CARDIAC MYOFILAMENTS AS TARGETS IN THE MANAGEMENT OF HEART FAILURE

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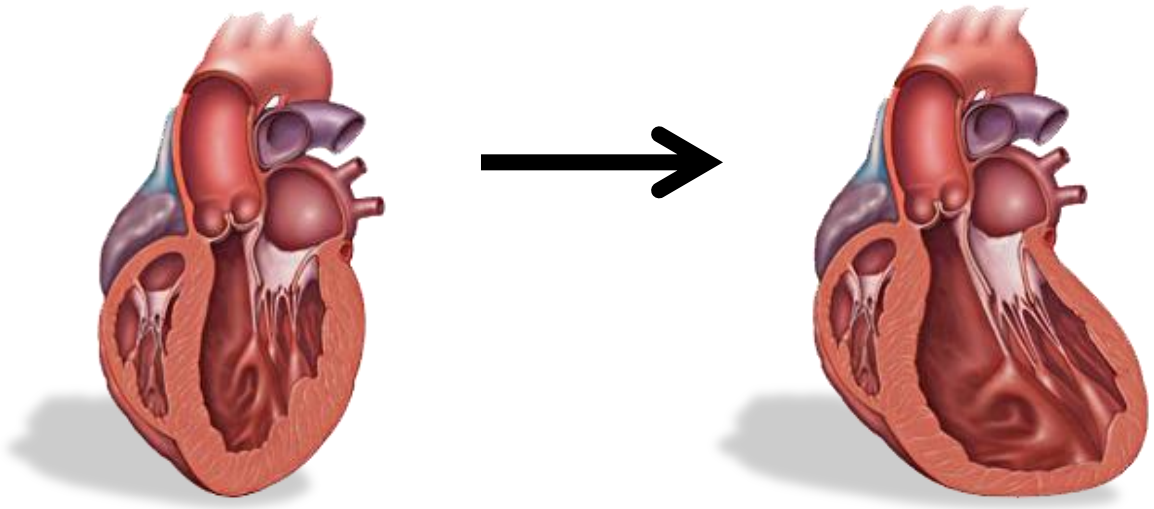
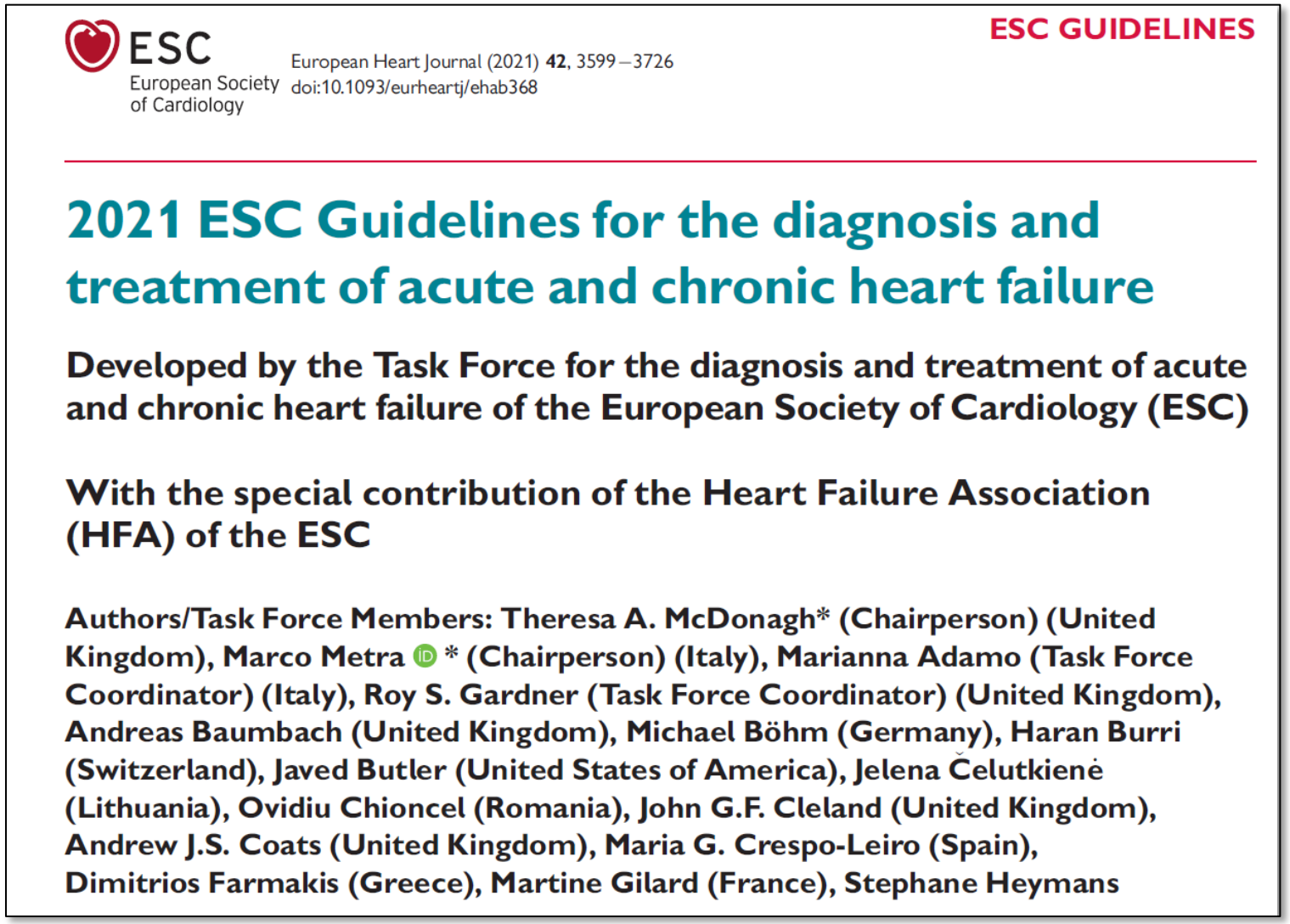
Czech Cardiovascular Research and Innovation Days
Prague, Czech Republic
28 November, 2022

Division of Clinical Physiology, Department of Cardiology
University of Debrecen
Hungary

How can we restore myocardial pump function during heart failure?



We follow rules!



ESC European Society of Cardiology

European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

McDonagh et al., European Heart Journal (2021) 42, 3599-3726

These drugs provide little help in increasing EF

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

McDonagh et al., European Heart Journal (2021) 42, 3599-3726

Ambiguity in classes of recommendation and levels of evidence for the treatment of acute and advenced heart failure

Recommendations	Class[a]	Level[b]
Oxygen and ventilatory support		
Oxygen is recommended in patients with SpO_2 <90% or PaO_2 <60 mmHg to correct hypoxaemia.	I	C
Intubation is recommended for progressive respiratory failure persisting in spite of oxygen administration or non-invasive ventilation.[448]	I	C
Non-invasive positive pressure ventilation should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SpO_2 <90%) and started as soon as possible in order to decrease respiratory distress and reduce the rate of mechanical endotracheal intubation.[448]	IIa	B
Diuretics		
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.[145]	I	C
Combination of a loop diuretic with thiazide-type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses.[145]	IIa	B
Vasodilators		
In patients with AHF and SBP >110 mmHg, i.v. vasodilators may be considered as initial therapy to improve symptoms and reduce congestion.[475–477,479,480]	IIb	B
Inotropic agents		
Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function.[387]	IIb	C
Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion.[387,467,478]	III	C
Vasopressors		
A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion.[485–487]	IIb	B
Other drugs		
Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.[494,495]	I	A
Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.[488,489]	III	C

AHF = acute heart failure; i.v. = intravenous; LMWH = low-molecular-weight heparin; PaO_2 = partial pressure of oxygen; SBP = systolic blood pressure; SpO_2 = transcutaneous oxygen saturation.
[a]Class of recommendation.
[b]Level of evidence.

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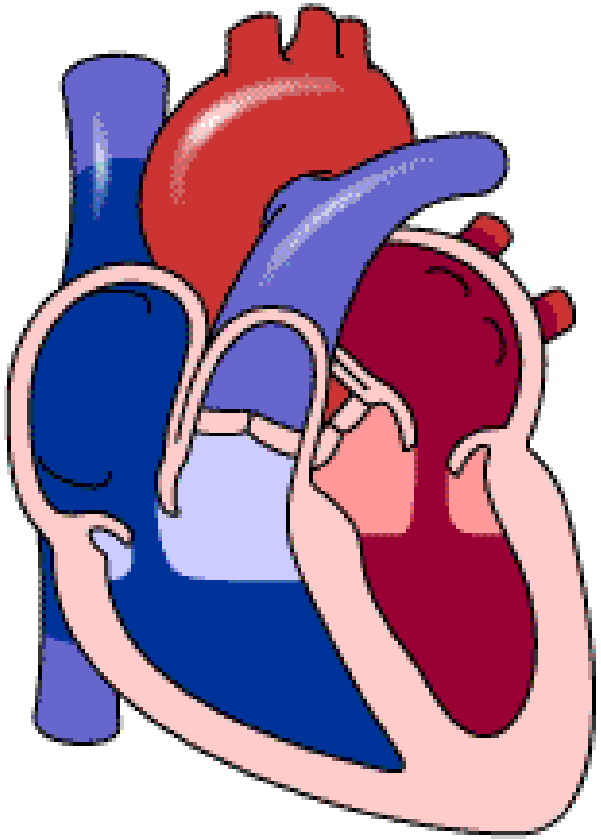
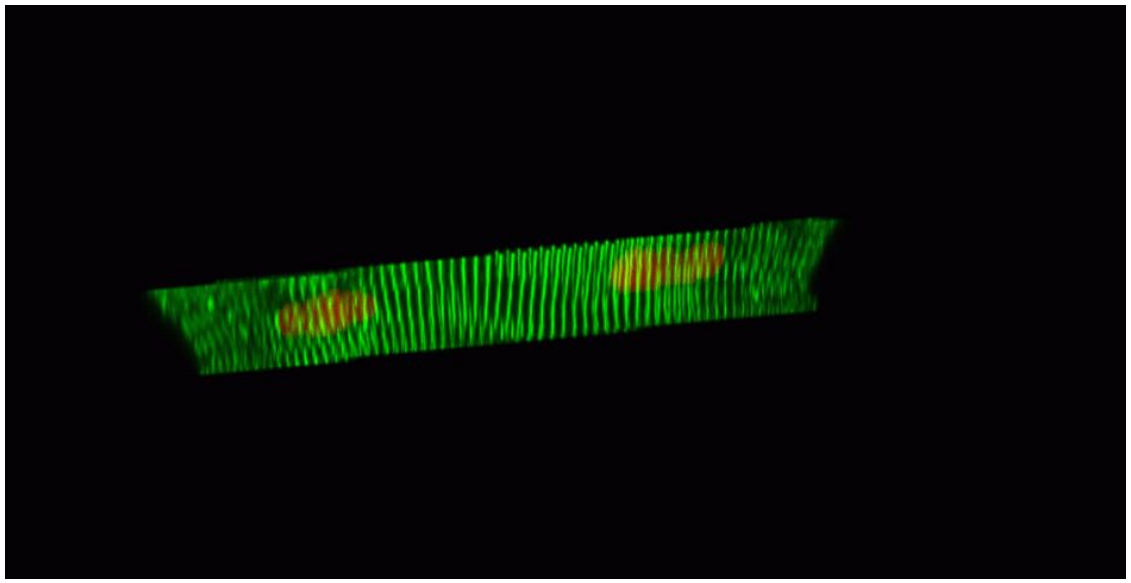
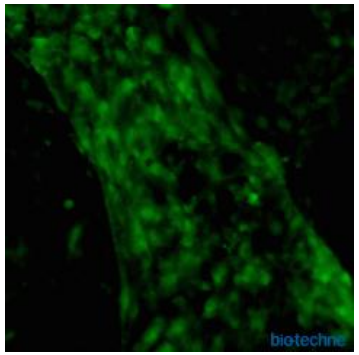
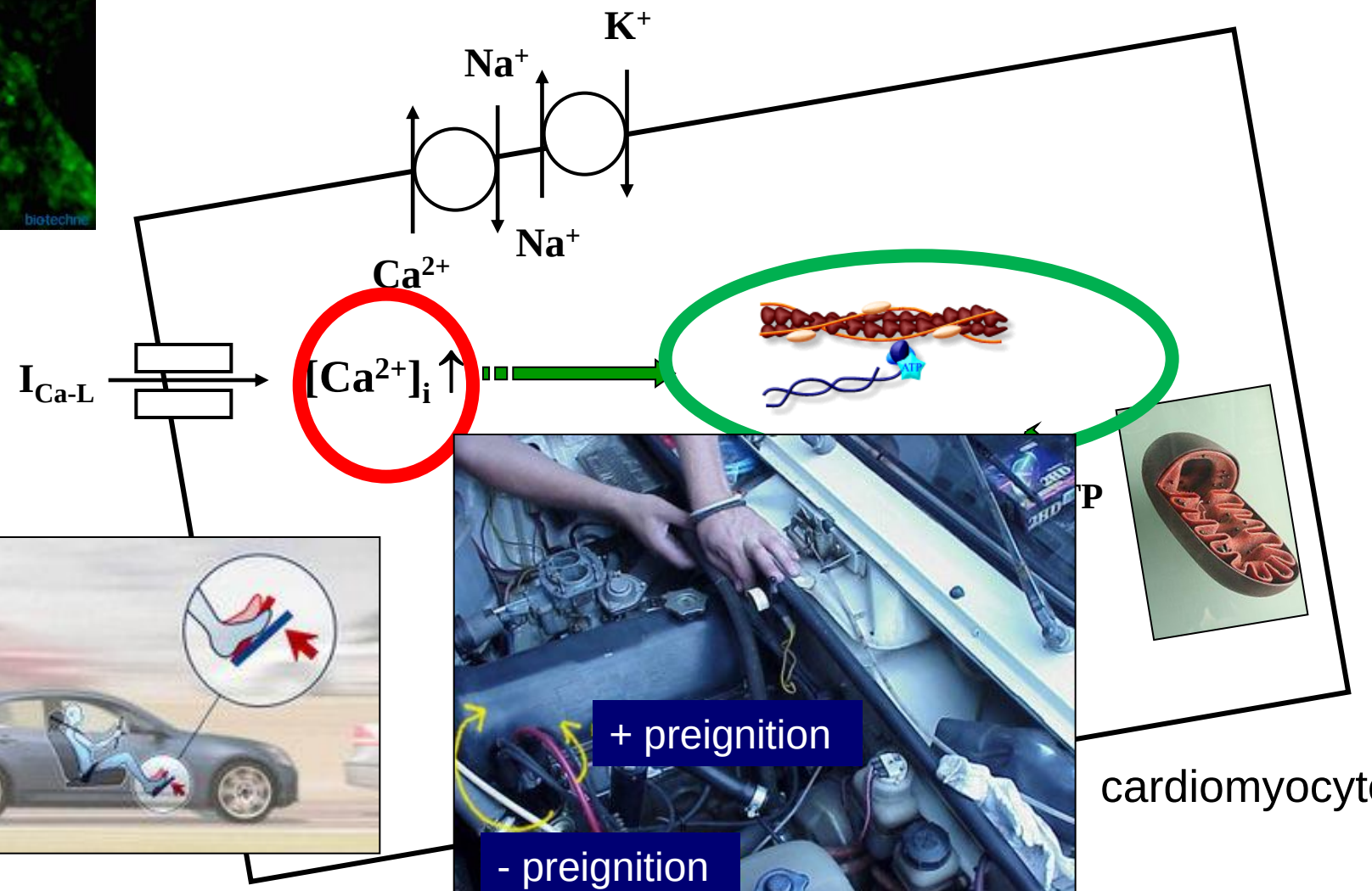
Heartbeats depend on the function of cardiomyocytes

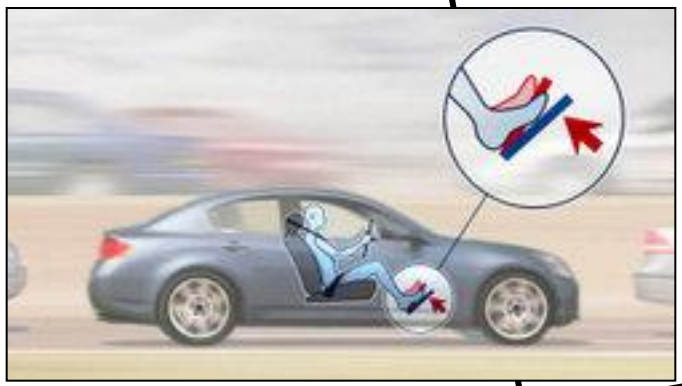




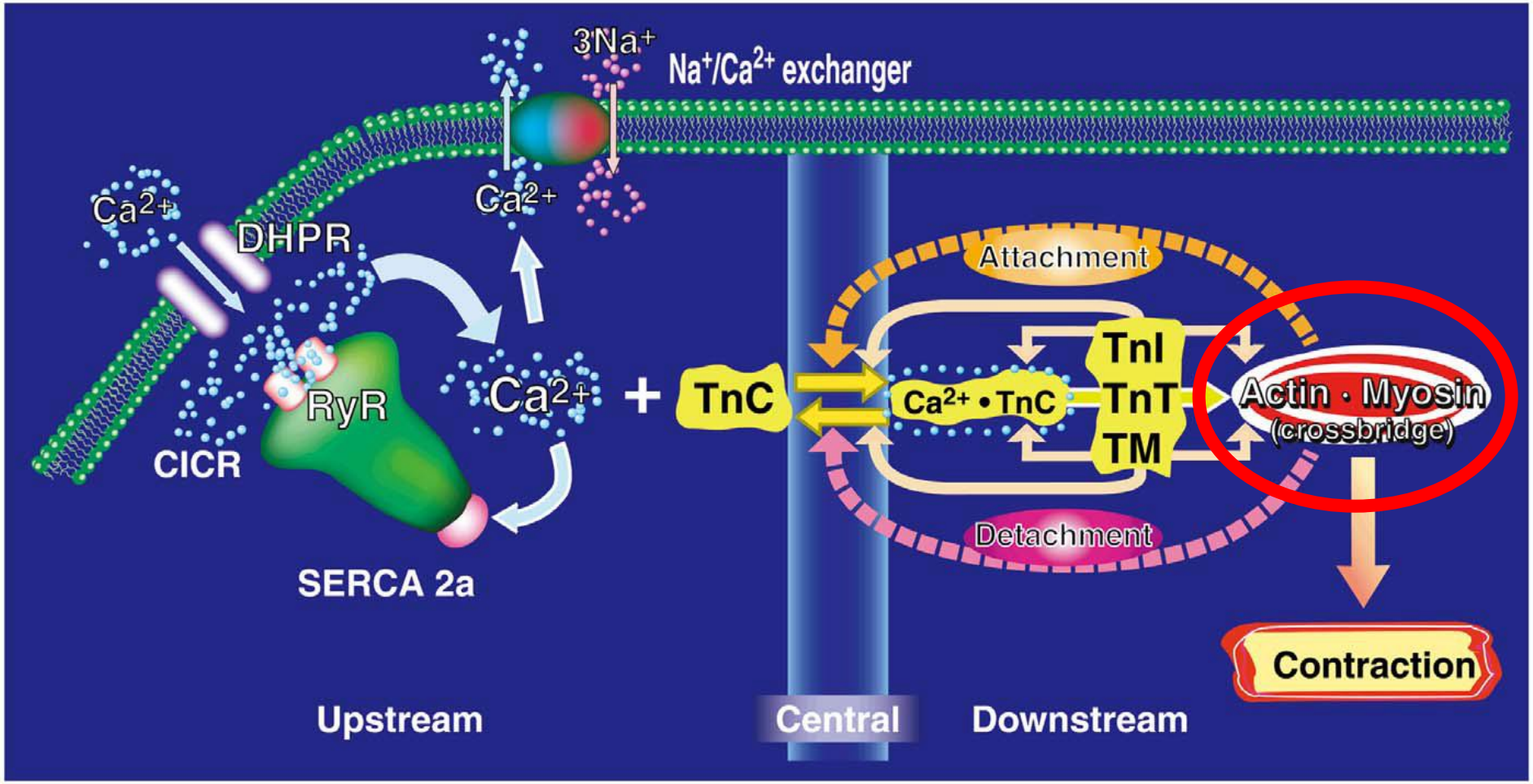
Myocardial contractility = Ca^{2+}-availibility + Ca^{2+}-responsiveness







Positive inotrope agents



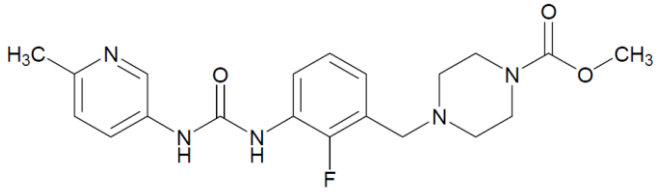
Ca²⁺-sensitizers **Direct myosin activators**

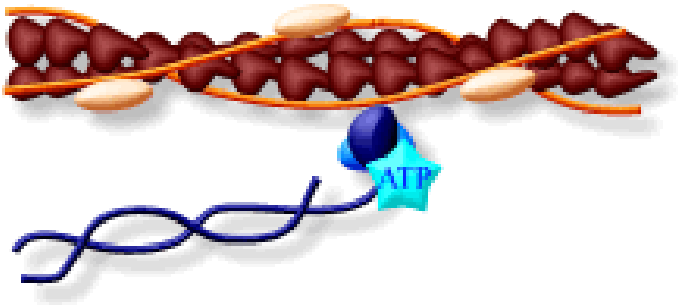
Calcitropes **Myotropes**

Endoh M.: Circ J (2008) 72:1915–1925

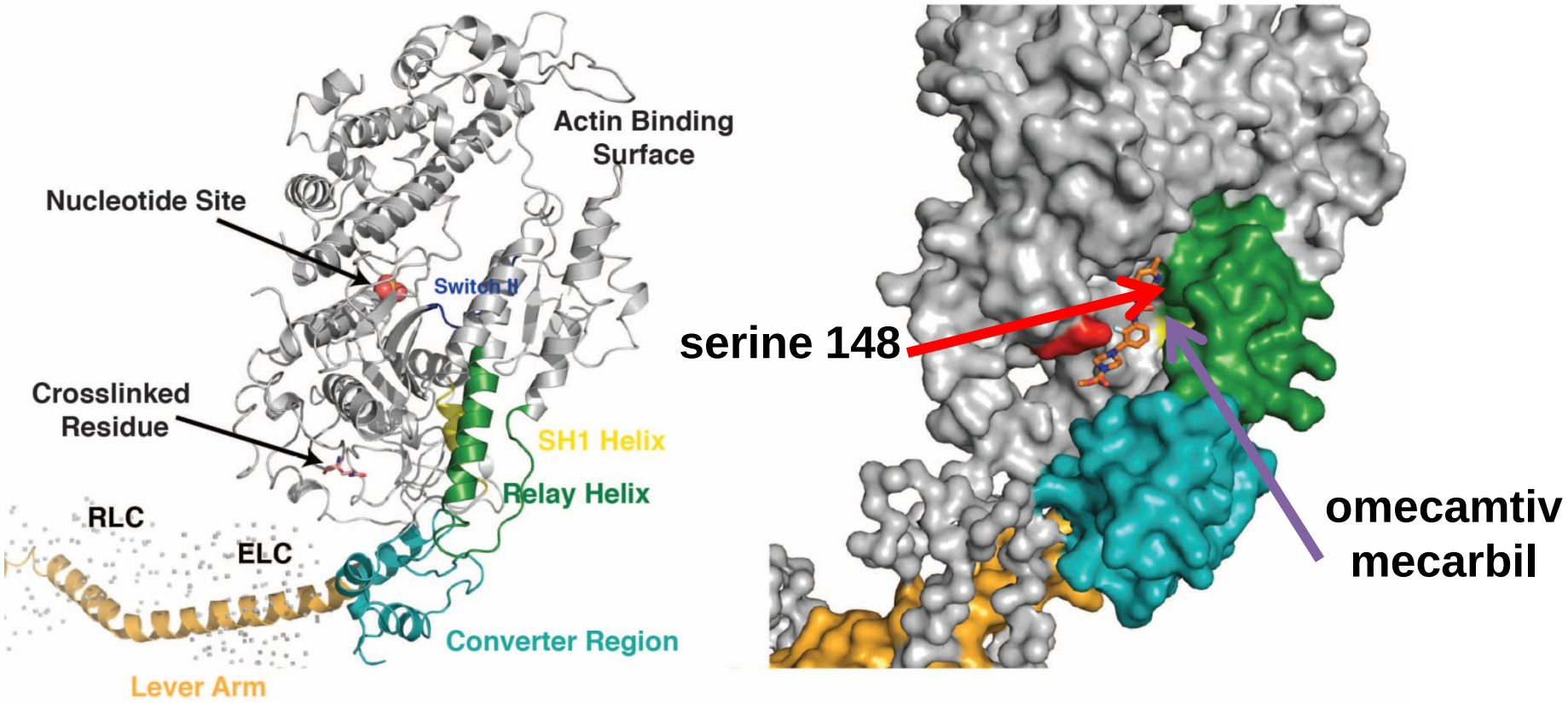
What do we know about direct myosin activators?

Omecamtiv mecarbil





Omecamtiv mecarbil binds to myosin S1 domain



Malik et al., Science 2011;331:1439–1443

Clinical trials with omecamtiv mecarbil

ATOMIC-AHF

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http://dx.doi.org/10.1016/j.jacc.2016.01.031

Acute Treatment With Omecamtiv Mecarbil to Increase ntractility in Acute Heart Failure

COSMIC-HF

Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial

GALACTIC-HF

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

J.R. Teerlir
A. Arias-Mendoza
U. Dahlström, L.
D.E. Lanfear, J. Li,
F.J.A. Ramires
A.A. Voors, M.

METEORIC-HF

JAMA | Original Investigation

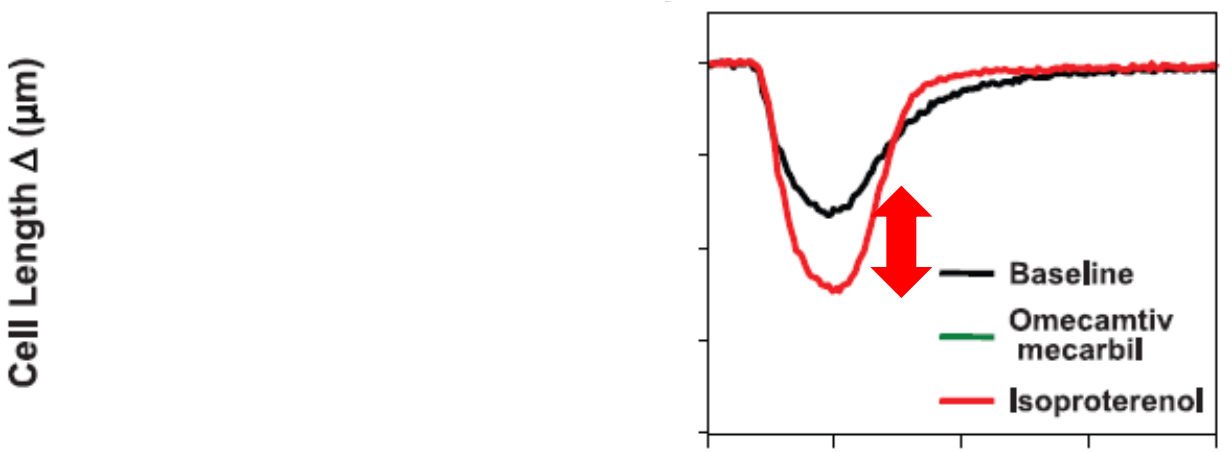
Effect of Omecamtiv Mecarbil on Exercise Capacity in Chronic Heart Failure With Reduced Ejection Fraction
The METEORIC-HF Randomized Clinical Trial

Gregory D. Lewis, MD; Adriaan A. Voors, MD, PhD; Alain Cohen-Solal, MD, PhD; Marco Metra, MD; David J. Whellan, MD, MHS; Justin A. Ezekowitz, MBBCh, MSc; Michael Böhm, MD; John R. Teerlink, MD; Kieran F. Docherty, BSc, MB, ChB; Renato D. Lopes, MD, PhD; Punag H. Divanji, MD; Stephen B. Heitner, MD; Stuart Kupfer, MD; Fady I. Malik, MD, PhD; Lisa Meng, PhD; Amy Wohltman, ME; G. Michael Felker, MD, MHS

Isoproterenol increases the Ca^{2+} transient

Isoproterenol

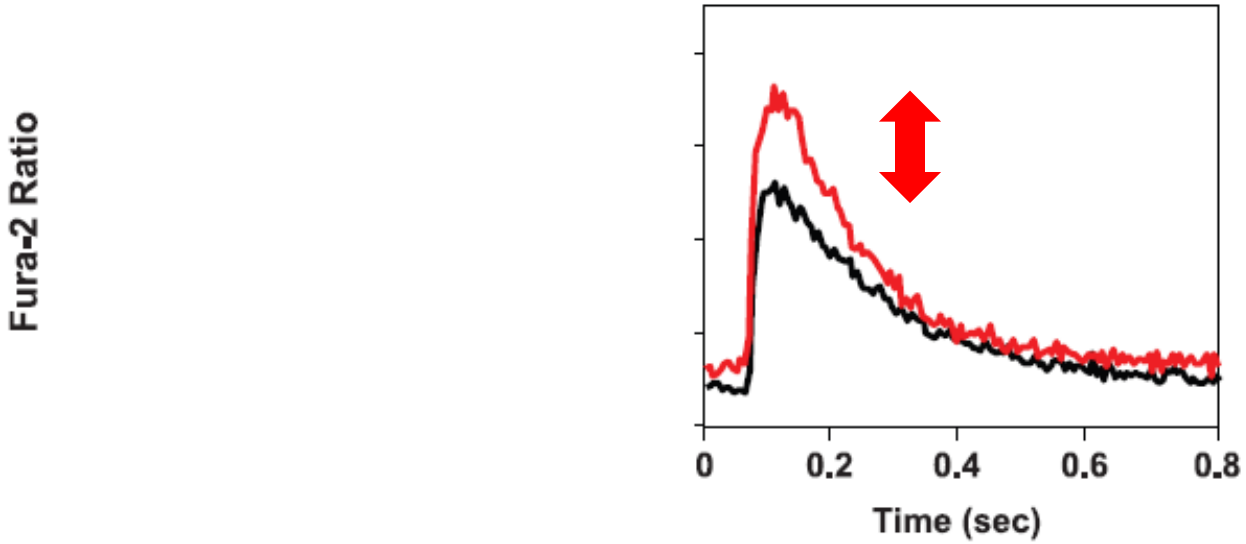
Contractility transient



diastole

systole

Ca^{2+} transient



systole

diastole

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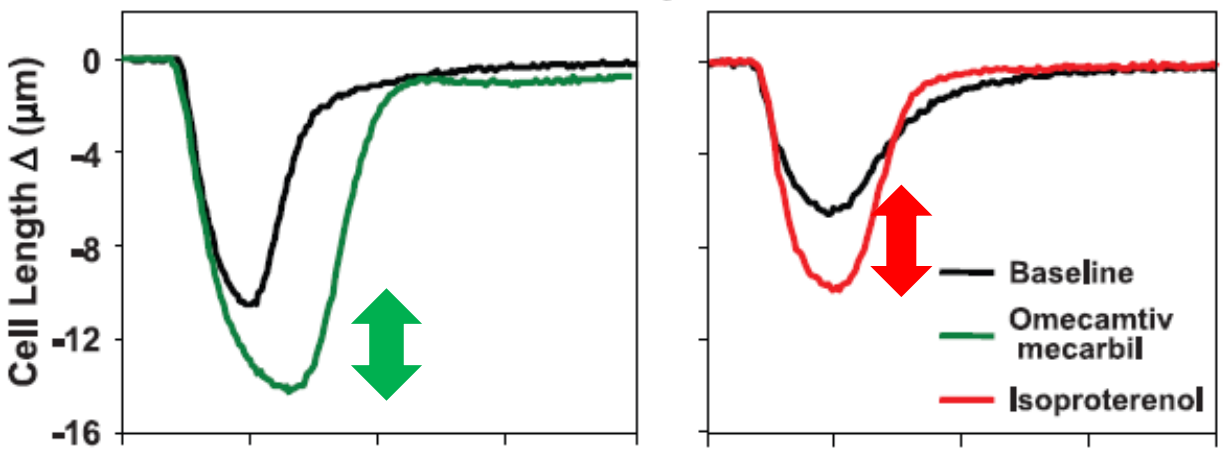
Omecamtiv mecarbil does not affect the Ca^{2+} transient

Omecamtiv mecarbil | Isoproterenol

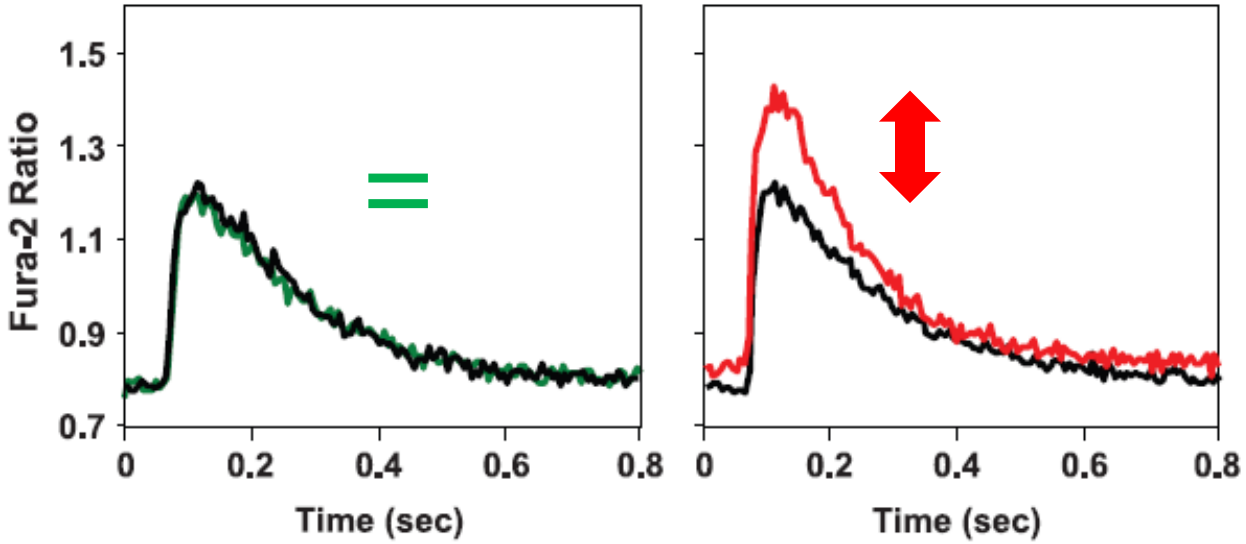
Contractility transient



diastole

systole

Ca^{2+} transient

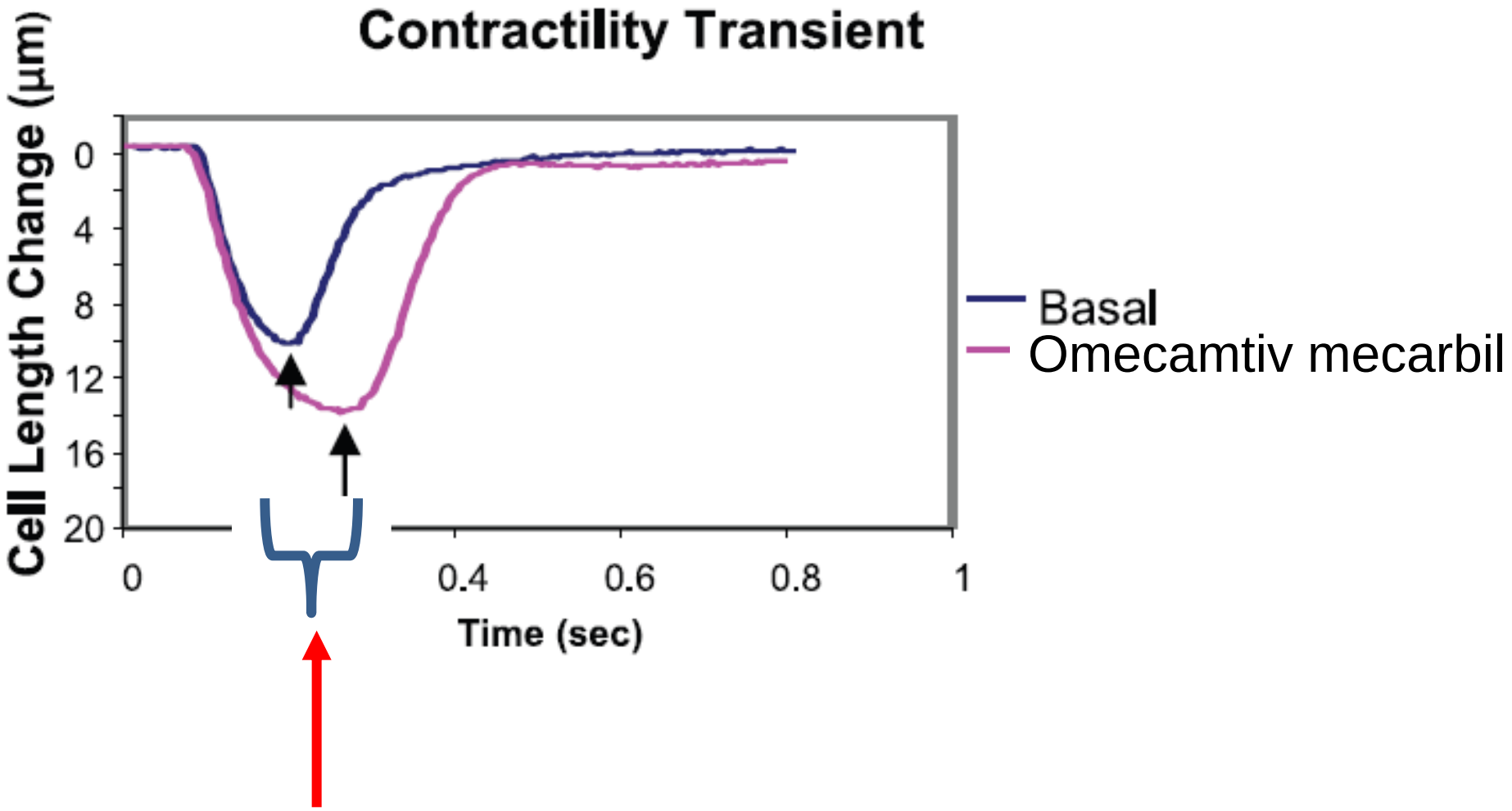


systole

diastole

Malik et al., Science 2011;331:1439–1443

Myosin activators increase systolic ejection time



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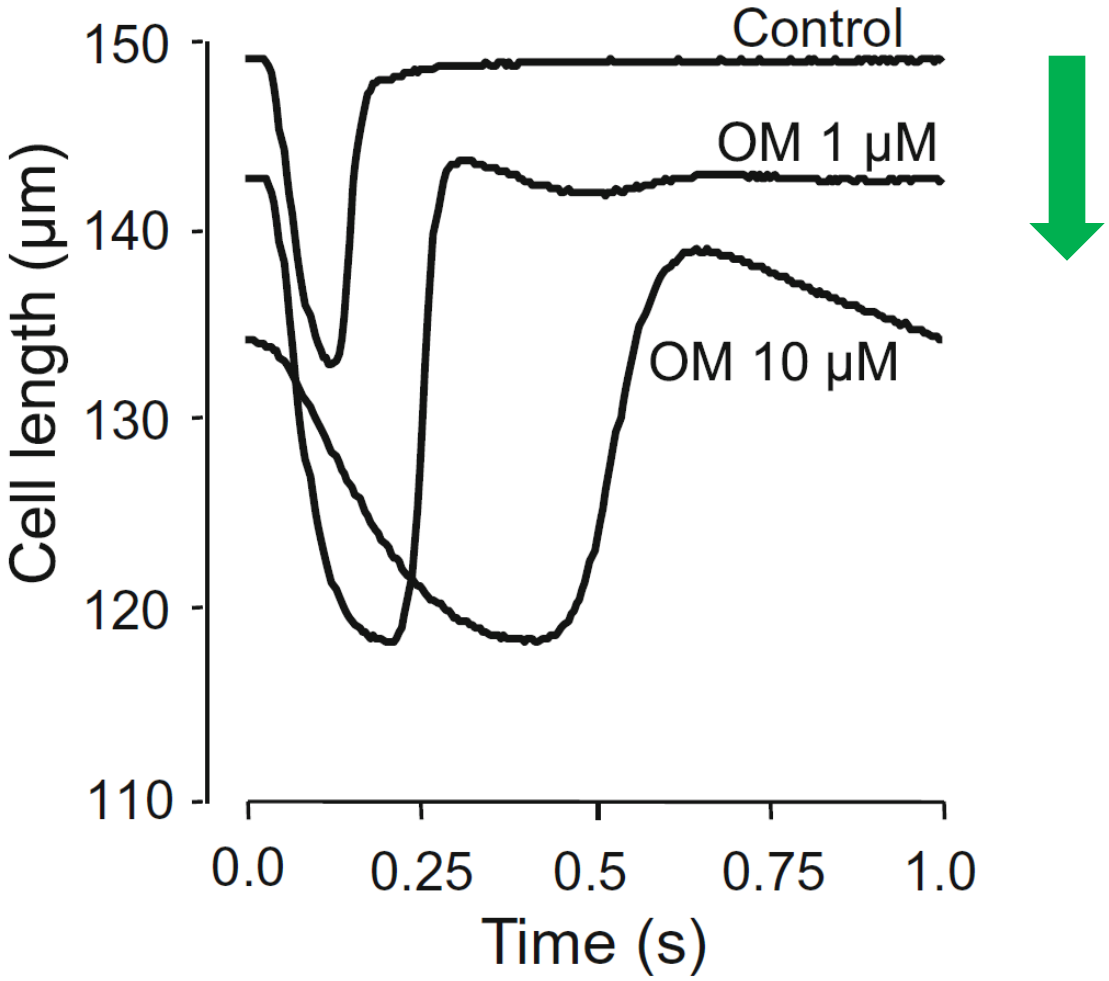
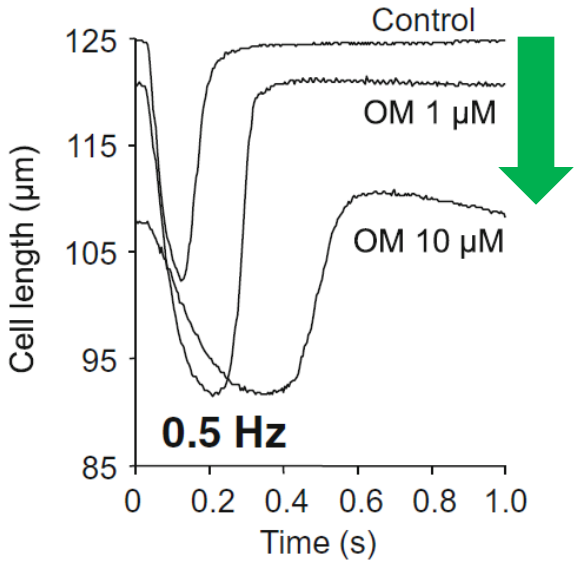
Omecamtiv mecarbil decreases diastolic cell length



Horvath B…Papp Z. et al. Naunyn Schmiedebergs Arch Pharmacol. (2017),390(12):1239-1246.

Diastolic cell length is also modulated by heart rate in the presence of omecamtiv mecarbil



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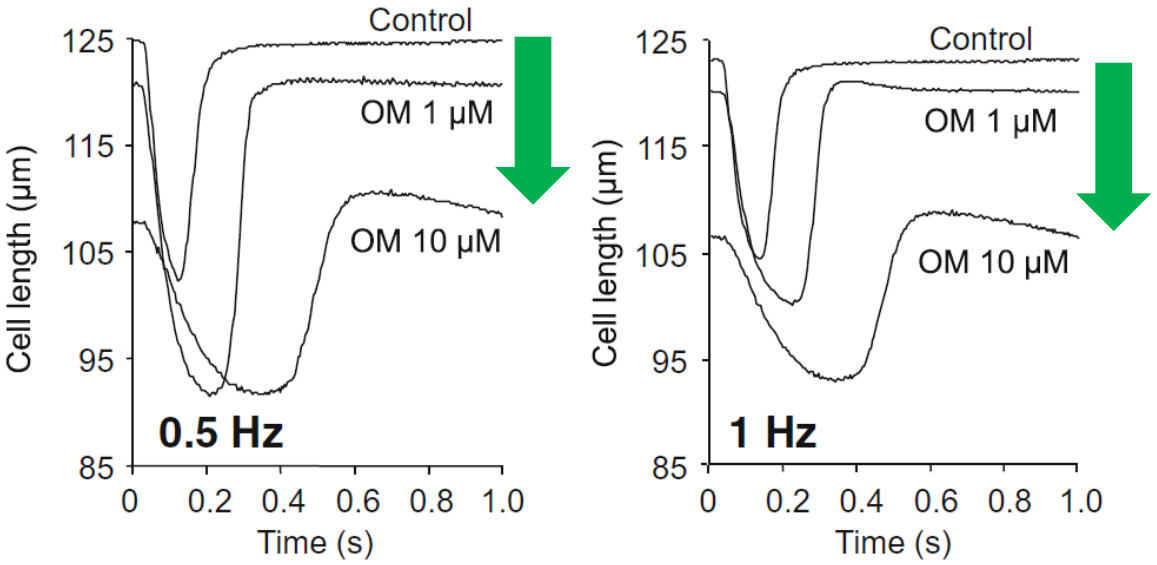

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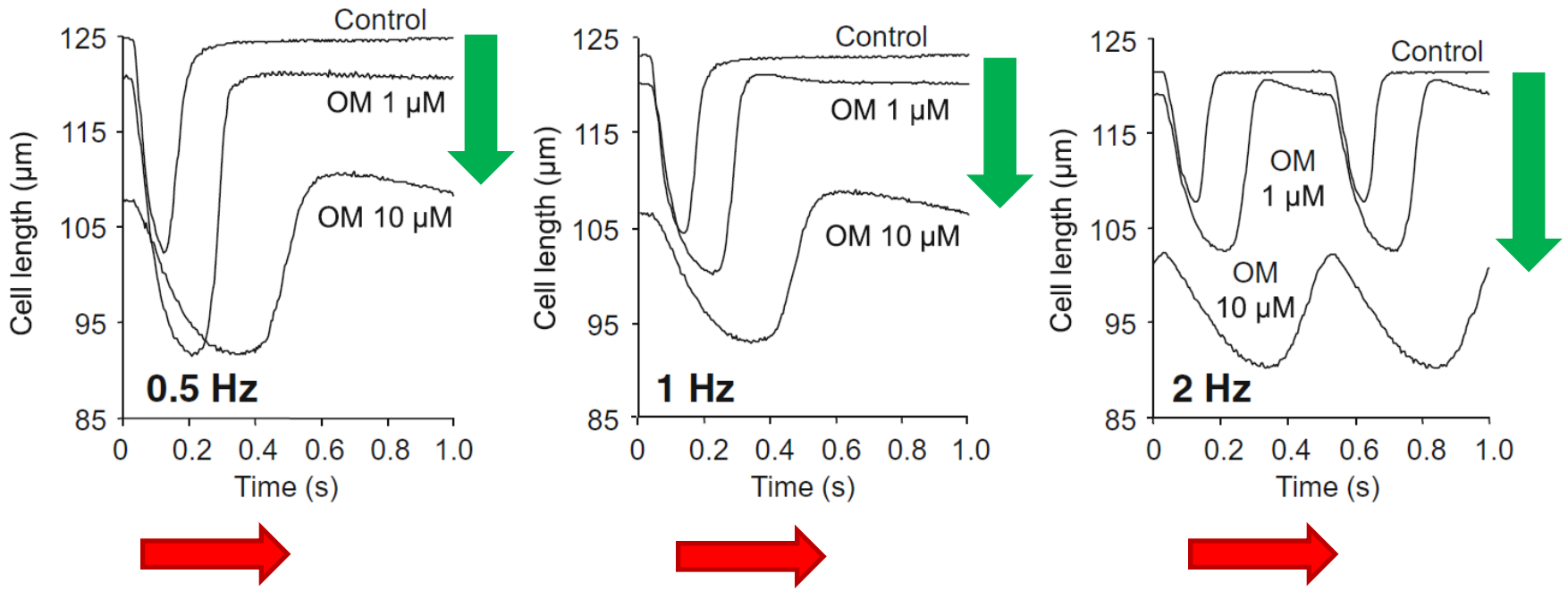

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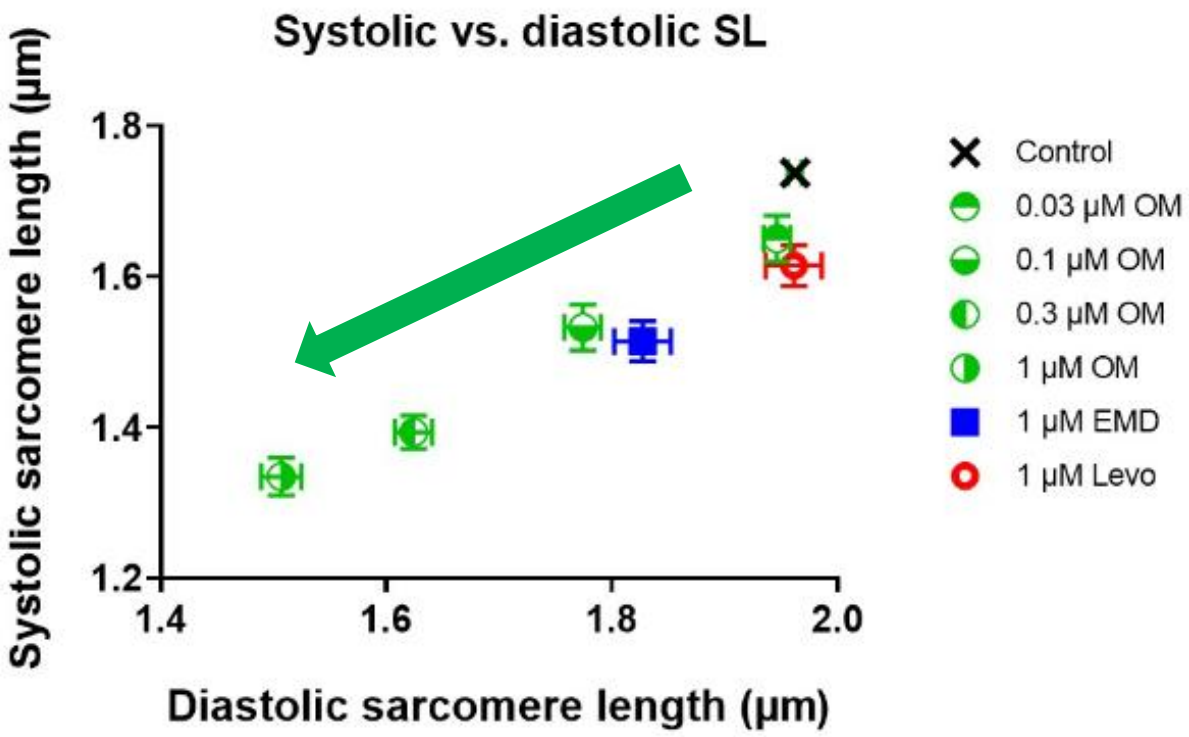
Changes in diastolic sarcomere length are associated with those in systolic sarcomere length/contraction duration



Ráduly A…Papp Z. et al. ESC Heart Failure, Pending on minor revision

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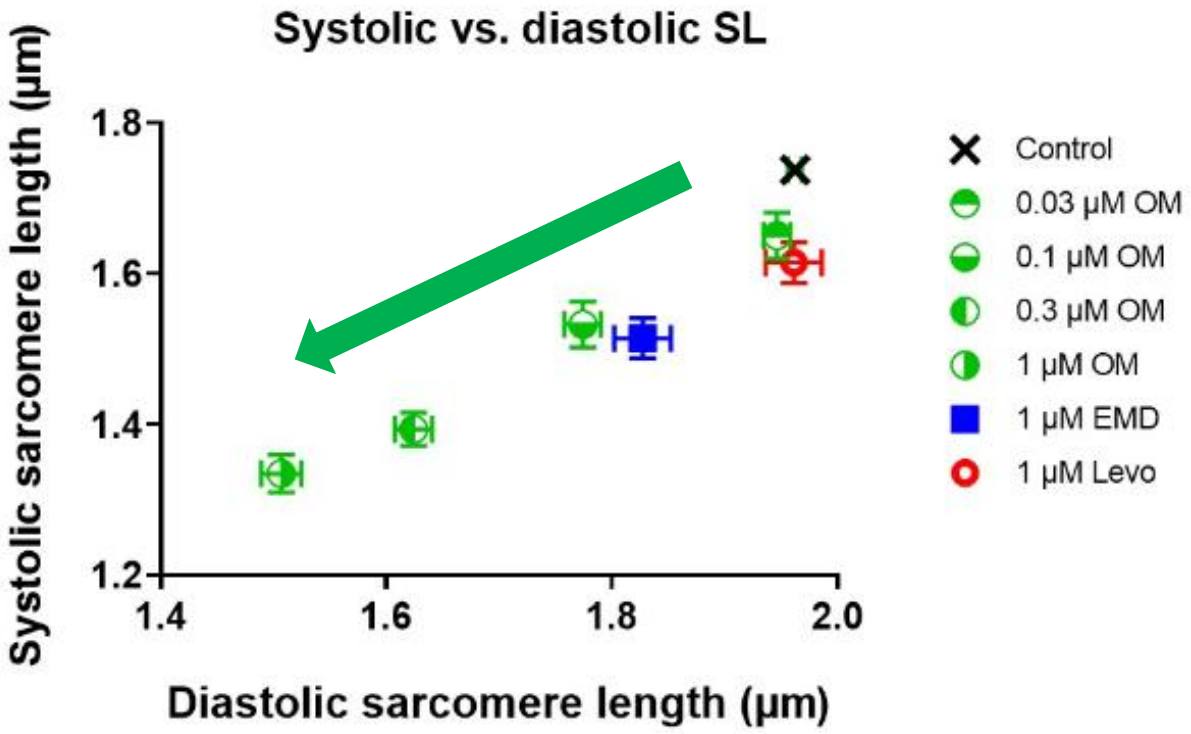
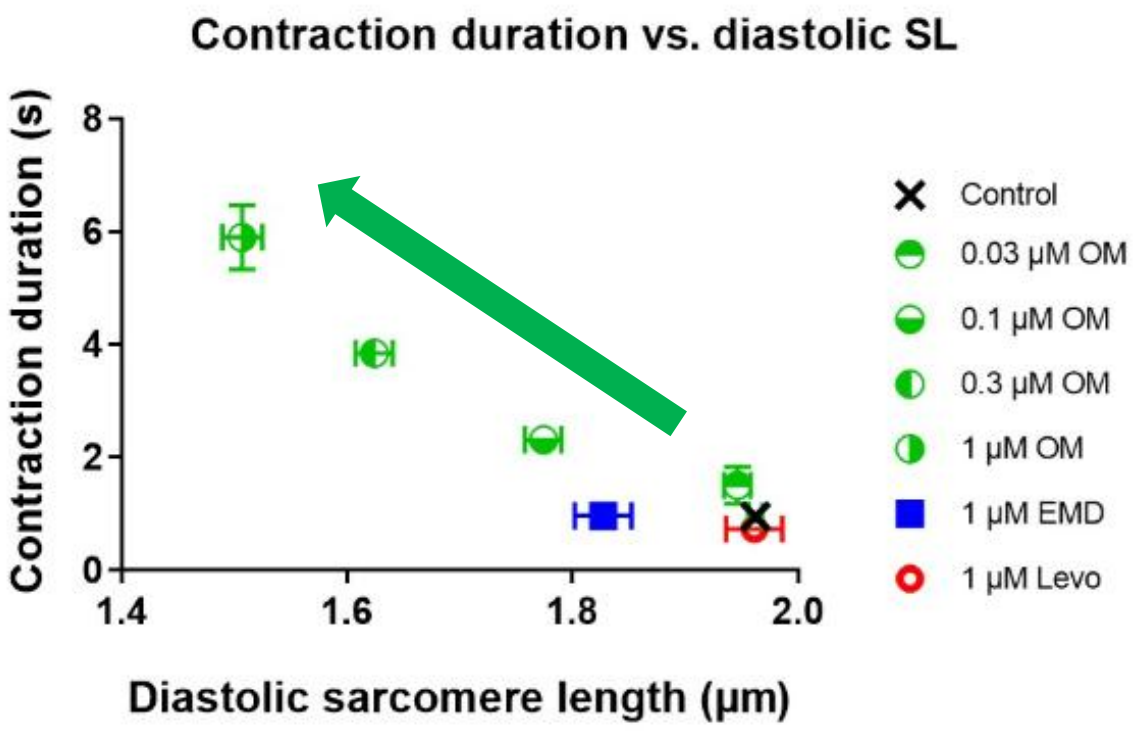
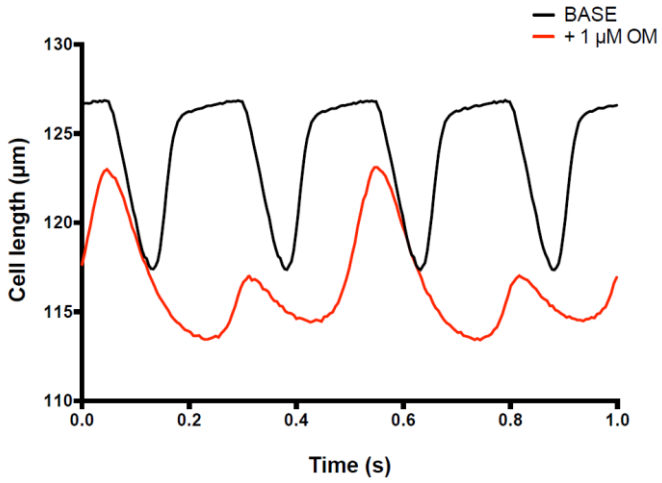
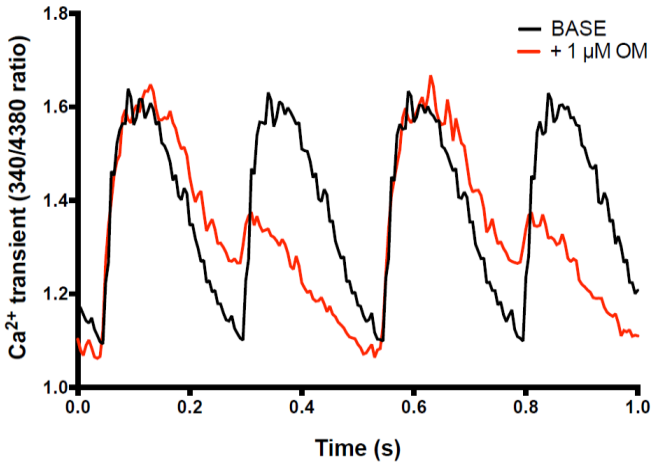


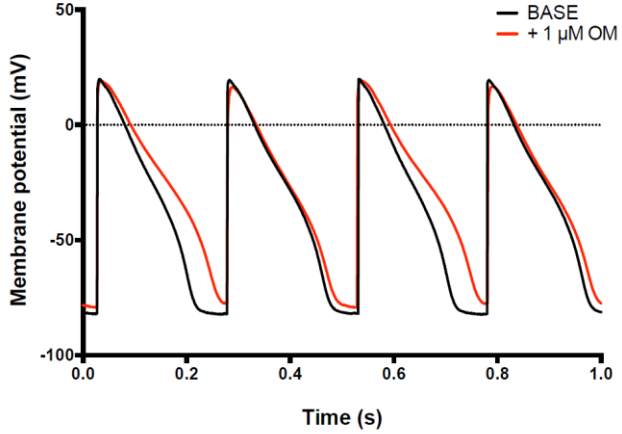


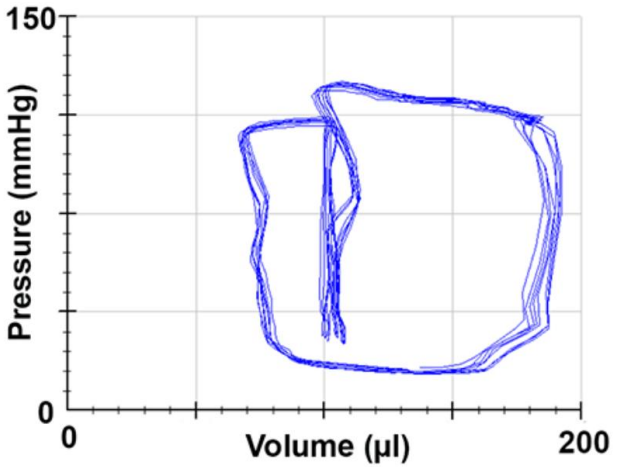
Ráduly A…Papp Z. et al. ESC Heart Failure, Pending on minor revision

Omecamtiv mecarbil evokes periodic electromechanical alternans



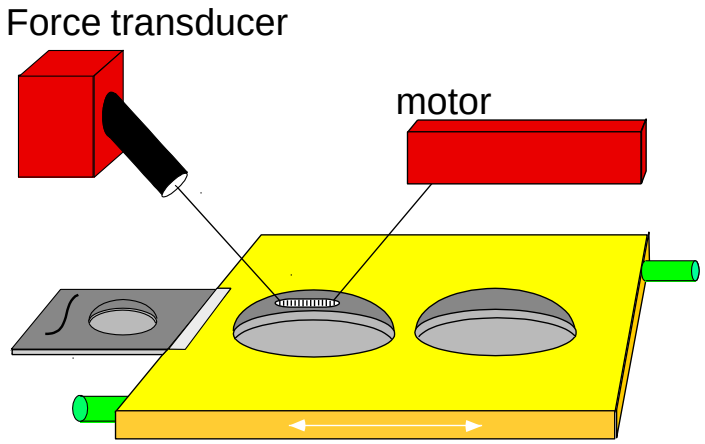


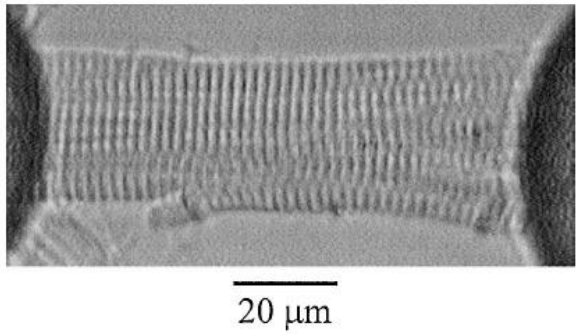


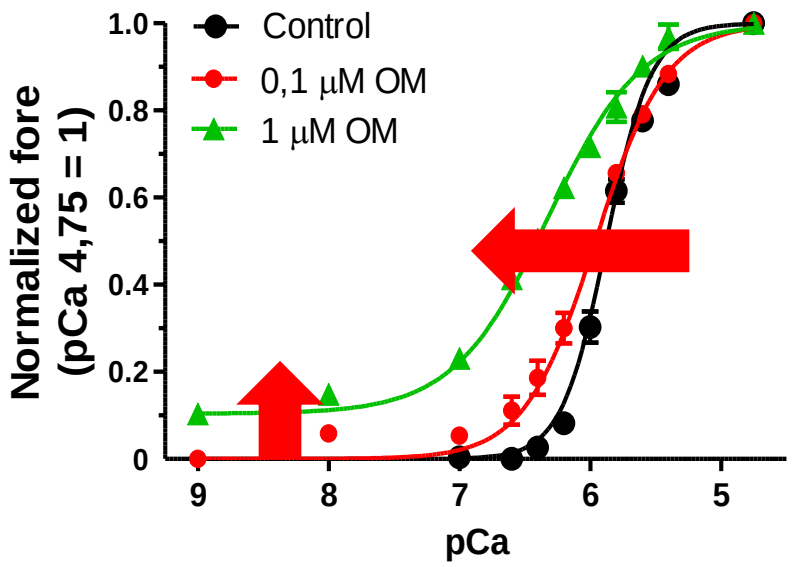


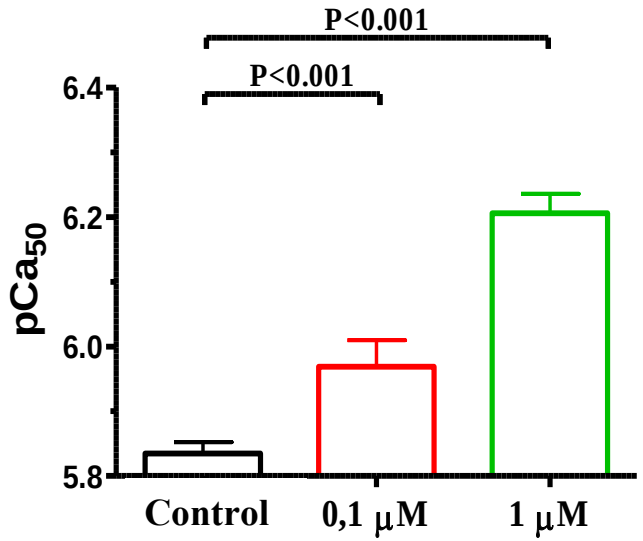
Fülöp G…Papp Z. et al. Basic Res Cardiol. 2021;116(1):24. doi: 10.1007/s00395-021-00866-8.

Omecamtiv mecarbil has a Ca^{2+}-sensitizer effect and may augment force production at low Ca^{2+} concentrations



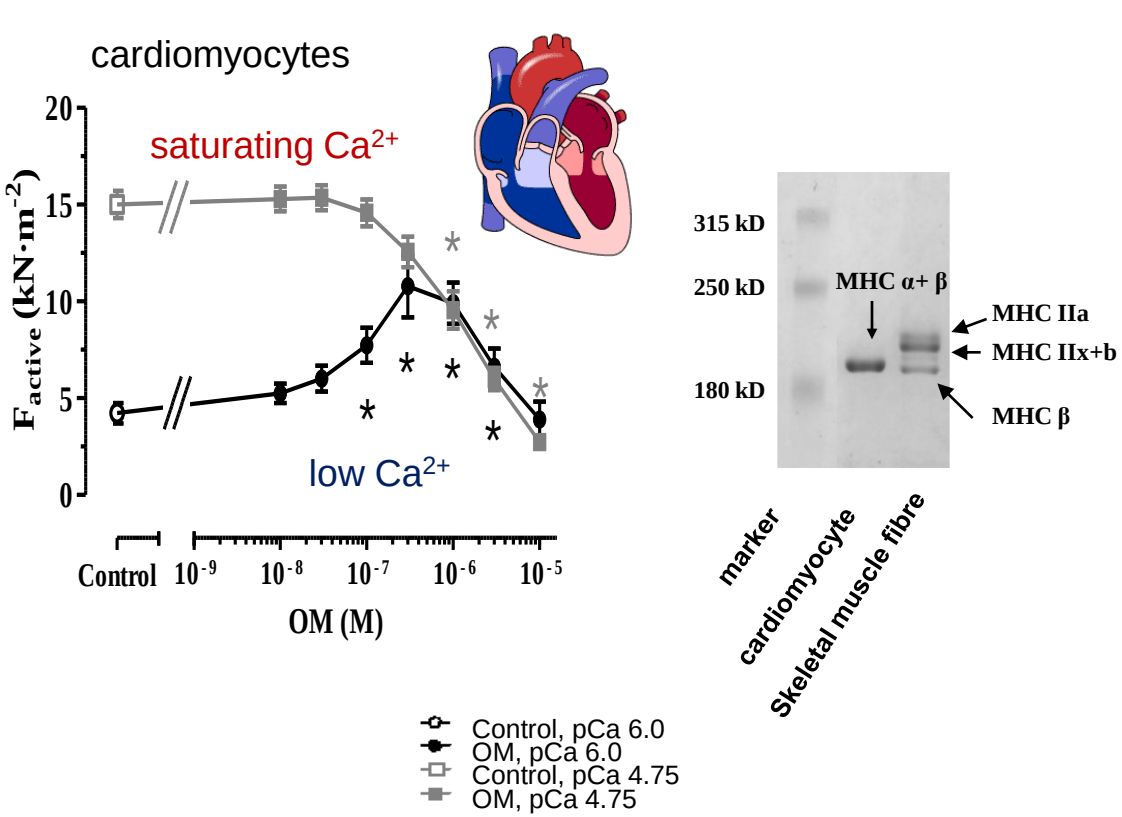


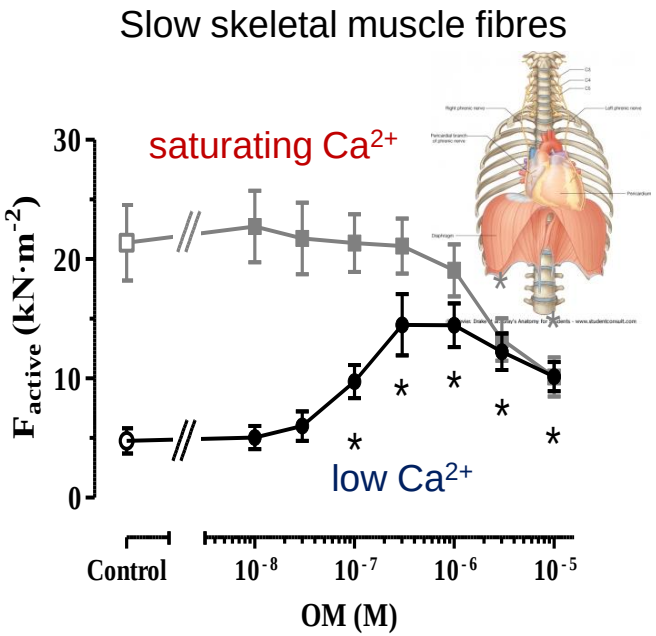




Nagy L… Papp Z. Br. J. Pharmacol. (2015) 172: 4506–4518.

Omecamtiv mecarbil is not selective for the heart

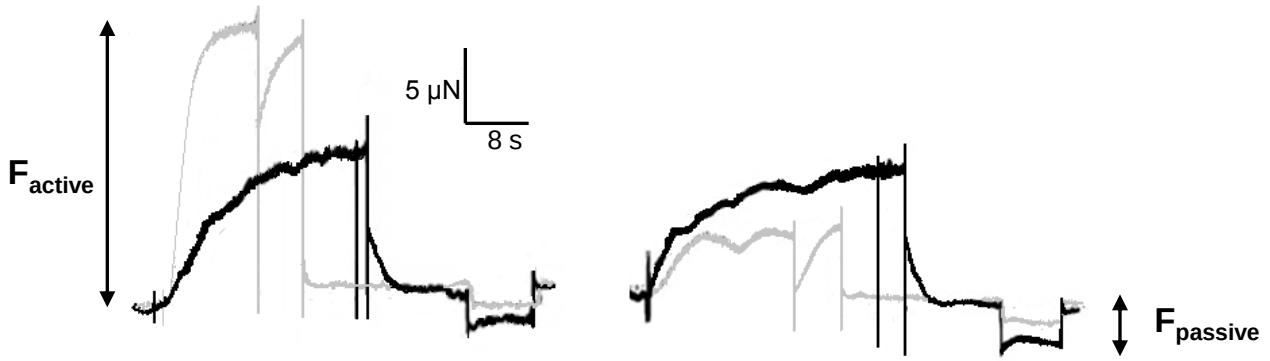


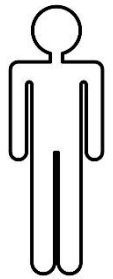


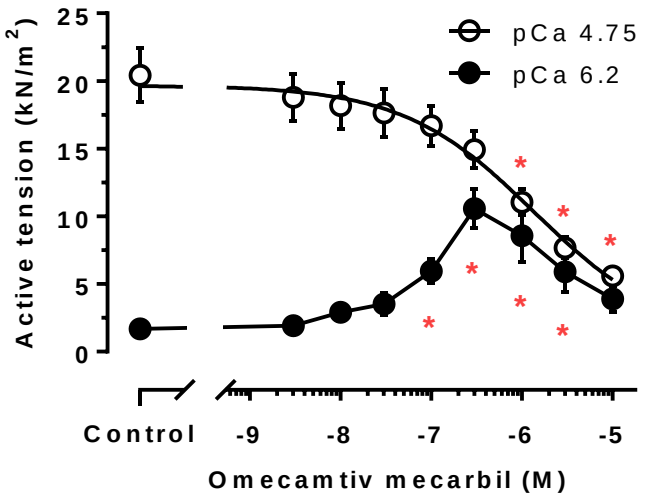
Nagy L… Papp Z. Br. J. Pharmacol. (2015) 172: 4506–4518.

Omecamtiv Mecarbil Enhances Cardiomyocyte Contractility in Humans

Human donor LV cardiomyocytes



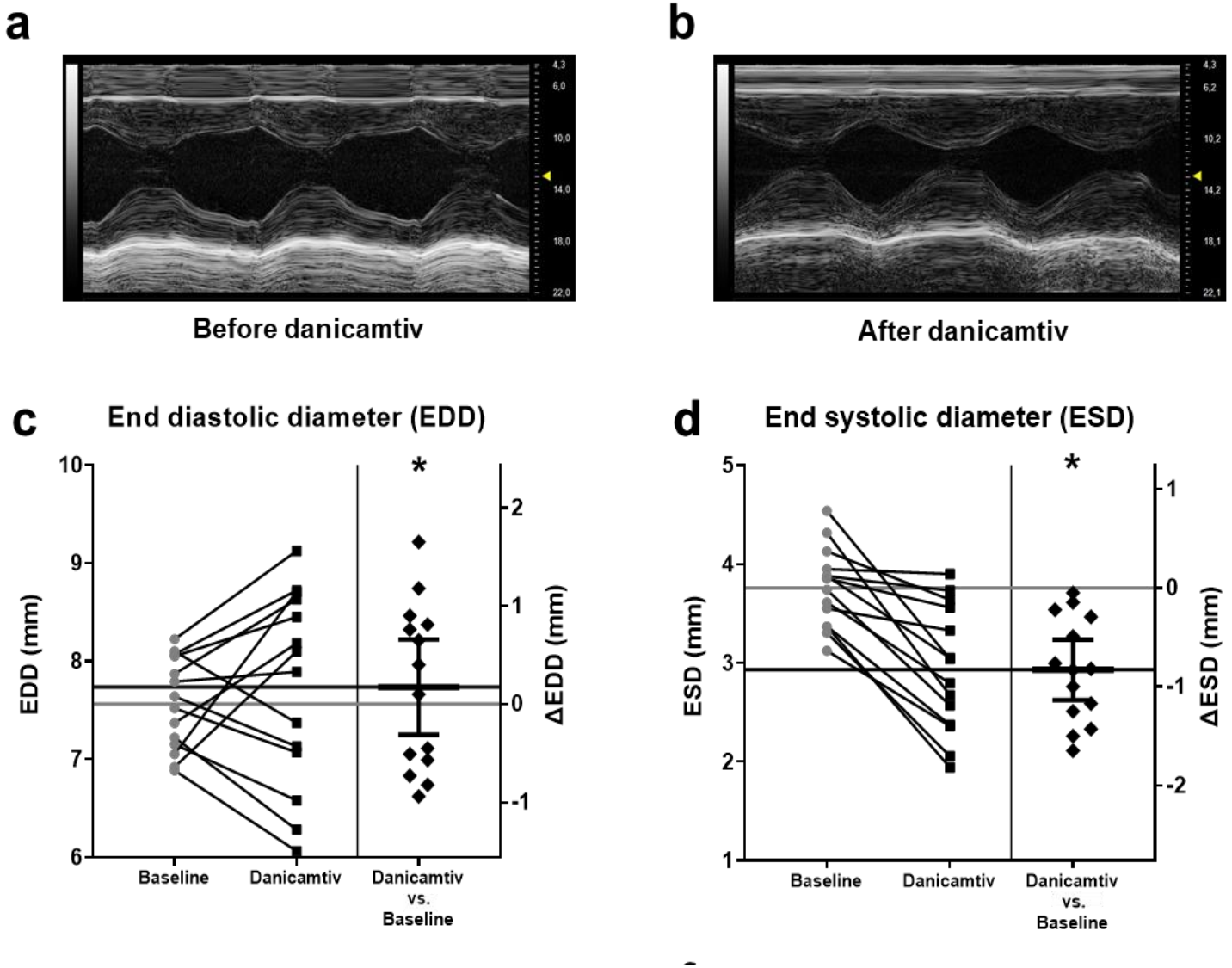




Fülöp G…Papp Z. et al. Basic Res Cardiol. 2021;116(1):24. doi: 10.1007/s00395-021-00866-8.

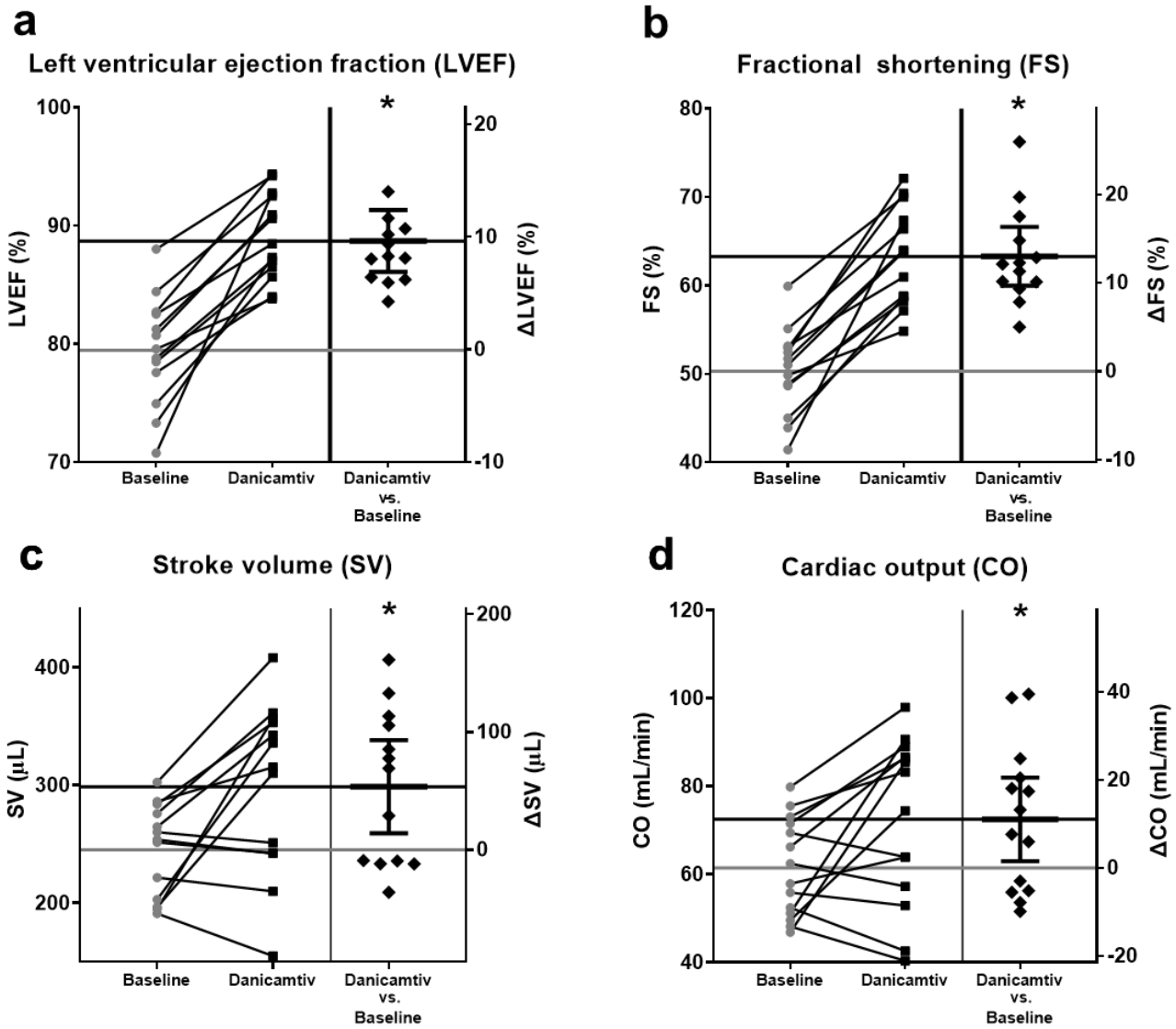

Simon Z.
Danicamtiv
A NEW HOPE

The danicamtiv evoked positive inotropy is similar to that observerd with omecamtiv mecarbil



Ráduly A…Papp Z. et al. Unpublished

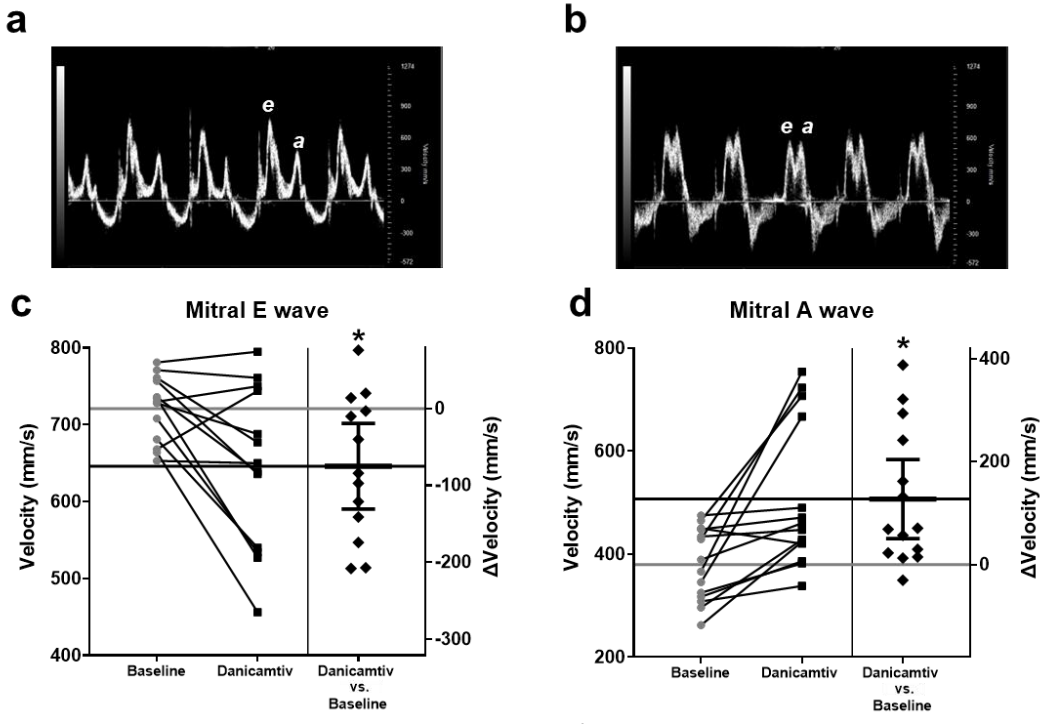
Danicamtiv is a potent positive inotrope



Ráduly A…Papp Z. et al. Unpublished

Danicamtiv evokes diatolic dysfunction, but augments atrial contractions

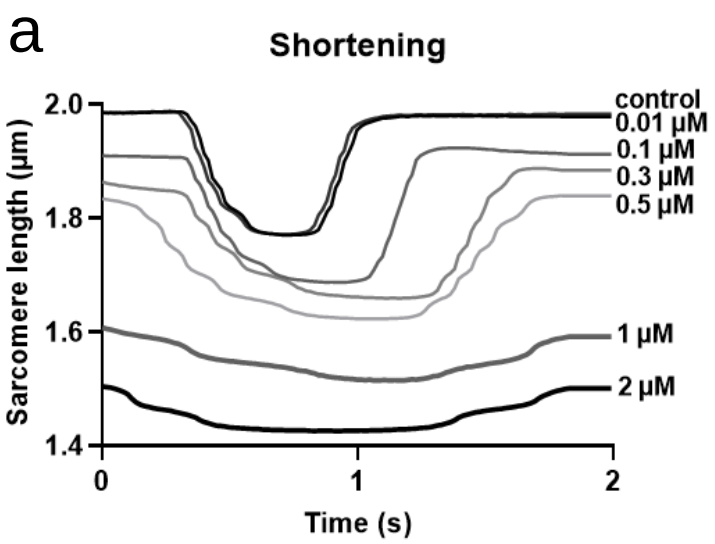
Baseline

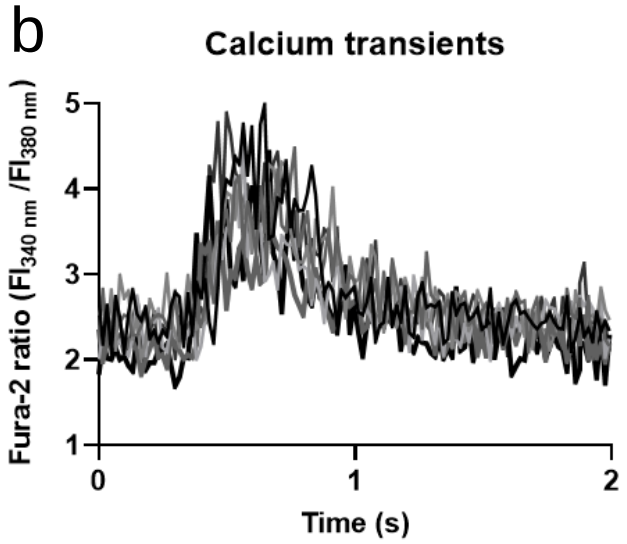


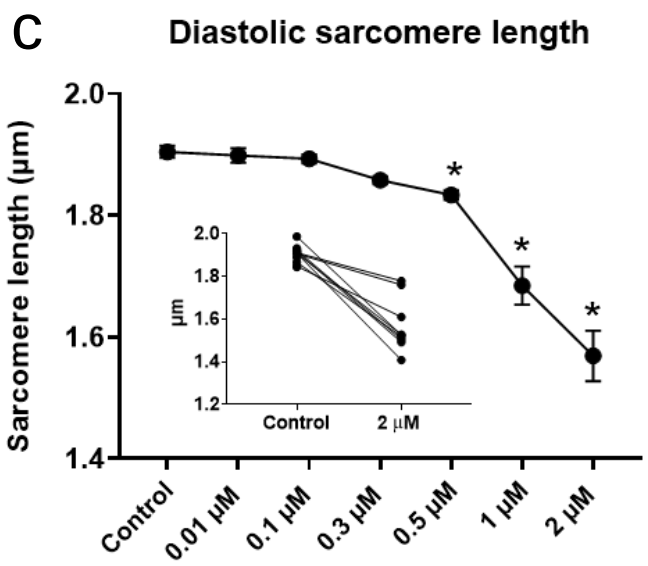
Danicamtiv

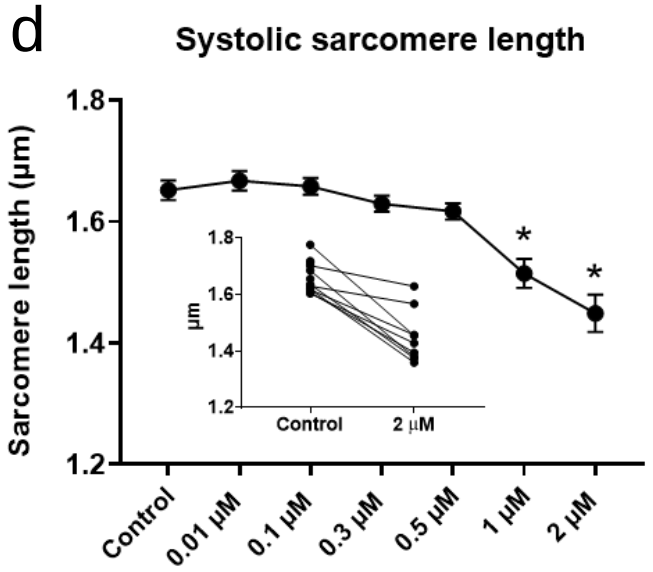
Ráduly A…Papp Z. et al. Unpublished

Danicamtiv decreases both systolic and diastolic SLs









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Direct myosin activation: everything comes with a price

Direct myosin activation: everything comes with a price

The two sides of the coin for direct myosin activators

positive inotropy
increase in systolic duration
slower contraction

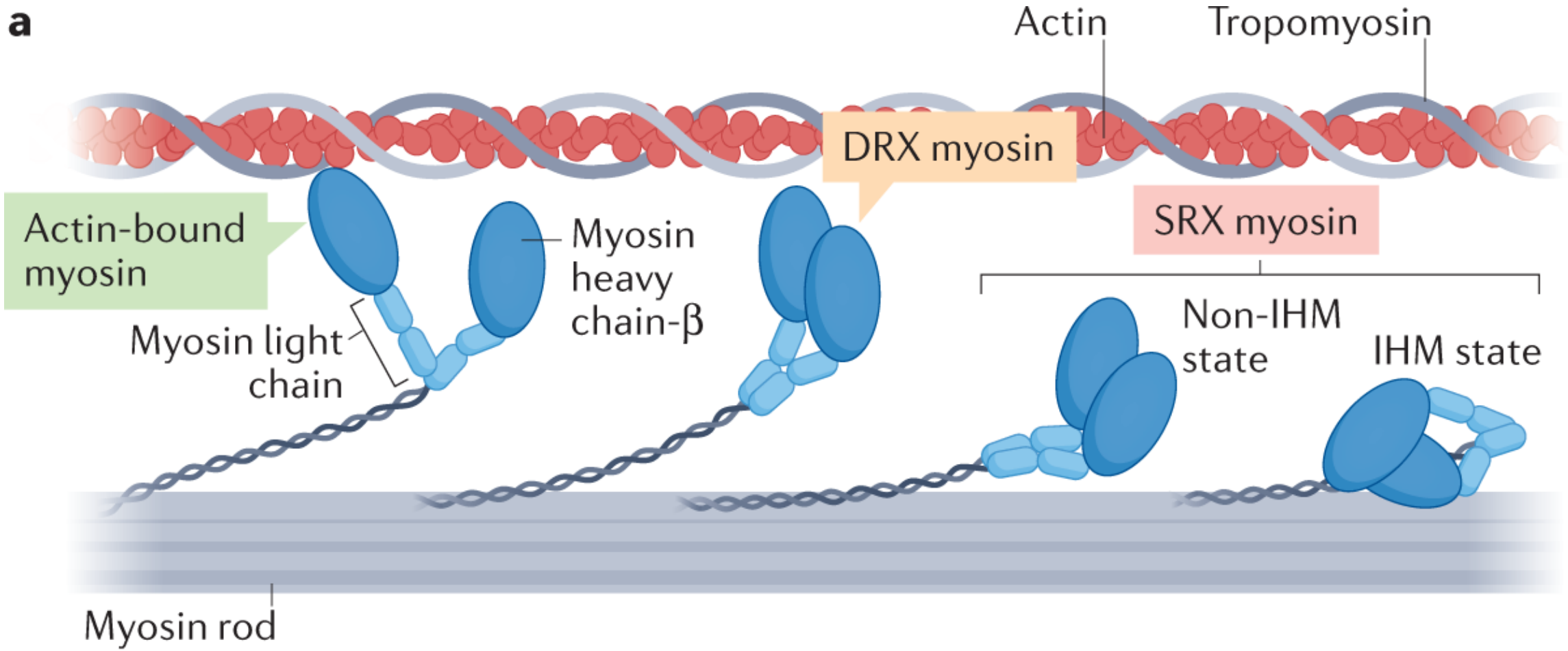
Direct myosin activation: everything comes with a price

The two sides of the coin for direct myosin activators

positive inotropy
increase in systolic duration
slower contraction

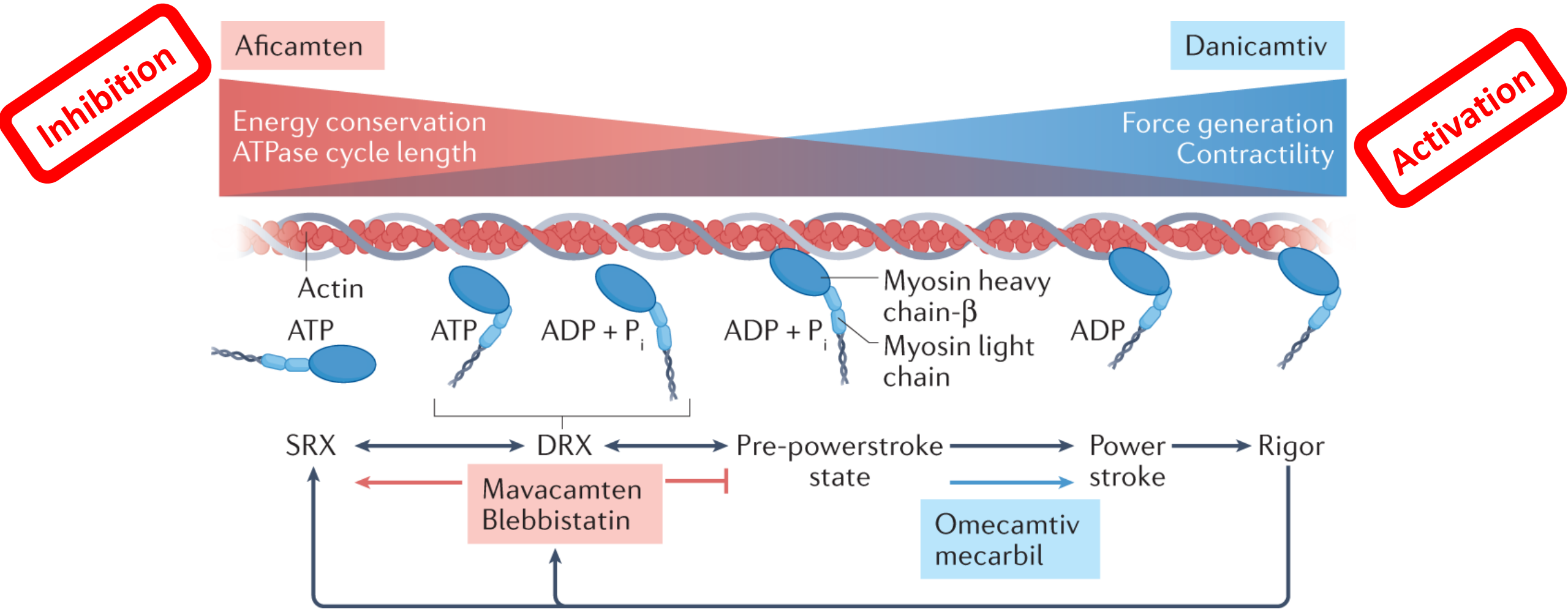
incomplete relaxation
decrease in diastolic duration
slower relaxation

The transitions betweem distinct states of myosin heads can be modulated by small molecules



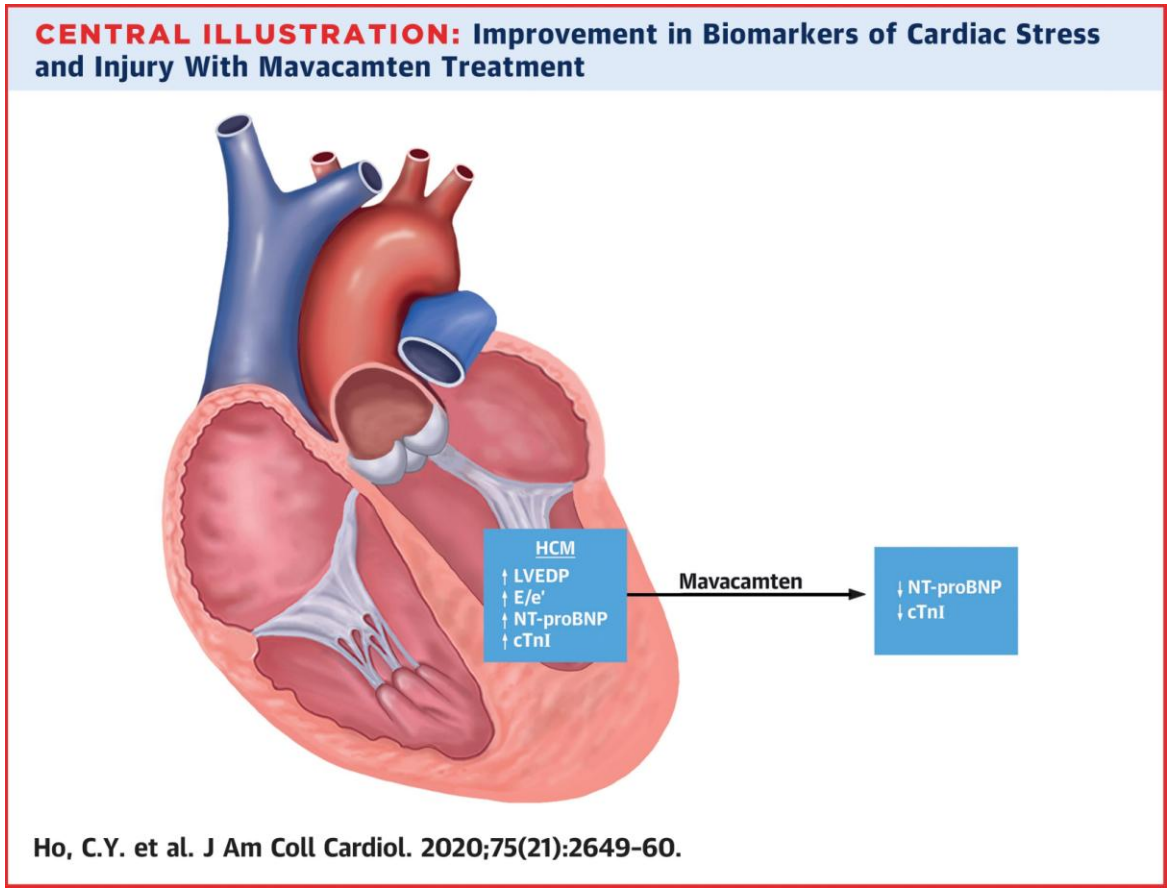
Lehman et al., Nature Reviews Cardiology (2022)19, 353–363

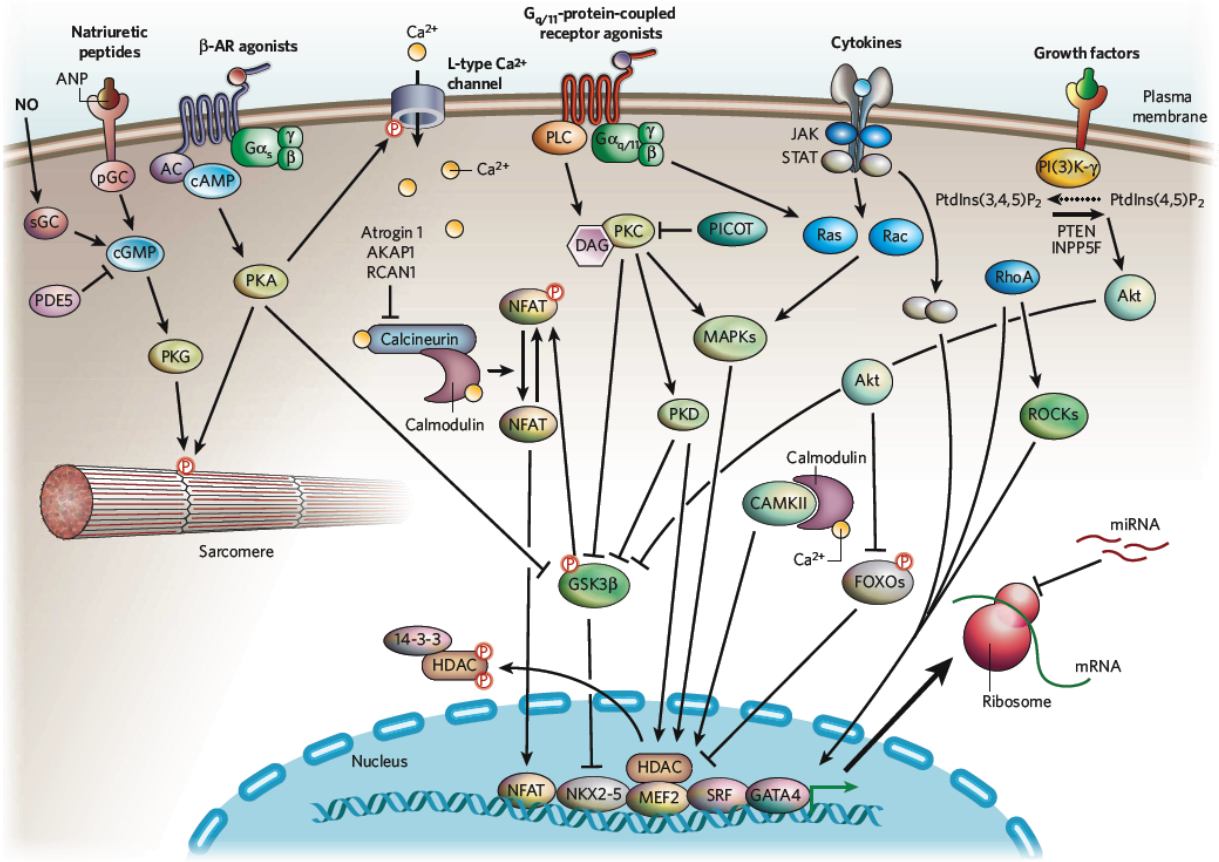
From myosin activation to myosin inhibition



Lehman et al., Nature Reviews Cardiology (2022)19, 353–363

Mavacamten may interfere with cardiomyocyte hypercontractility and signaling and may halt the progression of HCM





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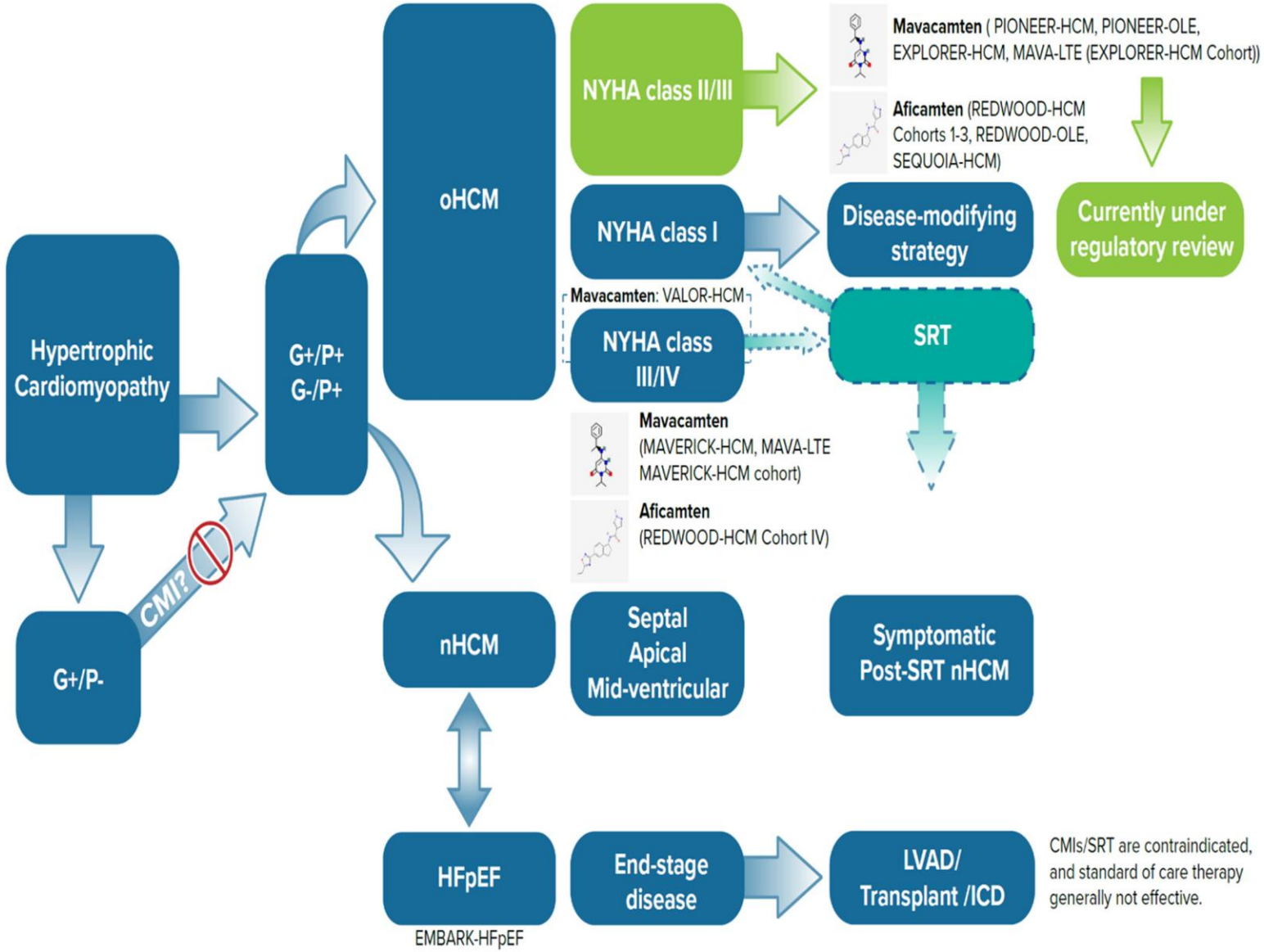
Current and future applications of cardiac myosin inhibitors (CMI)



Masri & OlivottoJ Am Heart Assoc. 2022;11:e024656.

Summary

1. Omecamtive mecarbil and danicamtiv evoke positive inotropic effects in murine, canine and human cardiac preparations in vitro and in vivo, consistently with their myosin activating and Ca^{2+}-sensitizing effects.
2. The myosin activator evoked increase in systolic performance was associated with an increased ejection time and altered contraction relaxation kinetics.
3. Myosin inhibitors hold promises for the treatment of HCM.

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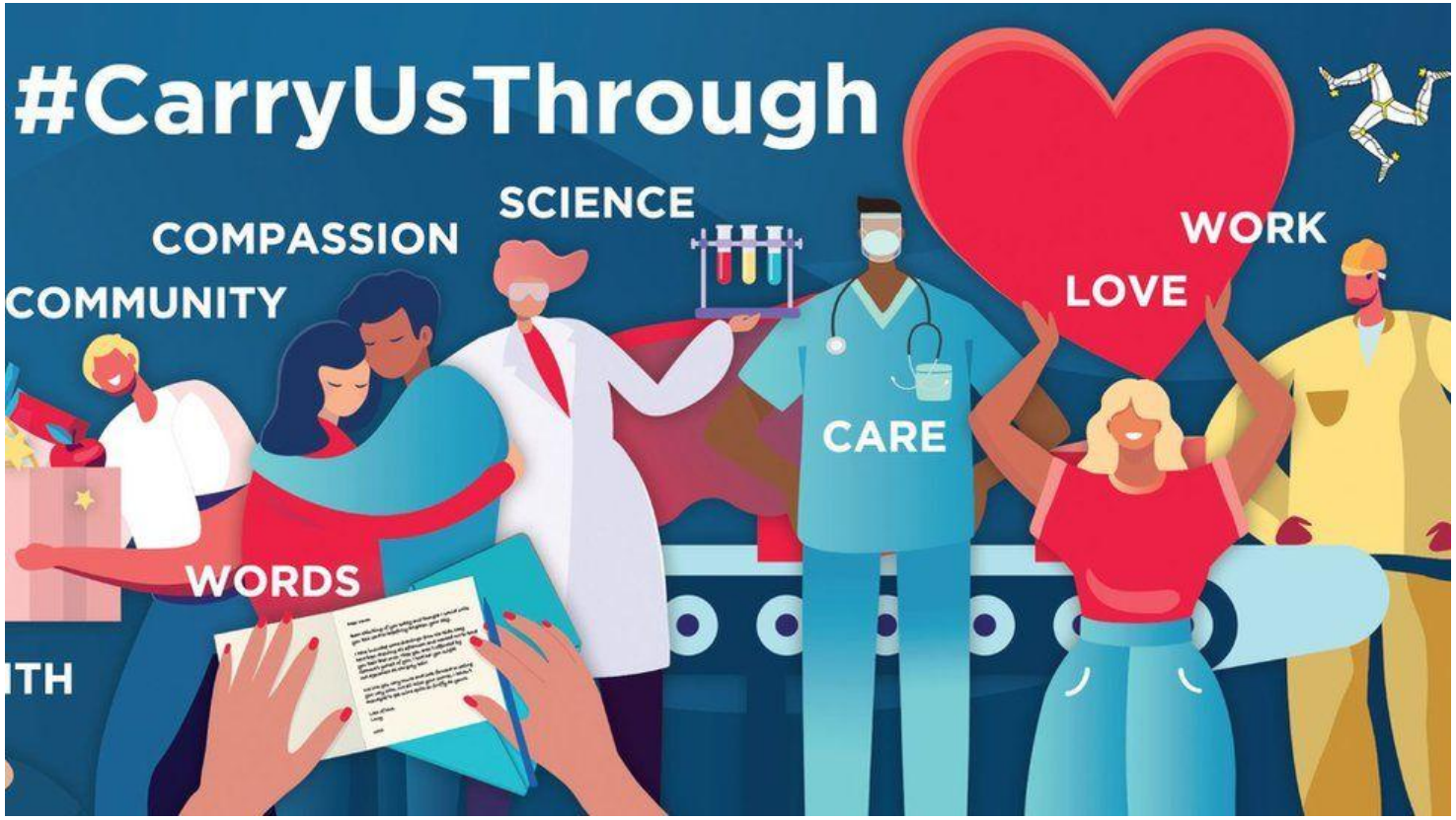
Thank you for your attention!



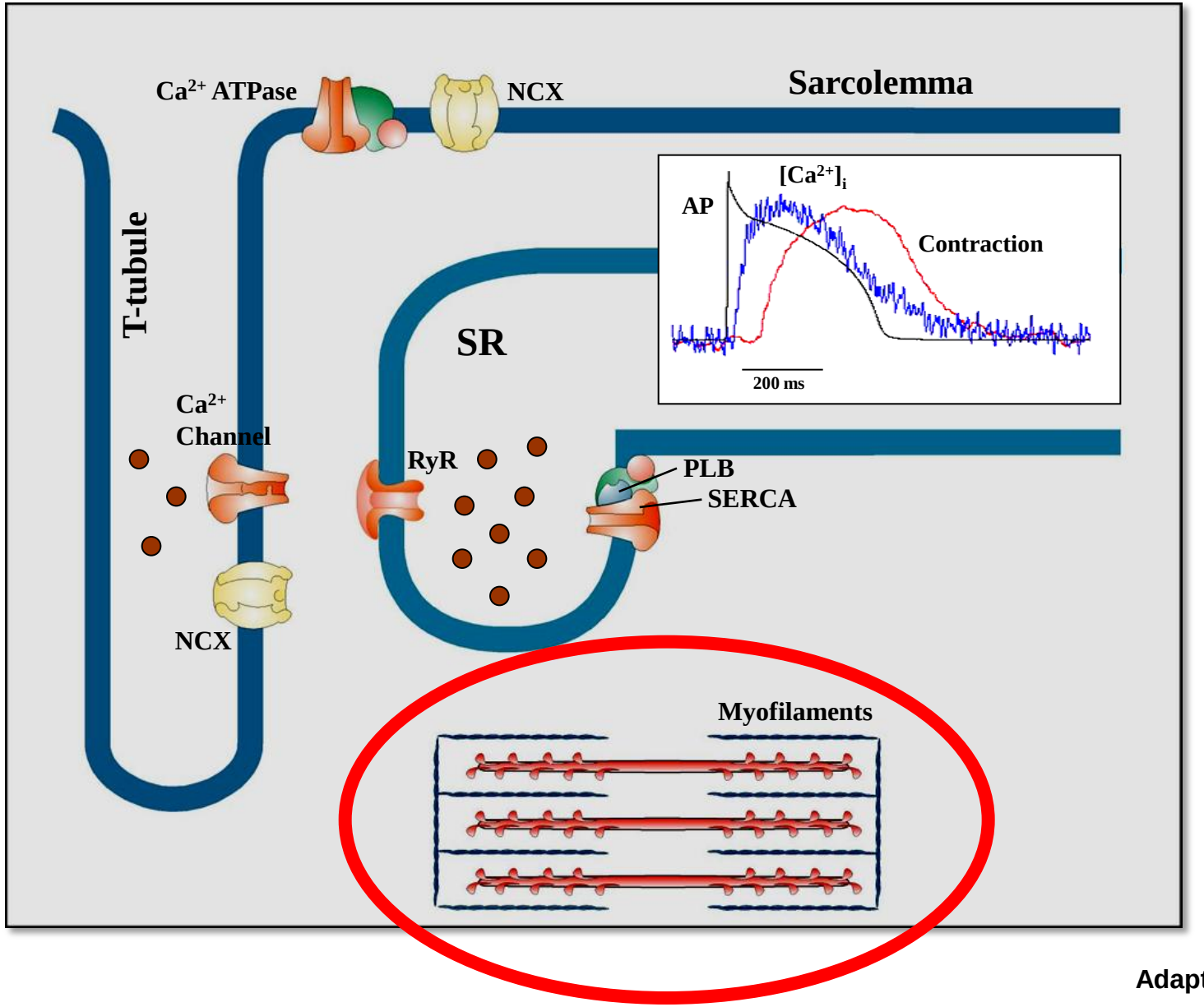
Myosin activators and myosin inhibitors

Molecule	Sarcomeric target	Molecular mechanism	Contractile effect	Clinical trial	Clinical effects
Sarcomeric contractile activators					
Omecamtiv mecarbil	Myosin heavy chain-β	Stabilizes the pre-powerstroke state of myosin	Increased owing to increased actomyosin interactions	GALACTIC-HF	Modest reduction in the rate of heart failure events and cardiac death; greatest improvement in function in patients with a left ventricular ejection fraction of ≤28%
				COSMIC-HF	Improved left ventricular systolic ejection time, stroke volume, end-diastolic diameter and volume, and heart rate; reduced plasma NT-proBNP level
Danicamtiv (MYK-491)	Myosin heavy chain-β	Unpublished	Increased	Phase II trial ongoing, recruiting participants with dilated cardiomyopathy	–
Sarcomeric contractile inhibitors					
Mavacamten (MYK-461)	Myosin heavy chain-β	Stabilizes the super-relaxed (SRX) state of myosin	Decreased owing to reduced myosin head availability	EXPLORER-HCM	Improved peak oxygen consumption and NYHA functional class; reduced left ventricular outflow tract obstruction
				PIONEER-HCM	Improved post-exercise peak left ventricular outflow tract gradient
				MAVERICK-HCM	Decreased risk of adverse events; decreased plasma NT-proBNP and cardiac troponin I levels
Aficamten (CK-274)	Myosin heavy chain-β	Slows phosphate release from myosin	Decreased owing to stabilization of weak actin-binding myosin conformation	REDWOOD-HCM	Reduced resting left ventricular outflow tract pressure gradient

NT-proBNP, N-terminal pro-B-type natriuretic peptide; PDE3, phosphodiesterase type 3.

Lehman et al.,
Nature Reviews Cardiology volume 19, 353–363 (2022)

Excitation-contraction coupling and Ca^{2+} transport



Adapted from Sjaastad et al., 2003