New inotropes in the management of acute heart failure

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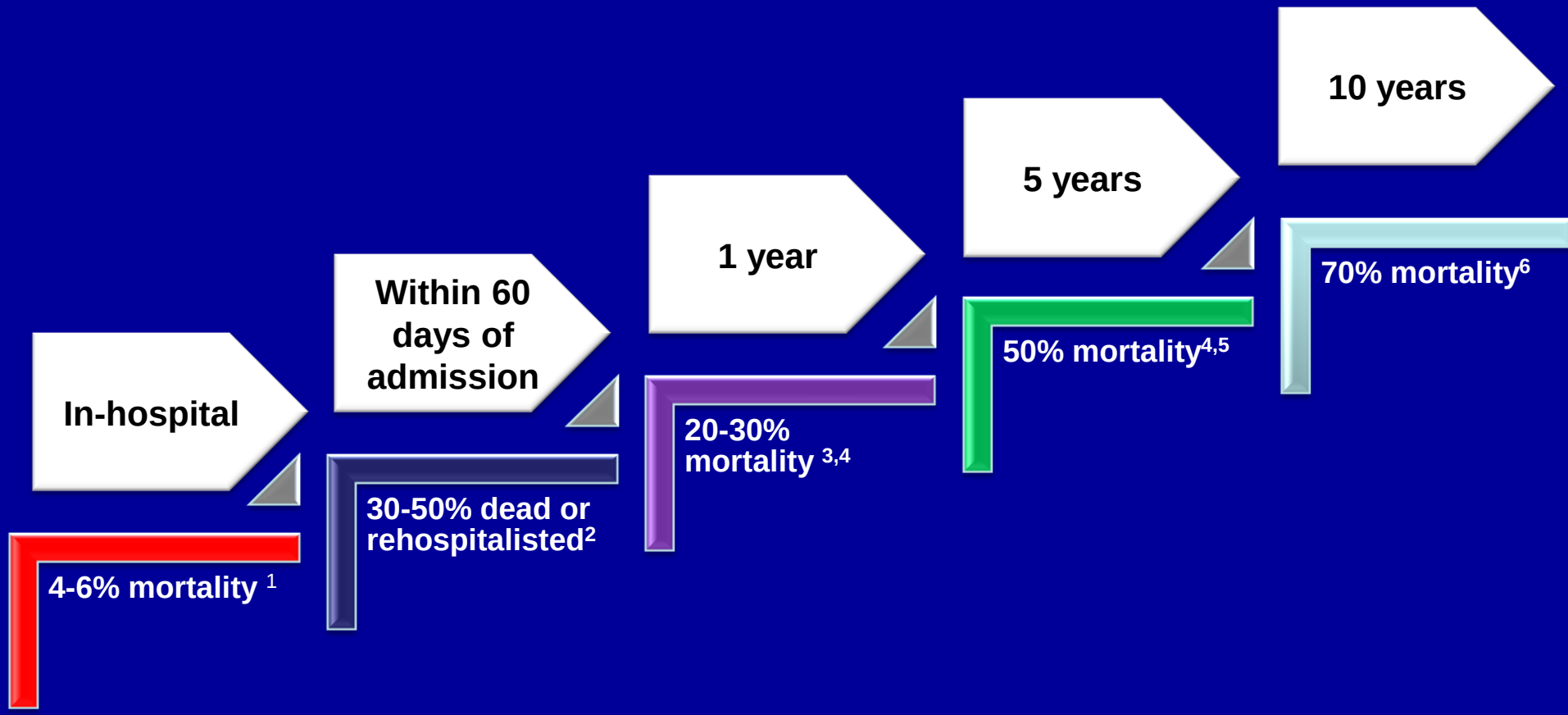
Disclosure

VM has received consultancy fees/honoraria from Bayer HealthCare AG, Novartis and CardioPep Pharma GmbH

Impact of Acute Heart Failure



1. Adams et al. *Am Heart J* 2008;149 209-16
2. Dickenstein et al/ *Eur Heart J* 2008; 29:2388-442
3. Chen et al. *JAMA* 2011;306:1669-78
4. Loehr et al. *Am J Cardiol* 2008; 101: 1016-22
5. Roger et al. *Circulation* 2012;125:e2-220
6. McMurray JJ, Pfeffer MA (2005). *Lancet* 365 (9474): 1877–89

Plus ça change, plus c'est la même chose

MEDICAL INTELLIGENCE

CURRENT CONCEPTS

Cardiac Decompensation

ALBERTO RAMÍREZ, M.D., AND
WALTER H. ABELMANN, M.D.

THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 28, 1974

- Morphine
- Oxygen (NIV)
- Loop diuretic
- (Turniquet/phlebotomy)
- Inotropes
- (Digitalis/aminophylline/ Isoproterenol)
- Nitroglycerin/nitroprusside phentolamine
- Cardioversion/pacing/IABP

Recent Drug Development Program in ADHF

Trial	Agent	Symptoms	Outcome
OPTIME-CHF n=951	Milrinone PDE-III Inh.	-	Negative
EVEREST n=4.133	Tolvaptan Vasopr. V_2-Ant.	+	Neutral
VERITAS n=1.448	Tezosentan Endothelin-Ant.	-	Neutral
SURVIVE n=1.327	Levosimendan Ca^{2+} Sensitizer	-	Neutral
PROTECT n=2.033	Rolofylline Adenosine A_1-Ant.	-	Neutral
ASCEND-HF n= 7.141	Nesiritide Natr. Pept. BNP	-	Neutral

Treatment of acute heart failure
Well almost an evidence free zone

JGF Cleland AHA 2010

Summary of guidelines (treatment)

	ESC	ACC/AHA	Canadian
Oxygen	I C	I C	-
Loop diuretic	I B	I B	I B
Vasodilators	I B	IIa C	I B
Non-invasive ventilation	IIa B	-	IIa B
Inotropes	IIa B	I C/IIb C	I B
Invasive monitoring	IIa B/IIa C	I C/IIa C	I B
Ultrafiltration	IIa B	IIa B	None
Coronary reperfusion	I C	IIa C	None

Not a single evidence-level A recommendation!

β-receptor dependent inodilators

Catecholamines *in ADHF*

meta analysis

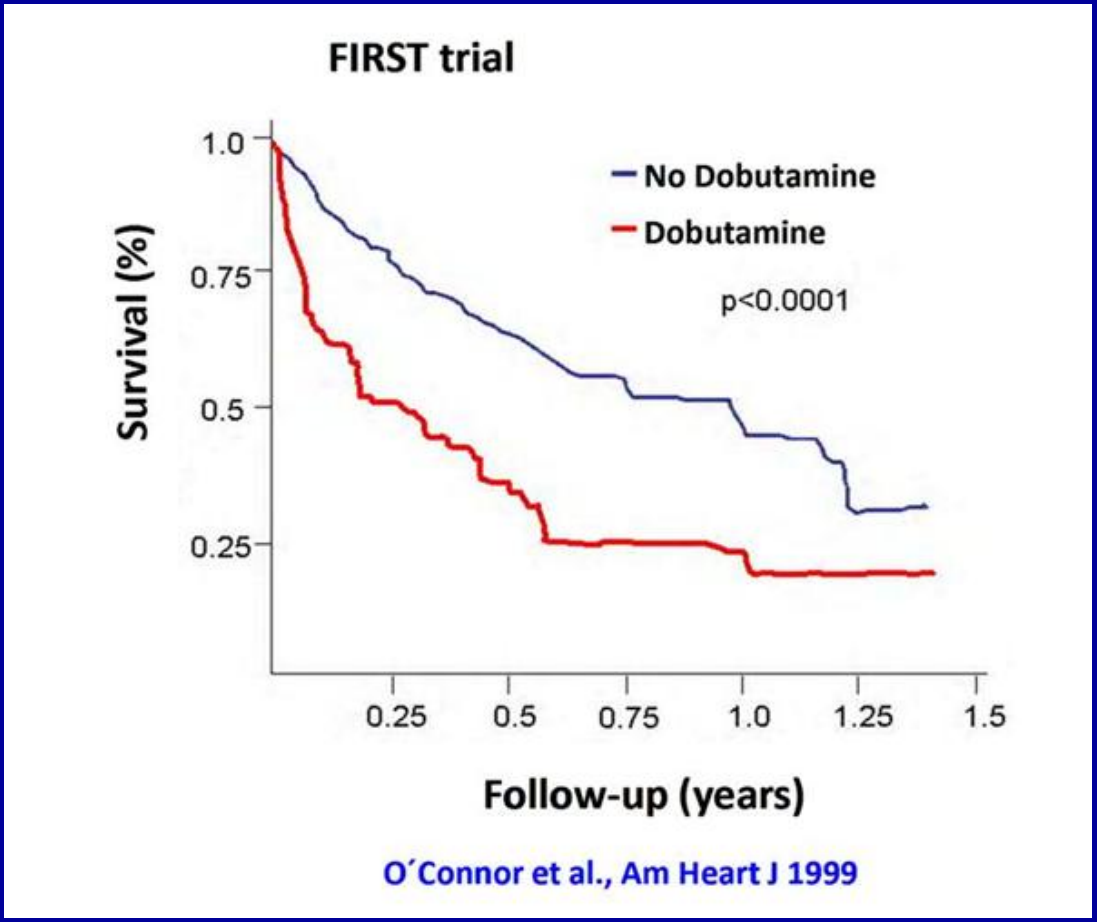
16 Trials, 474 Pts : Dobutamin, „highly dosed“- Dopamin

⇒ Symptoms ⇓ (NYHA Δ – 0.7)
(OR 1.50; 95%CI 0.51–3.92)

⇒ Lethality ⇑ (*OR 50; 95 % CI 0.51 – 3.92*)

Thackray et al: Eur J Heart Failure 2002;4:515-529

INOTROPES MAY INCREASE MORTALITY IN ACUTE HEART FAILURE



Disadvantages of Current Inotropes

Indirect Mechanism

↑ Calcium

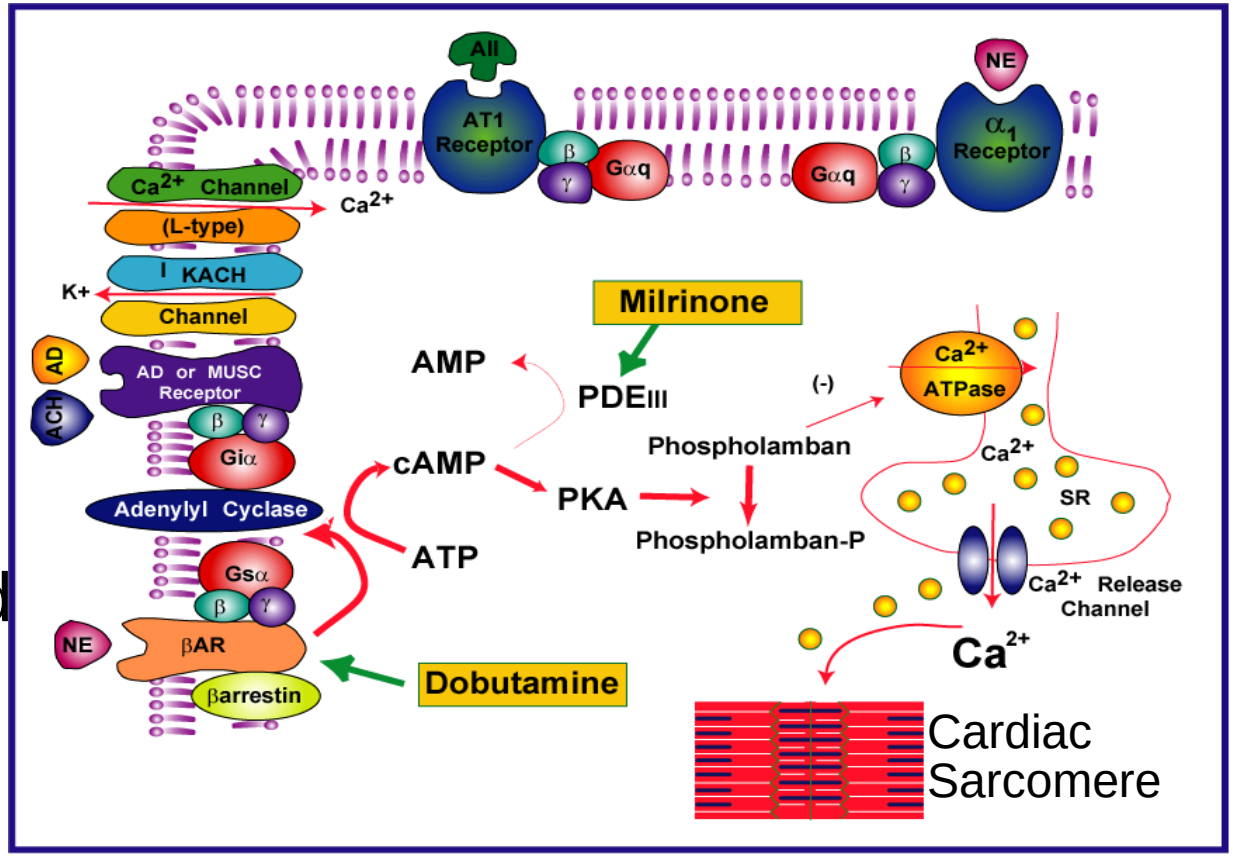
↑ Heart Rate

↓ Blood Pressure

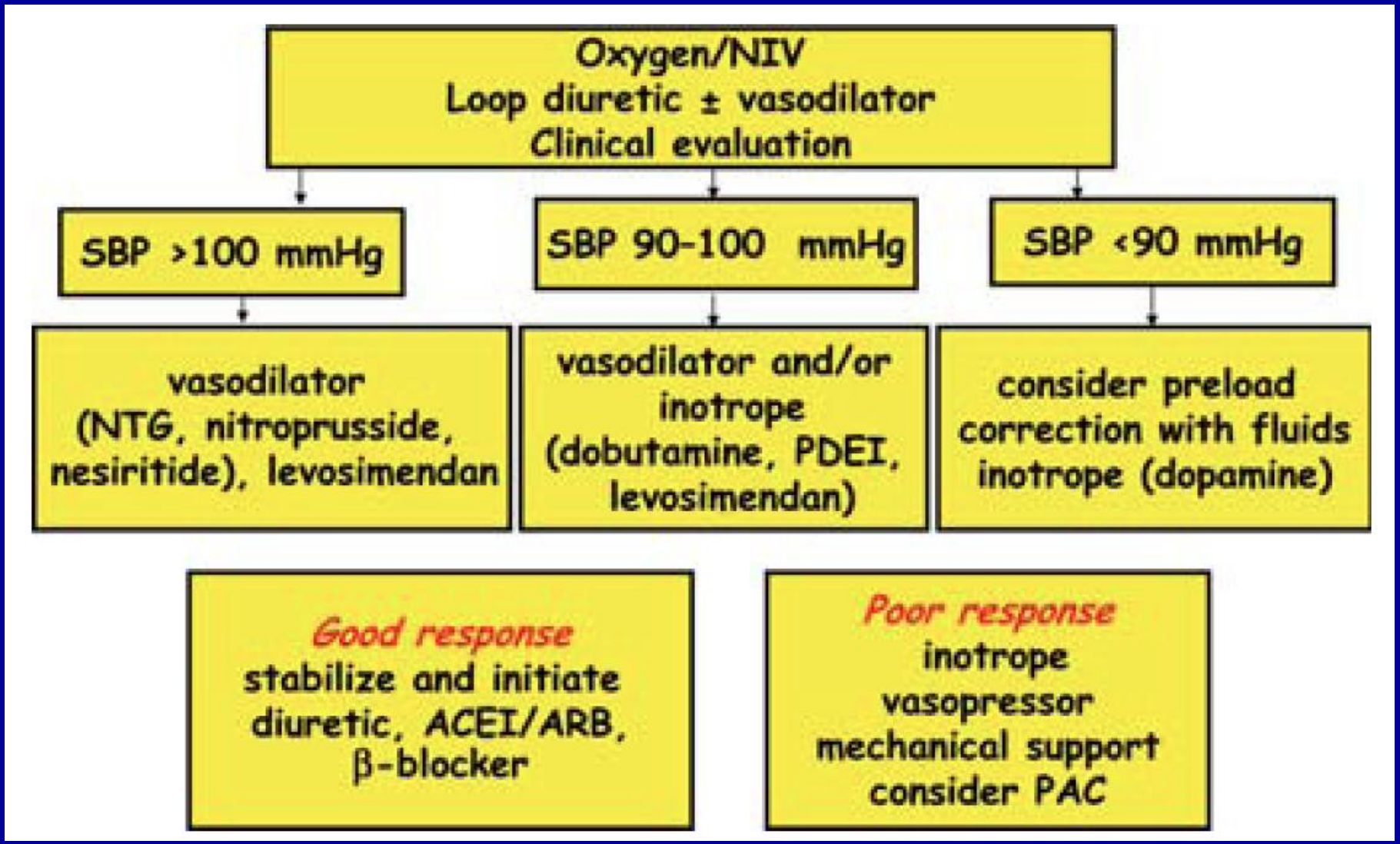
↑ Oxygen Demand

↓ Efficiency

↑ Arrhythmias



ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008‡



Dickstein EHJ 2008

New drugs on the horizon

Myosine Activator
(Omecamptiv Mecarbil)

Vasoactive Peptid
(Relaxin)

sGC-Modulators
(Cinaciguat, Riociguat)

New Natriuretic Peptides
(Ularitide, Nesiritide, CD-NP)

ECE + NEP-Inhibitors
(Daglutril)

AGE-Breakers
(TRC 4185)

Na^+-K^+ +SERCA-ATPase Inhibitors
(Istaroxime)

Aldosterone Syntase Inhibitors
(LCI, FAD 286)

MRA
(BAY 94-8862)

Small Molecules Can Improve Cardiac Function…

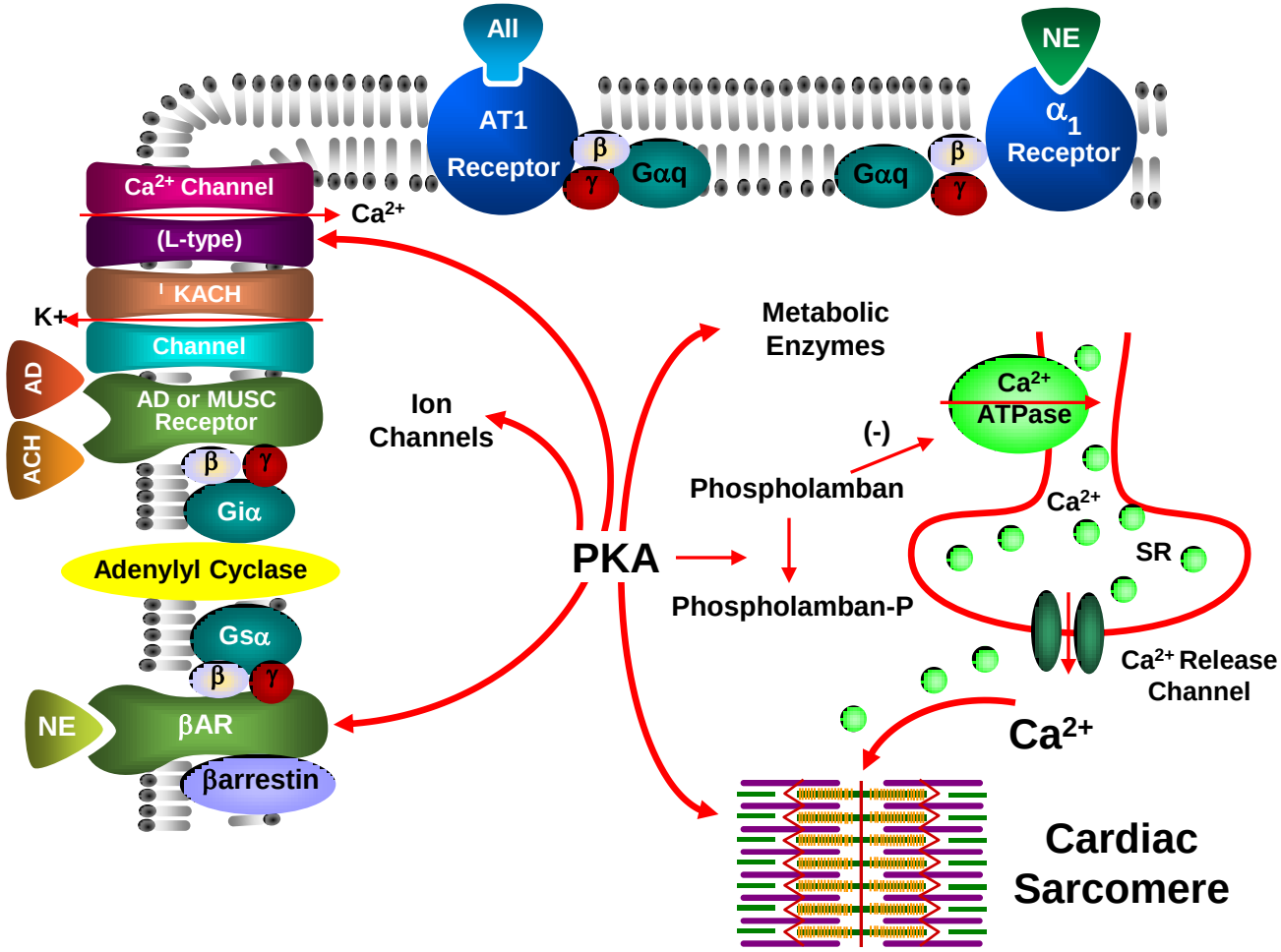
Indirect Mechanisms

PKA phosphorylates proteins throughout the myocyte

↓

Intracellular [Ca^{2+}] increases

↓



… But They Compromise CardiacPerformance

Indirect Mechanisms

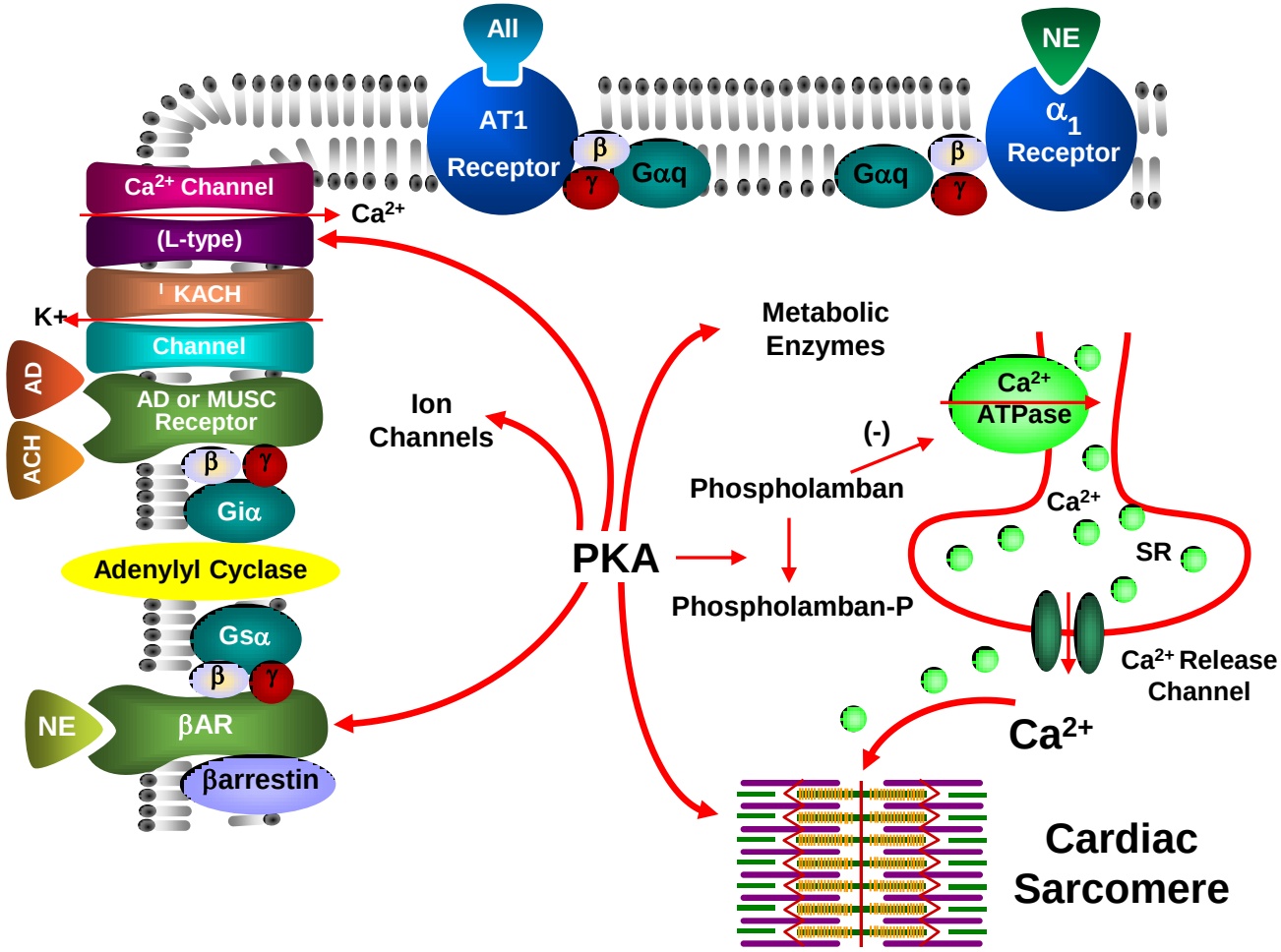
PKA phosphorylates proteins throughout the myocyte

↓

Intracellular [Ca^{2+}] increases

↓

- ↑ Contractility
- ↑ Heart rate
- ↓ Blood Pressure
- ↑ O_2 Demand
- ↓ Efficiency
- ↑ Arrhythmias



Dobutamine (β-agonist), Milrinone ($PDE3_i$)

Potential Advantages of Targeting the Sarcomere

Therapeutic Hypothesis

Directly target the sarcomere

Ø PKA activation

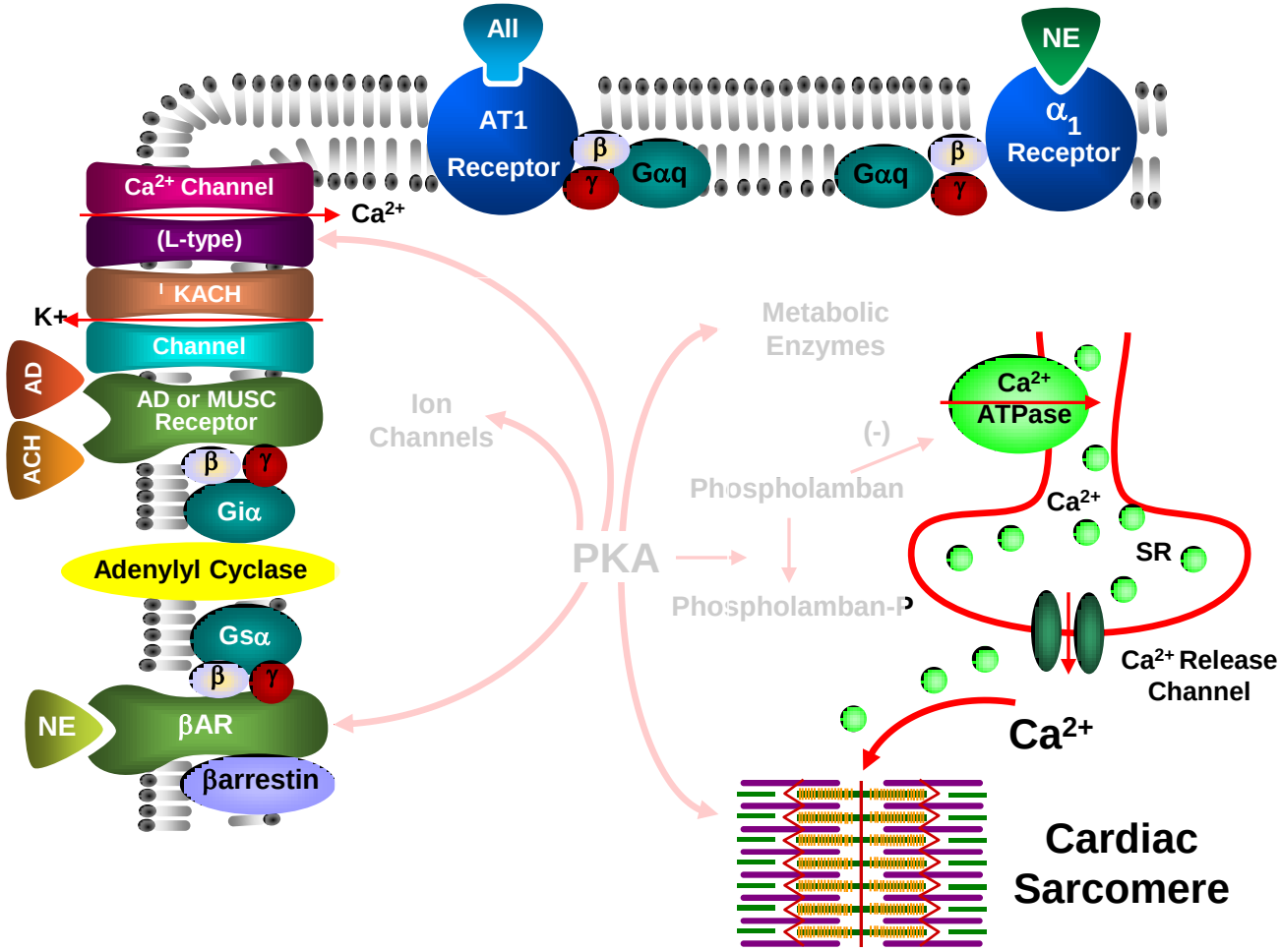
↓

Intracellular [Ca^{2+}] unchanged

↓

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

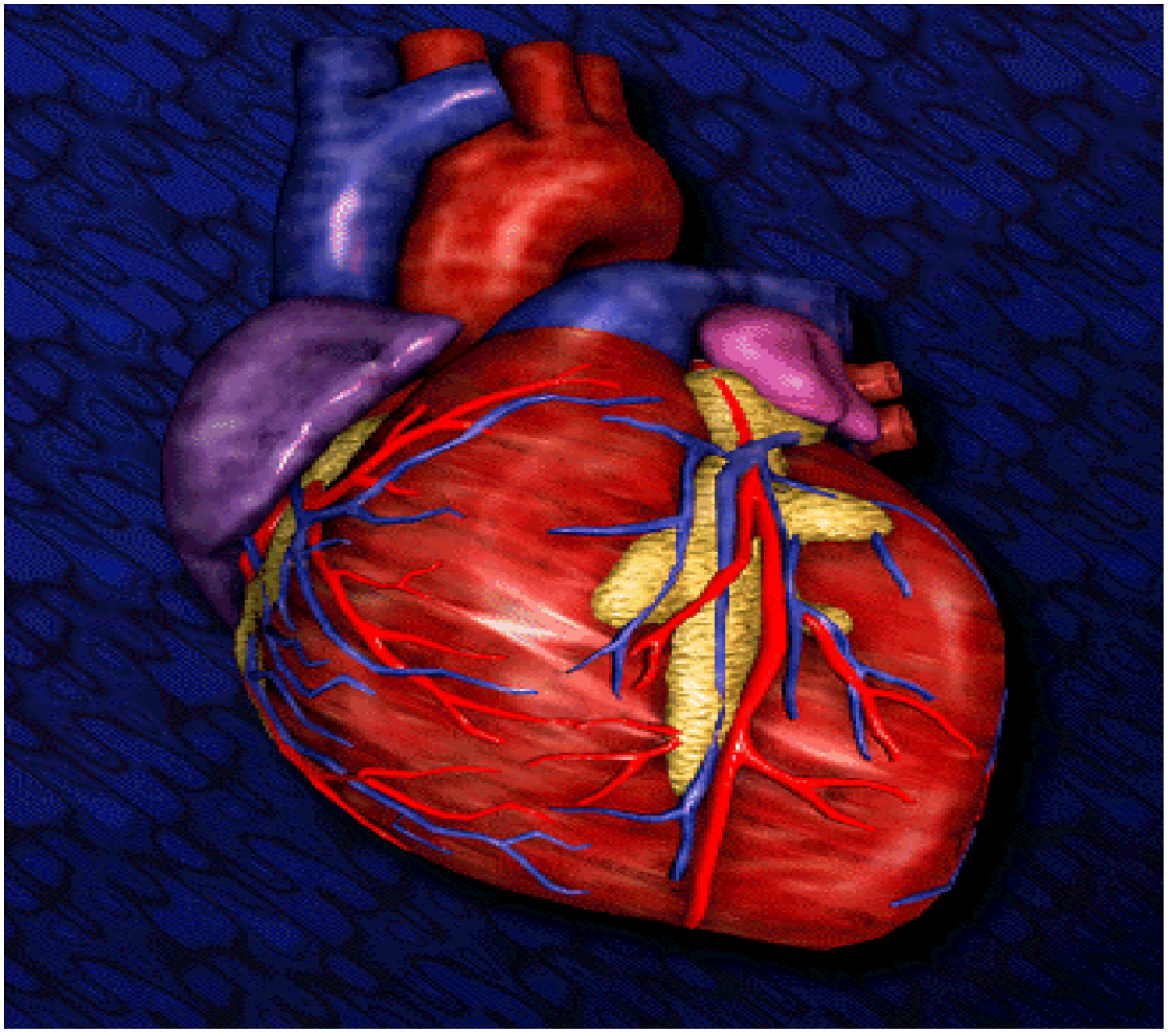
Effective Drug?



Inotropes

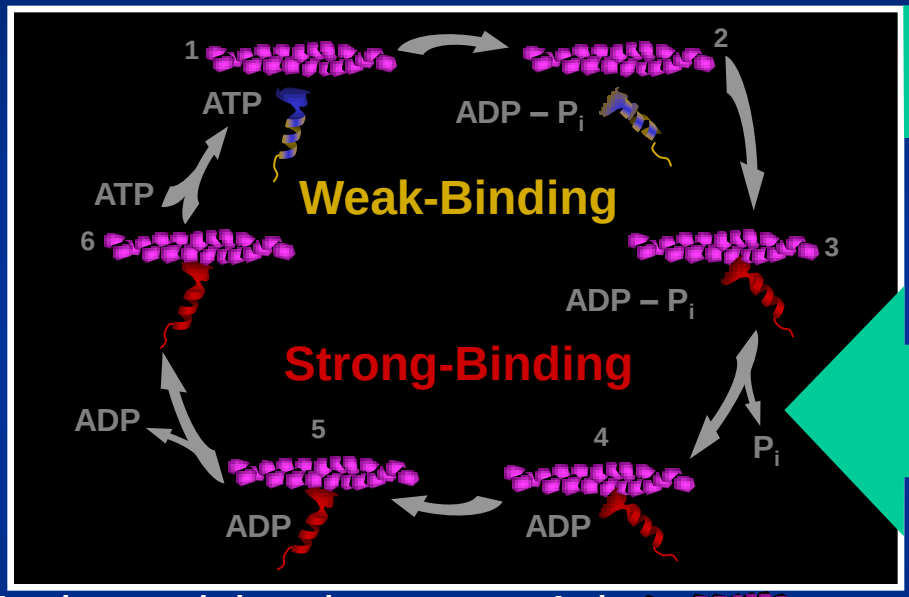
Omecamptiv Mecarbil

and Direct Cardiac Myosin Activation



Postulated Mechanism of Action for Cardiac Myosin Activators

Chemical and mechanical cycles are linked

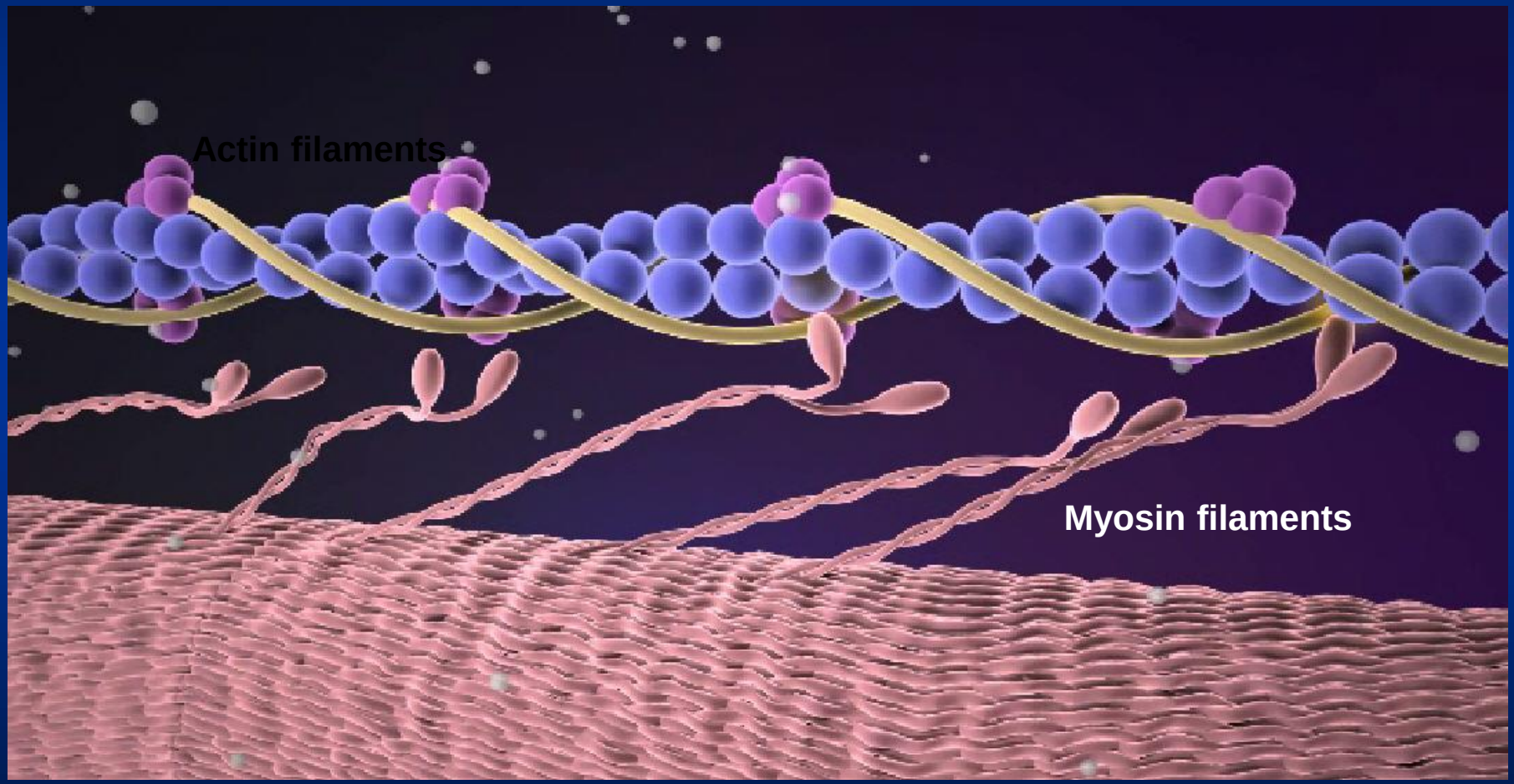


Cardiac myosin activators increase the actin-myosin transition rate from weak to strong binding states[1]

Cardiac myosin activators increase the number of "independent force generators" (myosin heads) interacting with the actin filament

1. Teerlink J. *Heart Fail Rev*. Published online ahead of print February 21, 2009. doi:10.1007/s10741-009-9135-0. 2. Malik F, et al. Poster presented at: 9th Annual Meeting of the Heart Failure Society of America; September 18-21, 2005; Boca Raton, FL. 3. Data on file, Amgen.

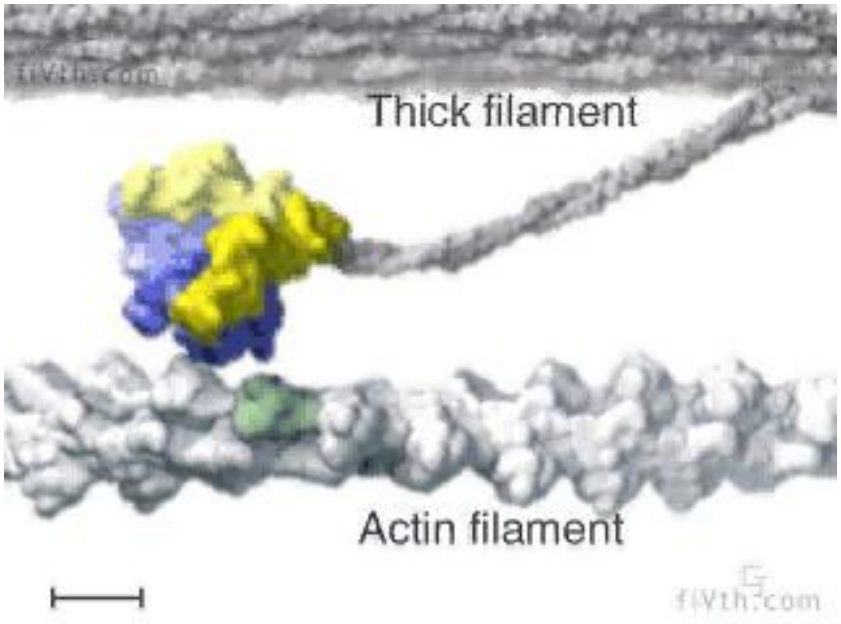
The Sarcomere: The Basic Contractile Unit of Muscle



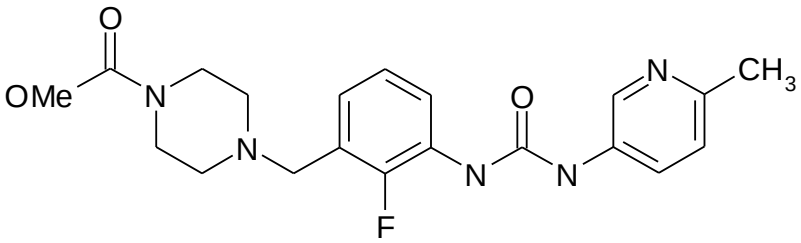
1. Adapted from: Guyton AC, et al. *Textbook of Medical Physiology*, 11th ed. 2006:chap 6.
2. Data on file, Amgen.

Omecamtiv Mecarbil a Cardiac Myosin Activator

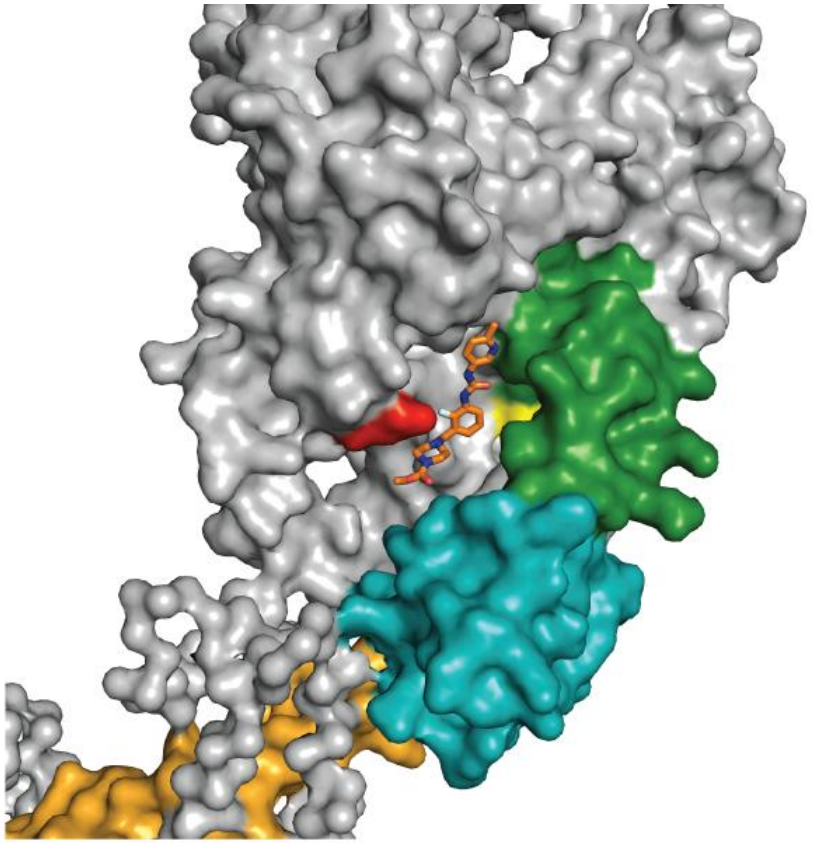
Omecamtiv Mecarbil Binds to the Mechanochemical Domain of Myosin



Vale and Milligan, Science 2000



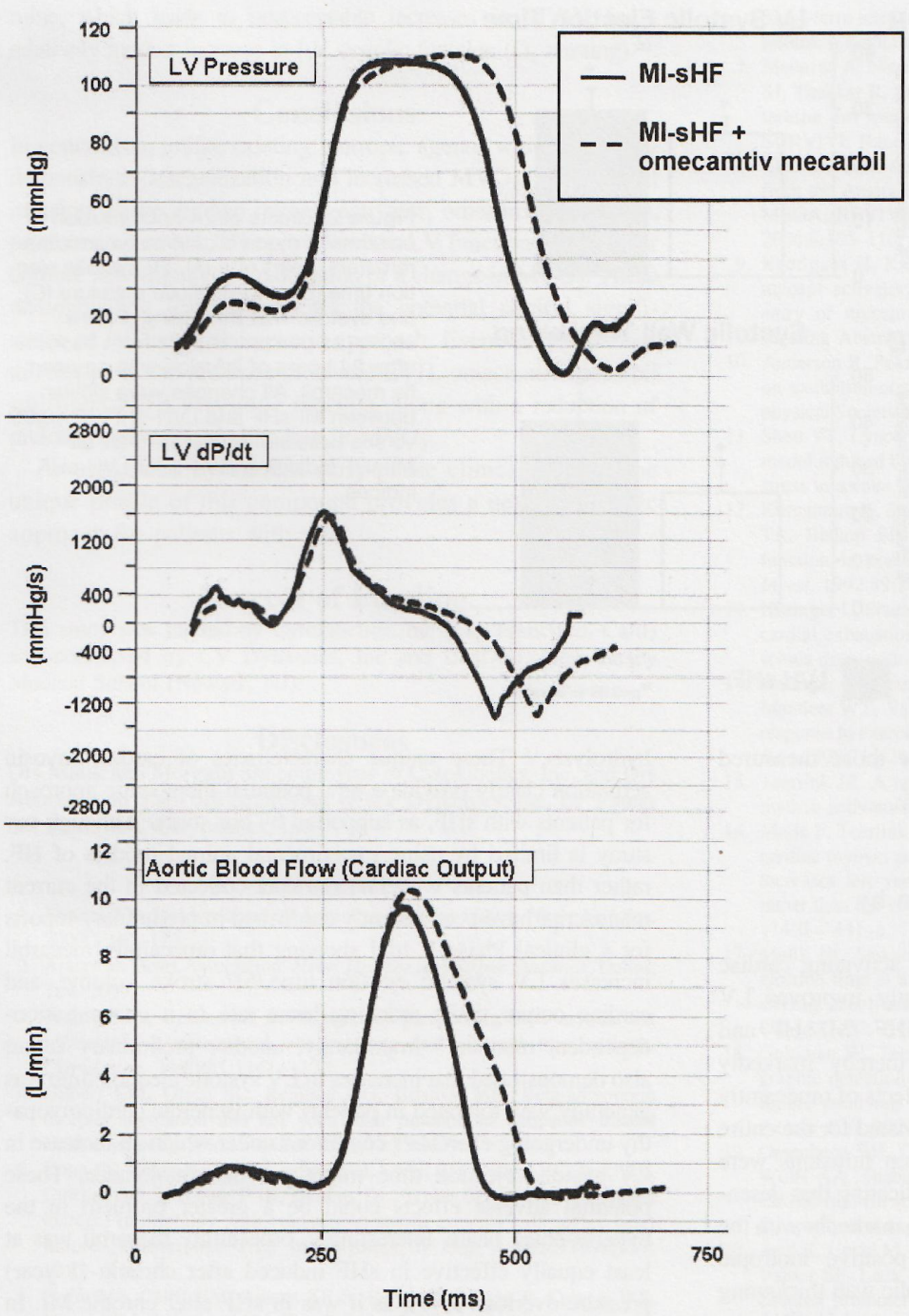
Omecamtiv Mecarbil
(MW = 401.43)



S1 Domain

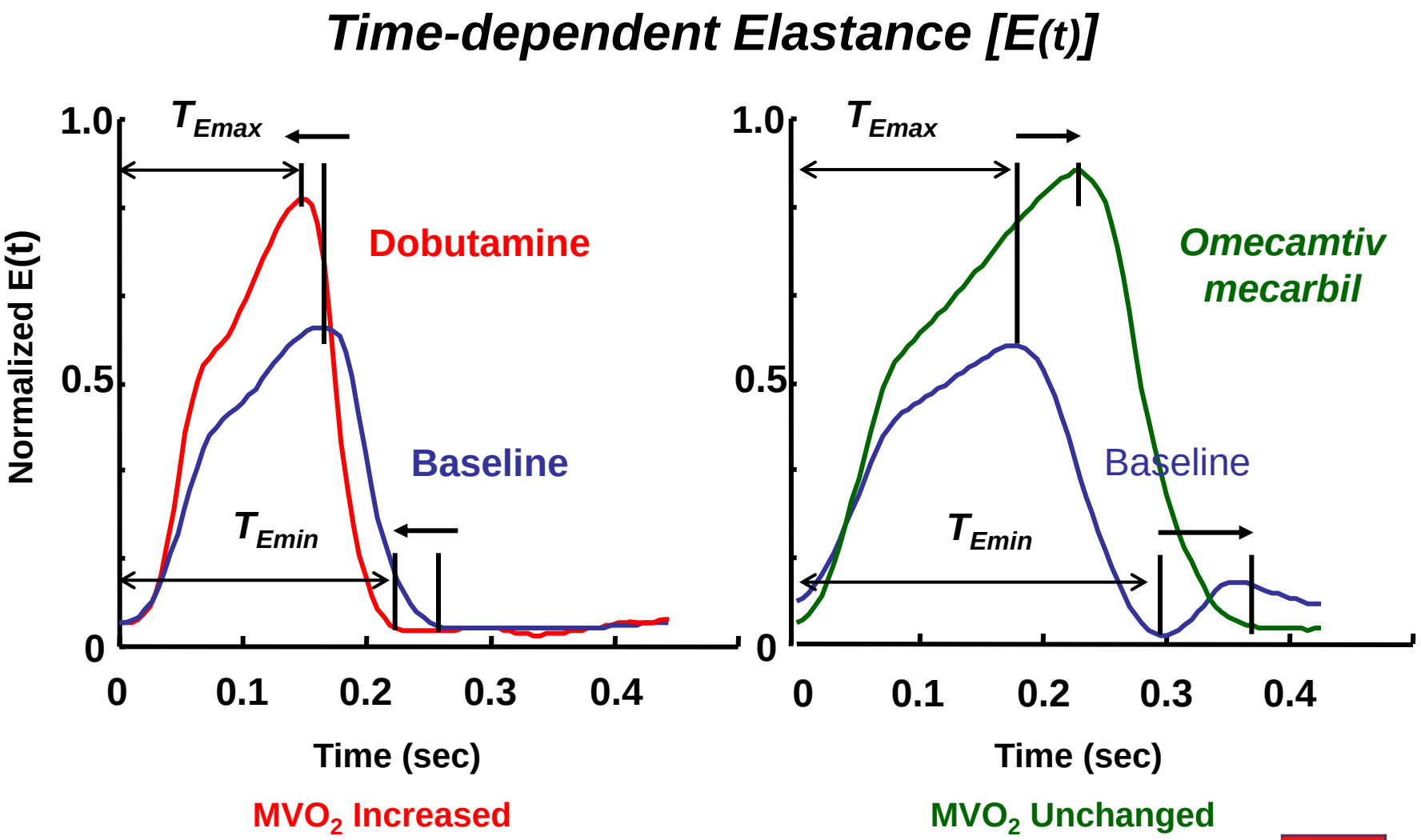
Science AAAS

Malik et al, 2011


LV Pressure
MI-sHF
MI-sHF + omecamtiv mecarbil
(mmHg)
120
100
80
60
40
20
0
LV dP/dt
(mmHg/s)
2800
2000
1200
400
0
-400
-1200
-2000
-2800
Aortic Blood Flow (Cardiac Output)
(L/min)
12
10
8
6
4
2
0
0
250
500
750
Time (ms)

Omecamtiv Mecarbil: Dog Heart Failure Model

Increases Duration but not Velocity of Contraction

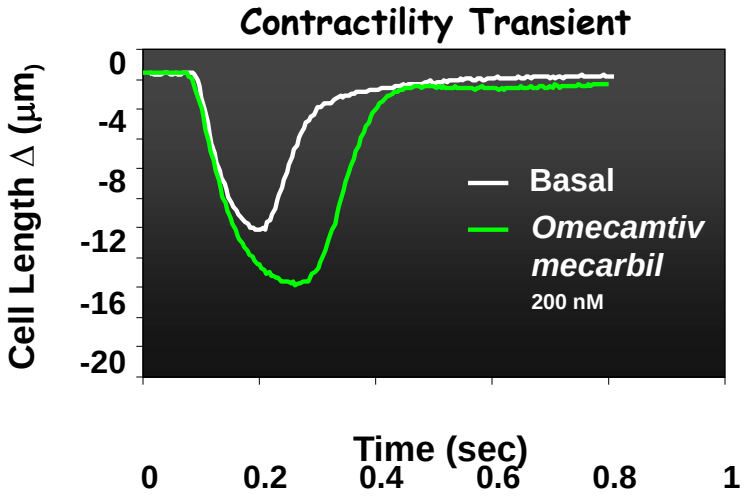


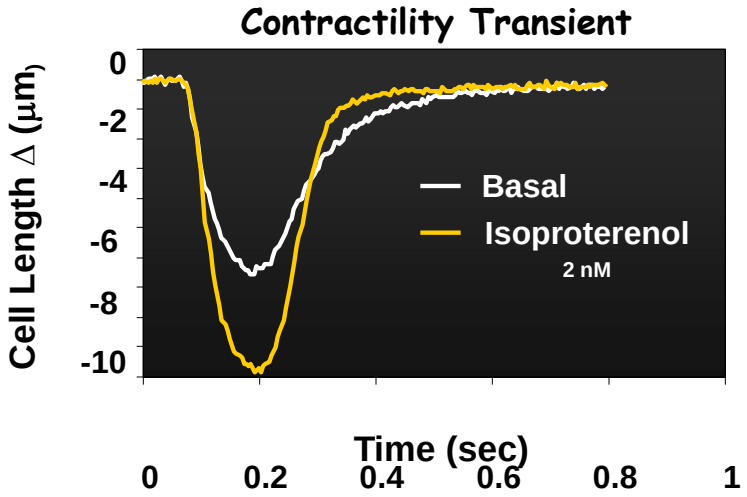
Science AAAS

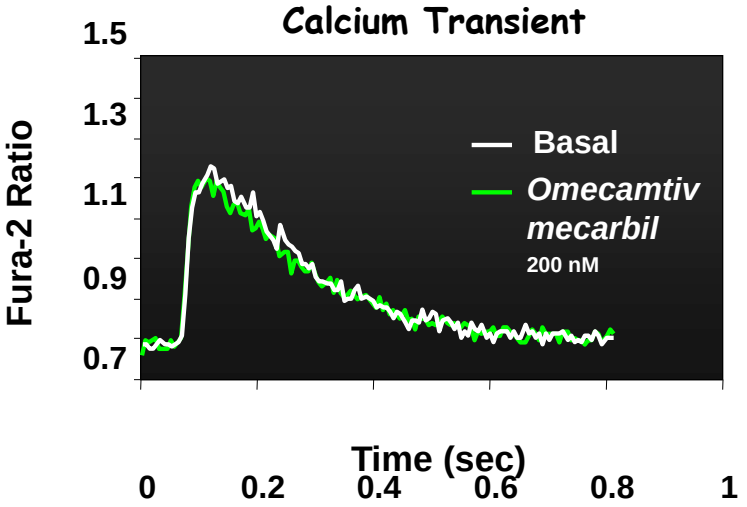
Malik et al, 2011

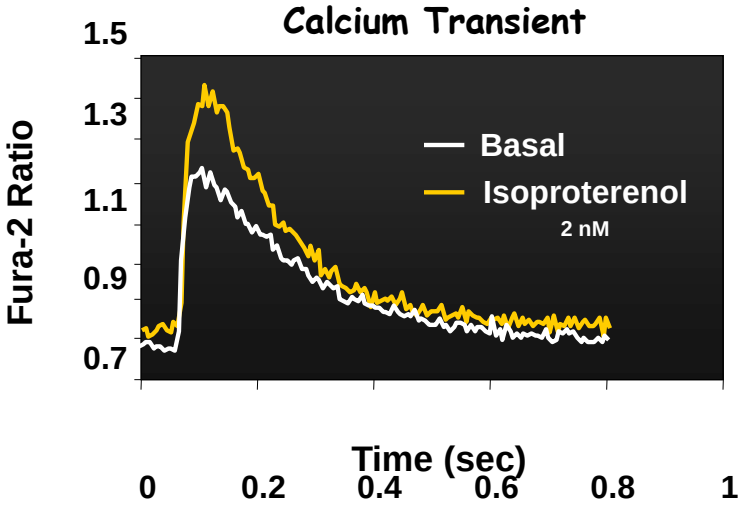
Omecamtiv Mecarbil: Rat Adult Cardiac Myocytes

Does Not Alter the Ca^{2+} Transient







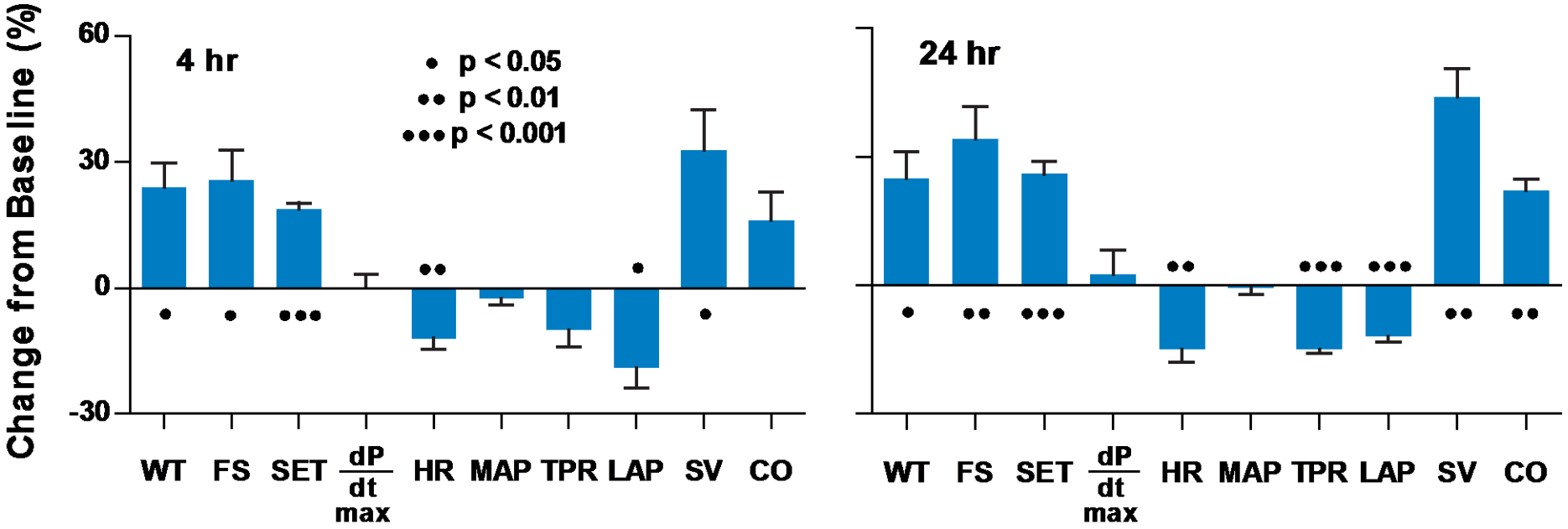


Science AAAS

Malik et al, 2011

Omecamtiv Mecarbil: Dog Heart Failure Model

Cardiac Function and Hemodynamics



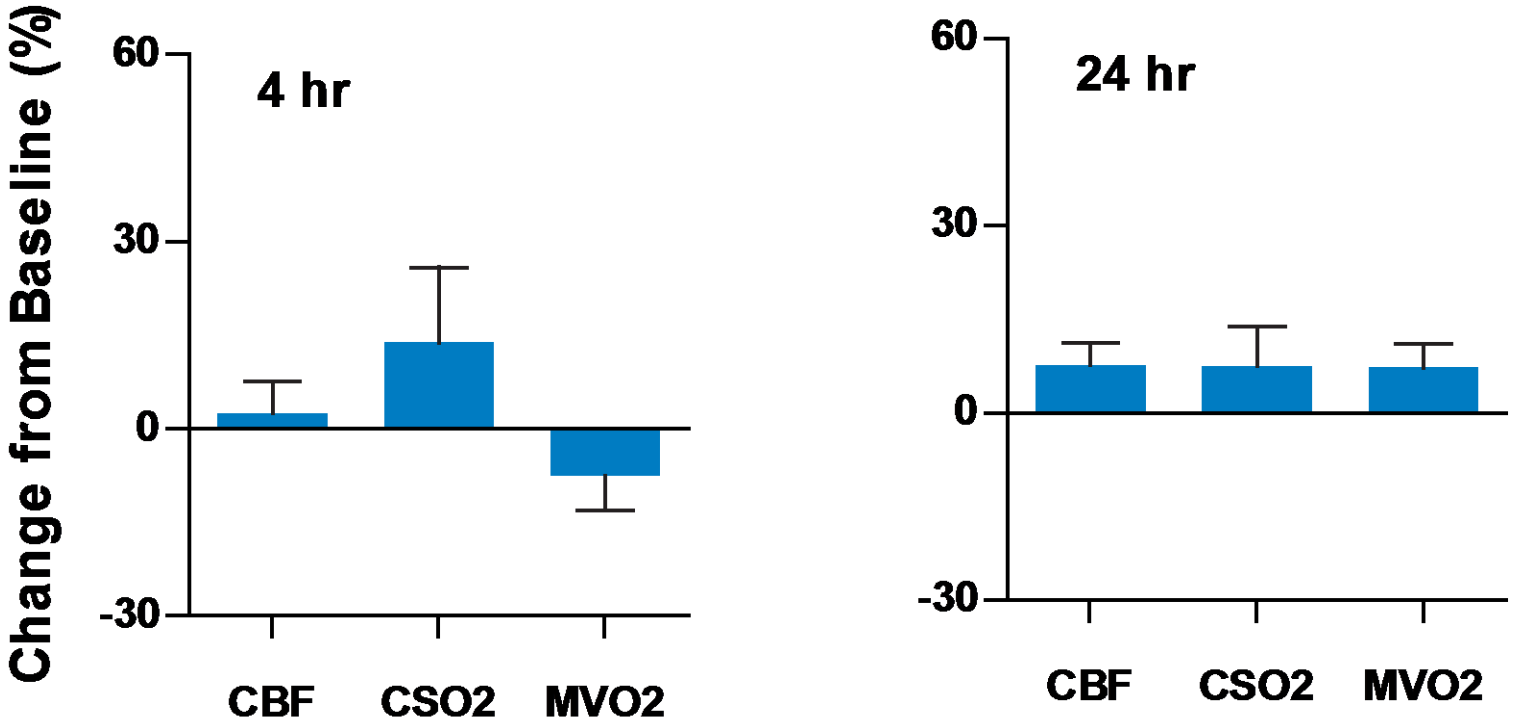
WT	:	Wall thickening	MAP	:	Mean Arterial Pressure
FS	:	Fractional shortening	TPR	:	Total Peripheral Resistance
SET	:	Systolic ejection time	LAP	:	Left Atrial Pressure
dP/dt	:	Rate of pressure change	SV	:	Stroke Volume
HR	:	Heart Rate	CO	:	Cardiac Output

Circulation Heart Failure

Shen YT, et al. 2010

Omecamtiv Mecarbil: Dog Heart Failure Model

Does not Increase Oxygen Consumption



CBF : Coronary Blood Flow
CSO2 : Coronary Sinus Oxygen Content
MVO2 : Myocardial Oxygen Consumption

Circulation Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Shen YT, et al. 2010

Overview of Completed Phase 1-2a Development Program

Phase 1 Healthy Volunteers (N = 124)	Phase 2 Heart Failure Subjects (N = 776)
CY 1111 First in human 6 hr IV (N = 35)	**CY 1121** PK, PD, safety, and tolerability ≤ 72 hr IV (N = 45)
CY 1011 Oral bioavailability 1 hr IV, 1 PO dose, fasted/fed (N = 10)	**CY 1221** Safety/tolerability in ischemic cardiomyopathy 20 hr IV followed by 7 d PO (N = 94)
CY 1013 Oral drug-drug interaction (CYP 2D6/3A4) 1 PO dose (N = 25)	**CY 1124** PD and Energetics 2 hrs IV (N = 2)
CY 1015 Single- and multiple-dose PK ≤ 7 days PO (N = 40)	**CY 1021** MR and IR PK 10 days PO (N = 35)
CY 1016 MR and IR PK 1 PO dose (N = 14)	ATOMIC-AHF PK,PD,safety and efficasy in ADHF 48hrs IV (N=600)

600 subjects studied – 569 exposed to omecamtiv mecarbil
for up to 3 days IV and 10 days PO

CY 1111

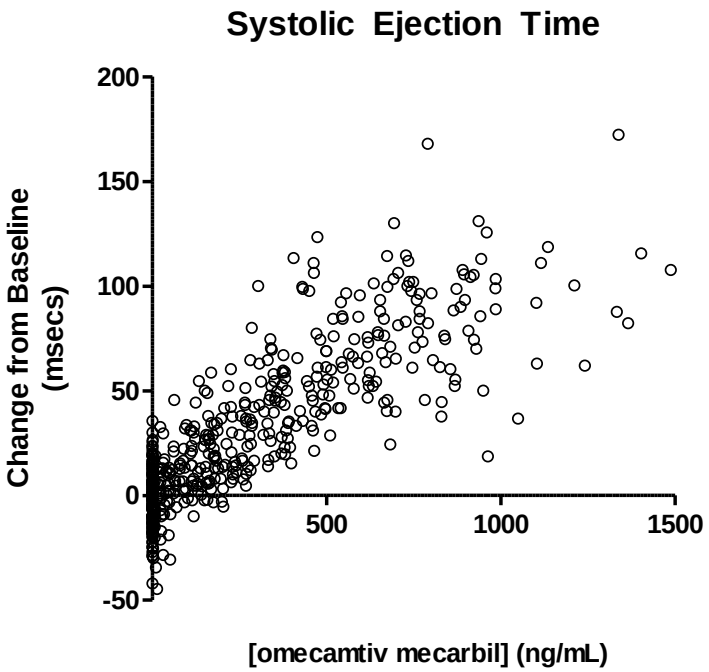
Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous *Omecamtiv Mecarbil* in Healthy Volunteers

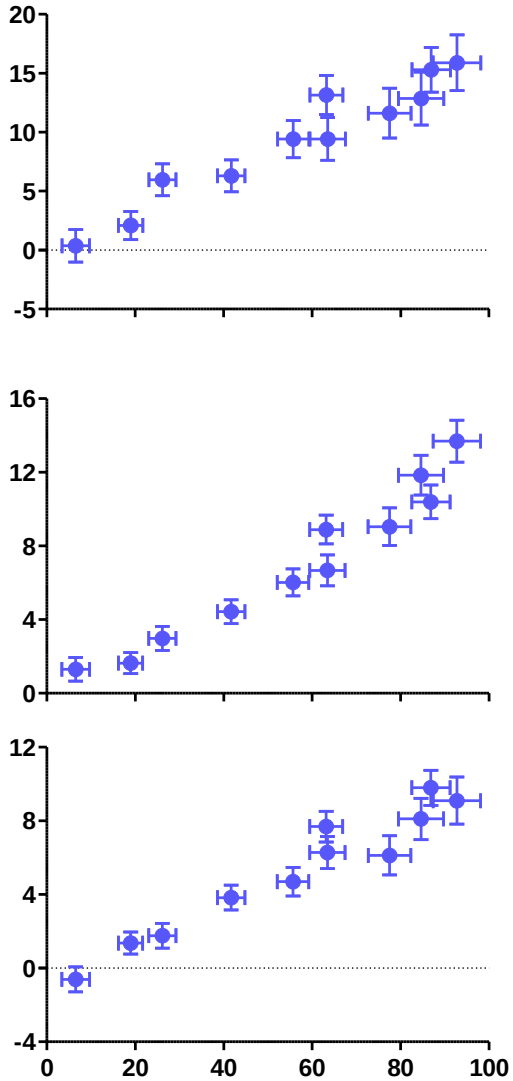
Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study

John R Teerlink, Cyril P Clarke, Khalil G Saikali, Jacqueline H Lee, Michael M Chen, Rafael D Escandon, Lyndsey Elliott, Rachel Bee, Mohammad Reza Habibzadeh, Jonathan H Goldman, Nelson B Schiller, Fady I Malik, Andrew A Wolff

***Lancet* 2011; 378: 667–75**

Increases in Systolic Ejection Time Underlie Increases in Cardiac Function





Δ Stroke Volume (mL)

Δ Fractional Shortening (% points)

Δ Ejection Fraction (% points)

Δ = placebo corrected change from baseline
Mean ± SEM

CY 1121

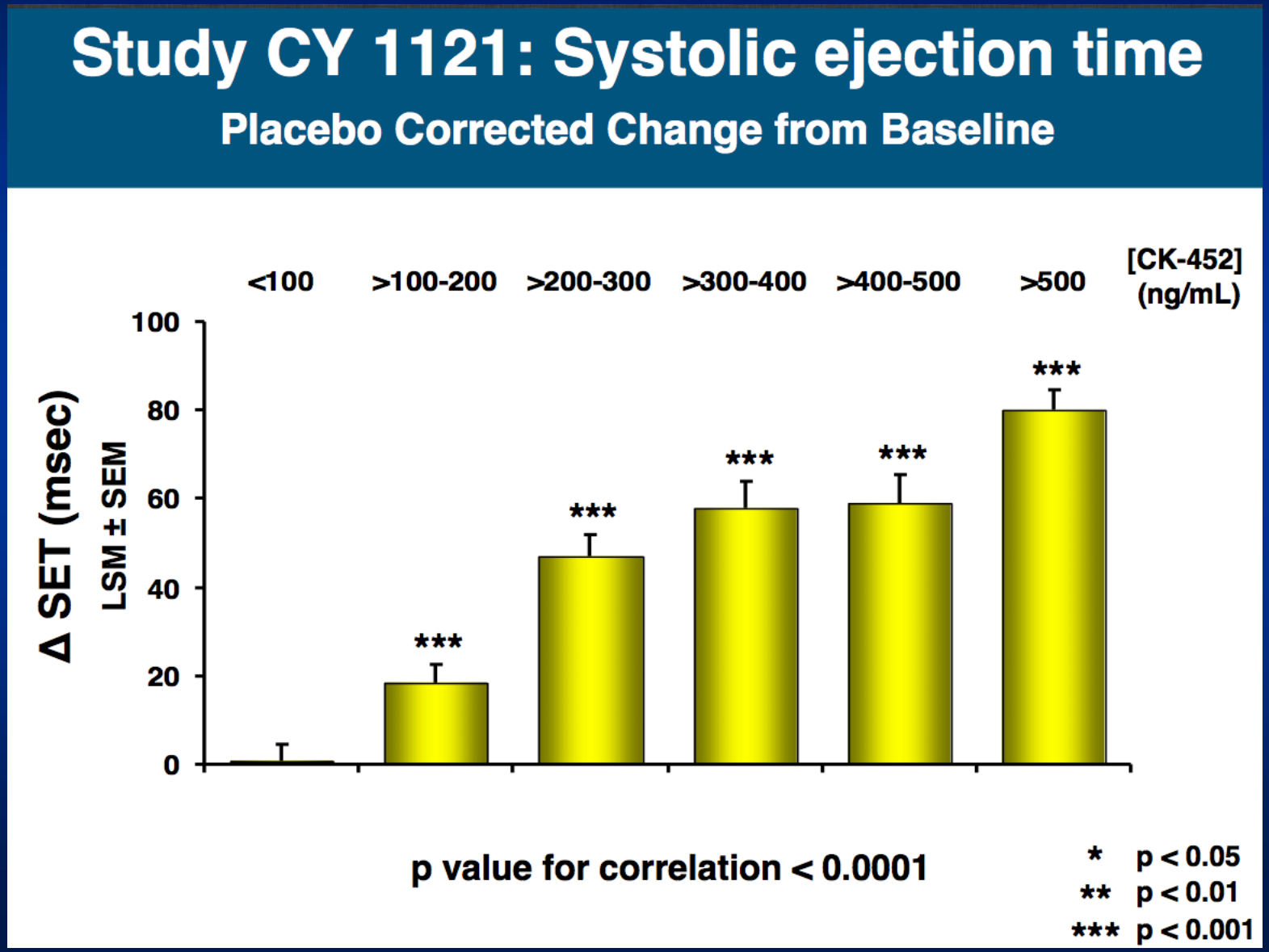
Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous *Omecamtiv Mecarbil* in Patients with Stable Heart Failure

The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial

John G F Cleland, John R Teerlink, Roxy Senior, Evgeny M Nifontov, John J V Mc Murray, Chim C Lang, Vitaly A Tsyrlin, Barry H Greenberg, Jamil Mayet, Darrel P Francis, Tamaz Shaburishvili, Mark Monaghan, Mitchell Saltzberg, Ludwig Neyses, Scott M Wasserman, Jacqueline H Lee, Khalil G Saikali, Cyril P Clarke, Jonathan H Goldman, Andrew A Wolff, Fady I Malik

***Lancet* 2011; 378: 676–83**

OM proof of concept study (45 patients)



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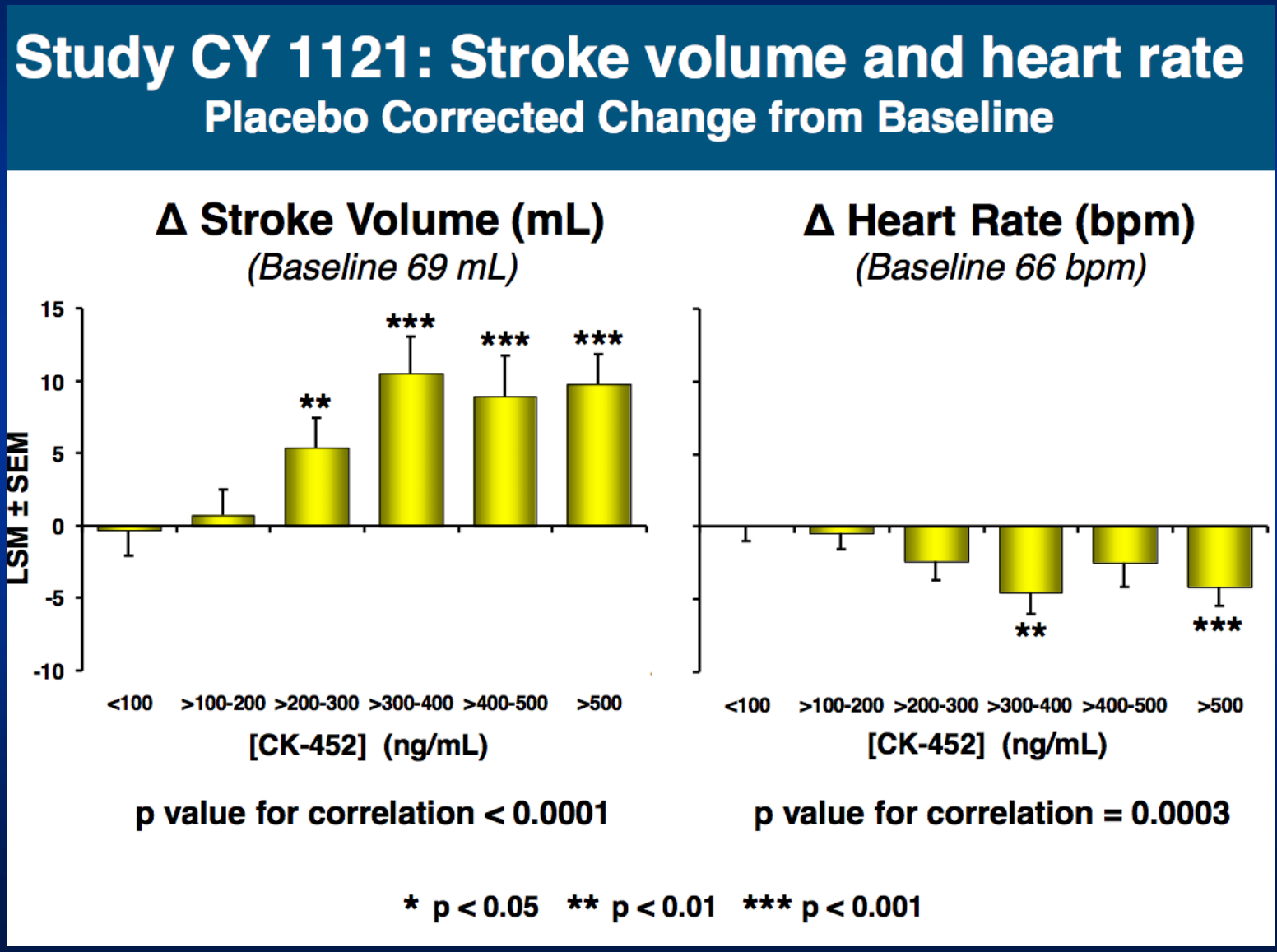

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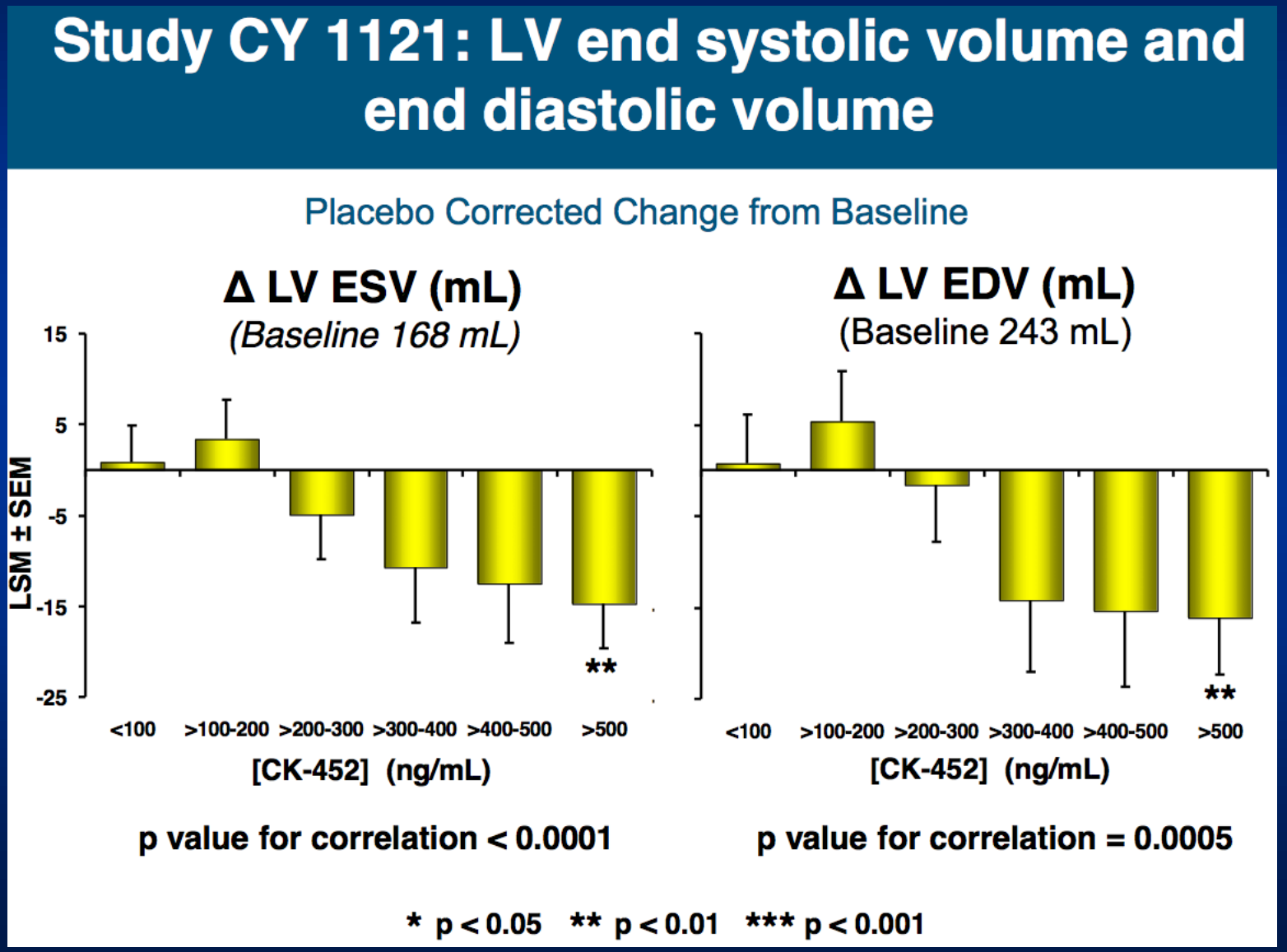
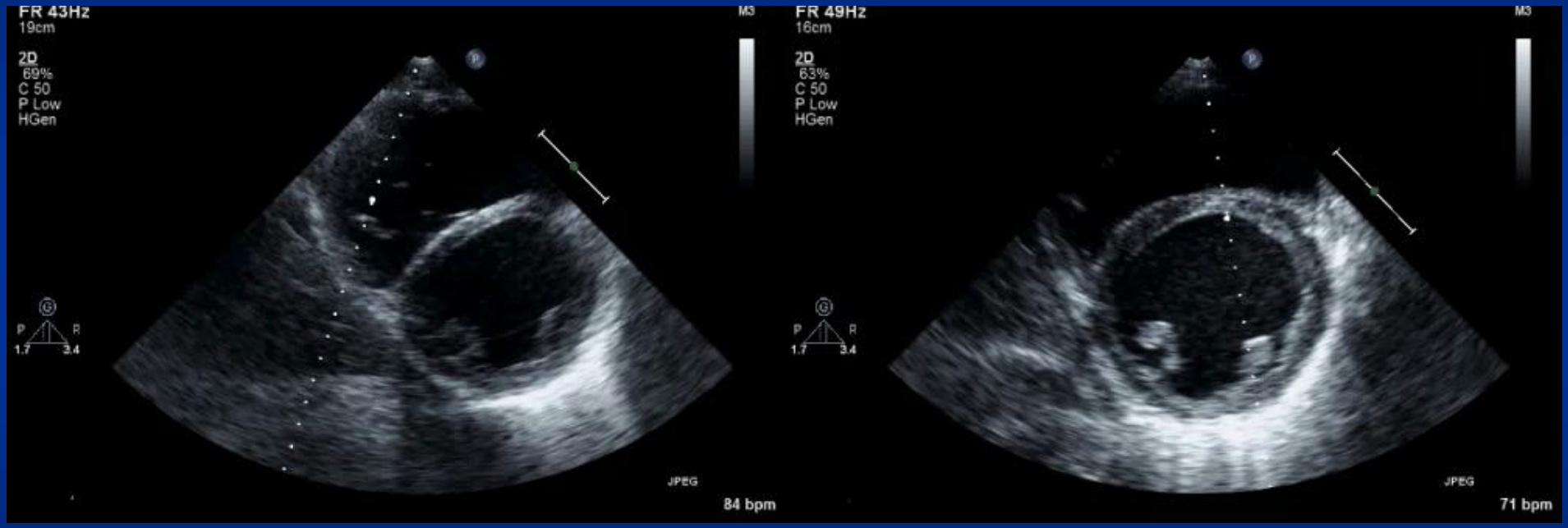


CY 1121: Effect of Omecamtiv Mecarbil in a Subject with Stable Heart Failure

24 hour infusion

Peak [*omecamtiv mecarbil*] = 378 ng/mL



Baseline *24 hours*

	SET (msec)		LVOT SV (mL)		EF (%)		HR (bpm) – supine ECG	
	Baseline	24 hrs	Baseline	24 hrs	Baseline	24 hrs	Baseline	24 hrs
Omecamtiv mecarbil	216	311	23	54	18	23	88	57
Placebo	234	225	26	24	18	18	85	86

CY 1121: Effect of Omecamtiv Mecarbil in a Subject with Stable Heart Failure

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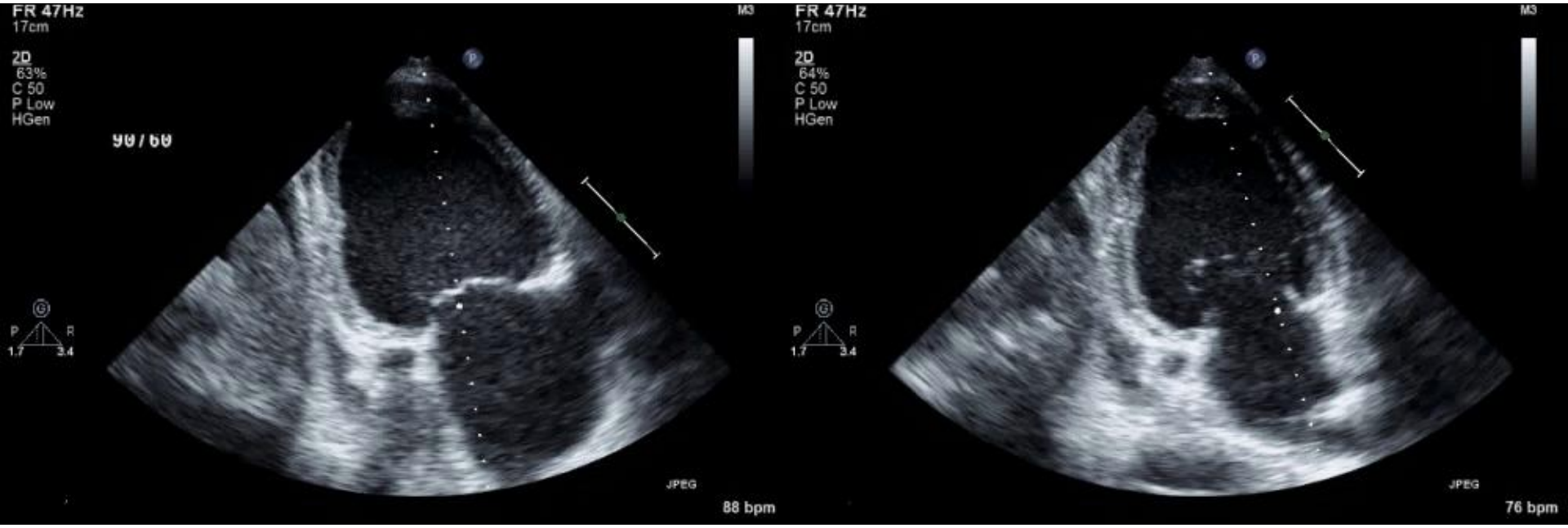


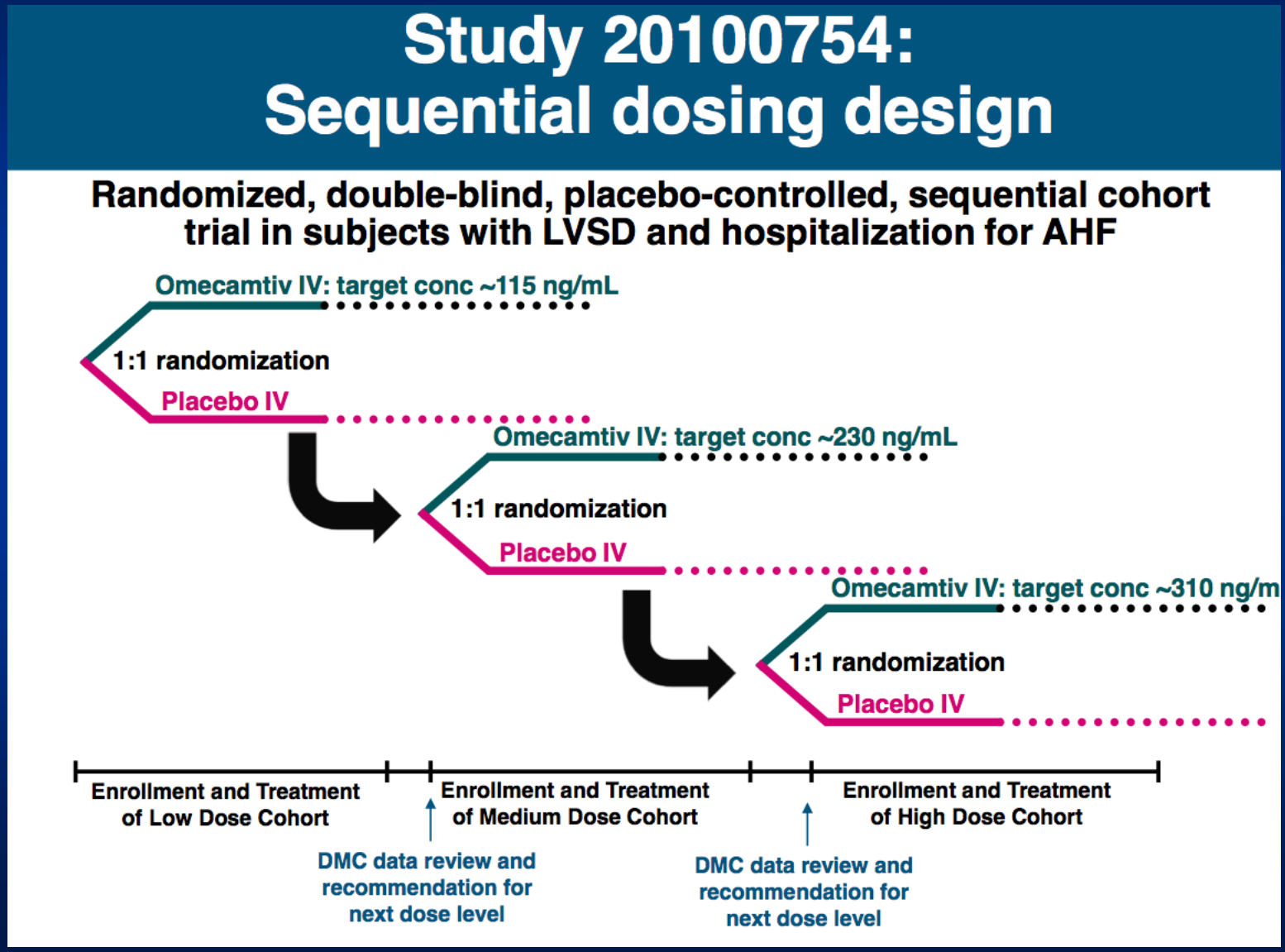
	SET (msec)		LVOT SV (mL)		EF (%)		HR (bpm) – supine ECG	
	Baseline	24 hrs	Baseline	24 hrs	Baseline	24 hrs	Baseline	24 hrs
Omecamtiv mecarbil	216	311	23	54	18	23	88	57
Placebo	234	225	26	24	18	18	85	86

ATOMIC-AHF

*A*cute *T*reatment with *O*mecamtiv *M*ecarbil to *I*ncrease *C*ontractility in *A*cute *H*eart *F*ailure (ClinicalTrials.gov NCT01300013

- 48 hr infusion of omecamtiv mecarbil vs. placebo
- Ascending dose cohorts (200 pts per cohort)
- Pts admitted for decompensated heart failure with dyspnea; EF≤40%; within 24 hrs of initial i.v. diuretic

OM aktuelle klinische Studie (geplant 600 Pat.)



Baseline Characteristics (1)

Characteristic	Pooled Placebo (N = 303)	Cohort 1 OM (N = 103)	Cohort 2 OM (N = 99)	Cohort 3 OM (N = 101)
Age , mean (SD)	66 (11)	65 (12)	67 (10)	68 (10)
Gender – male, %	76	76	82	76
Region, %	*			
Eastern Europe	53	45	56	62
North America	25	37	24	18
Australia	2	0	1	0
Western Europe	21	18	19	20
Ischaemic heart disease, %	62	62	59	66
Years from HF diagnosis, mean (SD)	6 (6)	6 (6)	6 (5)	6 (5)
Most recent LVEF (%), mean (SD)	26 (8)	26 (8)	25 (7)	28 (7)
Persistent Atrial Fibrillation or Flutter, %	33	29	32	36
Diabetes Mellitus, %	45	49	41	42
Hypertension, %	81	84	81	82

*$p < 0.05$ for a difference in cohorts 1-3 Placebo arms compared to each other

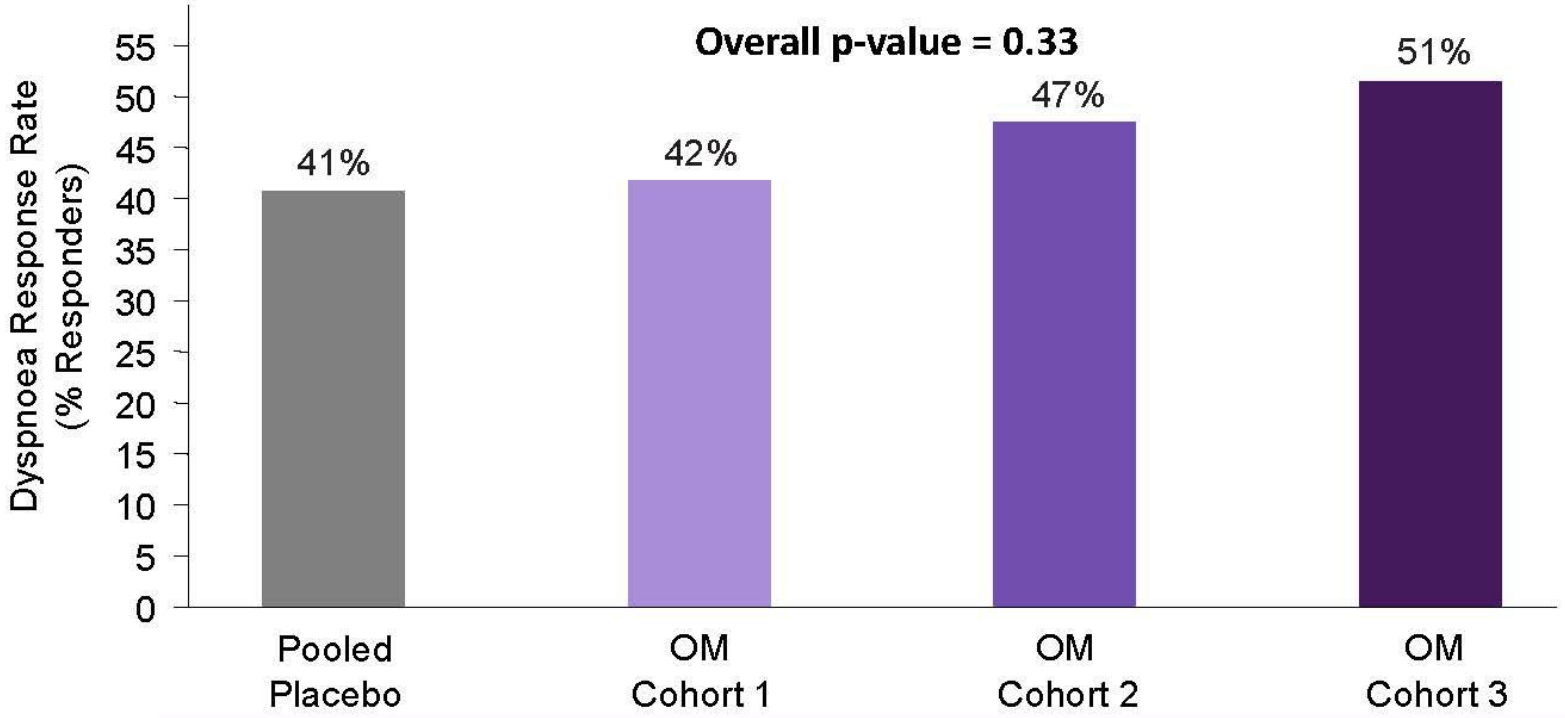
Baseline Characteristics (2)

Characteristic	Pooled Placebo (N = 303)	Cohort 1 OM (N = 103)	Cohort 2 OM (N = 99)	Cohort 3 OM (N = 101)
Systolic BP (mmHg), mean (SD)	119 (18)*	118 (18)	117 (17)	117 (15)
Heart rate (beats/min), mean (SD)	78 (13)	78 (13)	79 (13)	78 (14)
Dyspnoea Numerical Rating Scale (NRS), Mean (SD)	6 (2)	6 (2)	6 (2)	6 (2)
ACE inhibitors/Angiotensin Receptor Blockers, %	78	79	74	84
Beta blocker, %	86*	90	87	90
Digoxin, %	20	28	26	22
Mineralocorticoid Receptor Antagonist, %	55	54	59	58
Ivabradine, %	3	4	4	6
Troponin-I, median (URL 0.04 ng/mL)	0.044*	0.060	0.044	0.056
NT-proBNP (pg/mL), median	9026	7674	10488	10416
eGFR (mL/min/1.73m^2), mean (SD)	53 (18)*	52 (18)	53 (19)	50 (18)
Time from presentation to randomisation, mean (SD)	15 (8)*	12 (8)	16 (10)	15 (9)

*$p < 0.05$ for a difference in cohorts 1-3 Placebo arms compared to each other;
URL= upper reference limit

Primary Efficacy Endpoint: Dyspnoea Response (Likert Scale)

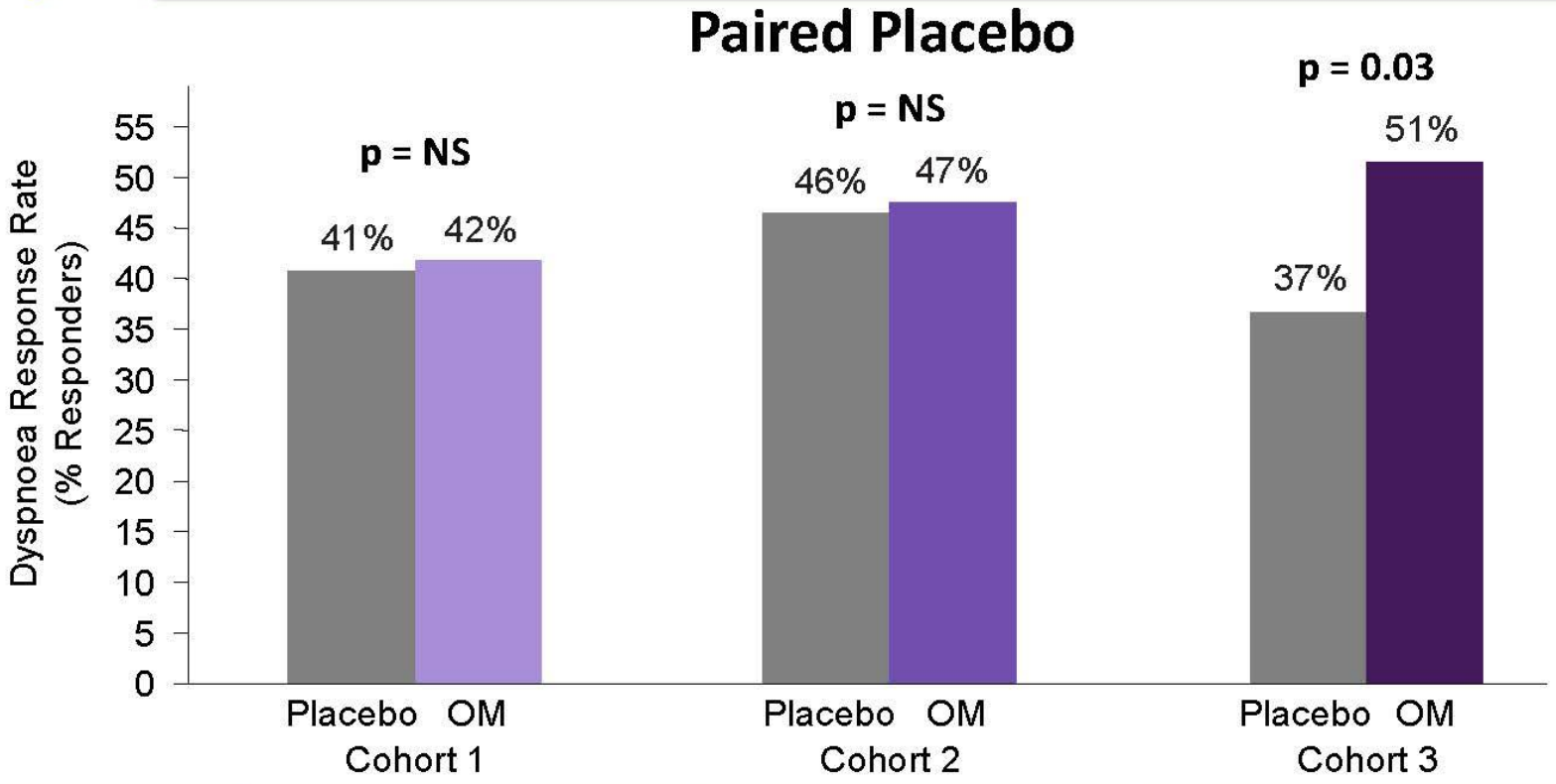
Pooled Placebo



Response Rate Ratio*	**1.03**	**1.15**	**1.23**
95% CI	**(0.79, 1.35)**	**(0.90, 1.47)**	**(0.97, 1.55)**

*Ratio of response rate to Pooled Placebo
p-value of a CMH test among all 3 Placebo arms = 0.32

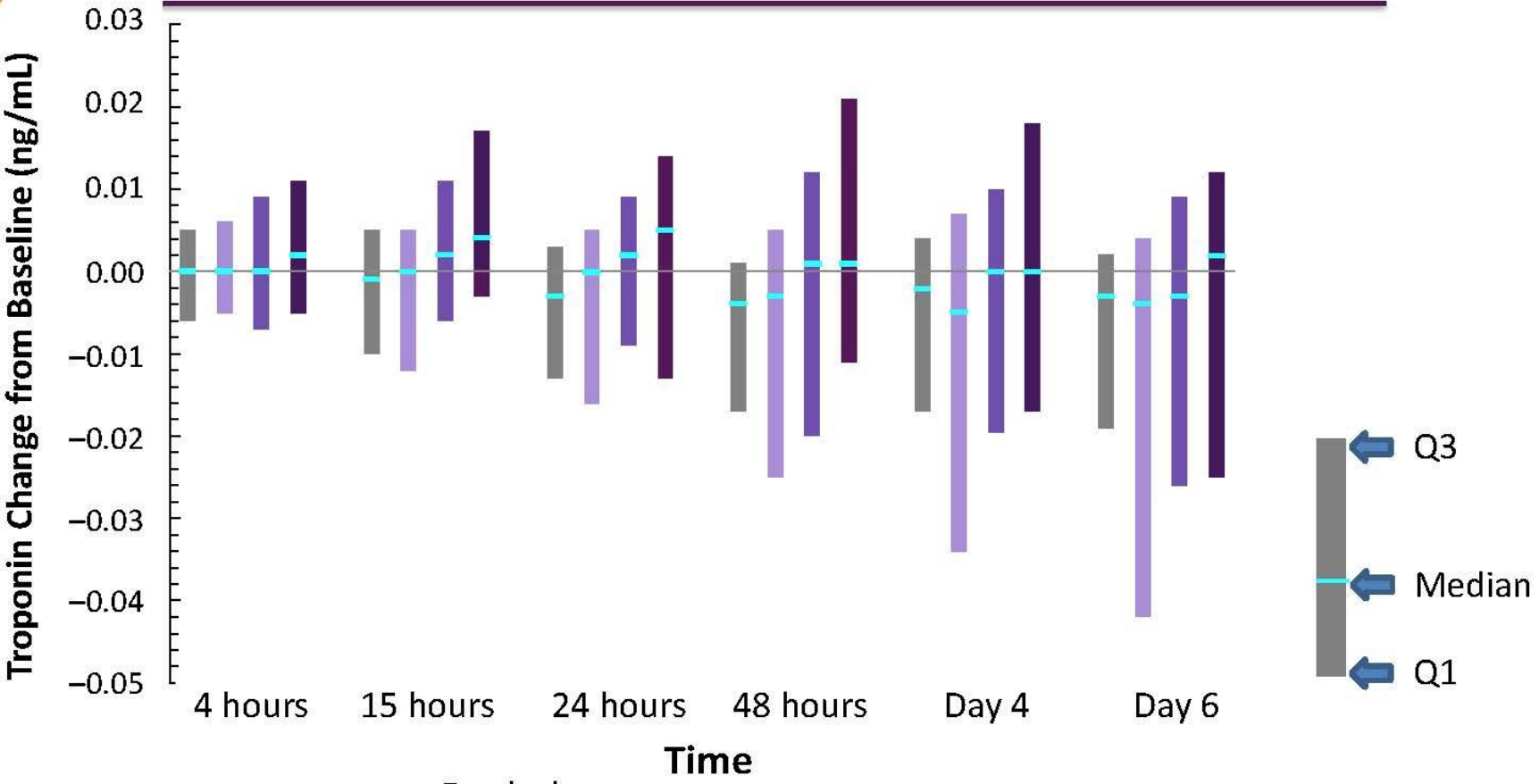
Supplemental Primary Analysis: Dyspnoea Response (Likert Scale)



Response Rate Ratio	**1.02**	**1.02**	**1.41**
95% CI	**(0.74, 1.42)**	**(0.76, 1.37)**	**(1.02, 1.93)**

Response rate ratio: ratio of response rate to Placebo within each cohort

Troponin-I Change from Baseline (ng/mL) Compared with Pooled Placebo



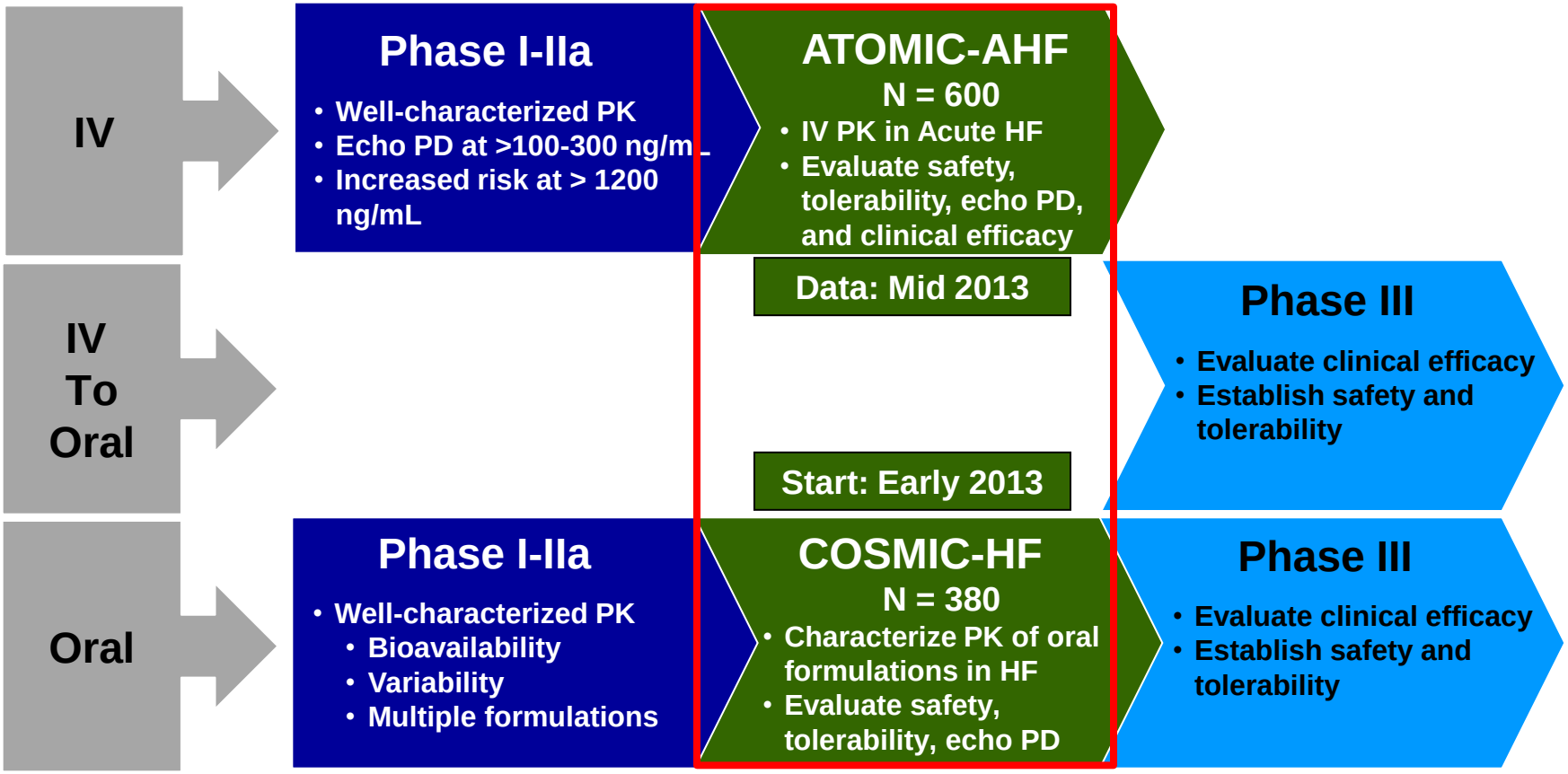
Baseline TnI (ng/mL)	Pooled Placebo	Cohort 1	Cohort 2	Cohort 3
Median	0.044	0.060	0.044	0.056
(Q1, Q3)	0.023, 0.080	0.028, 0.141	0.030, 0.084	0.026, 0.092

Change in Heart Rate and SBP

PK Concentration Bin Analysis	Control	OM Conc. Bin 1	OM Conc. Bin 2	OM Conc. Bin 3
OM concentration range (ng/ml)		≥88-200	>200-300	>300-787
Heart Rate (beats/min)				
LS means	-4.3	-4.4	-6.3	-6.5
Difference from control		-0.1	-2.0	-2.3
95% CI		(-1.4, 1.1)	(-3.6, -0.4)	(-3.9, -0.6)
p-value		0.835	0.016	0.008
Linear regression slope	p < 0.0001			
SBP (mmHg)				
LS means	-4.6	-4.4	-4.0	-2.2
Difference from control		0.3	0.6	2.4
95% CI		(-1.2, 1.7)	(-1.2, 2.4)	(0.6, 4.2)
p-value		0.719	0.521	0.009
Linear regression slope	p = 0.0017			

N: number of patients in the bin, n: number of observations in the bin. Heart rate measured by ECG. 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.

Omecamtiv Mecarbil: Development Across Continuum of Care



IV and oral formulations enable evaluation of *omecamtiv mecarbil* across a range of heart failure patient populations

Summary

- Efficacy
  - OM did not meet the 1° endpoint of dyspnoea relief
  - Appeared to improve dyspnoea in Cohort 3
  - Trends towards reduction of worsening HF
- Safety
  - Overall SAE profile and tolerability similar to placebo
  - Increase in troponin; no clear relationship to OM concentration
  - Numerical imbalance in MIs in Cohort 3
  - No evidence of pro-arrhythmia
- Pharmacology
  - PK similar to healthy volunteers and stable HF patients
  - Systolic ejection time significantly increased consistent with MOA
  - Small fall in heart rate & rise in systolic BP at higher doses


Thank You!

ATOMIC-AHF: Study Objectives

Study Objectives

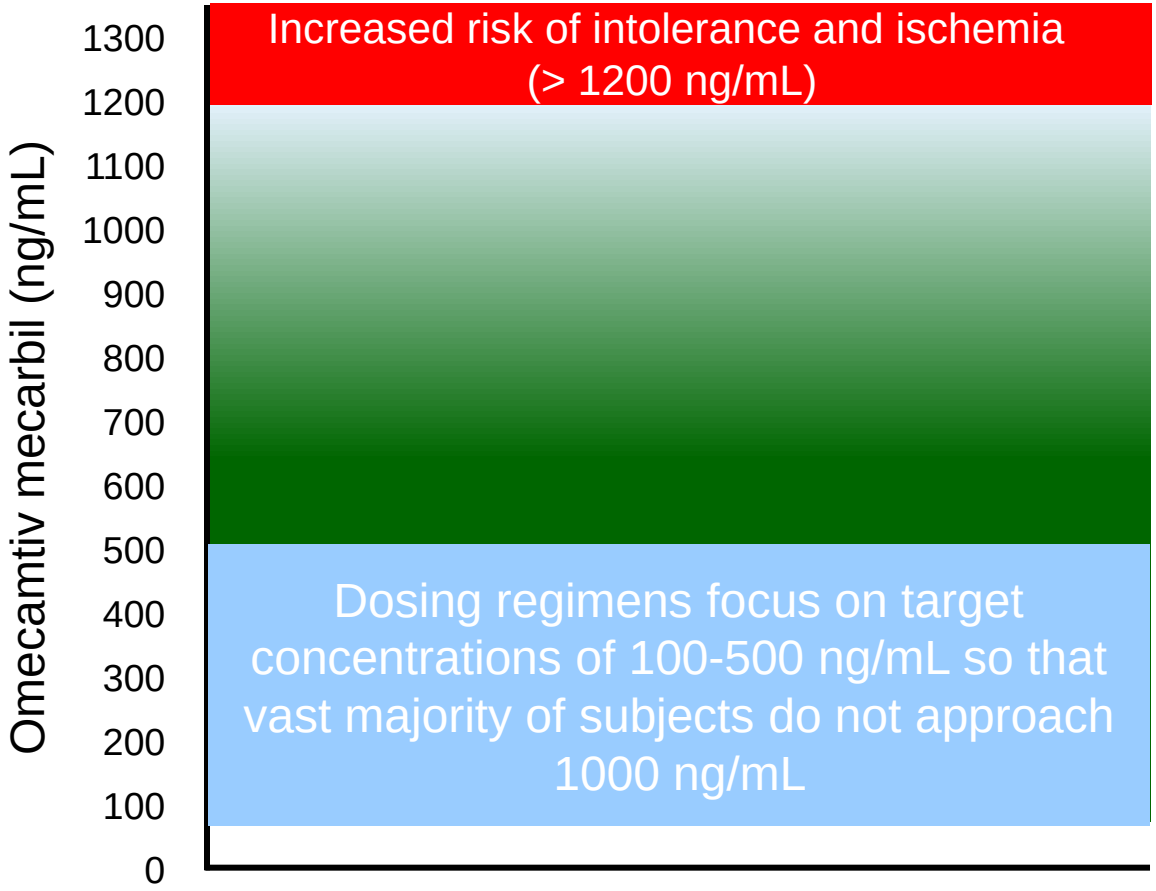
- Primary
  - Evaluate the effect of 48 hours of intravenous (IV) omecamtiv mecarbil (OM) compared with placebo on dyspnea in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure (AHF)
- Secondary
  - Assess the safety and tolerability of 3 dose levels of IV omecamtiv mecarbil (OM) compared with placebo in subjects with left ventricular systolic dysfunction hospitalized for AHF
  - Evaluate the effects of 48 hours treatment with IV OM on dyspnea (different measurement than primary), patient global assessment (PGA), change in NT-pro BNP and short-term clinical outcomes
  - Characterize PK of OM, including major metabolites, following IV infusion and evaluate the relationship between OM plasma concentration and echocardiographic parameters in subjects with acute heart failure

ATOMIC-AHF: Inclusion Criteria

KEY Eligibility Criteria – Inclusion

- Male/female ≥ 18 and ≤ 85 years of age at the time of randomization
- History of chronic heart failure (defined as requiring treatment for heart failure for a minimum of 30 d before hospitalization)
- History of left ventricular ejection fraction (LVEF) ≤ 40% (echocardiogram, radionuclide ventriculography, cardiac magnetic resonance imaging, or contrast ventriculography) without an intervening value of > 40%
- Dyspnea, due to heart failure, at rest or with minimal exertion
- Screening BNP ≥ 400 pg/mL or NT-proBNP ≥ 1600 pg/mL during screening (BNP ≥ 600 pg/mL or NT-proBNP ≥ 2400 pg/mL if the subject has atrial fibrillation)

Omecamtiv Mecarbil: Pharmacodynamics and Tolerability are Concentration-dependent



PK/PD Substudy Endpoint: 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.

Efficacy Endpoints

Primary:

- Dyspnoea symptom response (7-point Likert scale) through 48 hours

Secondary:

- Death (any cause) and/or worsening heart failure within 7 days
- Dyspnoea area under the curve (AUC) (baseline to 5th day or discharge) as measured by subject self-assessed Numerical Rating Scale (NRS)
- Dyspnoea by 7-point Likert scale at each scheduled assessment
- Patient Global Assessment response through 48 hours
- Change from baseline in NT-proBNP
- Length of initial hospital stay
- Days alive out of hospital until day 30

PK/PD (Echo) Sub-study

ATOMIC-AHF

Acute **T**reatment with **O**mecamtiv **M**ecarbil to **I**ncrease **C**ontractility in **A**cute **H**eart **F**ailure

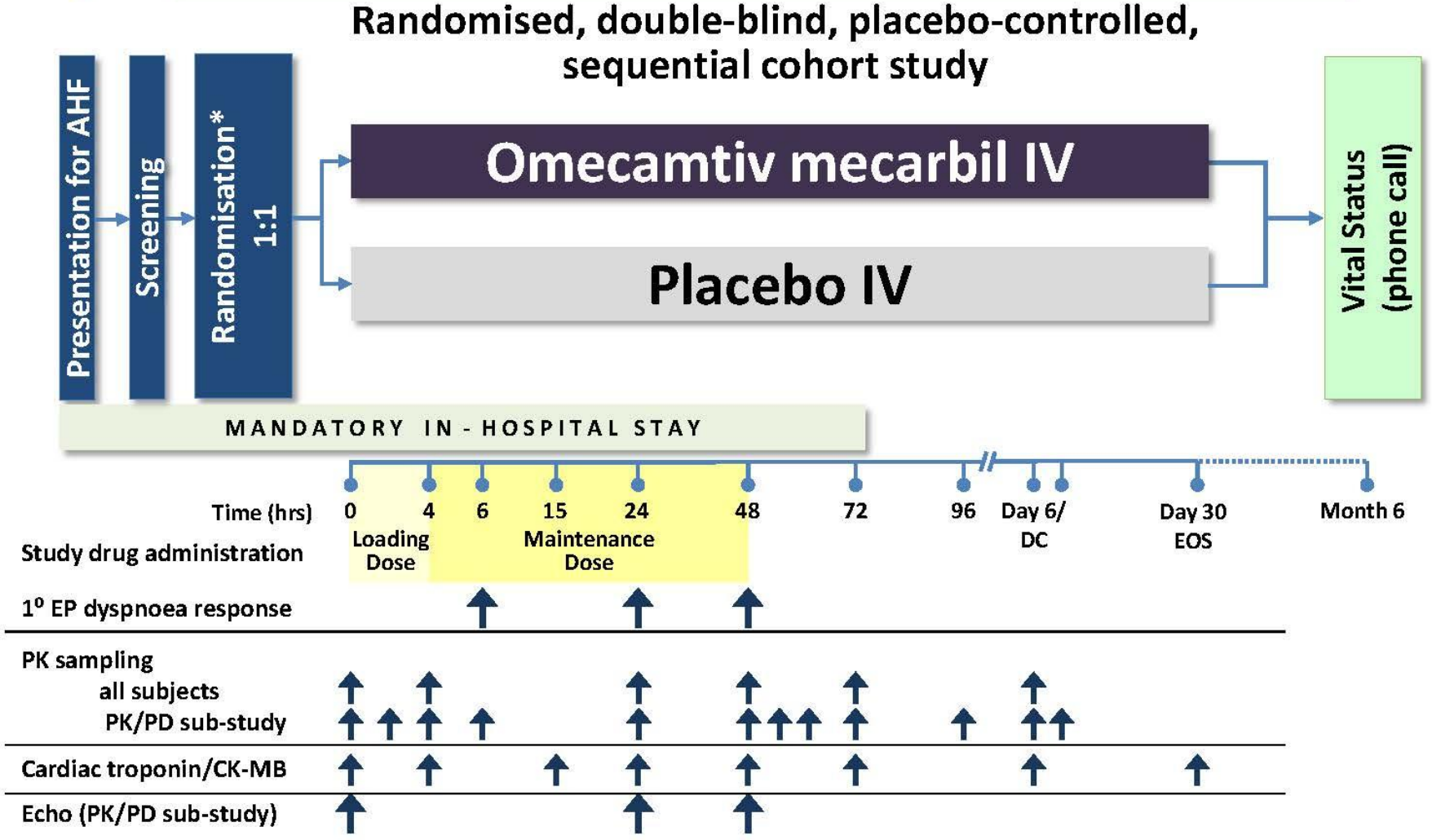
Objective:

- To evaluate the safety, pharmacokinetics/ pharmacodynamics, and efficacy of IV omecamtiv mecarbil (OM) in patients with acute heart failure (AHF)

Hypothesis:

- At least 1 dose level of IV OM will be well tolerated and will result in improvement of dyspnoea in subjects with left ventricular systolic dysfunction hospitalised for AHF

Study Design



* Randomisation within 24 hours of initial IV diuretic (Amendment 2)

OM aktuelle klinische Studie (geplant 600 Pat.)