TURIN,
October
25th-27th
2018
Starhotels
Majestic

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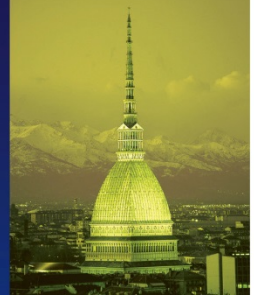


UNIVERSITÁ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

The First Choice for Functional Mitral Regurgitation Using the Coronary Sinus

Laura Vaskelyte, Ilona Hofmann, Markus Reinartz, Predrag Matić, Bojan Jovanović, Kolja Sievert, Sameer Gafoor, Stefan Bertog, Horst Sievert

CardioVasculäres Centrum Frankfurt

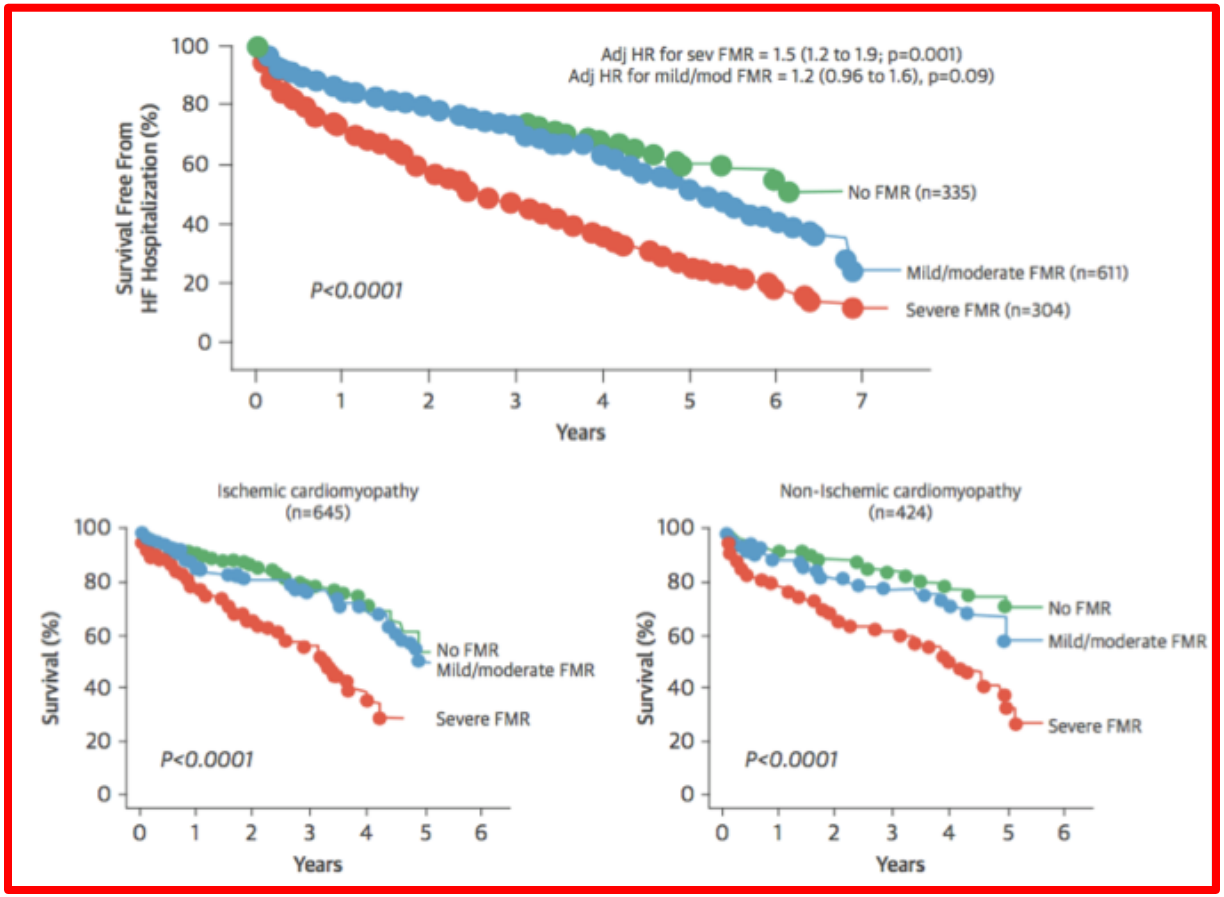
Disclosures

personal fees and travel expenses from

- Abbott Vascular
- NeoChord

Correlation between Survival and MR Severity

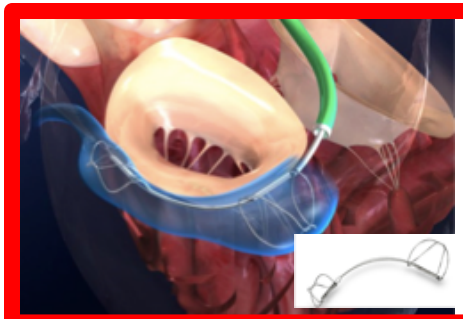
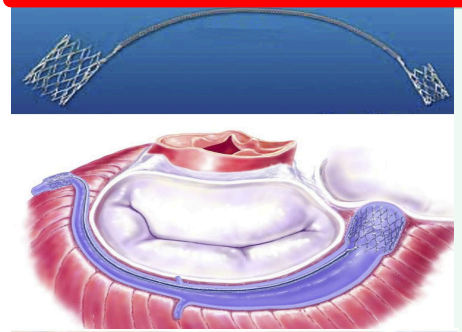
1 256 Pts with secondary MR



In patients with heart failure, FMR is associated with increased morbidity and mortality

Asgar et al. Secondary Mitral Regurgitation JACC VOL. 65, 2015:1231–48

Device Landscape for Indirect Annuloplasty Using CS

	CARILLON™ Mitral Contour System™ (Cardiac Dimensions Inc)	Two-Anchor design, repositionable, retrievable	TITAN I, TITAN II, AMADEUS, **REDUCE-FMR**
	MONARC (Edwards Lifesciences)	Two-anchor design for chronic CS reshaping (6 weeks) by a foreshortening bridge	EVOLUTION
	PTMA (Viacor Inc)	Tri-lumen catheter, metallic rods, reshapable, possibility of multiple long term adjustment	PTOLEMY

Paul T.L. Chiam, and Carlos E. Ruiz JCIN 2011;4:1-13

Cardiac Dimensions

Carillon™ Mitral Contour System™

Implant

- Venous jugular access 10 F
- CS anatomy and LCx anatomy dependent
- Distal and proximal anchors to ensure shortening by 4-5 cm
- Retrievable until final release and keeps all further Tx options

Distal Anchor
(in great cardiac vein)

Proximal Anchor
(in coronary sinus)

Implant lengths:
60 - 80 mm

Anchor sizes:
Individually selected for each patient

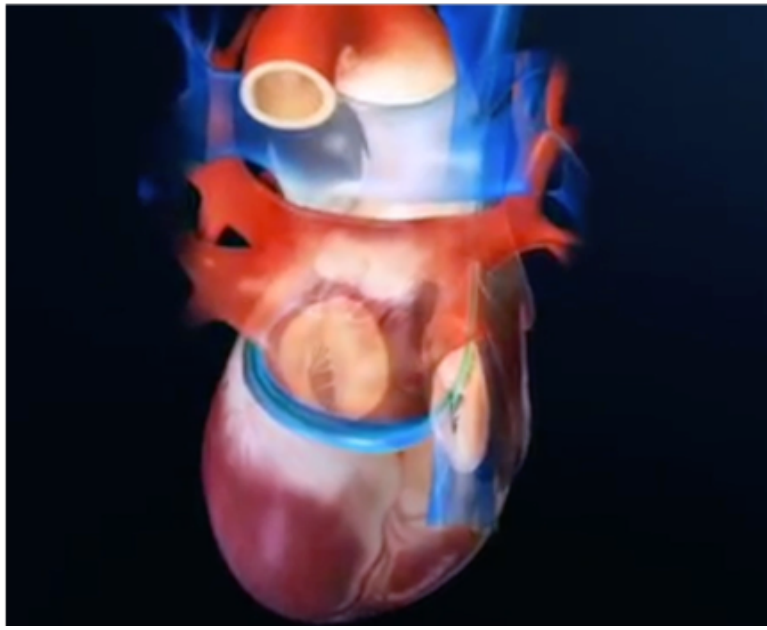
Delivery System

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use. Pivotal trial in US.

Cardiac Dimensions

Carillon™ Mitral Contour System™

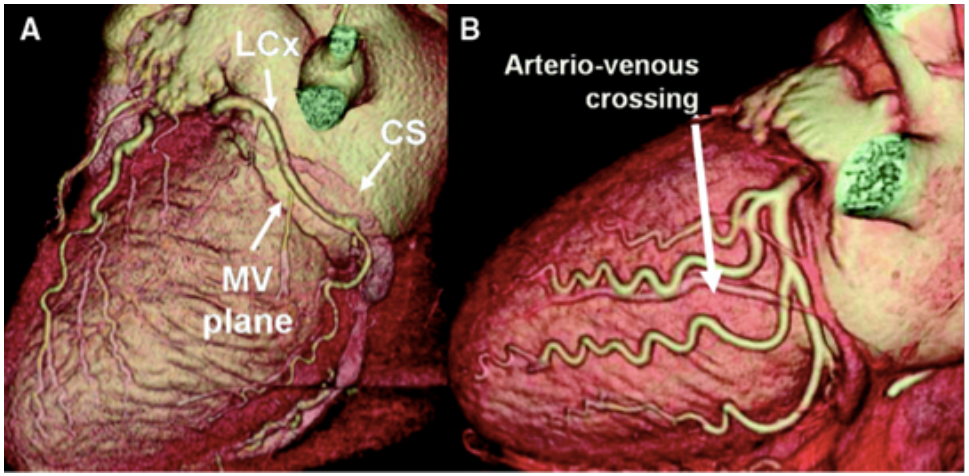
- Transjugulary venous access
- Introdution of 10F sheath in CS
- Device deployment under tension
- Cinching & leaflets approximation
- Retrievable till final release
- Preserving valve anatomy, all other treatment options remain open



Limitations of Coronary Sinus Approach

- CS typically lies on the atrial side of the mitral annulus rather than immediately in the plane of the annulus

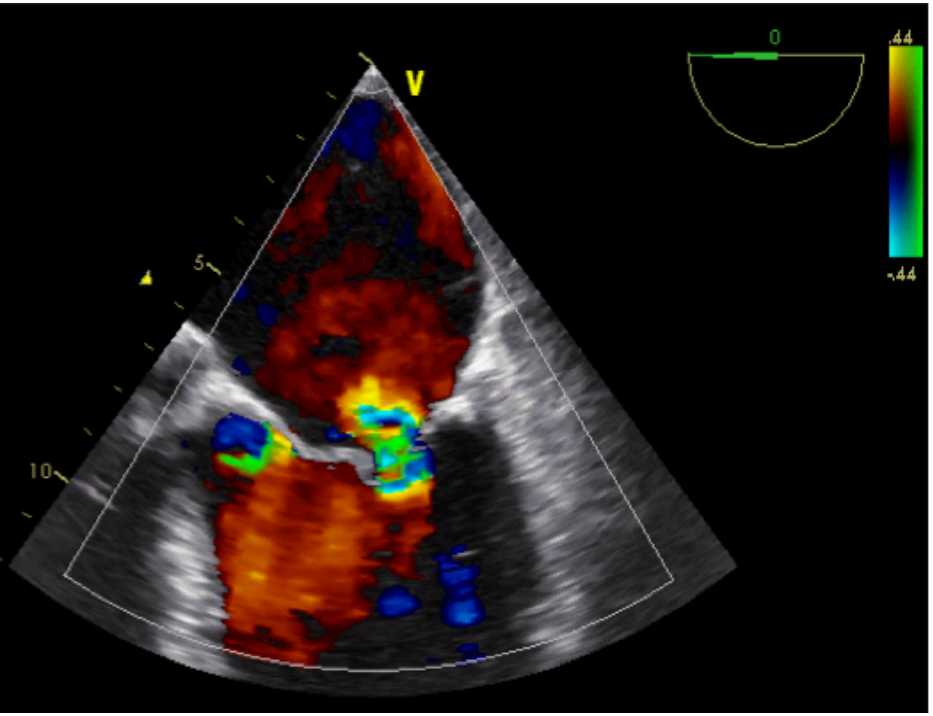
- Number of postmortem, CT and MRI studies demonstrated a highly variable anatomic relationship between MV and CS

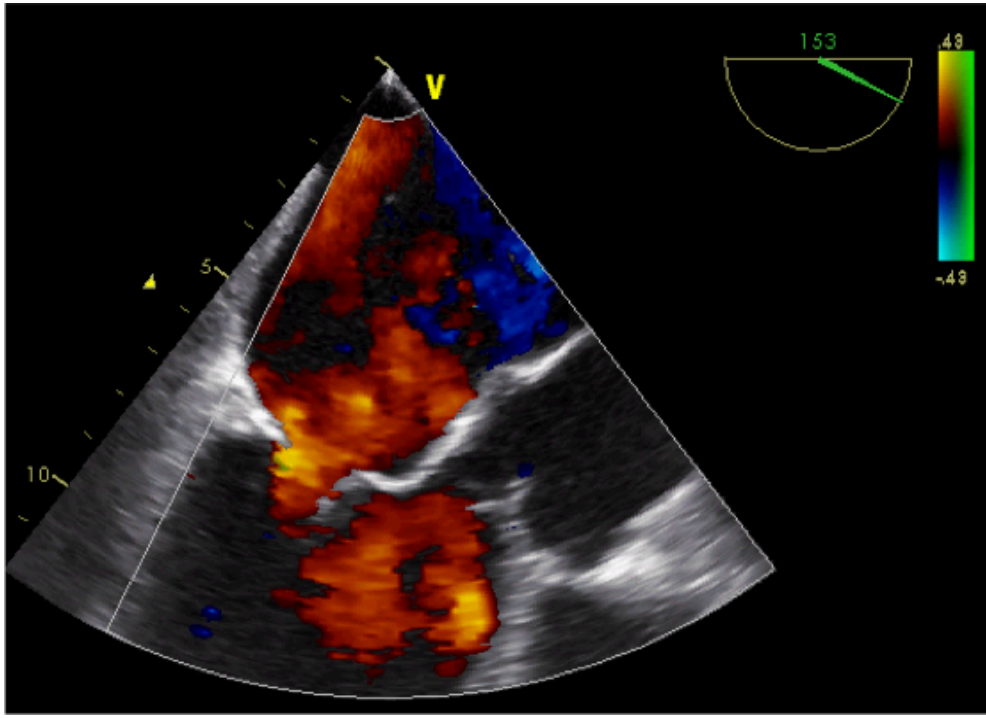


Percutaneous Treatment of Mitral Regurgitation, Volume: 2, Issue: 2, Pages: 140-146, DOI: (10.1161/CIRCINTERVENTIONS.108.837781)

Case Exemple

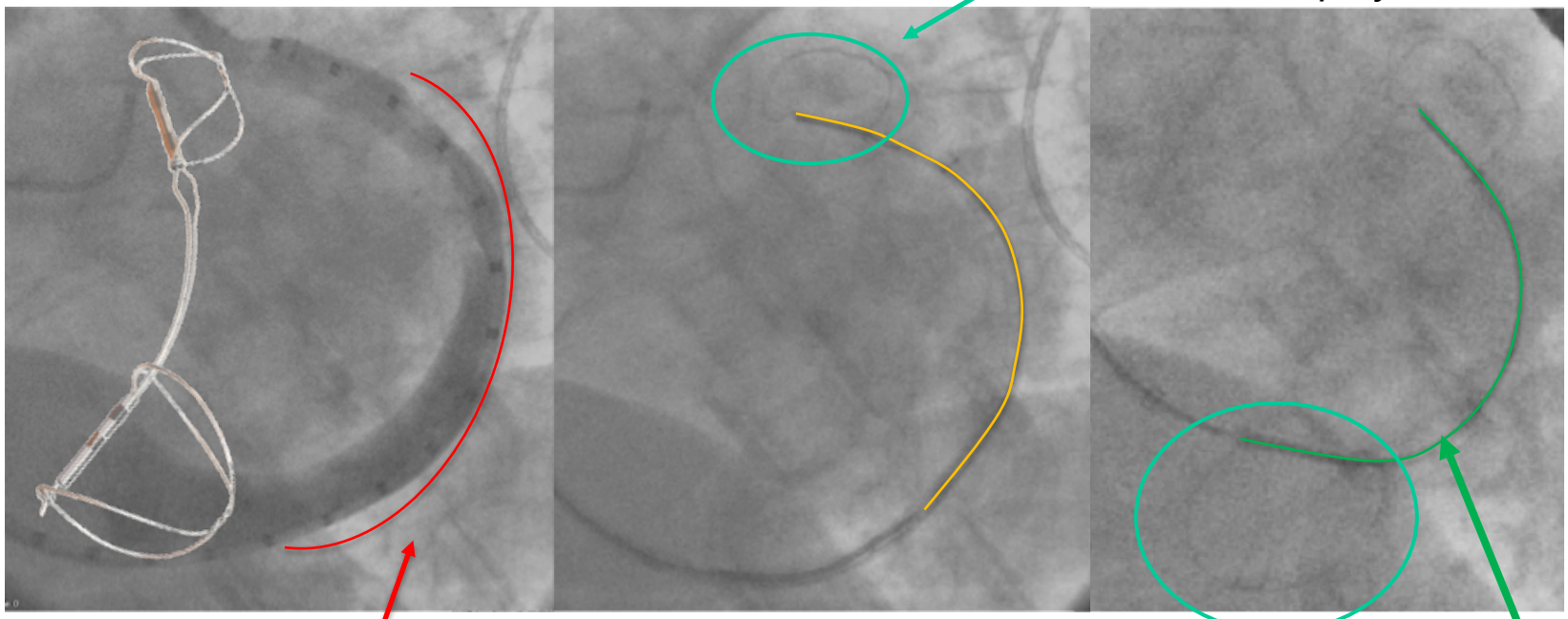
- 70 year old male
- Inflammatory DCM
- EF 40%
- Prostate Carcinoma
- Repetitive Hospitalizations due to worsening of the heart failure





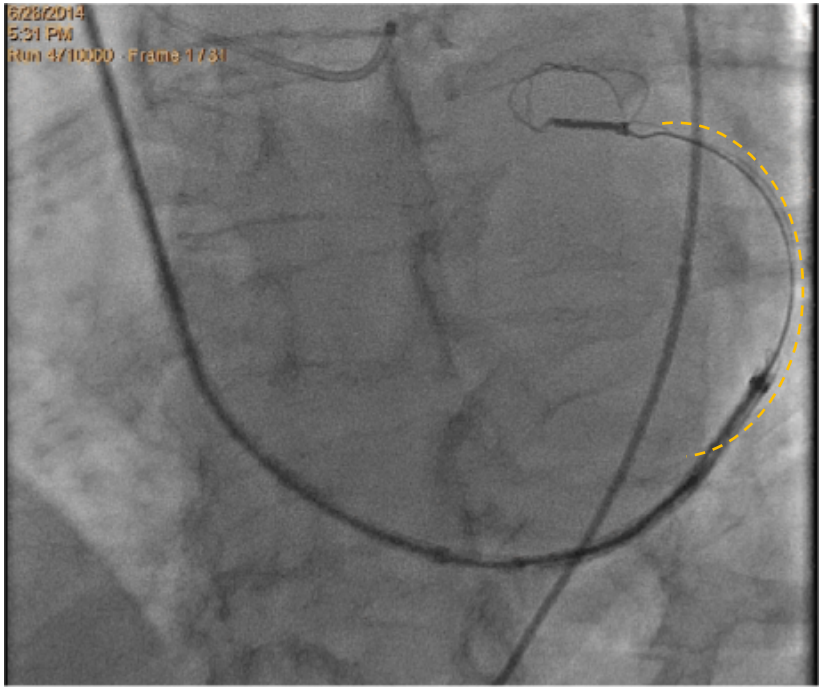
Carillon™ Mitral Contour System™

Device Deployment and Cinching

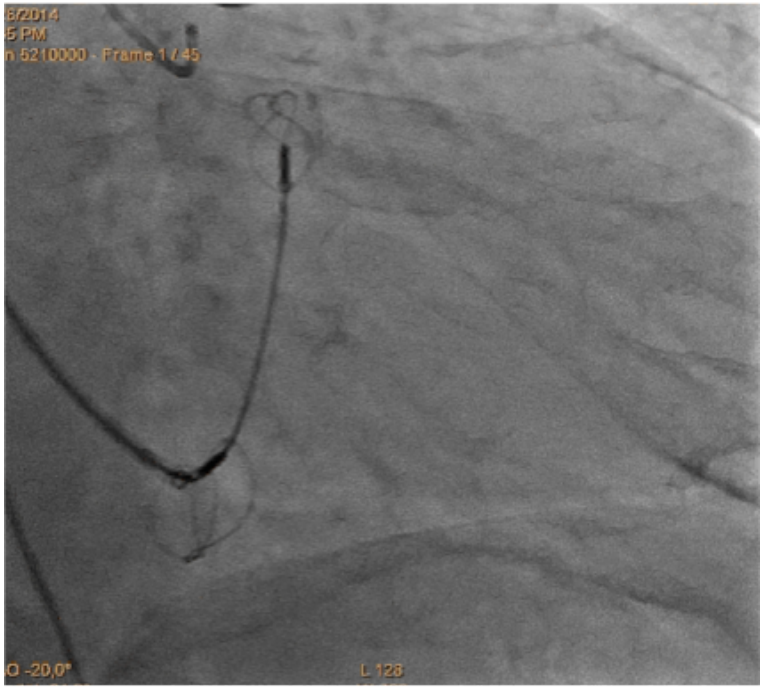


Fluoroscopy

Device deployment and tensioning

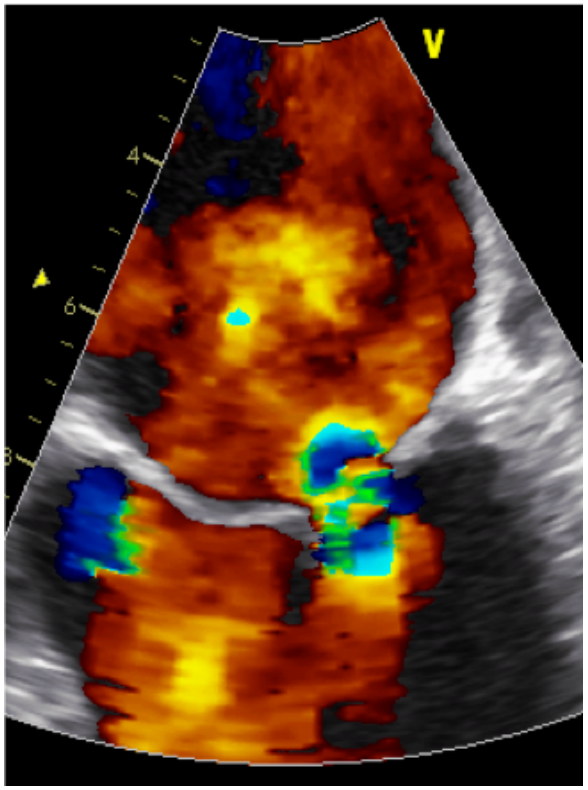


No interference between device & LCx

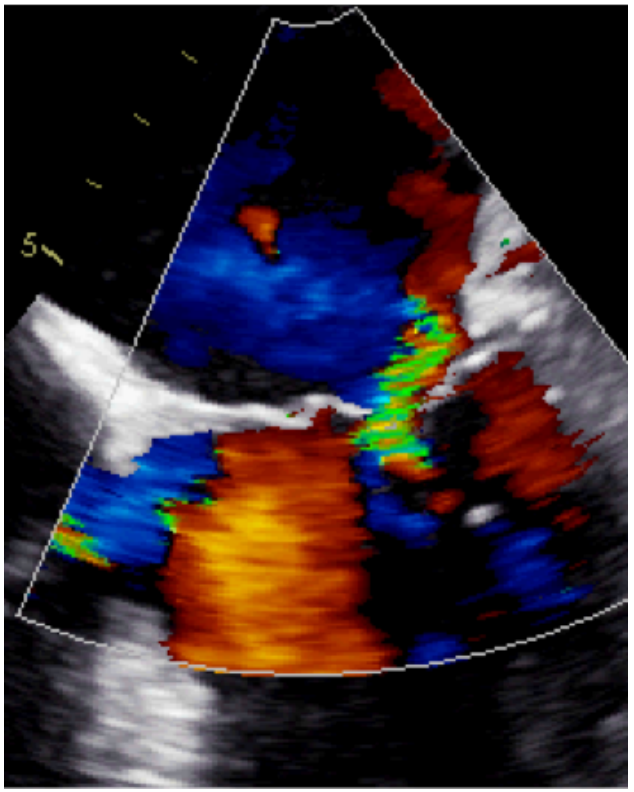


Improvement of MR over the Time

baseline



@ 6 Months



Improvement over the Time

	baseline	**@ 6 M**
LA Area	30 cm^2	26 cm^2
LA Volume	124 cc	86 cc
LVEDD	66 mm	62 mm
LVEDS	50 mm	46 mm
EF	40 %	52 %
E/E‘	18	10
TR	II°	I°
sPAP	85 mmHg	20 mmHg
NYHA	II-III	0-I

Myths about Mitral Valve Annuloplasty with Carillon™ Mitral Contour System™

Carillon is not very effective

- Can not be implanted in many patients
- Limited effect in patients in whom it can be implanted

Fact is, that data are limited

- But now they are looking good!

Carillon™ Mitral Contour System™

- Clinical experience:
  - Carillon device usually reduces, but rarely eliminates MR
  - Results improving over time

EVIDENCE:

- Previous small studies with Carillon device **AMADEUS**[1],**TITAN**[2] and **TITAN II**[3] have shown evidence of reduced MR and LV size

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: A Sham-Controlled Randomized Trial of Transcatheter Indirect Mitral Annuloplasty in Heart Failure Patients with Functional Mitral Regurgitation

Horst Sievert, MD

CardioVascular Center Frankfurt - CVC
Frankfurt, Germany

On behalf of the REDUCE-FMR Investigators

REDUCE FMR – Sham Control and Study Blinding

- All patients were heavily sedated, blindfolded and received noise canceling headphones
- Randomization was done after coronary sinus angiogram (for study eligibility)
- Echo core lab was blinded to patient randomization as well as timing of echoes
- Patient questionnaires on blinding at each follow-up visit
  - patients indicated uncertainty of treatment 96% of the time
- Assessors were blinded to patient randomization through 1-year follow-up assessment

REDUCE FMR – Analysis Populations and Endpoints

Intention to Treat (**ITT**): *As randomized regardless of implantation status*
As-Treated (**AT**): All patients with device implants at the end of the procedure
Per Protocol (**PP**): As-treated and patients who met inclusion and exclusion criteria

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

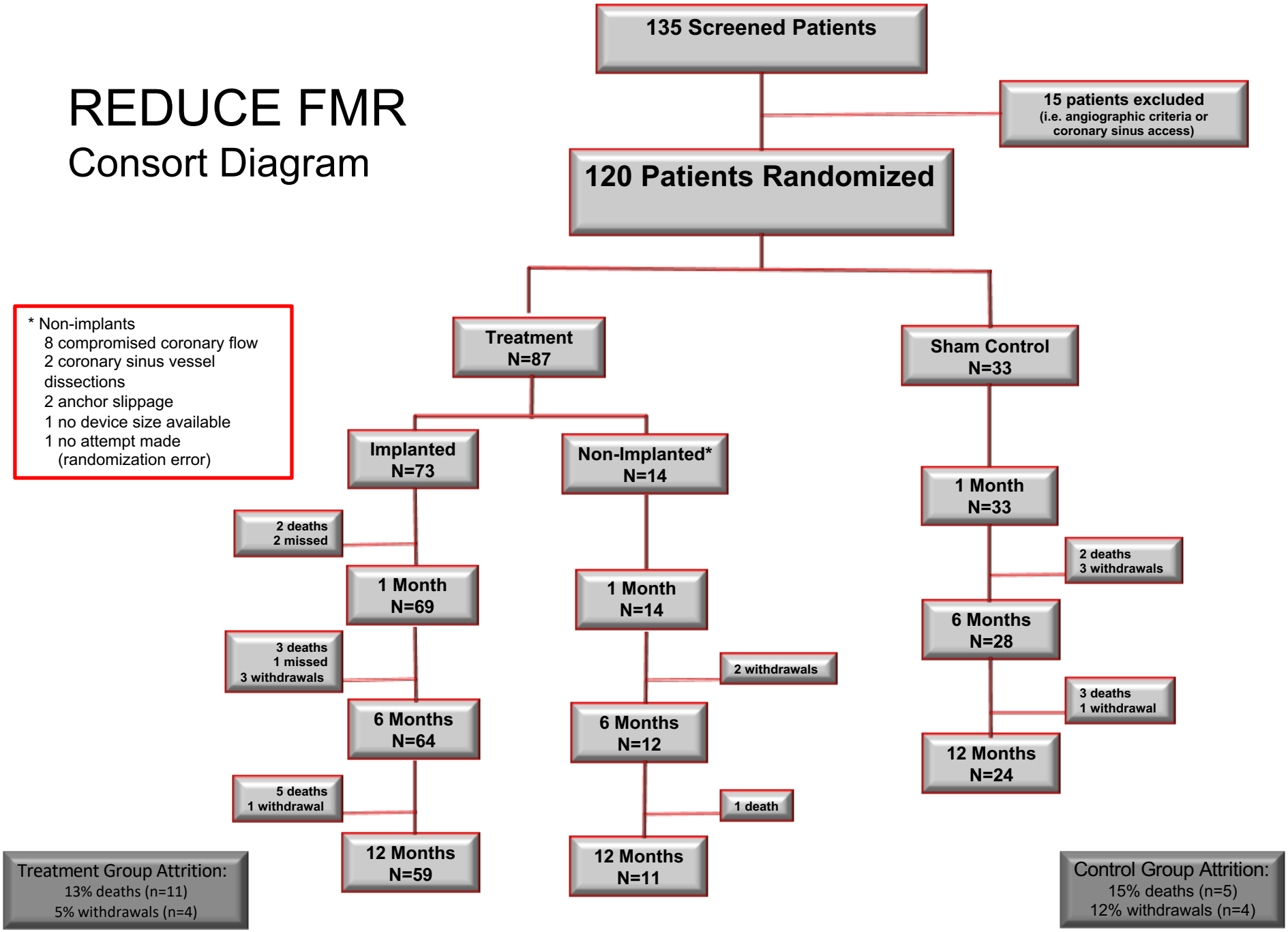
Inclusion:

- Dilated ischemic or non-ischemic cardiomyopathy
- 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



H.Sievert TCT 2018

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 (mm^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)	

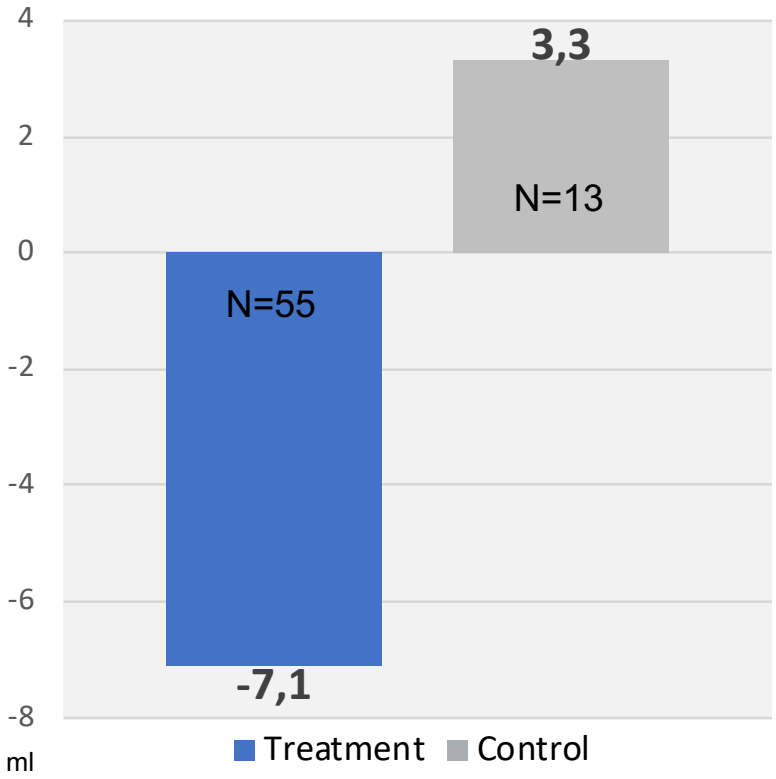
- MR was less severe than planned: baseline RV was 39 ml, 30% had MR 1+
- Less sick patient population than in most other heart failure trials

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)



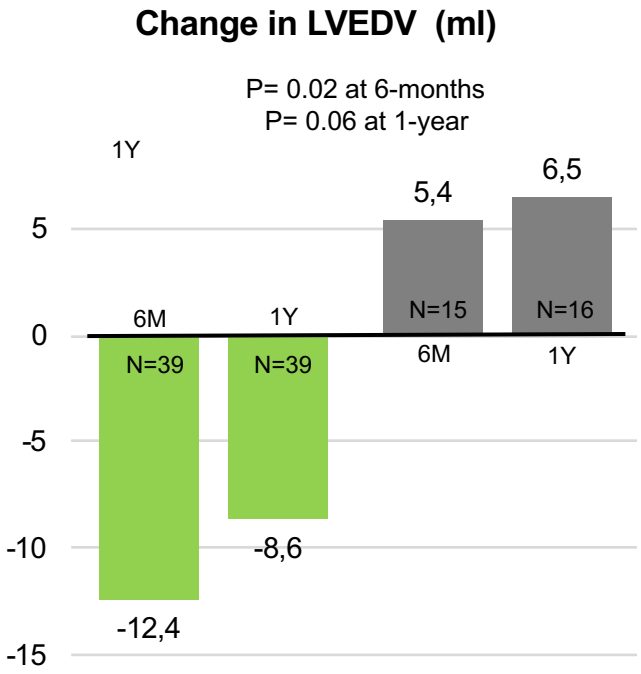
Mean RV Change – Paired data (ml)

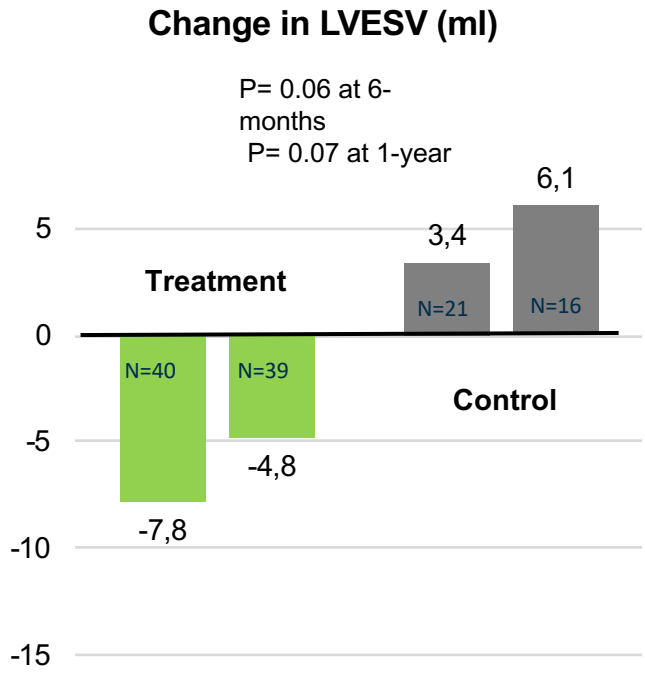
p = 0.03

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

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

REDUCE-FMR: Limitations

- The sample size of this sham-controlled randomized trial is too small to draw definitive conclusions on treatment effects of the secondary clinical endpoints (e.g. death, QoL and 6MWD)
- The frequency of MR 1+ (30%) in the ITT analysis population was unintended and negatively influenced overall improvements in regurgitant volumes in the treatment arm
- Echo follow-up assessments of quantitative MR proved to be difficult – further influencing treatment results

REDUCE-FMR: Conclusions

- Despite all the limitations, the primary endpoint, reduction in regurgitant volume (RV) at 1-year, **was met**
- The reduction in RV was amplified in patients in whom the device was implanted (AT), and in the 'intended' patient population (PP)
- Safety was similar in the treatment vs. sham-controlled groups with a MAE at 1 year of 16.1% in the treatment group vs. 18.2% in the control group
- Echo indicators of positive remodeling from LVESV and LVEDV were also observed in the as treated group (AT)

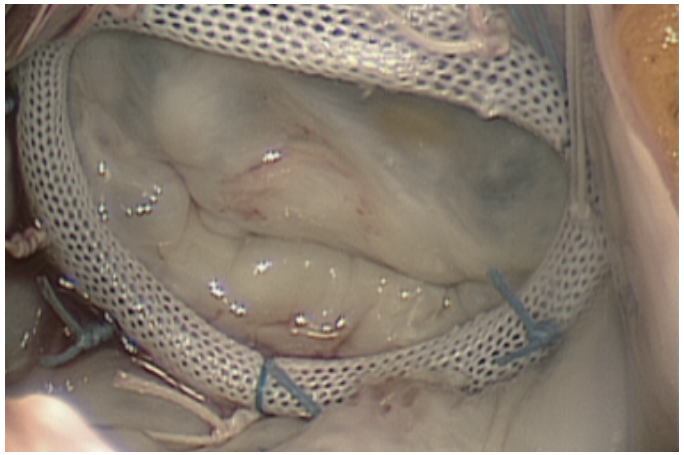
Carillon™ Mitral Contour System™

- *The ongoing CARILLON FDA pivotal randomized FMR trial is sham-controlled, with echo pre-screening of MR severity, and is powered to a hierarchical endpoint which includes clinical endpoints*

When Using the Coronary Sinus Approach for FMR Could Be the First Choice?

Surgical Annuloplasty

Implantation of an undersized ring



- Good results immediately
- Reccurence of MR 2+
  - after 6-12 months 15-33%
  - after 5 years 70%
- Predictors for MR recurrence:
  - Use of open or flexible ring
  - Severe LV dilatation (LVEDD >65 mm)
  - Tethering >11mm, PML-angle >45°
  - Severe MR pre-OP
  - Aneurysm or dyskinesia in basal segments

Ann Cardiothorac Surg 2015;4(3):278-283

When Could Using the Coronary Sinus Approach for FMR as a **Stand-Alone** Procedure Be the First Choice?

- CS lies close to the MV plane
- Atrial (Afib) MR
- Central Jet
- LV mild/ moderate dilated
- Tethering < 1 cm

Carillon™ Mitral Contour System™

- Fact is, that data is encouraging!
- In carefully selected patients, Carillon can be quite effective!

Thank you for your attention!