

PLACE



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

Centro Congressi
di Confindustria

**Auditorium
della Tecnica**

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2022



CARDIOMIOPATIA IPERTROFICA: UPDATE TERAPIA MEDICA OTTIMIZZATA E NUOVE TERAPIE FARMACOLOGICHE

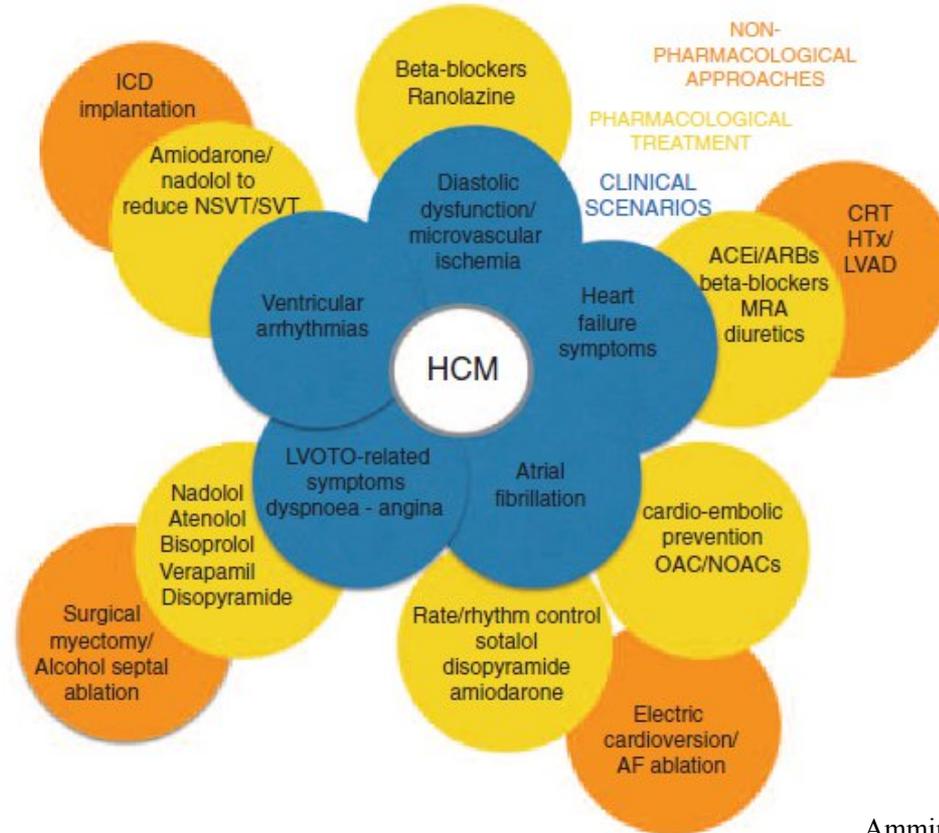
Iacopo Olivotto

Disclosures - Prof. Olivotto

Research Grants: BMS-Myokardia, Sanofi Genzyme, Shire Takeda, Amicus, Bayer, Menarini International.

Advisory board, invited speaker: BMS-Myokardia, Cytokinetics, Sanofi Genzyme, Shire Takeda, Amicus, Bayer, Tenaya

WHY DO WE USE DRUGS IN HCM ?



Ammirati et al, Eur J Heart Fail 2016

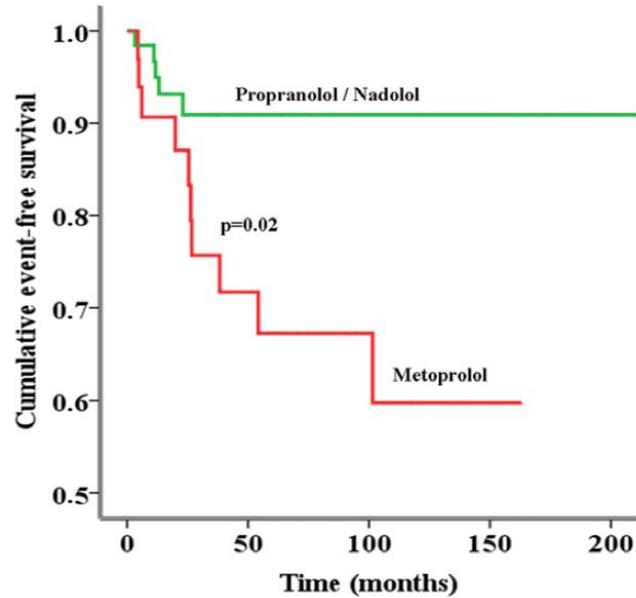
MAKING THE MOST OF WHAT WE HAVE

Beta-Blockers

- ✓ Atenolol: selective, anti-hypertensive, does not cross BB barrier
- ✓ Bisoprolol: selective, HF drug
- ✓ Nadolol: non-selective, good OD drug, well tolerated
- ✓ Metoprolol, Propranolol
- ✓ Carvedilol
- ✓ Nebivolol

Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

Higher Recurrence of Events Under Metoprolol

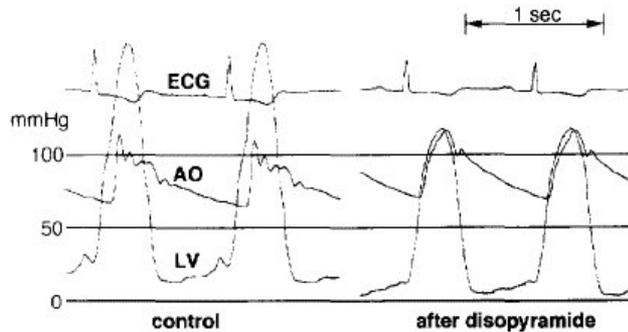


Chockalingam et al, JACC 2012

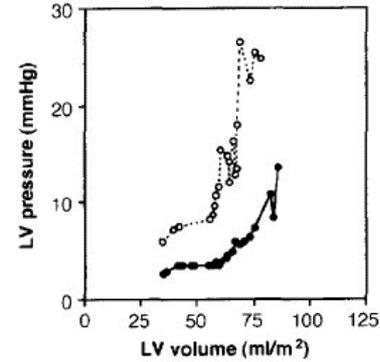
Salutary Effect of Disopyramide on Left Ventricular Diastolic Function in Hypertrophic Obstructive Cardiomyopathy

HIROMI MATSUBARA, MD,* SATOSHI NAKATANI, MD, SEIKI NAGATA, MD,
FUMINOBU ISHIKURA, MD, YUICHI KATAGIRI, MD, TOHRU OHE, MD, FACC,
KUNIO MIYATAKE, MD, FACC

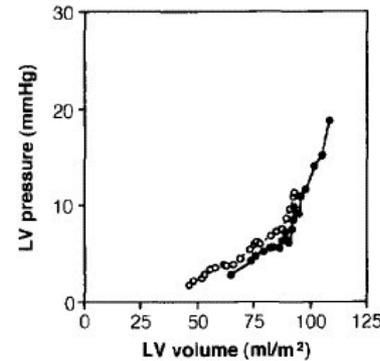
Osaka, Japan



J Am Coll Cardiol, 1995



HOCM

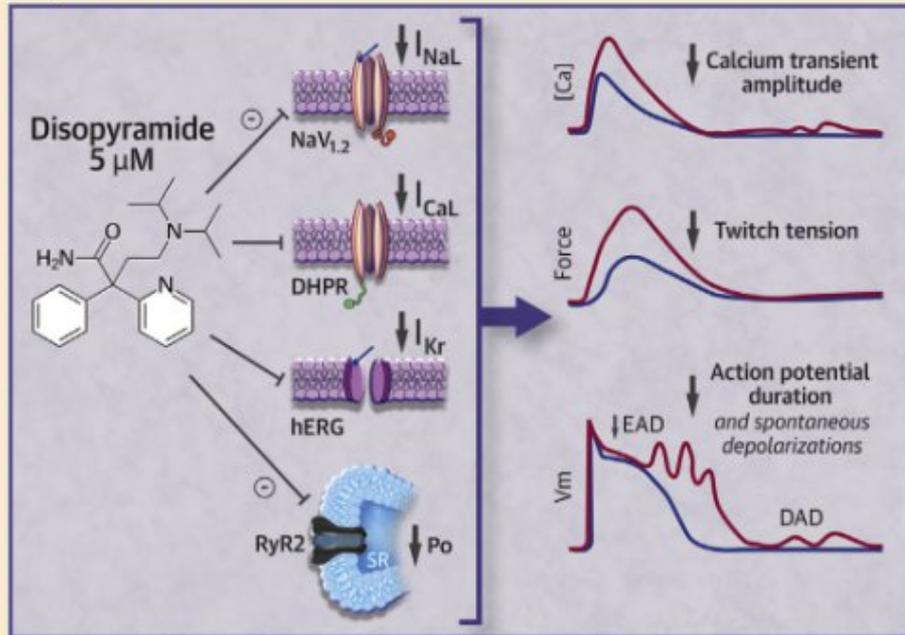


HNCM



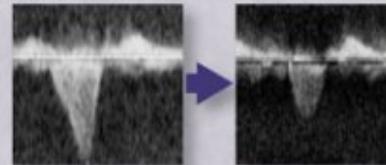
Key Results

In Vitro

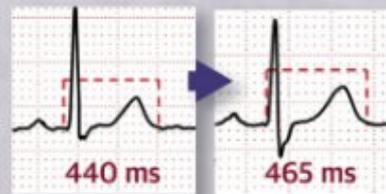


Clinical

- Reduction of gradient and symptoms

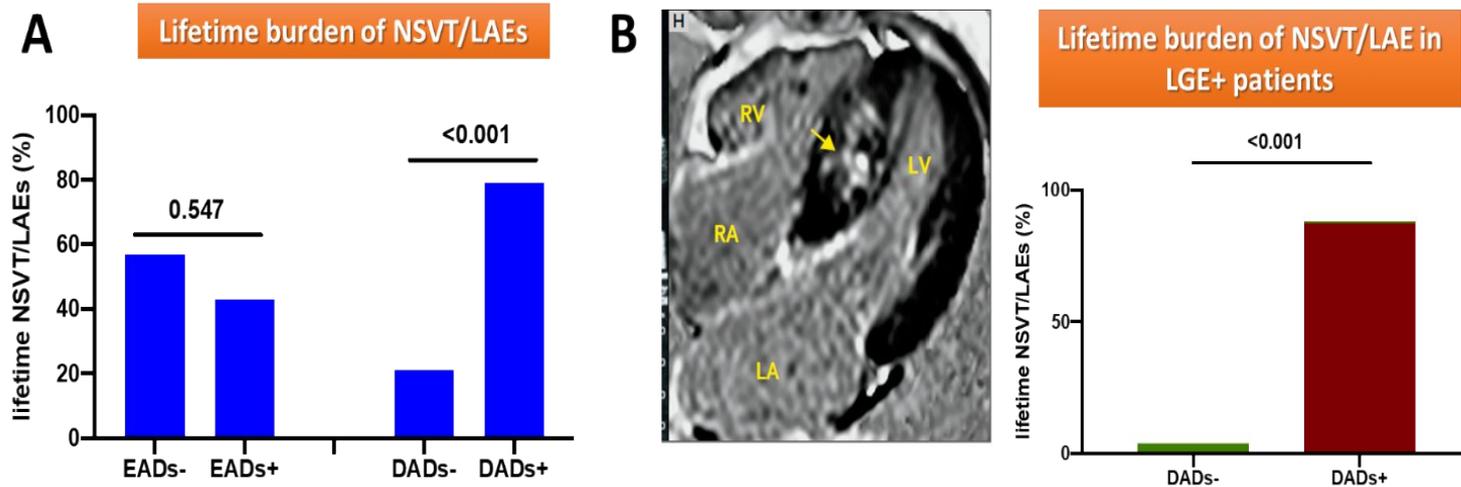


- Minimal QTc interval prolongation



- No arrhythmias

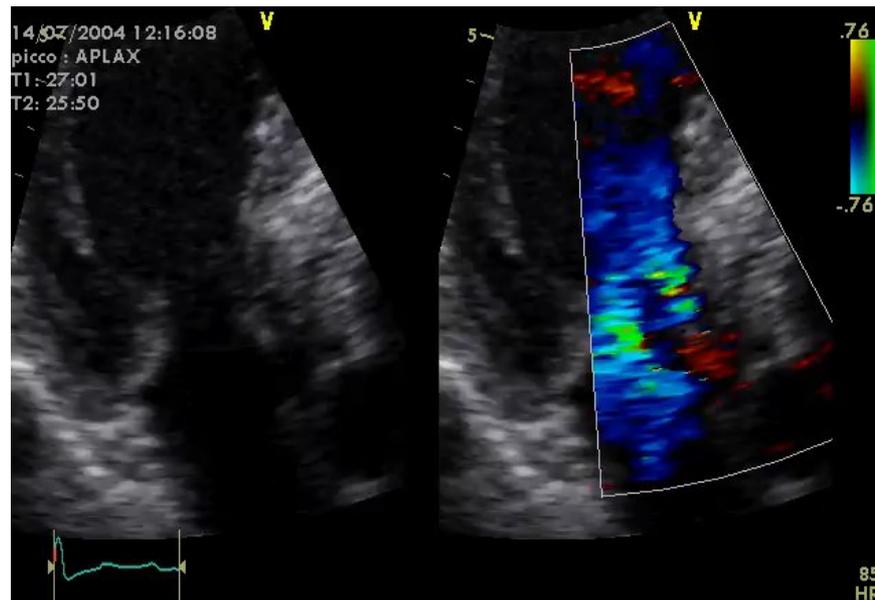
IMPACT OF ION CHANNEL DYSFUNCTION IN HCM



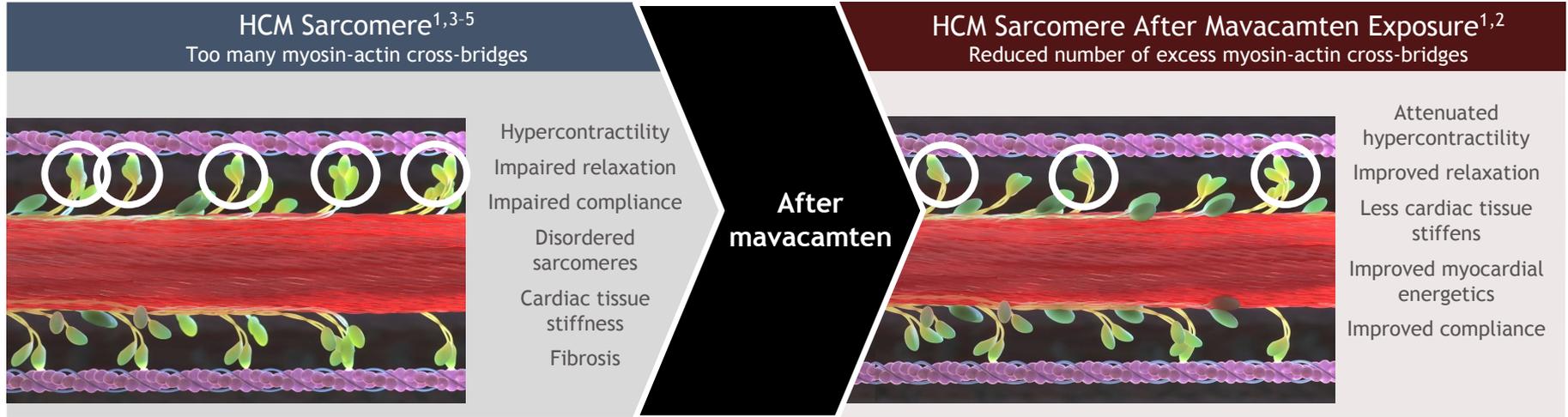
Electrophysiological basis of Ventricular Arrhythmias in patients with HCM: implications for prognostic stratification. A) Lifetime burden of NSVT and LAEs in myectomy patients with and without EADs or DADs; B) Lifetime burden of NSVT and LAEs in selected LGE+ myectomy patients with and without EADs or DADs

Ferrantini, Coppini, Zocchi et al, in preparation

TRATTARE IL PAZIENTE O TRATTARE IL GRADIENTE ?



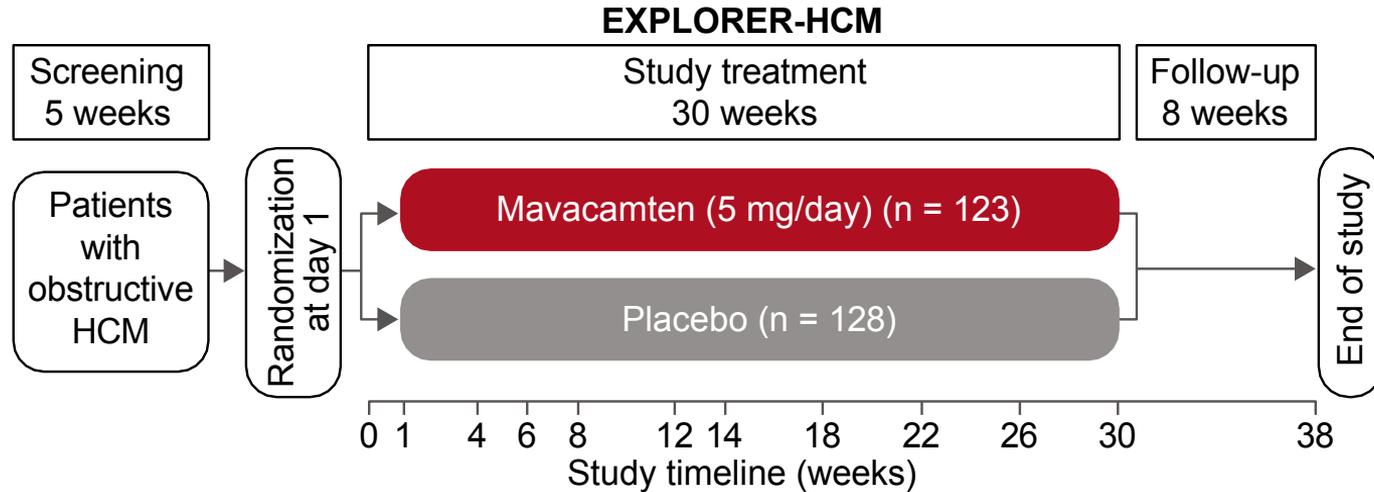
Mavacamten is a cardiac-specific myosin inhibitor designed to target the underlying pathophysiology of HCM^{1,2}



ATP, adenosine triphosphate; HCM, hypertrophic cardiomyopathy; LV, left ventricular.

1. Anderson RL et al. *Proc Natl Acad Sci U S A* 2018;115:E8143–E8152. 2. Green EM et al. *Science* 2016;351:617–621. 3. Ho CY et al. *Circ Heart Fail* 2020;13. doi:10.1161/CIRCHEARTFAILURE.120.006853. 4. Sequeira V et al. *FEBS Lett* 2019;593:1616–1626. 5. Alamo L et al. *eLife* 2017;6. doi:10.7554/eLife.24634.

EXPLORER-HCM Study Design



- **Primary endpoint**

- Composite of **type 1 response** (≥ 1.5 mL/kg/min increase in pVO_2 and at least one NYHA class reduction) or **type 2 response** (≥ 3.0 mL/kg/min increase in pVO_2 without NYHA class worsening)

- **Secondary endpoints^a**

- Postexercise LVOT gradient
- pVO_2
- Proportion of patients with ≥ 1 NYHA class improvement
- KCCQ-CSS
- HCMSQ-SoB subscore

- **Exploratory endpoints**

- Resting and Valsalva LVOT gradients
- Serum NT-proBNP concentrations
- Serum cTnI concentrations
- VE/ VCO_2 slope

^aChange from baseline to week 30. cTnI, cardiac troponin I; HCMSQ-SoB, HCM Symptom Questionnaire-Shortness of Breath; KCCQ-CSS, Kansas City Cardiomyopathy-Clinical Summary Score; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2 , peak oxygen consumption; VE/ VCO_2 , minute ventilation to carbon dioxide production

Primary Endpoint

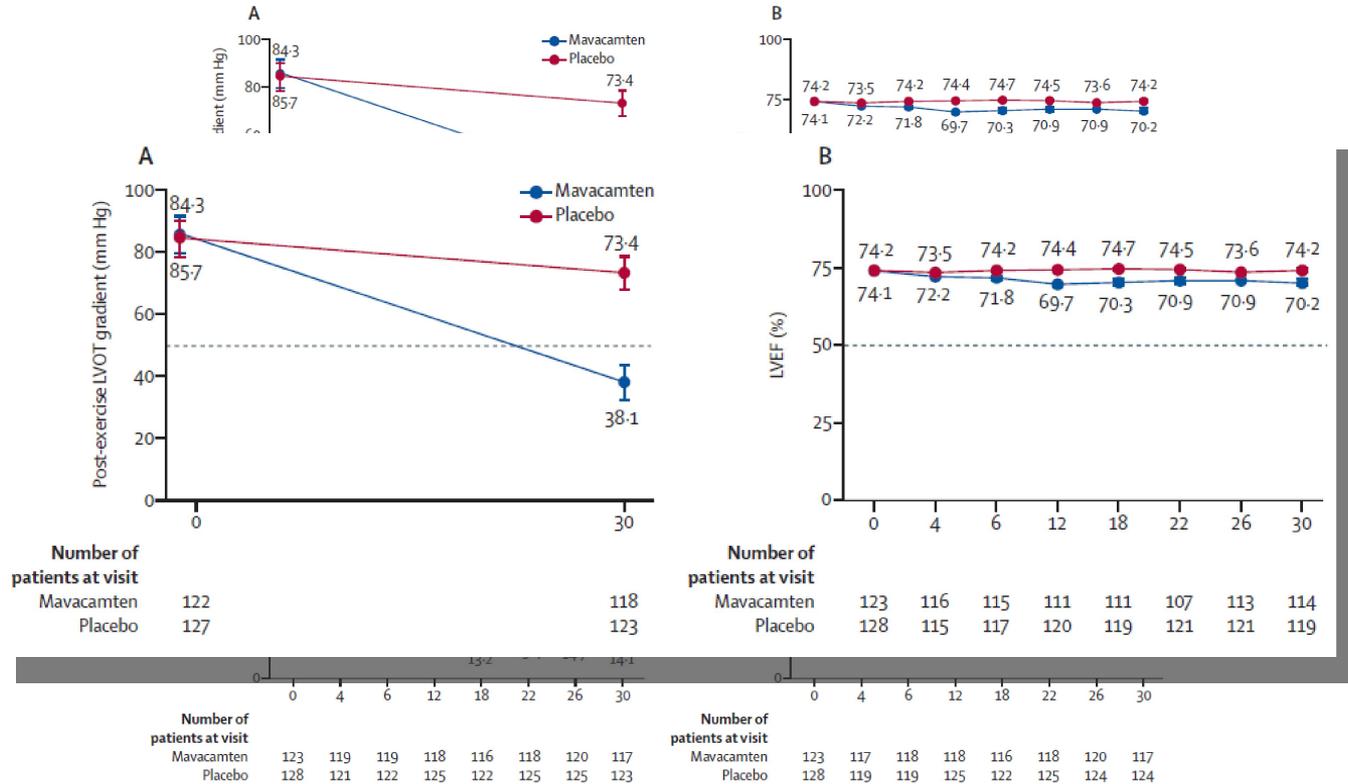
	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)	Difference (95% CI) P value
<u>EITHER</u> ≥1.5 ml/kg/min increase in pVO ₂ with ≥1 NYHA class improvement OR ≥3.0 ml/kg/min increase in pVO ₂ with no worsening of NYHA class	45 (36.6)	22 (17.2)	19.4 (8.7, 30.1) 0.0005
<u>BOTH</u> ≥3.0 ml/kg/min increase in pVO ₂ AND ≥1 NYHA class improvement	25 (20.3)	10 (7.8)	12.5 (4.0, 21.0) 0.0005*

*P value not alpha-controlled

NYHA, New York Heart Association; pVO₂, peak oxygen consumption.

Olivotto et al, Lancet 2020

LVOT Gradients and LVEF Over Time



Methods: Predefined Thresholds for Clinical Improvement

Parameter, direction of improvement	Much improved threshold	Improved threshold	Not improved threshold
LVOT gradient, mm Hg	≥ 50 at BL; < 30 at W30	1) 30–50 at BL; < 30 at W30 2) ≥ 50 at BL; 30–50 at W30	1) 30–50 at BL; ≥ 30 at W30 2) ≥ 50 at BL; ≥ 50 at W30
pVO ₂ , mL/kg/min ^a , ↑	≥ 1.5	–	< 1.5
VE/VCO ₂ slope ^a , ↓	≥ 2	–	< 2
NT-proBNP, pg/mL, ↓	> 50%	25–50%	< 25%
cTnl, pg/mL, ↓	> 25%	10–25%	< 10%
NYHA class, ↑	≥ 2 classes improvement	1 class improvement	No class improvement
KCCQ-CSS, ↑	≥ 10	5–10	< 5
HCMSQ-SoB subscore ^a , ↓	≥ 2.5	–	< 2.5

Thresholds were defined using clinical criteria to assign improvement status based on changes from baseline to week 30

^aParameter with binary classifications and a single accepted threshold

↓, decrease; ↑, increase; BL, baseline; W30, week 30

EXPLORER-HCM: General Trend of Patients' Responses by Group

Group 1

(1° EP +; Other EP +)

Patients who met the primary endpoint and improved in secondary and/or exploratory endpoints

Group 2

(1° EP -; Other EP +)

Patients who did not meet the primary endpoint but improved in secondary or exploratory endpoints

Group 3

(1° EP +; Other EP -)

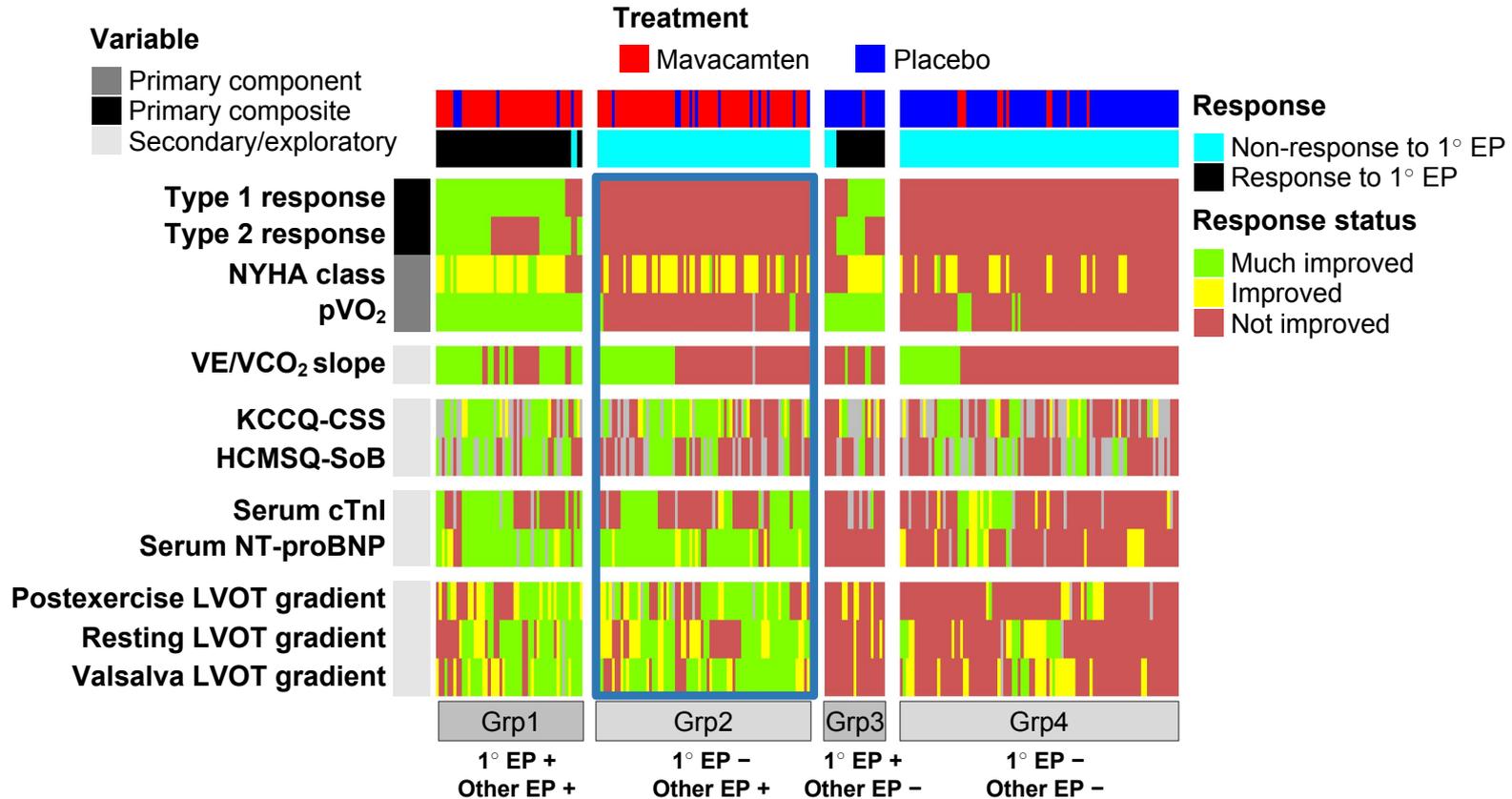
Patients who met the primary endpoint but had negligible responses to secondary or exploratory endpoints

Group 4

(1° EP -; Other EP -)

Patients without appreciable clinically relevant responses from this analysis

Results: Hierarchical Clustering of EXPLORER-HCM Patients



Grp, group



- Efficacia sui sintomi
 - Protezione
 - Efficacia emodinamica
 - Impatto prognostico
-
- Effetti collaterali / QOL
 - Insufficienza cronotropica
 - Compliance
 - Costi

