When and how for percutaneous treatment?

Francesco Maisano MD, FESC Valve Center IRCCS San Raffaele University Hospital





Disclosure Statement of Financial Interest and Potential for Conflicts of Interest

I, Francesco Maisano, have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

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Cardiovalve, Magenta, SwissVortex, Transseptalsolutions, Occlufit, 4Tech, Perifect





ESC HF guidelines 2021

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IIb

Secondary mitral regurgitation

Percutaneous edge-to-edge mitral valve repair should be considered in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, who are symptomatic^c despite OMT and who fulfil criteria^d for achieving a reduction in HF hospitalizations.⁶¹²

In patients with HF, severe secondary mitral regurgitation and CAD who need revascularization, CABG and mitral valve surgery should be considered.

Percutaneous edge-to-edge mitral valve repair may be considered to improve symptoms in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, highly symptomatic despite OMT and who do not fulfil criteria for reducing HF hospitalization.⁶¹⁷



OSPEDALE SAN RAFFAELE

HF and VHD guidelines are in line

Two randomized trials, MITRA-FR and COAPIT, evaluated the effectiveness of percutaneous edge-to-edge mitral valve repair plus OMT compared to OMT alone, in symptomatic patients with reduced LVEF (15-40% in MITRA-FR and 20-50% in COAPT) and moderate-to-severe or severe SMR [effective regurgitant orifice area (EROA) \geq 20 mm² in MITRA-FR and EROA \geq 30 mm² in COAPT].⁶¹⁰⁻⁶¹² MITRA-FR failed to show any benefit from the intervention on all-cause mortality or HF hospitalization at 12 months (primary endpoint; HR 1.16, 95% CI 0.73-1.84) and at 24 months.^{610,611} In contrast, COAPT showed a significant reduction in hospitalization for HF at 24 months (primary endpoint; HR 0.53, 95% CI 0.40-0.70) and mortality (secondary endpoint; HR 0.62, 95% CI 0.46-0.82).⁶¹² Differences in patient selection, concomitant MT, echocardiographic assessment, procedural issues and severity of SMR in relation to the degree of LV dilatation may be responsible for the diverging results of the MITRA-FR and COAPT trials.⁶¹³⁻⁶¹⁵ Thus, percutaneous edge-to-edge mitral valve repair should be considered for outcome improvement only in carefully selected patients who remain symptomatic (NYHA class II-IV) despite OMT, with moderate-to-severe or severe SMR (EROA \geq 30 mm²), favourable anatomical conditions, and fulfilling the inclusion criteria of the COAPT study (i.e. LVEF 20-50%, LV end-systolic diameter <70 mm, systolic pulmonary pressure <70 mmHg, absence of moderate or severe RV dysfunction, absence of severe TR, absence of haemodynamic instability) (Figure 17).^{615,616}





TEER should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the therapy.

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In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased chance of responding to TEER, the Heart Team may consider in selected cases a TEER procedure or other trans-catheter valve therapy if applicable, after careful evaluation for ventricular assist device or heart transplant.

OSPEDALE SAN RAFFAELE

Key elements of the decision

- Functional MR resistant to GDMT
- high risk or inoperable
- Severe regurgitation
- EF>20%
- LVESD<70 mm





Functional or Secondary MR and Heart Failure.

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., Editor

Secondary Mitral Regurgitation

Patrick T. O'Gara, M.D., and Michael J. Mack, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 75-year-old man presents with dyspnea and fatigue that occur with less than moderate physical activity. He had an ST-segment elevation myocardial infarction involving the inferior and posterior segments of the left ventricle 10 years ago, and since then the left ventricular ejection fraction (LVEF) has decreased from 40% to 25%, accompanied by increasing mitral regurgitation. An implantable cardioverter-defibrillator (ICD) was placed for primary prevention 6 months ago. His medications include metoprolol succinate, spironolactone, and torsemide. How would you further evaluate and treat this patient? European Society of Cardiology doi:10.1002/ejhf.2115

POSITION PAPER

Universal definition and classification of heart failure:

A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association.

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Bozkurt et al. European Journal of He



Functional mitral regurgitation

Valve structure is preserved (not really) Left ventricular and/or atrial function/shape are abnormal

Phenotypes	Etiology	Mechanisms		
Ischemic acute MR	Acute AMI	Regional motiona abnormalities, Papillary muscle rupture (complete or partial)		
PM dysfunction	Permanent or transitory ischemia of PM	Lack of PM contraction		
Ischemic regional chronic MR	Previous Infero-posterior AMI	Asymmetric tethering		
Ischemic global chronic MR	Previous massive AMI or multiple AMIs	Mostly symmetric tethering, annular dilation, reduced closing forces		
Non-ischemic functional MR	Dilatated Cardiomyopathy	Mostly symmetric tethering, annular dilation, reduced closing forces		
PM dissynchrony	Left bundle branch block or PM induced dyssynchrony	Dissynchrony between PMs and wall motion		
Atrial functional MR	Atrial fibrillation	Annular dilation and disfunction Atriogenic annular tethering		



SAN RAFFAELE

Functional mitral regurgitation: a disease of the ventricle....a secondary problem



The Consequences of FMR

- Reduced cardiac output
- Ongoing volume overload stress-induced remodeling
- Left atrial remodeling and structural derangement (Afib)
- Increased pulmonary vascular resistance
- Compliance to therapy
- Acute decompensations
- 30% decrease of work efficiency energy spent/work produced





Functional MR is one of many components of the CHF complex



OSPEDALE SAN RAFFAELE

- Ischemia stunning
- Hybernation
- Fibrosis
- Dilatation -Remodeling
- Functional MR
- Atrial Fibrillation
- LV Dyssynchrony
- Malignant arrythr
- Neurohumoral de



FMR in heart failure

OSPEDALE SAN RAFFAELE

- 1256 pts with ischemic or non-ischemic DCM (mean EF 32%) from 4 Italian istitutions, retrospective analysis
- Presence of MR is associated with increased mortality



Morbidity is proportional to the degree of MR in FMR



Rossi 2011¹: Hospitalization-free survival decreased with increased MR severity.

Bursi 2010²: Transplant-free survival decreased wi increased MR severity.

- 1. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure: a quantitative analysis of 1256 patients with ischemic and non dilated cardiomyopathy. *Heart*. 2011;97(20):1675-1680.
- 2. Bursi F, Barbieri A, Grigioni F, et al. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: a long-term outcome study. *Eur J Heart Fail*. 2010;12(4):382-388.





ATTEND registry



50% of patient have improvement of FMR with uptitration of GDMT

Figure 3 New York Heart Association (NYHA) class (left) and mitral regurgitation (MR) (right) response to optimize treatment. Thickness of the line corresponds to the number of patients.





Lotte E. de Groot ESC Heart Failure 2019; **6**: 936–943



ARNI and FMR, the PRIME STUDY

Circulation

ORIGINAL RESEARCH ARTICLE

P

Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation **PRIME Study**

Editorial, see p 1366

Duk-Hyun Kang, MD,

BACKGROUND: The morbidity and mortality of patients with functional mitral regurgitation (MR) remain high, but no pharmacological therapy has been proven effective. The hypothesis of this study was that sacubitril/ valsartan would be superior to valsartan alone in improving functional MR via dual inhibition of the renin-angiotensin system and neprilysin.

METHODS: In this double-blind trial, we randomly assigned 118 patients with heart failure with chronic functional MR secondary to left ventricular (LV) dysfunction to receive either sacubitril/valsartan or valsartan, in addition to standard medical therapy for heart failure. The primary end

PhD*

Sung-Ji Park, MD, PhD* Sung-Hee Shin, MD, PhD Geu-Ru Hong, MD, PhD Sahmin Lee, MD, PhD Min-Seok Kim, MD, PhD Sung-Cheol Yun, PhD Jong-Min Song, MD, PhD Seung-Woo Park, MD, PhD Jae-Joong Kim, MD, PhD

Table 4. Outcomes in Completers



		Baseline			12 Months		Change						ľ V	
	Outcome	Valsartan (n=53)	Sacubitril/ Valsartan (n=51)	<i>P</i> Value	Valsartan (n=53)	Sacubitril/ Valsartan (n=51)	P Value	Valsartan (n=53)	Sacubitril/ Valsartan (n=51)	Difference (95%Cl)	۴) ر	7	- Con	
OSPEDALE	Primary end point													
SAN RAFFAELE	EROA of MR, cm ²	0.208±0.109	0.200±0.099	0.70	0.178±0.151	0.123±0.074	0.021	-0.030±0.096	-0.077±0.080	-0.047 (-0.081 to -0.013)		-		

CRT therapy can improve MR in selected patients

• MIRACLE trial (450 pts with LVEF < 35% and QRS>130 sec)





Non responder to CRT are at high risk of mortality if MR remains untreated





Van Bommel Circulatio







About 10 years of FMR treatment in Europe

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CLINICAL RESEARCH

OSPEDALE SAN RAFFAELE **Interventional Cardiology**

Percutaneous Mitral Valve Interventions in the Real World

Early and 1-Year Results From the ACCESS-EU, A Prospective, Multicenter, Nonrandomized Post-Approval Study of the MitraClip Therapy in Europe

Francesco Maisano, MD,* Olaf Franzen, MD,† Stephan Baldus, MD,‡ Ulrich Schäfer, MD,§ Jörg Hausleiter, MD,|| Christian Butter, MD,¶ Gian Paolo Ussia, MD,#** Horst Sievert, MD,†† Gert Richardt, MD,‡‡ Julian D. Widder, MD,§§ Tiziano Moccetti, MD,|||| Wolfgang Schillinger, MD¶¶

Milan, Italy; Copenhagen, Denmark; Hamburg, Munich, Berlin, Frankfurt, Bad Segeberg, Hannover, and Göttingen, Germany; Catania, Italy; and Lugano, Switzerland

 Objectives
 The purpose of this article is to report early and mid-term outcomes of the ACCESS-EU study (ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe), a European prospective, multicenter, nonrandomized post-approval study of MitraClip therapy (Abbott Vascular, Inc., Santa Clara, California).

 Background
 MitraClip has been increasingly performed in Europe after approval; the ACCESS-EU registry provides a snapshot of the real-world clinical demographic data and outcomes.

Methods A total of 567 patients with significant mitral valve regurgitation (MR) underwent MitraClip therapy at 14 European





COAPT TRIAL A leapfrog in the history of functional mitral valve treatment

Primary Effectiveness Endpoint All Hospitalizations for HF within 24 months



Powered Secondary Endpoints

- Tested in hierarchical order¹ -

	P-value
1. MR grade ≤2+ at 12 months	<0.001
2. All-cause mortality at 12 months ²	<0.001
3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)	<0.001
4. Change in QOL (KCCQ) from baseline to 12 months	<0.001
5. Change in 6MWD from baseline to 12 months	<0.001
6. All-cause hospitalizations through 24 months	0.03
7. NYHA class I or II at 12 months	<0.001
8. Change in LVEDV from baseline to 12 months	0.003
9. All-cause mortality at 24 months	<0.001
10. Death, stroke, MI, or non-elective CV surgery for device-related	

¹All powered for superiority unless otherwise noted; ²Powered for noninf vs. the control group; ³Powered for noninferiority against an objective





NNT TO PREVENT 1 ALL-CAUSE DEATH*



* Data from different trials

* Incremental benefits due to test drug/device above background therapy

SAN RAFFAELE



COAPT

Three-Year Outcomes from a Randomized Trial of Transcatheter Mitral Valve Leaflet Approximation in Patients with Heart Failure and Secondary Mitral Regurgitation

> Michael Mack William T. Abraham JoAnn Lindenfeld Gregg W. Stone On behalf of the COAPT Investigators





COAPT (NCT01626079)

Primary Effectiveness Endpoint All Hospitalizations for HF within 36 months All patients, ITT, including crossovers



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Primary Effectiveness Endpoint All Hospitalizations for HF within 36 months All patients, ITT, including crossovers



OSPEDALE

COAPT vs MitraFR

- Does the design of each trial impact the results?
- Is there a mechanistic explanation for each trial's results?
- What can we learn from the outcomes of the control group of the two trials?
- Is there a need for a tie-breaker?
- Would a meta-analysis of the two trials be meaningful?
- Do the differences in sample size, operator experience and trial follow-up explain the different results?
- Industry sponsored vs independent?

OSPEDALE

SAN RAFFAELE



Patient selection: According to COAPT and MitraFR, patients with larger degree of MR and smaller ventricles have higher chance of improvement



OSPEDALE SAN RAFFAELE

VHD guideoines 2021 Severity MR threshold in SMR (ERO from 0.2 to 0.4)

Table 7 Severe mitral regurgitation criteria based on 2D echocardiography

	Primary mitral regurgitation	Secondary mitral regurgitation
Qualitative		
Mitral valve morphology	Flail leaflet, ruptured papillary muscle, severe retraction, large perforation	Normal leaflets but with severe tenting, poor leaflet coaptation
Colour flow jet area	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size
Flow convergence	Large throughout systole	Large throughout systole
Continuous wave Doppler jet	Holosystolic/dense/triangular	Holosystolic/dense/triangular
Semiquantitative		
Vena contracta width (mm)	≥7 (≥8 mm for biplane)	≥7 (≥8 mm for biplane)
Pulmonary vein flow	Systolic flow reversal	Systolic flow reversal
Mitral inflow	E-wave dominant (>1.2 m/s)	E-wave dominant (>1.2 m/s)
TVI mitral/TVI aortic	>1.4	>1.4
Quantitative		
EROA (2D PISA, mm ²)	≥40 mm ²	\geq 40 mm ² (may be \geq 30 mm ² if elliptical regurgitant orifice area)
Regurgitant volume (mL/beat)	≥60 mL	\geq 60 mL (may be \geq 45 mL if low flow conditions)
Regurgitant fraction (%)	≥50%	≥50%
Structural		
Left ventricle	Dilated (ESD ≥40 mm)	Dilated
Left atrium	Dilated (diameter ≥55 mm or volume ≥60 mL/m²)	Dilated

6.2.1 Evaluation

The echocardiographic criteria to define severe SMR do not differ from those used in PMR and an integrative approach should be used (Table 7).^{24,268} However, it should be acknowledged that when guantifying EROA and regurgitant volume in SMR, lower thresholds may be applied to define severe SMR. In heart failure patients, the total forward LV stroke volume is lower and that may lead to lower estimated regurgitant volume (<60 mL/beat). Calculation of regurgitant fraction in those circumstances could account for lower flows and has shown prognostic implications.³²⁰ In addition, the crescent shape of the regurgitant orifice, characteristic of SMR, may lead to underestimation of the vena contracta width and of the EROA. An EROA \geq 30 mm² by 2D proximal isovelocity surface area (PISA) likely corresponds to severe SMR. In contrast, whether an EROA \geq 20 mm² defines severe SMR remains controversial. In heart failure patients, even mild mitral regurgitation is associated with poor prognosis³²¹ and evidence that surgical or transcatheter treatment of moderate SMR does not seem to impro

the change in definition of sev



OSPEDALE SAN RAFFAELE

MitraClip therapy is not an alternative to ECMO, VAD or HTx







Disproportionately Severe FMR



. Adapted from Graybun et al. JACC Cardiovasc Imaging. 2018 Dec 6. pii: S1936-8

OSPEDALE SAN RAFFAELE

What is severe MR?



Morning







Obadia JF et al. NEJM. 2018 Aug 27. doi: 10.1056/NEJMoa1805374

Stone GW et al. NEJM. 2

Learning Curve and Expertise (TVT registry)



Procedural Success: Learning Curve Analysis*







Hemodynamic assessment

Continuous LAP measurements







MITRACLIP G4 DESIGN: 4th GENERATION SYSTEM EXPANDED CLIP OPTIONS



With Four Clip sizes of the MitraClipTM G4 system

EXPAND TRIAL: MR REDUCTION BY MR ETIOLOGY

83.5% MR \leq 1+ AT 1 YEAR IN SUBJECTS WITH BASELINE MR \geq 3+

ECL Adjudicated MR Severity by Etiology



Mitral Valve Etiology, Pathology and Lesions



Source: Daniel Drake, "Axial Echocardiography", Michigan Society of Thoracic and Cardiovascular Surgeons

mitral valve replacement / implantation



Cardiovalve TMVR: 1, 2, 3...



The full spectrum of mitral interventions





Continuum of care of patients with HF

European Journal of Heart Failure (2017) doi:10.1002/ejhf.951 **EDITORIAL COMMENT**



Mitral interventions in heart failure: time to deliver on the promise

Francesco Maisano* and Frank Ruschitzka







Clinical stabilization (prevent Hospitalizations)

Improve quality of life and performance

Improve prognosis



Disease

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Care

Treatment

managemer

life-time