TCTAP 2019
Seoul, Korea, April 27-30, 2019

The REDUCE-FMR Trial

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On behalf of the REDUCE FMR Investigators

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Frankfurt, Germany

Disclosures

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

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

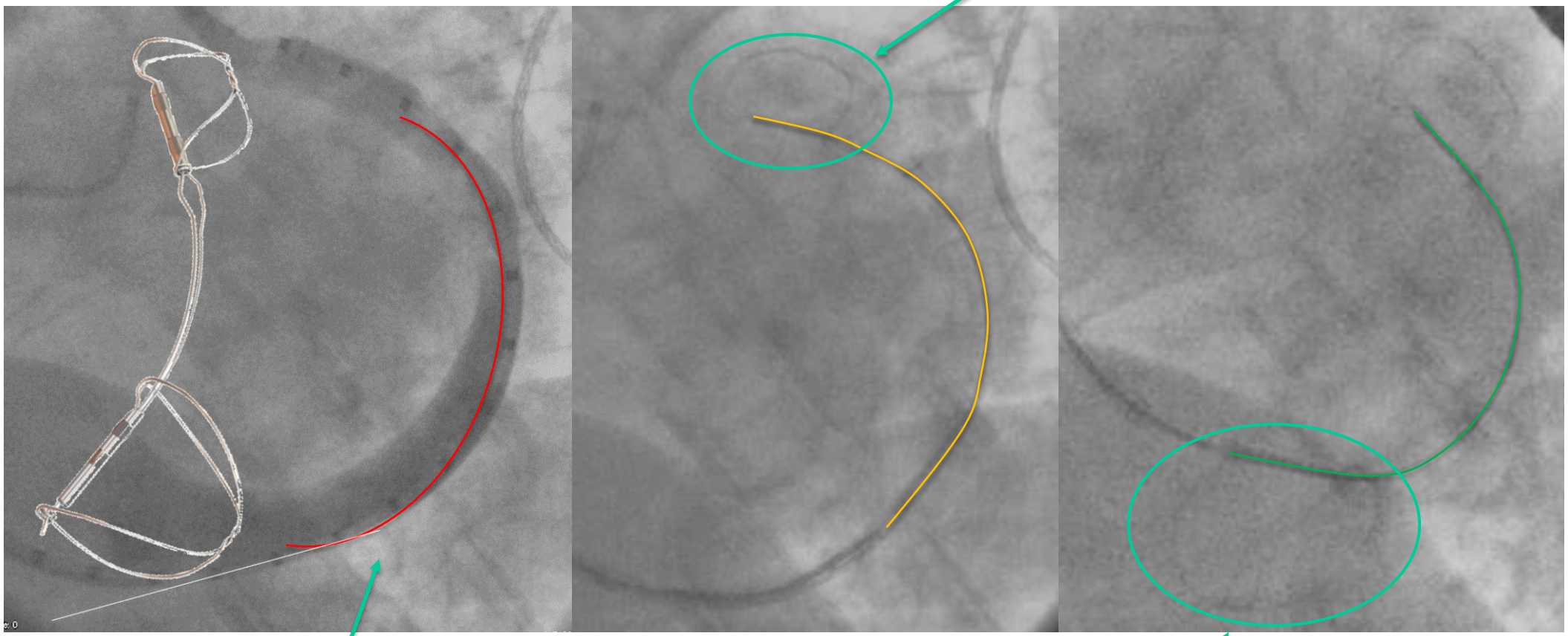
Distal Anchor
(in great cardiac vein)

Proximal Anchor
(in coronary sinus)

Anchor sizes are individually selected for each patient

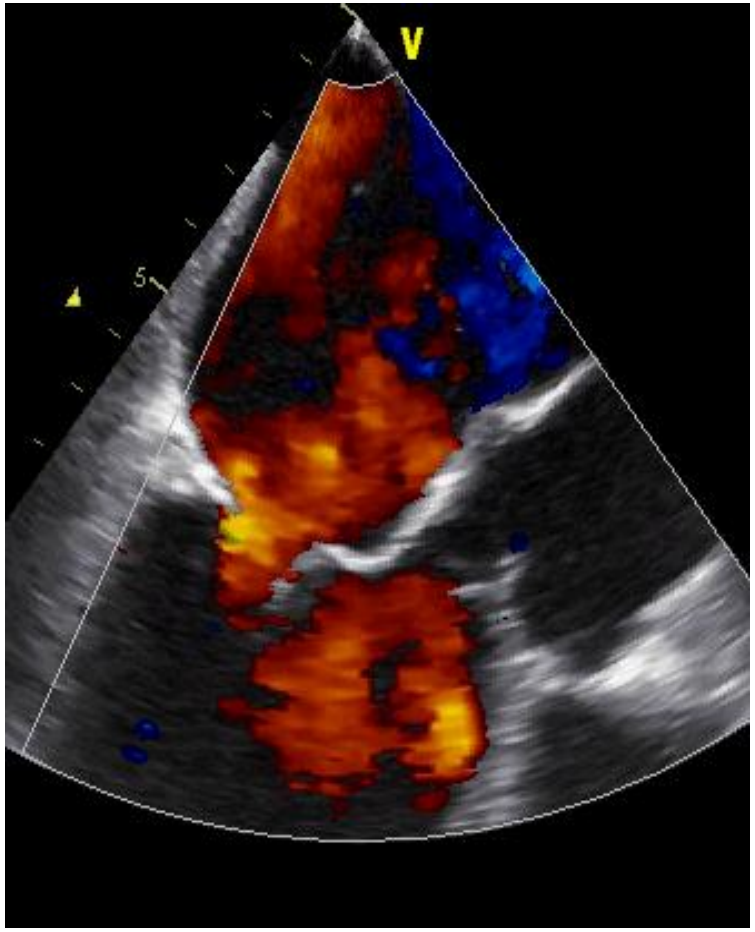
Trans-jugular Delivery System

Carillon Device Deployment and Cinching

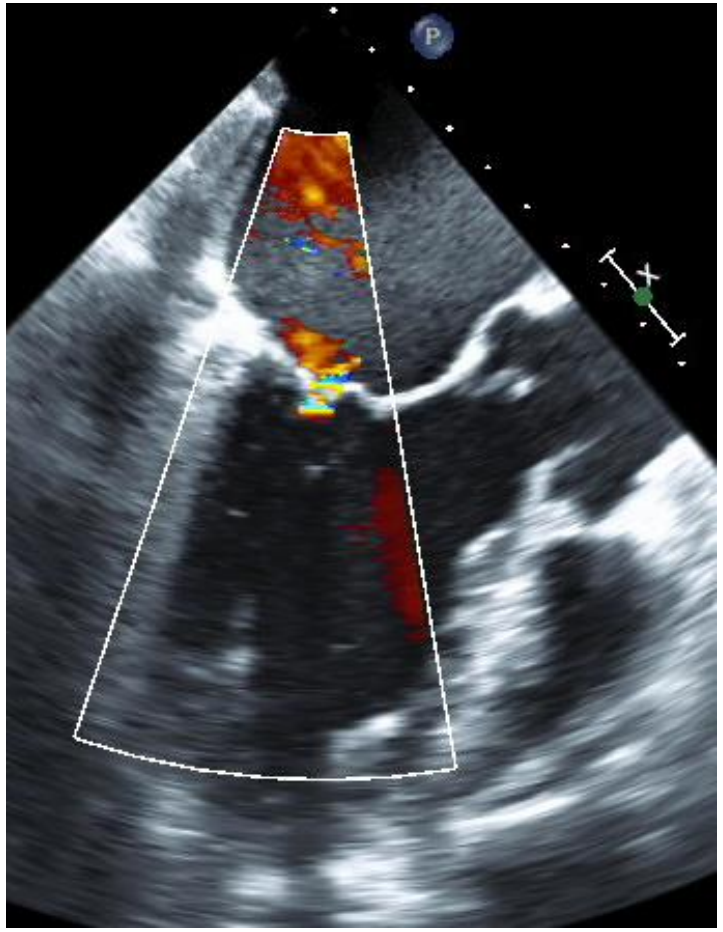


Carillon

before



after 1 month



Advantages

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

REDUCE FMR – Background and Objective

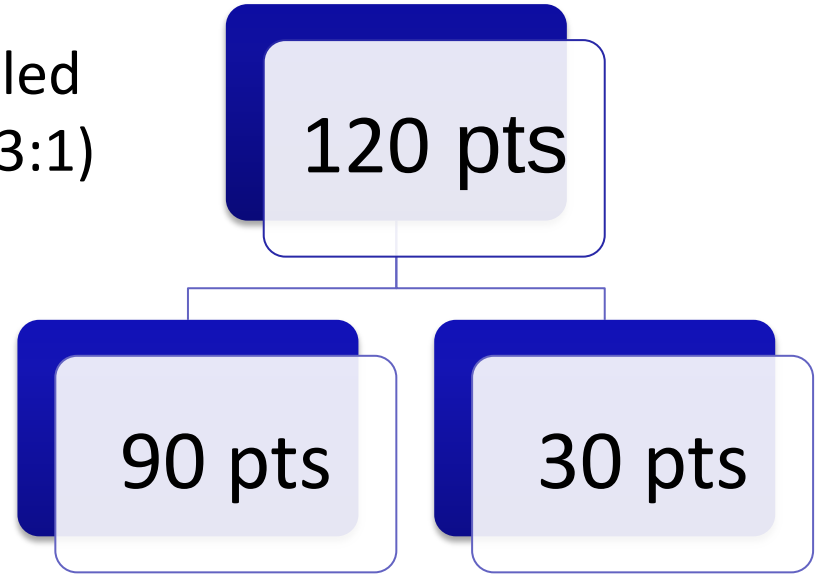
- Previous small studies with the Carillon device (AMADEUS[1], TITAN[2], and TITAN II[3]) have shown evidence of reduced mitral regurgitation (MR) and left ventricle (LV) remodeling
- The objective of REDUCE FMR was to demonstrate - in a **sham-controlled** randomized study - a decrease in **quantitative MR** with the Carillon device in heart failure patients with FMR

[1] Schofer et al. Circulation;120:326-333 [2] Siminiak et al. EU J of Heart Failure (2012 14, 931-938. [3] Lipiecki et al. Open Heart 2016;3:3000411

REDUCE FMR – Intended Randomization and Primary Endpoint

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

Sham-controlled
randomized (3:1)



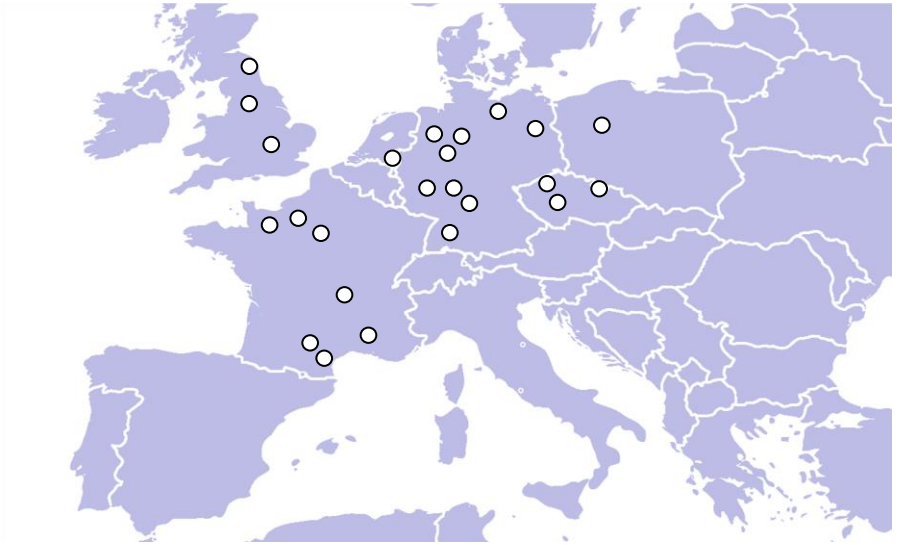
Treatment arm

Control arm

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

REDUCE FMR – Investigator Sites

(Top enrollers in **bold**)



Australia
- **Monash Health- R. Gooley and I. Meredith**
- The Alfred Hospital- S. Duffy and D. Kaye
- Royal North Shore Hospital- R. Bhindi
- Royal Prince Alfred Hospital- M. Adams
- Flinders Medical Centre- C. De Pasquale
- The Prince Charles Hospital- C. Raffel and D. Walters

Czech Republic
- University Hospital Olomouc- M. Táborský
- Na Homolce Hospital- P. Neužil
- Institute for Clinical and Experimental Medicine (IKEM)- J. Kautzner

France
- **Clinique du Millénaire- C. Piot**
- **Pole Santé République- J. Lipiecki**
- Hospital Georges Pompidou- C. Spaulding
- Hospital Charles Nicolle- E. Durand
- Clinique Saint Hilaire- J. Berland
- Rangueil University Teaching Hospital- D. Carrie
- Hopital Prive Saint Martin- J. Morelle

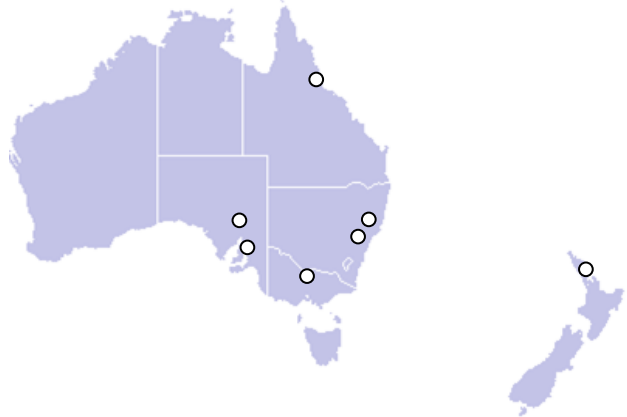
Germany
- CardioVascular Center Frankfurt- H. Sievert
- Sana Kliniken Lübeck- J. Weil
- Hospital Frankfurt Höchst- H. Hink
- Klinikum Lüdensheid- B. Lemke
- University Hospital Freiburg- J. Reinhöl
- Charité Universitätmedizin Berlin- U. Landmesser
- Augusta Kranken Anstalt gGmbH Bochum- M. Prull
- Elisabeth Krankenhaus Recklinghausen- T. Lawo
- Universitätsklinikum Frankfurt- S. Fichtlscherer

Netherlands
- University Hospital Maastricht- J. Vainer

New Zealand
- Auckland City Hospital- P. Ruygrok

Poland
- **HCP Medical Center- T. Siminiak**

United Kingdom
- **Leeds Teaching Hospital NHS Trusts- C. Malkin and K Witte**
- Harefield Hospital- M. Mason
- Freeman Hospital- M. Egred



REDUCE FMR – an innovative trial in many respects

- Inclusion of patients with lesser degrees of MR (2+)
  - 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
  - Recommended by echo societies and guidelines, but it has never been used as a primary endpoint in a device study
  - Difficult to achieve enough high quality echos
- 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
  - Tests the simplicity of the therapy and reproducibility in many operators hands

REDUCE FMR – Study Administration

Imaging Core Lab
C5 Research
Cleveland Clinic Foundation
Cleveland, Ohio

Data Safety Monitoring Board
Prof. Martin Cowie
Prof. Emmanual Lagarde
Prof. Keith Oldroyd

Clincal Events Committee
Prof. Andreas Baumbach
Dr. Robert Byrne
Dr. John Parissis

Imaging Training and Standards: Sonographer-focused technical training on echo quality and protocol requirements. Assessment of patient inclusion criteria was done site based

Site Training: Interventionists trained on device and protocol. Proctors were on-site for case support

Core Lab Image Read Standards: After initial quality review by core lab, the echo images were read in consensus format for MR grade and over-read for quantitative measures

100% Source Data Monitoring: All data monitored by independent CROs

REDUCE FMR – Endpoints

Primary Endpoint (Efficacy)

Change in 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 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

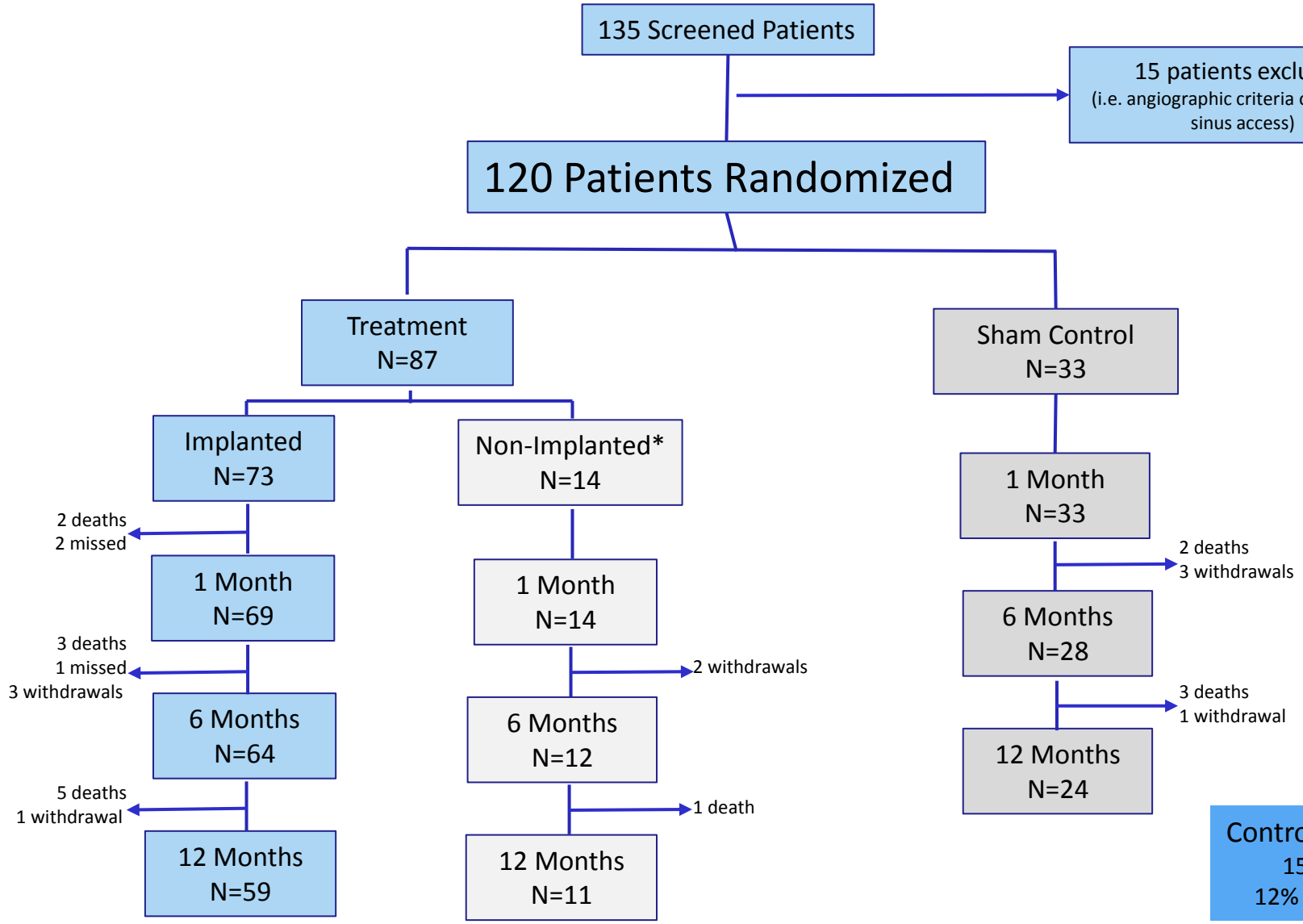
- **Dilated cardiomyopathy** (ischemic or non-ischemic)
- Functional mitral regurgitation moderate to severe defined as: **2+, 3+ or 4+**
- **NYHA II, III, or IV**
- LVEF ≤ 50%
  - 40-50% LVEF must be MR3+/4+ AND NYHA III/IV
- LVEDD > 55mm, or LVEDD/BSA > 3.0 cm/m^2
- **Stable heart failure medication**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

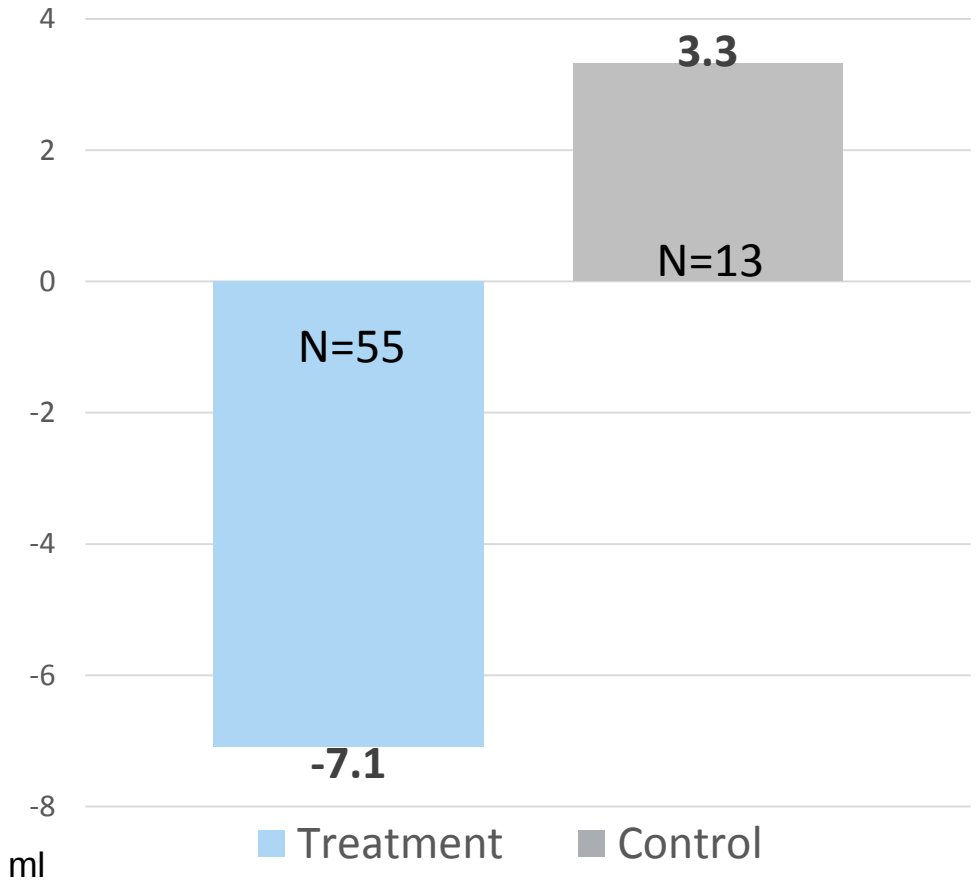
	Treatment	Control
COAPT EROA (mm^2)	41	40
MitraFR EROA (mm^2)	31	31

REDUCE FMR – Safety (MAE) at 1-Year (ITT)

	Treatment (N=87)			Control (N=33)	
	30 Days		1-Year	30 Days	1 Year
	Device Related	Procedure Related			
Death	0% (0)	2.3% (2)*	12.6% (11)	0% (0)	15.2% (5)
MI	1.1% (1)	3.5% (3)*	3.5% (3)	0% (0)	3.0% (1)
Cardiac Perforation**	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Device Embolism	0% (0)	0% (0)	0% (0)	n/a	n/a
Surgery or PCI related to device	0% (0)	0% (0)	0% (0)	n/a	n/a
Cumulative MAE Rate	**16.1% (14)**			**18.2% (6)**	

- * One death and two procedural MIs adjudicated as “possibly” related to device, however definitive relationship could not be established
- ** Of a cardiac structure (heart, artery and/or vein) leading to hemopericardium and requiring percutaneous or surgical intervention

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



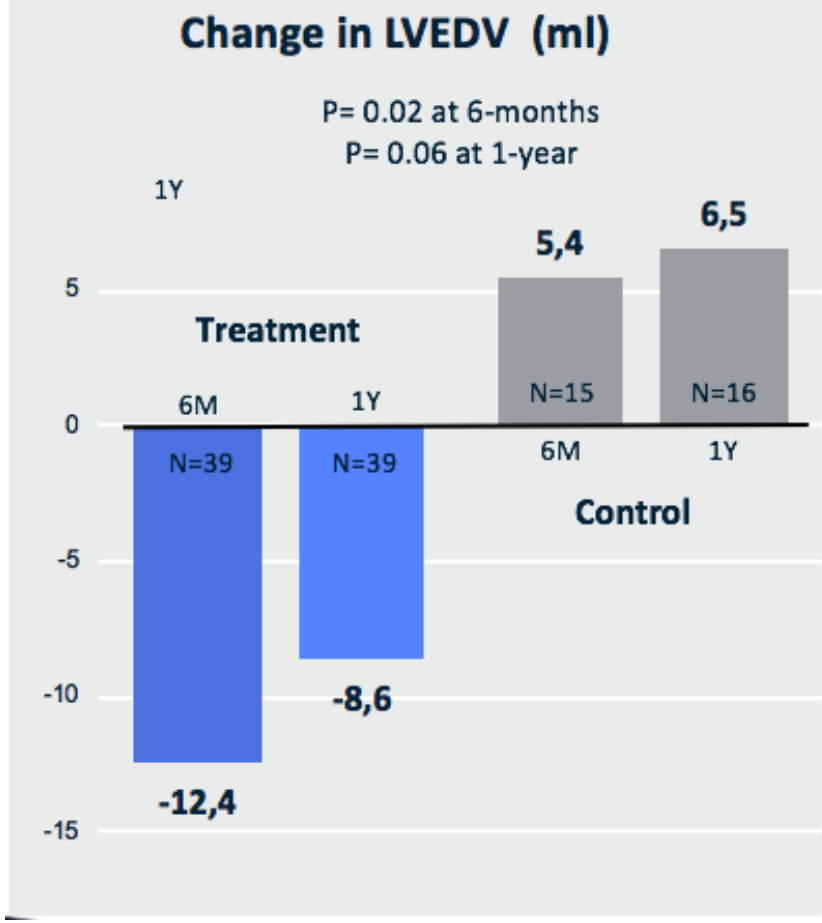
Mean RV Change – Paired data (ml)

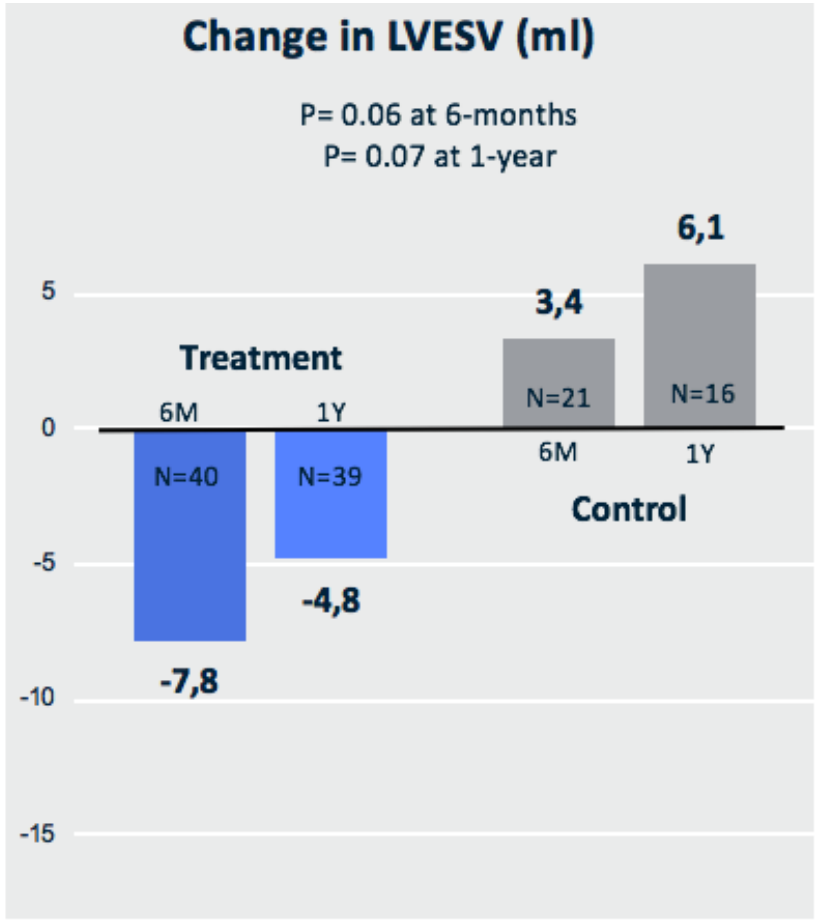
- 22% reduction in treatment group
- 8% increase in control group
- Absolute difference 10.4 ml

P = 0.03

Primary Endpoint Met

REDUCE FMR – Secondary Endpoint Analysis
Change in LVEDV and LVESV 1-Year (AT – As Treated)





- Secondary endpoints included change in LVEDV and LVESV at 1-year
- A volume reduction at 6-months and 12-months was observed in the treatment group
- The control group showed increased volumes at 6-months with further increased volumes at 1-year

Study Limitations

- The trial was not powered for clinical endpoints (e.g. death, QoL and 6MWD)
- The frequency of MR 1+ (30%) was unintended and made it more difficult to show a treatment effect
  - Despite this the trial was positive
- Echo follow-up of quantitative MR proved to be difficult
  - Despite this the trial was positive
- 14 patients did not receive the device but counted towards the treatment group (ITT analysis)
  - Despite this the trial was positive

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
- REDUCE FMR and COAPT demonstrated positive 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

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

Conclusions REDUCE FMR

- Catheter annuloplasty with the Carillon significantly reduced MR
- Adverse events were similar in the treatment vs. sham-controlled groups (MAE at 1 year 16.1% in the treatment group vs. 18.2% in the control group)
- Echo FU showed positive remodeling (LVESV and LVEDV)
- It may make sense to interrupt the vicious circle of LV dysfunction and mitral regurgitation (MR) not when the MR has become severe but as early as possible
- A larger randomized trial with clinical endpoints is ongoing

Thank you!

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