The COAPT Trial
Why the Trial Succeeded

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Consultant	• Neovasc, Ancora, Valfix, Gore
• Equity/options	• Ancora
• Institutional conflict	• My employer, Columbia University, receives royalties for sale of the MitraClip from Abbott

The MITRA-FR Trial

304 pts with SMR due to LV dysfunction with LVEF 15-40%, NYHA II-IV, HF hospitalization within the prior 12 months

MR defined by EU “severe” criteria as EROA >20 mm² or RVol >30 mL/beat. Both groups with “real-world” HF meds (not maximally-tolerated GDMT)

Randomize 1:1
at 37 French centers

MitraClip + MT
N=152

MT alone
N=152

Primary endpoint

Freedom from death or HF hospitalizations through 12 months

The COAPT Trial

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in 614 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR (US ASE criteria) who remained symptomatic despite maximally-tolerated GDMT and CRT if appropriate

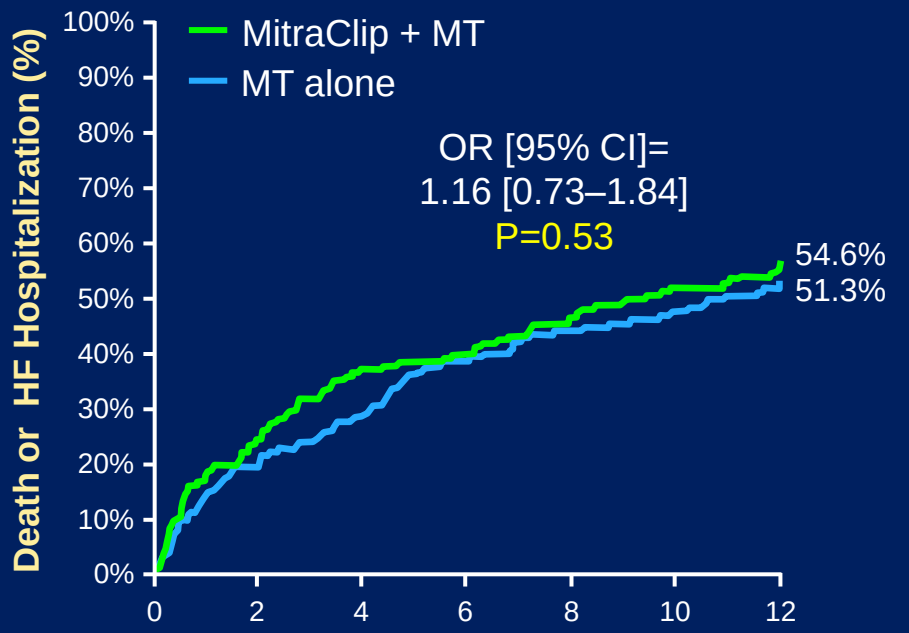
Primary endpoint

All HF hospitalizations through 24 months

Stone GW et al. N Engl J Med. 2018;379:2307-18

COAPT vs. MITRA-FR:
12-Month Death or HF Hosp

MITRA-FR

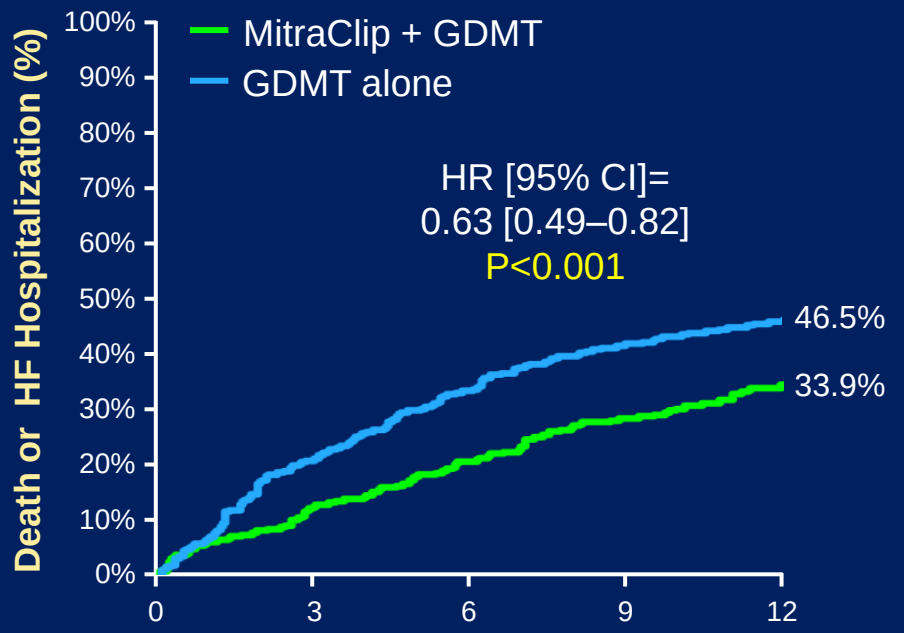


No. at Risk:

Control Group	152	123	109	94	86	80	73
Device Group	151	114	95	91	81	73	67

Obadia JF et al. N Engl J Med. 2018;379:2297-306

COAPT



No. at Risk:

Control Group	312	244	205	174	153
Device Group	302	264	238	215	194

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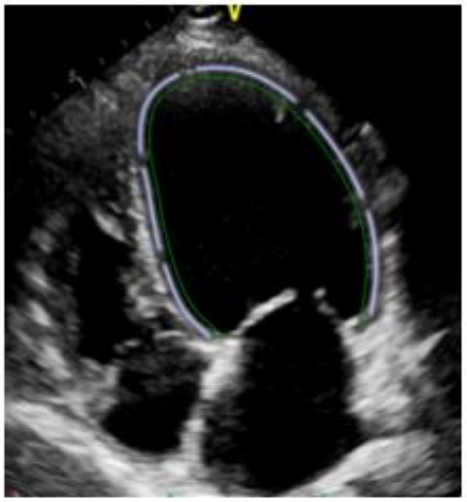
COAPT vs. MITRA-FR

	MITRA-FR	COAPT
N pts	304	614
N centers	37	89
Geography	France	US and Canada
SMR grade	Severe	Severe
Cardiomyopathy	Ischemic or non-isch	Ischemic or non-isch
LVEF	15% - 40%	20% - 50%
Primary effectiveness endpoint	Death or HF hosp at 1 year	All HF hosps at 2 years
Primary safety endpoint	-	Device-related complications at 1 year
Powered secondary endpoints	-	10 (death, all hosp, QOL, 6MWT, NYHA, MR↓)

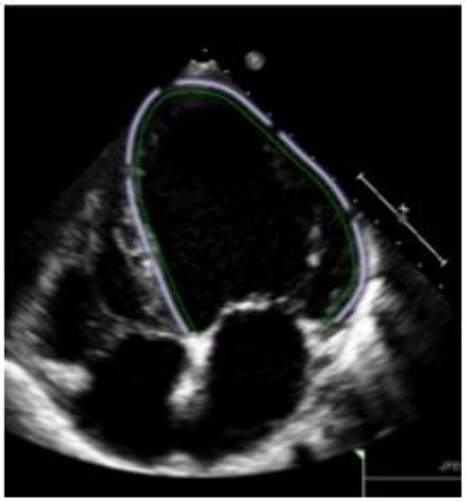
Why are the COAPT Results so Different from MITRA-FR? Possible Reasons

	MITRA-FR (n=304)	COAPT (n=614)
Severe MR entry criteria	Severe FMR by EU guidelines: EROA >20 mm^2 or RV >30 mL/beat	Severe FMR by US guidelines: EROA >30 mm^2 or RV >45 mL/beat or PSVFR or other
EROA (mean ± SD)	31 ± 10 mm^2	41 ± 15 mm^2
LVEDV (mean ± SD)	135 ± 35 mL/m^2	101 ± 34 mL/m^2

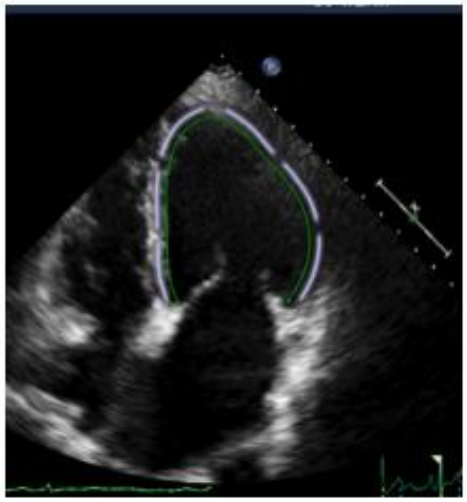
3 Patients with EROA of 30 mm^2



LVEF 22%
LVEDV 310 mL
GLS -6.8%



LVEF 36%
LVEDV 197 mL
GLS -8.4%



LVEF 60%
LVEDV 140 mL
GLS -20.3%

LVAD, transplant, hospice

Spectrum of LV dysfunction

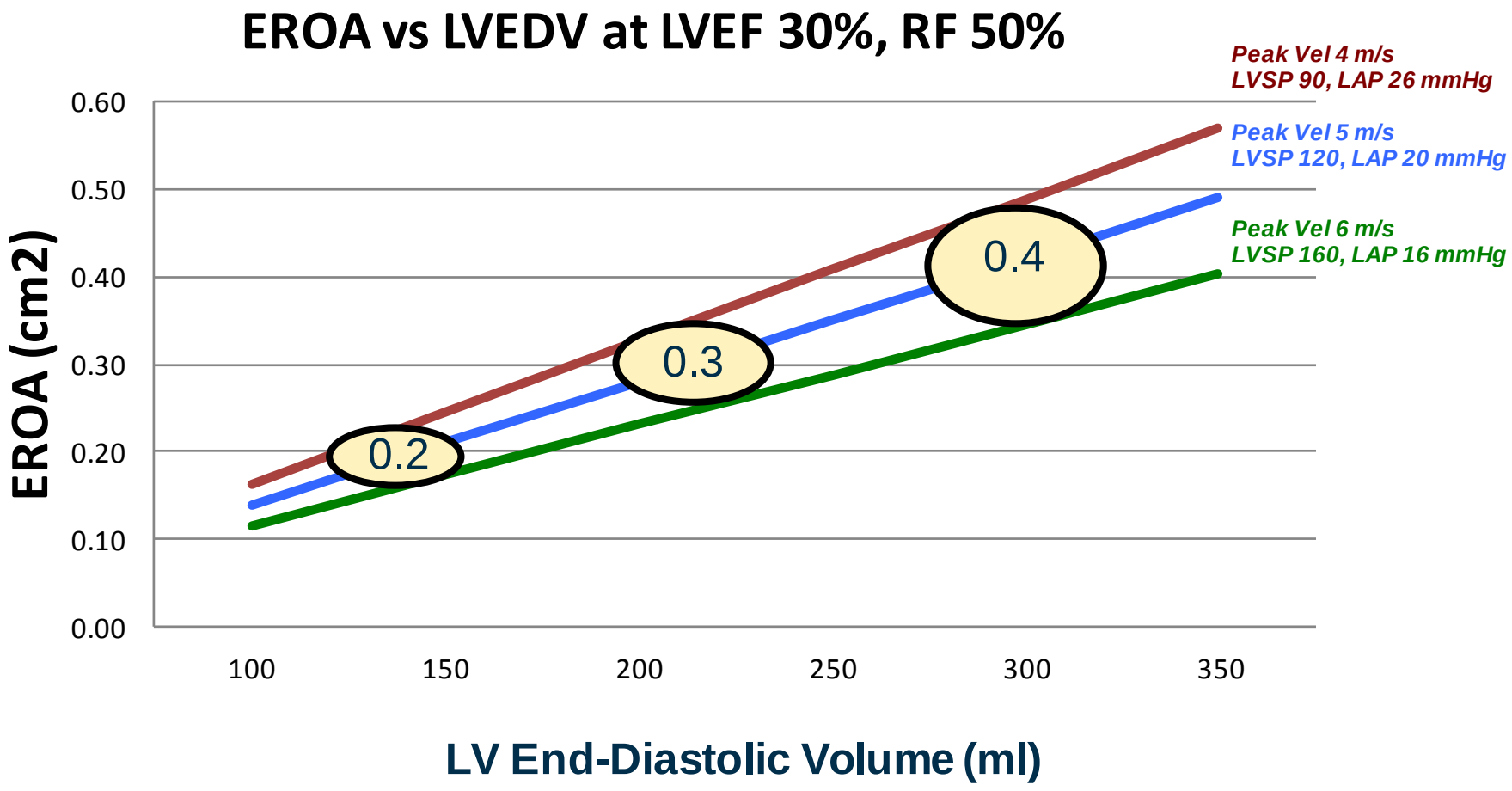
MR correction likely to be beneficial

LVEF, LV size, LV geometry
Severely abnormal

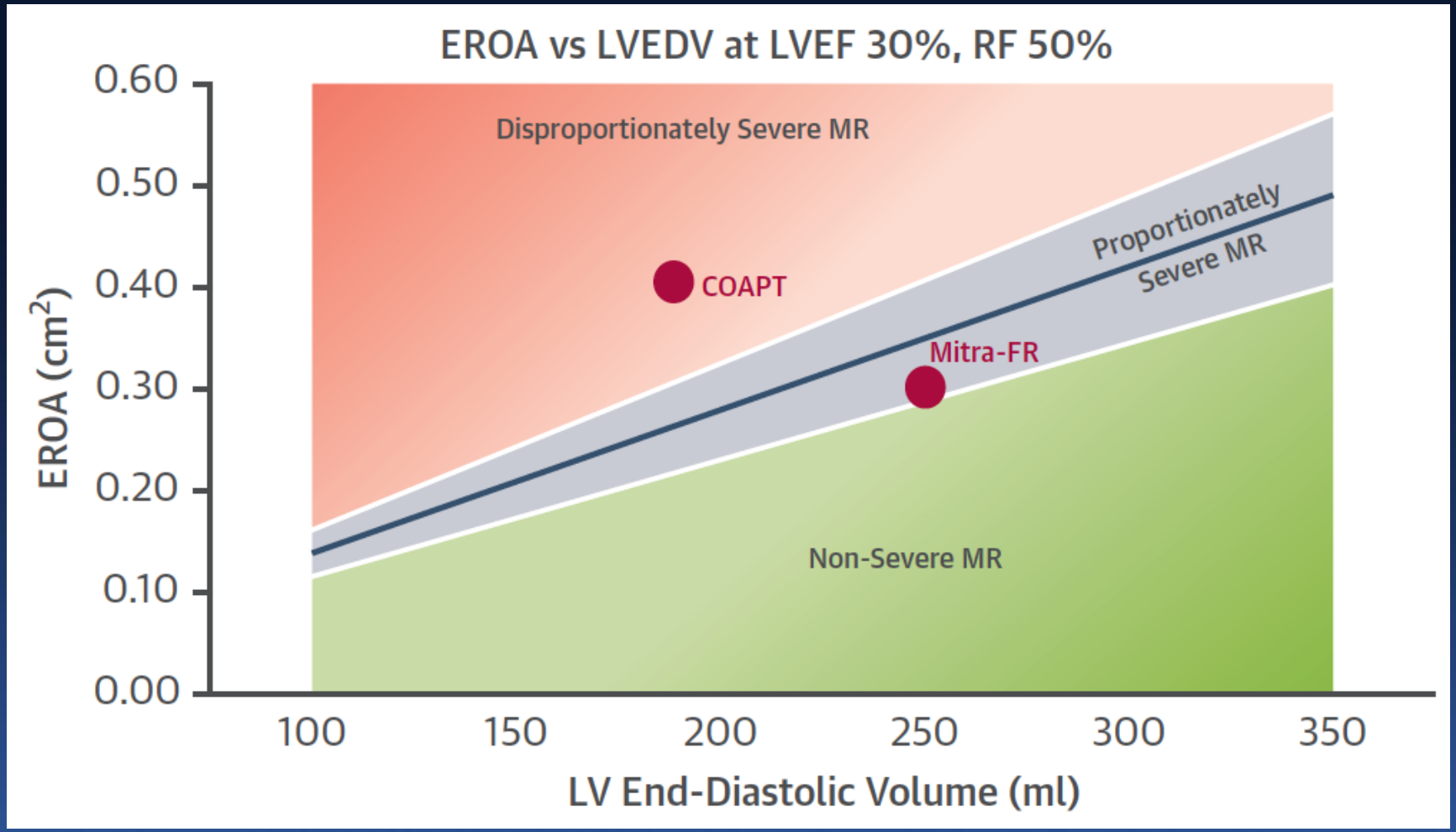
LVEF, LV size, LV geometry
Mild-to-moderately abnormal

LVEF, LV size, LV geometry
Normal

Importance of EROA and LV Size



Proportionate vs. Disproportionate MR: A conceptual framework



Grayburn PA et al. JACC CV Im 2019;12:353–62

COAPT TRIAL

Multiparametric Echocardiographic MR Assessment

Secondary MR, Severity 3+ or 4+ (graded by 1 of 3 criteria)

Tier 1

EROA ≥ 0.3 cm^2

or

PV systolic flow reversal

N=570 (85.7%)

Tier 2

EROA 0.2 cm^2 - <0.3 cm^2

With any 1 of the following:

- RV ≥ 45 ml/beat
- RF ≥ 40%
- VC width ≥ 0.5 cm

N=70 (10.5%)

Tier 3

EROA not measured or <0.2 cm^2

With at least 2 of the following:

- RV ≥ 45 ml/beat
- RF ≥ 40%
- VC width ≥ 0.5 cm
- PISA radius > 0.9 cm, but CW of MR jet not done
- Large (≥ 6.0 cm) holosystolic jet wrapping around LA
- Peak E velocity ≥ 150 cm/s

N=25 (3.8%)

+ LVEF 20-50% and LVESD ≤70 mm

No severe PHTN or RV failure

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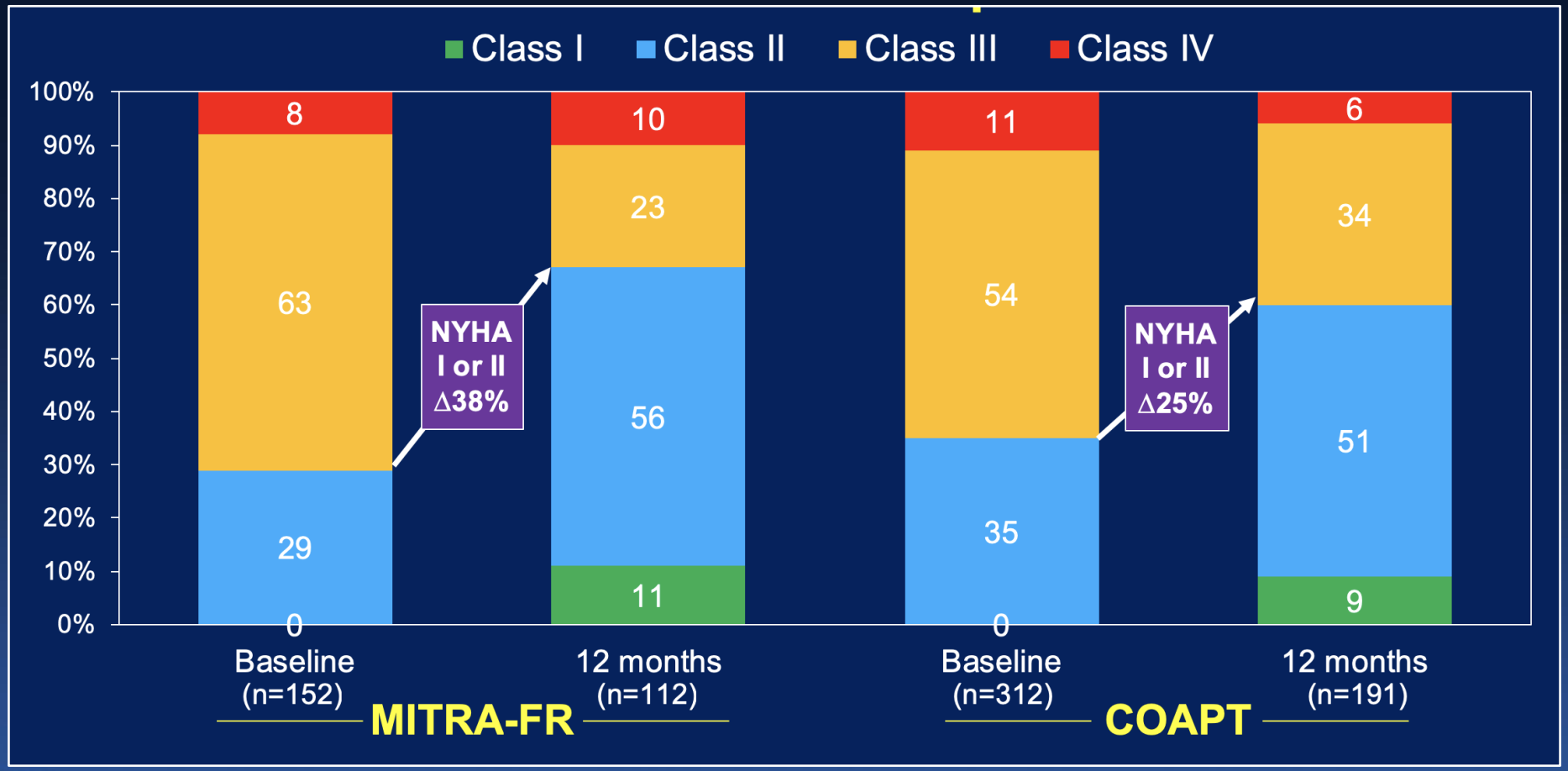
GDMT at baseline and FU	Receiving HF meds at baseline – allowed variable adjustment in each group during follow-up per "real-world" practice	CEC confirmed pts were failing maximally-tolerated GDMT at baseline – few major changes during follow-up

COAPT vs. MITRA-FR: Change in NYHA

Unpaired, all pts at baseline, surviving pts at 12 months

Control group



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Central Echo Core Lab and Eligibility Committee Review

1. A Central Echo Core Lab confirmed the presence of 3+4+ SMR
2. Potentially eligible pts were then presented by the local site investigators on weekly calls to a Central Eligibility Committee consisting of at a minimum a HF specialist and expert MV surgeon
3. The CEC confirmed that all eligibility criteria were met, especially 1) use of maximally-tolerated GDMT for HF, and Rx with CRT, defibrillators and revascularization if appropriate, and that 2) MV surgery would not be offered to the pt, even if randomized to control
4. Pts not meeting these criteria were rejected, or in some cases were deferred and could be re-presented after suitable GDMT had been instituted if the pt remained symptomatic and repeat echo still showed 3+-4+ SMR

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Acute results: No clip / ≥3+ MR	9% / 9%	5% / 5%
Procedural complications*	14.6%	8.5%
12-mo MitraClip <3+ MR	83%	95%

*MITRA-FR defn: device implant failure, transf or vasc compl req surg, ASD, card shock, cardiac embolism/stroke, tamponade, urg card surg

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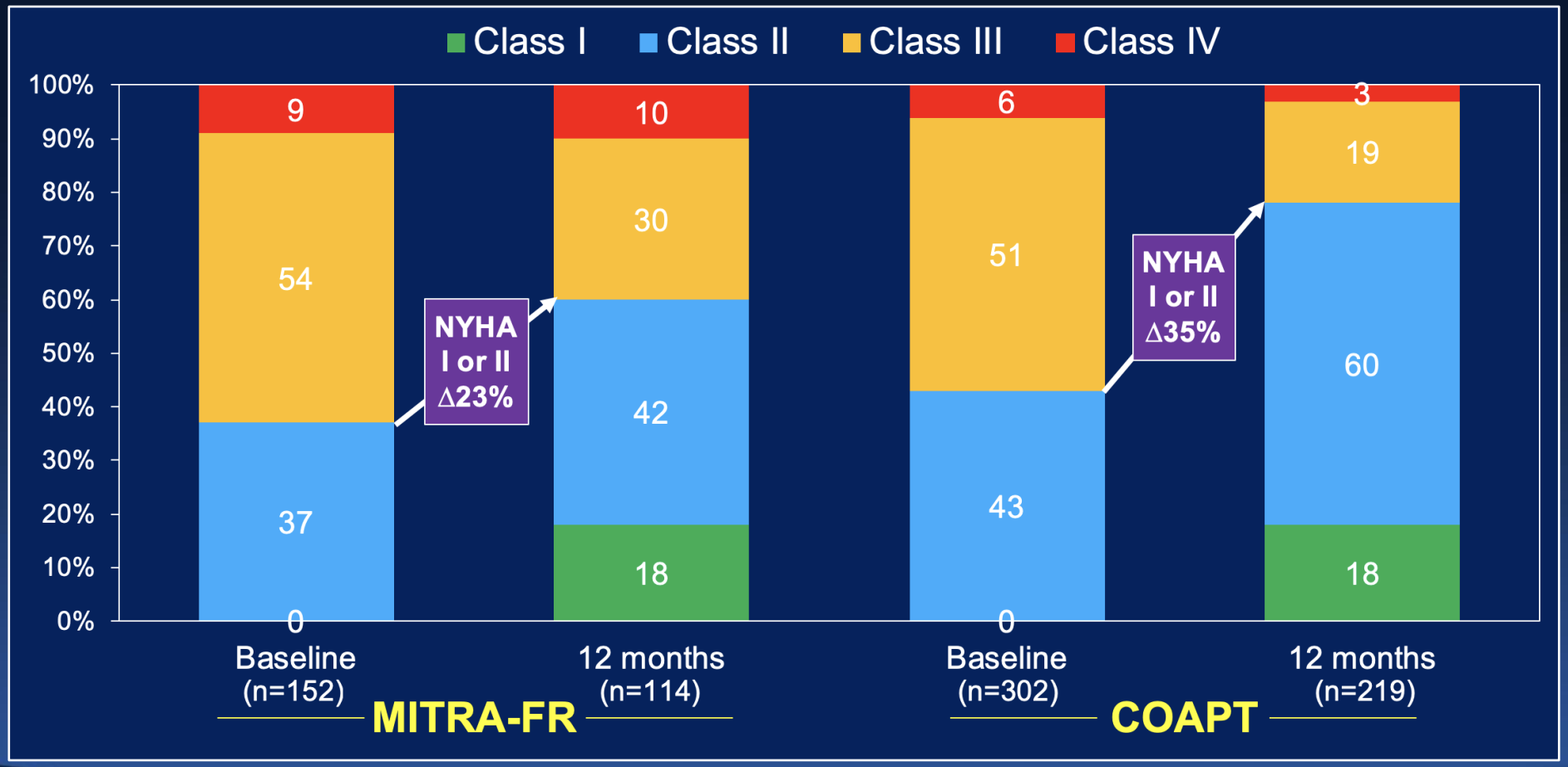
MitraClip group



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Implications of the COAPT and MITRA-FR Trials

- It is essential to identify high-risk heart failure pts with secondary MR in whom the MitraClip will prolong survival, reduce hospitalizations and improve QOL and functional capacity
- In this regard, the COAPT and MITRA-FR trials provide complementary insights, distinguishing pts with heart failure who will and will not benefit from MitraClip treatment
- Strict application of the COAPT eligibility criteria and study processes should allow operators and centers to duplicate the COAPT results in the ”real-world” and avoid over-treatment of pts unlikely to benefit