# Clinical Trials in **Functional** Mitral Regurgitation **Gregg W. Stone, MD Columbia University Medical Center NewYork-Presbyterian Hospital** Cardiovascular Research Foundation





#### **Disclosure Statement of Financial Interest**

None





#### Global or Regional LV Dysfunction can Result in Secondary (Functional) MR: The disease is the LV!

# Ischemic cardiomyopathy



Asgar, Mack, Stone. JACC 2015;65:1231–48

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## The Vicious Cycle of Secondary MR



# **MitraClip System and Implant**









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Feldman T et al. NEJM 2011;364:1395-406





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



Feldman T et al. NEJM 2011;364:1395-406

ventilation >48 hrs, new permanent AF, GI complication

requiring surgery, transfusion ≥2U

#### 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





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







2017 ESC/EACTS Valve; 2017 ACC/AHA/HFSA HF; 2017 ACC/AHA Valve

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# MitraClip Therapy Global Use, November 2017

Centers	>760
Patients	>50,000
Implant rate	97%
Functional MR	64%
Degenerative MR	22%
Mixed	14%

Data source: Abbott Vascular



#### **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



Goliasch G et al. EHJ 2018;39:39-46

#### Comparison of MitraClip to Conservative Therapy in High-risk MR: A Matched Registry Analysis

239 high risk MitraClip pts with 3+-4+ MR were propensity matched to 239 conservatively treated pts with 3+-4+ MR from the Duke Echo Lab Database 87% FMR; mean age 74 yrs; mean LVEF 42%; mean STS score 12%





Velazquez EJ et al. AHJ 2015;170:1050-9



#### Comparison of MitraClip to Conservative Therapy in FMR: A Matched Registry Analysis

60 high-risk MitraClip pts with 3+-4+ FMR were propensity matched to 60 conservatively treated pts with 3+-4+ FMR from a single center in Italy Mean age 75 yrs; mean LVEF 34% (52% ICM); median FU 515 days



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Giannini C et al. Am J Cardiol 2016;117:271-7

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Pls: Gregg W. Stone and Michael Mack Sponsor: Abbott Vascular

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### MitraClip RCTs in Functional MR (i)

	COAPT	<b>RESHAPE-HF-2</b>
N patients, sites	610 pts @ 100 NA and EU sites	380 pts @ 50 EU sites
Control arm	GDMT ± CRT	GDMT ± CRT
FMR grade	≥3+ (EROA ≥30 mm² and/or Rvol >45 mL by ECL)	≥3+ (EROA ≥30 mm² and/or Rvol >45 mL by ECL)
NYHA class	II, III, or ambulatory IV	III or ambulatory IV
Other inclusion criteria	HF hosp within 12 months or BNP ≥300 pg/ml or nT-proBNP ≥1500 pg/ml within 12 months; MV surgery is not local standard of care	HF hosp within 12 months or BNP ≥350 pg/ml or nT-proBNP ≥1400 pg/ml within 90 days; not eligible for MV surgery
LVEF	≥20% - ≤50%	≥15% - ≤40%
LV volumes	LVESD ≤70 mm	LVEDD ≥55 mm
Primary efficacy endpoint	Recurrent HF hospitalization at 24 months	Death or recurrent HF hospitalization at 24 months
Primary safety endpoint	SLDA, device embolizations, endocarditis/MS/device-related complications requiring non-elective CV surgery, LVAD, OHT at 12 mo	All-cause mortality, stroke, MI, new renal replacement therapy, non-elective CV surgery for device related complications
Total follow-up	5 years	5 years
Pls	GW Stone, M Mack	P Ponikowski, S Anker

#### MitraClip RCTs in Functional MR (ii)

	MITRA-FR	MATTERHORN
N patients, sites	288 pts @ 22 French sites	210 pts @ 15 EU sites
Control arm	GDMT ± CRT	MV Surgery
FMR grade	Severe (EROA >20 mm <sup>2</sup> + Rvol >30 mL) by ECL	≥3+
NYHA class	II - IV	≥III
Other inclusion criteria	HF hosp within 12 months; not eligible for MV surgery	_
LVEF	≥15% - ≤40%	≥20% - ≤45%
LV volumes	_	-
Primary efficacy endpoint	Death or recurrent HF hospitalization at 12 months	Death, HF rehosp, reintervention, assist device implantation or stroke at 12 months
Primary safety endpoint	_	Major adverse events at 30 days
Total follow-up	2 years	1 year
Pls	JF Obadia	J Hausleiter

# MitraClip RCTs in Functional MR

 4 trials randomizing <u>~1488 patients</u> with heart failure and secondary (functional) MR to MitraClip vs. GDMT or MV Surgery • As of April 10<sup>th</sup>, 2018, 1304 patients have been randomized: - COAPT - 614/610 (101%) - enrolled! - MITRA-FR – 288/288 (100%) – enrolled! - RESHAPE-HF-2 - 330/380 (87%) - MATTERHORN - 72/210 (34%)



#### **Novel MV Repair Devices with Ongoing US Pivotal Randomized Trials in FMR**

	AML	
	Cardiac Dimensions Carillon	Edwards Cardioband
Mechanism and study population	Coronary sinus mediated posterior annulus cinching	LA semi-rigid posterio partial annuloplasty bar with anchor cinching





# Novel MV Repair Devices with Ongoing US Pivotal Randomized Trials in FMR





	Cardiac Dimensions Carillon	Edwards Cardioband
Trial acronym	CARILLON NCT03142152	ACTIVE NCT03016975
N rand	N=400 2:1 vs. GDMT	N=375 2:1 vs. GDMT
Primary endpoints	<ul> <li>1-year efficacy: Requires superiority of both a) hierarchical composite endpoint of death, HF hospitaliza- tion, and improvement in 6MWD; b) change in regurgitant vol</li> <li>1-year safety: Device-related major adverse events (PG)</li> </ul>	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)





## Clinical Trials for Secondary MR Status 2018

- Patients with LV dysfunction may develop severe secondary MR, which can increase volume overload, decrease forward CO and worsen HF
- COAPT and other randomized trials are being performed to determine whether reducing secondary MR improves the prognosis of patients with HF



