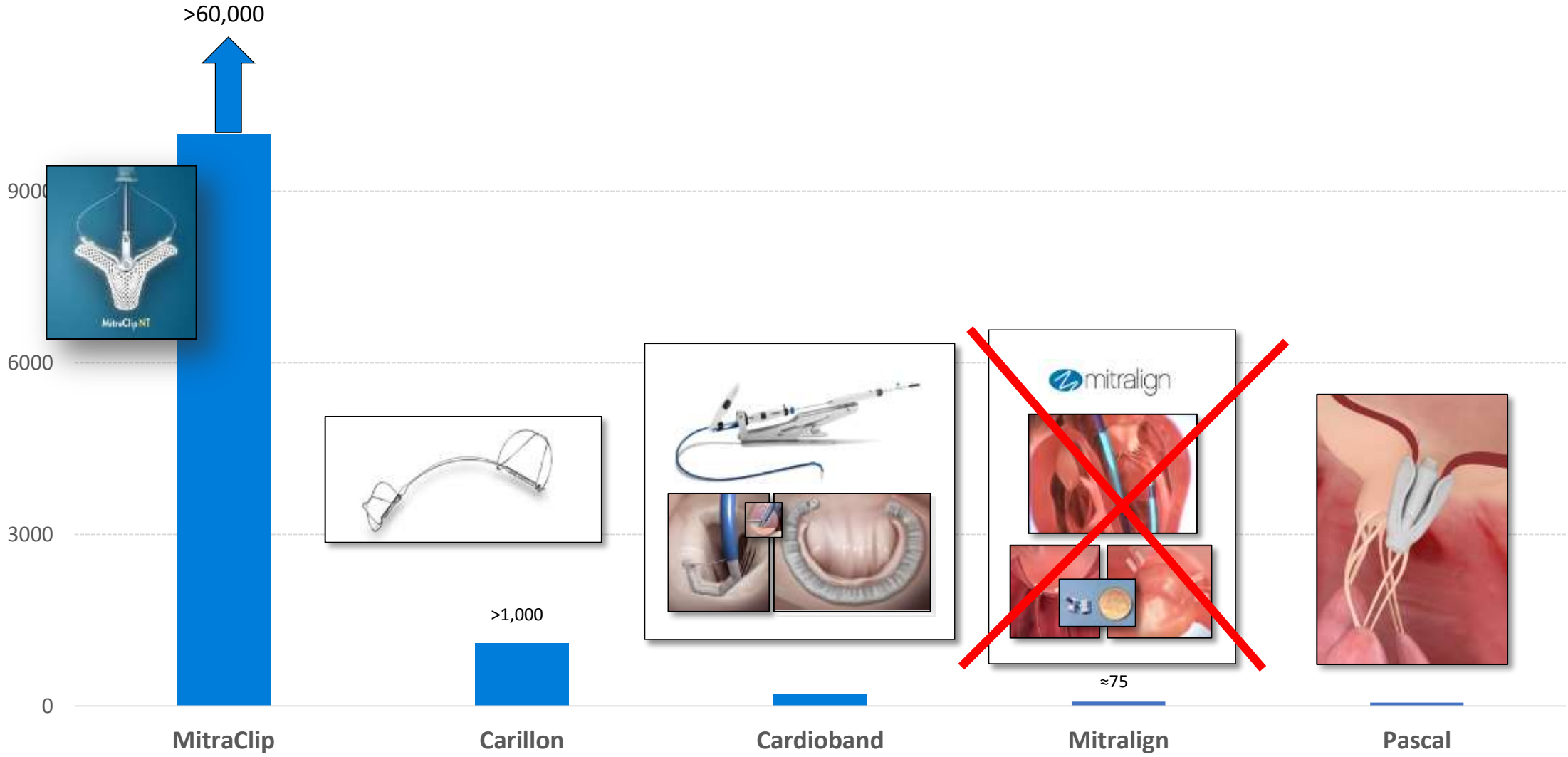
TMVR – CE certified Therapy Options

2008 → 2015 → 2016 → 2017



Waiting for CE approval:

Mitral Repair Devices in Use



Mitral Regurgitation
Unmet Need

- Surgical treatment of MR yields acceptable results, especially for primary MR

- However, patients with severe mitral regurgitation are denied surgery. Reasons include:

  ✓ Impaired LVEF
  ✓ Older Age
  ✓ Comorbidities / surgical risk status

➢ Transcatheter treatment strategies are needed for this large group of patients

[1]Dziadzko, et al., *Lancet* 2018; 391: 960-69; [2]Mirabel, et. al. , *Eur Heart J* 2007; 28: 1358-1365

Mitral Valve Repair

Transcatheter Repair Devices

A number of devices targeting the MV leaflets, chordal apparatus, and mitral annulus are under development. This presentation will focus on some. Overall, TMV repair (TMVr) devices show good safety outcomes, but improvements in ease of use and efficacy are required.

Anatomic Target	Device	Description	Main Indications	Status	Reported # of Treated Patients
Mitral Leaflets  	MitraClip	Edge-to-Edge	Primary and Secondary MR	FDA Approved CE Mark	>80,000
	Pascal	Edge-to-Edge	Primary and Secondary MR	CE Mark	>62
Mitral Annulus   	Carillon	Coronary Sinus cinching	Secondary MR	CE Mark	>1000
	Cardioband	Direct annuloplasty	Secondary MR	CE Mark	>100
	Millipede	Direct annuloplasty	Secondary MR	-	>65
Chordal Apparatus  	NeoChord	Artificial chordal implantation	Posterior leaflet flail/prolapse	CE Mark	>1100
	Harpoon	Artificial chordal implantation	Posterior leaflet flail/prolapse	-	>65

Mitral Interventions
Annulus MV Repair Systems

- ***Direct Annuloplasty***
  - *Mitralign*
  - Valcare AMEND
  - Cardiac Implants
  - Edwards Cardioband
  - BSC IRIS Millipede Ring

- ***Ventricular Repair***
  - Ancora
- ***Indirect Annuloplasty***
  - Carillon (coronary sinus approach)
  - Mitral Cerclage
  - MVRx

2017 AHA/ACC 2ry MR Valve Guidelines

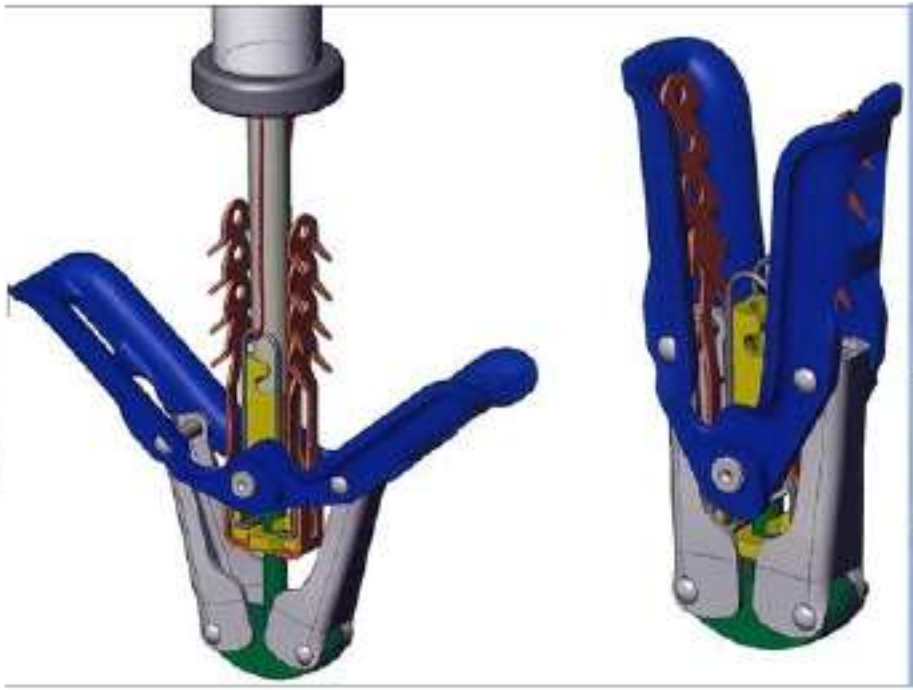
Class of recommendation	Level of evidence
IIb	B

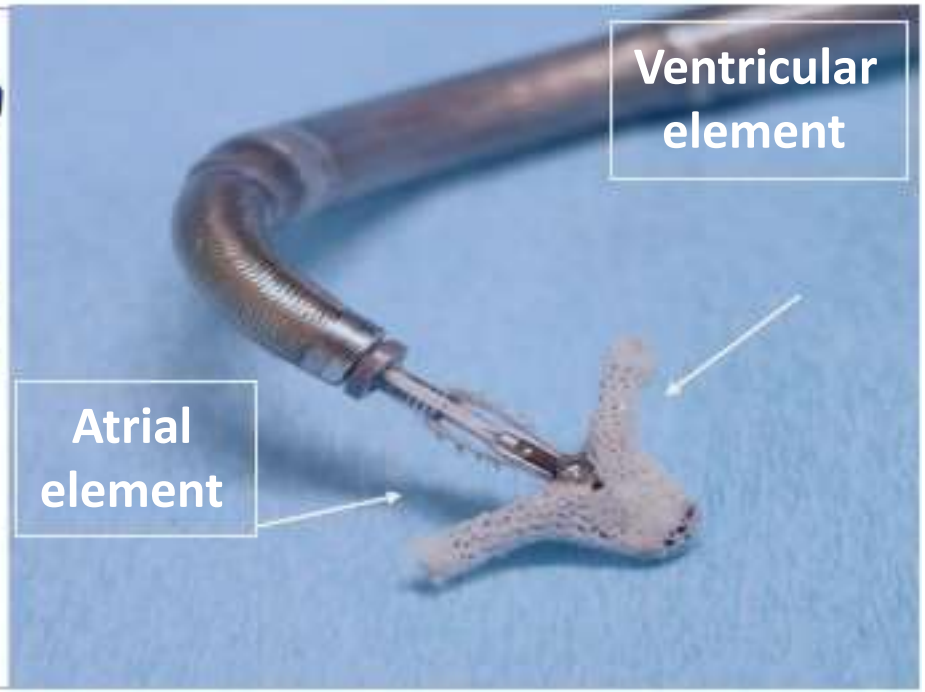
[Surgical] mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for heart failure

No recommendation for transcatheter MV repair

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

Imitate Prof Alfieri

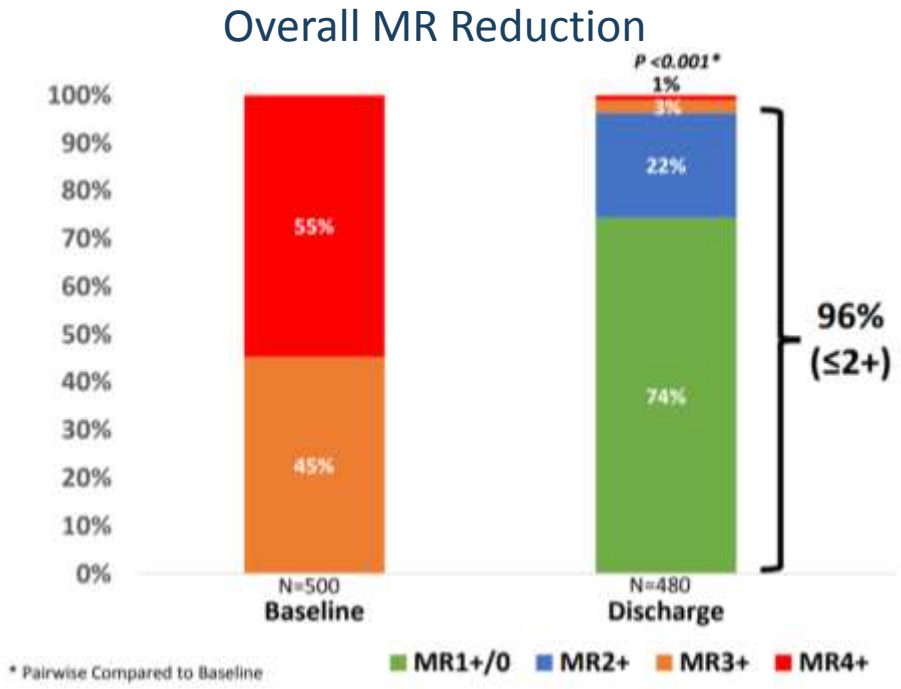


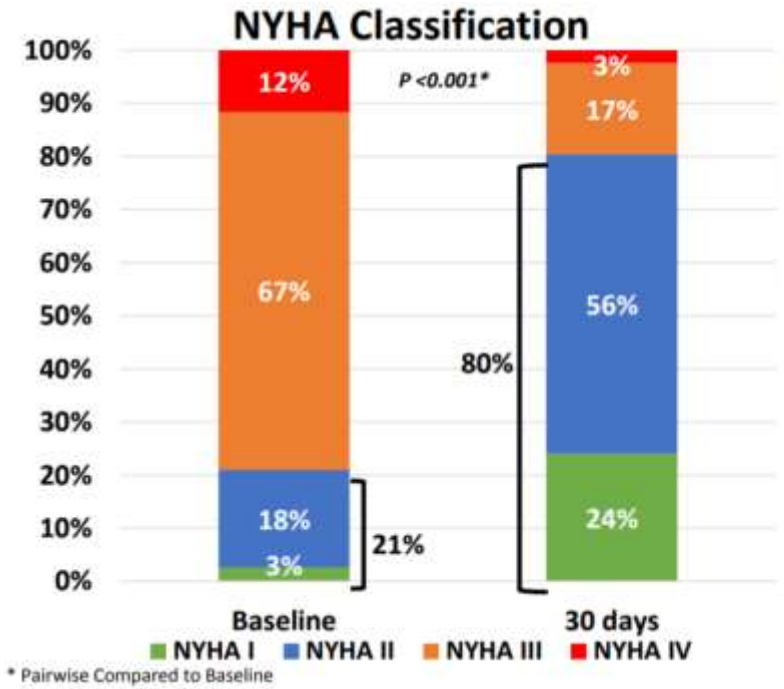


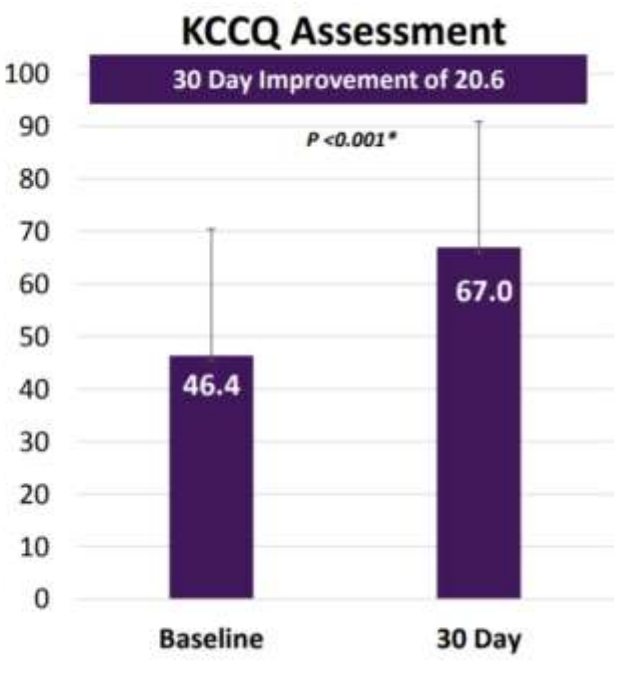
Leaflet Repair

MitraClip | Next Generation

Next generation MitraClip devices aim to improve ease-of-use. The EXPAND observational study is currently enrolling and an interim analysis of the first 500 patients showed significant MR reduction and improvements in QoL. In addition, it provided considerations for NTR and XTR device selection.







Adapted from Hausleiter, presented at EuroPCR 2019

MV World after COAPT
Words of Caution

STS/ACC TVT Registry (n= 2.952 pts)

MitraClip TVT Registry

pt, 2015; linked records to CMS claims data

de 4
de 3
de 2
de 0/1

40% with post-procedural MR ≥ 2

SLDA, 1.5%

In-hospital mortality = 2.7%

85.9% discharged home

Median LOS, 2 days

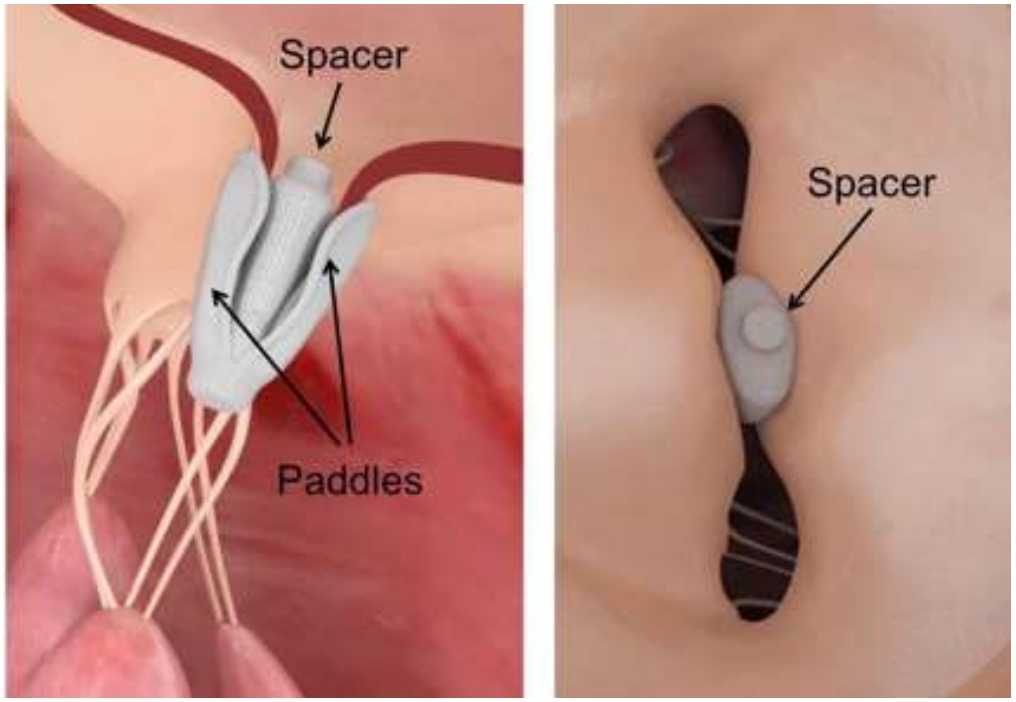
(1, 5 days)

Acute procedure success = 91.8%

The „Mitral World“ after COAPT

- Increased optimism with MV therapies
- Trial recruitement for other devices will become more difficult
- If the Clip becomes standard of care it might become the comparator for other mitral innovations
- HF specialists are now more actively involved
- Safety of the Clip procedure will be difficult to match
- The results of the COAPT trial are difficult to replicate in all patients. More devices are needed.
- Surgery remains an option for DMR in younger patients and more complex anatomies....

Leaflet Repair
PASCAL

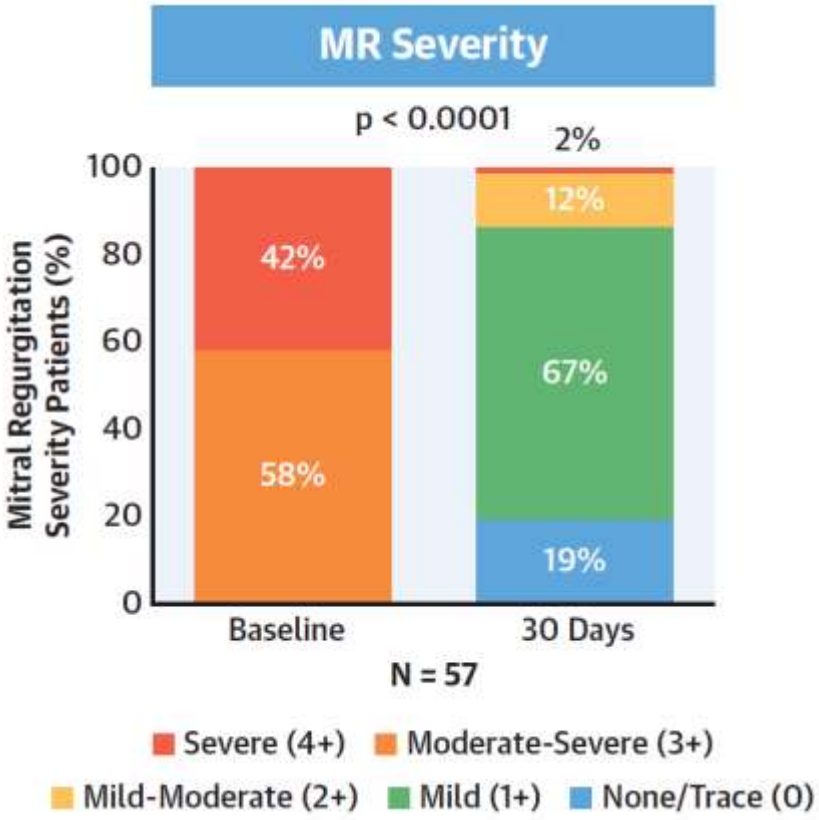


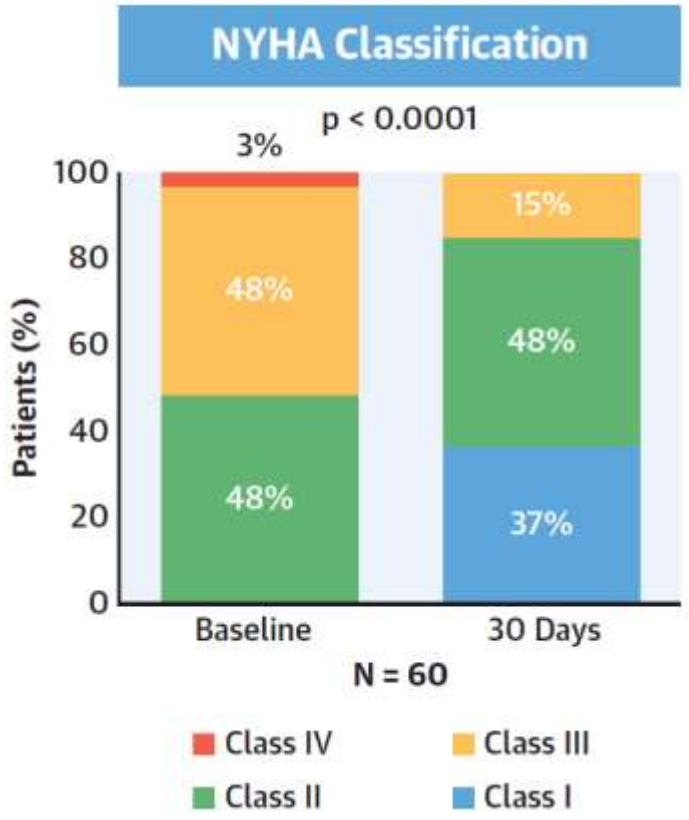
- Edge-to-edge repair
  - Based on Alfieri edge-to-edge suture approach
- System consists of
  - 22 Fr steerable guide sheath
  - Steerable catheter
  - Pascal device
    - Spring-loaded paddles
    - 10 mm central spacer
- Transseptal approach

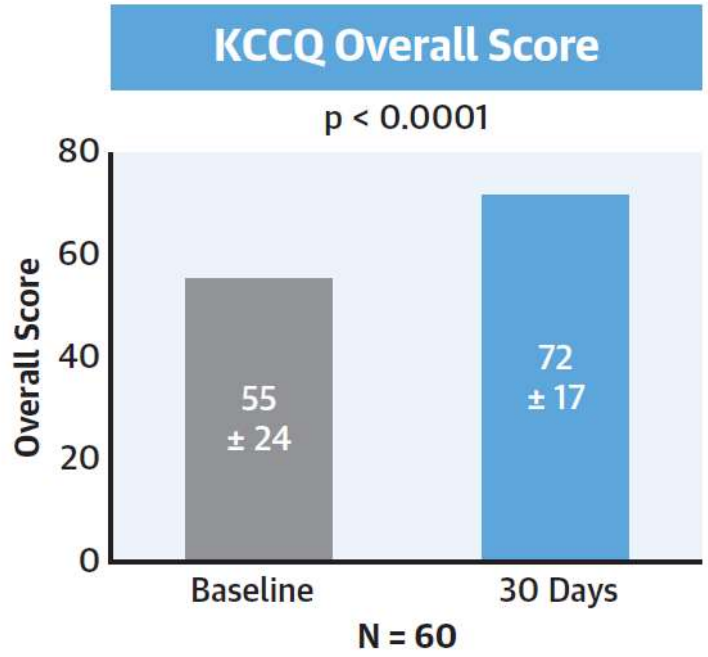
[1]Adapted from Feldman, presented at CRT 2019

Leaflet Repair
PASCAL

30-Day outcomes of the CLASP Early Feasibility Study showed significant improvements in MR severity, NYHA Functional class, and quality of life.





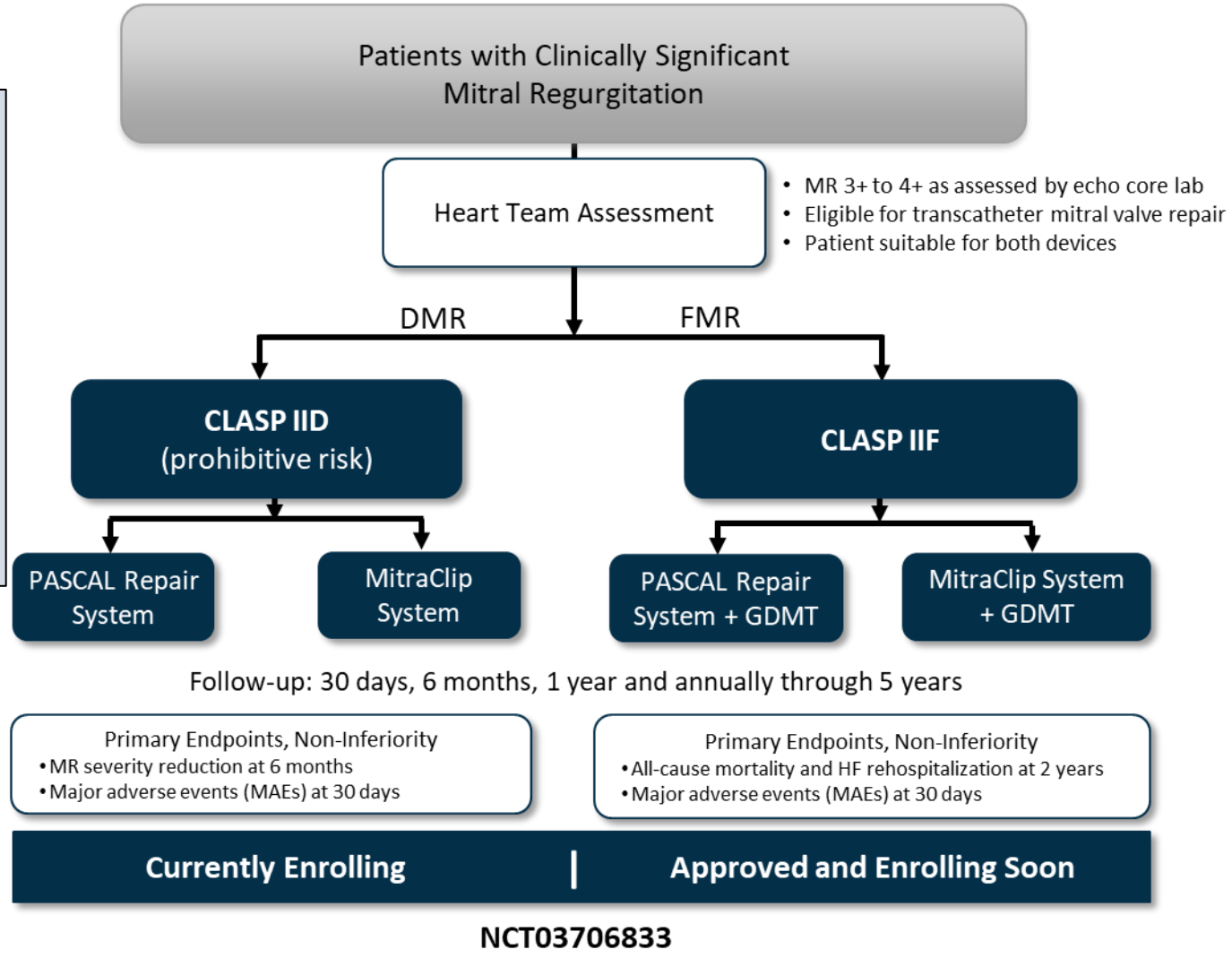


[1]Lim et. al. , *J Am Coll Cardiol* 2019; 22(14): 1369-1378

Leaflet Repair
PASCAL

The PASCAL device received CE Mark in February 2019.

The CLASP IID/IIF Pivotal Trial is currently underway and will evaluate the safety and effectiveness of PASCAL compared to MitraClip in patients with primary and secondary MR.

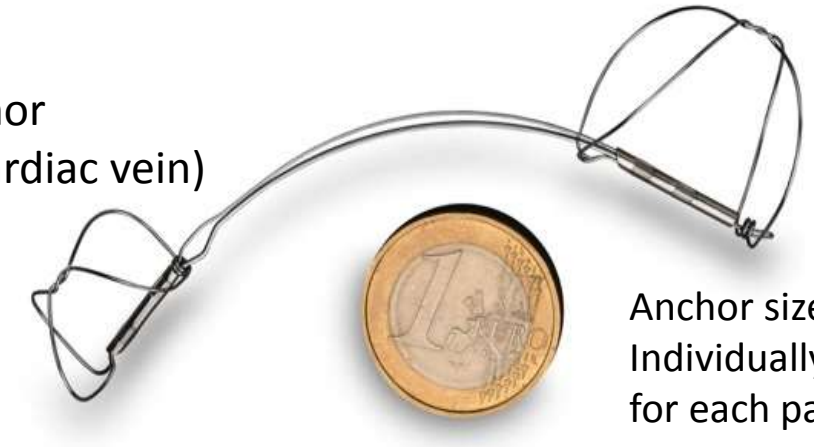


[1]Lim, presented at TVT 2019

Annular Repair
Carillon

Proximal Anchor
(in coronary sinus)

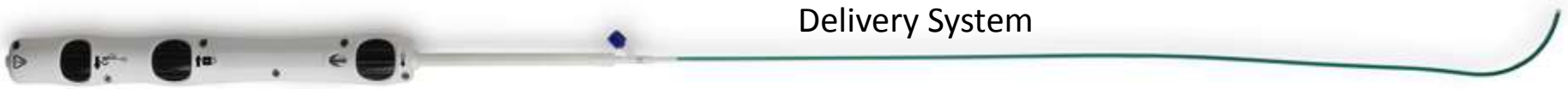
Distal Anchor
(in great cardiac vein)



Anchor sizes:
Individually selected
for each patient

Implant lengths:
60 - 80 mm

- Coronary sinus cinching
- System consists of
  - 9 Fr delivery catheter
  - Fixed-length, double-anchor, self-expanding nitinol device
  - Positioned with the coronary sinus/great cardiac vein
  - Once in place device cinched and tethered
- Transjugular/Coronary sinus access



Delivery System

[1]Adapted from Kapadia, presented at CRT 2019

Annular Repair
Carillon

Results of the randomized, sham-controlled REDUCE-FMR trial that assessed the safety and efficacy of transcatheter mitral annuloplasty with the Carillon device were presented in September, 2018.

	Implanted (n=73)	Control (n=33)
Age, Yr.	70±9	69±9
Male	78%	73%
Etiology, Ischemic	68%	64%
Prior MI	52.1%	51.5%
NYHA Class		
II	47.9%	44.5%
III	49.3%	51.5%
IV	5.5%	0
A Fib	58.6%	60.6%
HFH in Prior Year	46%	42%
LVEF (%)	32.8 ± 8.6	37.1 ± 8.7
LVEDD (cm)	6.5 ± 0.9	6.4 ± 0.9
EROA (cm^2)	0.25 ± 0.15	0.24 ± 0.14
RV (ml)	38.6 ± 23.5	38.1 ± 24.0
MR Grade (%)*		
1+	34.2%	32.3%
2+	37.0%	25.8%
3+	23.3%	35.5%
4+	5.5%	6.5%

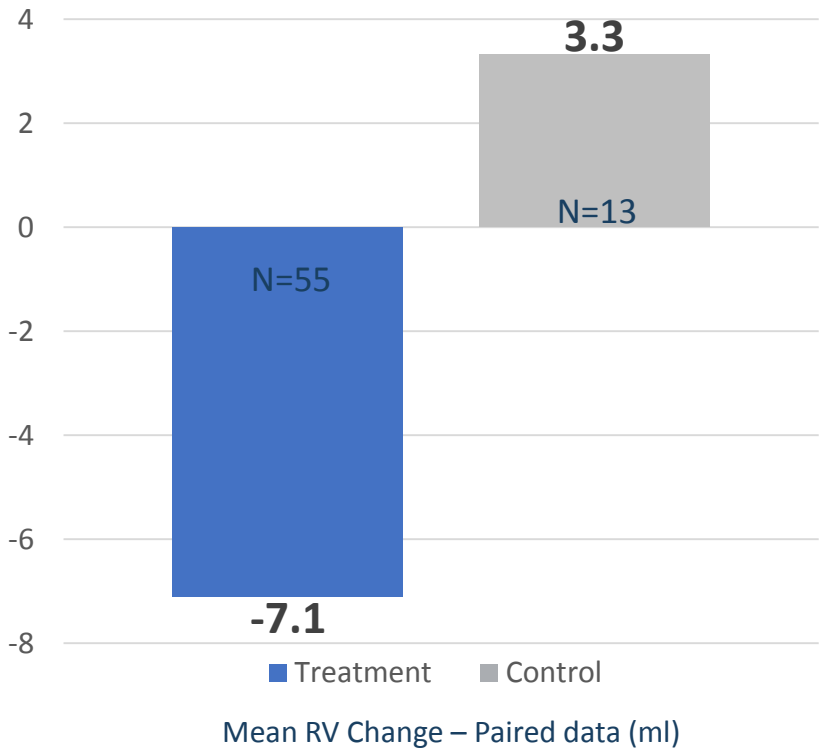
[1]Adapted from Sievert, presented at TCT 2018

Annular Repair
Carillon

After 12 months, investigators showed

- No difference in the cumulative major adverse event rates between the study and sham procedure arms (16.1% vs 18.2%).
- ***Those who received the Carillon device saw a 22% reduction in regurgitant volume compared with an 8% increase in those who had sham procedures*** (*P* = 0.03, ITT population).
- Trends for positive remodeling were observed in the as-treated analysis.

Change in Regurgitant Volume (RV) at 1-year (ITT)



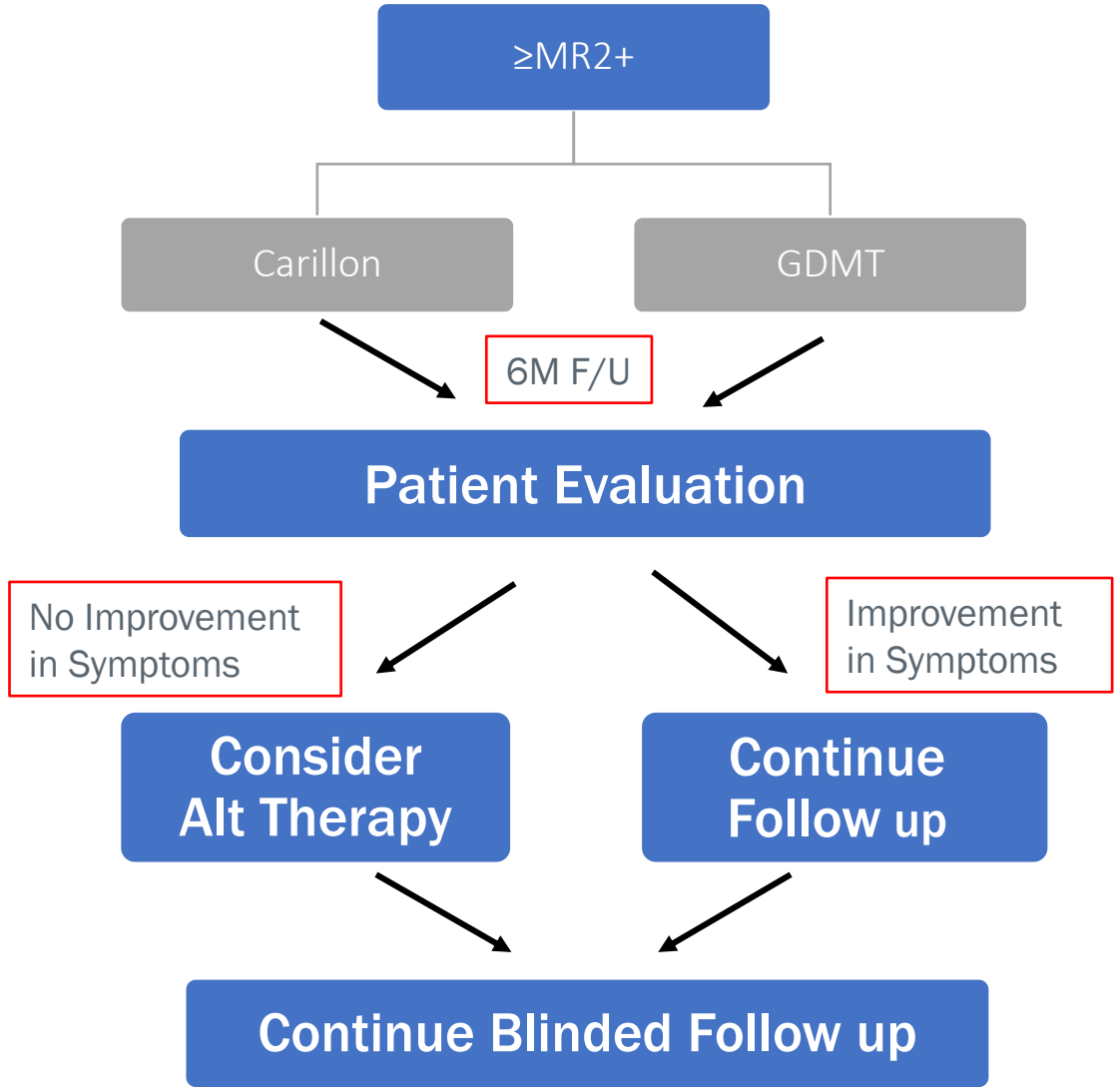
[1]Adapted from Sievert, presented at TCT 2018

Annular Repair
Carillon

The Carillon Pivotal Study design in the US was recently revised in light of the U.S. MitraClip approval

Key Changes:

- Randomization scheme changed from 2:1 to 1:1
- New clinically relevant hierarchical endpoint
  - Accommodates alternative therapies with 24 month follow up
  - Trial becomes a viable option for physicians who embrace COAPT, as well as those who remain skeptical based on Mitra-FR
- Primary Endpoint analysis timeframe extended to 2 years
  - Acknowledging relative benefits seen in COAPT between year one and year two
- Blinded Central Review Committee
  - Provides consistent patient selection and adjudication of alternative therapy primary endpoint events



[1]Adapted from Kapadia, presented at TVT 2019

Annular Repair
Cardioband

- Percutaneous annuloplasty
- System consists of
  - 24 Fr steerable guide catheter and implant catheter
  - Variable length tubular Dacron band with helicoidal anchors that fix implant into annulus
- Transseptal

[1]Adapted from Maisano, presented at CRT 2019

Annular Repair
Cardioband

The CE Mark Trial showed a favorable safety profile with reduced MR that was sustained out to 2 years. Technical success in this early experience was only 78.3% due to anchor disengagement. Recent device iterations aim to improve this complication.

Adjudicated Events[1]	30 Days n (%)
Death	2 (3.3)
Intracranial hemorrhage[2]	1 (1.6)
Multi-organ failure and sepsis following elective mitral surgery[2]	1 (1.6)
Myocardial infarction	1 (1.6)
Major bleeding complications	2 (3.3)
Renal failure	4 (6.6)
Cardiac tamponade	1 (1.6)
Respiratory failure	0 (0.0)

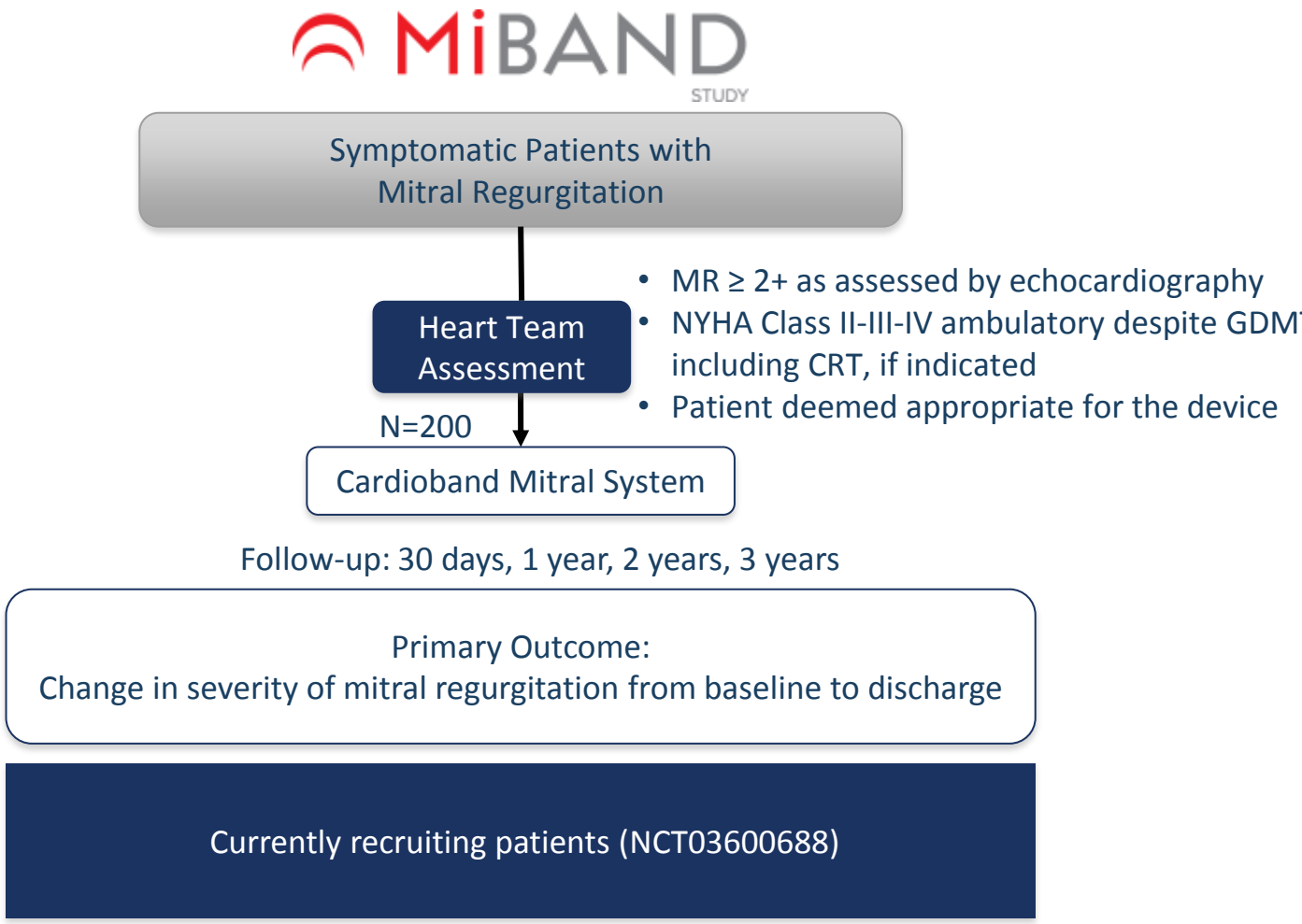
Mitral Regurgitation

[1]Adapted from Maisano, presented at TCT 2016

Annular Repair
Cardioband

The MiBAND Trial is a Prospective, multicenter, single arm European Post-Market Study

The purpose is to assess the safety and efficacy of the Cardioband Mitral System

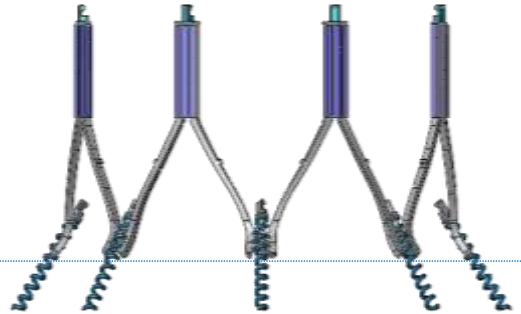


[1]Whisenant, presented at TVT 2019

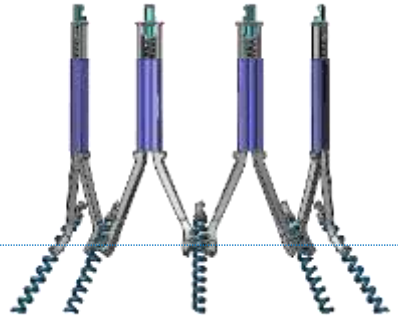
Annular Repair
Millipede

- Percutaneous annuloplasty
- System consists of
  - 23 Fr delivery catheter
  - Complete, semi-rigid, nitinol ring
  - Pre-attached anchors
  - Repositionable and retrievable until ring released
  - Implemented ICE catheter
- Transseptal

Placement



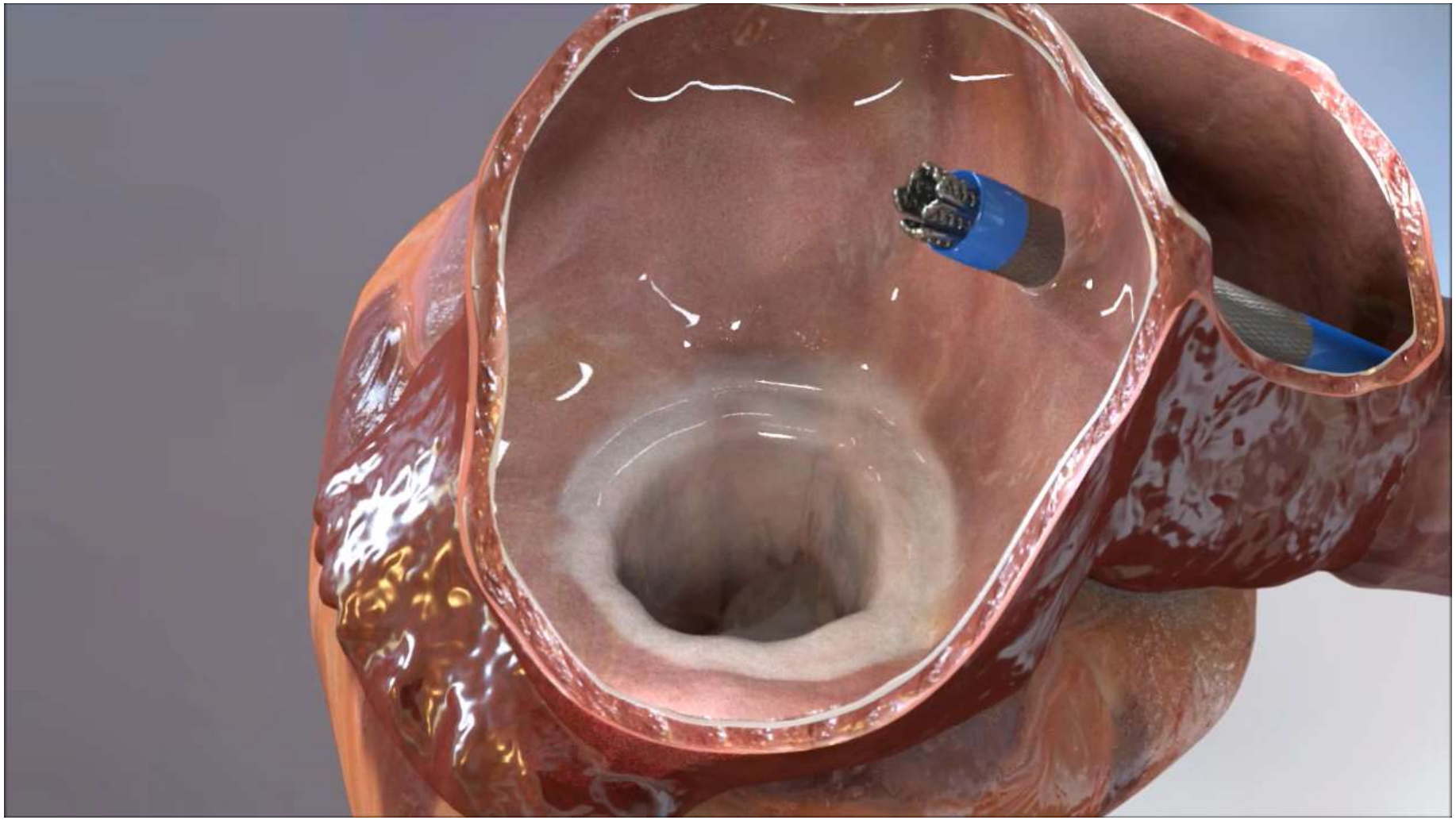
Anchor



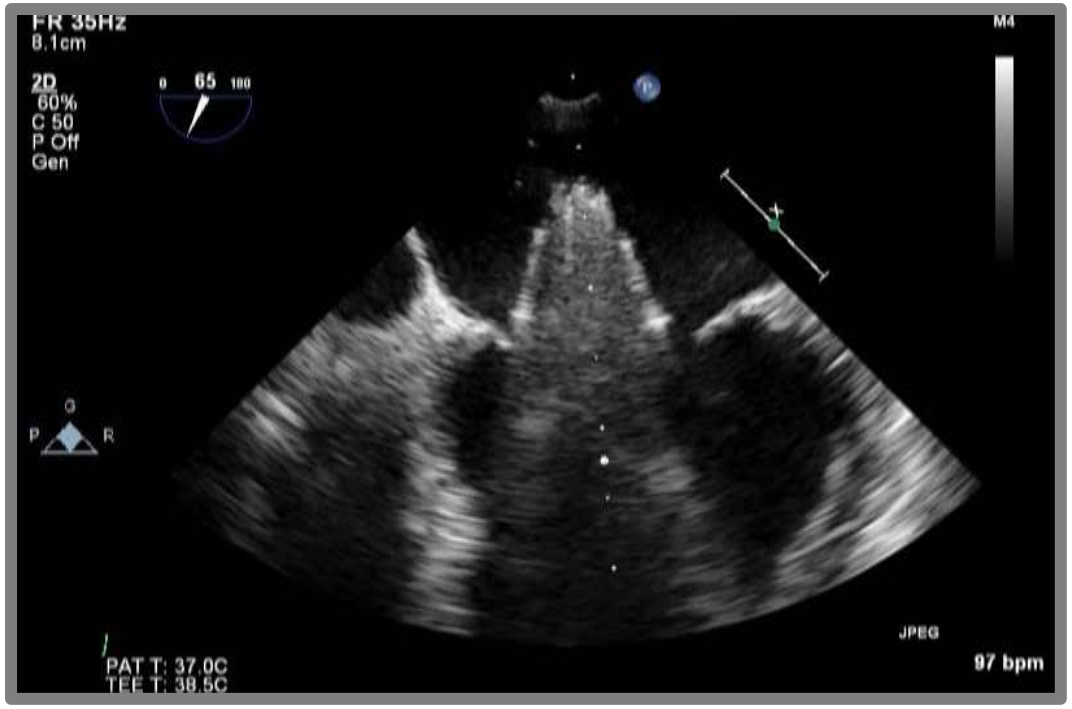
Actuate

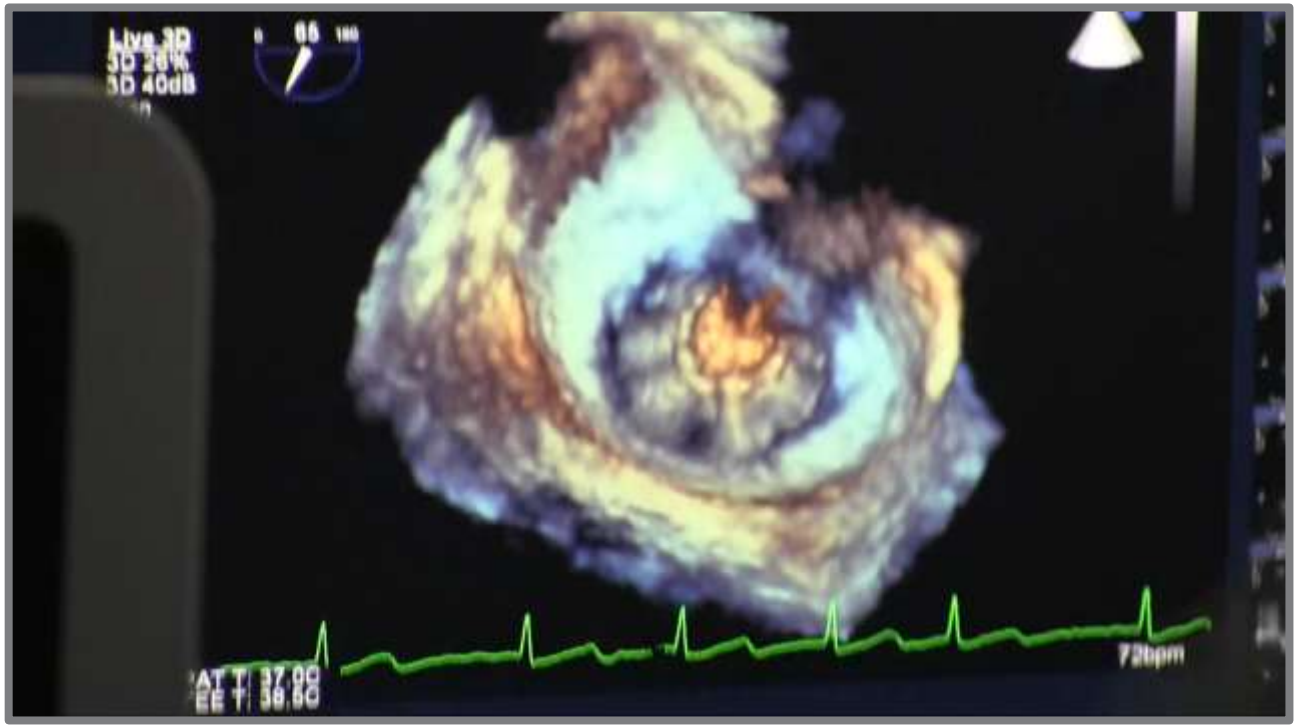
[1]Adapted from Bolling, presented at CRT 2019

Millipede Transcatheter Annuloplasty Ring System with Integrated ICE Imaging



Boston Scientific Millipede IRIS™
Transcatheter Mitral Repair System





2D and 3D Echo Positioning

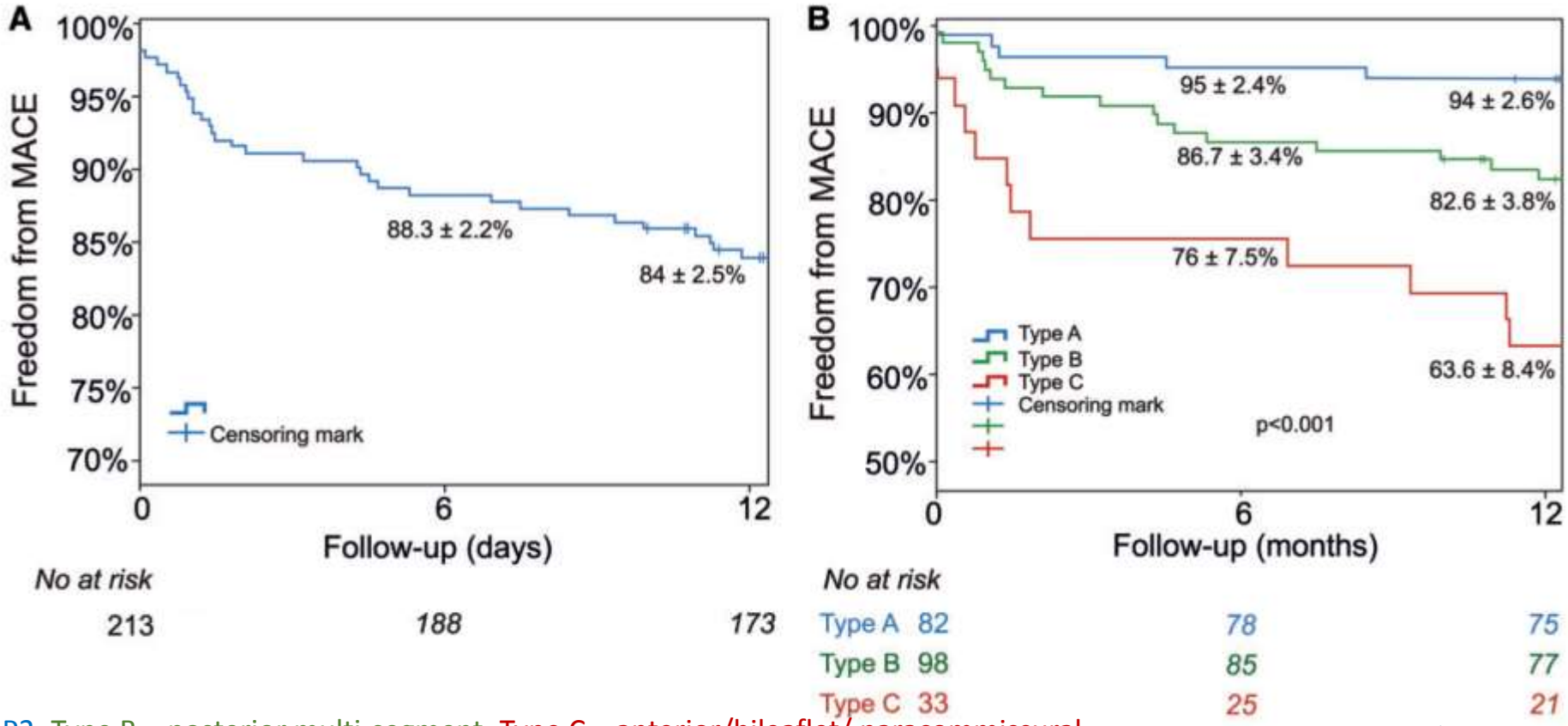
Chordal Repair Devices
Neochord

- Chordal implant
- System consists of
  - Delivery instrument with leaflet grasping tip and needle
    - Leaflet grasp confirmed by fiber optics in the tip
  - Needle pre-loaded with PTFE suture used to fix MV leaflet to LV apex
- Transapical access

[1]Adapted from Sievert, presented at CRT 2015

Chordal Repair Devices
Neochord

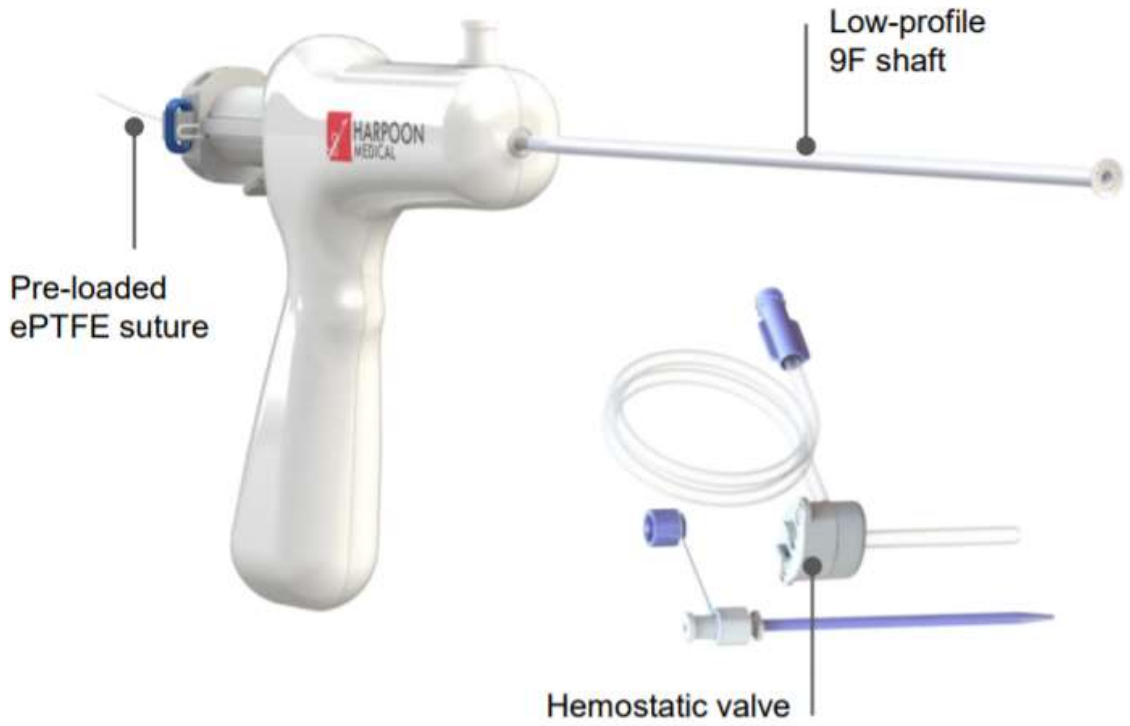
The experience with NeoChord is relatively large with >1100 patients treated. Early European experience in 213 patients helped to identify those patients who are most likely to benefit from chordal repair with the NeoChord system.



Type A = isolated P2; Type B = posterior multi-segment; Type C = anterior/bileaflet/ paracommissural

[1]Colli et. al. , *Eur J Cardio-Thoracic Surg* 2018; 0:1-7

Chordal Repair Devices
Harpoon



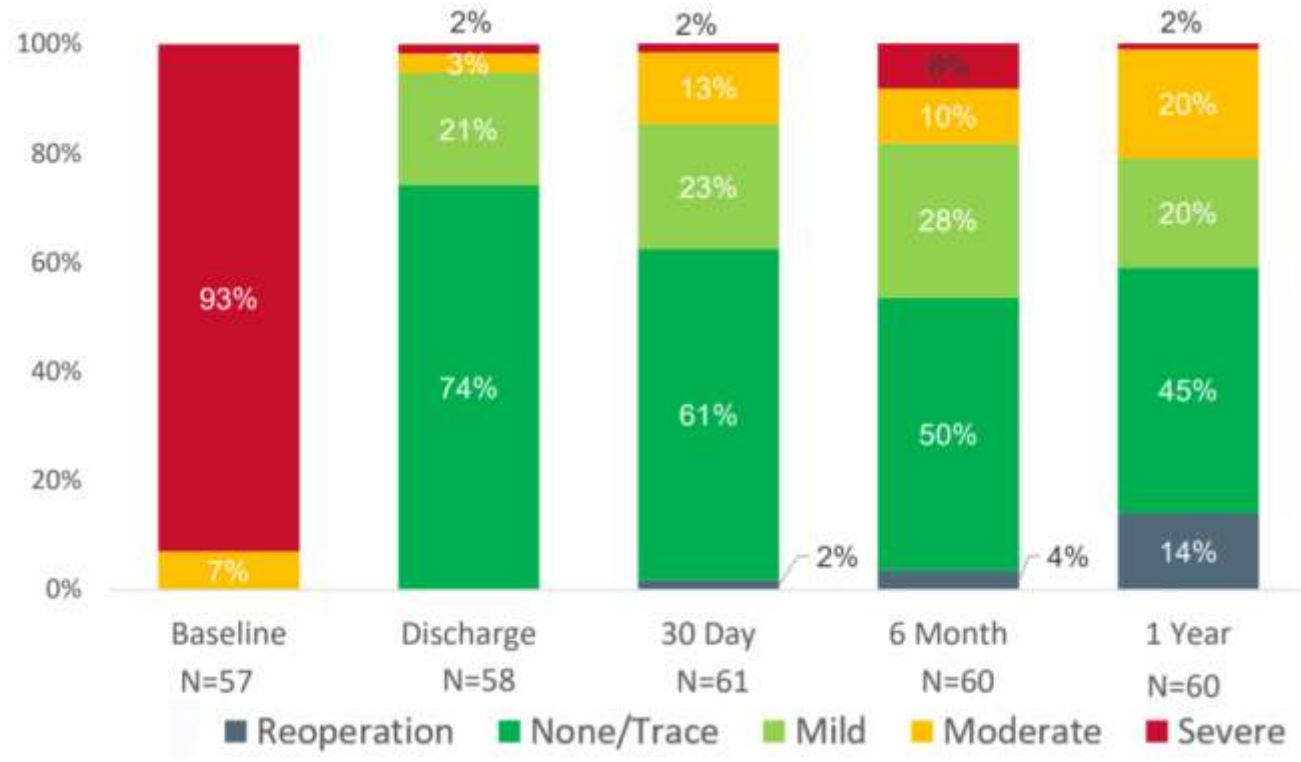
- Chordal implant
- System consists of
  - 9 Fr delivery system
  - Needle with ePTFE suture used to fix MV leaflet to LV apex
- Transapical access

[1]Adapted from Gammie, presented at TVT 2019

Chordal Repair Devices

Harpoon

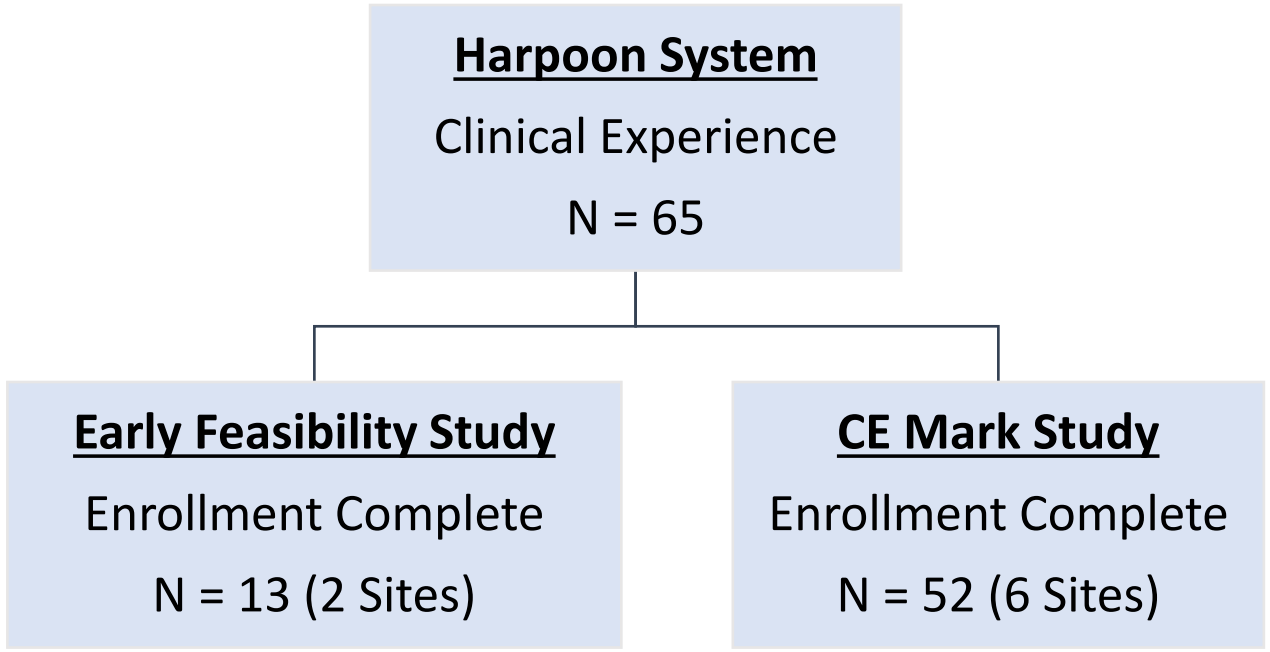
Successful implantation of cords with MR reduction to mild or less occurred in 95% of patients at discharge. The procedure was safe with no deaths or strokes. At 1-year MR was mild or less in 79% of patients, and favorable cardiac remodeling was observed.



[1]Gammie, presented at TVT 2019

Chordal Repair Devices
Harpoon

Future Study Summary: 65 Subjects in Two Studies in EU



- Follow up is ongoing
- Current status: 48 subjects completed 1 yr, and 19 completed 2 yr follow-ups
- Enrollment in Harpoon clinical studies is currently on pause

"In April 2018, a very small number of patients from the Harpoon studies were diagnosed with recurrent severe mitral regurgitation and subsequently underwent reoperation."

"Edwards decided to temporarily pause study enrollment until the potential root causes of these reoperations can be better understood."

- Dr. Bartus, TCT 2018

[1]Adapted from Bartus, presented at TCT 2018

Summary

- Transcatheter options are needed to treat the large group of patients with secondary MR who are currently denied surgery.
- Recent results with the MitraClip device show select patients with secondary MR can benefit from TMVr therapy.
- Current devices target the MV leaflets, chordal apparatus, and mitral annulus.
- Experience with TMVr devices is limited, with the exception of MitraClip.
- Overall, TMVr devices show good safety outcomes, but improvements in ease of use and efficacy are required.