31 Giornate Cardiologiche Torinesi
Turin, Italy, Oct 24-26, 2019

Transcatheter Mitral Valve Annuloplasty

Horst Sievert,

Kolja Sievert, Ilona Hofmann, Sameer Gafoor, Stefan Bertog, Predrag Matić, Markus Reinartz, Bojan Jovanovic, Shahrak Zaker, Iris Grunwald, Nalan Schnelle, Robert Andel, Anja Vogel, Pamela Ilioska, Kai Ruffmann, Gerhard Sell

CardioVascular Center Frankfurt - CVC,

Frankfurt, Germany

Disclosures

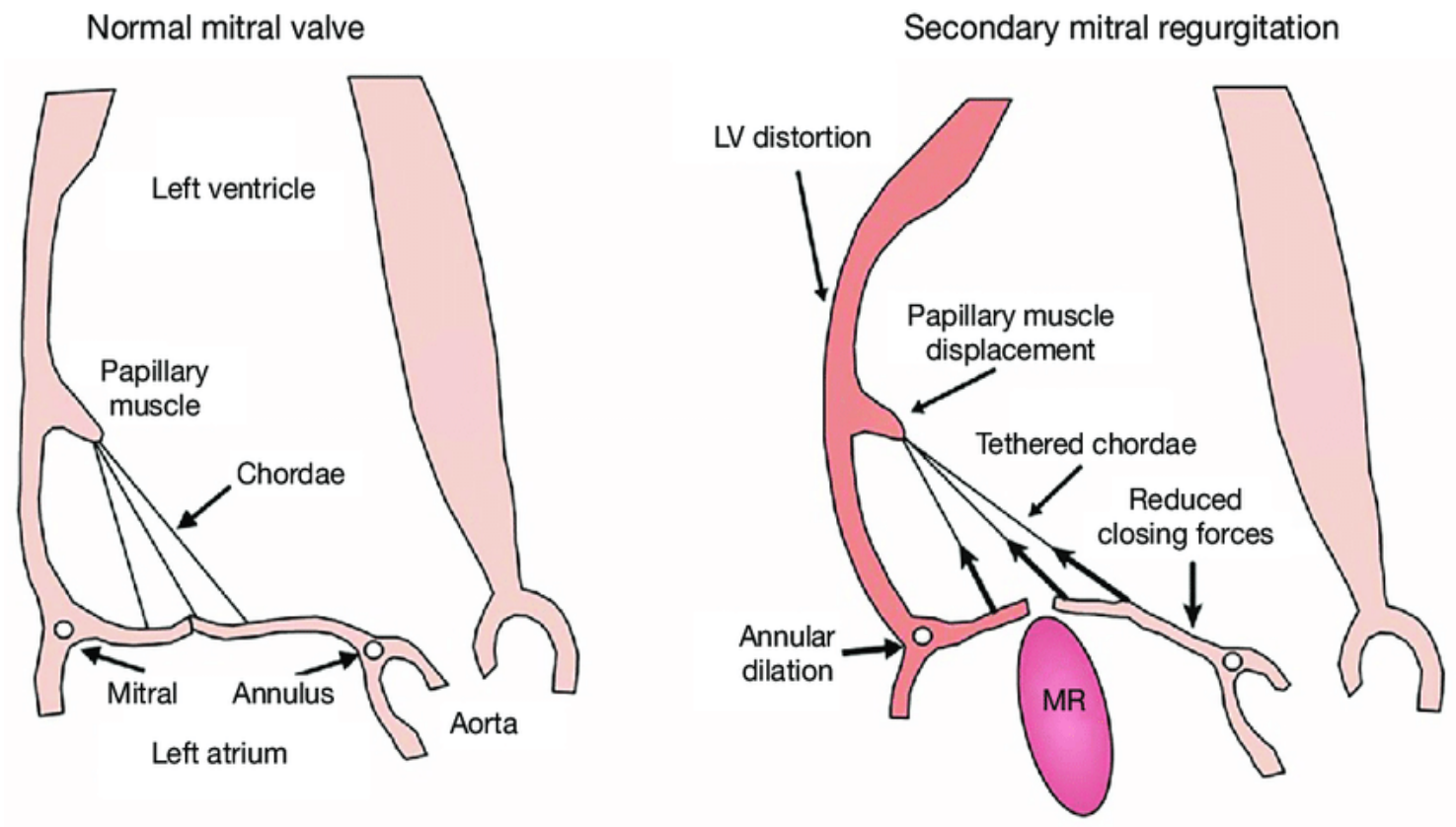
Physician name	Company	Relationship
Horst Sievert	4tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Append Medical, Bavaria Medizin Technologie GmbH, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, Cardimed, Celonova, Comed B.V., Contego, CVRx, Dinova, Edwards, Endologix, Hemoteq, Hangzhou Nuomao Medtech, Holistick Medical, Lifetech, Maquet Getinge Group, Medtronic, Mokita, Occlutech, Recor, Renal Guard, Terumo, Vascular Dynamics, Vectorious Medtech, Venock, Venus, Vivasure Medical	Study honoraria to institution, travel expenses, consulting fees to institution

Two Types of Mitral Regurgitation

Degenerative MR: Prolapse/Flail

Functional MR: annulus dilated due dilation of the left ventricle and/or the left atrium

Functional mitral regurgitation is not a disease of the valve, it is a disease of the left ventricle:



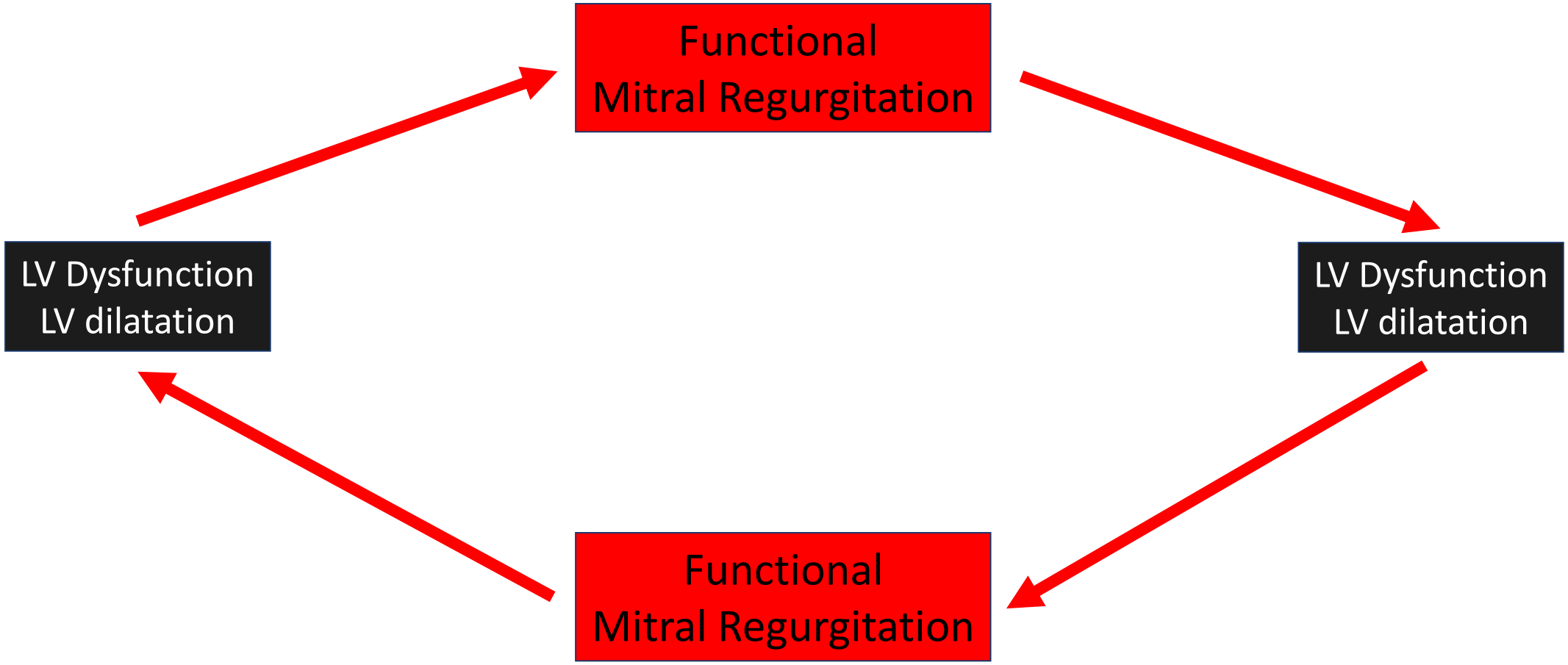
- The papillary muscles are displaced
- The chordae are under tension
- The annulus is dilated
- The "closing force" on the leaflets is lower
  - due to low systolic pressure in the LV and higher LA pressure
- The leaflets are normal

Paul A. Grayburn, TVT 2019

Functional mitral regurgitation (FMR) is not a disease of the valve, it is a disease of the left ventricle

So why to even consider treating the valve?

Because FMR is part of a vicious circle:



Obviously, elimination of mitral regurgitation may interrupt this circle

There is no question that we should **always** start with optimal medical therapy!

But "Optimal Medical Therapy" is not optimal!

In fact, ...it's terrible !!

ERO

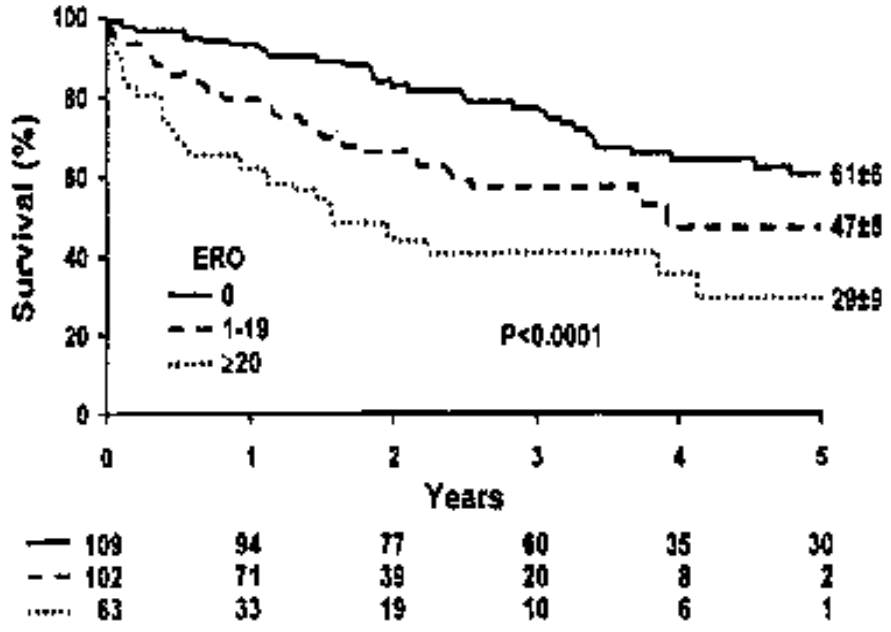


Figure 3. Survival (±SE) after diagnosis according to degree of MR as graded by ERO ≥20 mm^2 or <20 mm^2. Numbers at bottom indicate patients at risk for each interval.

RVol

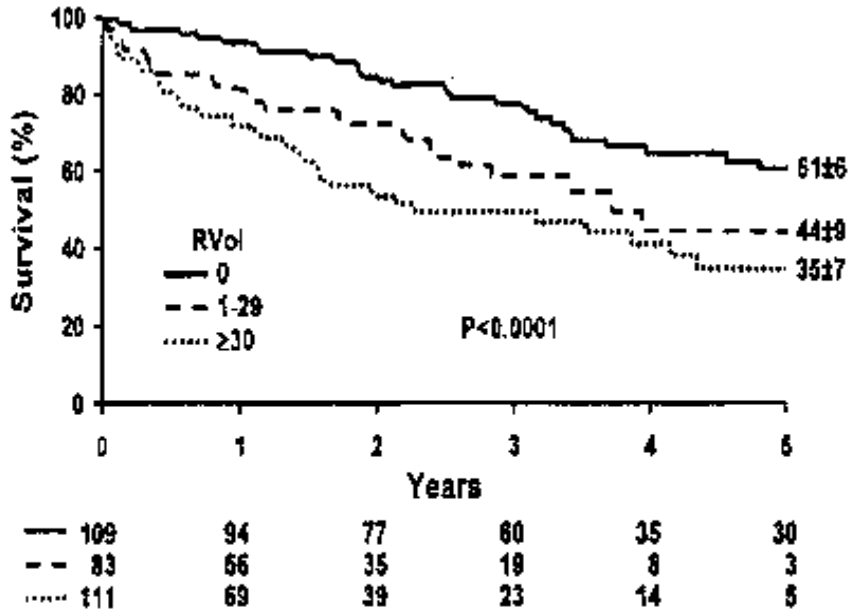
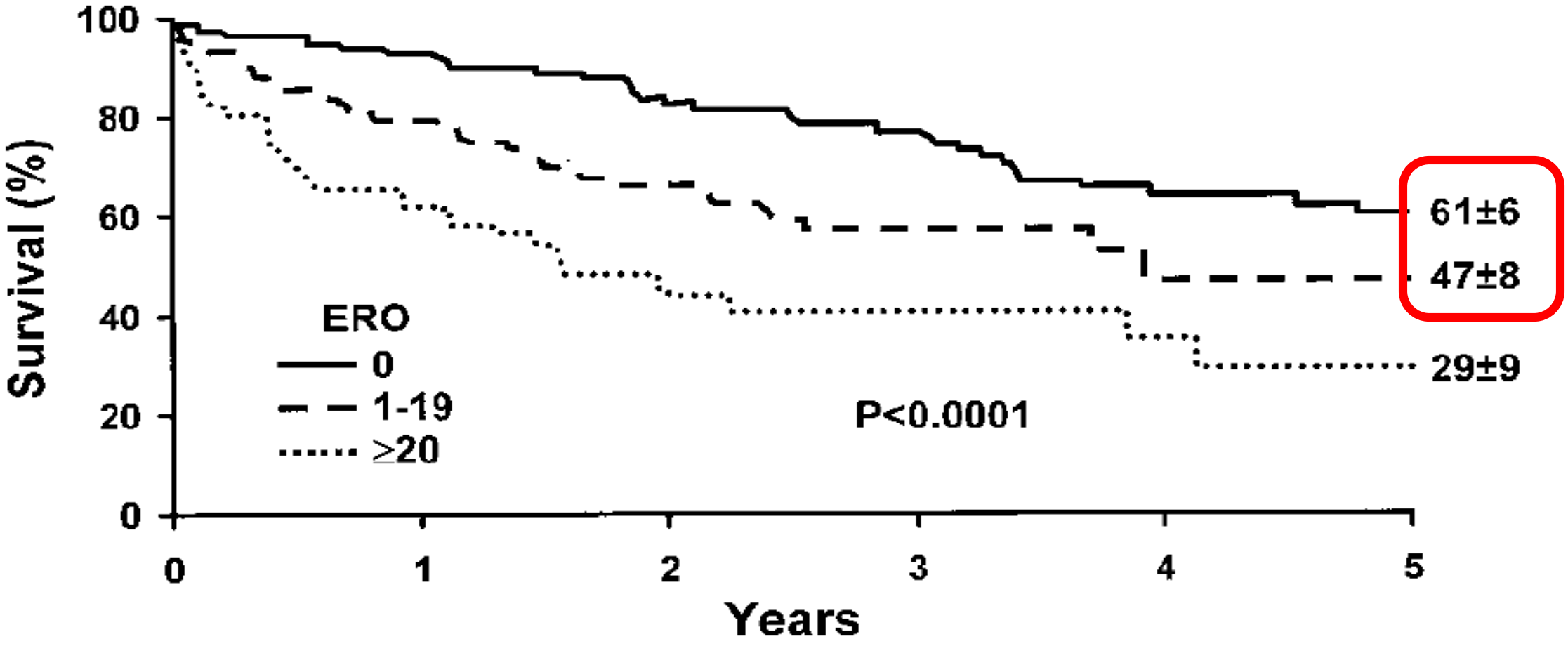


Figure 2. Survival (±SE) after diagnosis according to degree of MR as graded by RVol ≥30 mL/beat or <30 mL/beat. Numbers at bottom indicate patients at risk for each interval.

In heart failure with severe FMR, mortality is 70 %
in 5 years despite optimal medical therapy!

Grigioni et al: Circulation 103:1759, 2001

Survival is reduced even if FMR is only mild



May be even mild FMR should be treated

Grigioni et al,Circulation 2001;103:1759-63)

How to repair the mitral valve by catheter techniques?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

J.-F. Obadia, D. Messika-Zeitoun, G. Leurent, B. Iung, G. Bonnet, N. Piriou, T. Lefèvre, C. Piot, F. Rouleau, D. Carrié, M. Nejjari, P. Ohlmann, F. Leclercq, C. Saint Etienne, E. Teiger, L. Leroux, N. Karam, N. Michel, M. Gilard, E. Donal, J.-N. Trochu, B. Cormier, X. Armoiry, F. Boutitie, D. Maucort-Boulch, C. Barnel, G. Samson, P. Guerin, A. Vahanian, and N. Mewton, for the MITRA-FR Investigators*

ORIGINAL ARTICLE

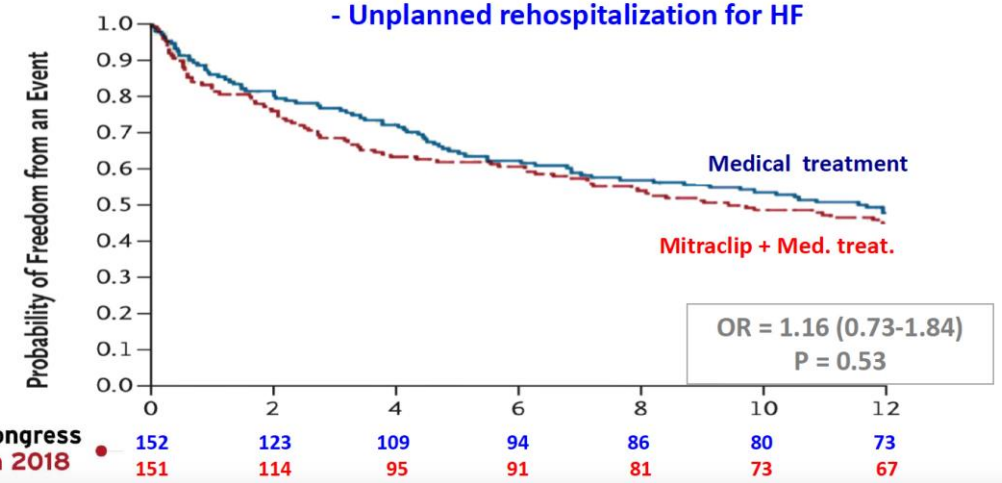
Transcatheter Mitral-Valve Repair in Patients with Heart Failure

G.W. Stone, J.A. Lindenfeld, W.T. Abraham, S. Kar, D.S. Lim, J.M. Mishell, B. Whisenant, P.A. Grayburn, M. Rinaldi, S.R. Kapadia, V. Rajagopal, I.J. Sarembock, A. Brieke, S.O. Marx, D.J. Cohen, N.J. Weissman, and M.J. Mack, for the COAPT Investigators*

Mitra.fr

Primary composite endpoint *(99% follow-up)*

- All-Cause Death
- Unplanned rehospitalization for HF

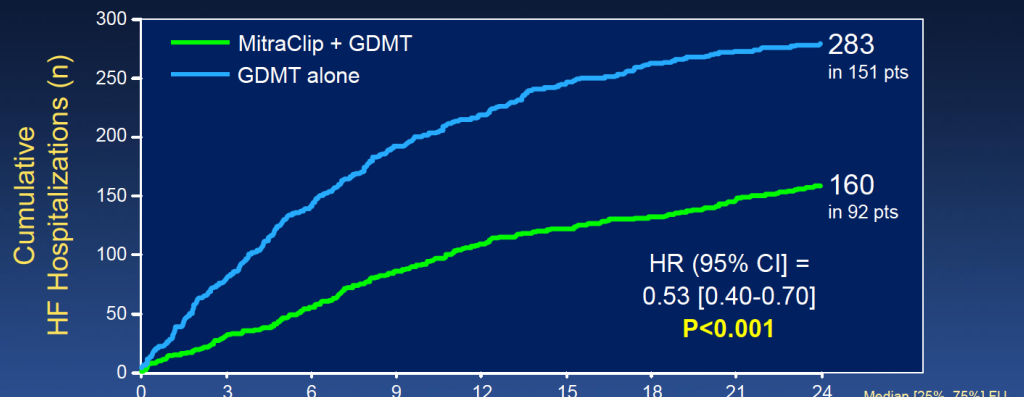


ESC Congress Munich 2018

COAPT TRIAL

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



Together with

ESC Congress Paris 2019 World Congress of Cardiology

Mitra-FR

COAPT

Over the last decade more than 35 percutaneous mitral valve repair techniques have been developed

- Annuloplasty approaches
  - Coronary sinus annuloplasty
    - Edwards Monarc — stopped
    - Cardiac Dimensions Carillon — CE mark
    - Viacor Shape Changing Rods (PTMA) — stopped
    - NIH-Cerclage — in patients
    - St. Jude Medical — stopped
    - Ample PS3 → MVRx — in patients
  - Direct annuloplasty
    - Mitralign Suture-based Plication — CE mark, stopped
    - Ancona Heart Accucinch — in patients
    - Cordis Direct Plication Annuloplasty — stopped
    - ReCor Medical — stopped
    - QuantumCor RF Annulus Remodeling — stopped
    - Valtech Cardioband — in patients
    - MiCardia variable size ring (hybrid) — in patients
    - Mitral Solutions (hybrid)
    - Millipede IRIS — in patients
    - Valcare Amend — in patients
    - Cardiac Implants

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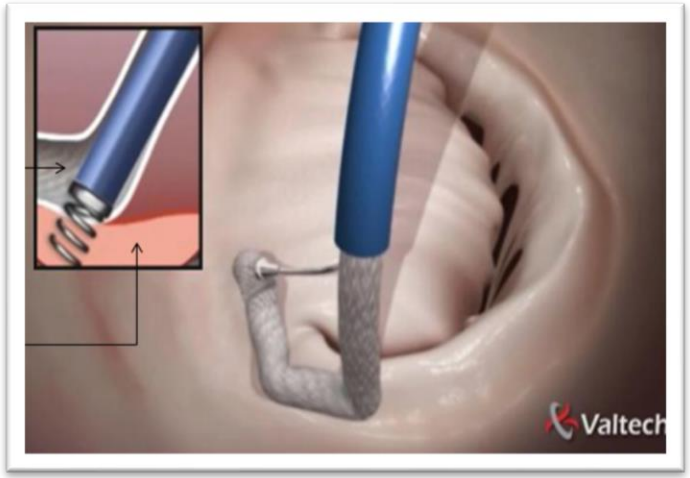
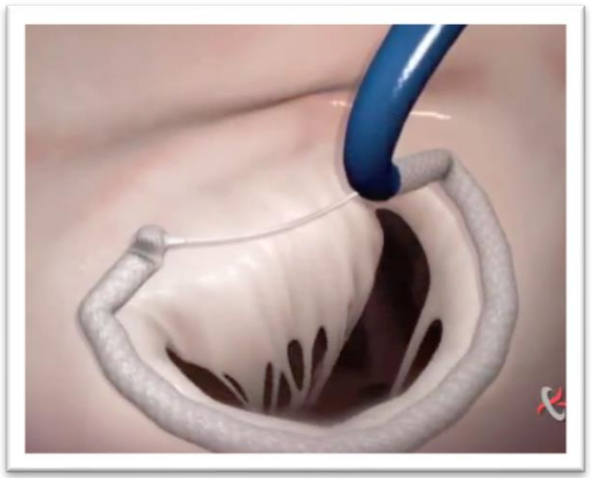
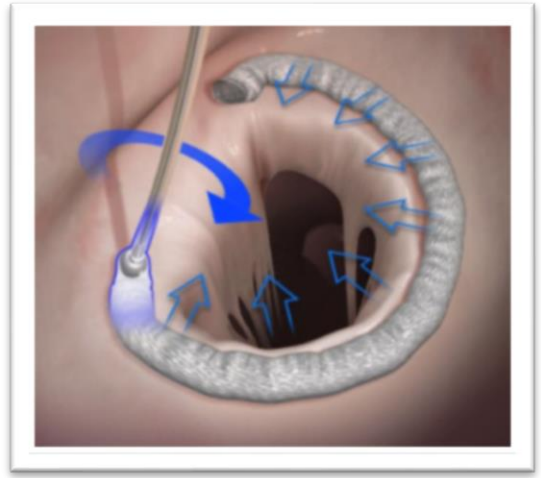
    - Valcare Amend — in patients
    - Cardiac Implants

- Many projects have been stopped for various reasons
- 7/17 had been used in humans
  - But they will not be available in clinical practice before 2022
- So I think we should focus on the two devices which have CE mark
  - Cardioband
  - Carillon

Valtech-Cardioband
Direct Annuloplasty With A Surgical-like Ring Implanted Percutaneously



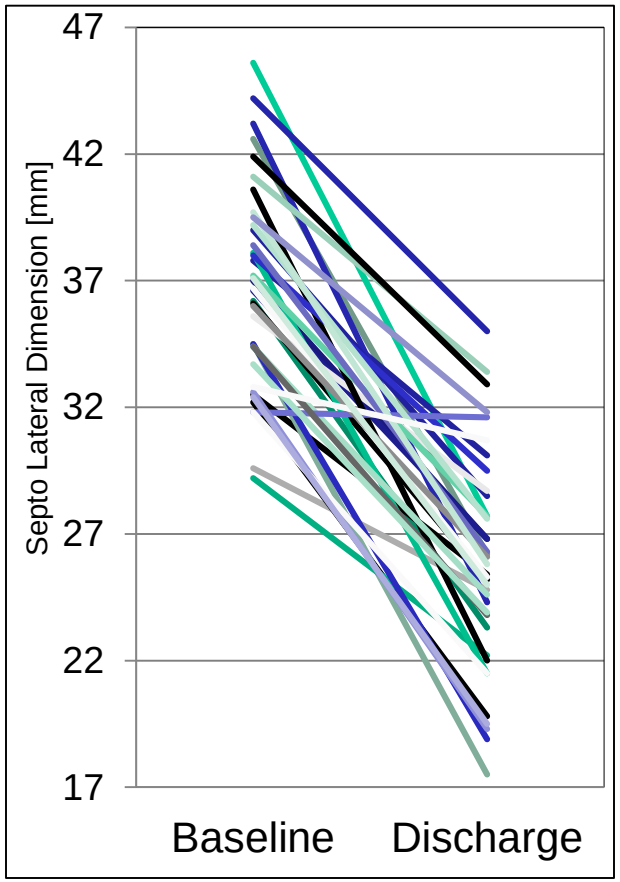


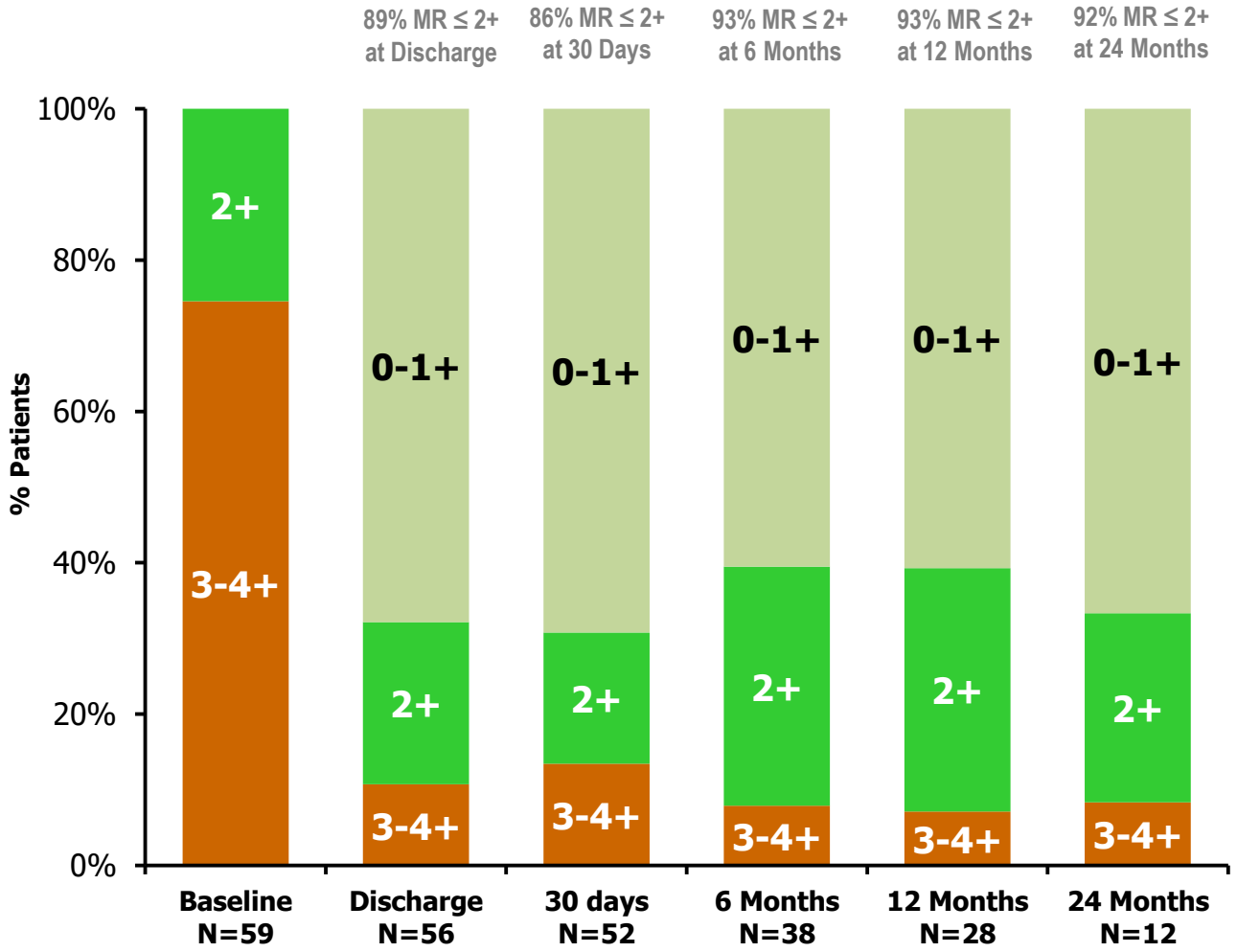


- Supraannular fixation by anchors
- Implanted via a transeptal approach
- Echo/fluoroscopic guidance

Result: Acute Animal

Annular Reconstruction by 30% Reduction in Septo Lateral (A-P) Dimension, 90% patients with MR≤2+ At 12 Months By Core Lab





The Carillon Mitral Contour System – an Indirect (Coronary Sinus) Annuloplasty Device

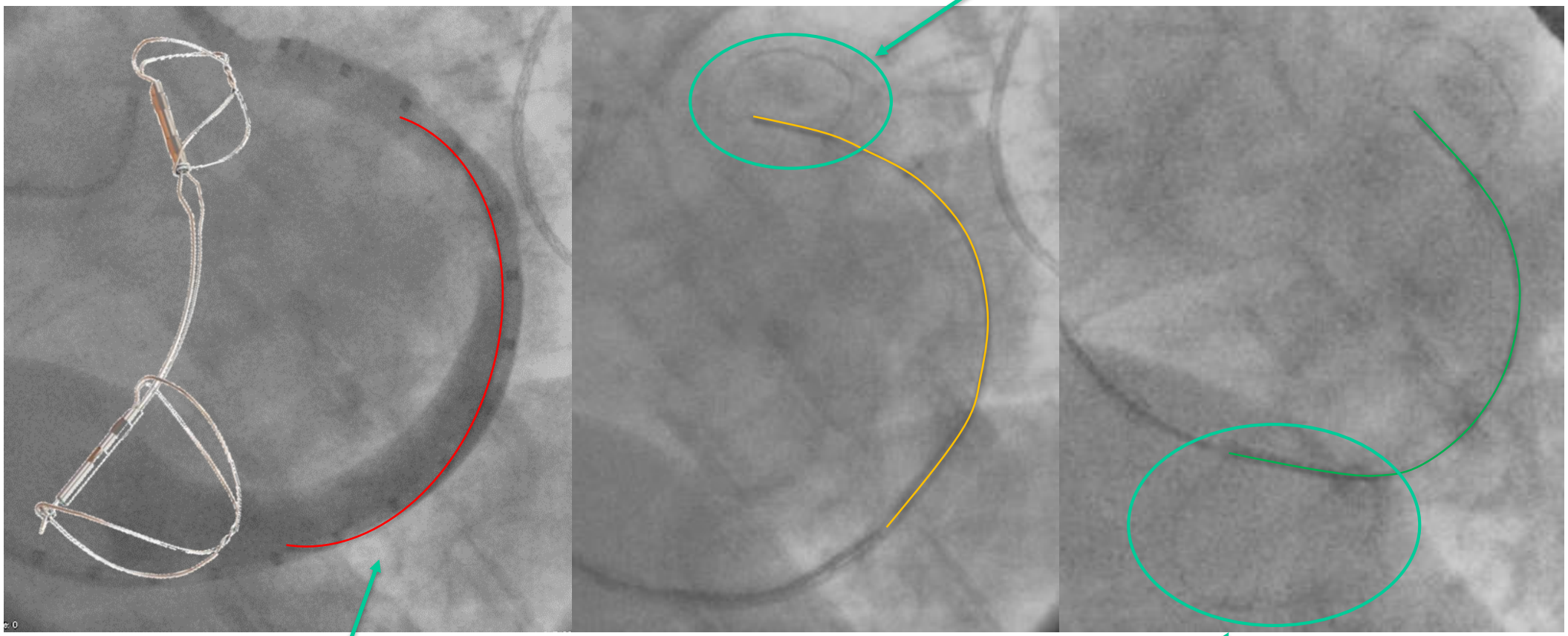
Distal Anchor
(in great cardiac vein)

Proximal Anchor
(in coronary sinus)

Anchor sizes are individually selected for each patient

Trans-jugular Delivery System

Carillon Device Deployment and Cinching

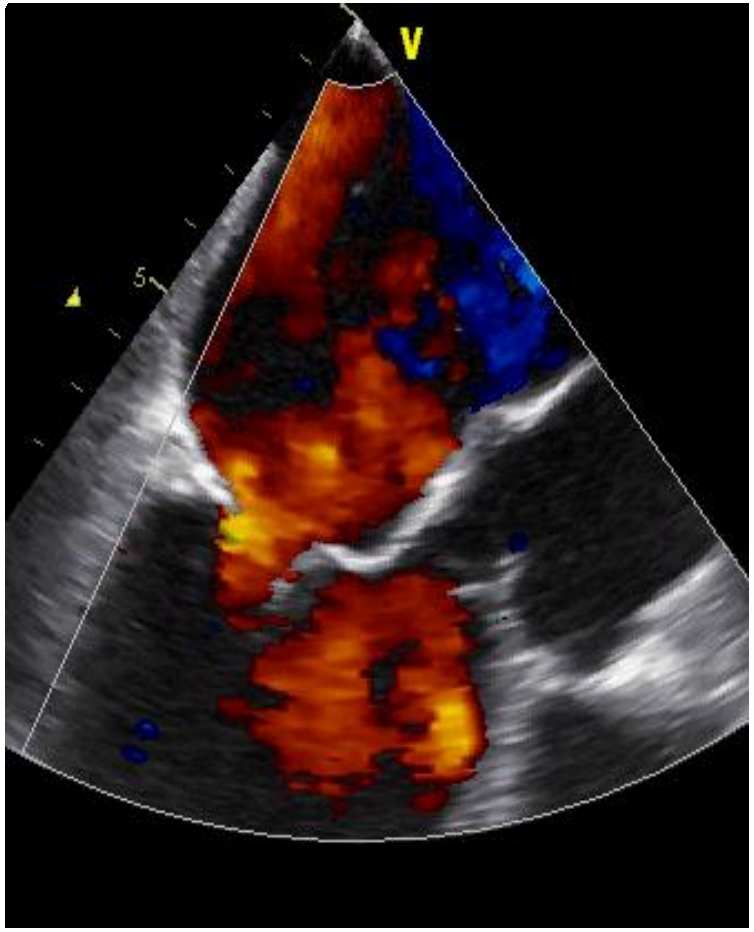


Advantages of Carillon

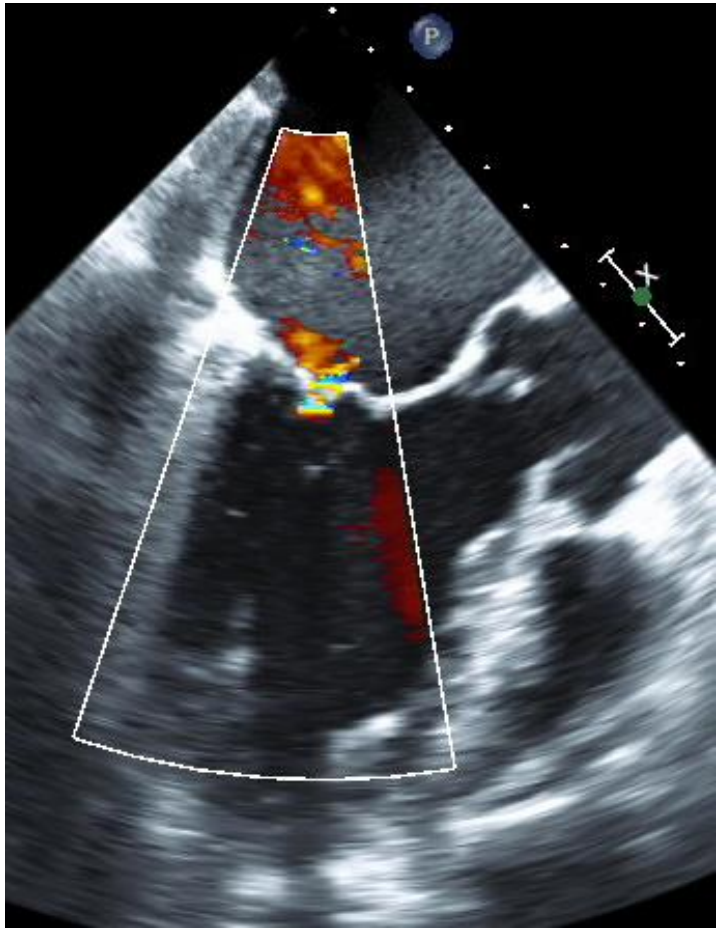
- Less invasive than other mitral valve repair techniques
- Easier to perform
- Valve leaflets are not touched
- Leaves all other options open

Carillon

before



after 1 month

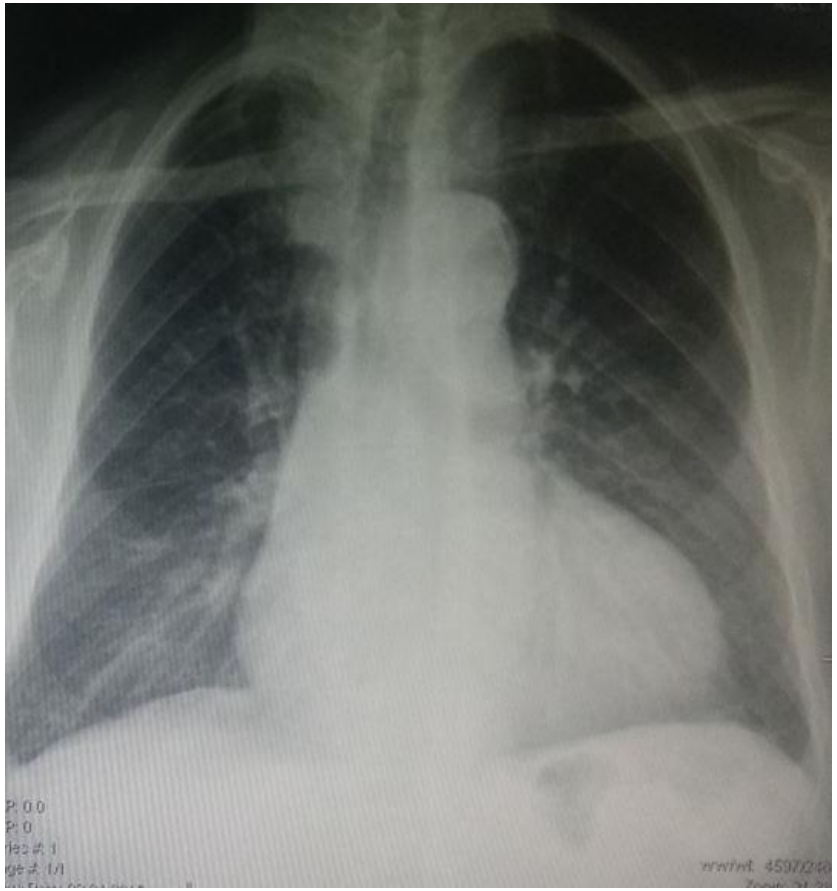


Carillon Mitral Contour System – Chest X-Ray FU

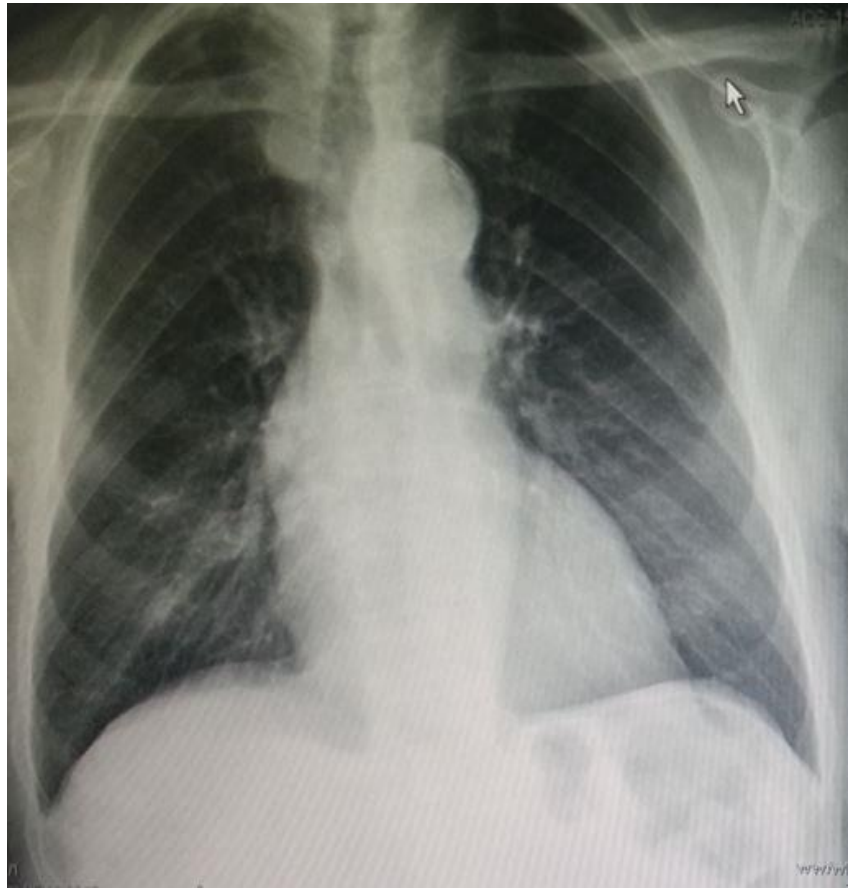
EF 15%

MR 3+

1 grade MR reduction on table



Before Carillon



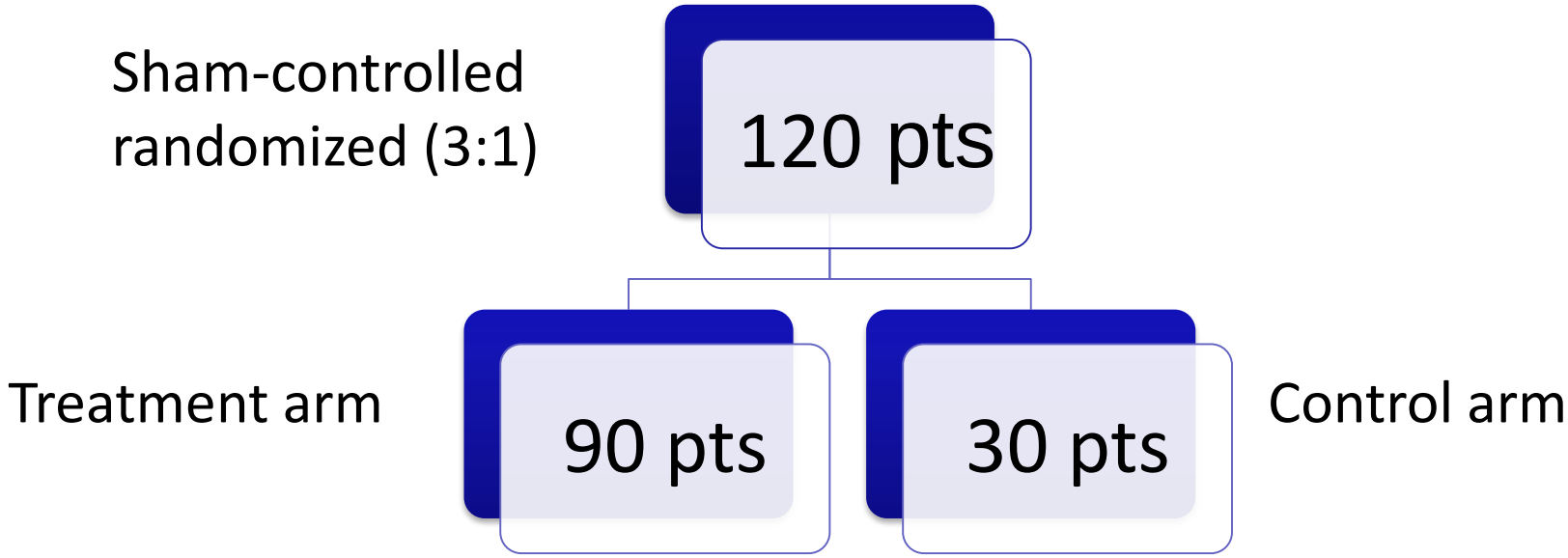
5 months after Carillon

Dr. Dayimi Kaya, Hospital Ishmir (Turkey)

REDUCE FMR

A multicenter randomized sham-controlled trial

120 patients at 31 sites in Europe and Australia, and New Zealand



Primary endpoint (ITT):
change in MR (regurgitant volume = RV)
assessed by a blinded echo core lab at 1-year

REDUCE FMR – an innovative trial in many respects

- Inclusion of patients with lesser degrees of MR (2+)
  - because it may be better to intervene earlier
  - But it makes it more difficult to prove a treatment effect
- Use of quantitative echo parameters as primary endpoint
  - which is recommended by echo societies and guidelines, but it has never been used as a primary endpoint in a device study
- The only blinded, sham-controlled randomized device trial in valve therapy
  - Everybody was blinded except operator and cath lab staff
  - Echo core lab blinded to patient randomization **and timing** of echoes
- Many sites were inexperienced – they just started their program
  - which means that this trial tested the simplicity of the therapy and reproducibility in many operators hands

REDUCE FMR – Endpoints

Primary Endpoint (Efficacy)

Change in MR (regurgitant volume =RV) at 1-year assessed by the blinded echo core lab (ITT analysis)

Secondary Endpoints

Efficacy

- Heart Failure Hospitalizations at 1-year
- Change in MR (regurgitant volume = RV) at 1-year (AT and PP analyses)
- Change in LVEDV and LVESV (baseline to 1-year)

Safety

- Major Adverse Events at 1-month and 1-year, defined as: death, MI, device embolization, vessel perforation requiring intervention, PCI or surgery associated with device failure

Key Selection Criteria

Inclusion

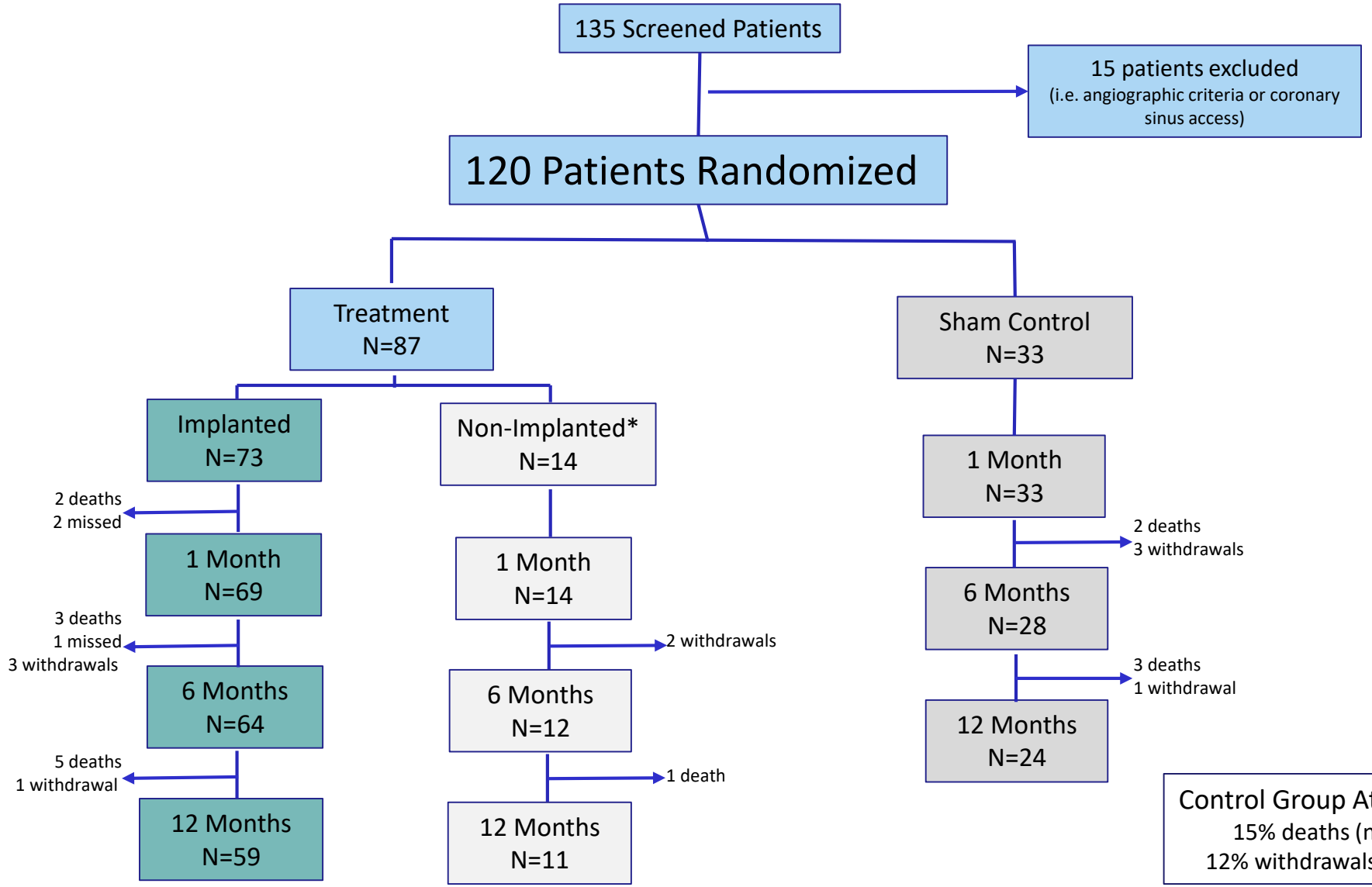
- **Dilated cardiomyopathy** (ischemic or non-ischemic)
- Functional mitral regurgitation moderate to severe defined as: **2+, 3+ or 4+**
- **NYHA II, III, or IV**
- LVEF ≤ 50%
  - 40-50% LVEF must be MR3+/4+ AND NYHA III/IV
- LVEDD > 55mm, or LVEDD/BSA > 3.0 cm/m^2
- **Stable heart failure medication** for at least 3-months

Exclusion

- Hospitalization in past 3-months due to MI, CABG, or unstable angina
- Hospitalization in past 30 days for coronary angioplasty or stent placement
- Expected to require any cardiac surgery within 1- year
- **Presence of coronary artery stent** under the CS/GCV, **in the implant target zone**
- Severe mitral annular calcification
- **Significant organic mitral valve pathology**

REDUCE FMR

Consort Diagram



* Non-implants
- 8 compromised coronary flow
- 2 coronary sinus vessel dissections
- 2 anchor slippage
- 1 no device size available
- 1 no attempt made (randomization error)

Treatment Group Attrition:
13% deaths (n=11)
5% withdrawals (n=4)

Control Group Attrition:
15% deaths (n=5)
12% withdrawals (n=4)

14 non-implanted patients counted towards the treatment group

A higher drop out rate was seen in the control arm

REDUCE FMR – Clinical Baseline Demographics (ITT)

	Treatment (N=87)	Control (N=33)	P Value
Age, yr	70.1 ± 9.7	69.1 ± 8.9	0.59
Male	72.4% (63/87)	72.7% (24/33)	0.97
BMI	26.7 ± 5.3	28.1 ± 6.2	0.22
Etiology – Ischemic	67.8% (59/87)	63.6% (21/33)	0.67
Prior MI	49.4% (43/87)	51.5% (17/33)	0.84
NYHA Class			0.92
II	44.8% (39/87)	48.5% (16/33)	
III	52.9% (46/87)	51.5% (17/33)	
IV	2.3% (2/87)	0.0% (0/33)	
Median NT-BNP (IRQ) -ng/l	2505 (1085-4432)	2410 (1079-5283)	0.33
Atrial Fibrillation	58.6% (51/87)	60.6% (20/33)	>0.99
Prior HFH in last year	44.8% (39/87)	45.5% (15/33)	>0.99

- Most patients were NYHA III
- Almost half of the patients were NYHA II – less sick than in most other heart failure trials

REDUCE FMR – Echo Baseline Demographics (ITT)

	Treatment (N=87)	Control (N=33)	P Value
LVEF (%)	33.5 ± 8.9	37.1 ± 8.7	0.09
LVEDD (cm)	6.4 ± 0.9	6.4 ± 0.9	0.92
EROA (- m^2)	25 ± 15	24 ± 14	0.56
Regurgitant Volume (ml)	39.4 ± 23.5	39.3± 23.7	>0.99
MR Grade			0.54
1	28.7% (25/87)	32.3% (10/31)	
2	39.1% (34/87)	25.8% (8/31)	
3	26.4% (23/87)	35.5% (11/31)	
4	5.7% (5/87)	6.5% (2/31)	

- MR was less severe than planned: baseline RV was 39 ml, 30% had MR 1+
- Less sick patient population than in most other heart failure trials

	Treatment	Control
COAPT EROA (mm^2)	41	40
MitraFR EROA (mm^2)	31	31

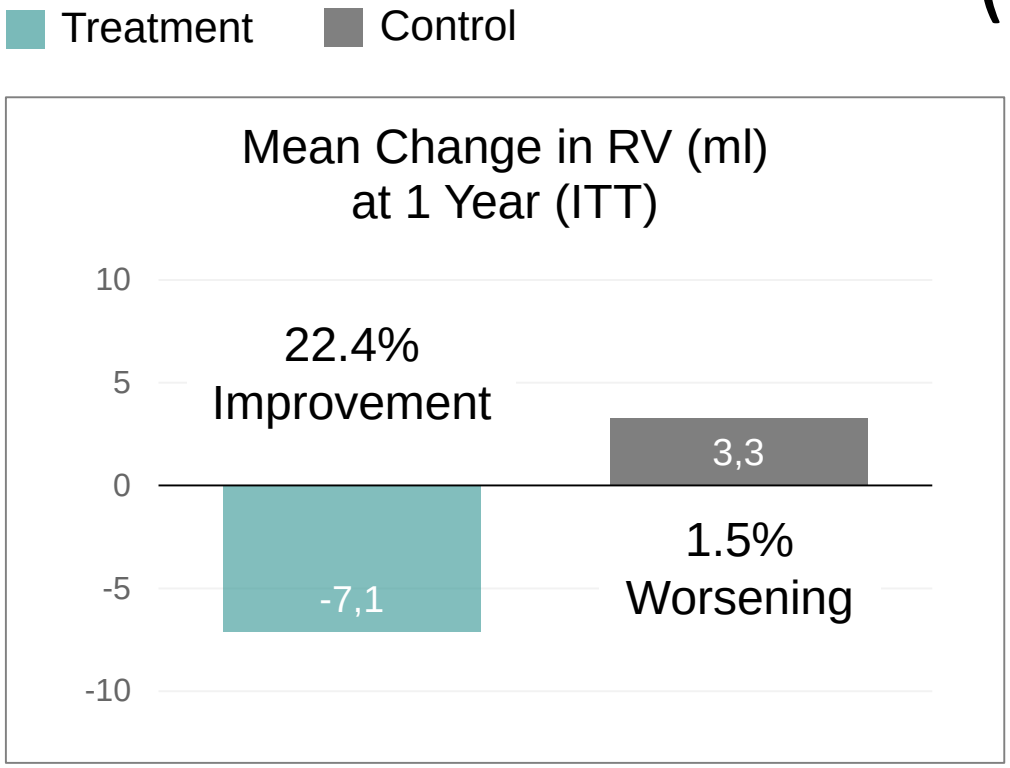
REDUCE FMR adverse events

98.9%
freedom from
device-related
MAE at 30 days

	TREATMENT (N=87)	CONTROL (N=33)
	1-Year MAE Rate	
Death	12.6% (11)	15.2% (5)
MI	3.5% (3)	3.0% (1)
Cardiac Perforation	0% (0)	0% (0)
Device Embolism	0% (0)	n/a
Surgery or PCI related to device	0% (0)	n/a
Total MAE Rate	16.1% (14)	18.2% (6)

Sievert, H. 2018. REDUCE-FMR: A Sham Controlled Randomized Trial of Transcatheter Indirect Mitral Annuloplasty in Heart Failure Patients with Functional Mitral Regurgitation. Presented at TCT 2018, San Diego, CA.

REDUCE FMR – Primary Endpoint
Change in MR (Regurgitant Volume = RV) at 1-year (ITT)



- 22.4% reduction in treatment group
- 1.5% increase in control group
- Absolute difference 10.4 ml

$P < 0.05$

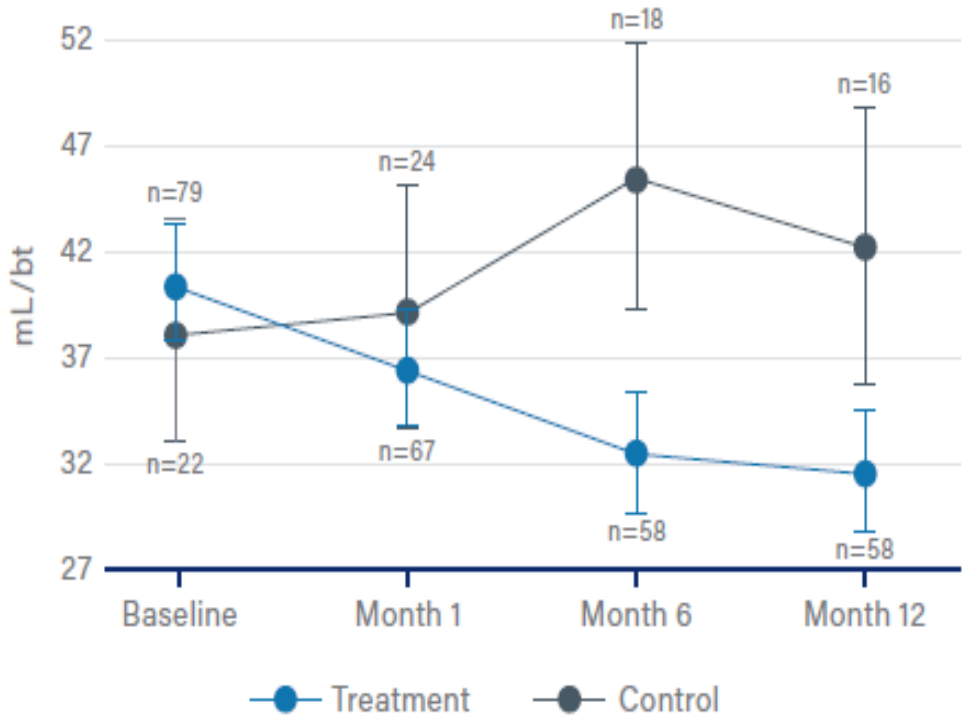
ITT = Intention-to-Treat Population

1. Witte K, et al. A Randomized Sham-Controlled Study of Percutaneous Mitral Annuloplasty in Functional Mitral Regurgitation: The REDUCE FMR Trial. J Am Coll Cardiol HF. DOI: 10.1016/j.jchf.2019.06.011.
2. Kramer DG, et al. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am Coll Cardiol. 2010 Jul 27;56(5):392-406.

As in prior studies, the treatment effect is a delayed effect

Significant Reduction in MR

Change in Mean Mitral Regurgitant Volume (ITT)



Primary Endpoint Met p<0.05

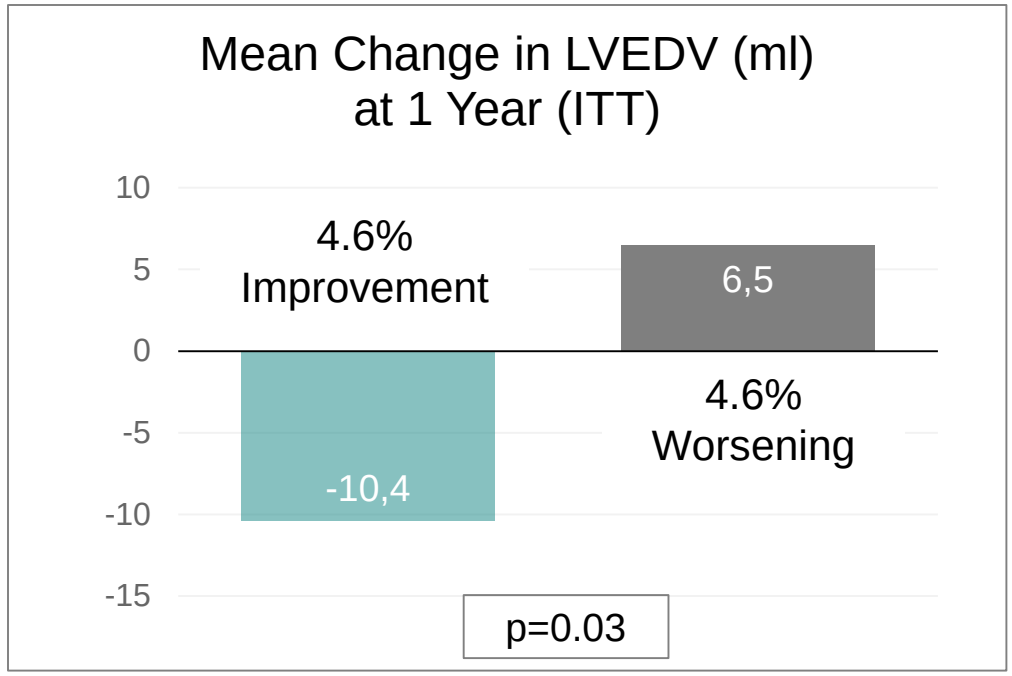
- **7.1 mL/bt reduction at 12 months** (median 22.4% decrease)
- **3.3 mL/bt increase at 12 months** (median 1.5% increase)

Patients with baseline MR grade ≥3+ implanted with the devise experienced the greatest reduction in MR

Change in MR volume at 12 months

- Treatment: 12.8 mL/bt mean reduction (n=15)
- Control: 0.6 mL/bt mean increase (n=8)

REDUCE FMR – Secondary Endpoint
Change in LVEDV at 1-year (ITT): Significant remodeling



- 4.6% reduction in treatment group
- 4.6% increase in control group
- Absolute difference 16.9 ml

P < 0.05

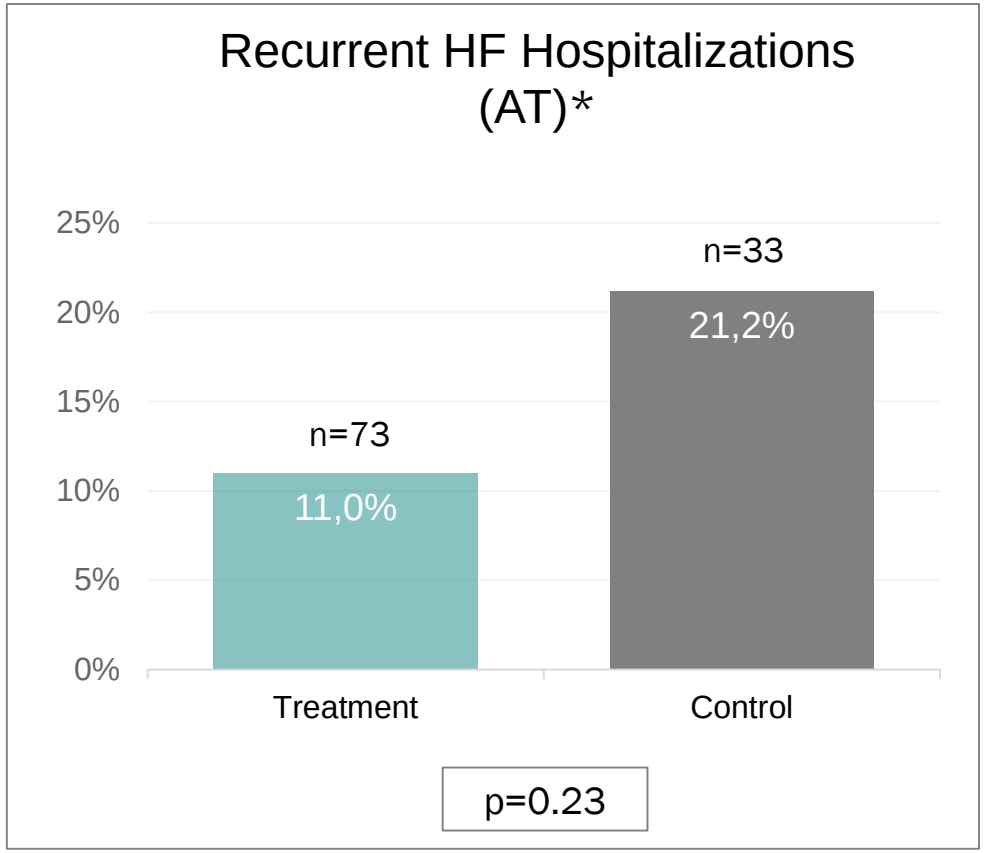
According to Kramer et al[2], LVEDV reduction of >10ml results in improved survival

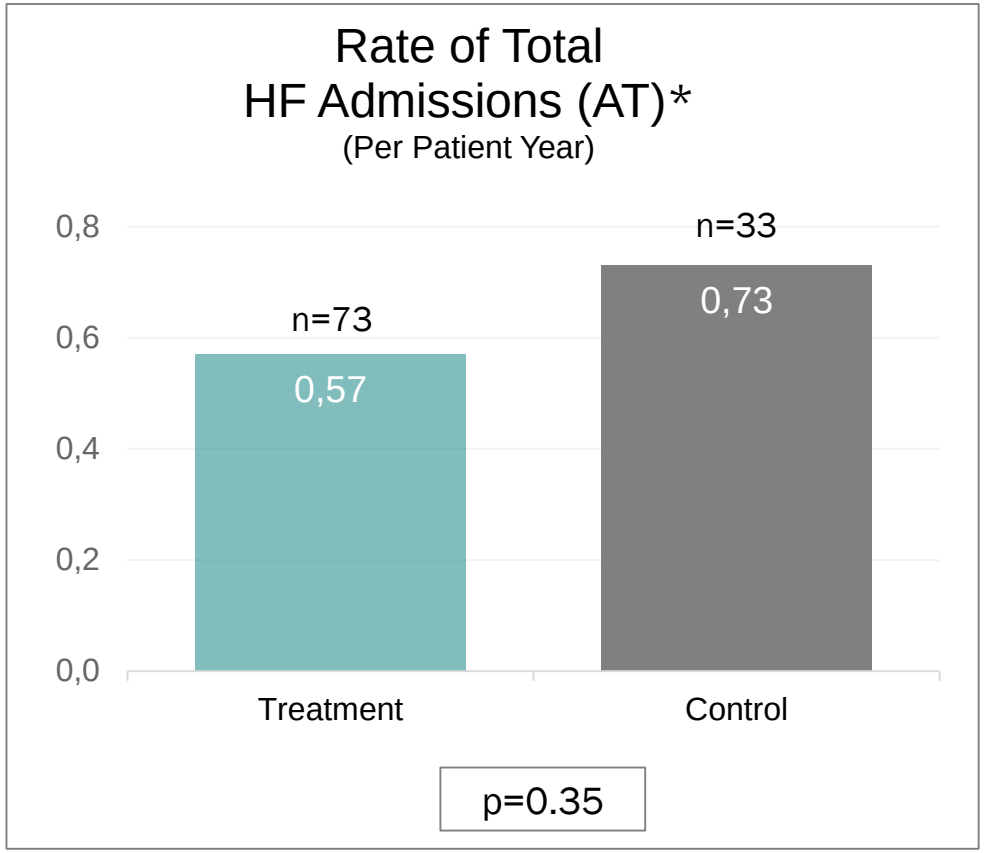
ITT = Intention-to-Treat Population

1. Witte K, et al. A Randomized Sham-Controlled Study of Percutaneous Mitral Annuloplasty in Functional Mitral Regurgitation: The REDUCE FMR Trial. J Am Coll Cardiol HF. DOI: 10.1016/j.jchf.2019.06.011.
2. Kramer DG, et al. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am Coll Cardiol. 2010 Jul 27;56(5):392-406.

Fewer recurrent HFH and total HF admissions

Favorable trends observed in the treatment group





*REDUCE FMR Trial was not powered to detect statistical differences in HF Hospitalizations

AT = As-Treated Population

Sievert, H. 2018. REDUCE-FMR: A Sham Controlled Randomized Trial of Transcatheter Indirect Mitral Annuloplasty in Heart Failure Patients with Functional Mitral Regurgitation. Presented at TCT 2018, San Diego, CA.

MV Repair Trials: Echo Parameters and Outcomes

- EROA was 0.4 in COAPT, 0.31 in MITRA FR and 0.25 in REDUCE FMR
- LVEDV Index was 136 in MITRA FR and 100 in COAPT and REDUCE FMR
- All cause mortality at 30 days was similar amongst trials and treatment groups
- REDUCE FMR and COAPT showed similar improvement in Death/HFH at 12 months
- Only REDUCE FMR but not COAPT und Mitra FR demonstrated favorable remodeling

	REDUCE FMR[1]		COAPT[2]		MITRA.fr[3]	
	Treatment (N=73)	Control (N=33)	Treatment (N=302)	Control (N=312)	Treatment (N=152)	Control (N=152)
Echo Parameters						
EROA ,cm^2	0.25	0.24	0.41	0.40	0.31	0.31
LVESV, ml	132	122	136	134		
LVEDV, ml	192	189	194	191		
LVEDV Index, ml/m^2	100	100	101		136	135
LVEF	33.5%	37.1%	31.3%	31.3%	33.3%	32.9%
30 Day Outcomes						
Death all cause	2.3%	0	2.3%	1.0%	3.3%	2.6%
12 Month Outcomes						
Death	12.6%	15.2%	~19%**	~22%**	24.3%	22.4%
HFH*	27.4%	39.3%	~24%**	~40%**	48.7%	47.4%
Death or HFH*	31.5%	42.4%	33.9%	46.5%	54.6%	51.3%
NYHA I & II	69.5%	58.3%	72.2%	49.6%	~68%	~70%
LVEDV Change from BL (ml)	-8.6	6.5	-1.1	18.6	-2	7

* COAPT HFH includes study exit for LVAD or Heart Transplant. Modified to include REDUCE FMR study exits for Mitra Clip, Heart Transplant / surgery or LVAD

** KM estimate extrapolated

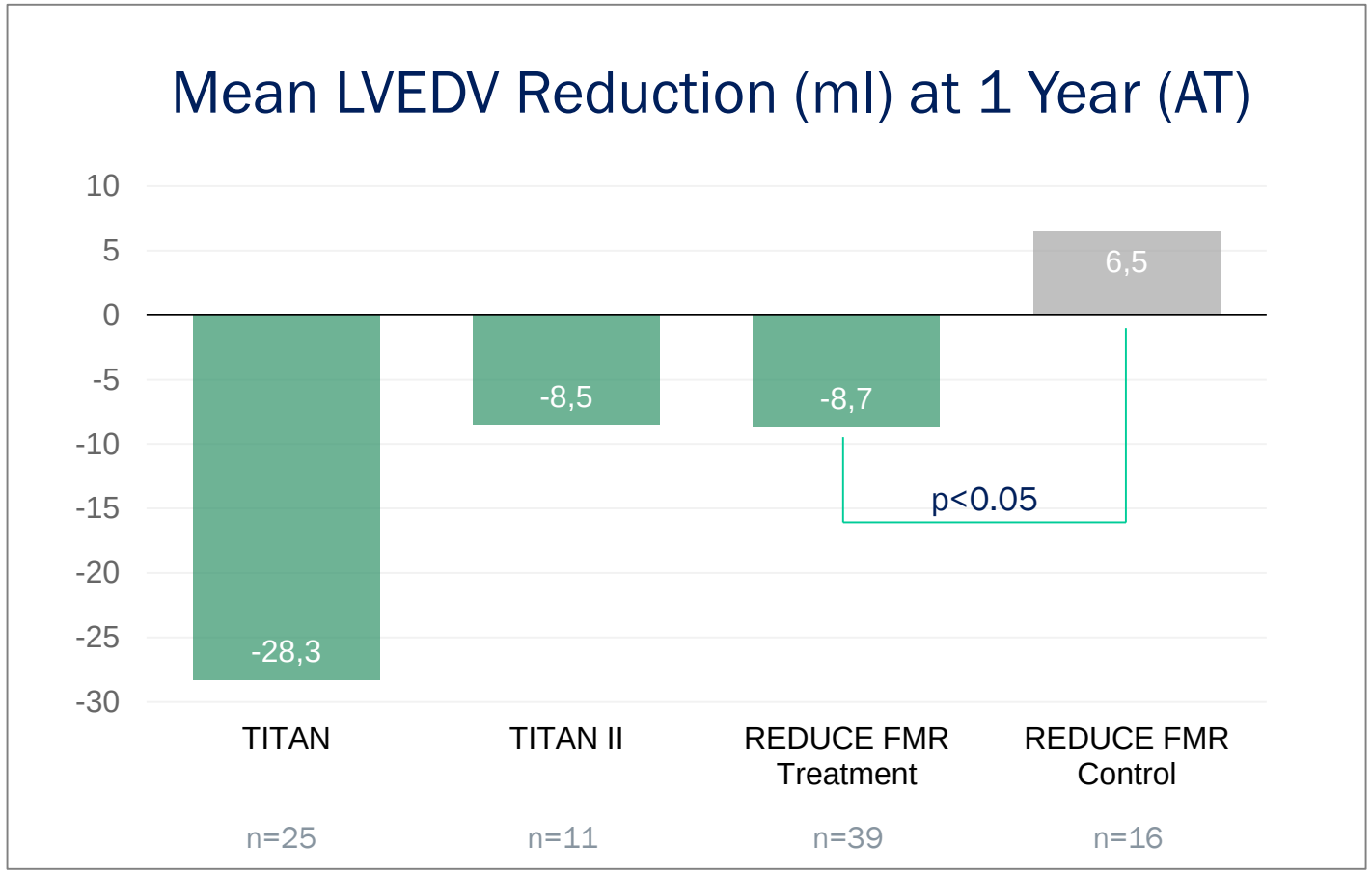
Sievert et al, TCT 2018, September 21-25, San Diego, CA
Stone et al. NEJM 2018 DOI: 10.1056/NEJMoa1806640; G. Stone TCT 2018, September 21-25, San Diego, USA
Obadia et al. NEJM 2018 DOI: 10.1056/NEJMoa1805374

REDUCE FMR Severe MR Group vs COAPT vs MITRA-FR
Only Carillon decreased LVEDV (positive remodeling)

	REDUCE FMR - MR 3+/4+		COAPT		MITRA.FR	
Baseline Clinical & Echo Parameters	**Treatment* (N=21)**	**Control (N=13)**	**Treatment**	**Control**	**Treatment**	**Control**
Age (mean)	70.3	72.1	71.7	72.8	70.1	70.6
NYHA III & IV (%)	47.6	46.2	57.0	64.6	63.1	71.1
Ischemic Etiology (%)	66.7	61.5	60.9	60.6	62.5	56.3
History of Afib (%)	66.7	69.2	57.3	53.2	34.5	32.7
EROA ,cm^2	0.40	0.37	0.41	0.40	0.31	0.31
Regurgitant Volume (ml)	62.7	57.4	59.7	59.9	45	45
LVESV, ml	153	125	136	134	NA	NA
LVEDV, ml	226	197	194	191	NA	NA
LVEDV Index, ml/m^2	120	109	101	NA	136	135
LVEF (%)	33.5	37.6	31.3	31.3	33.3	32.9
12 Month Outcomes						
Death (%)	19.0	7.7	19.1	23.2	24.3	22.4
Death or HFH** (%)	38.1	46.2	33.9	46.5	54.6	51.3
Relative Risk Death or HFH	0.83		0.73		1.06	
RV Mean Change (ml)	-12.8	0.6	NA	NA	NA	NA
RV Median Change (ml)	-11.5	-2.3			-23.5	-4
LVEDV Mean Change from BL (ml)	-26.9	10.2	-1.1	18.6	NA	NA
LVEDV Median Change from BL (ml)	-31.3	15.0	NA	NA	-2	7

† REDUCE FMR echo parameters are implant only group. Clinical parameters are ITT
* REDUCE FMR implant only.
** COAPT HFH includes study exit for LVAD or Heart Transplant. Modified to include REDUCE FMR study exits for Mitra Clip, Heart Transplant / surgery or LVAD

Improvement in LVEDV has been shown in **all** Carillon trials



First TMVR therapy to demonstrate favorable LV remodeling

in a randomized, sham-controlled clinical study

AT = As-Treated Population

1. Siminiak T, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: Results of the TITAN Trial. Eur J Heart Fail. 2012;14:931-38.
2. Lipiecki J, et al. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial. BMJ Open Heart. 2016; 3: e000411.
3. Witte K, et al. A Randomized Sham-Controlled Study of Percutaneous Mitral Annuloplasty in Functional Mitral Regurgitation: The REDUCE FMR Trial. J Am Coll Cardiol HF. DOI: 10.1016/j.jchf.2019.06.011.

The CARILLON Trial

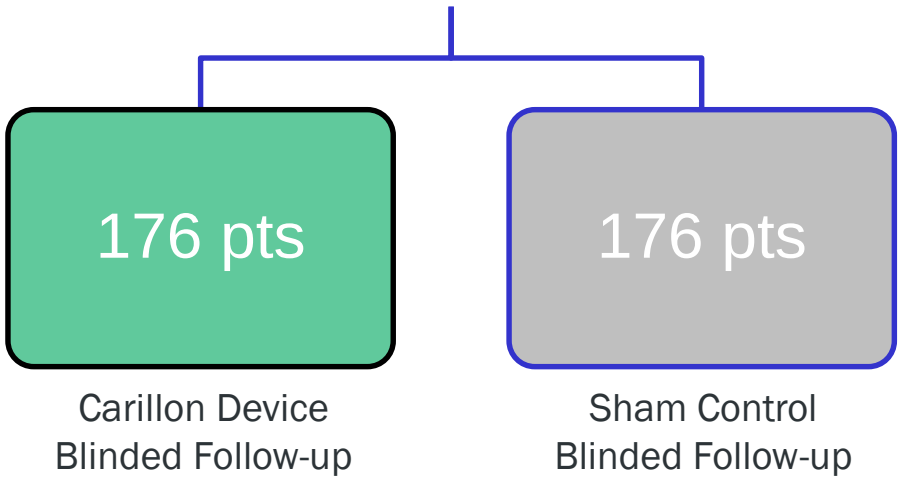
REVISED Protocol

Study Design

- 1:1 randomization
- Treatment vs Sham Control

Key Inclusion

- FMR Grade ≥ 2+
- NYHA Class ≥ 2
- LVEF ≤ 50%



Hierarchal Clinical Endpoint

1. Death
2. Alternative therapy
   - Heart Transplant or LVAD
   - Mitral valve surgery or percutaneous therapy
3. Heart Failure Hospitalization
   - Multiple heart failure hospitalizations
   - Single heart failure hospitalization
4. 6 minute walk at 12 months

Primary endpoint (ITT) Through 24 months Follow up
Hierarchical Endpoint primarily consisting of mortality and heart failure hospitalizations

Where should Carillon be placed in a treatment algorithm for FMR?

- After medical treatment
  - if moderate to severe FMR persists
- Before CRT
  - because Carillon after CRT is problematic for technical reasons
- Before edge-to-edge repair
  - because it is less invasive and leaves all other options open

Conclusions

- REDUCE FMR is the first sham-controlled double blind study in valve disease
- The primary endpoint - reduction in MR (regurgitant volume) - was met in the ITT - analysis
- Catheter anuloplasty with Carillon
  - is a very safe procedure (not more AE than in the control group)
  - reduces MR (primary endpoint)
  - results in significant LV remodeling
  - Shows a positive trend in all clinical endpoints
- Earlier treatment of FMR seems to make sense

Thank you for your time!

HorstSievertMD@aol.com