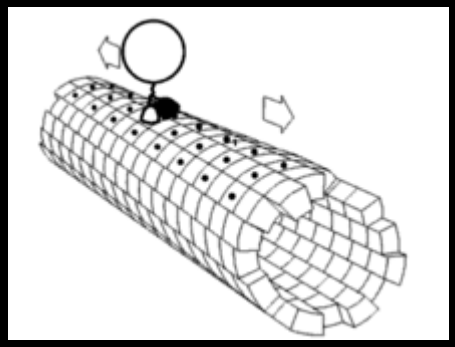
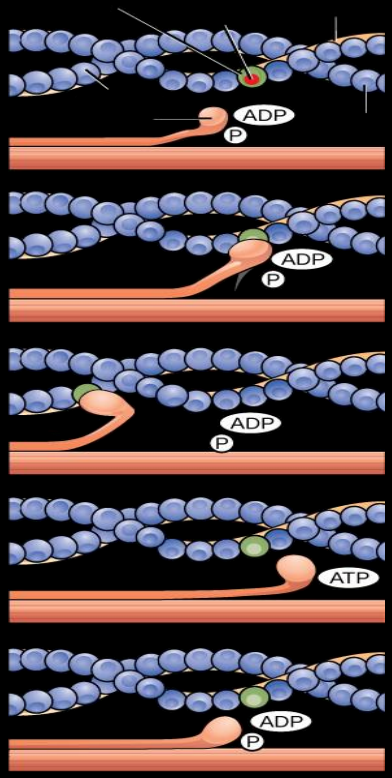
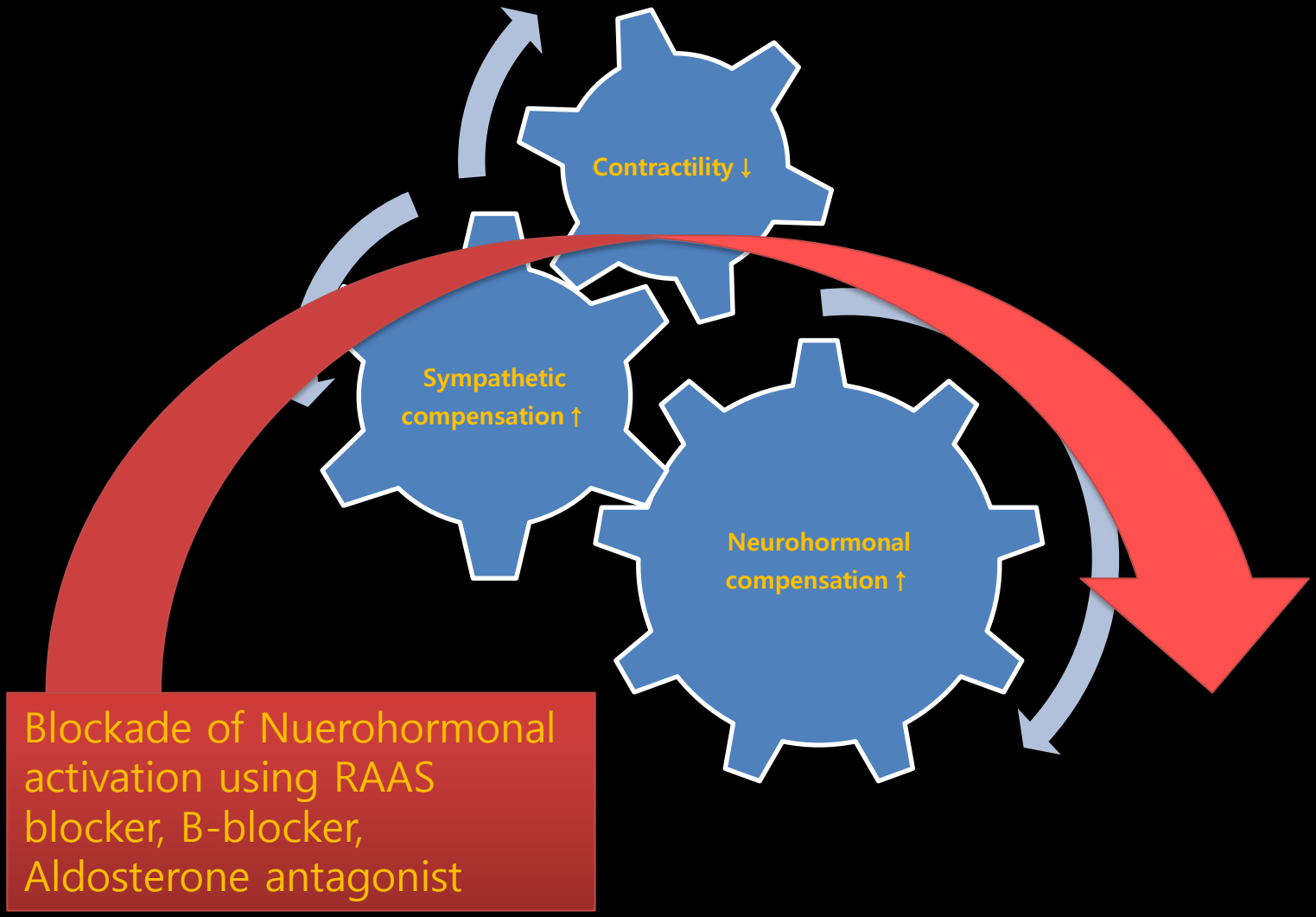
Cardiac Myosin Activator in Heart Failure



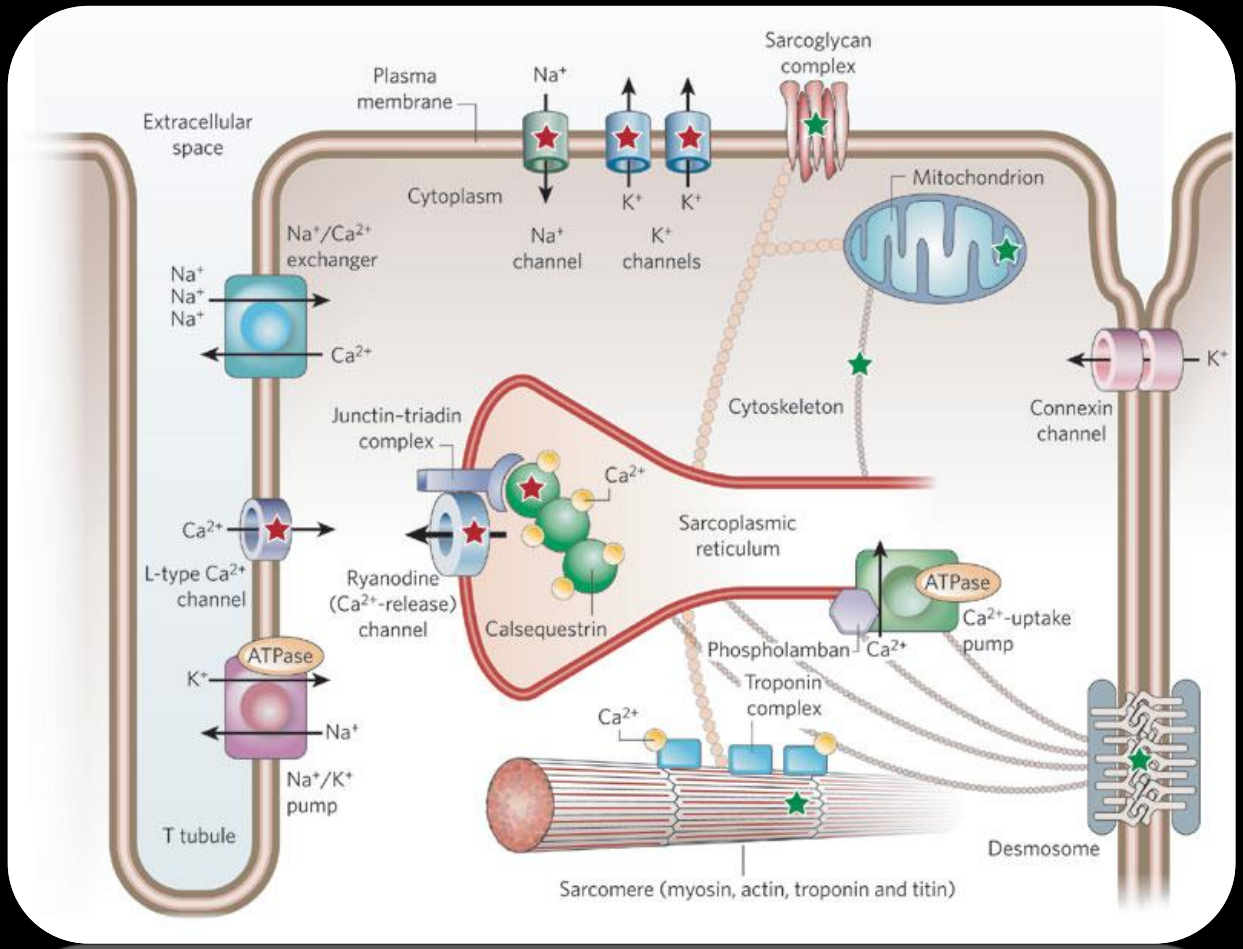


Choi seonghoon
Cardiology
Hallym University College of Medicine

HF treatment



Cardiac Excitation-contraction Coupling



Contraction

L-type Ca^{2+} channel

Na^{+}/Ca^{2+} exchange

Ryanodine receptor(RYRe)

: Ca2+ transient

Ca^{2+} -TroponinC

Relaxation

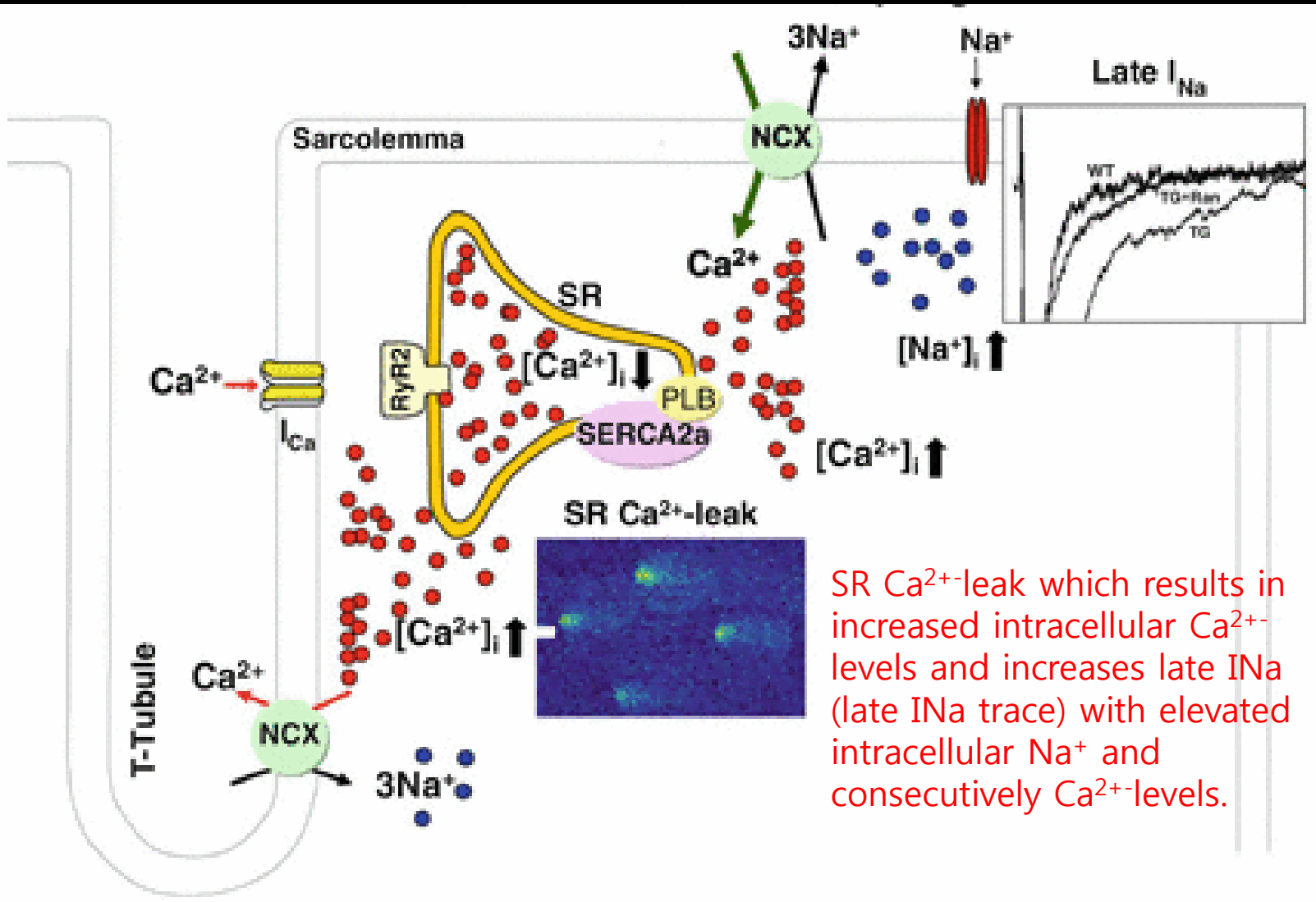
70% Ca^{2+} - SR Ca^{2+}ATPase(SERCA2a) → SR

28% Na^{+}-Ca^{2+} exchanger(NCX) → Extraccellular

<2% Ca^{2+} ATPase or mitrochondrial ca^{2+} uniport

Bers DM et al Nature 2002 Björn C. Nature 451, 929-936 2008)

Cardiac Excitation-contraction Coupling in HF myocardium



SR Ca^{2+}-leak which results in increased intracellular Ca^{2+}-levels and increases late INa (late INa trace) with elevated intracellular Na^+ and consecutively Ca^{2+}-levels.

Classic Inotropes

On Cardiac contraction/relaxation

- Hemodynamics, physiologic approach
- Inotrope : improvement & stabilization in hemodynamically unstable cases

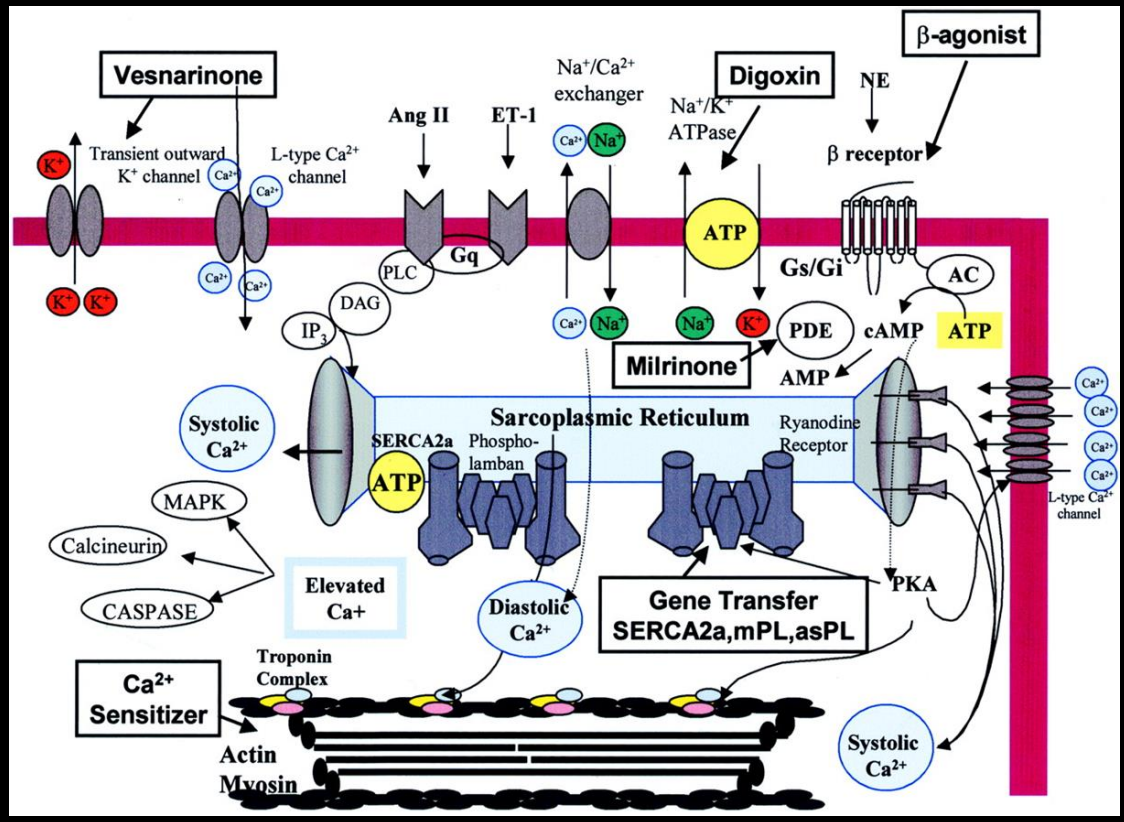
Classical inotropes

① Na^+/K^+ ATPase pump inhibitor : digoxin

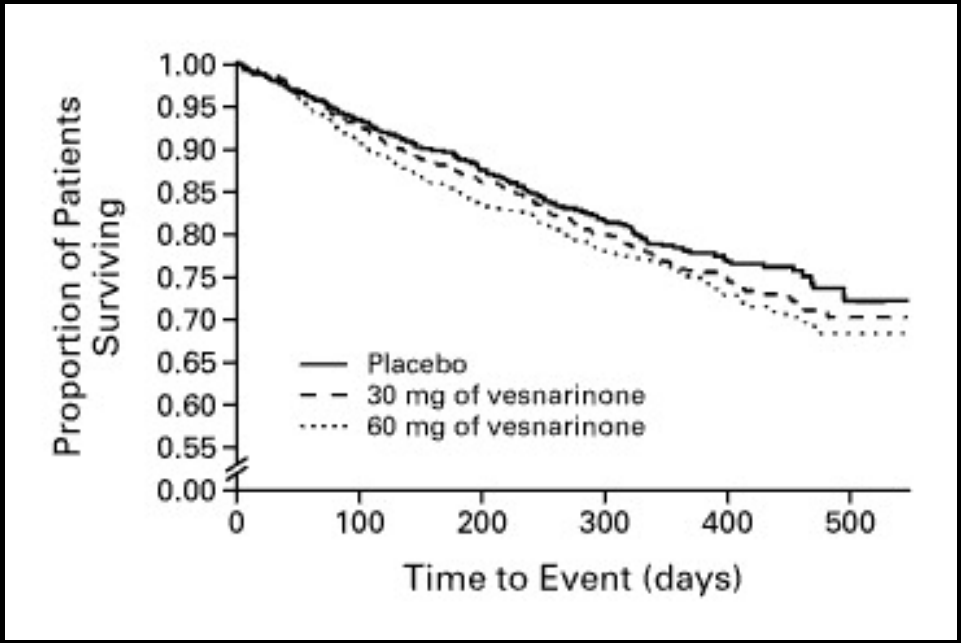
② β-adrenergic receptor agonist : β-agonists

③ Phosphodiesterase inhibitors : PDEI,

cAMP or intracelluar Ca^{2+} increase



A Dose-Dependent Increase in Mortality with Vesnarinone among Patients with Severe HF



Adverse effect or ↑ mortality

due to arrhythmia, myocardial ischemia, ↑ cardiac O_2 consumption

N Engl J Med 1998; 339:1810-1816

Indirect to Direct

B

Direct Mechanisms

Directly target the sarcomere

Ø PKA activation

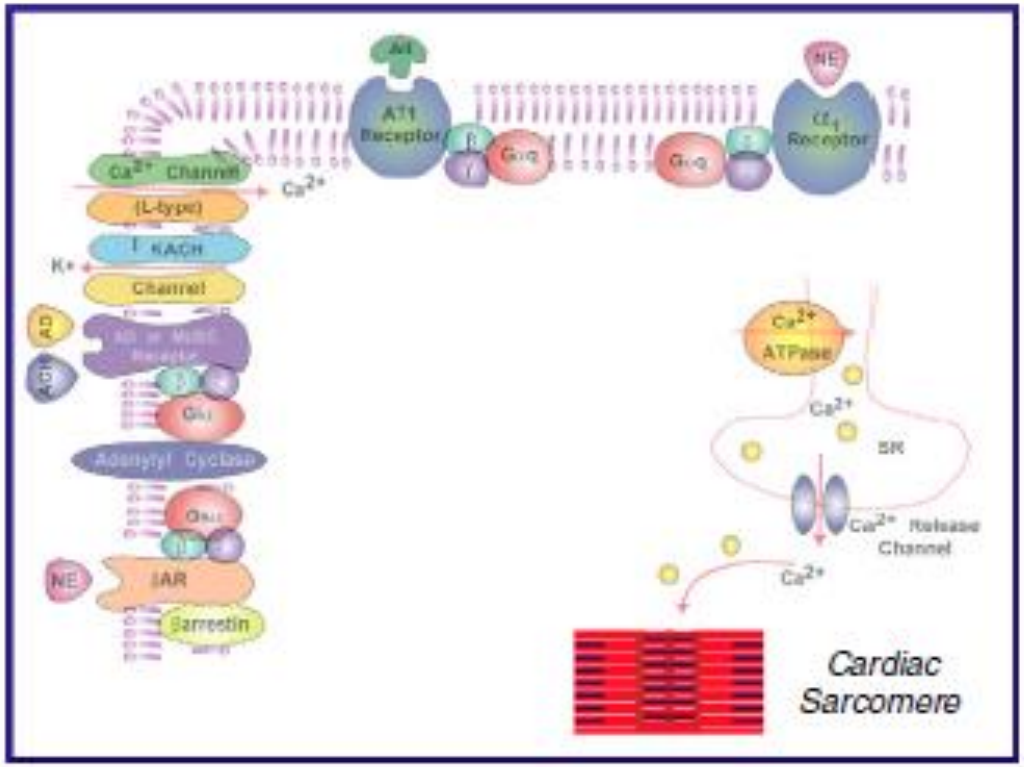
↓

Intracellular [Ca^{2+}] unchanged

↓

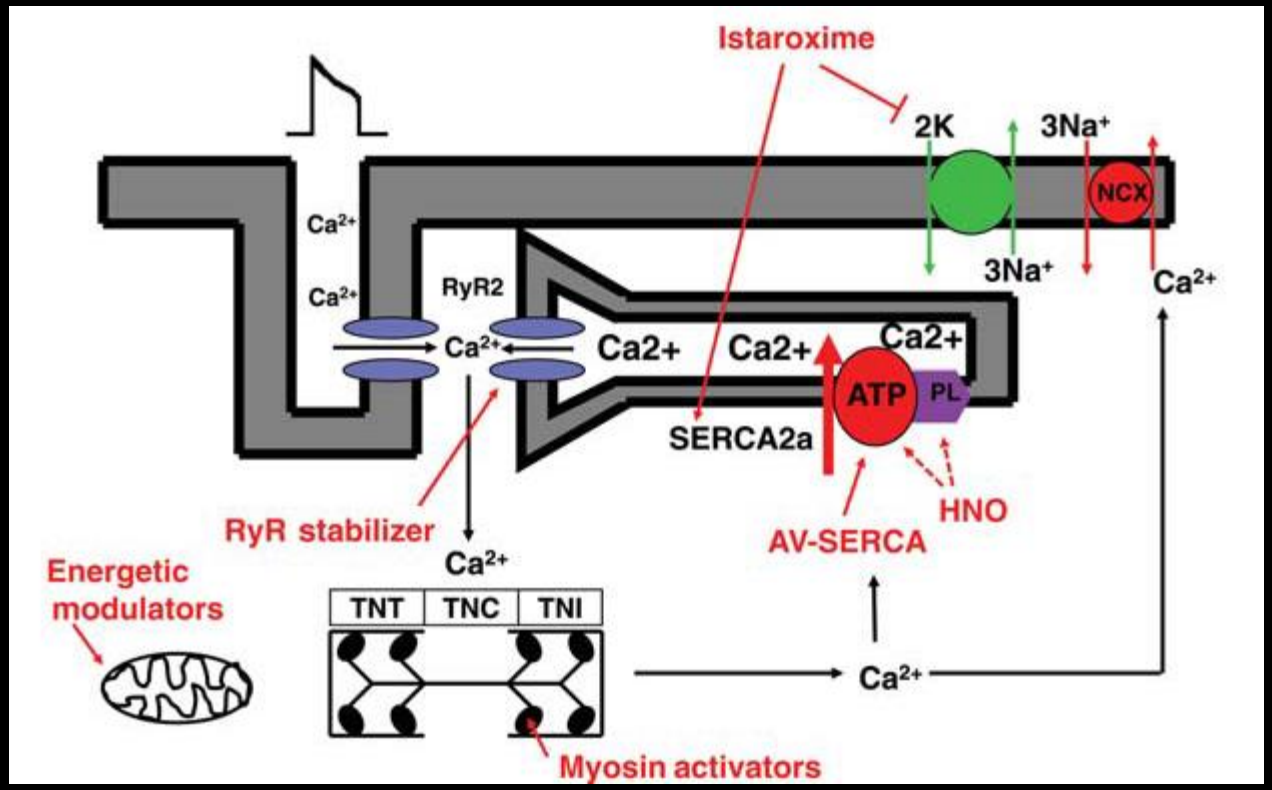
- ↑ Contractility
- ↔ Heart rate?
- ↔ Blood Pressure?
- ↔ O_2 Demand?
- ↑ Efficiency?
- ↔ Arrhythmias?

Effective Drug?



Newly developed inotropes

- Calcium sensitizer ; Levosimendan
- SERCA 2a stimulator (by inhibition of Na^+/K^+ ATPase pump; Istaroxime)
- Cardiac myosin activator (omecamtiv mecarbil: CK-1827452)

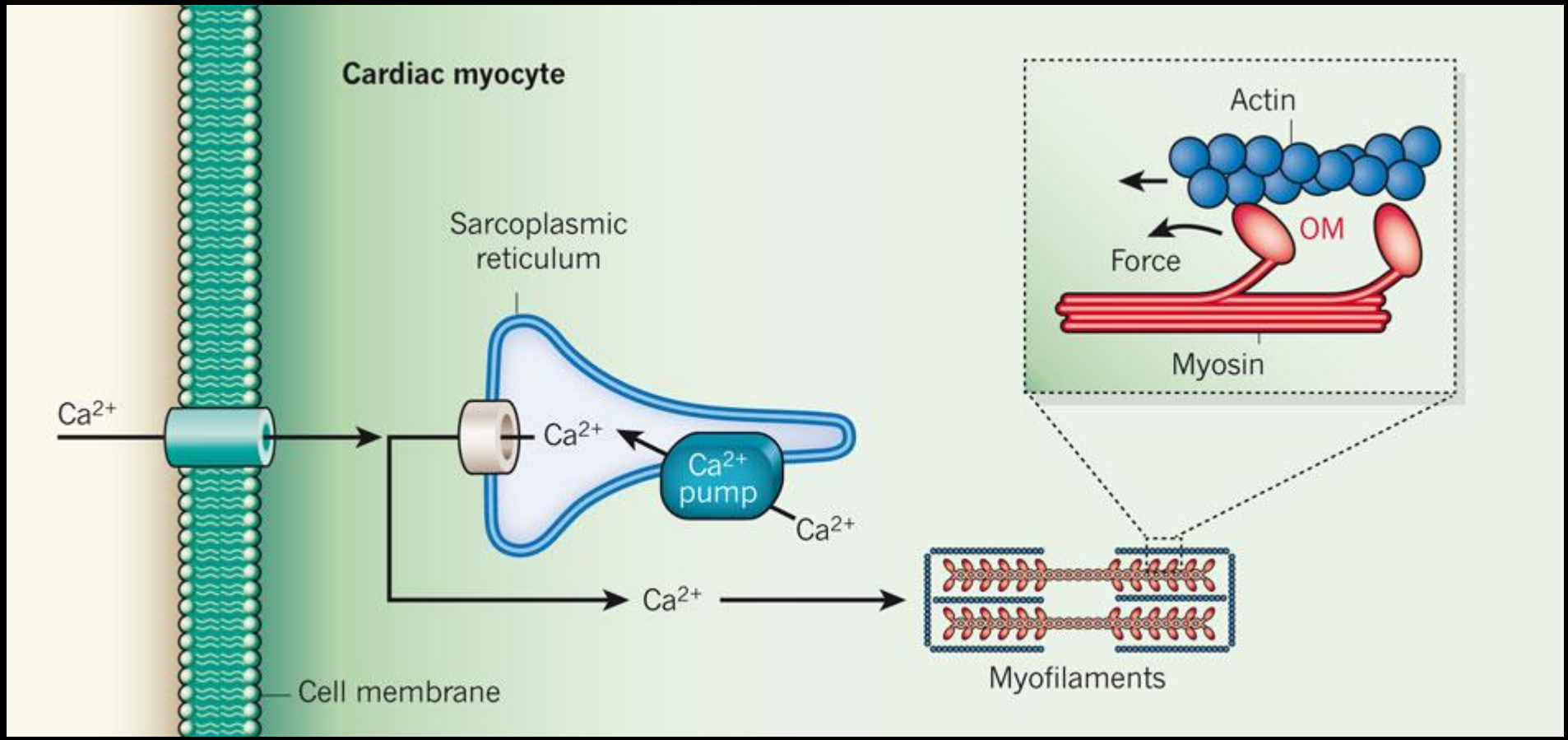


Inotrope - abstract

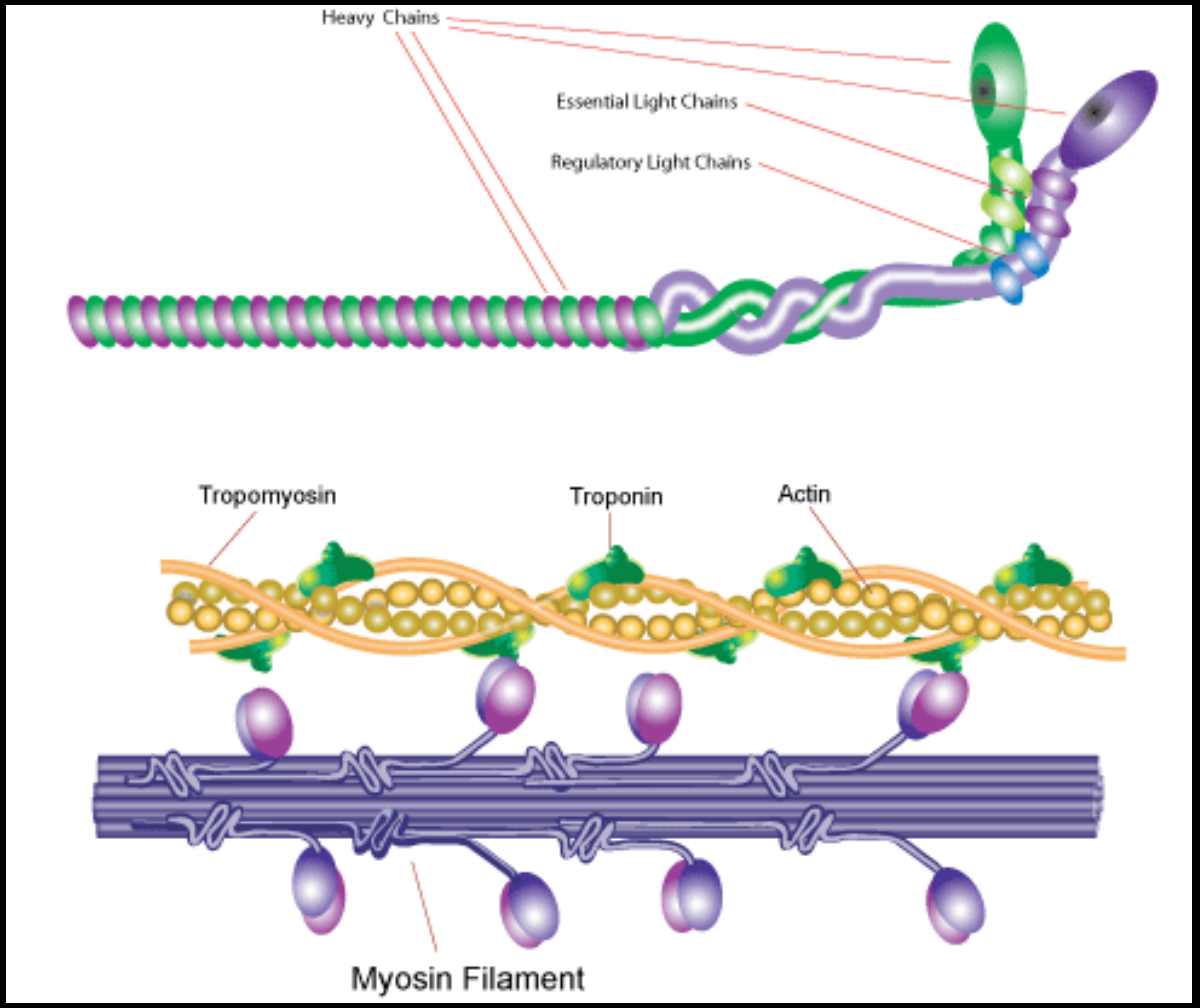
Inotrophic mechanism	Drugs
Na-K-ATPase inhibition	Digoxin
B-adrenergic stimulation	Dobutamine, dopamine
Phosphodiesterase inhibition	Enoximone, Milrinone
Calcium sensitization	Levosimendan
Na-K-ATPase inhibition + SERCA activation	Istaroxime
Acto-myosin cross-bridge activation	Omecamtive mecarbil
SERCA activation	Gene transfer
SERCA activation + vasodilation	Nitroxyl donor;CXL-1020
Ryanodine receptor stabilization	Ryanodine receptor stabilizer:S44121
Energetic modulation	Ectomoxir, pyruvate

Hasenfus G. et al, Eur Heart J 2011

Cardiac myosin activators



Myosin : ATP hydrolysis



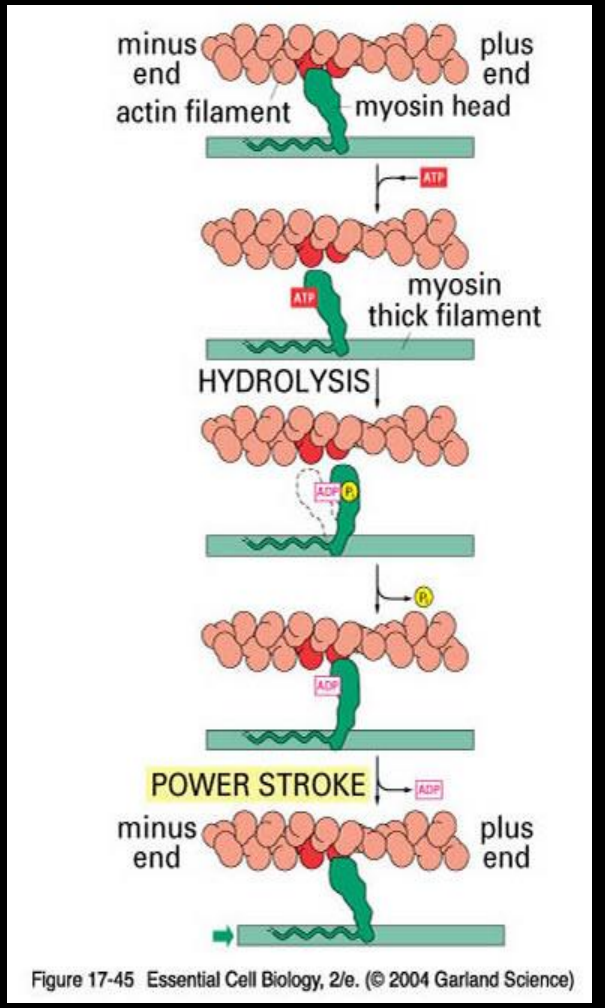
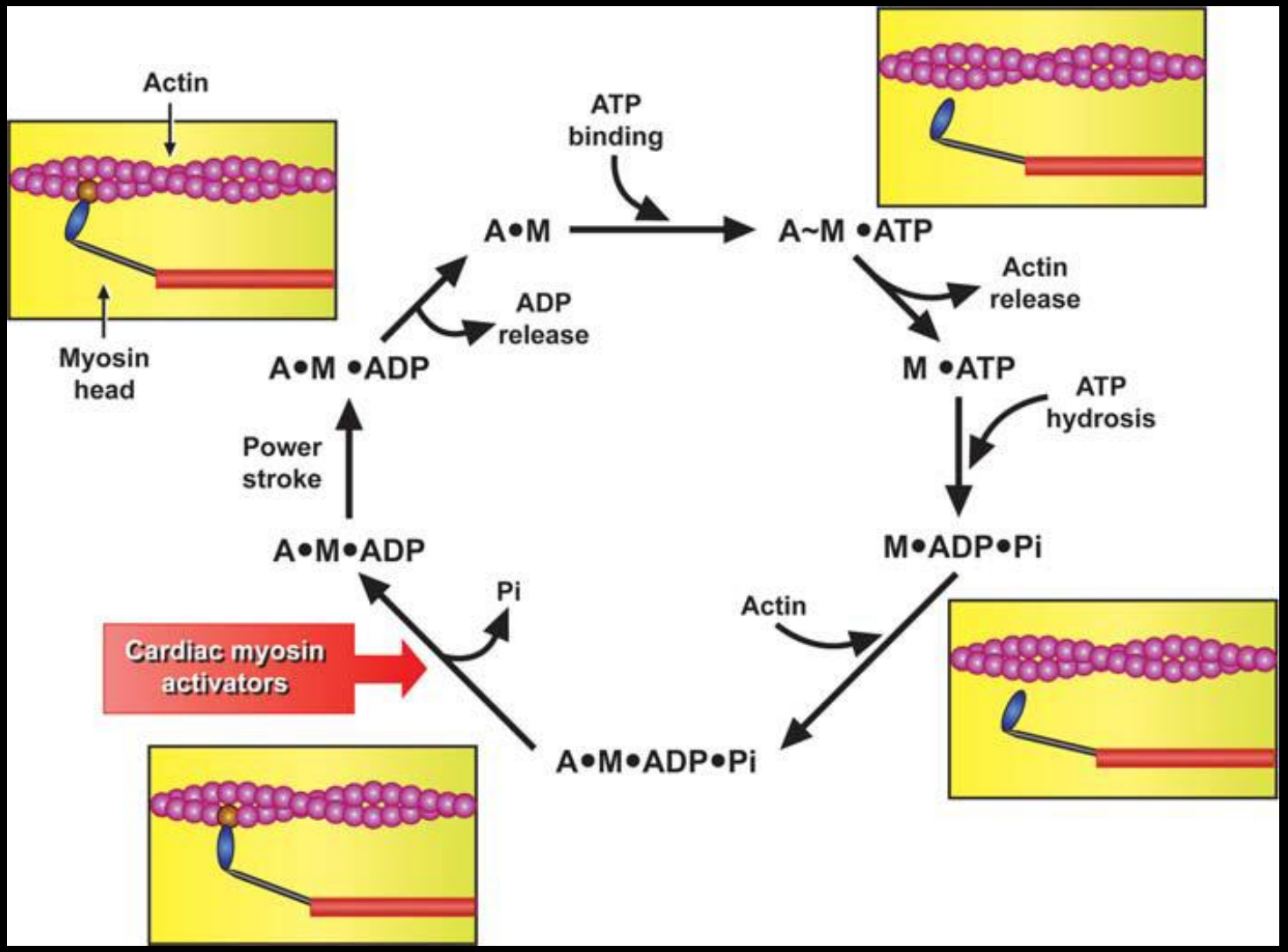


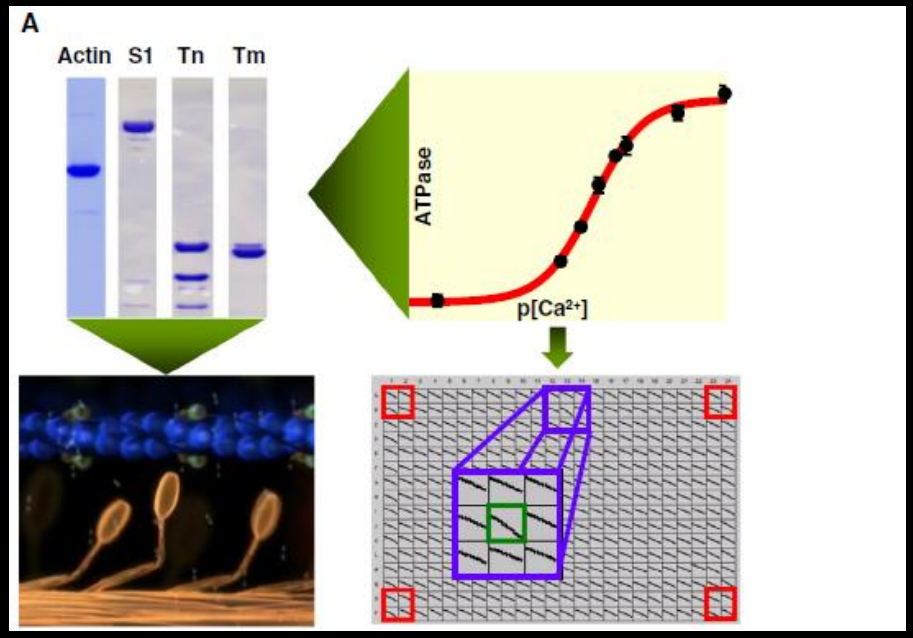
Figure 17-45 Essential Cell Biology, 2/e. (© 2004 Garland Science)

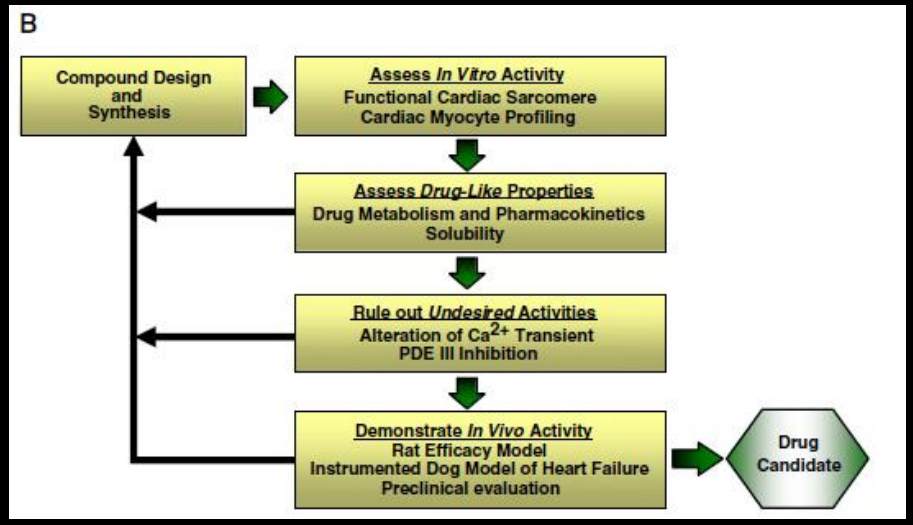
Mode of action of cardiac myosin activators



History

- 1998 inhibitors for mitotic kinesin
- Rather activation of biochemical activity of microtubule-based motor protein

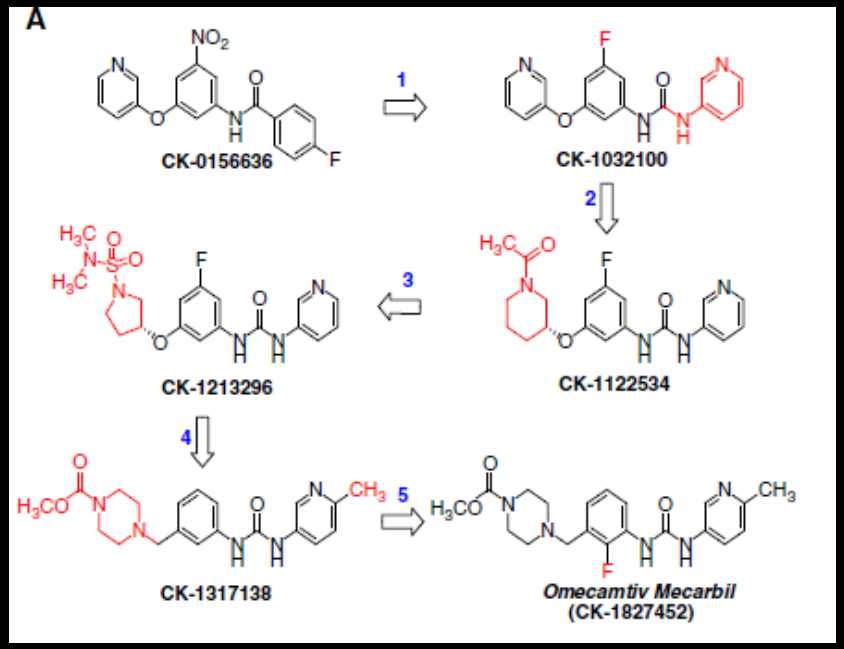


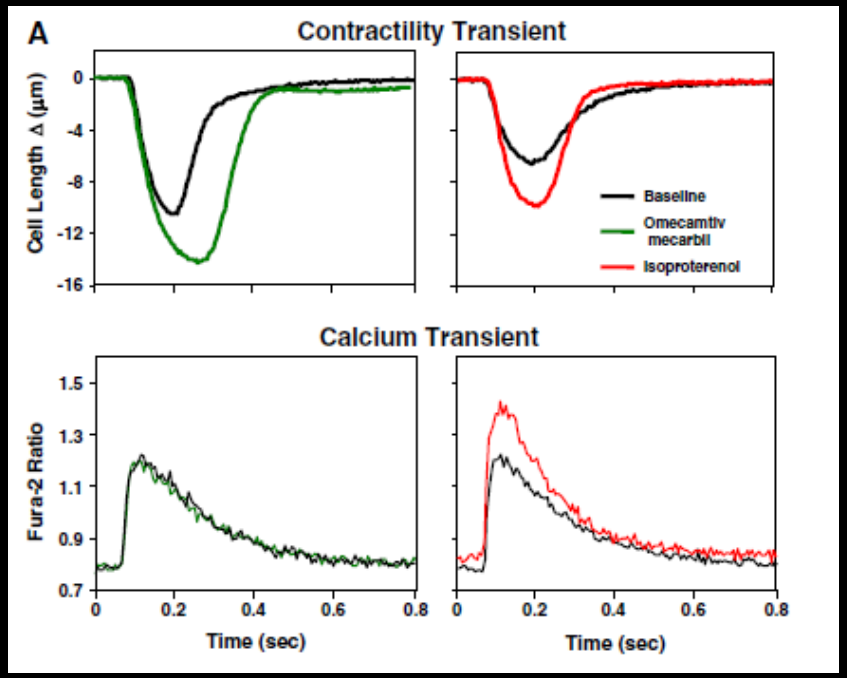


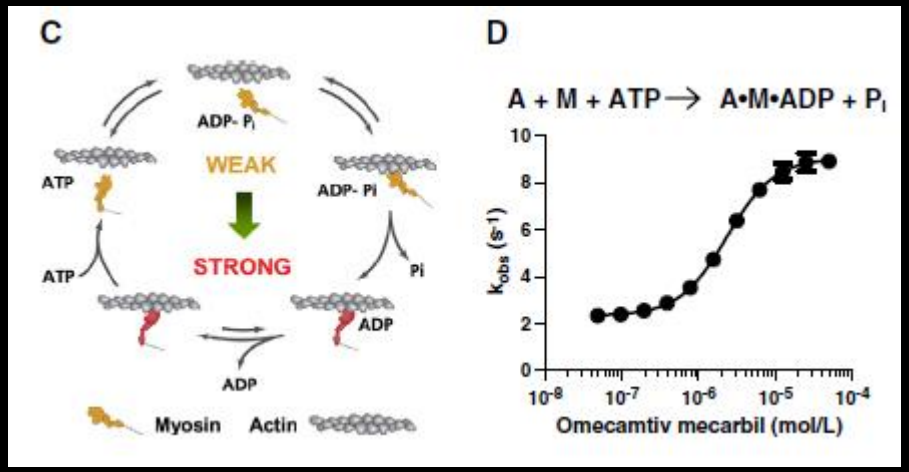
Fady I Malik, Bradley P.Morgan

Cardiac myosin activators

- Cardiac myosin ATPase activity with dose-dependent manner
- Direct influence on cross-bridge cycle
  - ① A … elease
  - ② W
  - ③ P … -bridge
  - ④ In … hosphate re
  - ⑤ R
- More … e cross-bridge … ce increases
- CK-0689705, CK-1122534, CK-1213296, and CK-1827452(omecamtiv mecarbil)


A
CK-0156636
CK-1032100
CK-1213296
CK-1122534
CK-1317138
Omecamtiv Mecarbil
(CK-1827452)


A
Contractility Transient
Cell Length Δ (μm)
Baseline
Omecamtiv mecarbil
Isoproterenol
Calcium Transient
Fura-2 Ratio
Time (sec)
Time (sec)

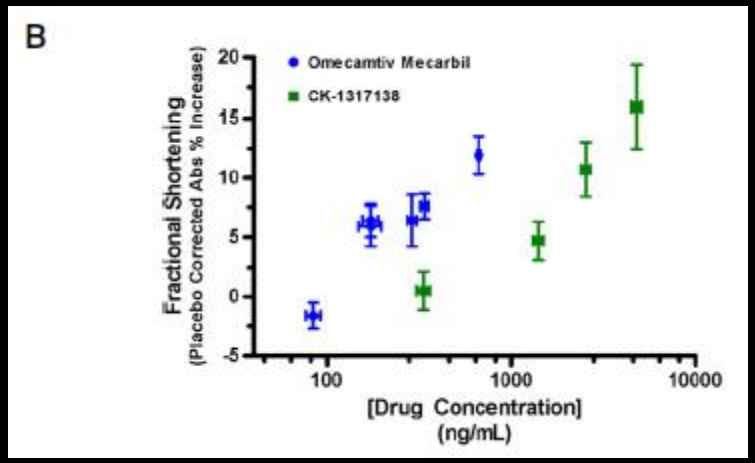

C
ADP- Pi
WEAK
ATP
ADP- Pi
STRONG
ATP
Pi
ADP
ADP
Myosin
Actin
D
A + M + ATP → A•M•ADP + Pi
kobs (s-1)
Omecamtiv mecarbil (mol/L)

Omecamtiv mecarbil

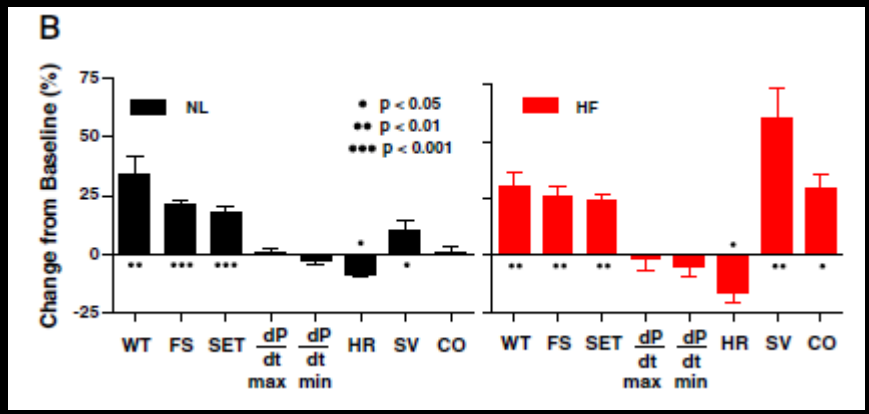
Two Dog model

① tachycardia-pacing-induced failure on top of myocardial infarction,

② pressure overload by constriction of the ascending aorta



- ↑SV, CO, and ↓LV EDP, HR.
- ↑LV systolic ejection time (SET) by 26%.
- Not associated with increased myocardial oxygen consumption.



YT Shen et al. Circ Heart Fail. 2010;3:522-527

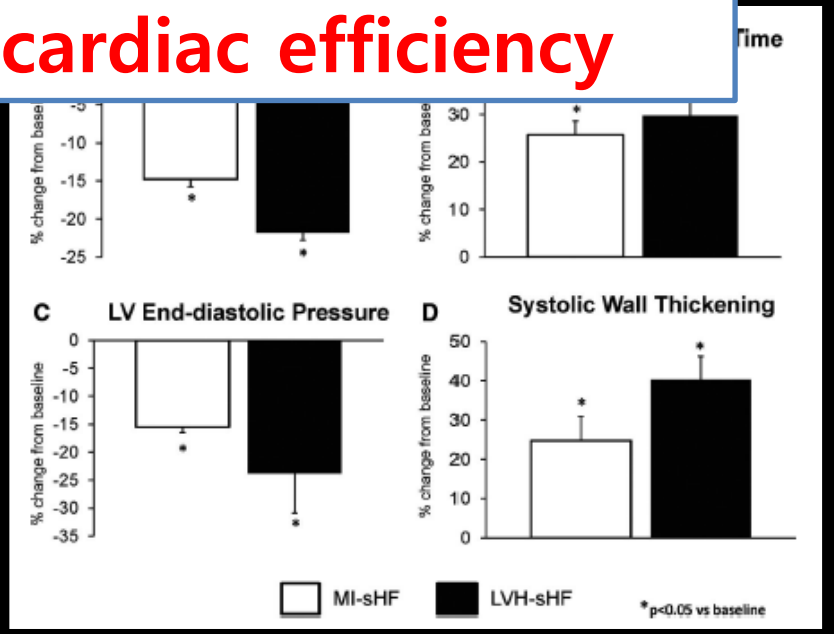
Table 2. Effects of Omecamtiv Mecarbil on LV Function in Conscious Dogs With MI-sHF

	n	Baseline	Omecamtiv Mecarbil Infusion (% Change From Baseline) 15 Minutes	4 Hours	24 Hours	72 Hours (n)‡
Mean arterial pressure, mm Hg	6	87±5.0	1.4±3.3	−2.5±1.5	−0.6±1.6	−3.6±2.2 (4)
Heart rate, beats/min	6	143±7.1	−15±3.5*	−12±2.7*	−15±3.0*	−12±3.5 (4)
Mean left atrial pressure, mm Hg	5	25±0.9	−25±7.0*	−19±4.7*	−12±1.3	−10.6±5.9 (4)
LV systolic ejection time, ms	6	156±5.7	23±4.8*	19±1.2*	26±2.9*	32±5.0 (4)
LV systolic pressure, mm Hg	6	101±5.2	4.9±1.9	−0.2±2.7	1.3±3.9	−2.2±3.5 (4)
LV end-diastolic pressure, mm Hg	6	28±2.4	−14±4.6*	−17±3.5*	−16±3.5*	−14±4.8 (4)
LV dP/dt max, mm Hg/s	6	1663±111	4.5±2.5	0.2±3.2	2.4±5.9	6.6±8.4 (4)
Systolic wall thickening, mm	6	1.5±0.2	18±5.2*†	24±5.8*	25±6.2*	41±9.4 (4)
Cardiac output, L/min	5	1.5±0.17	8±5.7	16±6.9	22±2.8*	32±8.2 (3)
Stroke volume,						±7.8 (3)
Total peripheral						±3.6 (3)

Stroke work 60% ↑ /no MVo2 increase
➔ 30% increase of cardiac efficiency

Table 3. Effects of Omecamtiv Mecarbil on MVO_2 in Conscious Dogs With MI-sHF

	n	Baseline	Omecamtiv Mecarbil Infusion 15 Minutes	4 Hours	24 Hours
Coronary blood flow, mL/min	6	34±5	36±6	36±6	37±6
Arterial O_2 content, mL/dL	5	15±1	16±2	15±1	15±0.7
Myocardial O_2 consumption, mL O_2/min	5	3±0.3	3±0.4	3±0.4	4±0.3
Coronary sinus O_2 content, mL/dL	5	4±1	5±1	4±0.8	4±0.4



YT Shen et al. Circ Heart Fail. 2010;3:522-527

Desirable effect

- Improving cardiac contraction without ↑ intracellular Ca^{2+}
  Decreasing of known adverse effect of classic inotropes (myocardial ischemia, arrhythmia, hypotension)

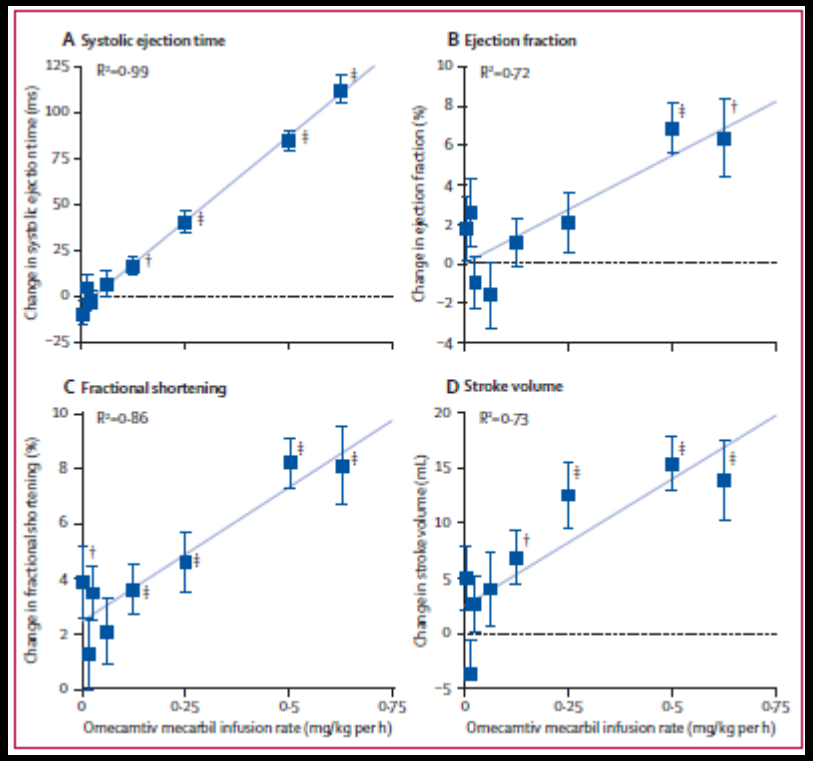
- Systolic ejection time increase (↑ duration of contraction)

- No change of velocity of contraction(dP/dt)

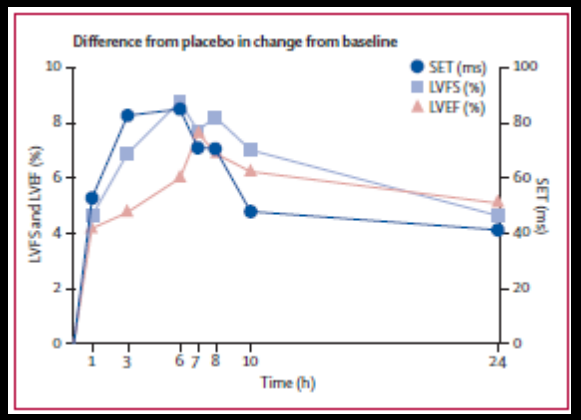
- Clinical merit : Improve cardiac function without compromising myocardial oxygen demand given the absence of changes in cellular calcium homeostasis

Phase I study

- dose-escalating, crossover study, 34 healthy men received a 6-h double-blind intravenous infusion of omecamtiv mecarbil or placebo once a week for 4 weeks.



MTD of 0.5 mg/kg/h



LVEF 6.8%
(P<0.0001
FS 9.2%
(p<0.0001)

No clinical relevant change in Diastolic function or
No significant dose-related adverse effect
The dose-limiting toxic effect : myocardial ischemia due to excessive prolongation of systolic ejection time

Teerling JR et al. J Card Fail 2006;12:763.

Phase I study

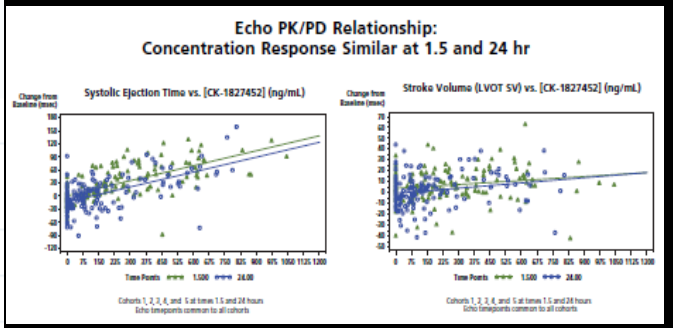
- Dose of 0.75 and 1.0 mg/kg/h : signs and symptoms of myocardial ischemia most likely due to excessive prolongation of the systolic ejection time, causing decreased diastolic coronary perfusion and decreased diastolic filling.

Phase II study

- multi-center, double-blind, placebo controlled trial sought to assess the effects of CK-452 in patients with stable heart failure.
- LVEF < 40% with ACEI(or ARB) and BB ± diuretics
- 3 infusion with escalating dose 1-week apart

		Placebo Corrected Changes from Baseline						P-Value for Correlation versus [CK-1827452]
[CK-452] (ng/mL)		1-100	>100-200	>200-300	>300-400	>400-500	>500-833	
Observations (n)		69	50	32	19	30	20	
	Baseline							
SET (ms)	318	3 ± 4	24 ± 5‡	54 ± 5‡	65 ± 7‡	72 ± 8‡	98 ± 7‡	p < 0.0001
SV (mL)	68	1 ± 2	1 ± 2	6 ± 2⋆	12 ± 3‡	14 ± 3‡	14 ± 3‡	p < 0.0001
FS (%)	17	1 ± 1	2 ± 1⋆	3 ± 1†	4 ± 1†	3 ± 1#	4 ± 1‡	p < 0.0001
EF (%)	32	0 ± 1	0 ± 1	1 ± 1	1 ± 1	1 ± 1	2 ± 1	p < 0.05

Least Squares Mean ± SEM #p ≤ 0.05 ⋆p ≤ 0.01 †p≤0.001 ‡p≤0.0001.



- HR : slight decline, no dose-related change in BP

Cleland JGF, et al J Card Fail 2008;14:67

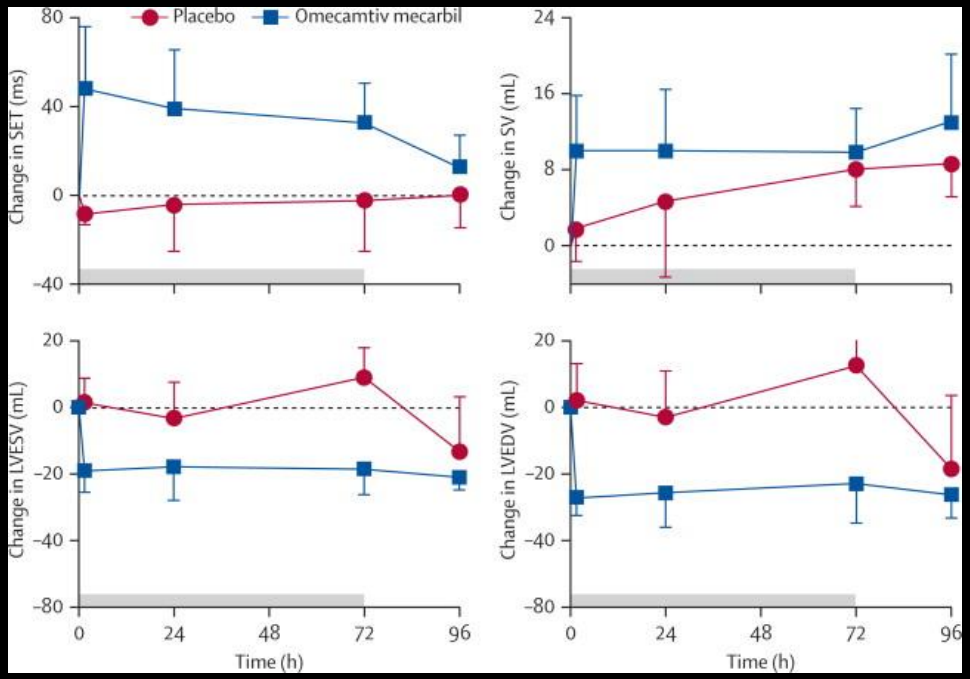
Phase II trial

- double-blind, placebo-controlled, crossover, dose-ranging,
- IV for 2, 24, or 72 h
- Stable systolic HF LVEF <40%, N=45

	Patient n=45
Sex	Male 39(87%) Female 6(13%)
Cause	Ischemic 29(64%) non-ischemic 16(36%)
ACEI or ARB	98%
BB	98%
LVEF	33%

Lancet. 2011 Aug 20;378(9792):676-83.

Phase II trial



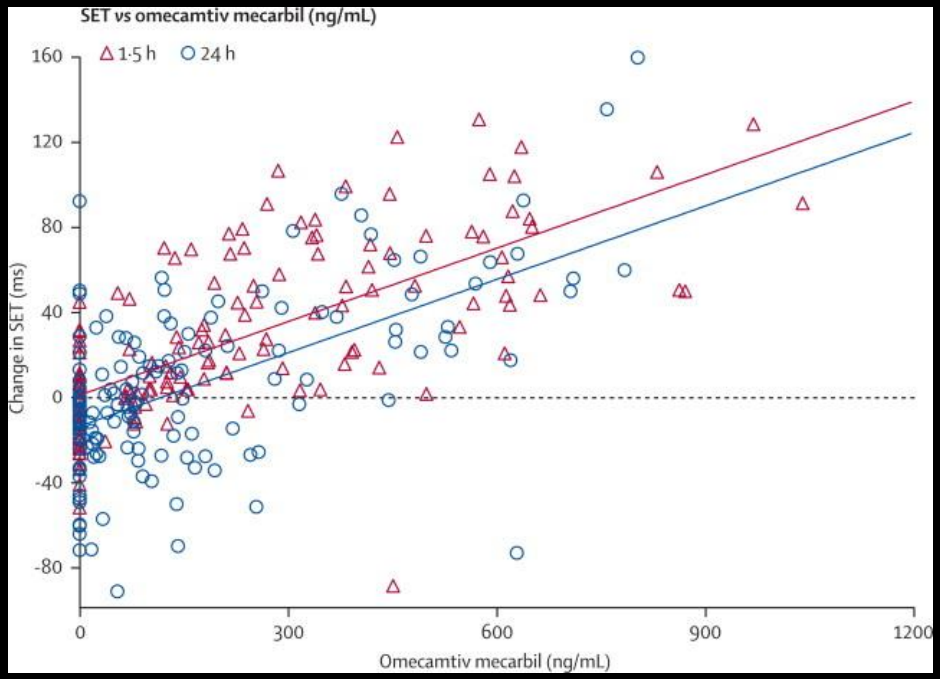


Figure 1 Time-
gram measure
ons of omecam
ow SEM. Patie

ystolic ejection time in
from baseline plotted f
east squares linear reg

Increase Stroke volume in patients with systolic HF

Lancet. 2011 Aug 20;378(9792):676-83.

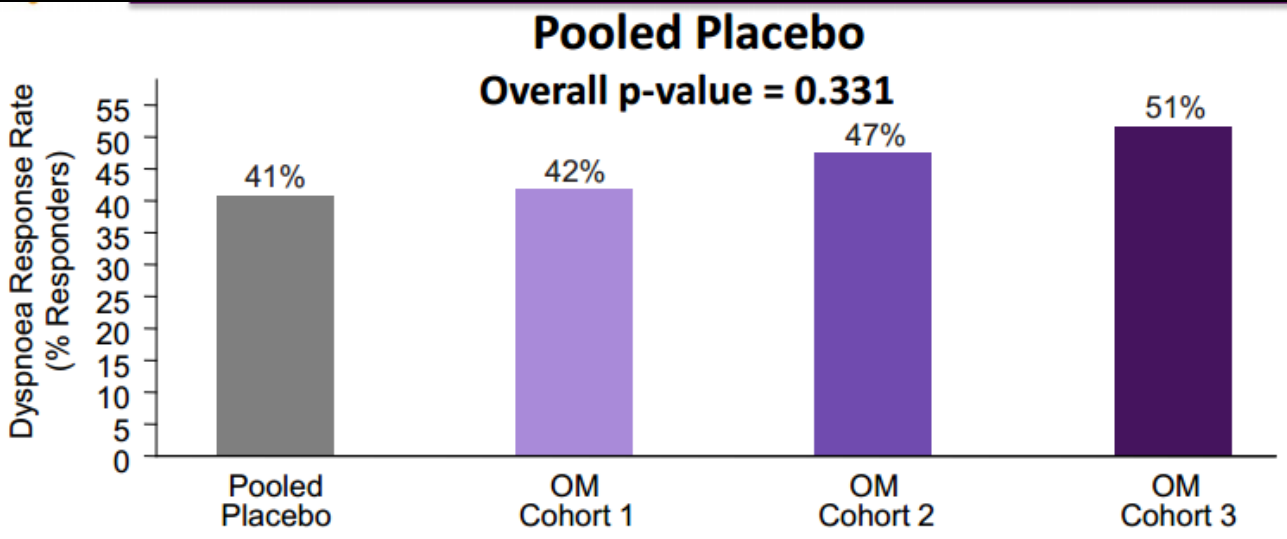
Phase IIb trial

- Acute Treatment with OM to Increase Contractility in Acute Heart Failure (ATOMIC-AHF) study
- Hospitalized HF patients due to acute HF(n=613), systolic dysfunction
- 48 hours IV infusion with three ascending dose cohorts or placebo
- Primary efficacy end point : effect of OM on dyspnea
- Secondary end points : safety, tolerability and effects on additional measures of dyspnea, patients' global assessments, change in NT-proBNP and short-term clinical outcomes

A Phase 2 Study of Intravenous Omecamtiv Mecarbil, A Novel Cardiac Myosin Activator, In Patients With Acute Heart Failure

John R. Teerlink, G. Michael Felker, John J. V. McMurray, Piotr Ponikowski, Marco Metra, Gerasimos S. Filippatos, Kenneth Dickstein, Justin A. Ezekowitz, John G. Cleland, Jae B. Kim, Lei Lei, Beat Knusel, Andrew A. Wolff, Fady I. Malik and Scott M. Wasserman
on behalf of the ATOMIC-AHF Investigators and Patients

Primary Efficacy points



Exploratory Analyses: Dose and Concentration Relationship

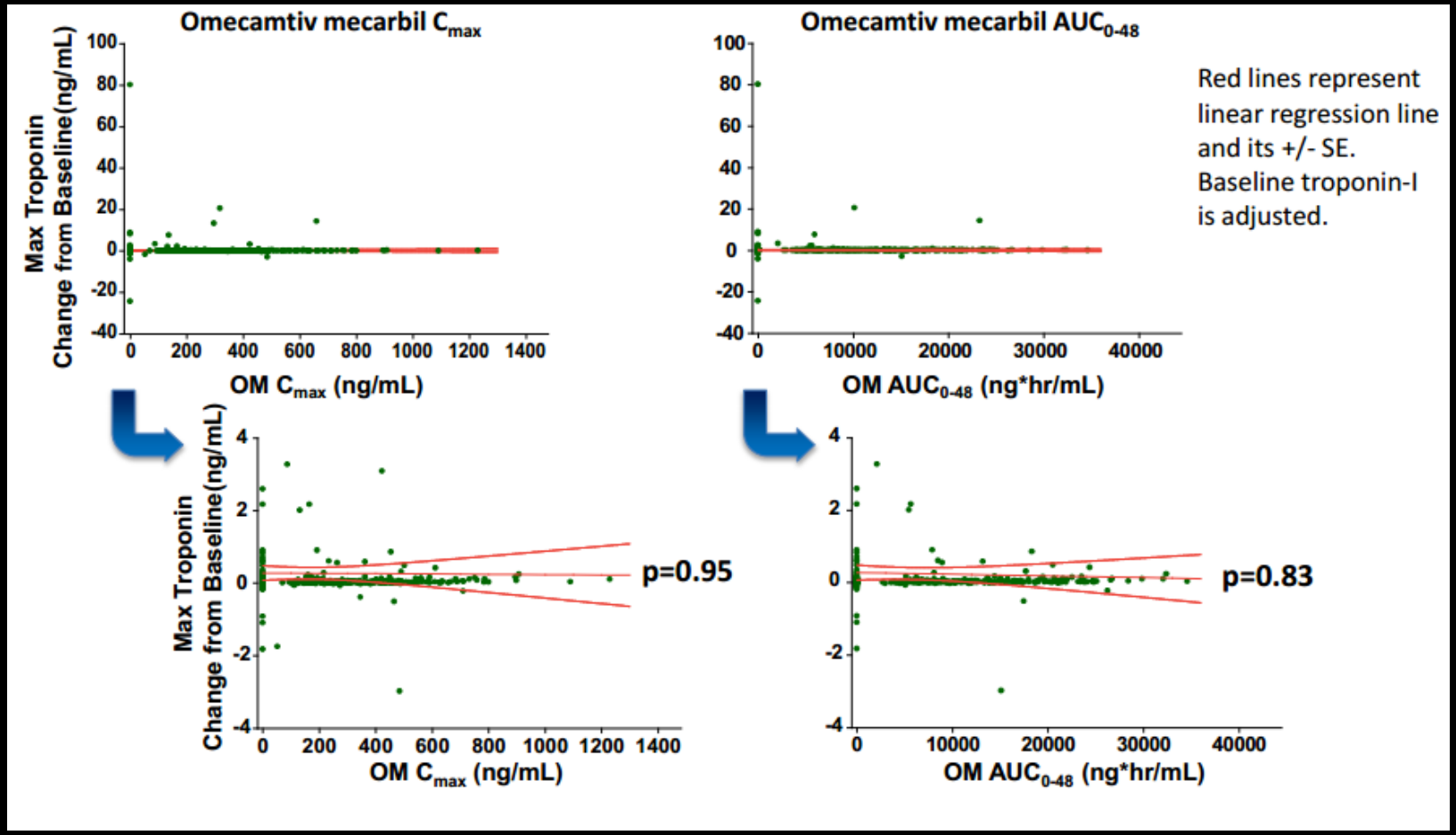
Dose & Concentration-Response	For Increases of…	Response Rate Ratio Increases…	95% CI	P-value
Dose*	50 mg total OM administered	5.5%	0.7% – 10.6%	0.025
Plasma concentration*	4000 hr*ng/mL AUC48h	6.4%	1.7% – 11.4%	0.007

Post-random Adjudicated Events

Patient Incidence, n (%)	Pooled Placebo (N = 303)	Pooled OM (N = 303)	Cohort 1 OM (N = 103)	Cohort 2 OM (N = 99)	Cohort 3 OM (N = 101)
Death	**10 (3.3)**	**8 (2.6)**	**1 (1.0)**	**4 (4.0)**	**3 (3.0)**
Cardiovascular	10 (3.3)	8 (2.6)	1 (1.0)	4 (4.0)	3 (3.0)
ACS/MI (fatal)	0	1 (0.3)	0	0	1 (1.0)
All Rehospitalisations	**37 (12.2)**	**29 (9.6)**	**11 (10.7)**	**11 (11.1)**	**7 (6.9)**
Acute MI	1 (0.3)	1 (0.3)	1 (1.0)	0	0
Unstable angina	0	0	0	0	0
Heart failure	19 (6.3)	22 (7.3)	6 (5.8)	11 (11.1)	5 (5.0)
Other	18 (5.9)	7 (2.3)	4 (3.9)	0	3 (3.0)
All Index hospitalisation MI (non-fatal)	**2 (0.7)**	**5 (1.7)**	**1 (1.0)**	**0**	**4 (4.0)**
Investigator reported	0 (0.0)	2 (0.7)	0 (0.0)	0	2 (2.0)
Troponin triggered	2 (0.7)	3 (1.0)	1 (1.0)	0	2 (2.0)
Total MIs (Fatal + Rehosp + Nonfatal Index Hosp)	**3 (1.0)**	**7 (2.3)**	**2 (1.9)**	**0**	**5 (5.0)**

ACS/MI = Acute Coronary Syndrome/Myocardial Infarction. 66 patients had 73 positively adjudicated rehospitalisations.

OM Concentration vs. Troponin-I maximal change from baseline



PK/PPD substudy Endopoint: Change in Systolic Ejection Time(SET)

PK Concentration Bin Analysis	Control	OM Concentration Bin 1	OM Concentration Bin 2	OM Concentration Bin 3
OM concentration range (ng/ml)		≥88-200	>200-300	>300-787
Change in SET (msec)				
N(n)	45 (88)	10 (18)	15 (23)	12 (19)
LS mean	-6.7	16.6	26.9	46.4
Difference from control		23.4	33.6	53.2
95% CI		(7.4, 39.4)	(19.8, 47.4)	(38.0, 68.3)
p-value		0.005	<0.0001	<0.0001
Linear regression slope	$p < 0.0001$			

Baseline systolic ejection time for all patients was 258 msec. N: number of patients in the bin, n: number of observations in the bin; Control = observations in Placebo + PK below quantification limit; PK bin concentration analysis: repeated measures analysis of covariance; Linear regression slope analysis: repeated measures multiple linear regression.

ATOMIC –AHF Summary

- Efficacy

① OM did not meet Primary endpoint of dyspnea itself
② Trends toward reduction of worsening HF

- Safety

① Overall SAE profile and tolerability similar to placebo
② Increase in Troponin; no clear relationship to OM concentration
③ No evidence of Pro-arrhythmia

- Pharmacology

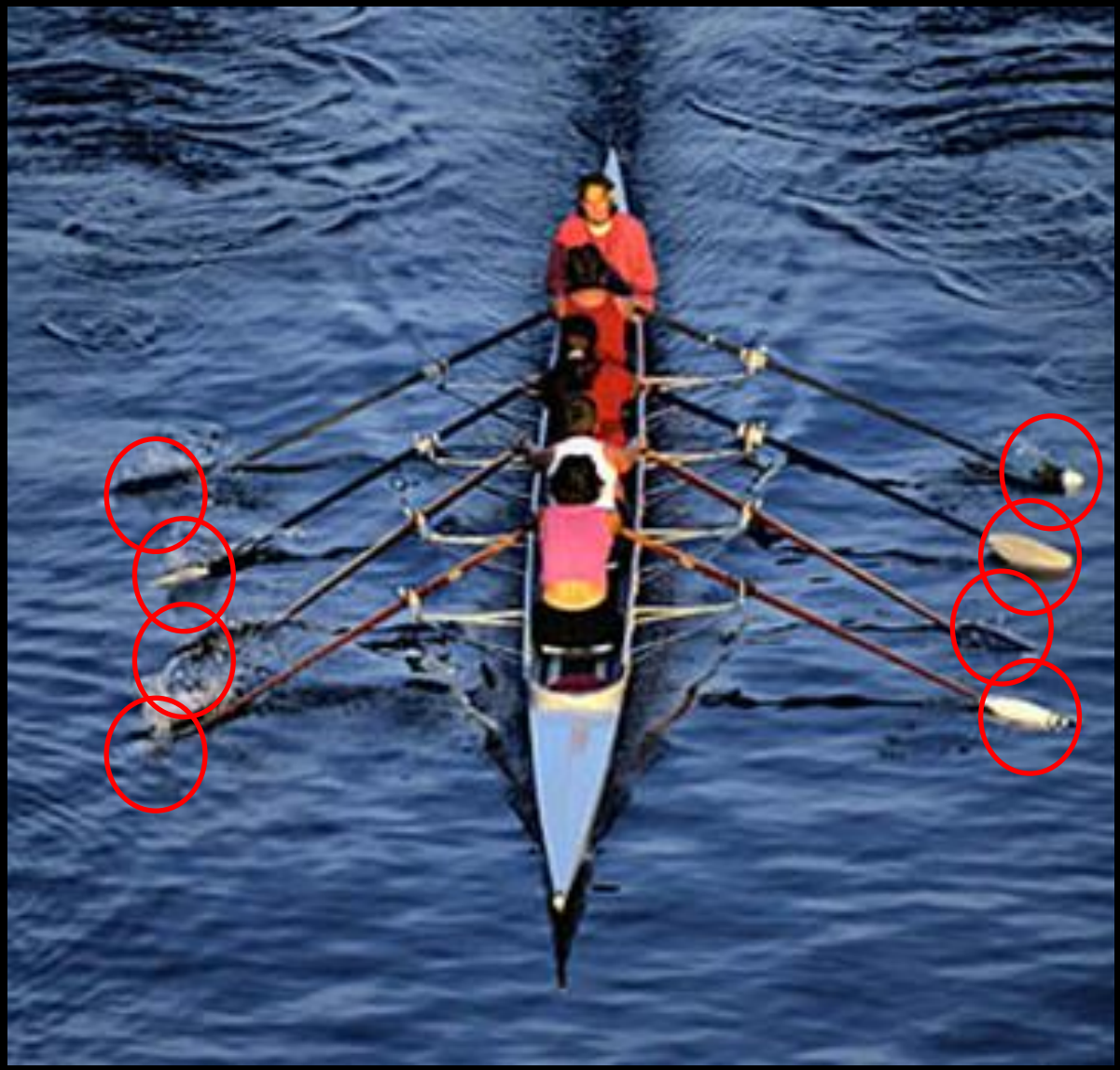
① PK similar to healthy volunteers and stable HF
② Systolic ejection time significantly increased consistent with MOA
③ Small fall in HR & rise in systolic BP at higher dose

On –going trial

- Double blind randomized placebo-controlled dose-finding trial
- COSMIC-HF(Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure)
- To select an oral modified release (MR) formulation and dose of OM for chronic twice daily (BID) dosing in subjects with HF and left ventricular systolic dysfunction (LVSD)
- To characterize its pharmacokinetics (PK) after 12 weeks of treatment

In Summary

- Classical Inotropes has limited effect on HF
- New agent targeting Systolic dysfunction without cAMP or Ca2+ is on developing state
- Omecamtive mercarbil is unique new drug for enhancing actin-myosin contraction with ATPase activity and effective contraction
- Animal & Phase I-II study showed enhanced SV, SET without increasing adverse effects (except higher dose).
- But phase IIb Study on Acute decompensated HF patients did not show improving Primary outcome(dyspnea).
- Another study for chronic stable HF is need & on-going(COSMIC-HF)



Thank you for your attention !!