Training course:
All About Clinical Trials

UPCOMING AND ONGOING CLINICAL TRIALS:
Heart Failure

Claudio Ceconi

ESC Working Group Cardiovascular Pharmacotherapy

Declaration of Conflict Of Interest

The existence of potential conflicts of interest does not necessarily indicate a bias. However it is our ethical obligation to inform organisers and participants so that they are made aware of any relationship that might cause unintentional bias. A potential conflict of interest may arise from various relationships, past or present, such as employment, consultancy, investments and stock ownerships, funding for research, family relationship etc.

✓ **I have no potential conflict of interest to report**

□ I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	
Receipt of honoraria or consultation fees:	
Participation in a company sponsored speaker's bureau:	
Stock shareholder:	
Spouse/partner:	
Other support (please specify):	

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Unmet needs

- **Effective treatments in Acute Heart Failure**
- **Effective treatments in Heart Failure with preserved heart LV function**

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The failure of new therapies

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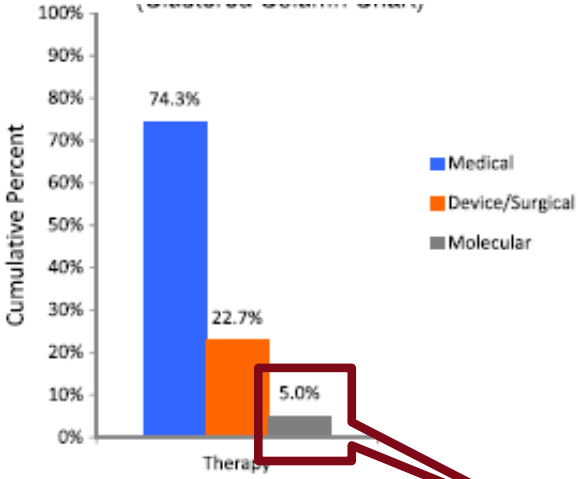
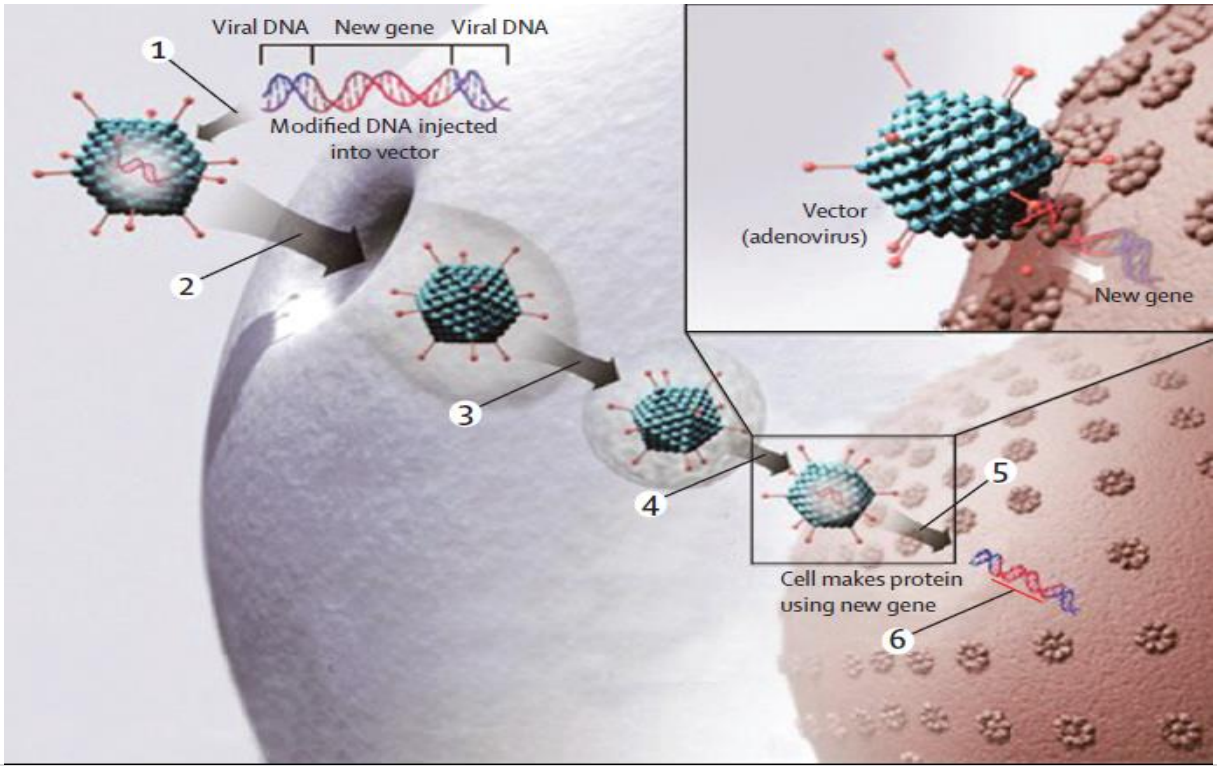


Inotropic mechanism	Drugs
Sodium-potassium-ATPase inhibition	Digoxin
β-Adrenoceptor stimulation	Dobutamine, dopamine
Phosphodiesterase inhibition	Enoximone, milrinone
Calcium sensitization	Levosimendan
Sodium-potassium-ATPase inhibition plus SERCA activation	Istaroxime
Acto-myosin cross-bridge activation	Omecamtiv mecarbil
SERCA activation	Gene transfer
SERCA activation plus vasodilation	Nitroxyl donor; CXL-1020
Ryanodine receptor stabilization	Ryanodine receptor stabilizer; S44121
Energetic modulation	Etomoxir, pyruvate

Gene transfer in the future for HF therapy ?



Braunwald E, Lancet http://dx.doi.org/10.1016/

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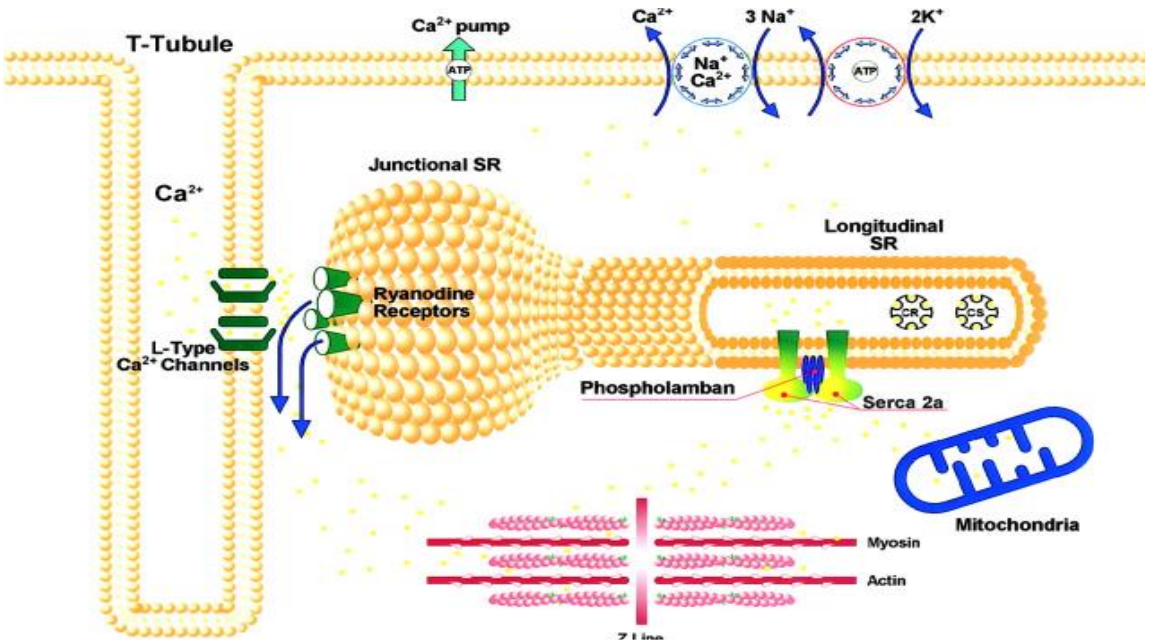
SERCA2a gene therapy in HF



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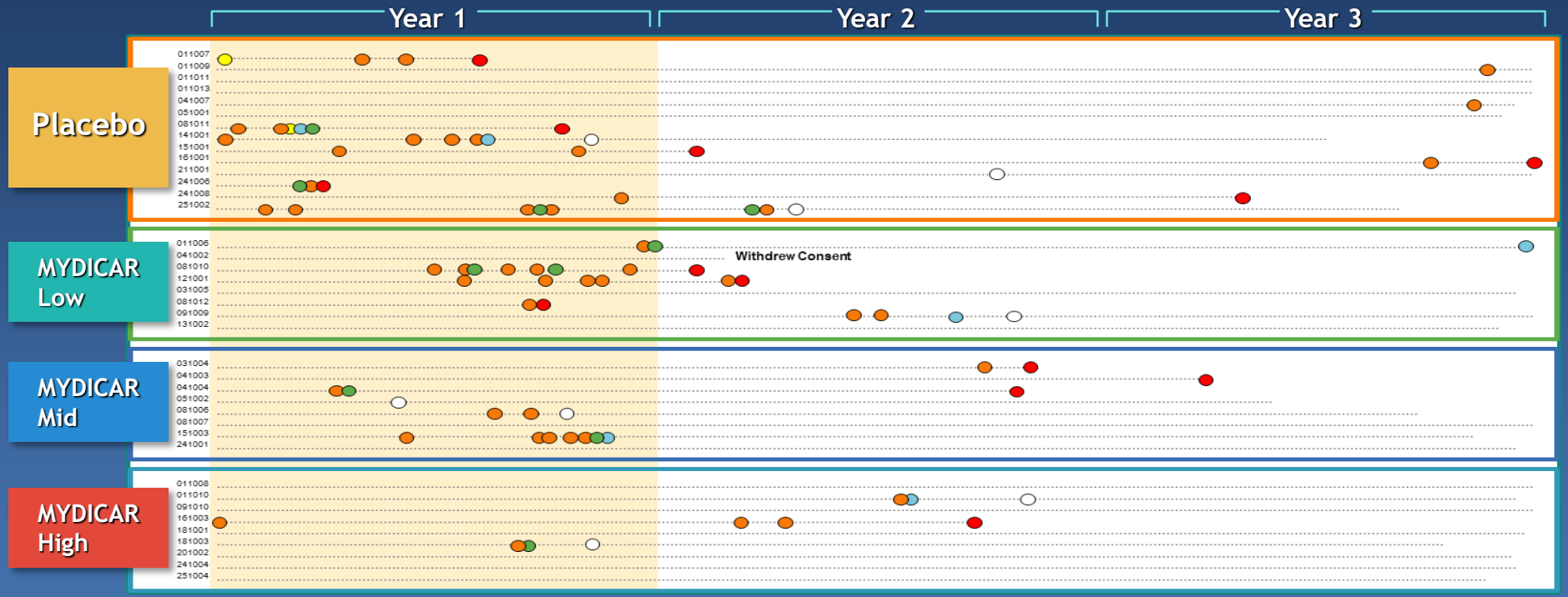
MYDICAR Reduced Adjudicated CV Clinical Events: 3-Year Follow-up



- 13 Deaths in Phase 2 Trial
- 6 in Placebo
- 3 in Low Dose
- 3 in Mid Dose

Zsebo K et al. Circ Res 2014;114:101-8

CUPID 2: A Phase 2b Confirmatory Ongoing International Study – Data April 2015

Enrolment | Conduct (12 Months o | Analysis 3 Months

Study Population

- 18-80 years of age
- Systolic HF
- Ischemic or non-ischemic
- EF ≤35%
- NYHA Class II to IV
- Maximal, optimized HF regimen

MYDICAR 1x10^{13} DRP, N=125

Placebo, N=125

Sample Size/Power:

N=125 per treatment group wi rent events provides:

83% power, 0.05 two-sided s evel, to detect at least a 45% risk reduction (HR=0.55)

All Subjects Foll arterly for Clinical Events Until:

Last enrolled sub es 12 months of observation AND

186 adjudicat ed hospitalizations have occurred

PRIMA OINT

Tim ent HF-related hospitalizations in presence of terminal events (a eath, heart transplant, and LVAD implantation)

DARY ENDPOINT

o-first terminal event (all-cause death, heart transplant, LVAD implantation)

DDITIONAL ENDPOINTS

Symptoms, Exercise Capacity and Quality of Life

Recurrent analysis showed inefficacy p=0.98

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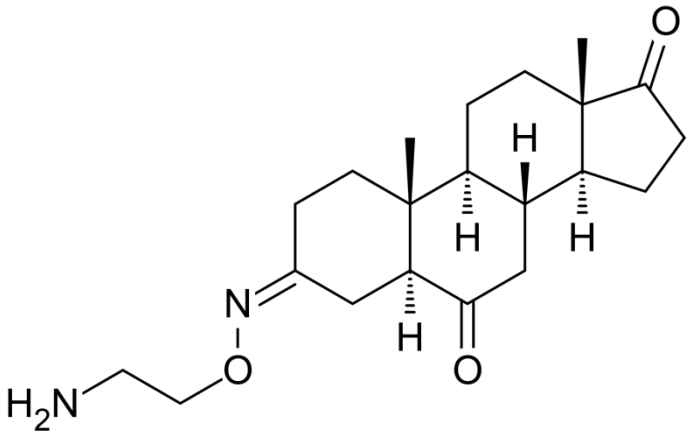
SERCA2a story is not over yet…

Istaroxime phase III in acute heart failure



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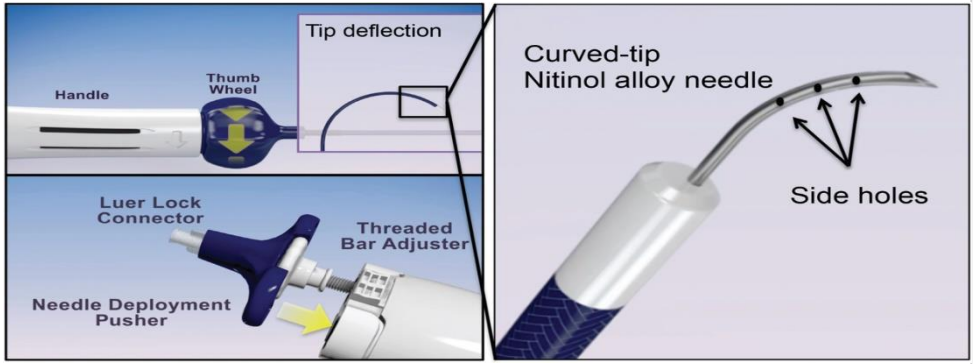
Cardiopoietic Stem Cell Therapy Improved Left Ventricular Remodeling - Longitudinal Results from the CHART-1 Study

John R. Teerlink, MD, HFA Congress 2017

- **Intramyocardial injections using retention-enhanced catheter (C-Cathez®)**
- **Up to 20 injections of 0.5 mL each spaced ~1 cm apart over LV where ≥ 8 mm thick**
  - **≤ 16 injections n=29**
  - **17/18/19 n=35**
  - **≥ 20 n=56**
- **Sham procedure did not have intramyocardial injections**



Bartunek J, *et al. Eur J Heart Fail* 2016;18:160-8.

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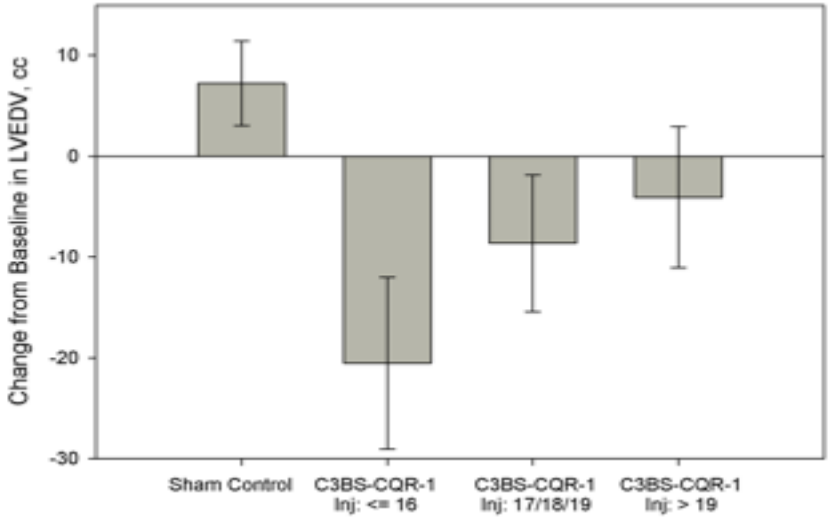
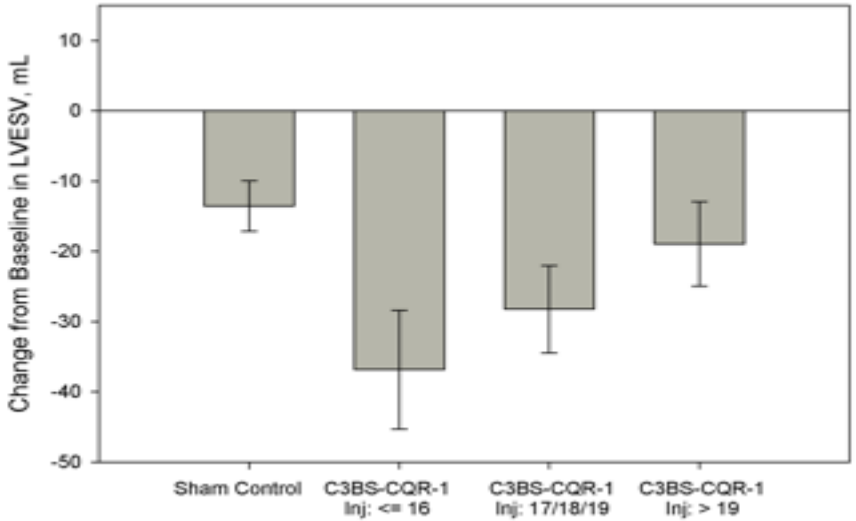
Changes in LVEDV and LVESV at Week 52 by number of cardiopoietic cell injections





In this population of patients with advanced HF, intramyocardial administration of cardiopoietic stem cells induced significant reverse LV remodeling

Effects on remodeling appear most pronounced in patients who received a moderate number of injections

John R. Teerlink, MD, HFA Congress 2017

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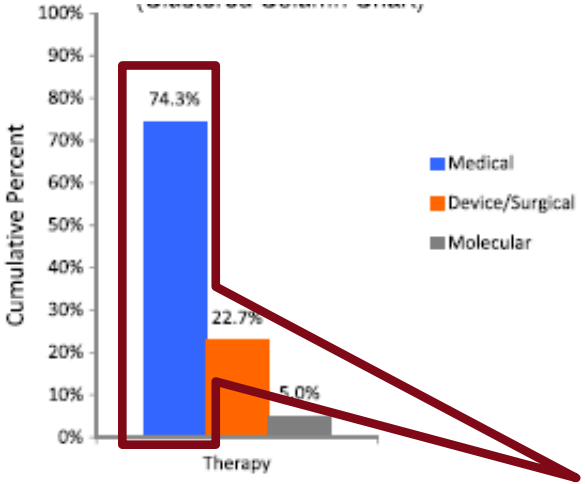

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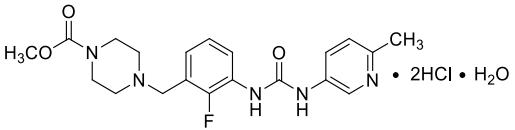
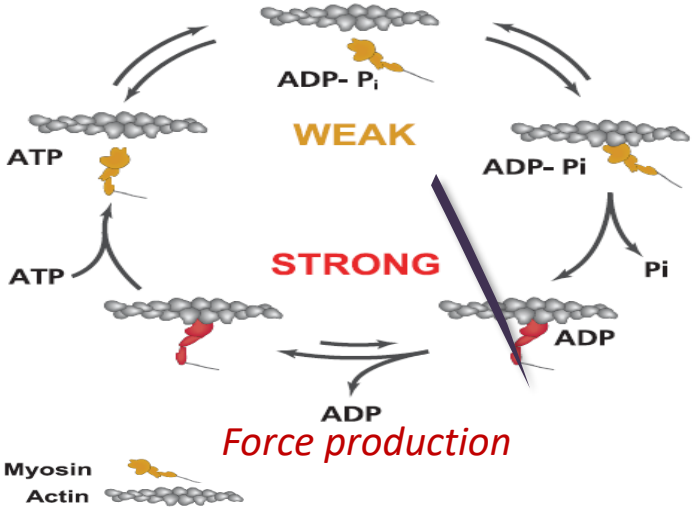
Omecamtiv Mecarbil (OM)
Selective Cardiac Myosin Activator



Omecamtiv mecarbil is a small molecule that directly activates cardiac myosin



OM binds directly to the enzymatic domain of cardiac myosin and, during systole, increases its rate of ATP hydrolysis

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_2

Malik FI, *et al.* *Science* 2011; 331:1439-43.

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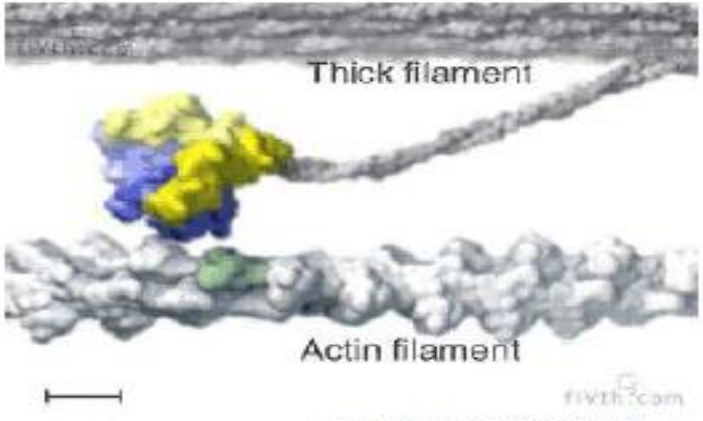
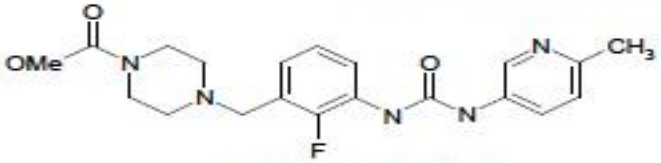
Omecamtiv Mecarbil: A Cardiac Myosin Activator

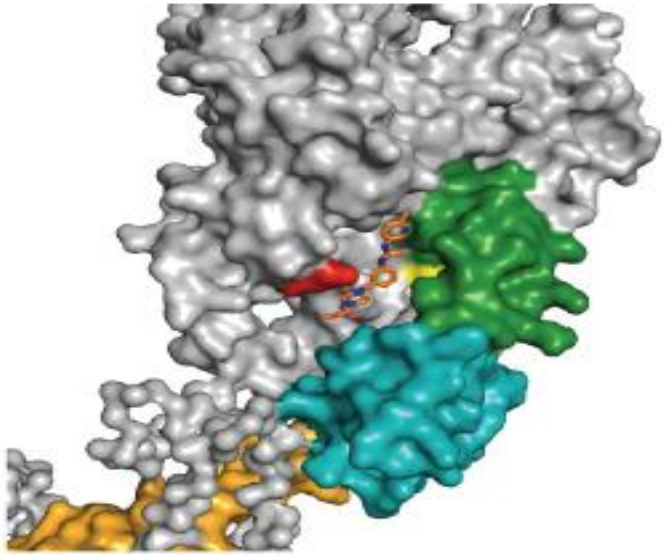
Omecamtiv Mecarbil Binds to the Mechanochemical Domain of Myosin



Vale and Milligan, *Science*. 2000.



Omecamtiv Mecarbil
(MW = 401.43)



S1 Domain

Malik et al. *Science*. 2011.

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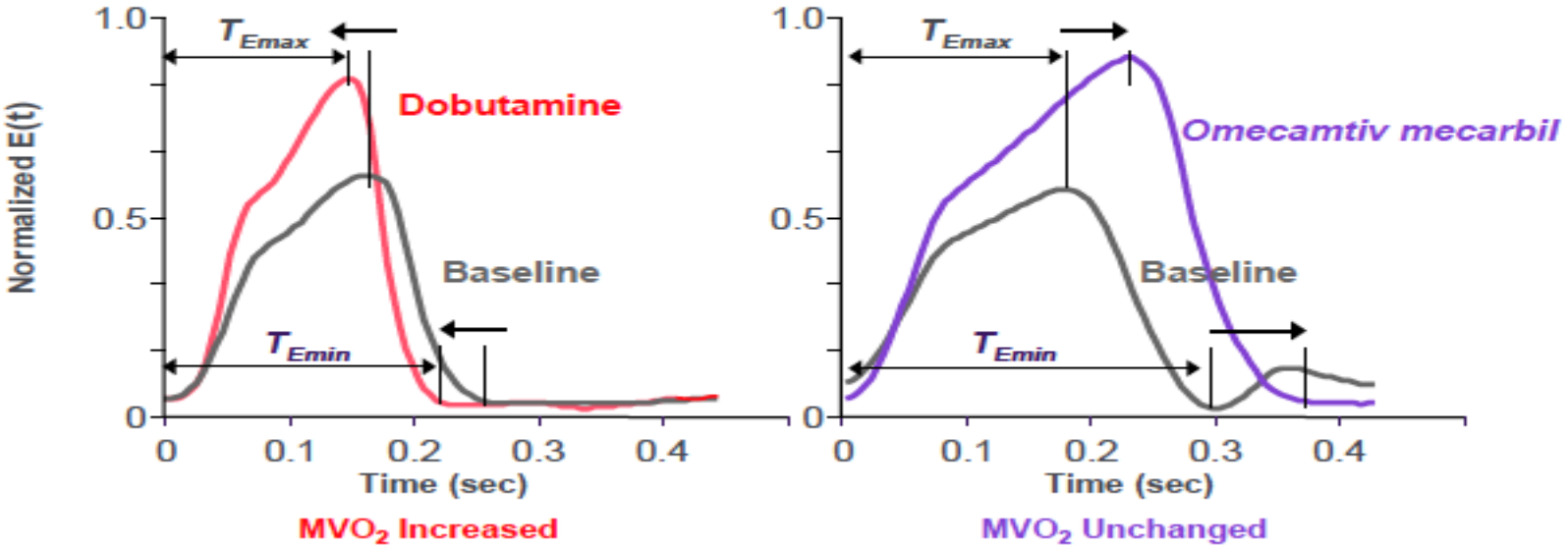
Omecamtiv Mecarbil: Preclinical Pharmacology in Dog Heart

Increases in Duration of Cardiac Contraction Underlie Increases in Cardiac Function

Time-dependent Elastance [E(t)]



Malik et al. *Science*. 2011.

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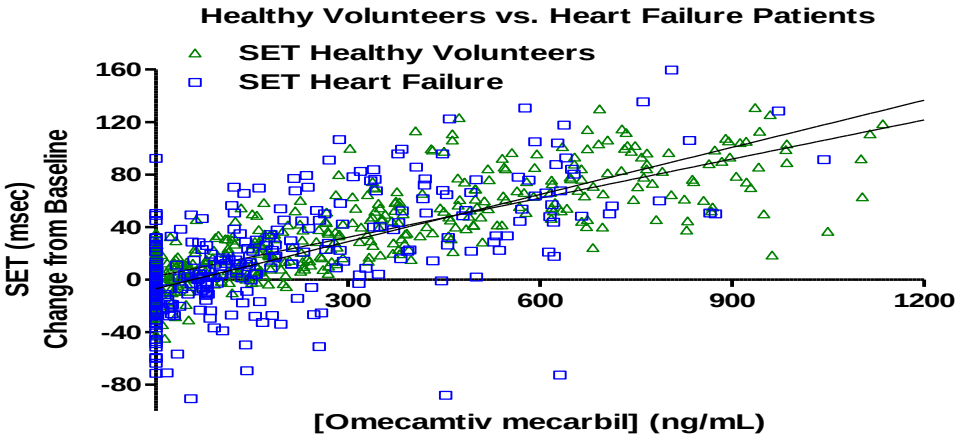
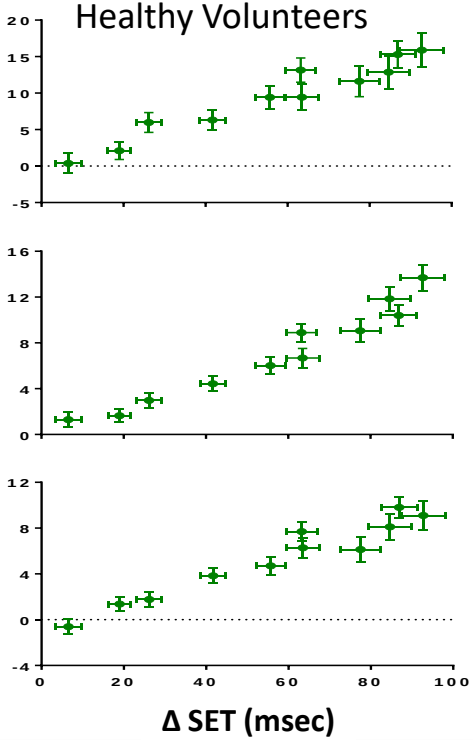
Increase in systolic ejection time underlies increase in cardiac function





Teerlink JR, et al. *Lancet* 2011; 378: 667–75.
Cleland JGF, et al. *Lancet* 2011; 378: 676–83.

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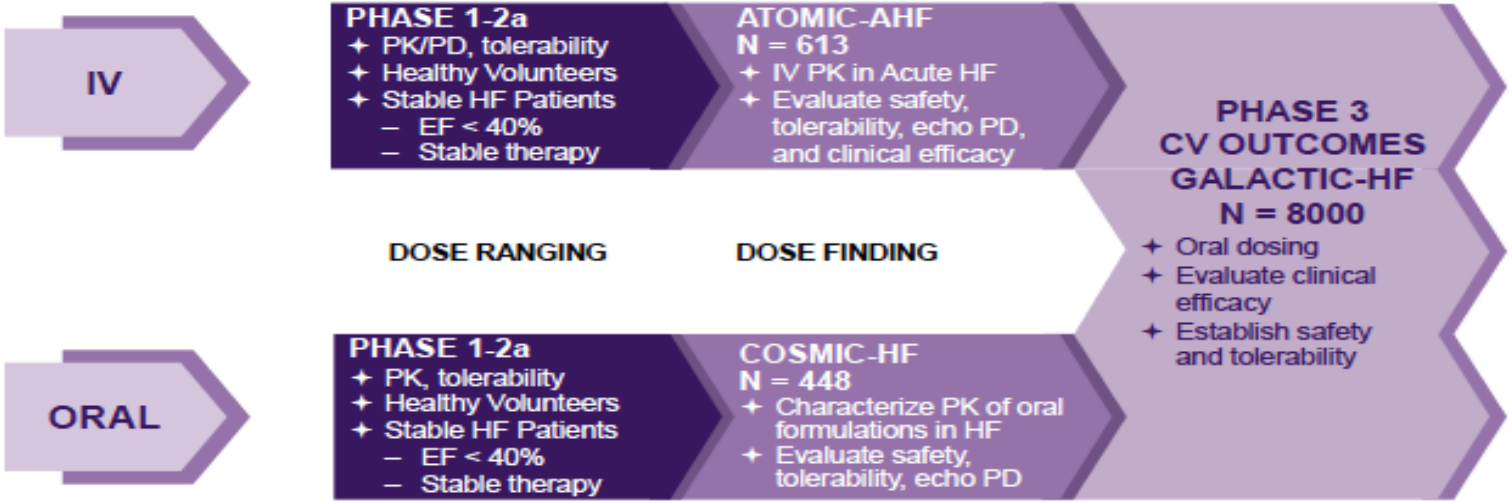
Omecamtiv Mecarbil: Overview of Development Program



Evaluation across a range of heart failure patient populations
14 phase 1 and 2 studies completed; > 1000 subjects dosed

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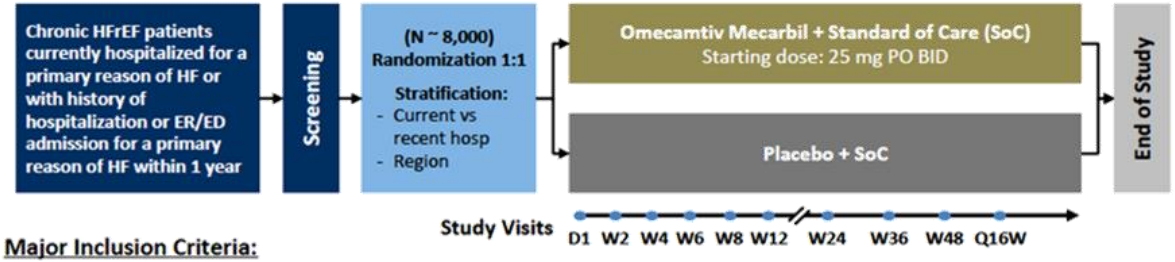
GALACTIC-HF

Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility (in Heart Failure)

A Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction



Major Inclusion Criteria:

- Chronic heart failure
- NYHA II-IV
- LVEF ≤35%; ↑ BNP/NT-proBNP
- Managed with Standard of Care therapy
- Current hospitalization for HF or history of hospitalization or ER/ED visit for HF within 12 months

- 1° endpoint:
  Time to CV death or first HF event
- Event driven trial

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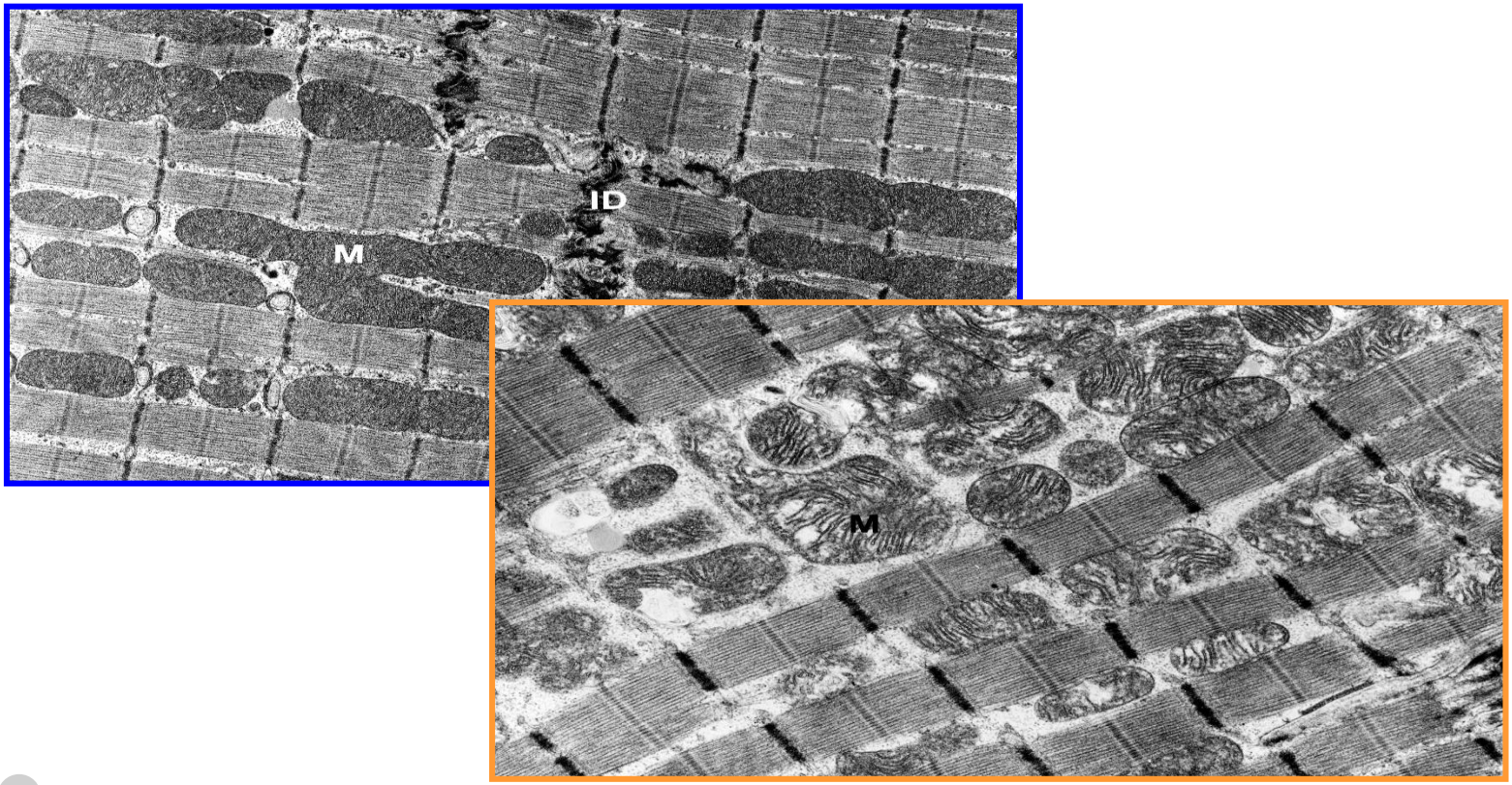
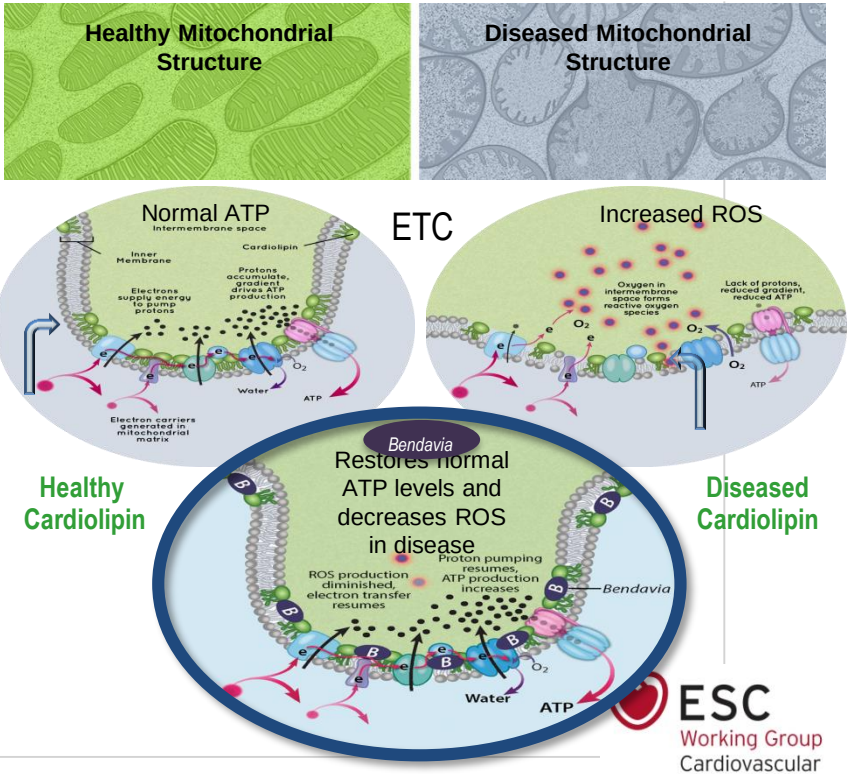
Mithocondrial therapies



Bendavia

Improves Mitochondrial Structure and Function

- **Cardiolipin shapes mitochondrial structure**
  - Foundation of electron transport chain (ETC)
  - Maintains healthy ATP levels and minimal ROS production
- **Bendavia reestablish healthy mitochondrial structure and function in disease**
  - Electrostatic interaction with cardiolipin, maintaining ETC
  - Restoring healthy ATP and ROS levels
  - Modifying disease



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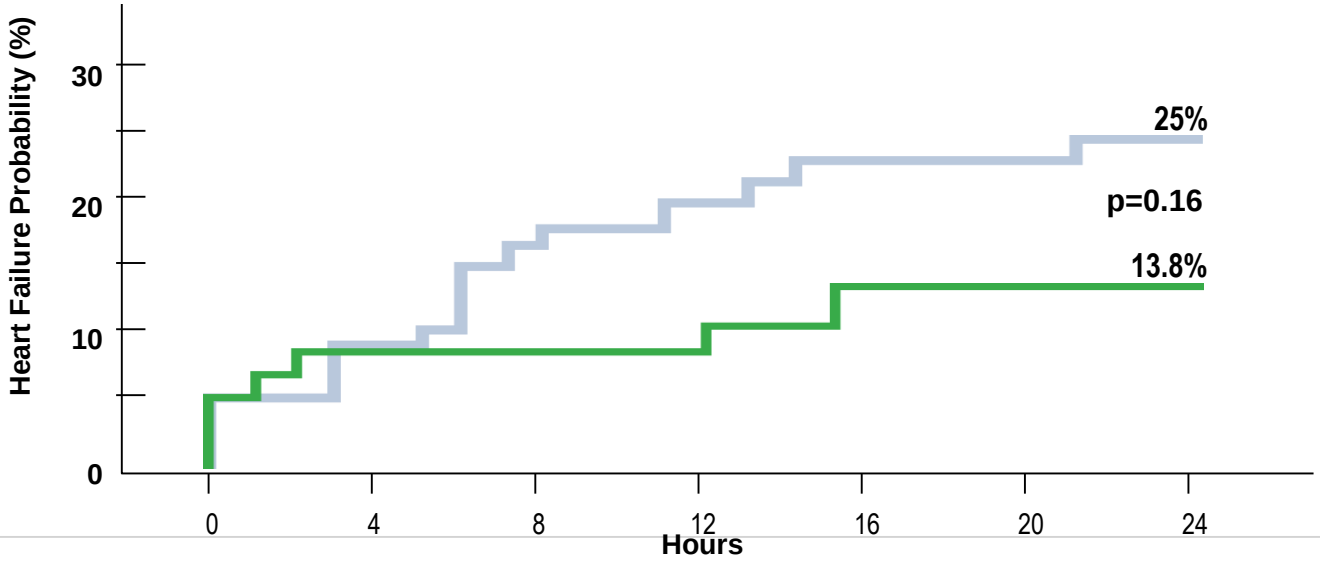
Bendavia in Acute Coronary Syndrome

EMBRACE Clinical Study

- Clinical outcomes and heart failure
  - Bendavia reduces the incidence of heart failure during the initial day after ACS
  - No differences in clinical safety and patient tolerability



Left Ventricular Ejection Fraction (LVEF)

41.9 ± 10.4 (n=55)

44.0 ± 11.0 (n=52)

Placebo

Bendavia

Gibson et al. ACC 2015

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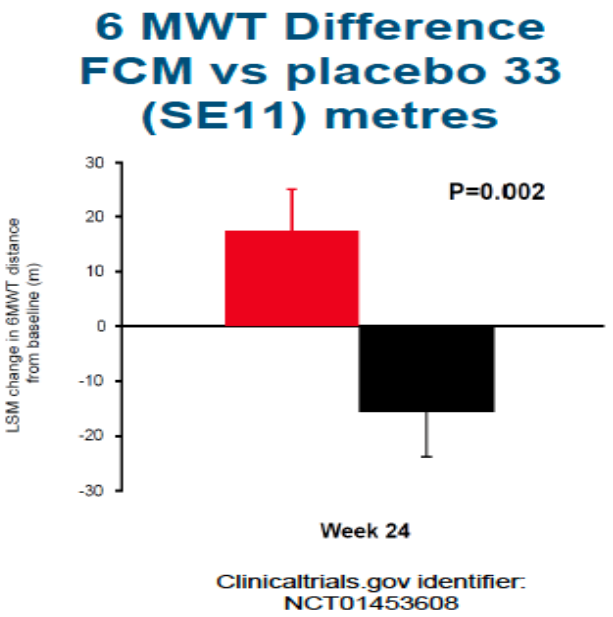
The hypothesis CONFIRM HF

European Heart Journal (2015) **36**, 657–668
doi:10.1093/eurheartj/ehu385

FASTTRACK ESC HOT LINE
Heart failure/cardiomyopathy

Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

Piotr Ponikowski[1,2]*, Dirk J. van Veldhuisen[3], Josep Comin-Colet[4], Georg Ertl[5,6], Michel Komajda[7], Viacheslav Mareev[8], Theresa McDonagh[9], Alexander Parkhomenko[10], Luigi Tavazzi[11], Victoria Levesque[12], Claudio Mori[12], Bernard Roubert[12], Gerasimos Filippatos[13], Frank Ruschitzka[14], and Stefan D. Anker[15], for the CONFIRM-HF Investigators



Speaker

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Choosing Quality vs Quantity of Life in Heart Failure

- … there was a **"strong preference for the symptom relief afforded by inotropes [illegible] he better sur[illegible] promise of optimal medical [illegible] vs 26%, p[illegible]** Maclver J, *J Heart Lung*

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FAIR-HF-2

Design: Multi-centre, international, randomised (1:1), double-blind, placebo-controlled

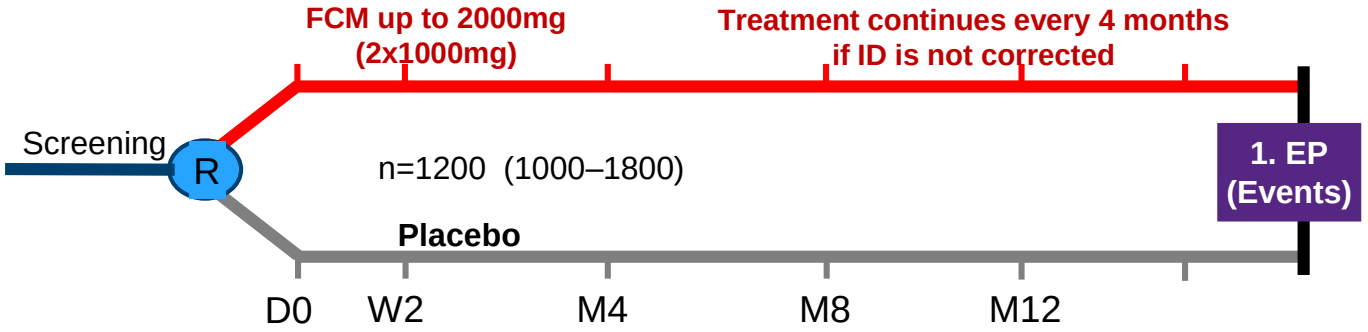
Main inclusion criteria:

CHF with LVEF ≤ 45% and NYHA class II / III

HF hospitalisation within 6 mo or BNP/NT-proBNP >100/>300 pg/mL or MRproANP>120 mmol/L

Iron deficiency: serum ferritin <100 µg/L or ferritin 100-299ng/mL with TSAT <20%

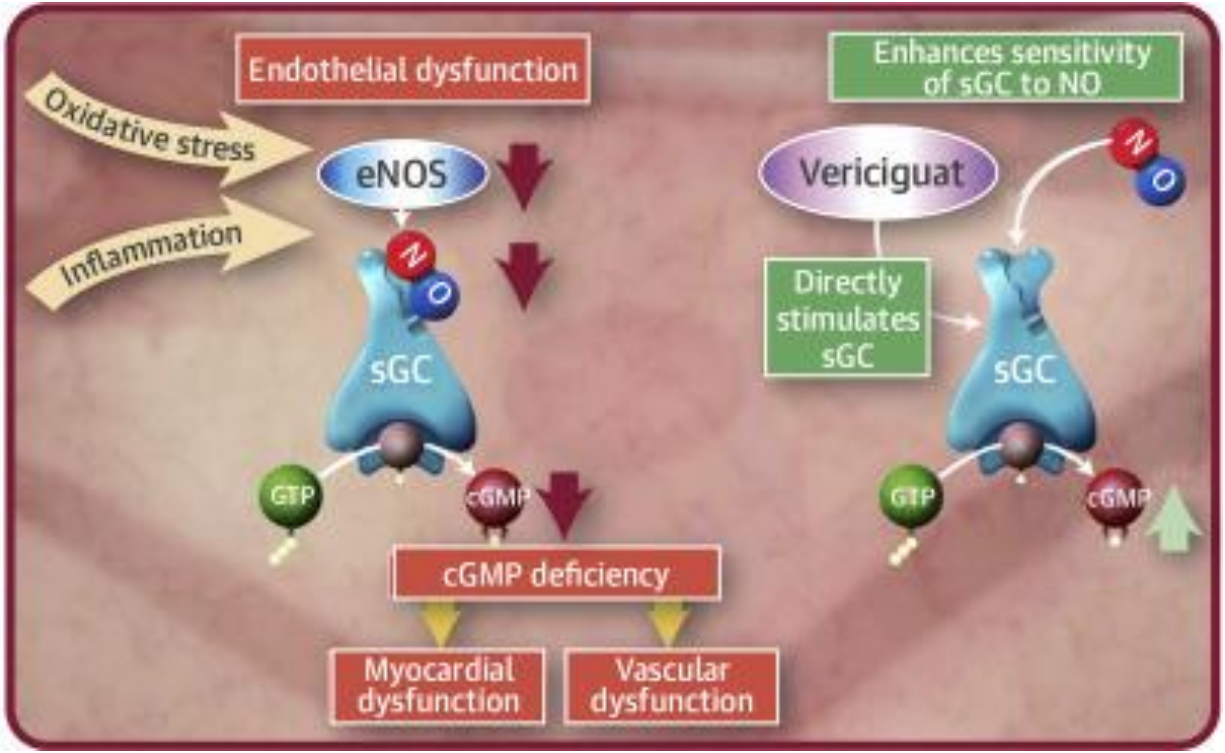
Hb: ≤ 14.0 g/dL



Primary endpoint

- Rate of recurrent hospitalisations for heart failure or CV death during follow-up.

Vericiguat


Endothelial dysfunction
Oxidative stress
Inflammation
eNOS
sGC
GTP
cGMP
cGMP deficiency
Myocardial dysfunction
Vascular dysfunction
Enhances sensitivity of sGC to NO
Vericiguat
Directly stimulates sGC
sGC
GTP
cGMP

VICTORIA[2]

- **Hypothesis:** Vericiguat will be superior to placebo, added to SOC, in patients with symptomatic chronic HF-REF (LVEF <45%)
- **Population:** 4872 patients; iv therapy for exacerbation of HF in past 3 months/hospitalization within 6 months and elevated NPs
- **Primary endpoint:** CV death or HF hospitalization: target 1561 events (powered for CV death).

[1]NCT01877915 [2]NCT02861534

The soluble guanylate cyclase stimulator reduced the composite endpoint of CV death or heart failure hospitalization compared with placebo when given on top of standard therapies. No additional details were provided

Monday, November 18, 2019

Antidiabetic drugs in HF: the case of SGLT-2inh

DAPA-HF Trial, *NEJM 2019*

- **Empaglifozin (23) and Canaglifozin (5)**
- **Mechanisms ?**
- **HFrEF vs. HFpEF ?**

Many other stories going on…

- Praliciguat
- Cimlanod
- Neucardin
- K+ binders
- Etomoxir
- Ryanodine receptor stabilizers
- Neuregulin 1β3
- A pletora of biosensors
- …

The great thing in this world is not so much where we stand, as in what direction we are moving

Oliver Wendell Holmes 1841-1935

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