INOVA
Heart and Vascular Institute
CARDIOVASCULAR SYMPOSIUM

Managing Heart Failure with Reduced Ejection Fraction in 2019

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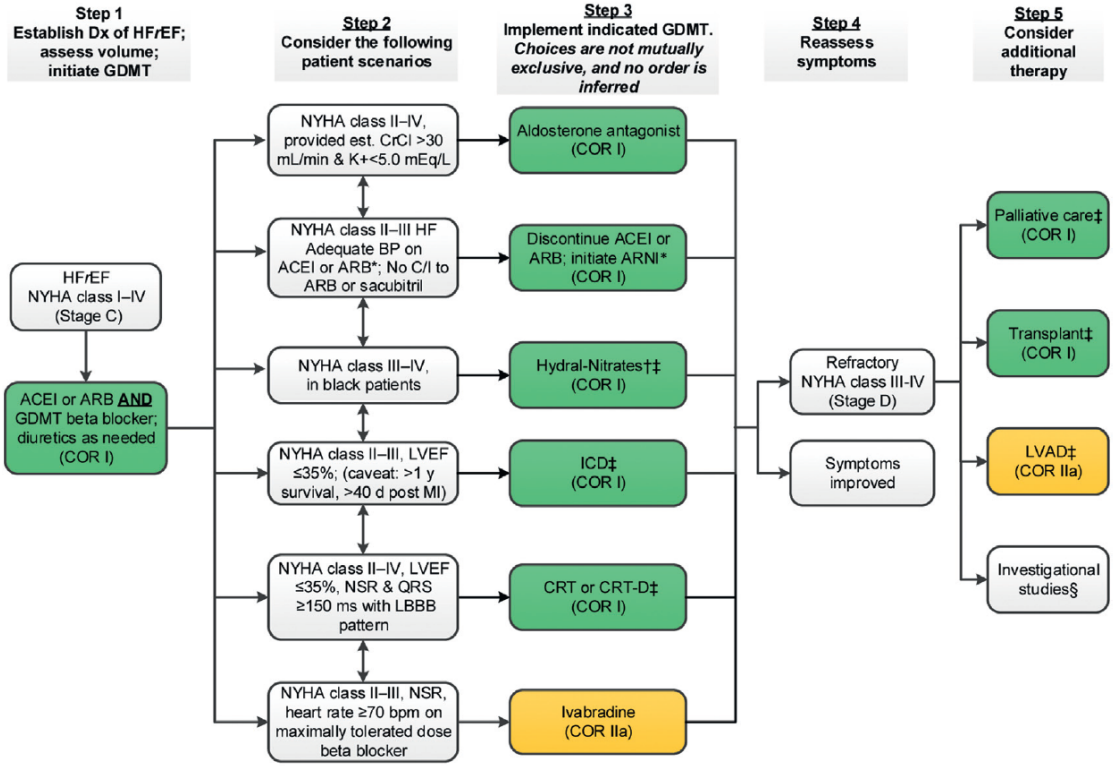
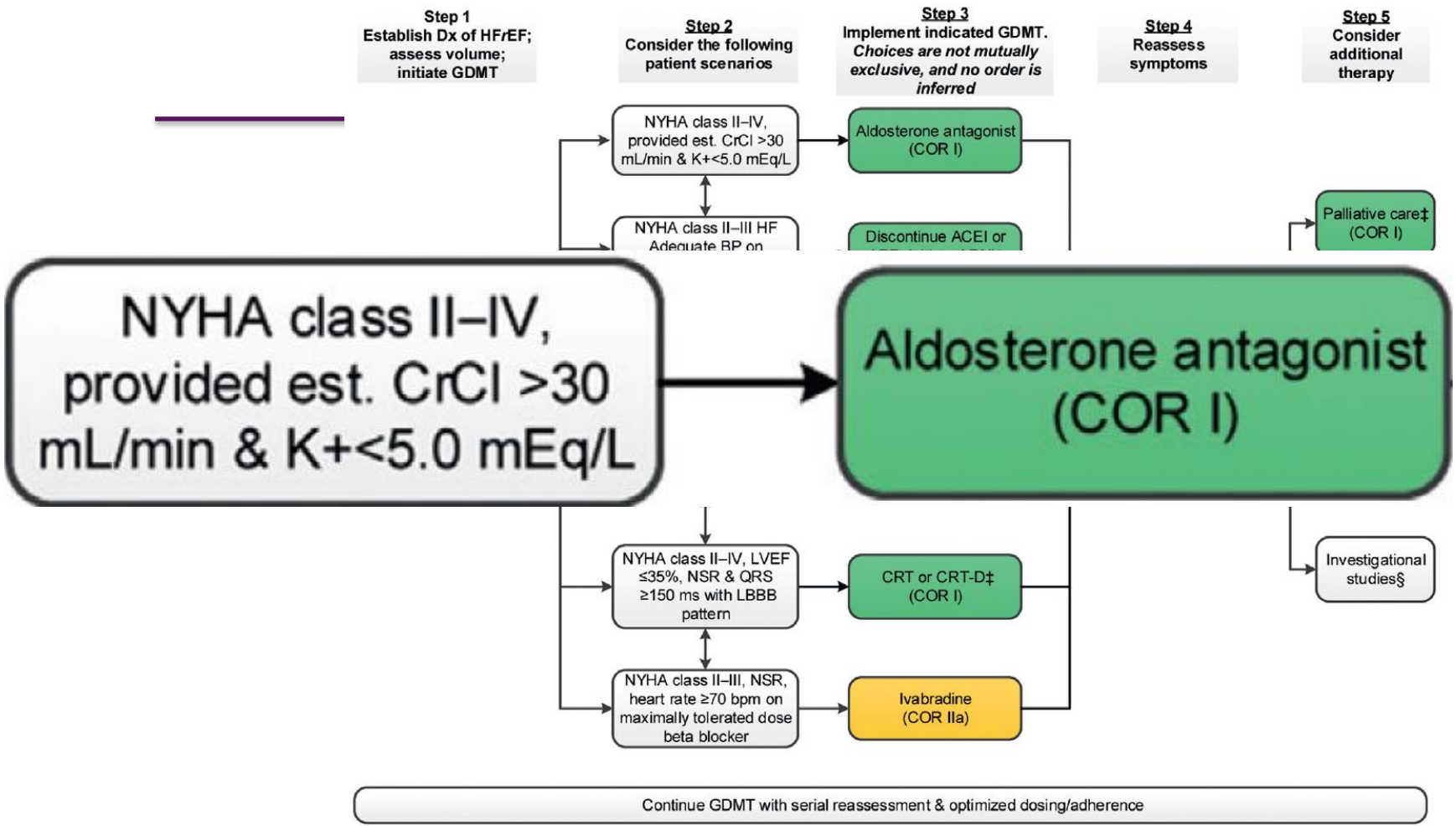
Declaration of Interest

- Financial Disclosure
  - J.R. Teerlink has received research grants and/or consulting fees from Abbott, Amgen, Astra Zeneca, Bayer, Bristol-Myers Squibb, Cytokinetics, Medtronic, Merck, Novartis, Relypsa, St. Jude, Trevena, and ZS Pharma.
- Unlabeled/unapproved uses disclosure
  - I will be discussing investigational therapies that are not approved by the FDA.

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

Yancy CW, *et al. J AM Coll Cardiol* 2017;70:776-803.




Step 1
Establish Dx of HFrEF; assess volume; initiate GDMT
Step 2
Consider the following patient scenarios
Step 3
Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred
Step 4
Reassess symptoms
Step 5
Consider additional therapy
NYHA class II–IV, provided est. CrCl >30 mL/min & K+<5.0 mEq/L
Aldosterone antagonist (COR I)
NYHA class II–III HF
Discontinue ACEI or
Palliative care‡ (COR I)
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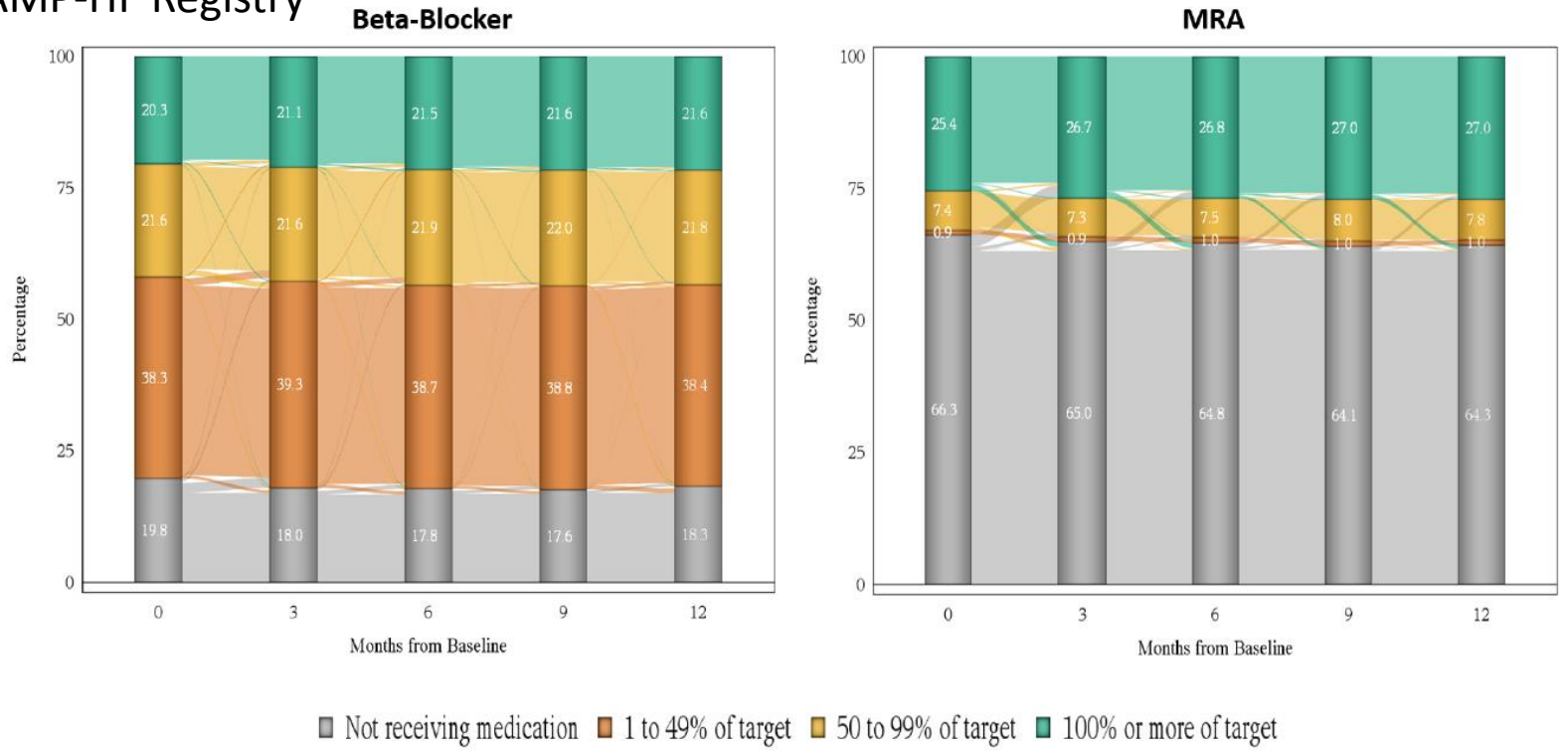
CRT or CRT-D‡ (COR I)
Investigational studies§
NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker
Ivabradine (COR IIa)
Continue GDMT with serial reassessment & optimized dosing/adherence


SUCKING AT SOMETHING
IS THE FIRST STEP TO BECOMING SORTA GOOD AT SOMETHING
apmeme

Continued Marked Underutilization of Guideline-directed Medical Therapy

Greene SJ, *et al. J Am Coll Cardiol* 2019; https://doi.org/10.1016/j.jacc.2019.02.015

CHAMP-HF Registry

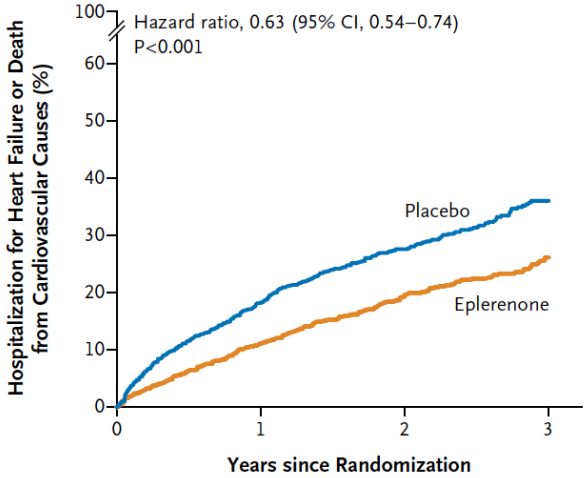


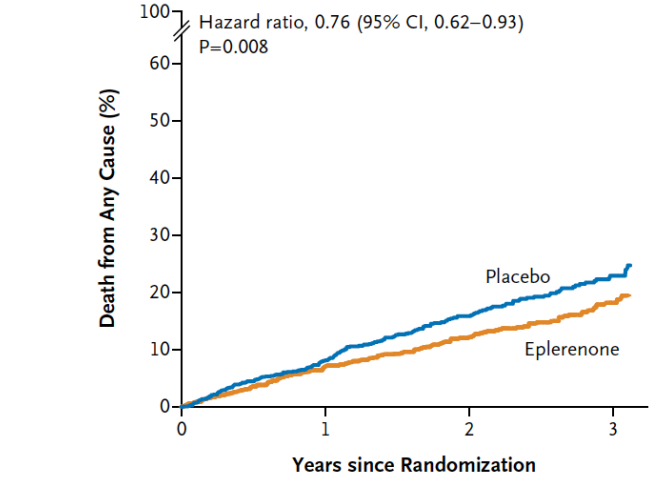
Eplerenone Improves Survival in Patients with HF (EMPHASIS-HF)

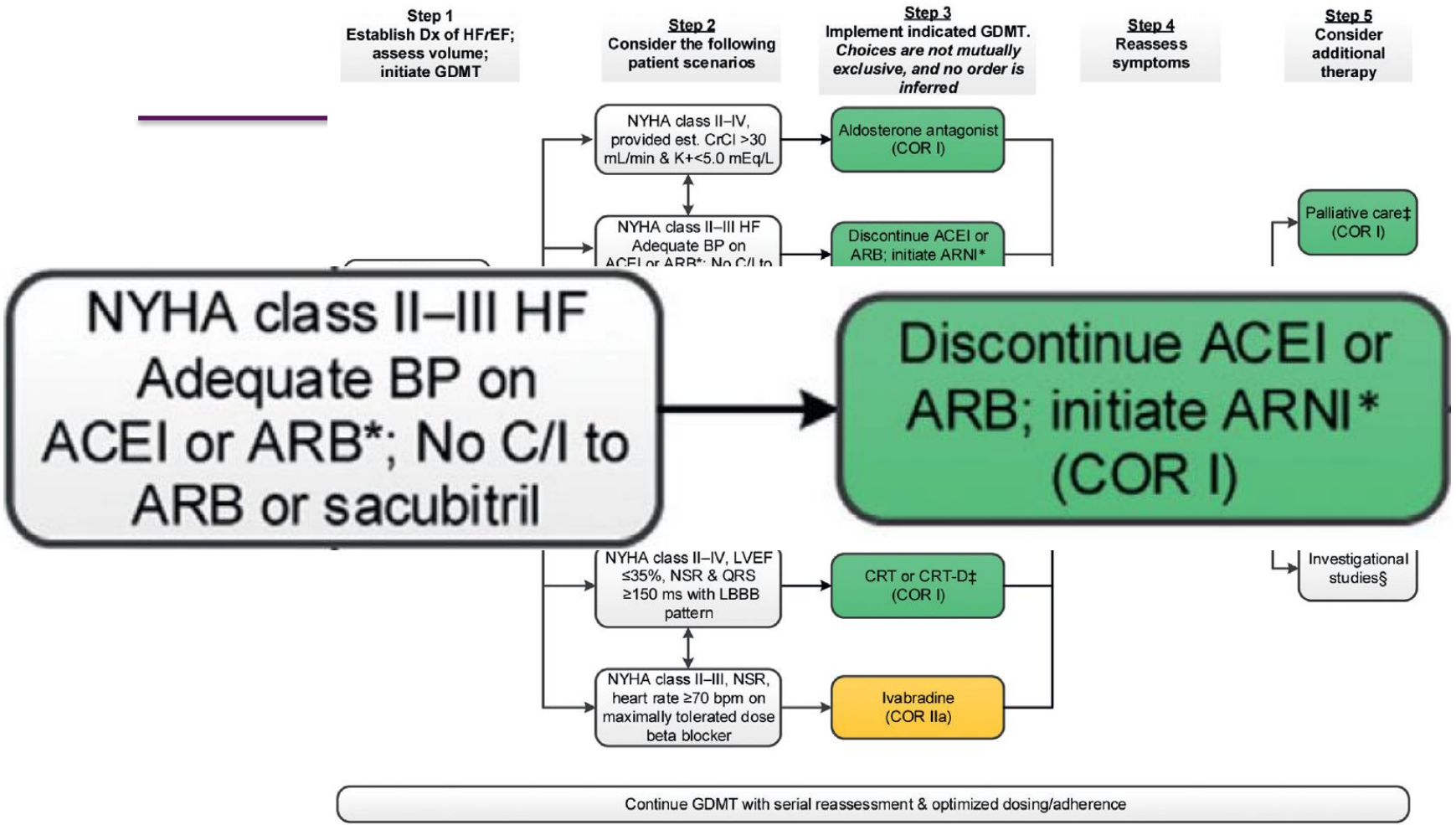
Zannad F, *et al. N Engl J Med*. 2011;364:11-21.

2737 patients
NYHA II
LVEF≤35%
Randomized to
- Eplerenone (≤50 mg qd)
- Placebo

K+ >5.5 in 11.8% Epl
vs 7.2% Placebo
(p<0.001)



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NYHA class II–III HF Adequate BP on ACEI or ARB*; No C/I to
Discontinue ACEI or ARB; initiate ARNI*
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NYHA class II–IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern
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Ivabradine (COR IIa)
Investigational studies§
Continue GDMT with serial reassessment & optimized dosing/adherence
NYHA class II–III HF Adequate BP on ACEI or ARB*; No C/I to ARB or sacubitril
Discontinue ACEI or ARB; initiate ARNI* (COR I)

PARADIGM-HF: Main Results

McMurray JJV, *et al. N Engl J Med* 2014;371:993-1004.

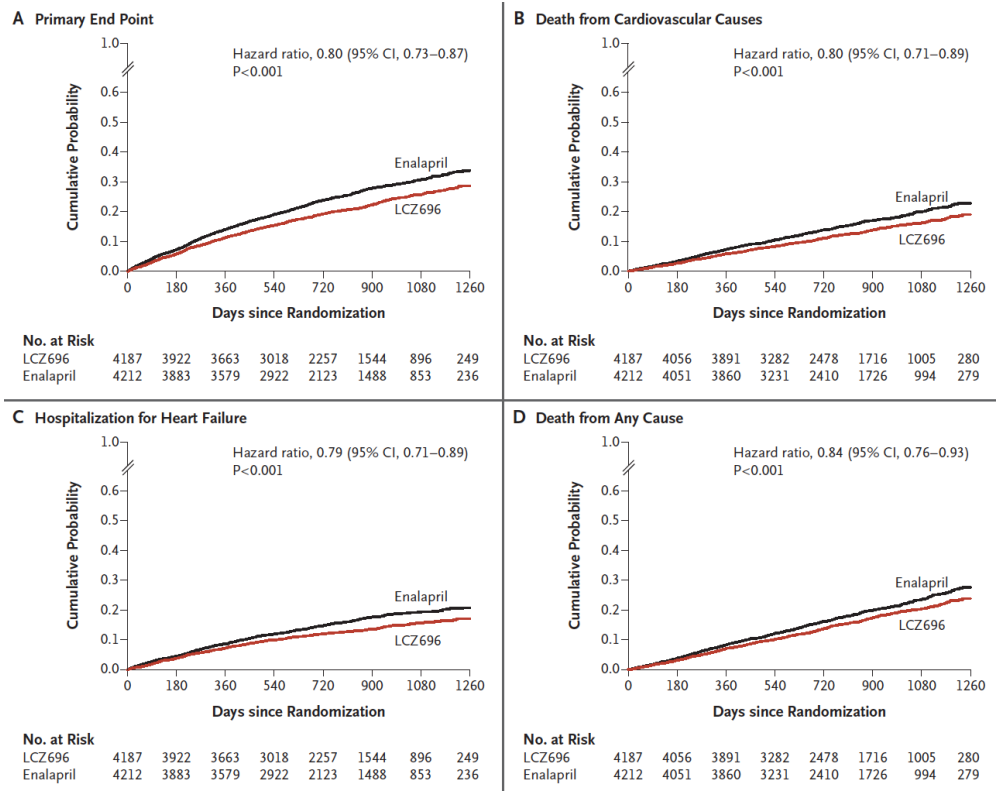
8442 patients, NYHA II, III, or IV LVEF≤ 40%

Randomized to:

Sacubitril/ valsartan (97/103 mg bid) or enalapril (10 mg bid),

1°: CV death or HF hospitalization

Stopped early due to overwhelming benefit, after a median follow-up of 27 months



PIONEER-HF

Velazquez EJ, *et al. N Engl J Med* 2019;380:539-48.

881 patients, admitted for ADHF, LVEF≤ 40%; elevated NPs. stable

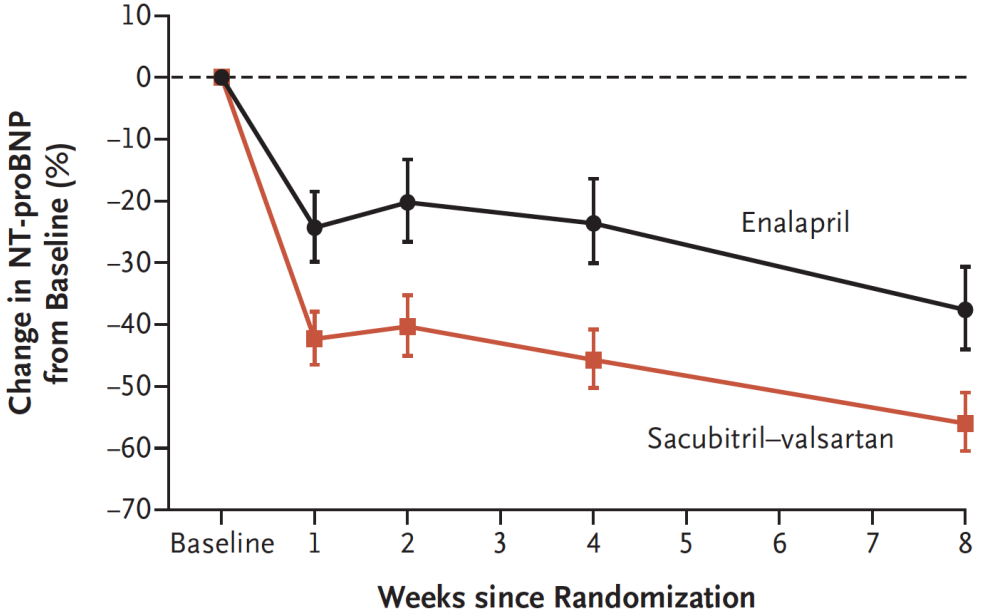
Enrolled in–hospital 24 hours-10 days post-admit (median 68 hours

Randomized to:

Sacubitril/ valsartan (97/103 mg bid) or enalapril (10 mg bid),

1°: Time-averaged proportional change in NT-proBNP concentration from baseline through weeks 4 and 8

No significant difference in rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema



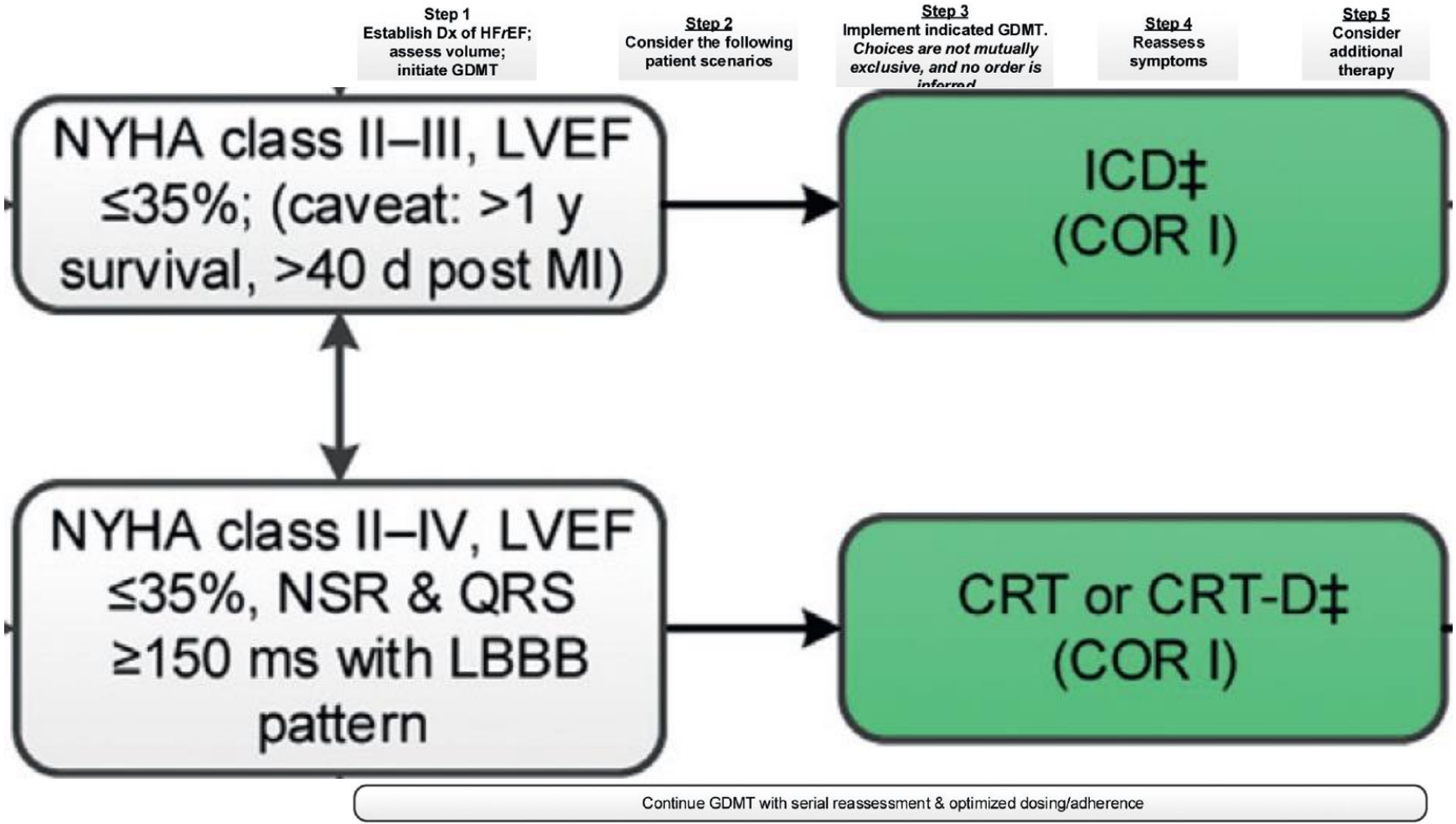
No. at Risk

Enalapril	394	359	351	350	348
Sacubitril–valsartan	397	355	363	365	349

PIONEER-HF

Velazquez EJ, *et al. N Engl J Med* 2019;380:539-48.

Exploratory clinical outcomes — no. (%)			Hazard ratio (95% CI)§
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)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ICD‡ (COR I)
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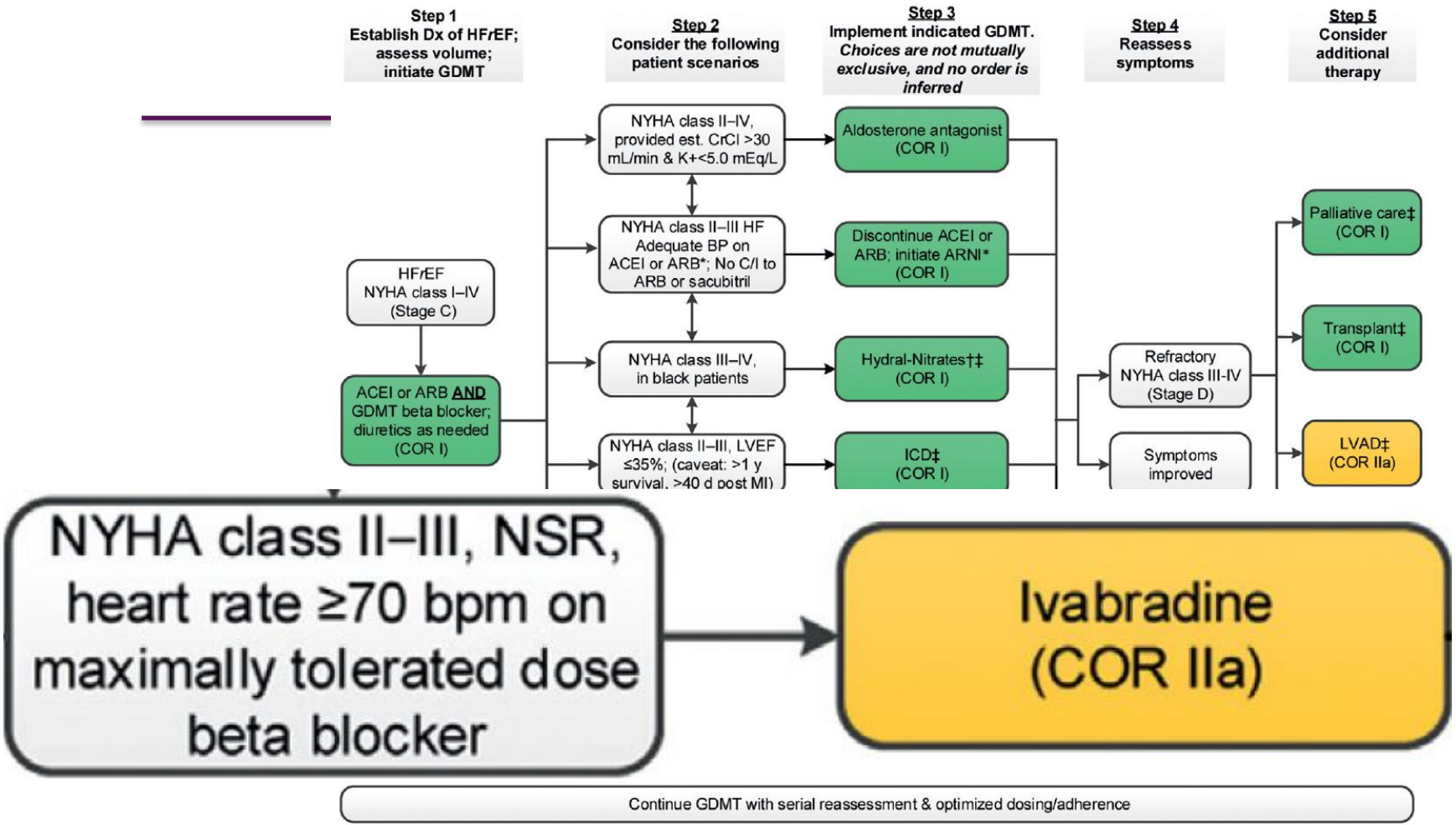
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HFrEF
NYHA class I–IV
(Stage C)
ACEI or ARB AND GDMT beta blocker; diuretics as needed
(COR I)
NYHA class II–IV, provided est. CrCl >30 mL/min & K+<5.0 mEq/L
Aldosterone antagonist
(COR I)
NYHA class II–III HF Adequate BP on ACEI or ARB*; No C/I to ARB or sacubitril
Discontinue ACEI or ARB; initiate ARNI*
(COR I)
NYHA class III–IV, in black patients
Hydral-Nitrates†‡
(COR I)
NYHA class II–III, LVEF ≤35%; (caveat: >1 y survival, >40 d post MI)
ICD‡
(COR I)
Refractory NYHA class III-IV
(Stage D)
Symptoms improved
Palliative care‡
(COR I)
Transplant‡
(COR I)
LVAD‡
(COR IIa)
NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker
Ivabradine
(COR IIa)
Continue GDMT with serial reassessment & optimized dosing/adherence

Future Directions in HFrEF

- Diuretic therapy:
  - Torsemide vs. Furosemide (TRANSFORM)
  - (SGLT2 inhibitors)
- Treatments for hyperkalemia/ Facilitating RAAS-inhibiting therapies
  - Patiromir
  - Sodium zirconium cyclosilicate (ZS-9)

Future Directions in HFrEF: COMMANDER-HF

Zannad F, *et al. N Engl J Med* 2018;379:1332-42.

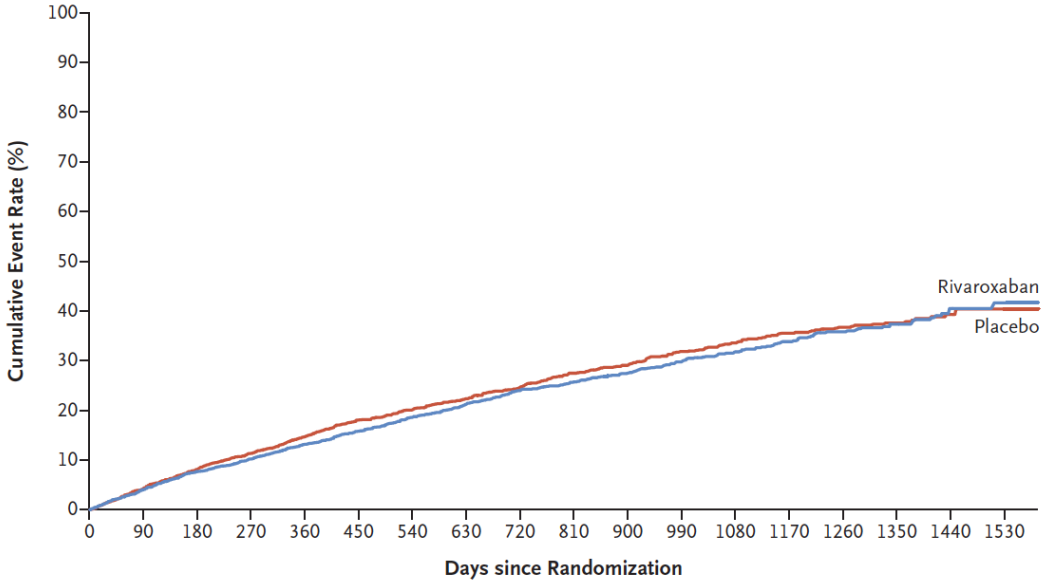
5022 patients; heart failure x3 mo., WHF within 21 days; LVEF ≤40%, coronary artery disease, elevated natriuretic peptides; without atrial fibrillation

Randomized to:

Rivaroxaban 2.5 mg bid or placebo

1° efficacy: death from any cause, myocardial infarction, or stroke.

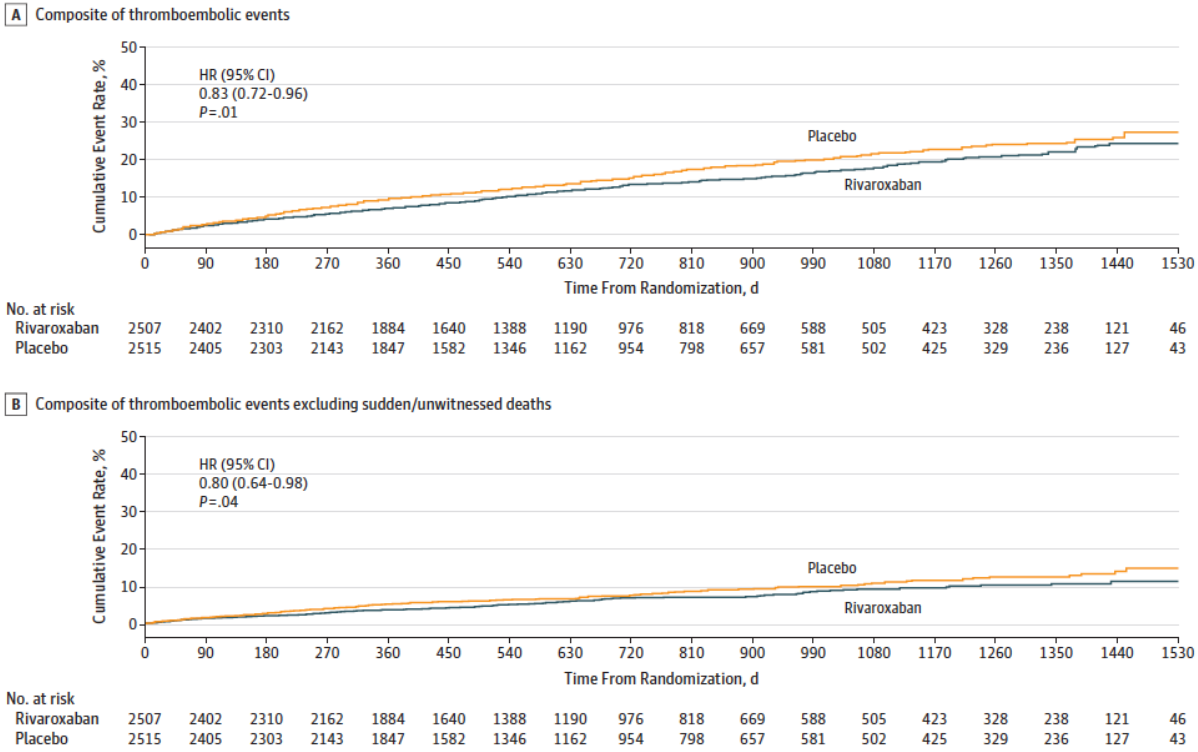
1° safety: fatal bleeding or bleeding into a critical space with a potential for causing permanent disability.



Future Directions in HFrEF: COMMANDER-HF

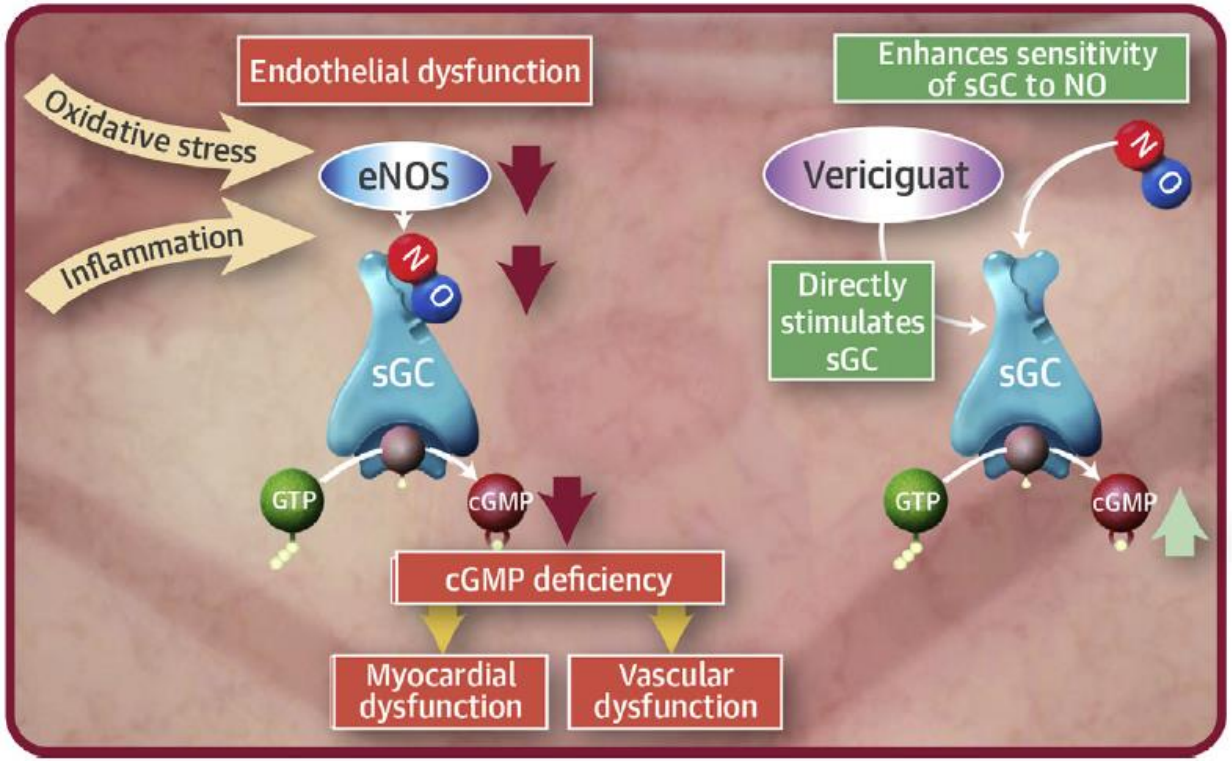
Greenberg BF, *et al. JAMA Card* 2019;379:1332-42.

Thromboembolic events:
MI, ischemic stroke, sudden/unwitnessed death, symptomatic pulmonary embolism, or symptomatic deep vein thrombosis.



Future Directions in HFrEF: Vericiguat, Soluble Guanylate Cyclase (sGC) Stimulator

Armstrong PW, *et al. J Am Coll Cardiol HF* 2018;6:96-104.



VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA)

Armstrong PW, *et al. J Am Coll Cardiol HF* 2018;6:96-104.

Target enrollment 4872

Vericiguat 2.5 mg uptitrated to 10 mg qd vs. Placebo

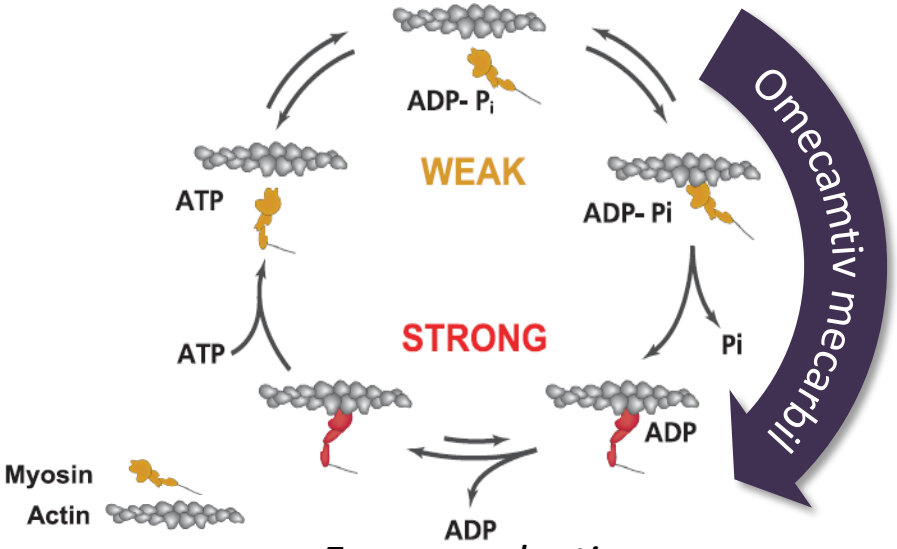
Primary Outcome Measure: Time to Cardiovascular (CV) Death or Heart Failure Hospitalization

Inclusion Criteria:

- History of chronic HF (NYHA Class II-IV) on standard therapy before qualifying HF decompensation
- Previous HF hospitalization within 6 months prior to randomization or intravenous (IV) diuretic treatment for HF (without hospitalization) within 3 months.
- BNP levels: NSR-≥ 300 pg/mL; A Fib-≥ 500 pg/mL and NT-proBNP levels: NSR- ≥ 1000 pg/mL; A Fib- ≥ 1600 pg/mL within 30 days prior to randomization
- LVEF<45% assessed within 12 months prior to randomization by any method

Future Directions in HFrEF:
Omecamtiv Mecarbil, Selective Cardiac Myosin Activator

Mechanochemical Cycle of Myosin



Force production

OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

"More hands pulling on the rope"

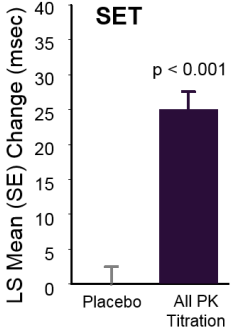
- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_2

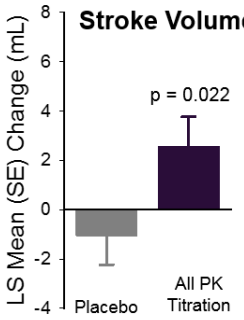
Malik FI, *et al. Science* 2011; 331:1439-43.
Shen YT, *et al. Circ Heart Fail* 2010;3:522-7.
Planelles-Herrero VJ, *et al. Nat Commun* 2017;8:190.

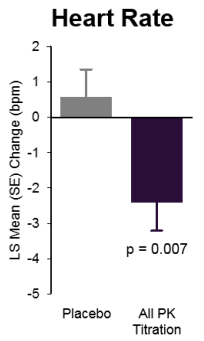
Overall Effects of Omecamtiv Mecarbil

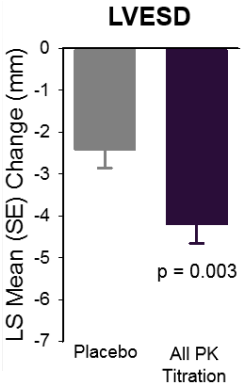
Teerlink JR, *et al*. *Lancet* 2016; 388: 2895-903.

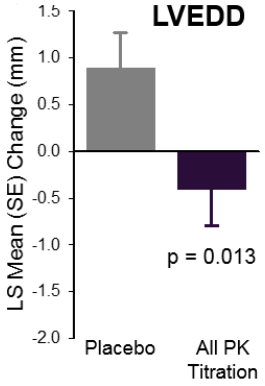
Placebo, n= 149;
All PK-Titration, n= 146

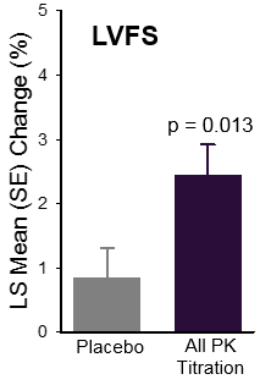


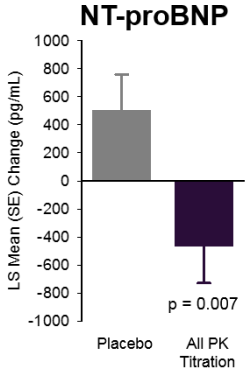












LS, Least square; LVEDD, LVESD: Left ventricular end-diastolic (systolic) dimension; LVFS, left ventricular fractional shortening; SE, standard error; SET, systolic ejection time

GALACTIC-HF

clinicaltrials.gov NCT02929329

- Chronic HF pts on standard of care therapy, LVEF ≤35%, NYHA II-IV, HF hospitalization within 12 months, elevated natriuretic peptides
- 1° endpoint: CV death & HF Hospitalization
- ~8,000 patient, event-driven trial, powered for CV death

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Thank you!

Heart Failure Society of America

www.hfsa.org