

Acute Heart Failure 2019

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FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE

Disclosures

- **Employment:** Duke University
- **Grant Support:** NHLBI, American Heart Association, Novartis, Amgen, Merck, Roche Diagnostics, Cytokinetics
- **Consulting:** Novartis, Amgen, Roche Diagnostics, Medtronic, BMS, GSK, Cytokinetics, EBR Systems, Abbott, Cardionomic, SC Pharma, Innolife, V-Wave, LivaNova, Alnylam
- **Journals:** Associate Editor, *JACC: Heart Failure*



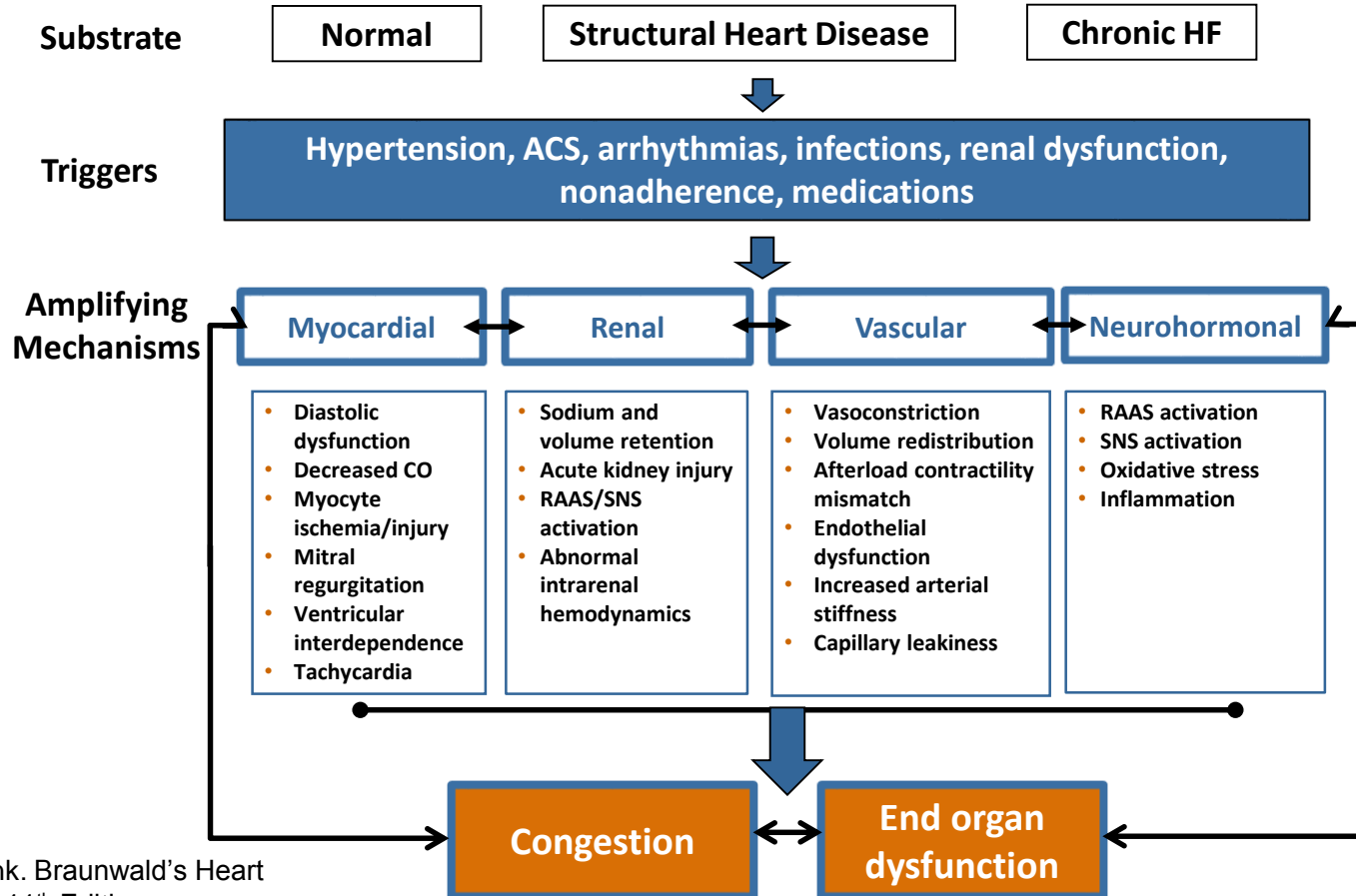
Does Acute Heart Failure = Hospitalization for Heart Failure?

- “Acute heart failure” is often not really acute
- Worsening heart failure can occur in both inpatient and outpatient settings
- This concept often conflates a clinical/biological process (worsening of heart failure) and a location of care (the hospital)

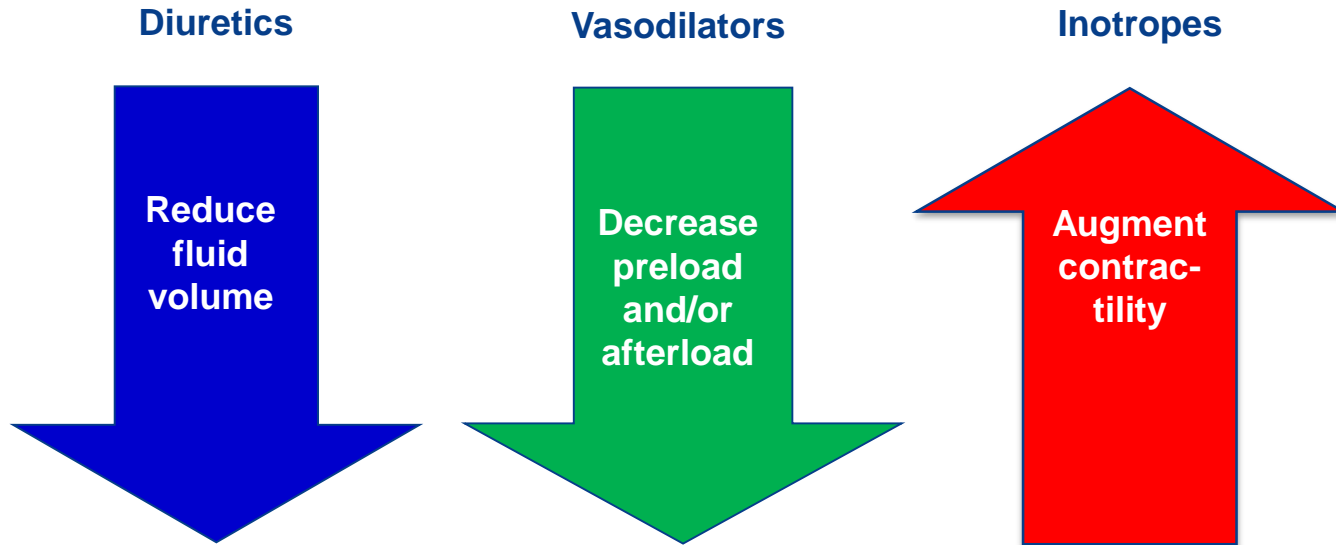
Goals of Care in Patients Hospitalized with HF

- Symptom relief
- Stabilize in-hospital course
- Optimize ICU/hospital length of stay
- Prevent in-hospital mortality
- Optimize chronic care
- Prevent post discharge events (death/rehosp)

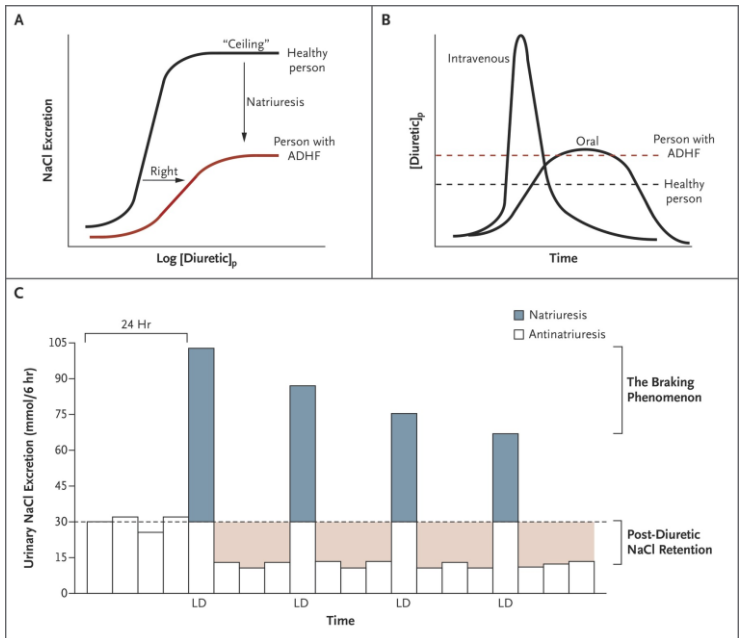
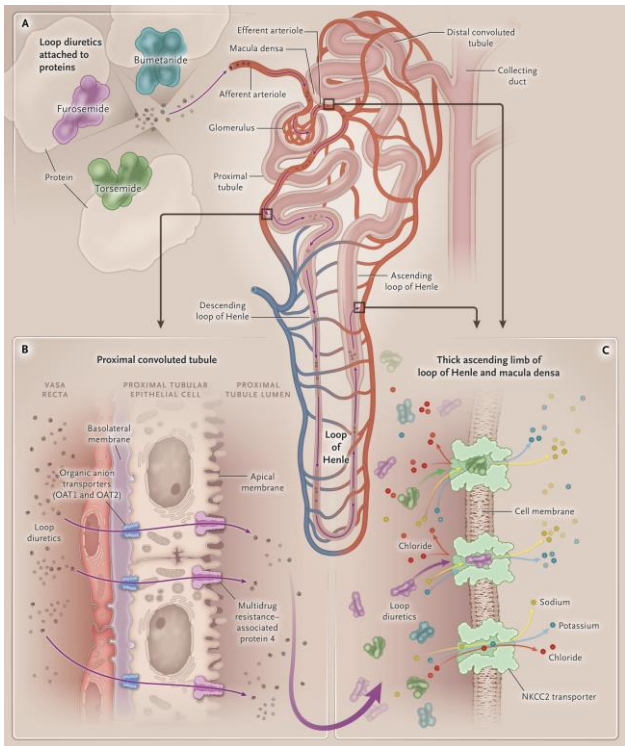
AHF Pathophysiology Remains Complex and Poorly Understood



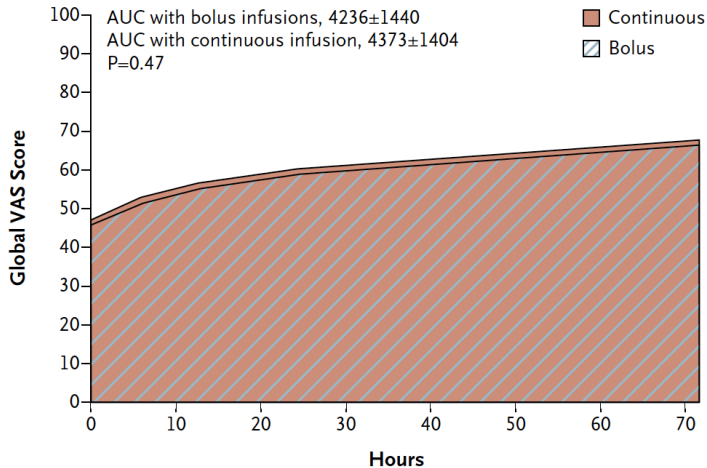
Current Treatments of HHF



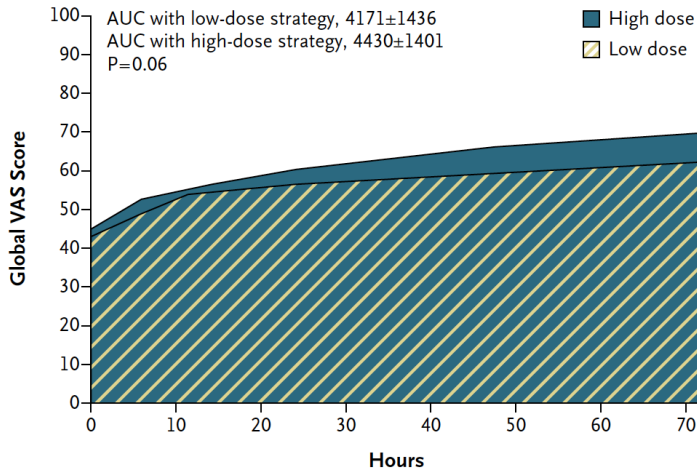
Loop Diuretics in Heart Failure



A Bolus vs. Continuous Infusion



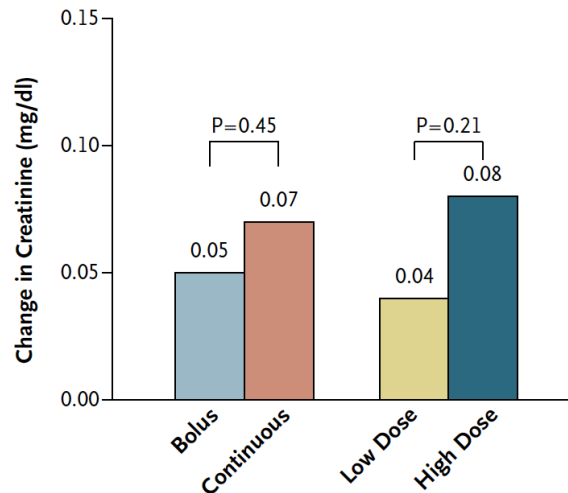
B Low-Dose vs. High-Dose Strategy



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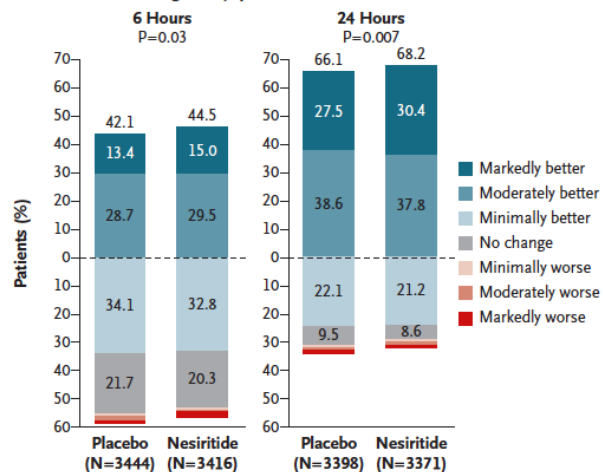
Secondary Endpoints: Low vs. High

	Low	High	P value
Dyspnea VAS AUC at 72 hours	4478	4668	0.041
% free from congestion at 72 hrs	11%	18%	0.091
Change in weight at 72 hrs	-6.1 lbs	-8.7 lbs	0.011
Net volume loss at 72 hrs	3575 mL	4899 mL	0.001
Change in NTproBNP at 72 hrs (pg/mL)	-1194	-1882	0.06
% Treatment failure	37%	40%	0.56
% with Cr increase > 0.3 mg/dL within 72 hrs	14%	23%	0.041
Length of stay, days (median)	6	5	0.55

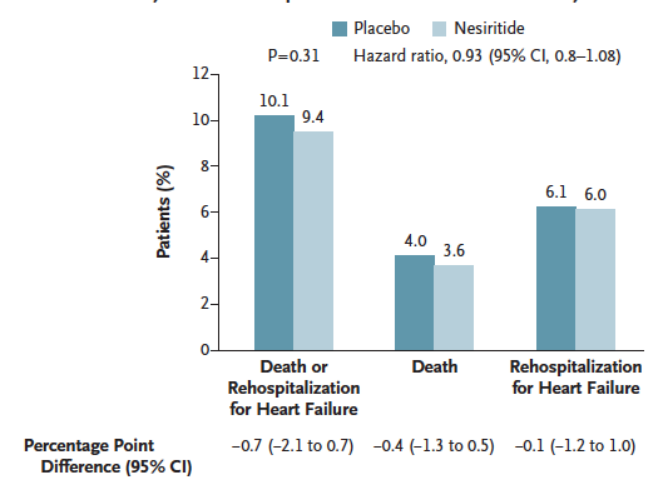
ORIGINAL ARTICLE

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

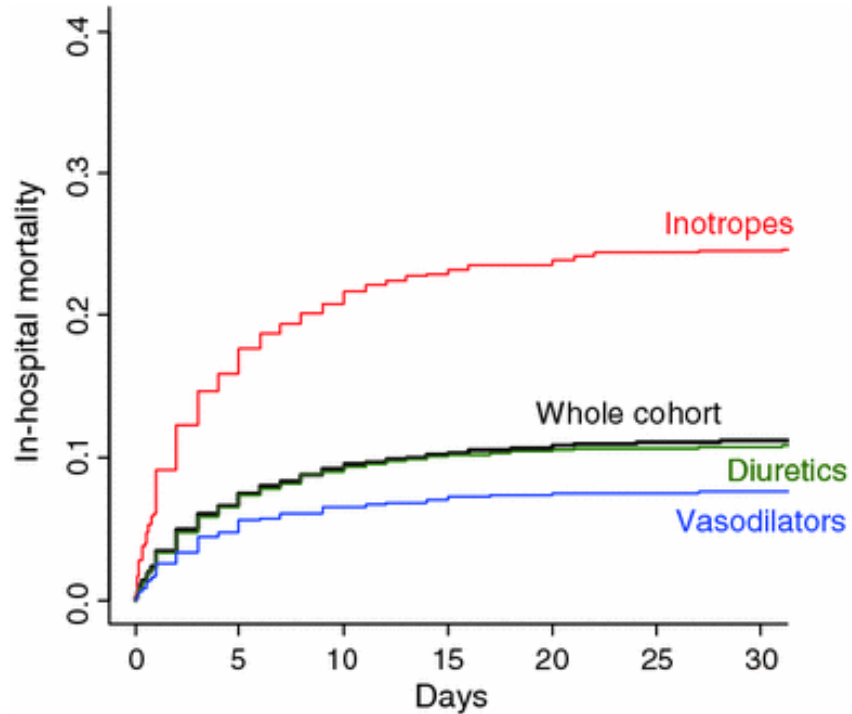
A Self-Assessed Change in Dyspnea at 6 and 24 Hours



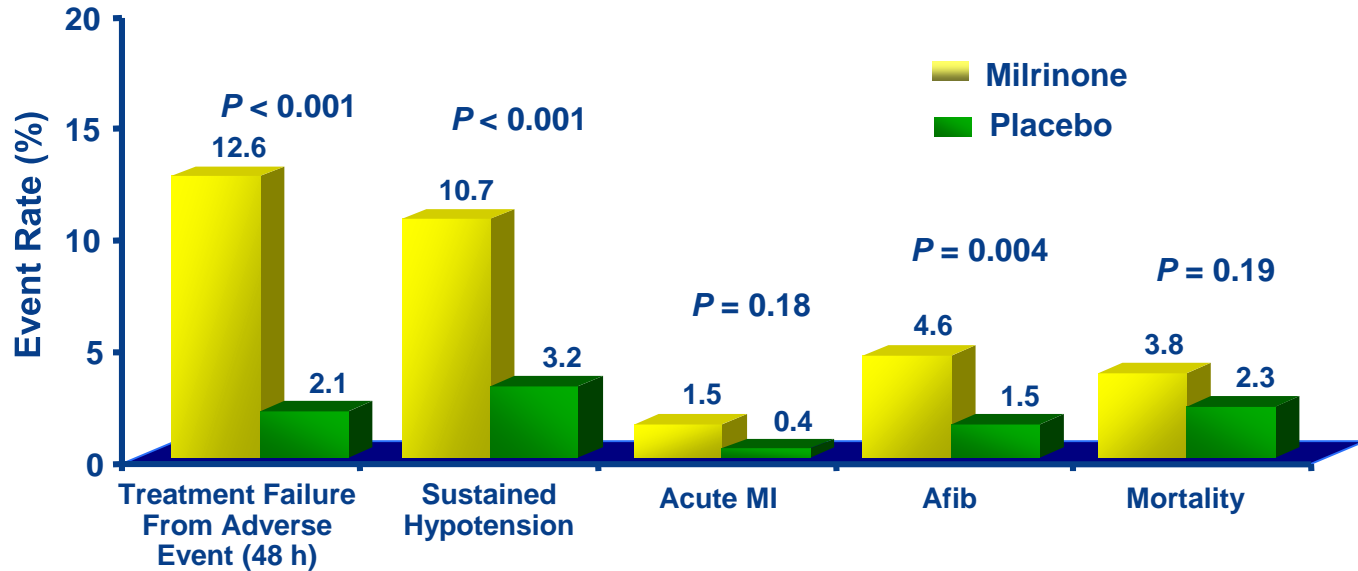
B Death from Any Cause or Rehospitalization for Heart Failure at 30 Days



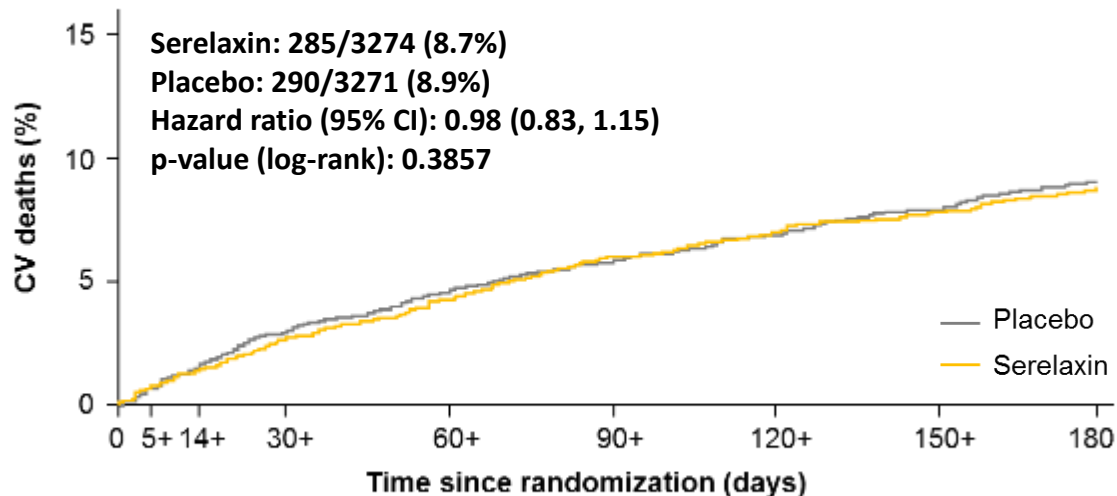
Inotropic Therapy for HF: ALARM Registry



In-hospital Adverse Events



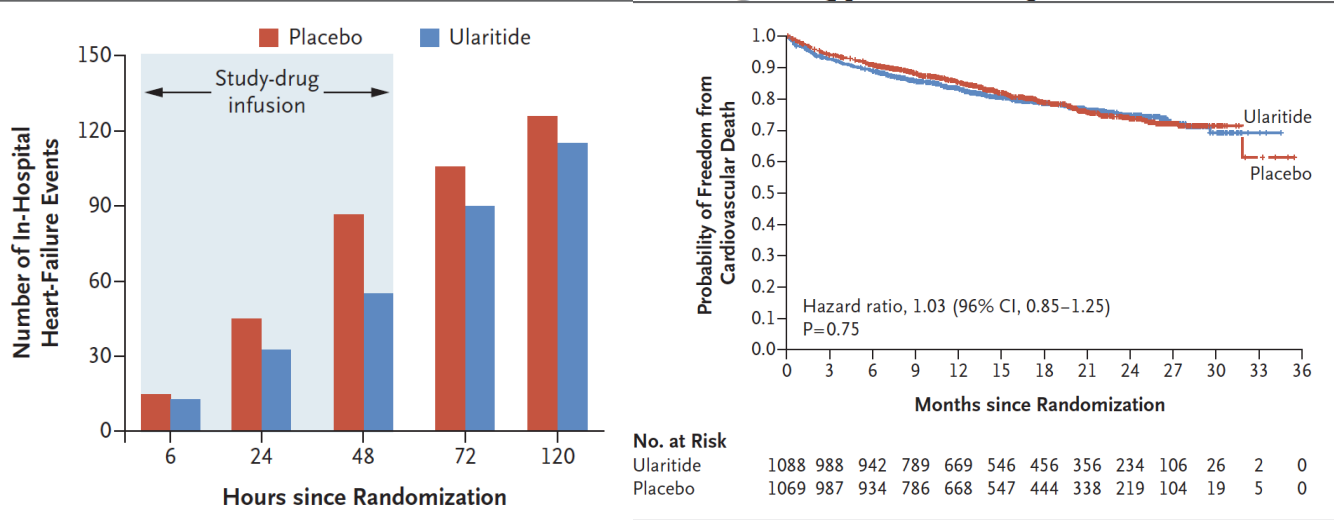
RELAX-AHF-2: CV mortality



Number at risk:

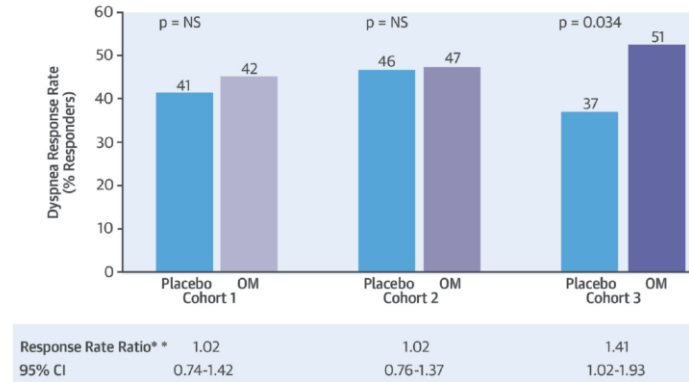
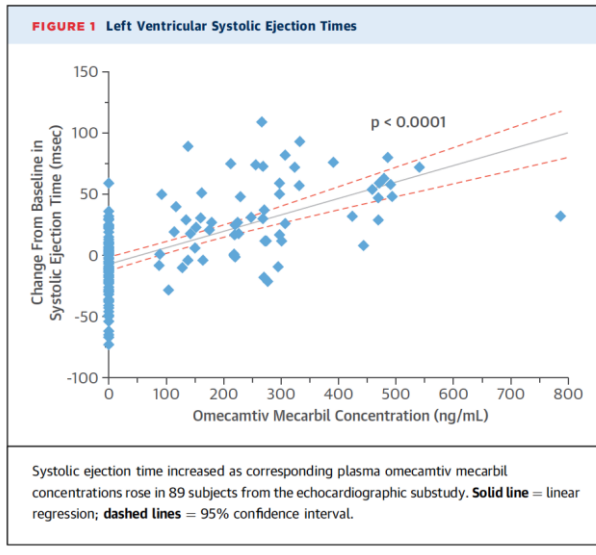
Placebo	3271	3244	3210	3149	3080	3018	2962	2912	2545
Serelaxin	3274	3247	3218	3165	3100	3032	2988	2949	2548

ORIGINAL ARTICLE





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



Teerlink, J.R. et al. J Am Coll Cardiol. 2016; 67(12):1444-55.

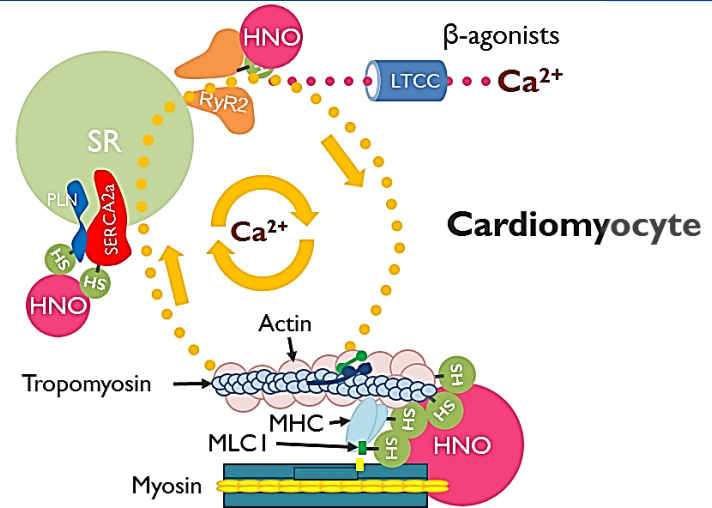
Nitroxyl (HNO): Mechanism of Action

Enhances contractility and relaxation by

- Increase in calcium release from ryanodine receptors¹
- Increase in sarcoplasmic reticulum (SR) calcium uptake due to activation of SERCA2A and PLB^{2,5,6}
- Increase in myofilament sensitivity (actin, MLC, and tropomyosin)^{3,4}
- No effect on L-type calcium channels

Vasodilation by

- Activation of soluble guanylate cyclase






Improved calcium cycling efficiency & increased myofilament sensitivity

References:

1. Kohr, et al., *Front Biosci*, 2009
2. Tocchetti, et al., *Circ Res*, 2007
3. Dai, et al., *J Physiol*, 2007
4. Murray et al., *JMCC*, 2009
5. Froehlich, et al., *Biochem*, 2008
6. Lancel, et al., *Circ Res*, 2009

What are the Hemodynamic “Buttons” We can Push?

BMS-986231

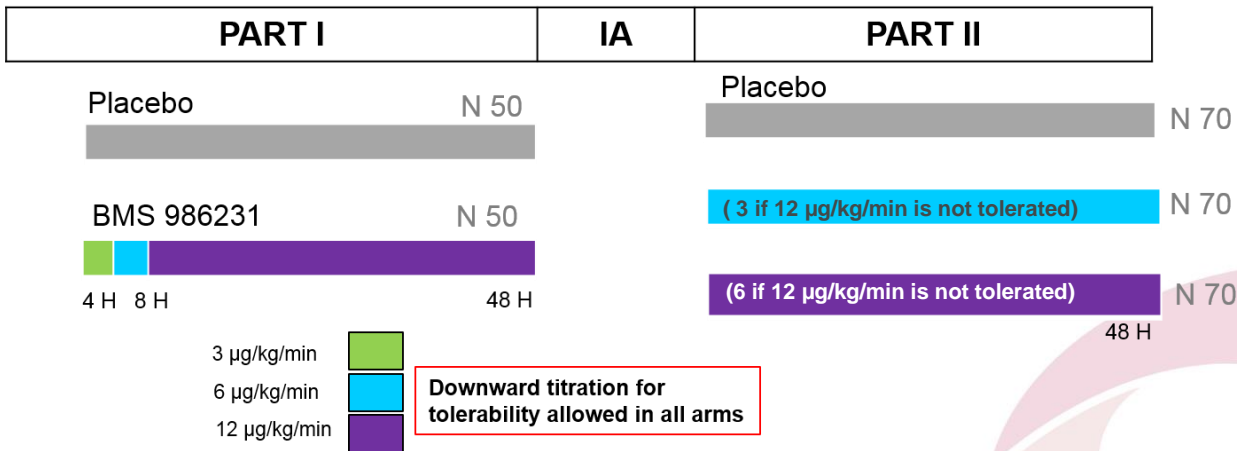
- Improve contractility (inotropy) 
- Improve relaxation/filling (lusitropy) 
- Optimize loading conditions 
 - Preload
 - Afterload

**Can we demonstrate that these mechanisms are operative
in patients with heart failure?**



STAND UP AHF: Study Design

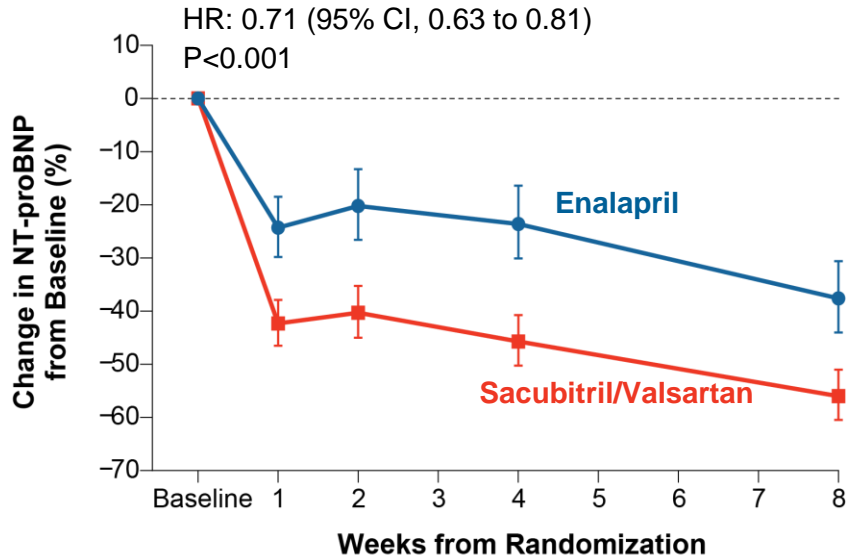
CV013-011



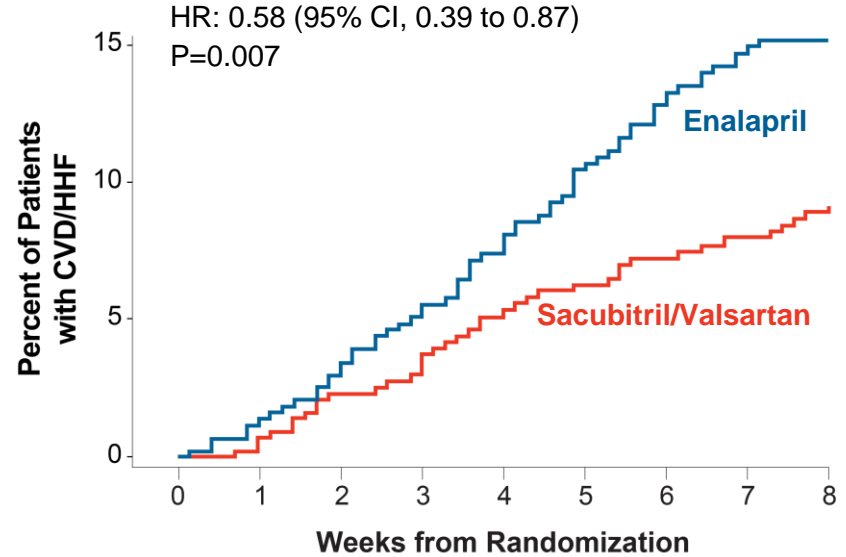
Part I/Cohort I
 100 subjects randomized in a 1:1 ratio to placebo or escalating dose of BMS-9862313

Part II/Cohort II
 210 subjects randomized in a 1:1:1 ratio to placebo or one of the 2 highest tolerated doses from Part I

PIONEER HF: In-Hospital Initiation of Sacubitril/Valsartan



Velazquez et al. N Engl J Med. 2019 Feb 7;380(6):539-548



Morrow et al. Circulation. In press.

Conclusions

- HHF is a highly symptomatic and morbid condition
- Standard of care therapy (diuretics) improve resting symptoms in most patients if dosed adequately
- Novel therapies to date without clear benefit
- In hospital optimization of GDMT (including ARNi) improves outcomes
- More to do!