Conoscere e Curare il Cuore 2019

SABATO 2 MARZO

TRATTAMENTO DELL'INSUFFICIENZA MITRALICA CON LA MITRACLIP

CONTRO

Edoardo Gronda

IRCCS MultiMedica, Sesto San Giovanni - MI

Dr. Edoardo Gronda

Disclosures:

NONE

Background

La valvola mitrale è una **struttura complessa** che comprende:

- lembi valvolari
- annulus valvolare
- corde tendinee
- muscoli papillari
- segmenti della parete ventricolare su cui poggiano i papillari

APPARATO SOTTOVALVOLARE

Insufficienza mitralica secondaria:

condizione complessa dovuta a mancata coaptazione di lembi strutturalmente normali, per alterazione:

- **della geometria**
- **del volume**
- **della funzione**

del ventricolo sinistro

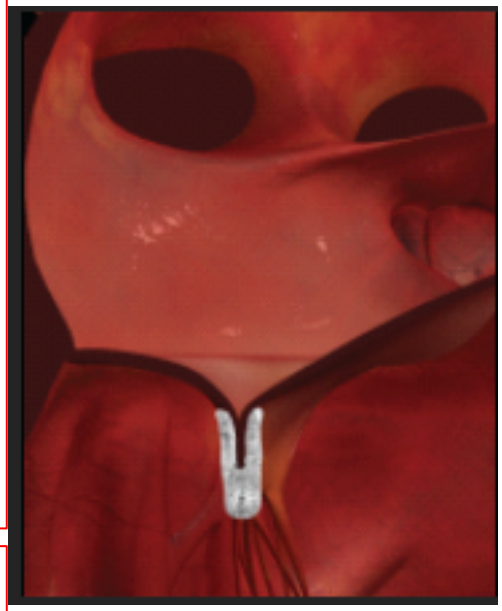
COAPT (COMPLEX) Study

Prospective, multicenter, randomized, parallel-controlled trial in a 1:1 ratio to:

- MitraClip device
- no MitraClip device

Patient selection based on:

- 13 inclusion criteria
- 30 exclusion criteria



★(2) **HF subjects (LVEF >20% - <50%)**

FMR [moderate-to-severe (3+)/severe (4+)]
be likely to benefit from **MR reduction**
Symptomatic **despite the use of**
★(3) **maximal doses** of guideline-directed medical therapy **deemed too high risk** to undergo mitral valve surgery.

"**Primary** effectiveness end point **all hospitalizations… for HF within 24 months of follow-up."**

★(5)(..**including recurrent events in patients with more than one event)**

In the published Study protocol:

★(4)**"analyzed when the last subject completes 12 months of follow-up"**

★(1) "Sites must have adequate volume of potential subjects who meet the eligibility criteria **(at least 1 subject per site per month)".**

No more than 15% of patients enrolled in each center

Qualified by an **Independent Central Eligibility Committee (Interventional, CT surgeon, HF physician, echocardiographer)**

Stone G et al. NEJM 2018

78 enrolling Sites in the United States and Canada

Recruitment Information	★(1)	
Recruitment Status ICMJE	Recruiting	
Estimated Enrollment ICMJE (submitted: January 31, 2017)	610	"The [highest] enrolling center, Cedars-Sinai in Los Angeles, included 46 pts in the enrollment period of close to 5 years. Less than one clip per month in the most active center in the COAPT trial." *Obadia JF MEDSCAPE Set 2018*
Original Estimated Enrollment ICMJE (submitted: June 21, 2012)	500	
Estimated Study Completion Date	July 2024	
Actual Primary Completion Date	July 2018	(Final data collection date for primary outcome measure)

https://clinicaltrials.gov/ct2/show/record/NCT01626079?term=COAPT+Stone+Gregg&cond=heart+failure+mitraclip&cntry=US&rank=1

History of Changes for Study: NCT01626079

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial)

Latest version (November 5, 2018) on ClinicalTrials.gov

1	◉	○	June 21, 2012	Nothing (earliest Version on record)
2	○	○	August 1, 2012	Contacts/Locations and Study Status
3	○	○	August 9, 2012	Outcome Measures and Study Status
4	○	○	October 12, 2012	Contacts/Locations and Study Status
5	○	○	December 13, 2012	Recruitment Status, Study Status and Contacts/Locations
6	○	○	December 19, 2012	Contacts/Locations and Study Status
7	○	○	January 2, 2013	Study Status and Contacts/Locations
8	○	○	January 23, 2013	Contacts/Locations and Study Status
9	○	○	January 30, 2013	Contacts/Locations and Study Status
10	○	○	February 4, 2013	Study Status and Contacts/Locations
11	○	○	February 26, 2013	Contacts/Locations and Study Status
12	○	○	March 7, 2013	Study Status, Contacts/Locations, Eligibility and Study Design
13	○	○	June 3, 2013	Outcome Measures, Study Status and Eligibility
14	○	○	July 22, 2013	Outcome Measures, Eligibility and Study Status
15	○	○	October 14, 2013	Contacts/Locations, Study Status, Eligibility and Outcome Measures
16	○	○	October 16, 2013	Contacts/Locations and Study Status
17	○	○	January 14, 2014	Study Status, Outcome Measures, Study Description, Study Identification, References, Eligibility, Study Design and Oversight
18	○	○	January 29, 2014	Contacts/Locations and Study Status
19	○	○	March 5, 2014	Contacts/Locations and Study Status
20	○	○	October 24, 2014	Contacts/Locations, Study Status, Eligibility and Study Identification
21	○	○	December 16, 2014	Contacts/Locations, Outcome Measures, Arms and Interventions,
22	○	○	March 11, 2015	Contacts/Locations, Study Description, Study Status, Eligibility, Outcome Measures and Conditions
23	○	○	April 23, 2015	Study Status and Contacts/Locations
24	○	○	June 3, 2015	Contacts/Locations and Study Status
25	○	○	October 9, 2015	Contacts/Locations and Study Status
26	○	○	February 10, 2016	Study Status and Contacts/Locations
27	○	○	June 6, 2016	Contacts/Locations, Study Status, Study Design and Study Description
28	○	○	January 31, 2017	Contacts/Locations, Outcome Measures, Study Description, Study Status, Study Identification, Eligibility and Study Design
29	○	○	July 14, 2017	Contacts/Locations, Study Status, Outcome Measures, Conditions, Study Description, References, Eligibility and Study Design
30	○	○	November 6, 2017	Contacts/Locations and Study Status
31	○	○	December 1, 2017	Study Status and Contacts/Locations
32	○	○	May 30, 2018	Contacts/Locations, Study Status, Outcome Measures and Study Description
33	○	○	September 10, 2018	Study Status, Study Description and Study Identification
34	○	◉	November 5, 2018	Study Status and Study Identification

Compare

Comparison Format: ◉ Merged ○ Side-by-Side

1. June 21, 2012 **(Inclusion C) ★(2)**

Left ventricular ejection fraction (LVEF) > 30% and left ventricular end-systolic dimension (LVESD) ≤ 60 mm

2. March 7, 2013 **(Inclusion C)**

Left ventricular ejection fraction (LVEF) ***> 20%*** and left ventricular end-systolic dimension (LVESD) ≤ 60 mm

3. June 3, 201[illegible] **(exclusion C)**

The subject has severe LV dysfunction …. (…defined as Left Ventricular End Systolic Dimension (LVESD) **>60mm or** Left Ventricular Ejection Fraction (LVEF) **<20%**) and confirmed by the Echocardiography Core Laboratory.

4. January 14, 2014 **(Inclusion C)**

Left Ventricular Ejection Fraction (LVEF) **is ≥20% and ≤50% within 90 days** prior to subject registration, assessed by the site using any one of the following methods: echocardiography, contrast left ventriculography, gated blood pool scan or cardiac magnetic resonance imaging (MRI).

5. October 24, 2014 **(Inclusion C)**

Left Ventricular End Systolic Dimension (LVESD) is **≤ 70 mm** assessed by site based on a transthoracic echocardiographic (TTE) obtained within 90 days prior to subject registration.

6. December 16, 2014 (**Inclusion C**)

Left Ventricular Ejection Fraction (LVEF) is ≥20% and ≤50% within 90 days prior to subject registration, assessed by the site using any one of the following methods: echocardiography, contrast left ventriculography, gated blood pool scan or cardiac magnetic resonance imaging (MRI). **Note: The method must provide a quantitative readout (not a visual assessment).**

https://clinicaltrials.gov/ct2/show/record/NCT01626079?term=COAPT+Stone+Gregg&cond=heart+failure+mitraclip&cntry=US&rank=1

Frazione d'eiezione e diametro ventricolare sinistro

- Il valore della frazione d'eiezione e del diametro diastolico del ventricolo sinistro sono stati indicati quali criteri **fondamentali** per la selezione dei pazienti da arruolare.

- Sul sito **clinicaltrials.gov dello studio** si riscontrano **5 modifiche** di questi parametri, eseguite nell'arco di 30 mesi, nello studio condotto in approssimativamente 5 anni.

- La variabilità di questi **fondamentali** criteri d'inclusione è durata per il 50% del tempo di arruolamento.

- L'inclusione nel trial di soggetti con differente profilo di rischio ha compromesso l'appropriata distribuzione del rischio stesso, nei 2 gruppi indagati.

La Popolazione dello Studio COAPT

"NYHA functional class II, III, or IV (ambulatory) despite the use of

★(3) stable maximal doses of GDMT and CRT

(if appropriate), which were administered in accordance with guidelines of professional societies."

Stone G et al. NEJM 2018

Baseline	Device Group (N = 302)	Control Group (N = 312)	
COAPT (IVTD 101 ± 34 ml/m2)			
ACEI, ARB or ARNI (Baseline)	71.5% (216/302)	62.8% (196/312)	p 0.02
NYHA IVa (ambulatory)	18/302 (6.0)	33/311 (10.6)	
N-terminal pro–BNP pg/ml	5174.3 ± 6566.6	5943.9 ± 8437.6	

Obadia JF et al. NEJM 2018

MITRA FR (IVTD 135 ± 37 ml/m)		
ACEi/ARB	111/152 (73.0)	113/152 (74.3)
ARNI	14/140 (10.0)	17/140 (12.1)
NYHA IV	14 (9.2)	12 (7.9)
N-terminal pro–BNP pg/ml	3407 (1948–6790)	3292 (1937–6343)

Popolazione dello Studio COAPT

"NYHA functional class II, III, or IV (ambulatory) despite the use of

★(3) stable maximal doses of GDMT and CRT

(if appropriate), which were administered in accordance with guidelines of professional societies."

One year FU

	Stone G et al. NEJM 2018		
COAPT (IVTD 101 ± 34 ml/m2)	**Device Group (N = 302)**	**Control Group (N = 312)**	
Beta-blocker	93.3% (222/238)	86.7% (195/225)	p 0.02
ACEI, ARB or ARNI	76.5% (182/238)	63.1% (142/225)	p 0.002
SBP mm Hg	NA	NA	
Heart Rate	NA	NA	
Deaths Any Cause (at 12 mos)	57 (19,1%)	70 (23.2%)	p<0.001
MITRA FR (IVTD 135 ± 37 ml/m)	*Obadia JF et al. NEJM 2018*		
Heart rate — beats/min	βb 88.2% 73 ± 13	90.8% 72 ± 13	
SBP mm Hg	109 ± 16	108 ± 18	
Deaths Any Cause (at 12 mos)	37 (24.3%)	34 (22.4%)	

Studio COAPT analisis dei Risultati

"**Primary** effectiveness end point was **all hospitalizations for heart failure within 24 months of follow-up ★(4) analyzed when the last subject completes 12 months of follow-up".**

Appendix
"Results" section
"Patients and treatments" subsection
"Primary and secondary end points" subsection.

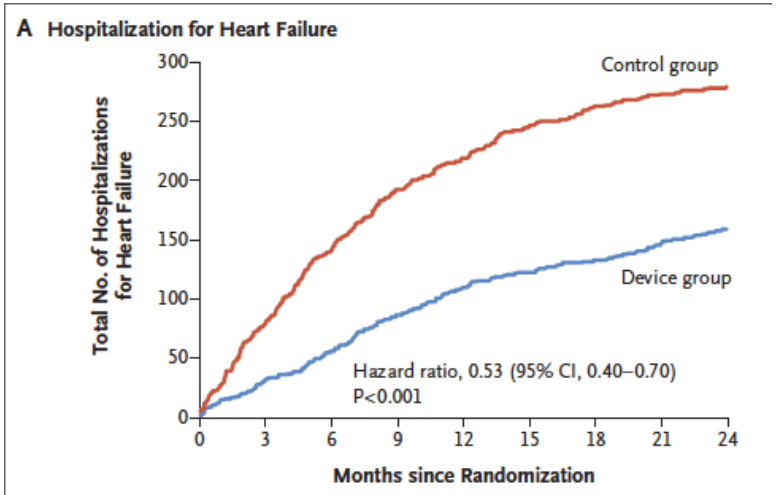
"All patients were evaluated along 12 months of follow-up (Table S7)".
"On August 3, 2018 the last patient had completed one year of follow-up".

	treated arm		control arm
Enrolled Patients N.	302	vs	312
Authors Reported Completed FU	**97.7%**		**94.2%**
Subjects with data on medication (Table S6)	238/302		225/312
	78,8%		**72,1%**

Stone G et al. NEJM 2018

Studio COAPT analisis dei Risultati

"Primary **effectiveness end point** was **all hospitalizations for HF within 24 months of follow-up … ★(5) including recurrent events in patients with more than one event…**



Version 8.0	Rationale for Change
Kaplan-Meier freedom from: (1) cardiovascular mortality (2) **the first** HF related hospitalization (3) **the first** cardiovascular hospitalization (4) **the first** HF related hospitalization **or all-cause mortality** at 12 months and 24 months and then yearly through 5 years	To clarify that Kaplan-Meier analysis will be performed based on time to the first event.

Section
Clinical Addition Clinical
Section 4 Clinical
Section 7 Clinical

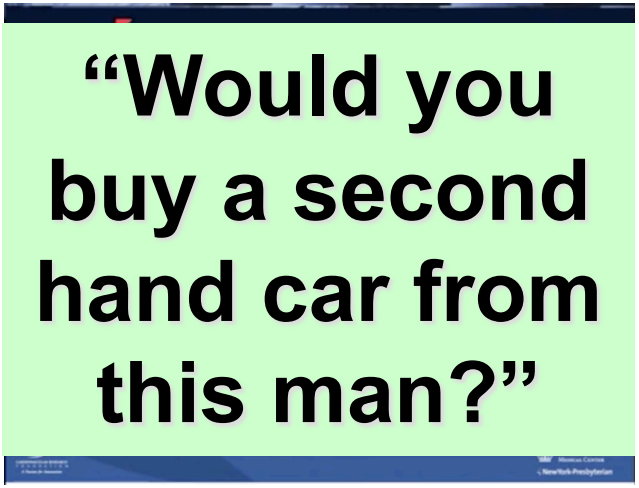
★(5) including recurrent events in patients with more than one event (??)

CONCLUSIONI

Figura 2 [1]
“Subgroup Analyses of Hospitalization for Heart Failure within 24 Months”

Il 30% dei soggetti arruolati nei due bracci dello studio COAPT non dispongono del follow up a 24 mesi.

Gregg Stone et al. assicurano che dopo aggiustamento statistico per le variabili mancanti il risultato sull’ end point primario rimane solido!



[1] G.W. Stone, J. Lindenfeld, W.T. Abraham, S. Kar, D.S. Lim, J.M. Mishell, et al.,Transcatheter mitral-valve repair in Patients with heart failure N. Engl. J. Med. (2018) https://doi.org/10.1056/NEJMoa1806640 [Epub ahead of print].