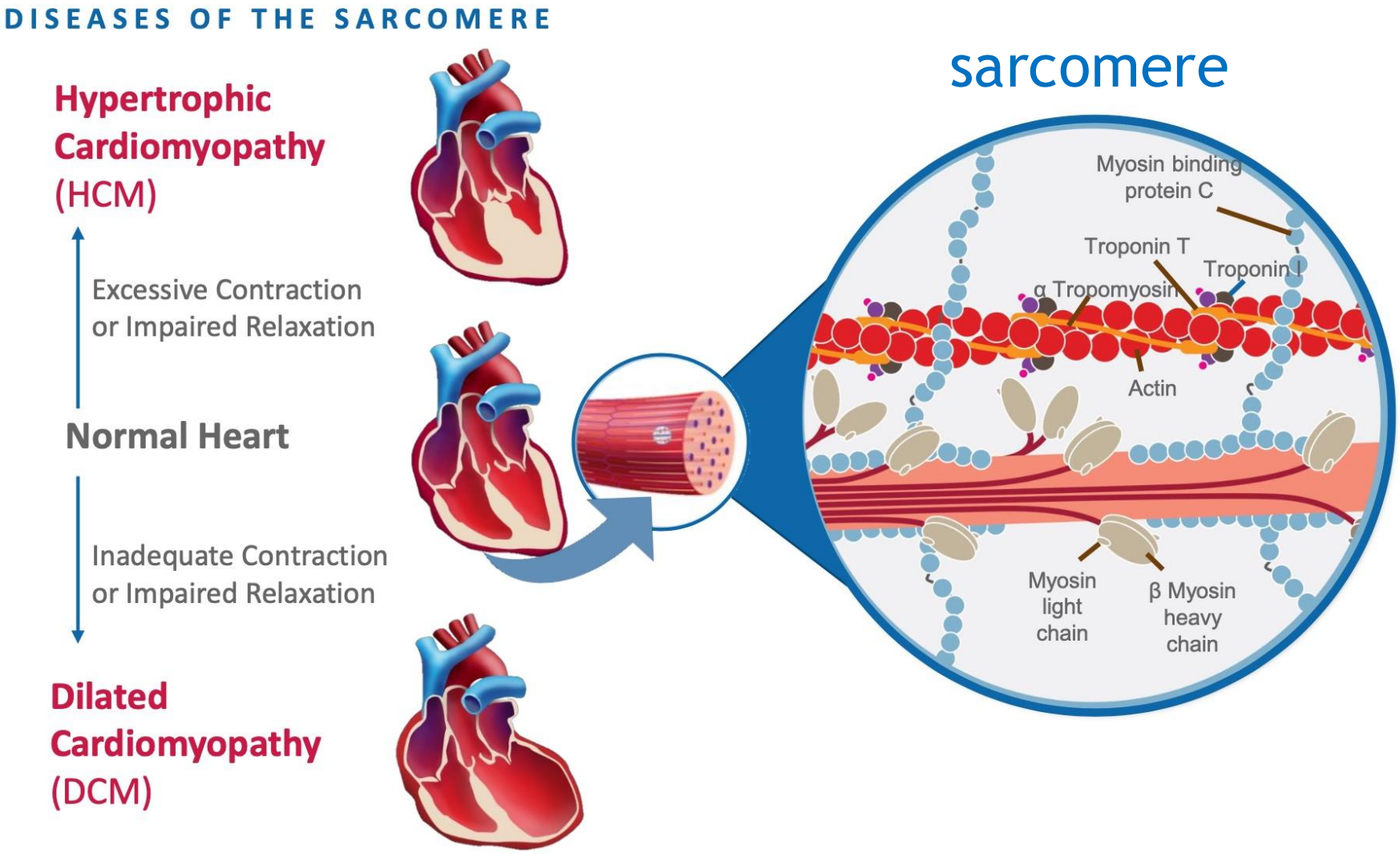
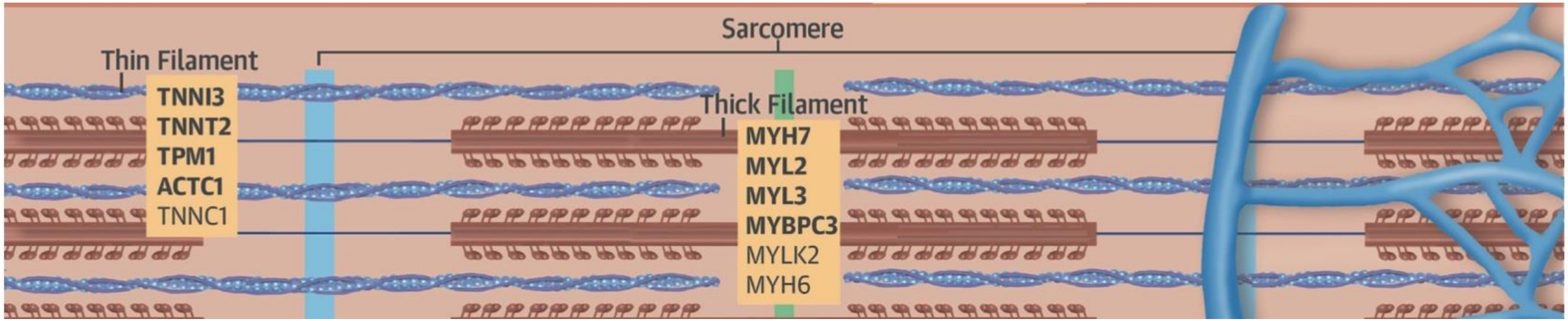
mavacamten case study – *MYH7*

Hypertrophic cardiomyopathy (HCM)



- HCM is linked to mutations in sarcomere proteins (next slide)
- HCM symptoms are related to dynamic outflow obstruction
- Current medical management for obstructive HCM (oHCM) includes beta-blockers, calcium channel blockers, or disopyramide.

Genetics of HCM point to 8 mutated sarcomere proteins

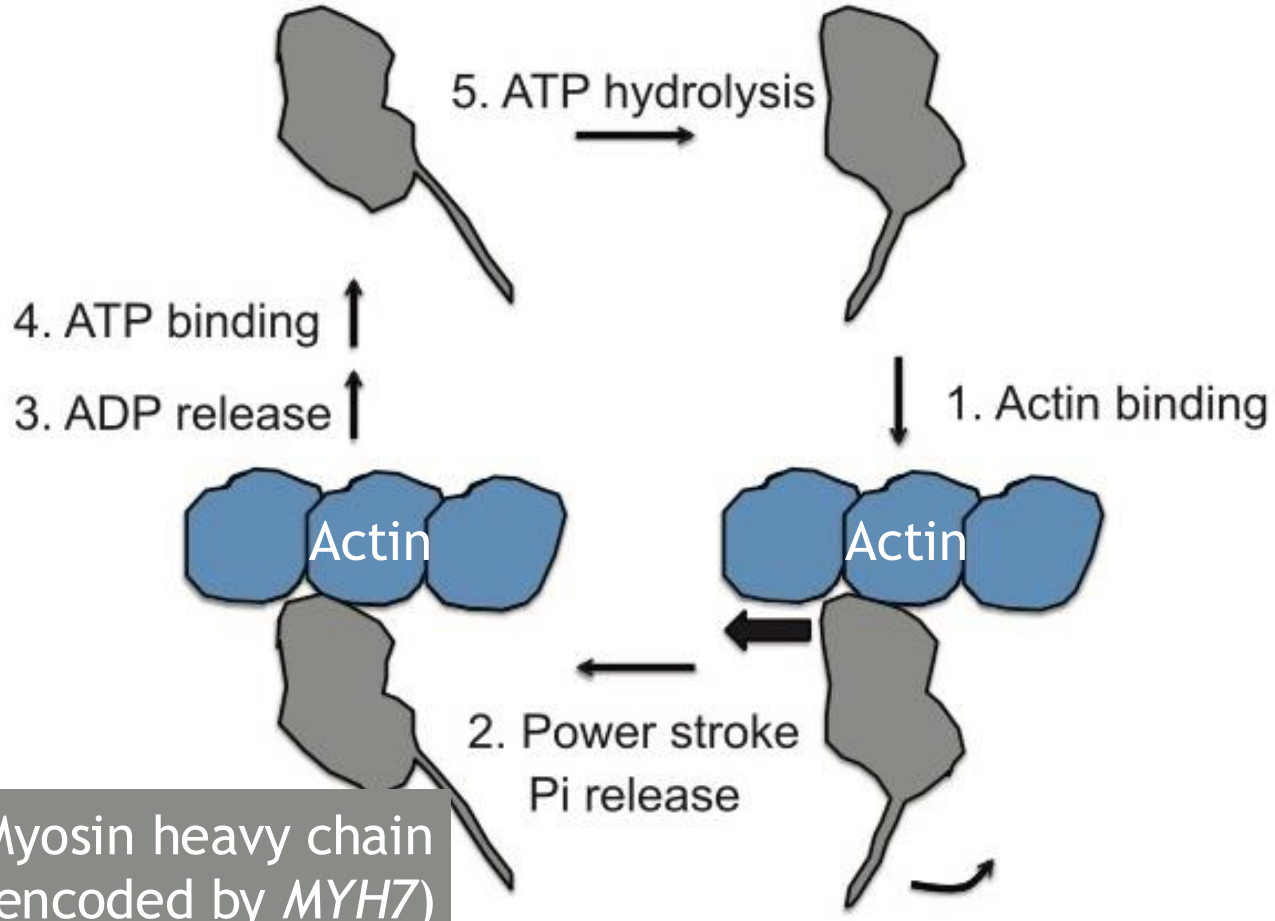


Burke *et al* JACC (2016)

***MYH7* gene**

- First *MYH7* mutation (R403Q) identified in 1990 [Geisterfer-Lowrance *et al* Cell (1990)]
- Since that time, >100 variants have been described in *MYH7*, which cluster in the myosin head and are enriched in HCM cases (14%) vs controls (1%) [Walsh *et al* Genet Medicine (2017)]
- Mechanism: structural, biochemical and molecular analyses in engineered human cells, reconstituted human protein systems, and *in vivo* animal models indicate that *MYH7* mutations **dysregulate actin-myosin cross-bridges**, leading to **(1)** enhanced contraction, **(2)** impaired relaxation, and **(3)** a persistent energetic burden –> *designed assay for a screen (next slide)*

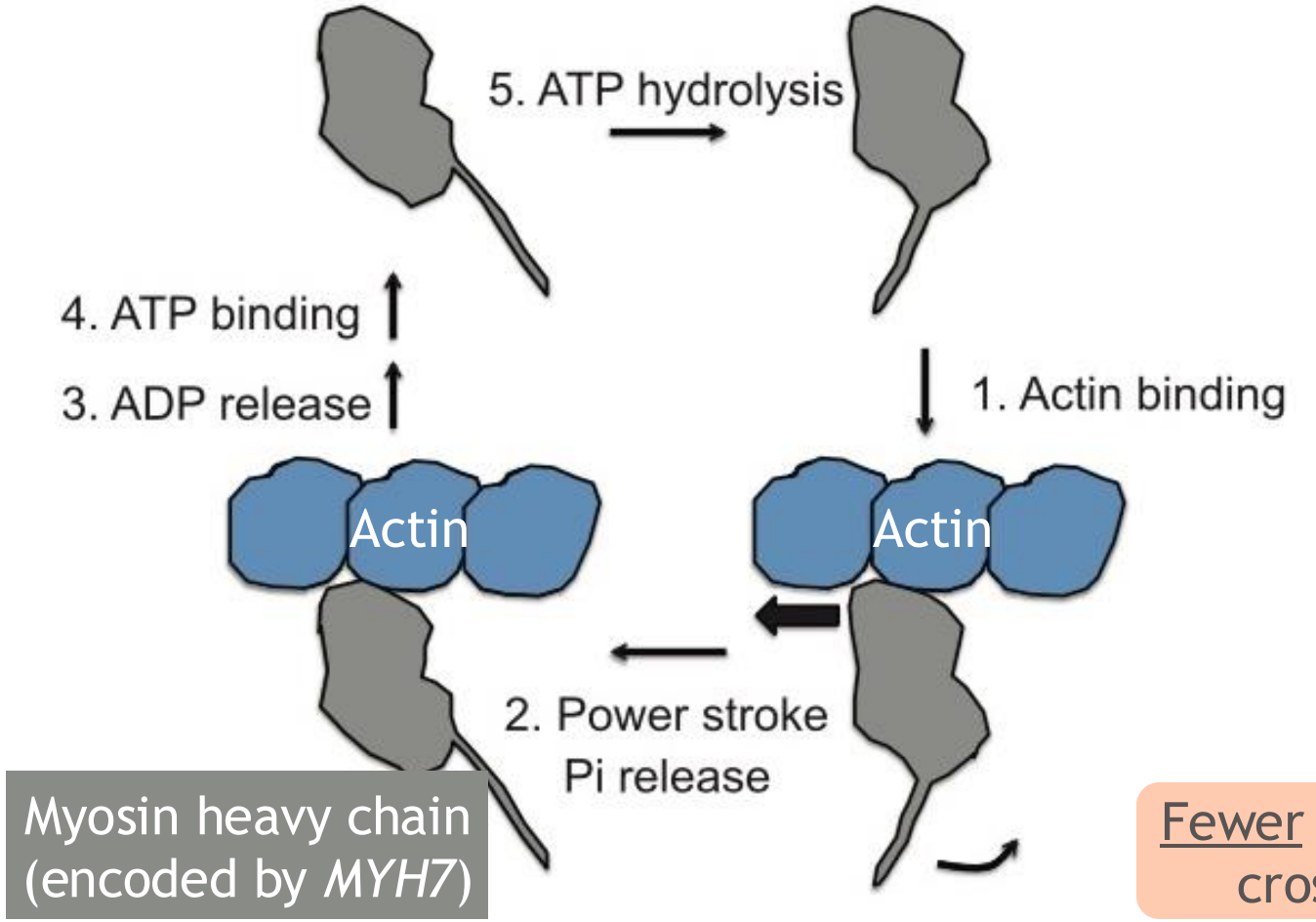
Human genetics as a guide to screen for small molecule actin-myosin “power cycle” inhibitors



ATPase rate as a proxy for the number of **actin-myosin cross-bridges** that form during a completed **power cycle**

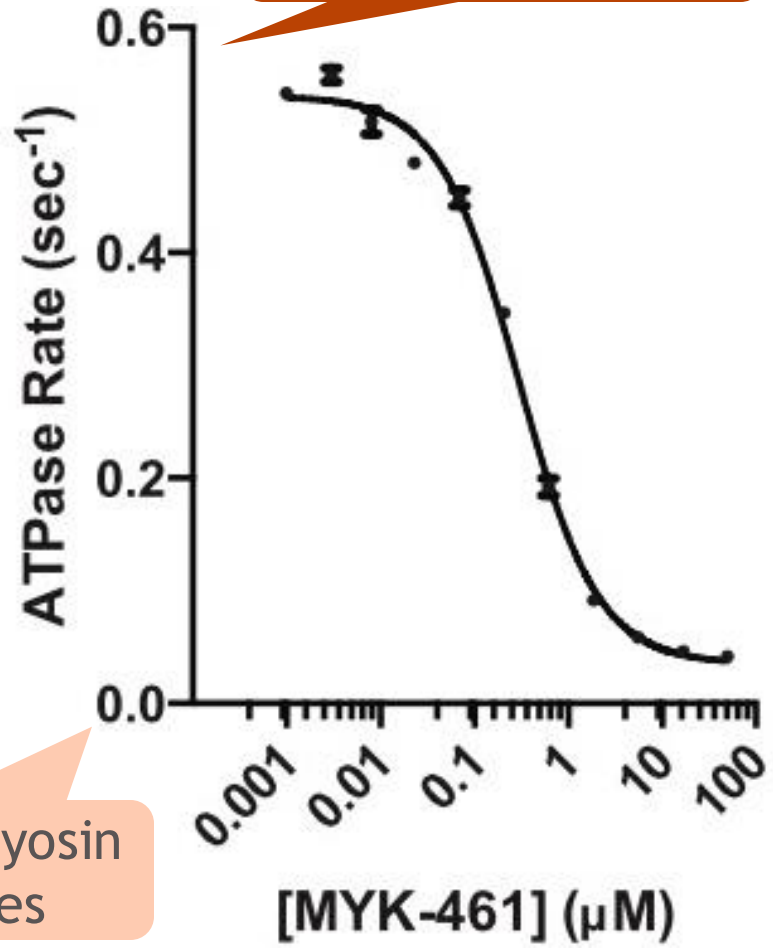
Green *et al* Science (2016)

Human genetics as a guide to screen for small molecule actin-myosin "power cycle" inhibitors



Myosin heavy chain (encoded by *MYH7*)

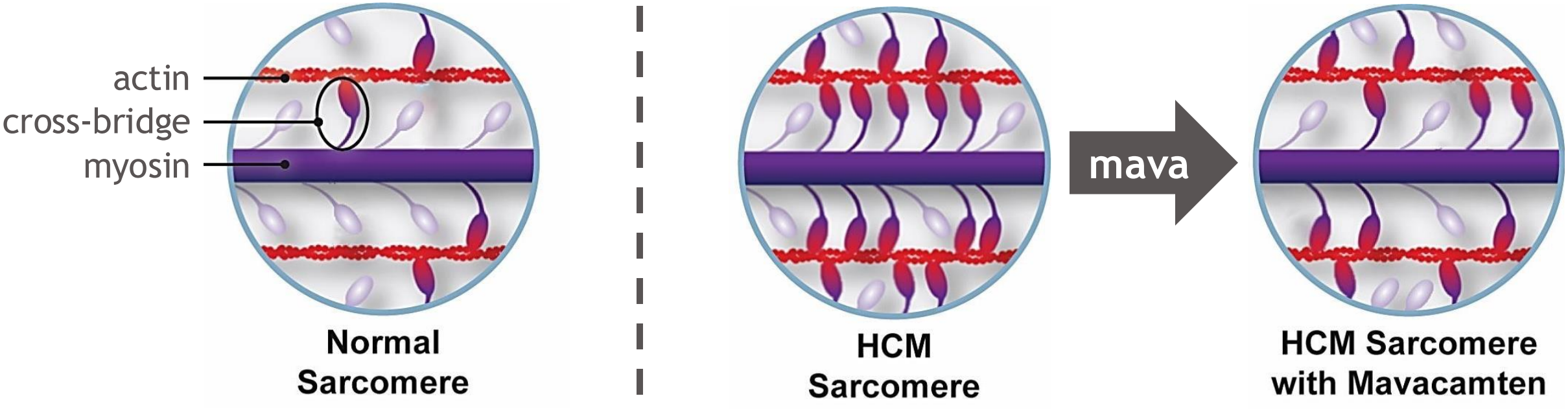
More actin-myosin cross-bridges



Fewer actin-myosin cross-bridges

Green *et al* Science (2016)

Mavacamten MoA: *reduce cross-bridges but retain function*



Normal Sarcomere	HCM Sarcomere	HCM Sarcomere with Mavacamten
Normal contractility Effective relaxation Normal energetics	Hypercontractility Impaired relaxation Altered energetics	less hypercontractility Improved compliance Improved energetics

- First-in-class, allosteric inhibitor of cardiac myosin (protein product of *MYH7* gene)
- Reduces the number of actin-myosin cross bridges ("thins the bench" of eligible myosins) while not disrupting the chemo-mechanical power cycle for those bridges that form

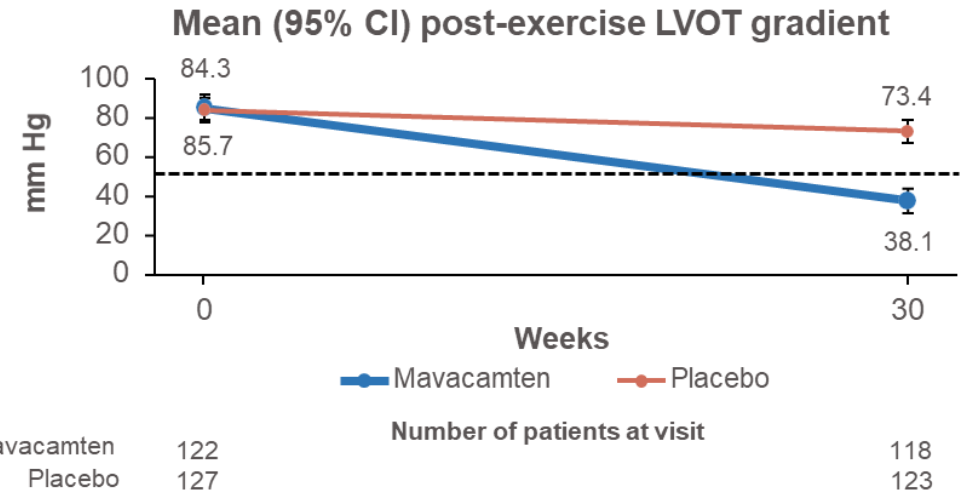
EXPLORER Ph3 trial met primary composite endpoint

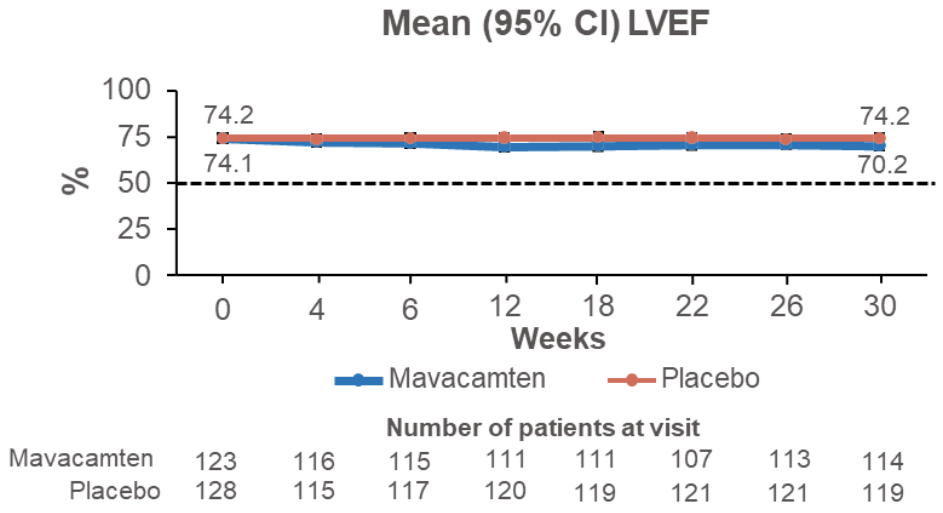
	Mavacamten n/N (%)	Placebo n/N (%)	Difference (95% CI) p-value
EITHER • ≥1.5 ml/kg/min increase in pVO2 with ≥1 NYHA class improvement OR • ≥3.0 ml/kg/min increase in pVO2 with no worsening of NYHA class	45/123 (36.6)	22/128 (17.2)	19.4 (8.7, 30.1) 0.0005
BOTH • ≥3.0 ml/kg/min increase in pVO2 AND • ≥1 NYHA class improvement	25/123 (20.3)	10/128 (7.8)	12.5 (4.0, 21.0) 0.0005*

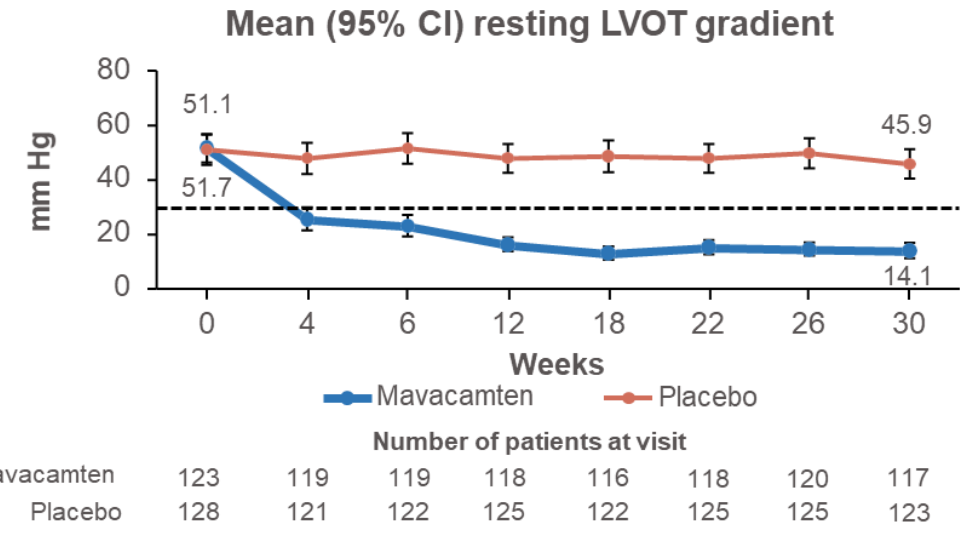
>25% of patients treated with mavacamten had *complete responses* vs 1% on placebo (NYHA class I and all LVOT gradients <30 mm Hg)

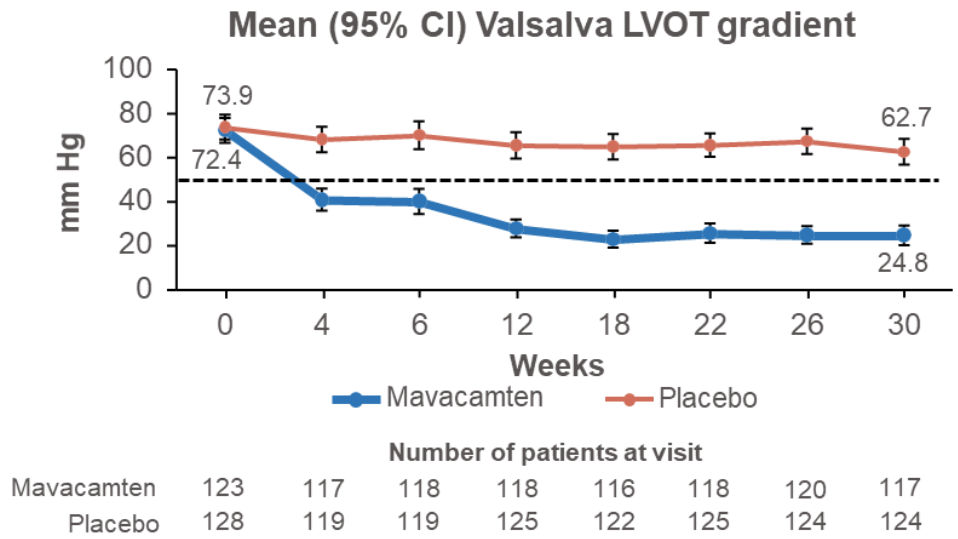
Olivotto *et al* Lancet (2020)	**32/117 (27.4%)**	**1/126 (0.8%)**	**26.6 (18.3, 34.8) *P<0.0001***

LVOT gradients normalized with minimal impact on LVEF









Olivotto *et al* Lancet (2020)

Mavacamten (*MYH7*) summary

- Mutations in 8 sarcomere proteins (including *MYH7*) lead to HCM and point to the critical role of the actin-myosin power cycle in disease pathogenesis
- HCM mutations lead to excessive actin-myosin cross-bridges by preventing myosin heads to remain locked in the “off” state (i.e., too many are “on”)
- A small molecule screen guided by human genetics identified an allosteric inhibitor of cardiac myosin, leading to fewer cross bridges while retaining function of the cross bridges that form
- EXPLORER-HCM trial demonstrated efficacy of mavacamten in obstructive HCM – primary and all secondary endpoints were met with high statistical significance.
- *Will specific mutations identify oHCM patients more likely to respond?*
- *Is it possible to subsets patients with heart failure w/ preserved ejection fraction (HFpEF) to identify those who will respond to mavacamten?*