What's New in the Treatment of Heart Failure

March 28, 2018

Ohio Chapter-ACC

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Disclosures

- Advisory board: Medtronic, Novartis
- Research funding: Corvia, NHLBI, Amgen

Outline

- Definitions
- HF Guideline Updates
- Process of Care
- HFrEF
- HFpEF
- Advanced HF

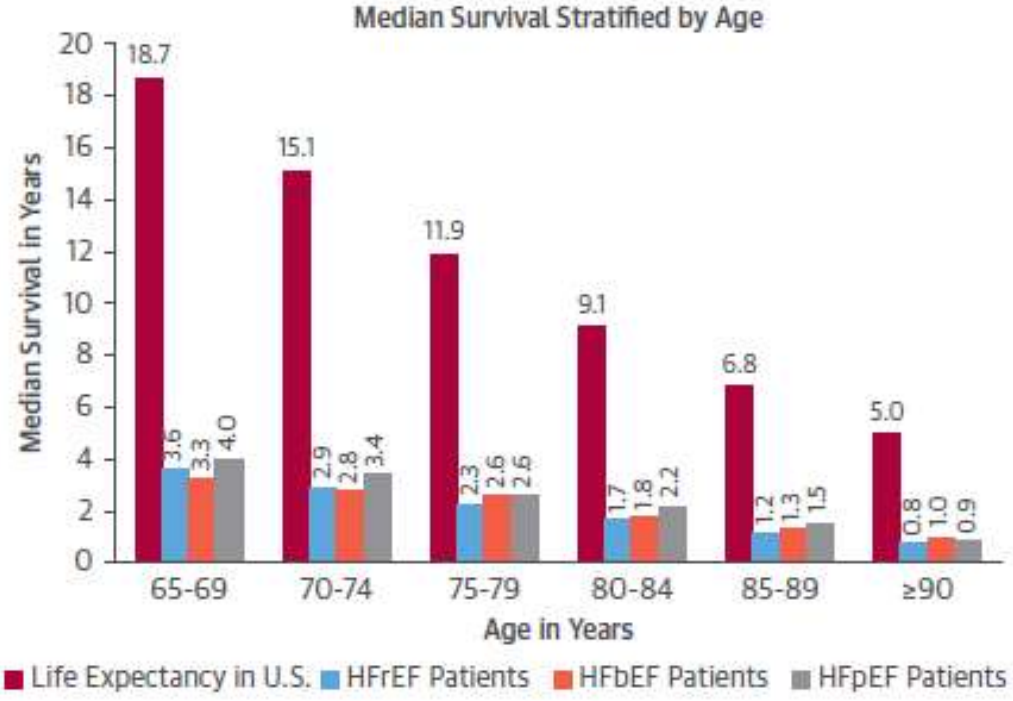
Outcomes HF; After Hospitalization

HFpEF ≥50%

HFbEF 41-49%

HFrEF ≤40%

FIGURE 2 Median Survival in Years by Age Group in HF Patients Compared With the Life Expectancy in the United States



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CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

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

A Report of the American College of Cardiology/American Heart Association
Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration with the American Academy of Family Physicians,
American College of Chest Physicians, and International Society for Heart and Lung Transplantation

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

TABLE 1 Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

GDMT

Guideline-Directed Management and Therapy

The term *guideline-directed management and therapy* (GDMT) encompasses clinical evaluation, diagnostic testing, and pharmacological and procedural treatments.

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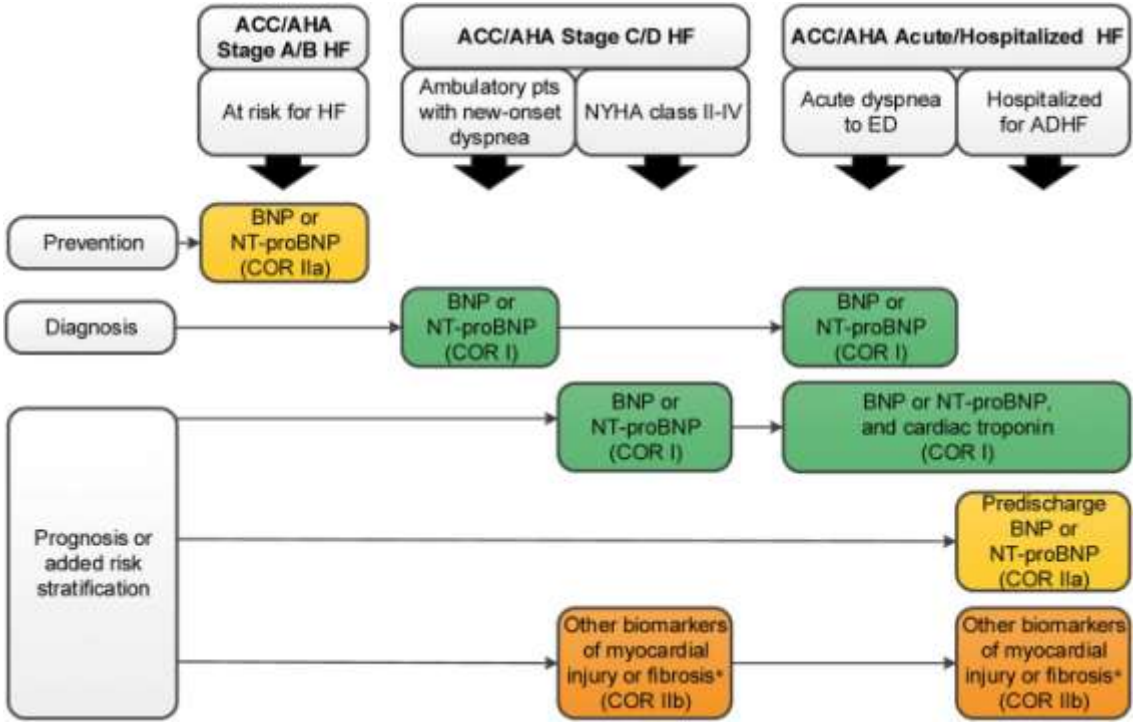
2017 HF Update Biomarkers



JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

ARNI Indications

NEW

COR	LOE	RECOMMENDATIONS
I	ACE-I: A ARB: A	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (128–133), OR ARBs *(Level of Evidence: A)* (134–137), OR ARNI *(Level of Evidence: B-R)* (138) in conjunction with evidence-based beta blockers (9,139,140), and aldosterone antagonists in selected patients (141,142), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.
	ARNI: B-R	

- ACEi or ARBs or ARNI **for HFrEF**
- W**hen ARNI not appropriate, continued use o**f an ACEi is recommended for all classes of HFrEF

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

ARNI Indications

NEW

In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (138).

ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (148,149).

ARNI should not be administered to patients with a history of angioedema.

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

Ivabradine

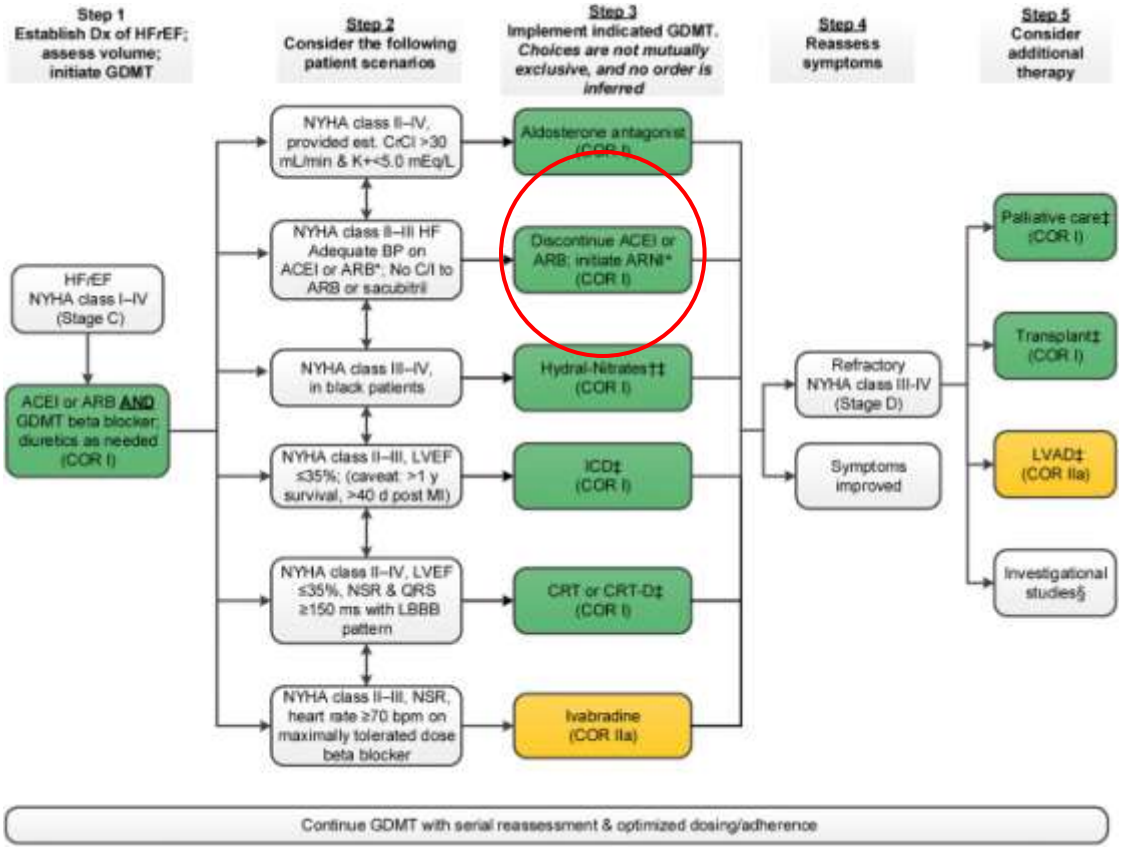
NEW

Recommendation for Ivabradine

COR	LOE	RECOMMENDATION
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM*, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (154–157).

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

2017 Update Treatment of HFrEF Stages C and D



JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

Recommendations for Stage C HFpEF

NEW

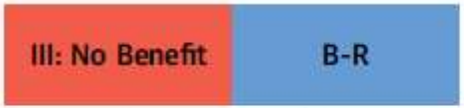
In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83,166,167).

Use of MRA based upon post hoc analyses and based upon geographic variation in outcomes

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

Recommendations for Stage C HFpEF

NEW



Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective (171,172).

2013 Recommendations Remain

- BP control target <130 mm Hg
- **Diuretics for volume control**
- CAD GDMT
- **AFIB GDMT**
- BP control with ACEi, ARB, BB is reasonable
- **Use of nutritional supplements NR**

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

COMORBIDITIES: ANEMIA

NEW

COR	LOE	RECOMMENDATIONS
IIb	B-R	In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and QoL (173,174).
III: No Benefit	B-R	In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality (176).

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

STAGE A HYPERTENSION

STAGE C HF rEF HYPERTENSION

NEW

COR	LOE	RECOMMENDATIONS
I	B-R	In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg (189–193).

COR	LOE	RECOMMENDATION
I	C-EO	Patients with HF*r*EF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg (191).

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

HYPERTENSION SUMMARY

2017 Focused Update

- Class I recommendation (Level of Evidence: B-R) for targeting an optimal blood pressure (BP) of <130/80 mm Hg in those with hypertension and at increased risk (stage A HF).
- Class I recommendation (Level of Evidence: C-EO) for titration of GDMT to attain systolic BP (SBP) <130 mm Hg in patients with HFrEF and hypertension.
- Class I recommendation (Level of Evidence: C-LD) for titration of GDMT to attain SBP <130 mm Hg in patients with HFpEF and persistent hypertension after management of volume overload.

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.
www.acc.org/latest-in-cardiology

COMORBIDITIES: SLEEP APNEA

NEW

COR	LOE	RECOMMENDATIONS
IIa	C-LD	In patients with NYHA class II–IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable (200,201).
See Online Data Supplement G.		
IIb	B-R	In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness (204).
See Online Data Supplement G.		
III: Harm	B-R	In patients with NYHA class II–IV HF*r*EF and central sleep apnea, adaptive servo-ventilation causes harm (203).
See Online Data Supplement G.		

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

SLEEP APNEA SUMMARY

2017 Focused Update

- Class IIa recommendation (Level of Evidence: C-LD) for a formal sleep assessment in patients with NYHA class II–IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness.
- Class IIb recommendation (Level of Evidence: B-R) for utilization of continuous positive airway pressure in patients with cardiovascular disease and obstructive sleep apnea, to improve sleep quality and daytime sleepiness.
- Class III recommendation: Harm (Level of Evidence: B-R) for use of adaptive servo-ventilation in patients with NYHA class II–IV HFrEF and central sleep apnea, as it causes harm.

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

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Heart Failure

Incremental Cost-Effectiveness of Guideline-Directed Medical Therapies for Heart Failure

Gaurav Banka, MD,* Paul A. Heidenreich, MD,† Gregg C. Fonarow, MD*

Los Angeles and Palo Alto, California

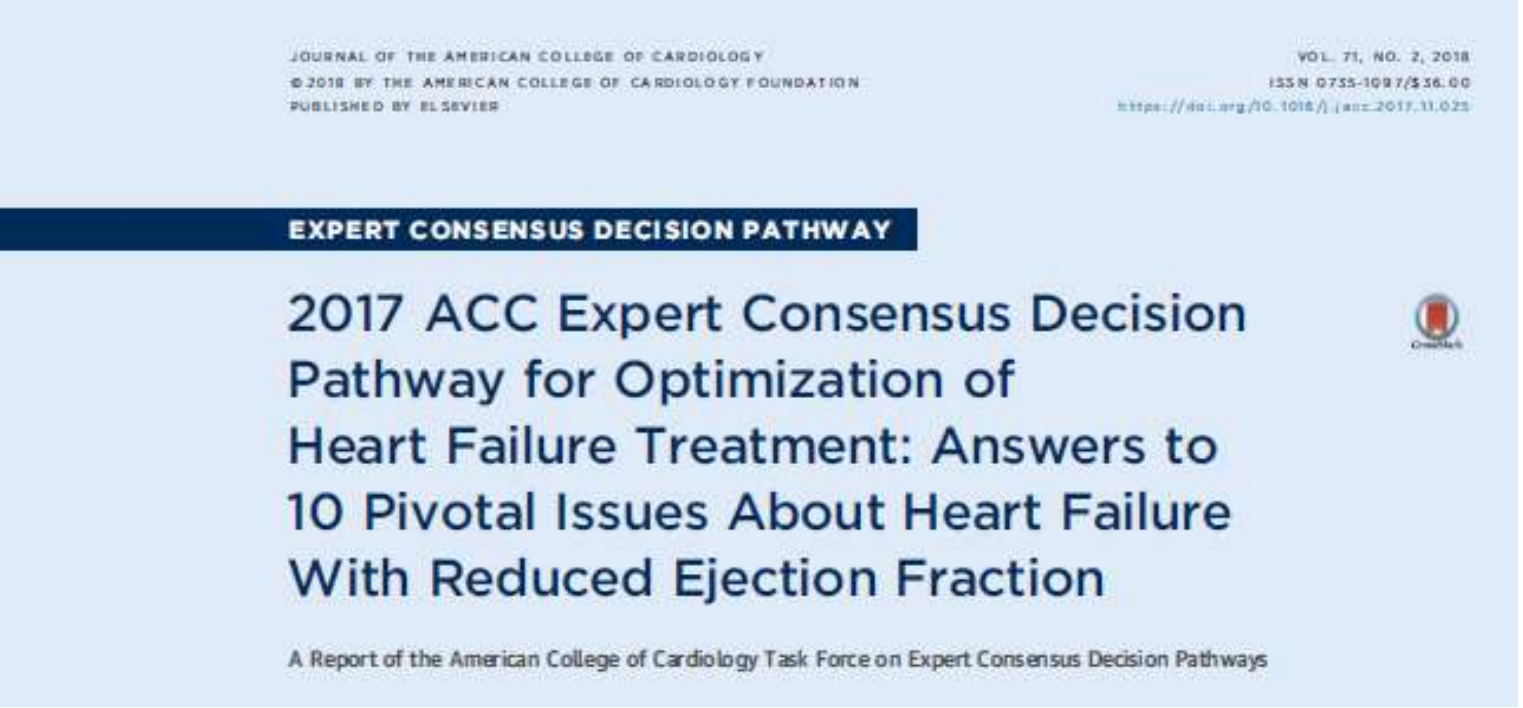
Our analysis demonstrates that medical tr st-effective and may even result in cost-savings. Greater efforts to ensure optimal ed medical therapy for HFrEF are warranted. (J Am Coll Cardiol 2013;61:1 ican College of Cardiology Foundation

Questions About Guidelines?

- Who reads them?
- Who follows them?
- Do patients have access to GDMT”
- What is gap between guidelines and implementation?

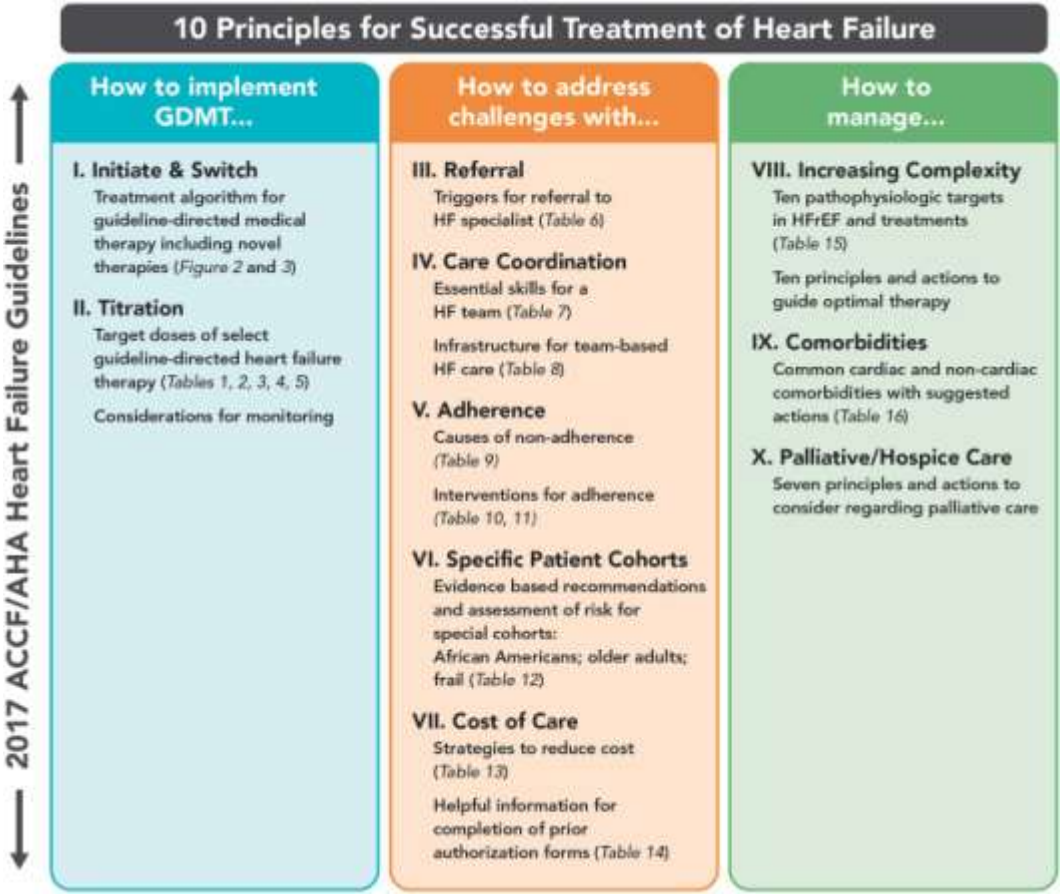
IMPLEMENTATION

realization that guidelines require effective translation to become reality



ACC.18

"provide practical guidance for transforming guideline recommendations into clinically actionable information"

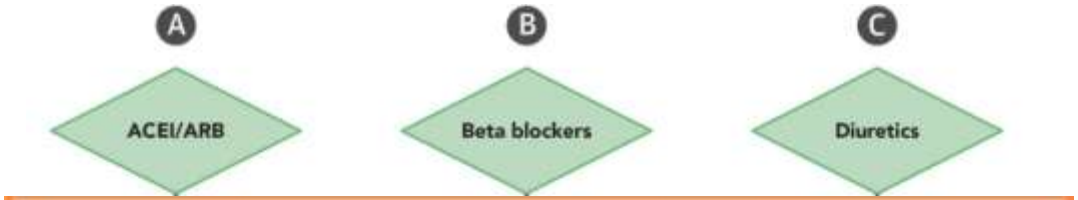


Clyde W. Yancy et al. JACC 2018;71:201-230

Ten Pivotal Issues in HFrEF

ACC.18

1. How to initiate, add, or switch therapy to new evidence-based guideline-directed treatments for HFrEF.
2. How to achieve optimal therapy given multiple drugs for HF including augmented clinical assessment that may trigger additional changes in guideline-directed therapy (e.g., imaging data, biomarkers, and filling pressures).
3. When to refer to an HF specialist.
4. How to address challenges of care coordination.
5. How to improve adherence.
6. What is needed in specific patient cohorts: African Americans, the frail, and older adults.
7. How to manage your patients' cost of care for HF.
8. How to manage the increasing complexity of HF.
9. How to manage common comorbidities.
10. How to integrate palliative care and transition to hospice care.



Consider increasing dose of beta blocker every 2 weeks until maximum tolerated or target dose is achieved

Monitor heart rate, blood pressure, and for signs of congestion after initiation and during titration

(ie equivalent of 120 mg of furosemide twice daily) consider

a. changing to a different loop diuretic or

b. adding thiazide diuretic, taken together with loop diuretic

Monitor blood pressure, electrolytes, and renal function after initiation and during titration

Clyde W. Yancy et al. JACC 2018;71:201-230

Patient with hypotension

ACC.18

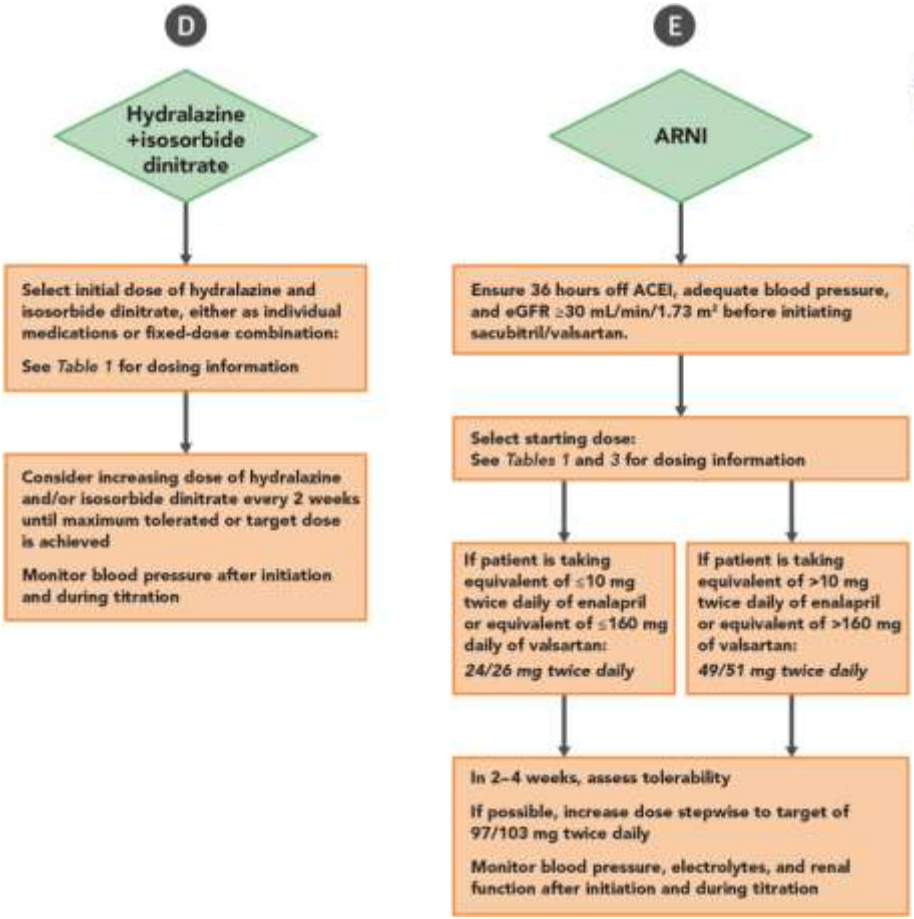
- 32 year old man with new onset HF, DCM, EF 15%
- Lisinopril 5 mg, carvedilol 6.25 mg BID, spironolactone 25 mg daily, furosemide 40 mg daily
- BP 92/70 HR 96

***Scenario 2**: Symptomatic hypotension.*

Hypotensive symptoms may be due to overdiuresis, other vasoactive medication, autonomic dysfunction, or taking multiple medications together. All of these should be addressed prior to deciding to lower doses of evidence-based therapies.

Action: After excluding other causes of hypotension, use best-tolerated doses of GDMT, accepting that less data exist for the impact of lower doses in HF management.

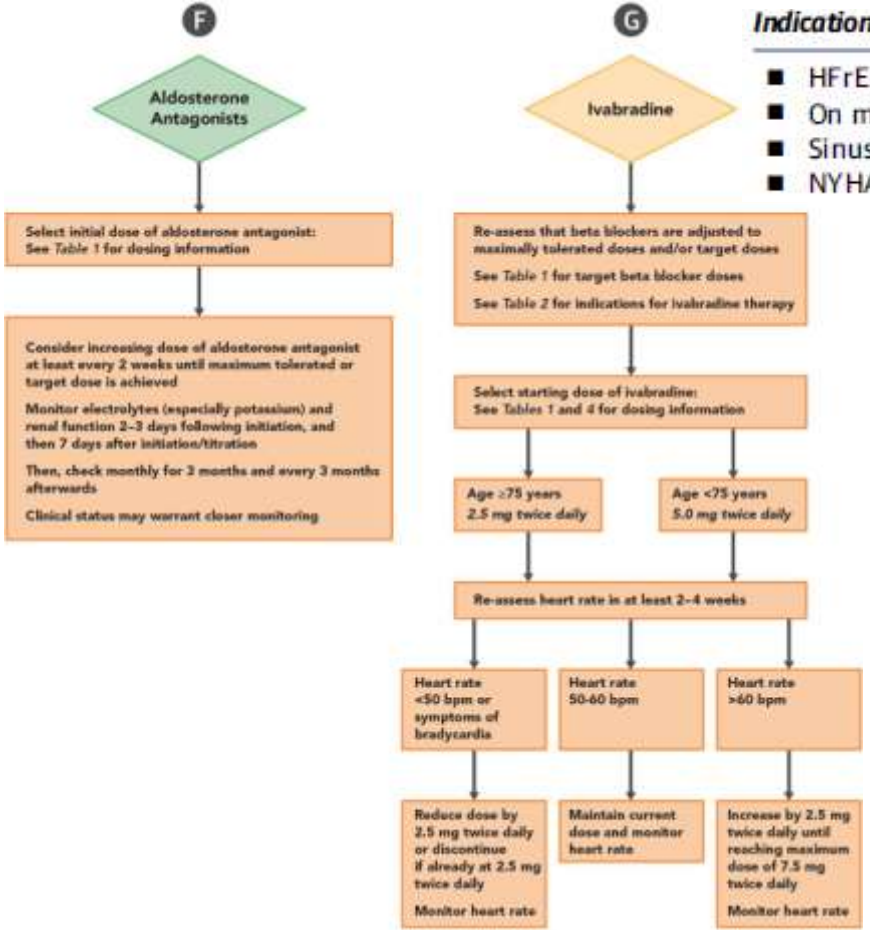
Principle 3: Optimal SNS modulation with target doses of beta blocker appears to have the best effect on HFrEF outcomes (cardiovascular mortality, pump failure mortality, and sudden cardiac death).



Indications for Use of an ARNI

- HFrEF (EF ≤40%)
- NYHA class II or III HF

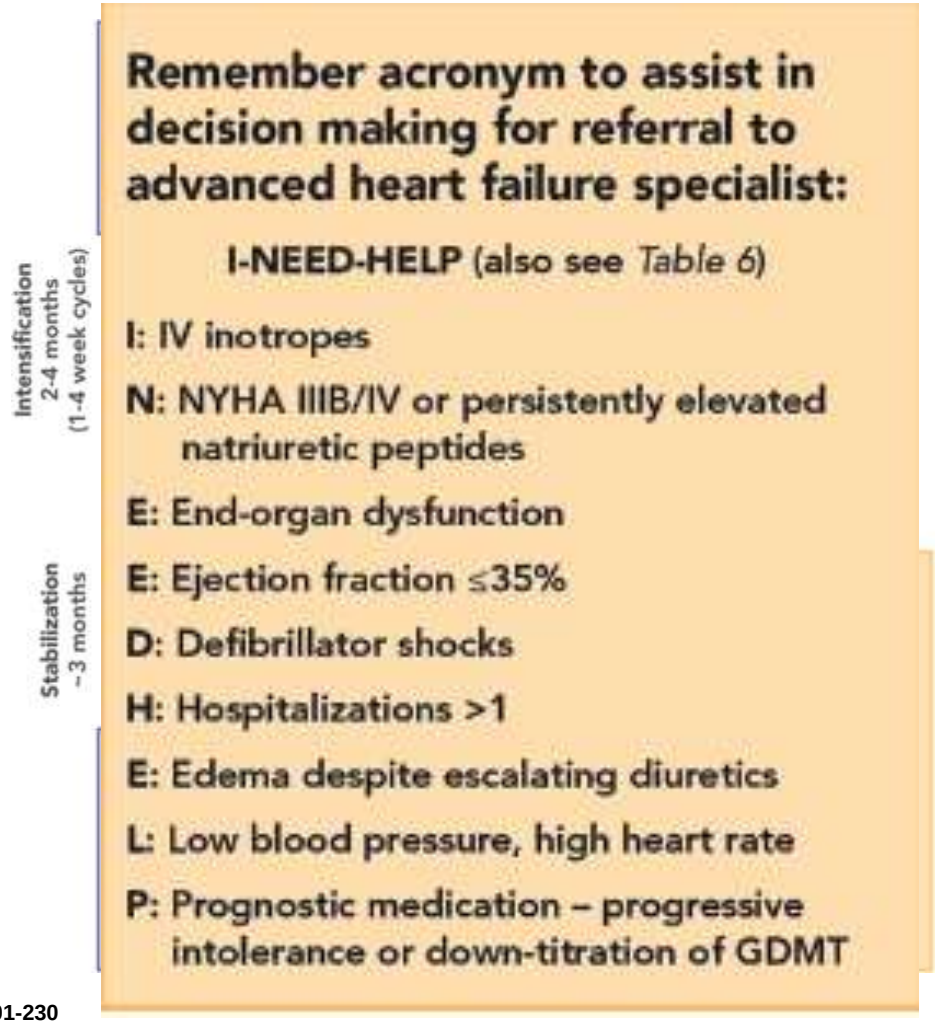
Clyde W. Yancy et al. JACC 2018;71:201-230



Indications for Use of Ivabradine

- HFrEF (EF ≤35%)
- On maximum tolerated doses of beta blocker
- Sinus rhythm with a resting heart rate ≥70 bpm
- NYHA class II or III HF

Clyde W. Yancy et al. JACC 2018;71:201-230



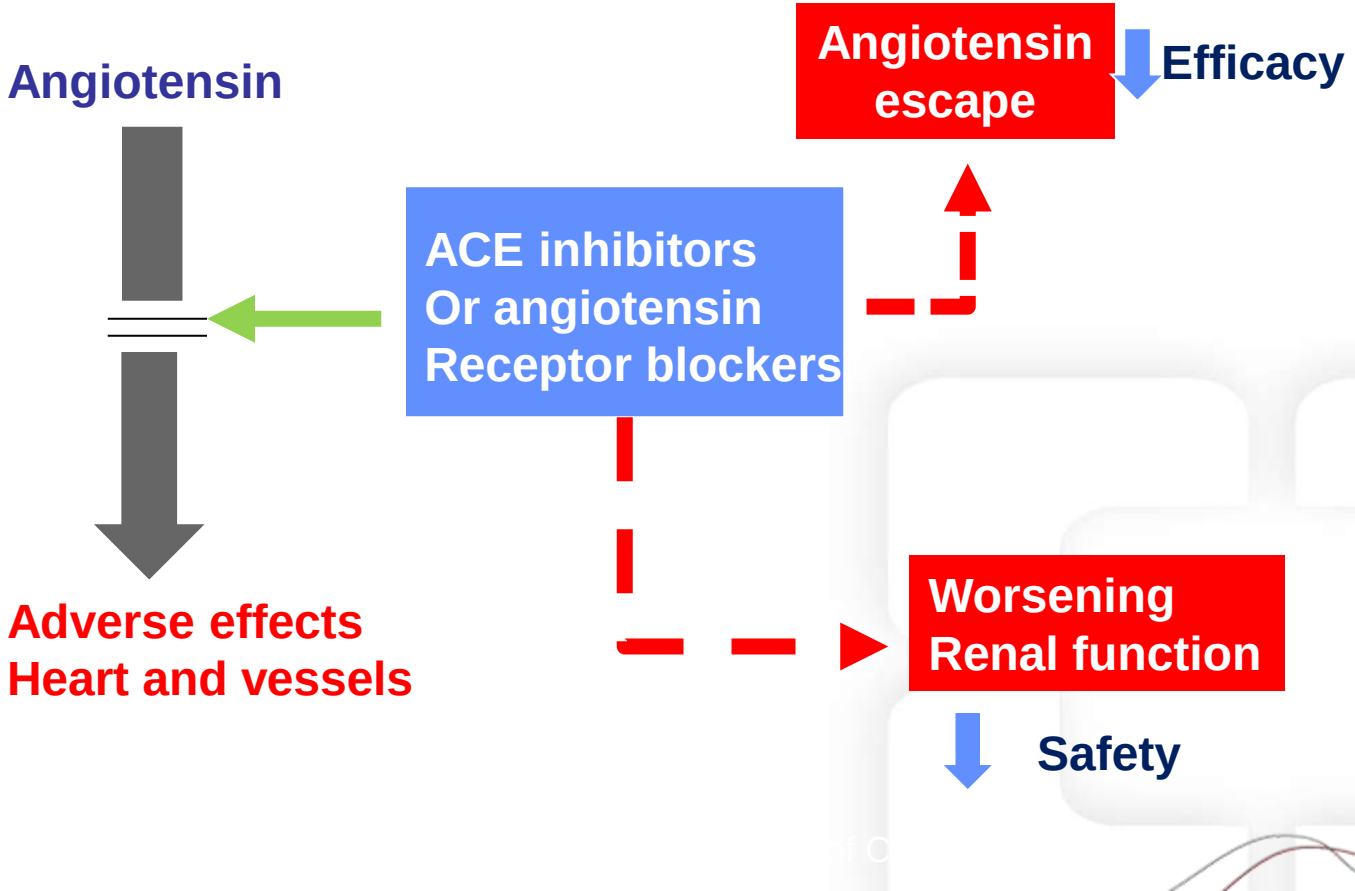
Clyde W. Yancy et al. JACC 2018;71:201-230

JACC

Emerging Drugs in USA Trials
HFrEF

- Omecamtiv mecarbil inotrope
- Sacubitril/valsartan ARNI
- Vericiguat cGMP promoter

Limitations with current Inhibitors of the Renin-Angiotensin System



Biological Antagonism of Neurohormonal Systems

Endogenous compensatory peptides

Bradykinin, natriuretic peptides, adrenomedullin, angiotensin, endothelin amyloid-ß peptide

NEPRILYSIN

Inactive metabolites

REDUCE

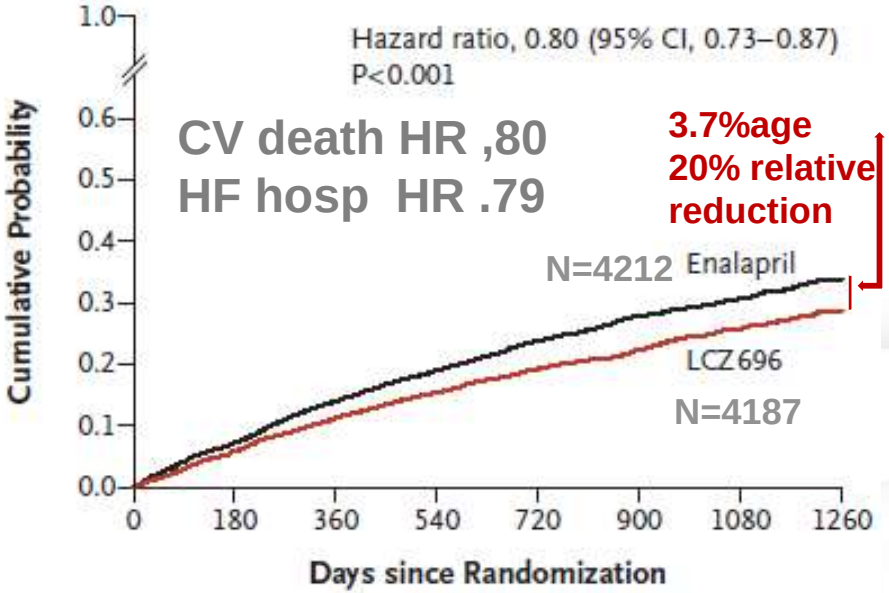
Neurohormonal Activation

Vascular tone

Cardiac remodelin

Sodium retention

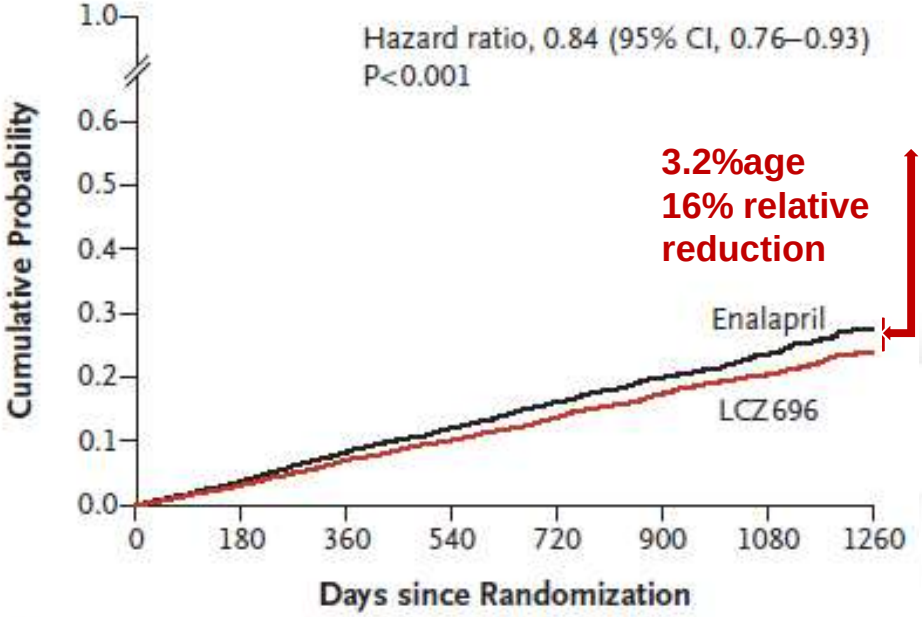
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

N Engl J Med 2014;371:993.

PARADIGM-HF: Death from any cause (secondary endpoint)



No. at Risk								
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

N Engl J Med 2014;371:993

PARADIGM-HF: Key secondary endpoints

Outcome	LCZ 696	Enalapril	HR	P Value
Change in KCCQ	-2.99	-4.63	1.64	0.001
New Onset AFIB	84(3.1)	83(3.1)	0.97	0.83
Decline in Renal Function	94(2.2)	108(2.6)	0.86	0.28

Fewer symptoms and physical limitations with sacubitril-valsartan

No increase in AFIB or decline in renal function

PARADIGM-HF:Adverse Events

Event	LCZ696 n=4187	Enalapril n=4214	P Value
Hypotension symptomatic	**588(14.0)**	388(9.2)	<0.001
Systolic BP <90 mm Hg	**112(2.7)**	59(1.4)	<0.001
Potassium >5.5 mmol/l	674(16.1)	727(17.3)	0.15
Potassium >6.0 mmol/l	181(4.3)	**236(5.6)**	0.007
Cough	474(11.3)	**601(14.3)**	<0.001
Angioedema*	10(0.2)	5(0.1)	0.19

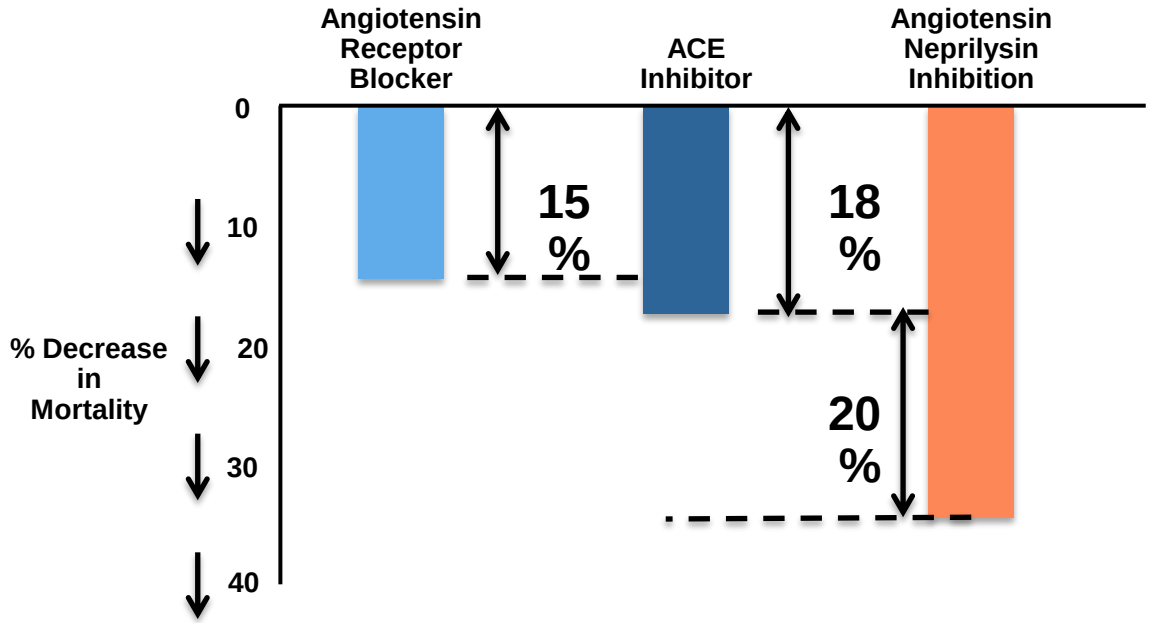
N Engl J Med 2014;371:993.

Sacubitril Valsartan: initiation

- 72 yrs WM 5 year history of HFrEF
  - DCM
  - CRT D
  - Metoprolol succinate 150 mg daily
  - Losartan 50 mg daily
  - Spironolactone 25 mg daily
  - Furosemide 10 mg daily prn
- NYHA Class III
- NT BNP 2200
- GFR 50
- BP 145/80 mm Hg

Options: increase losartan, add amlodipine, substitute ARNI for ARB

Incremental Decrease in Mortality



Effect of ARB vs placebo derived from CHARM-alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

Gaps with PARADIGM HF

Limited NYHA IV patients

FDA approval but not included in the guidelines

Perez A et al. JACC HF 2017

HEART FAILURE NETWORK

LIFE Trial

sacubitril/valsartan

Entresto™ (LCZ696) In Advanced Heart Failure

Protocol for the Heart Failure Clinical Research Network

INCLUSION

Advanced HFrEF defined as including ALL :

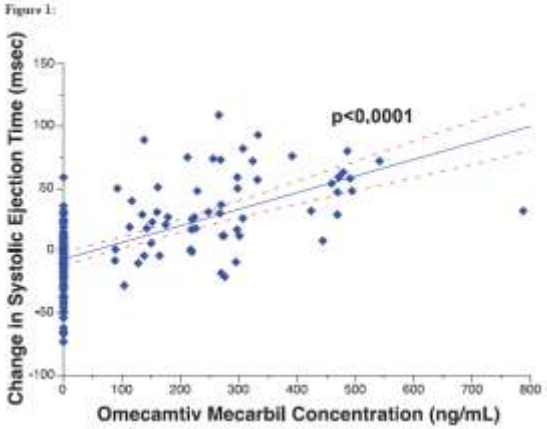
a. LVEF≤ 35% documented during the preceding 3 months
b. estimated GFR 20-60 mL/min/1.73m2
c. NYHA class IV symptomatology for the majority of the previous month
d. Minimum of 3 months GDMT for HF and/or intolerant to therapy

NCT02816736

Omecamtiv mecarbil: novel inotrope

ATOMIC-HF*
COSMIC-HF

Safety and
dose titration



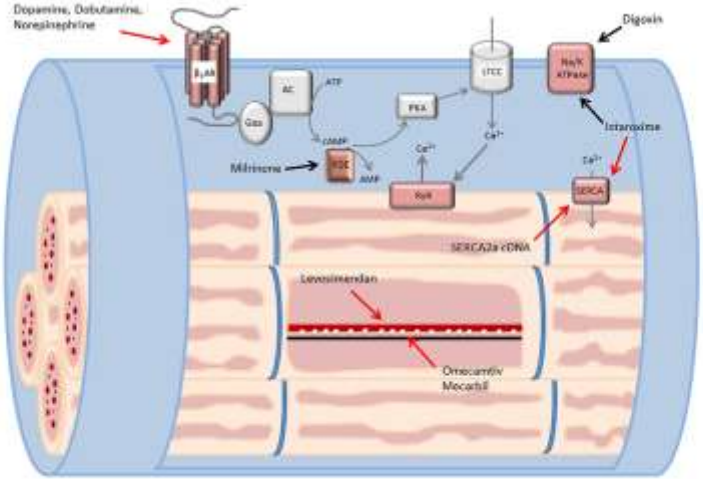


Figure 1 Diagram of Intracellular Signaling Cascades Within Cardiomyocytes Altered by Inotropes

JACC Vol. 63, No. 20, 2014
Teerlink J et al JACC 2016

GALACTIC-HF

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

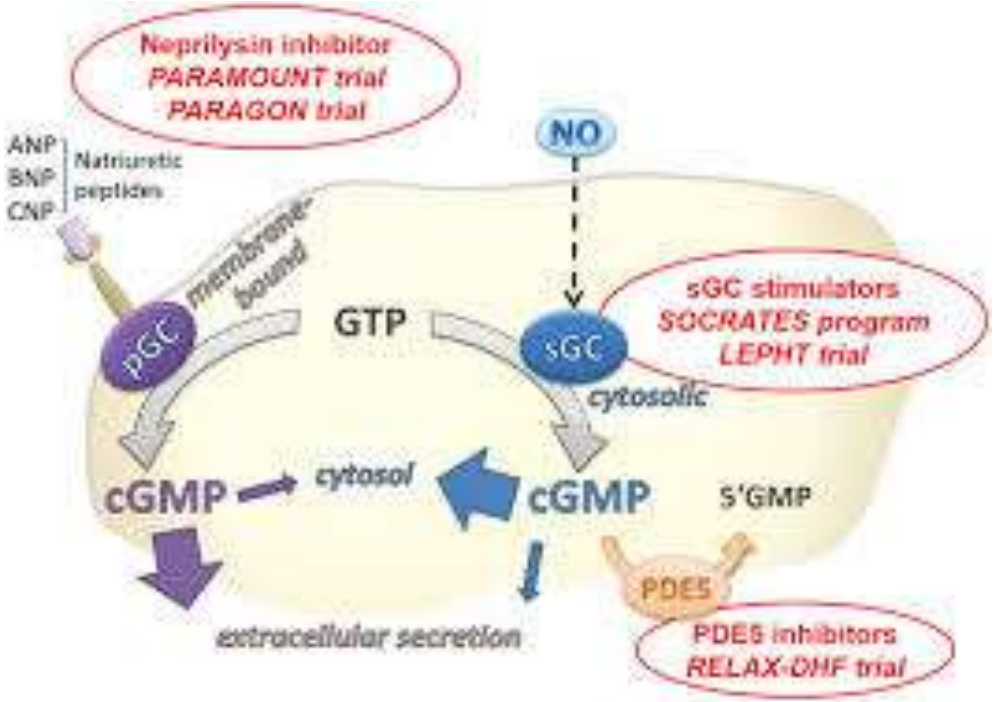
Primary Endpoint:
Measure time to cardiovascular death or first heart failure event

Evaluate the effect of omecamtiv mecarbil as compared with placebo in subjects with **chronic heart failure with reduced ejection fraction** receiving standard of care therapy

Dose based on plasma levels
Global n=8000

https://clinicaltrials.gov/ct2/show/NCT02929329

Relative deficit of cGMP in heart failure
role of oral soluble guanylate cyclase stimulators?



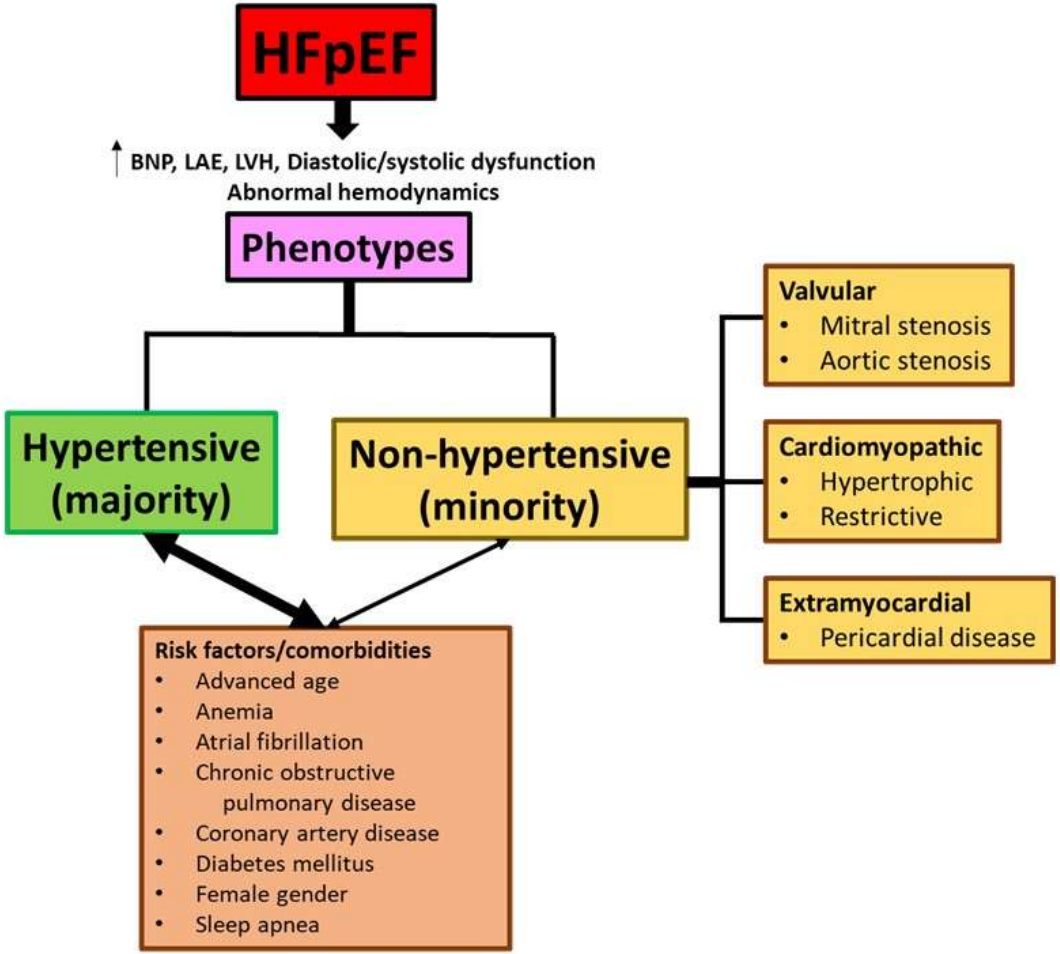
The primary hypothesis is vericiguat (MK-1242) is superior to placebo in increasing the time to first occurrence of the composite of cardiovascular (CV) death or heart failure (HF) hospitalization in participants with HFrEF

VICTORIA

NCT02861534

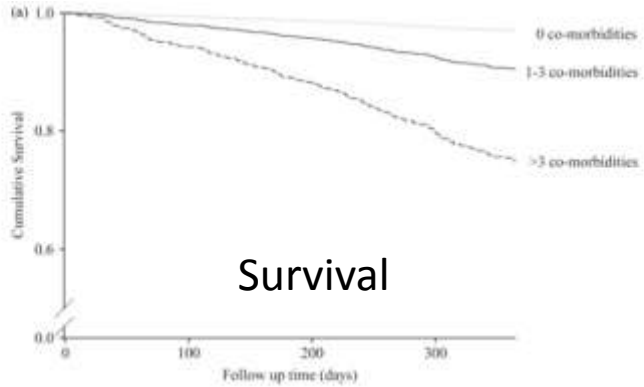
- HFrEF inclusion EF <45%
- n=4872
- Event Driven: time to 1st CV death or HF admit
- NYHA II-IV
- Hospitalization and BNP criteria
- Completion 2020

SOCRATES *JAMA*. 2015;314(21):2251-2262.

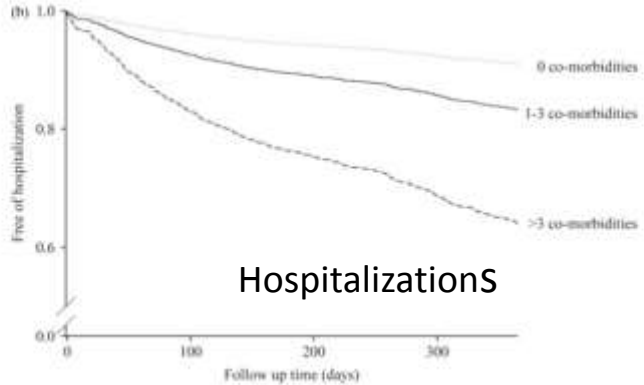


Xanthopoulos, Triposkiadis, Starling. Trends in Cardiovascular Medicine 2018.

Comorbidities and Outcomes



Survival



HospitalizationS

Worse Outcomes Based on Co-Morbidities!

Van Deursen et al. Eur J Heart Fail. 2014 Jan;16(1):103-11

HFpEF JS 74 yo retired RN, LV EF 60%

- BMI 38 BP 165/94 mm HG
- Chronic AFIB post PVI
- CKD GFR 38
- Anemia receives IV iron
- OSA and uses CPAP intermittently
- Syncope and bradycardia; now with DDD pacemaker
- Recurrent hospital admits with weight gain, edema,

- What to do next?

Insert echo video

Negative Trials:

ACEi
ARB
Nitrates
PDE5 inhibitors
Beta blockers

ARB? Candesartan
Reduced HF admissions

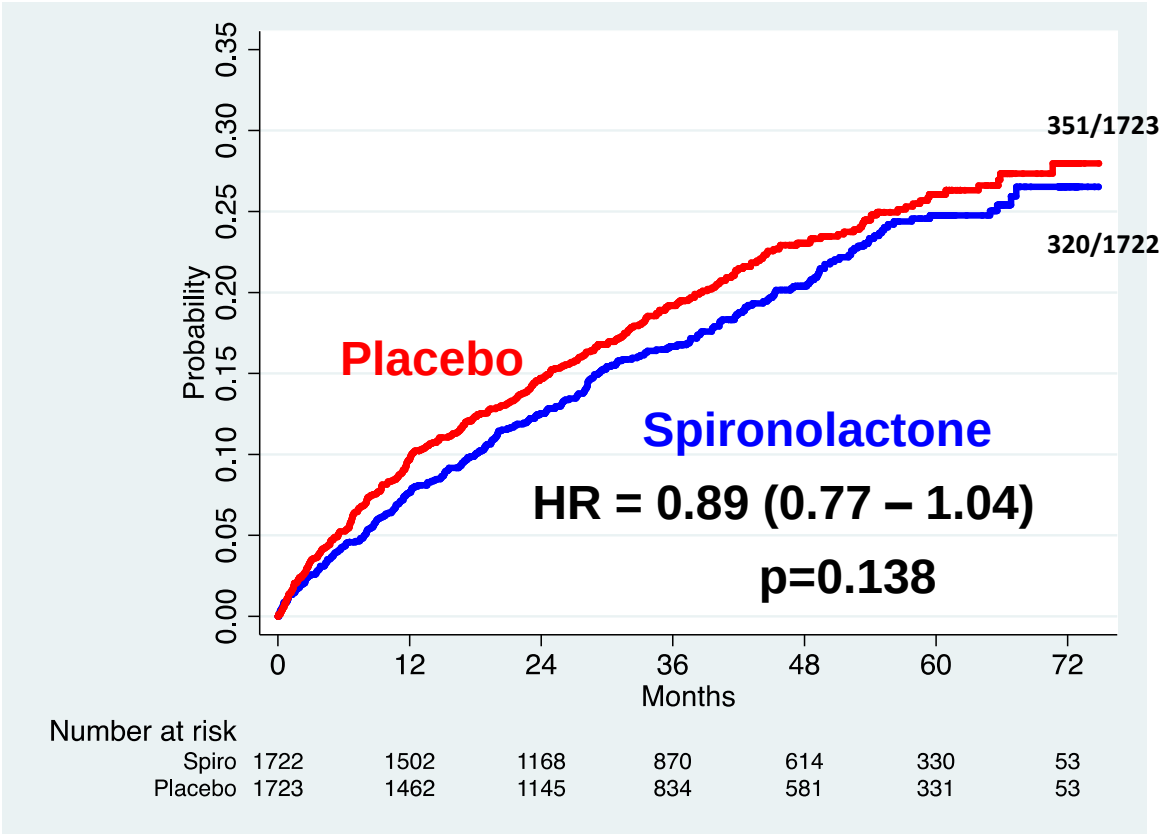
Table – Randomized trials in HFpEF.

Study	Region	Number of randomized patients	Ejection fraction cut-off	Primary endpoint	Intervention	Results
CHARM-preserved Yusuf et al., Lancet 2003;362: 777–781	26 countries (Europe, Australia, Asia, Africa, and America)	3025	>40%	CV death or unplanned admission to hospital for the management of worsening chronic HF	Candesartan	Fewer HF admissions
PEP-CHF Cleland et al., European Heart Journal 2006;27:2338–2345	Bulgaria, Czech Republic, Hungary, Ireland, Poland, Russia, Slovakia, and the United Kingdom	850	40-50%	All-cause mortality or unplanned HF-related hospitalization	Perindopril	Fewer HF admissions at 1 year, but differences were not significant for the entire duration of follow-up
I-PRESERVE Massie et al., The New England Journal of Medicine 2008;359:2456–2467	25 countries (Europe, America, Africa, and Australia)	4128	≥45%	Death from any cause or hospitalization for a CV cause	Irbesartan	Neutral
Kitzman et al. Kitzman et al. Circ Heart Fail 2010;3:477–485	United States	71	≥50%	Exercise capacity or aortic distensibility	Enalapril	Neutral
SENIORS van Veldhuisen et al., J Am Coll Cardiol 2009;53:2150–2158	Czech Republic, France, Germany, Hungary, Italy, Netherlands, Romania, Spain, Ukraine, and United Kingdom	2111	≥35% or ≥40% (post-hoc analyses)	All-cause mortality or hospital admissions for a CV cause	Nebivolol	Similar effect of nebivolol between HF patients with impaired ejection fraction and patients with preserved ejection fraction
ELANDD Conraads et al., Eur J Heart Fail 2012;14:219–225	Italy, Netherlands, Belgium, Spain, Portugal, Greece, Germany, Austria	116	>45%	6 Minutes walking distance	Nebivolol	Neutral
J-DHF Yamamoto et al., Eur J Heart Fail 2013;15: 110–118	Japan	245	>40%	Cardiovascular death or HF hospitalization	Carvedilol	Neutral
RAAM-PEF Derwal et al., Journal of Cardiac Failure 2011;17:634–642	United States	46	≥50%	6 Minutes walking distance	Eplerenone	Neutral
Aldo-DHF Edelmann et al., JAMA 2013;309:781–791	Germany and Austria	422	≥50%	Peak VO_2, change in E/e'	Spironolactone	– Peak VO_2 without a difference between groups – E/e' significantly declined with spironolactone
TOPCAT Pitt et al., The New England Journal of Medicine 2014;370: 1383–1392	United States, Canada, Brazil, Argentina, Russia, Georgia	3445	≥45%	Death from CV causes, aborted cardiac arrest, or hospitalization for HF	Spironolactone	Neutral
DIG Ahmed et al., Circulation 2006;114:397–403	United States and Canada	988	>45%	HF hospitalization or HF mortality	Digoxin	Neutral
RELAX Redfield et al., JAMA 2013;309: 1268–1277	United States and Canada	216	≥50%	Peak VO2	Sildenafil	Neutral

Xanthopoulos A, Triposkiadis F, Starling RC. Trends Cardiovasc Med. 2018 Jan 9. pii: S1050-1738(18)30005-7. doi: 10.1016/j.tcm.2018.01.001.

1° Outcome TOPCAT

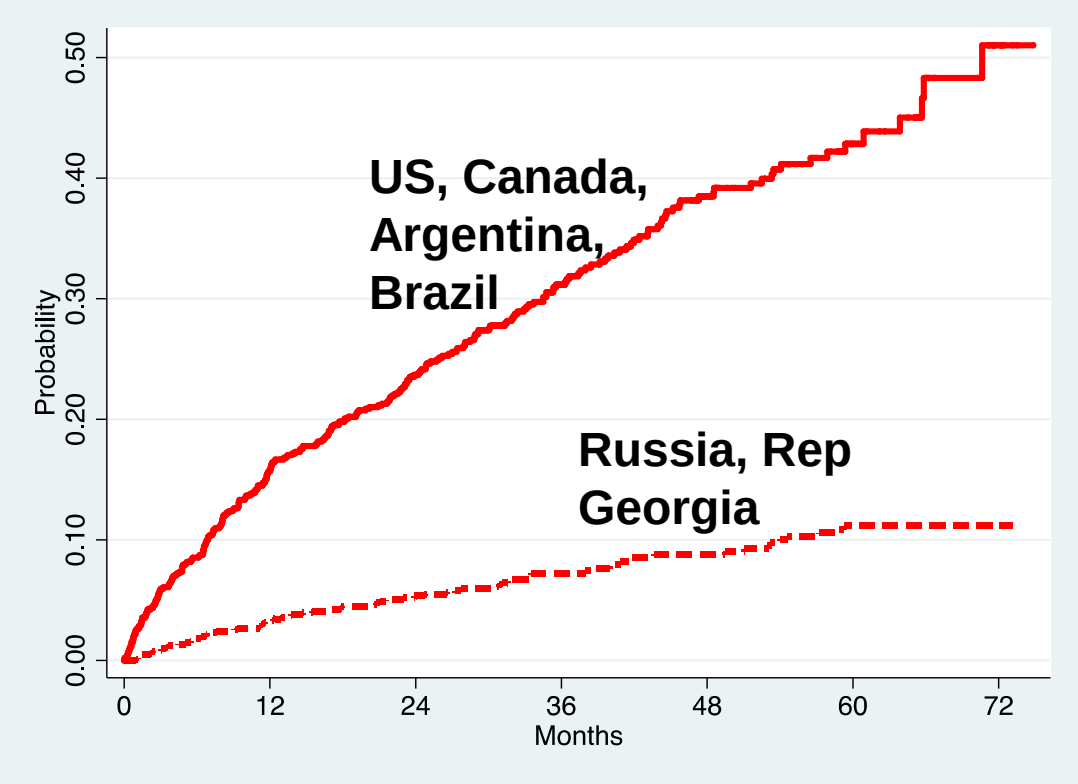
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)



N Engl J Med. 2014 Apr 10;370(15):1383-92.

TOPCAT Placebo Rates:

Primary Outcome, by region



Placebo:
280/881 (31.8%)

Placebo:
71/842 (8.4%)

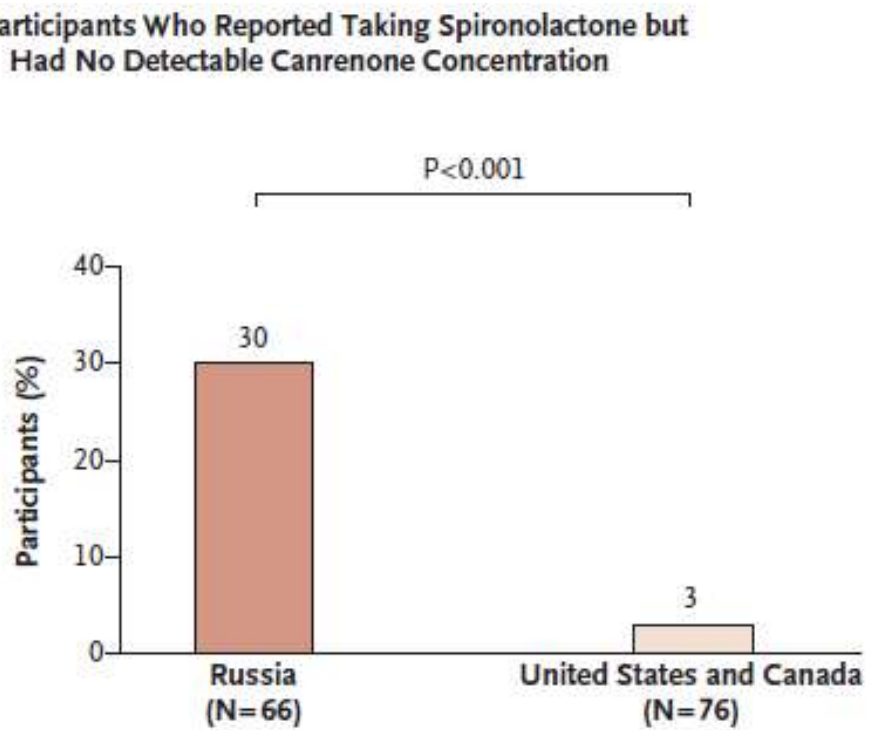
N Engl J Med. 2014 Apr 10;370(15):1383-92.

TOPCAT spironolactone for HFpEF ≥45%

Marked regional differences in outcomes

Drug metabolites not present

Trial results obtained in Russia do not reflect the true therapeutic response to spironolactone



N Engl J Med. 2017 Apr 27; 376(17): 1690–1692.

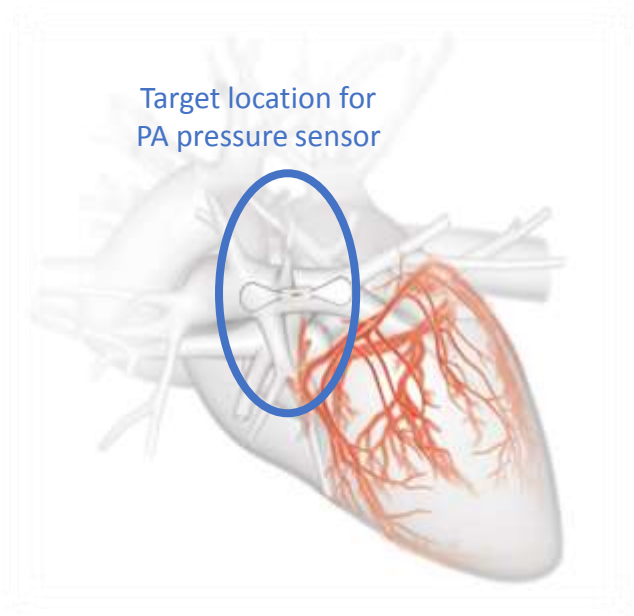
Hemodynamic-Guided HF Management

Cardiomems™ HF System

Pulmonary Artery Pressure Sensor

Patient Electronics System

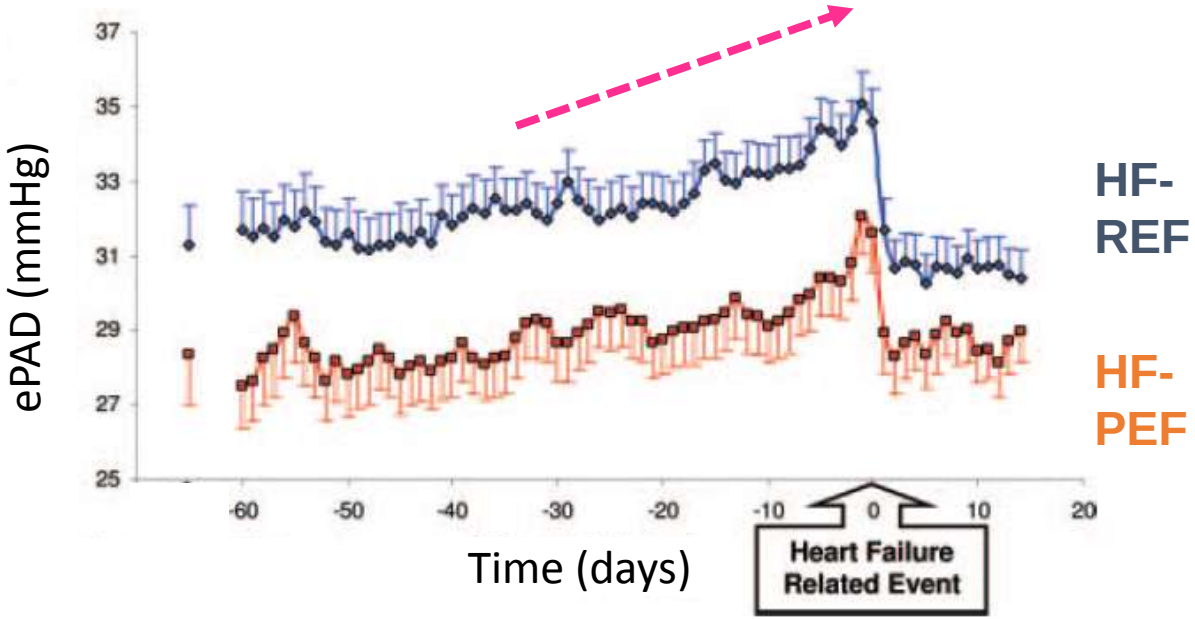
Merlin.net™ PCN



Abraham W, et al. Lancet, 2011;377(9766):658-66.

Progressive Rise in Filling Pressures Leads to Hospitalization

Transition from Chronic Compensated to Acute Decompensated HF



Zile M, et al. Circulation. 2008;118:1433-1441.

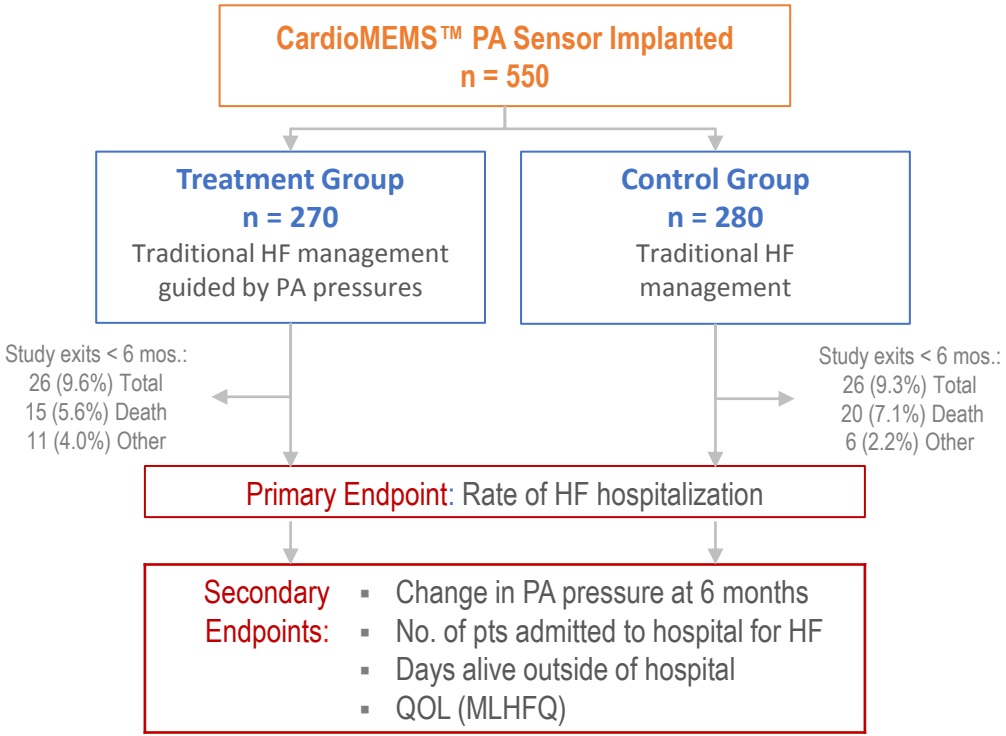
Hemodynamic-Guided HF Management

CHAMPION (n=550)

PURPOSE
Evaluate the safety and efficacy of the CardioMEMS™ HF System in reducing HF related hospitalizations in NYHA class III heart failure patients.

Treatment group managed to target PA pressures:

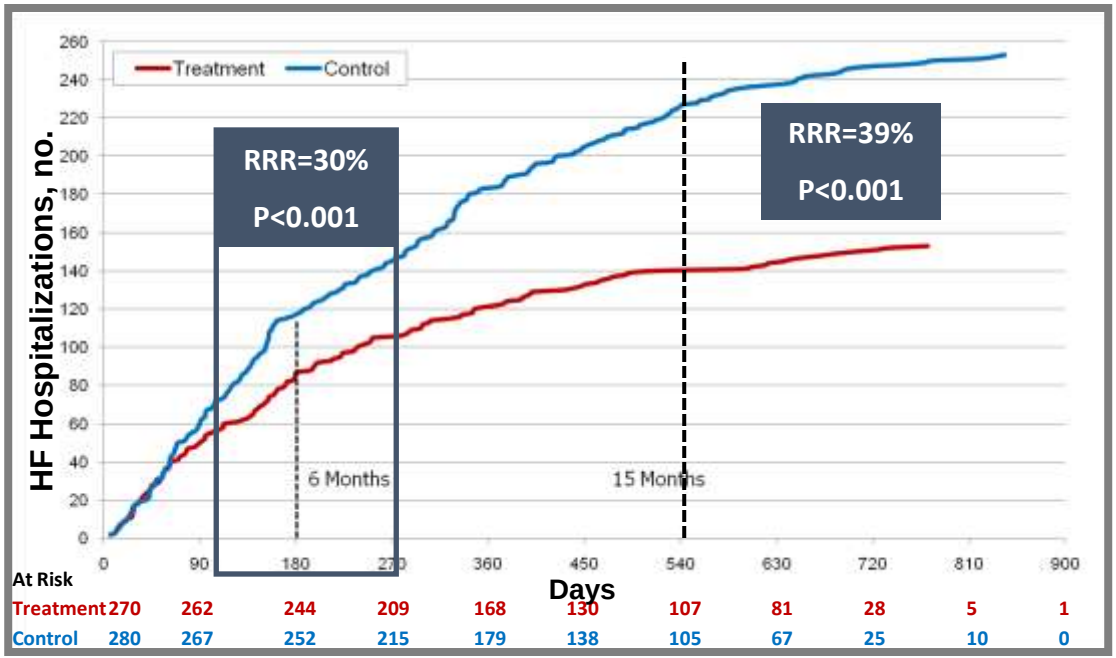
Systolic 15 – 35 mmHg
Diastolic 8 – 20 mmHg
Mean 10 – 25 mmHg



Abraham W, et al. Lancet, 2011;377(9766):658-66.

Hemodynamic-Guided HF Management

CHAMPION (n=550)

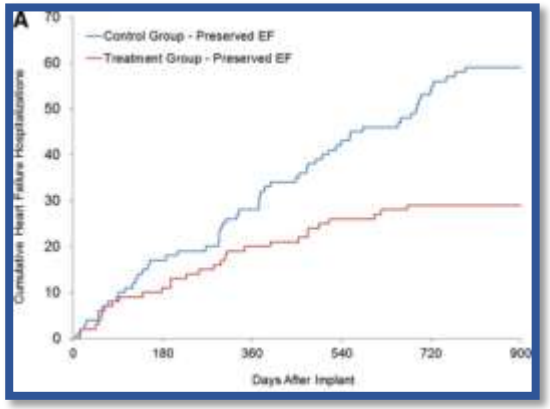


Abraham W, et al. Lancet, 2011;377(9766):658-66.

HFpEF pts made up 22% of the trial cohort

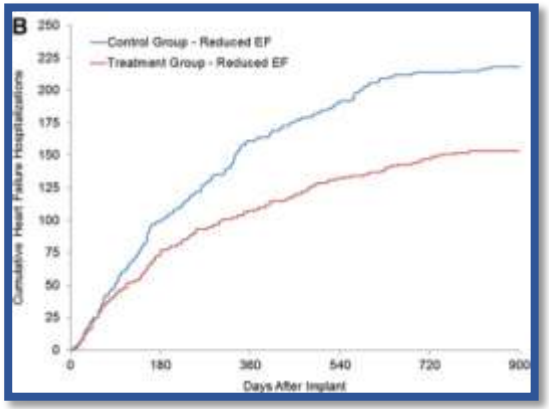
PURPOSE Evaluate the effect of PA pressure-guided therapy with the CardioMEMS™ HF System in patients with preserved ejection fraction (EF ≥ 40%), a group with no clinically proven therapies.

HFpEF



RRR 46% (HR 0.54, CI 0.38-0.70)

HFrEF

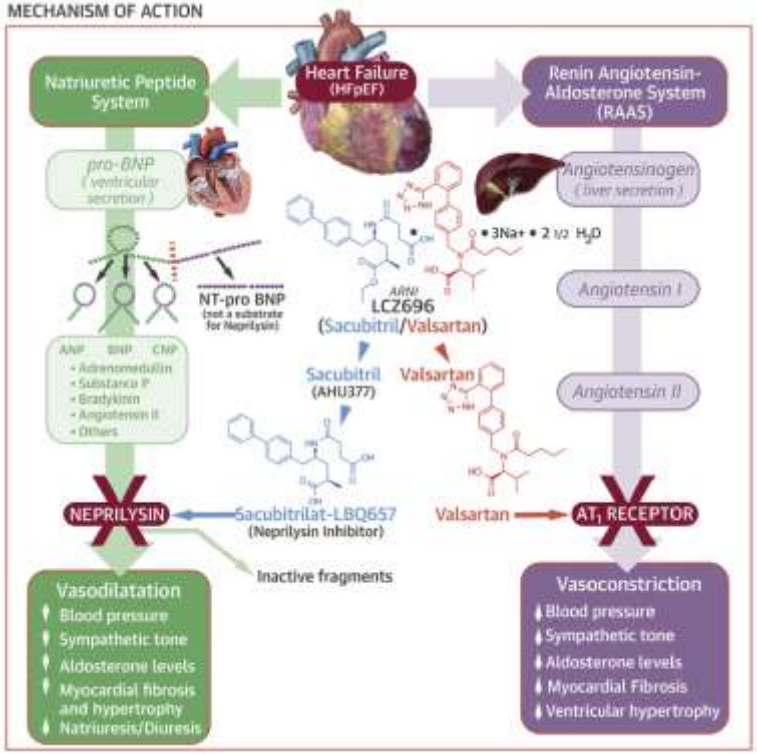


RRR 24% (HR 0.76, CI 0.61-0.91)

HF Hospitalization Reduction (18 mo follow-up)
n=115, p=0.0004

Adamson PB, et al. Circ Heart Fail, 2014;7:935-944

Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction (PARAGON-HF Trial)



Solomon, S.D. et al. J Am Coll Cardiol HF. 2017;5(7):471–82

Treatment for Heart Failure with preserved ejection fraction

- valsartan/sacubitril: PARAGON-HF n=4600 enrolling

- phase III
- EF ≥ 45%, NYHA II–IV, LA enlarged or LV hypertrophy
- Composite: CV death and total HF hospitalizations

NCT01920711

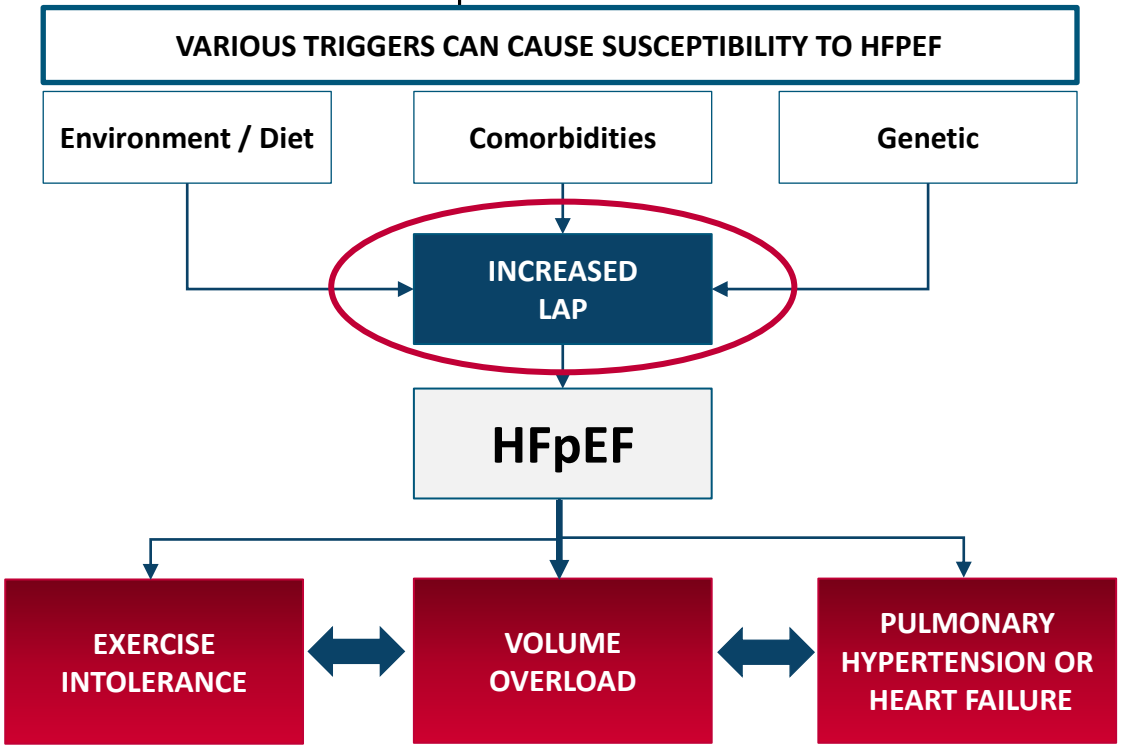
PARAMOUNT HF

Lancet Vol 380, No. 9851, p1387–1395

Solomon, S.D. et al. J Am Coll Cardiol HF. 2017;5(7):471–82

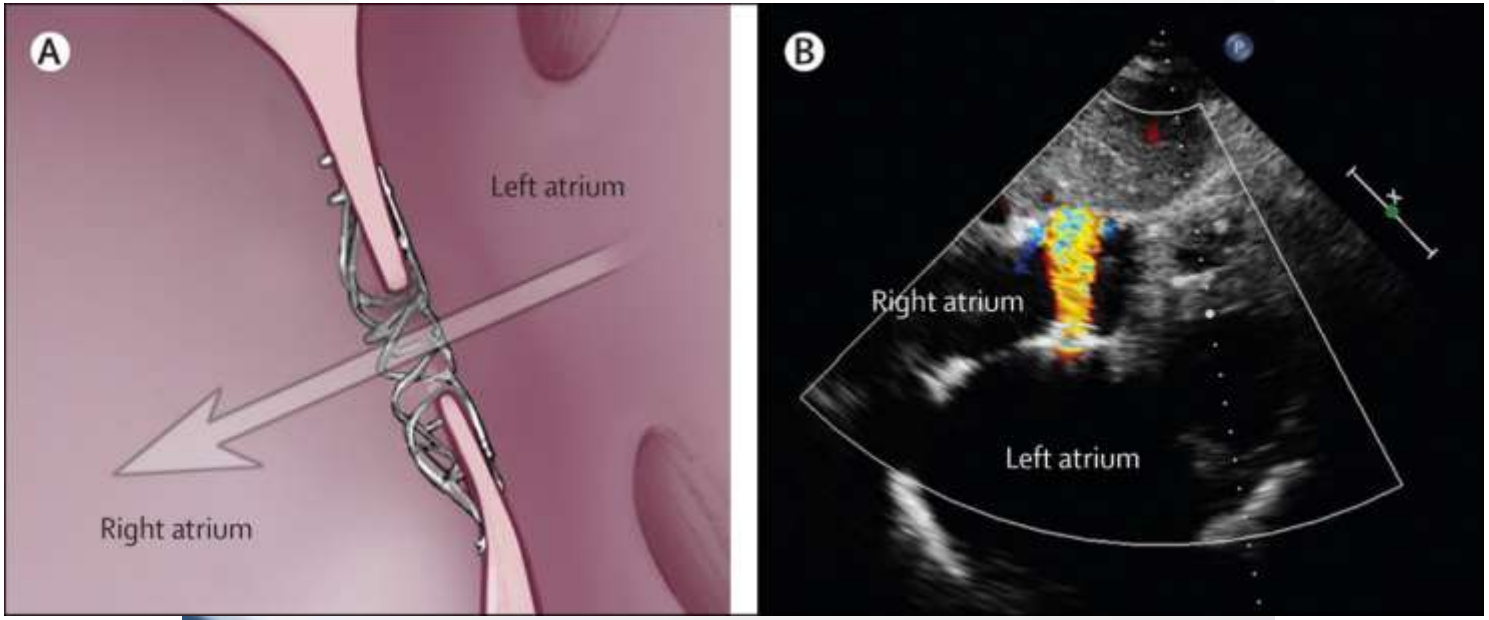
Increased LAP (Left Atrial Pressure)

The Common denominator in HFpEF

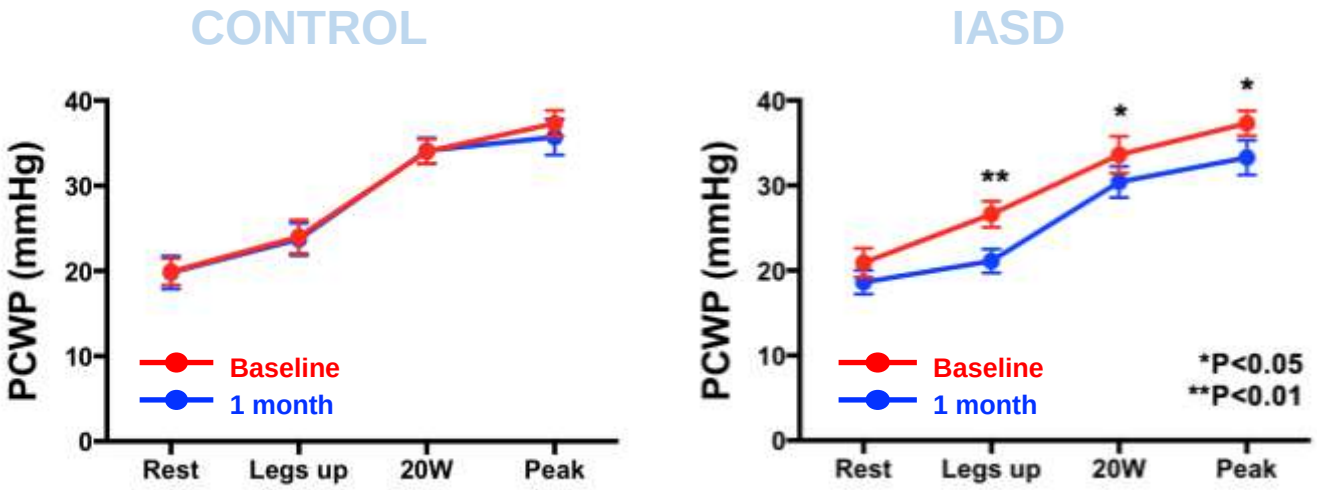


Shah SJ. JACC 2013

Inter Atrial Shunt Device IASD



Change in PCWP: Baseline to 1 month



REDUCE-LAP HF I Study Results

A Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure with Preserved Ejection Fraction (REDUCE LAP-HF I): A Phase 2, Randomized, Sham-Controlled Trial

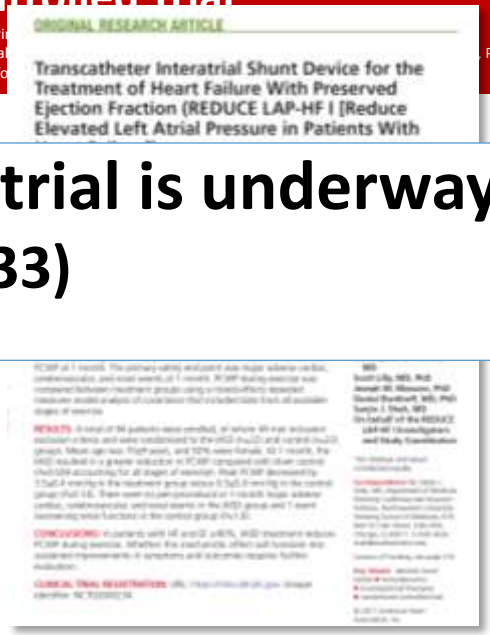
Ted Feldman, MD; Laura Mauri, MD, MSc; Rami Kahwash, MD; Sheldon Litwin, MD; Mark J. Ricciardi, MD; Pi
David M. Kaye, MD, PhD; Mark C. Petrie, MB, ChB, MRCP; Anupam Basuray, MD; Scott L. Hummel, MD, MS; Rhonda , PhD;
Joseph M. Massaro, PhD; Daniel Burkhoff, MD, PhD; Sanjiv J. Shah, MD; fo

successful and safe, no

REDUCE LAP-HF II pivotal trial is underway (NCT03088033)

leg position when compared to sham group

- This hemodynamic study demonstrates the beneficial mechanistic effect of the IASD
- The IASD could have beneficial clinical effects in


ORIGINAL RESEARCH ARTICLE

Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With

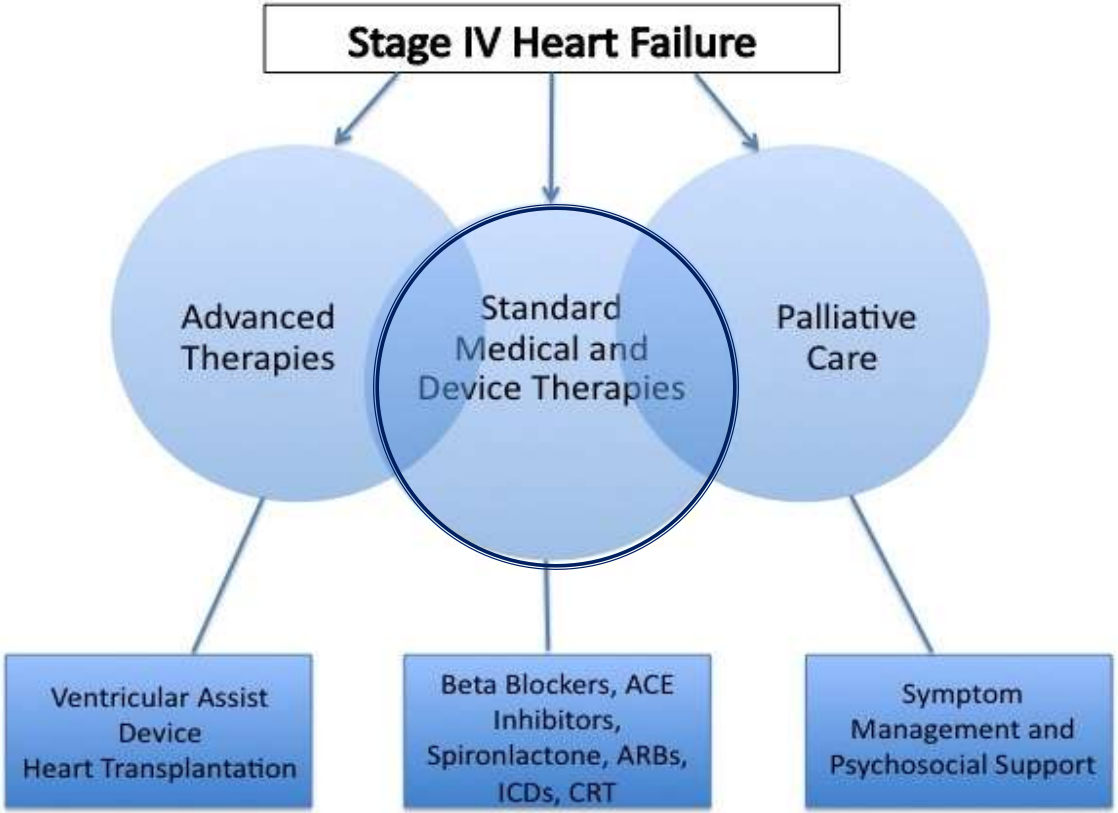
Circulation. 2018 Jan 23;137(4):364-375

Conclusions

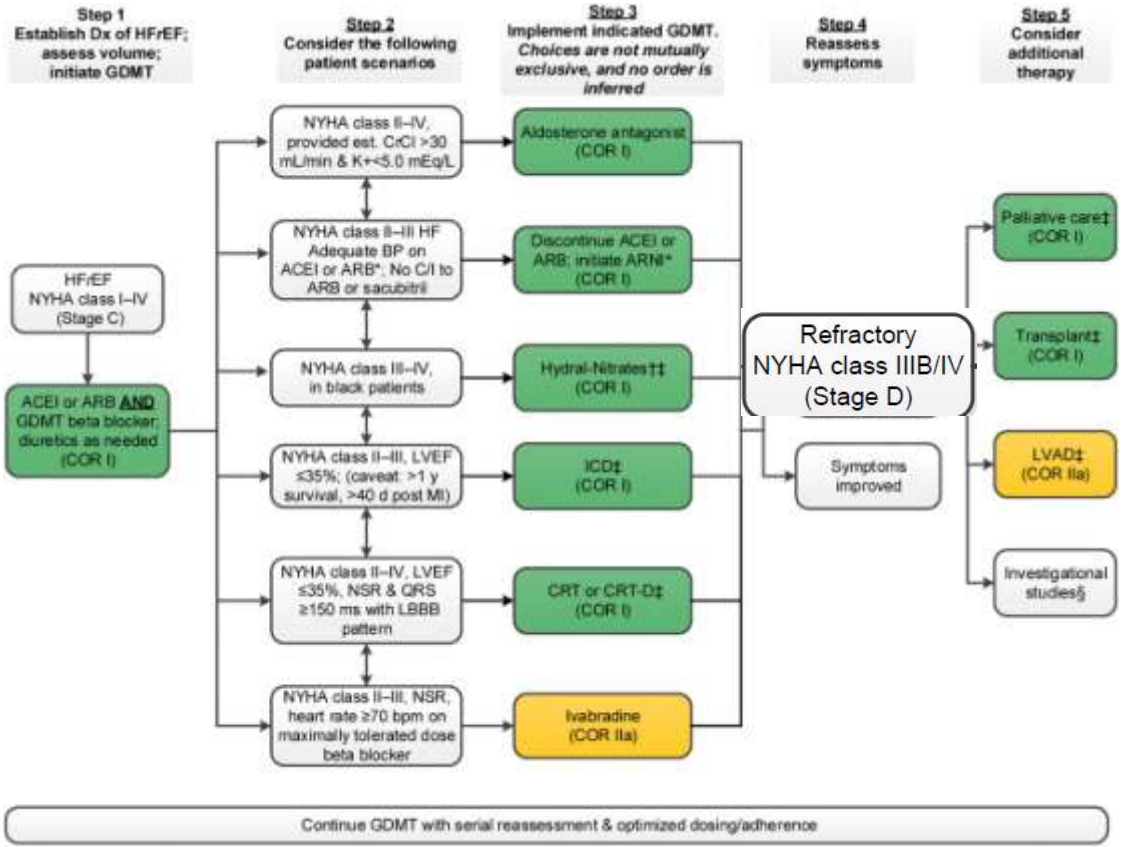
- Up to 50% of patients with HF have preserved LVEF(HFpEF)
- Morbidity and mortality in HFpEF and HFrEF as similar
- Comorbidities are frequent both in HFpEF and HFrEF
- There is **no specific proven treatment for HFpEF**
  - Sacubitril valsartan is being evaluated in the PARAGON HF trial
  - Aggressive management of hypertension and all comorbidities should be implemented
- The future identification of successful therapies for HFpEF will require defining specific phenotypes of HFpEF with targeted therapy addressing unique mechanisms

Advanced Heart Failure GUIDELINES

JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.



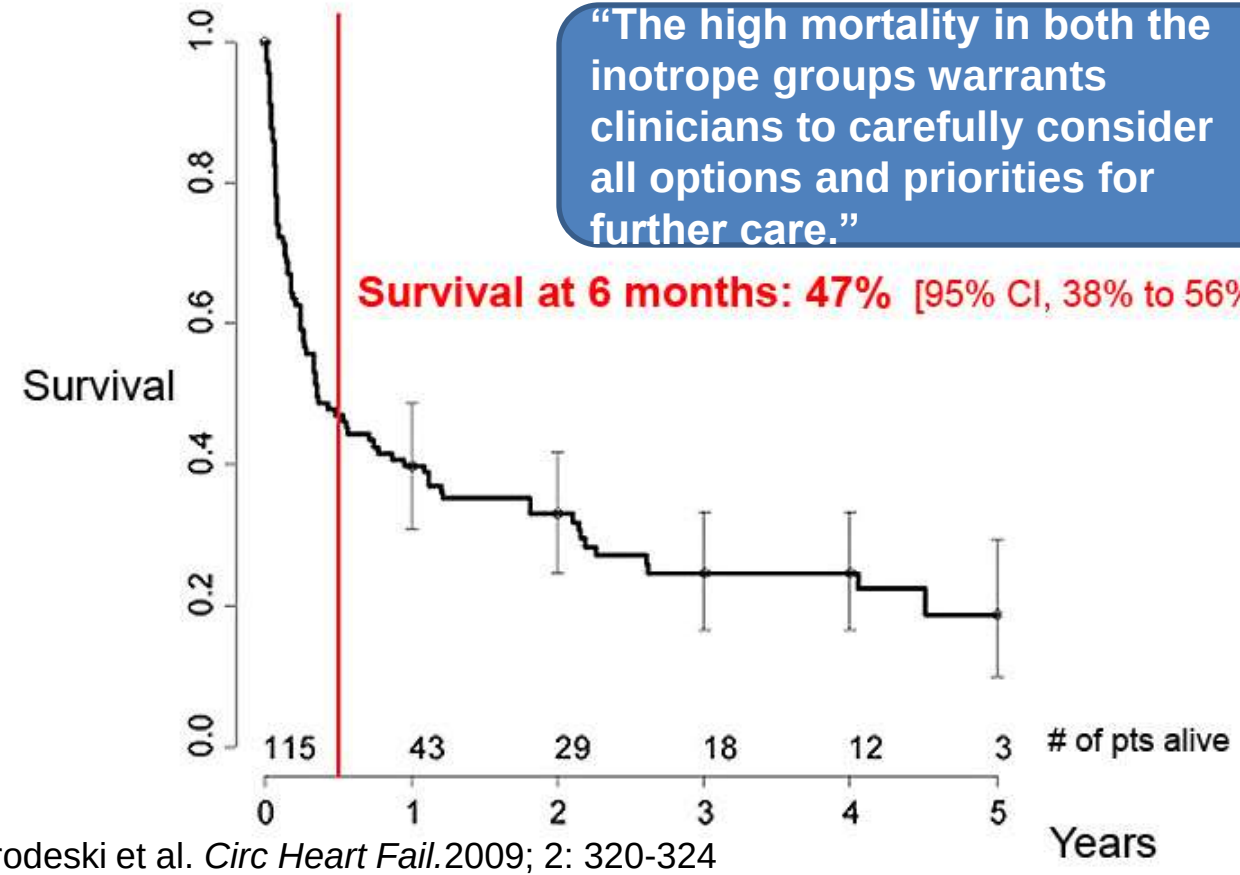
2017 Update Treatment of HFrEF Stages C and D



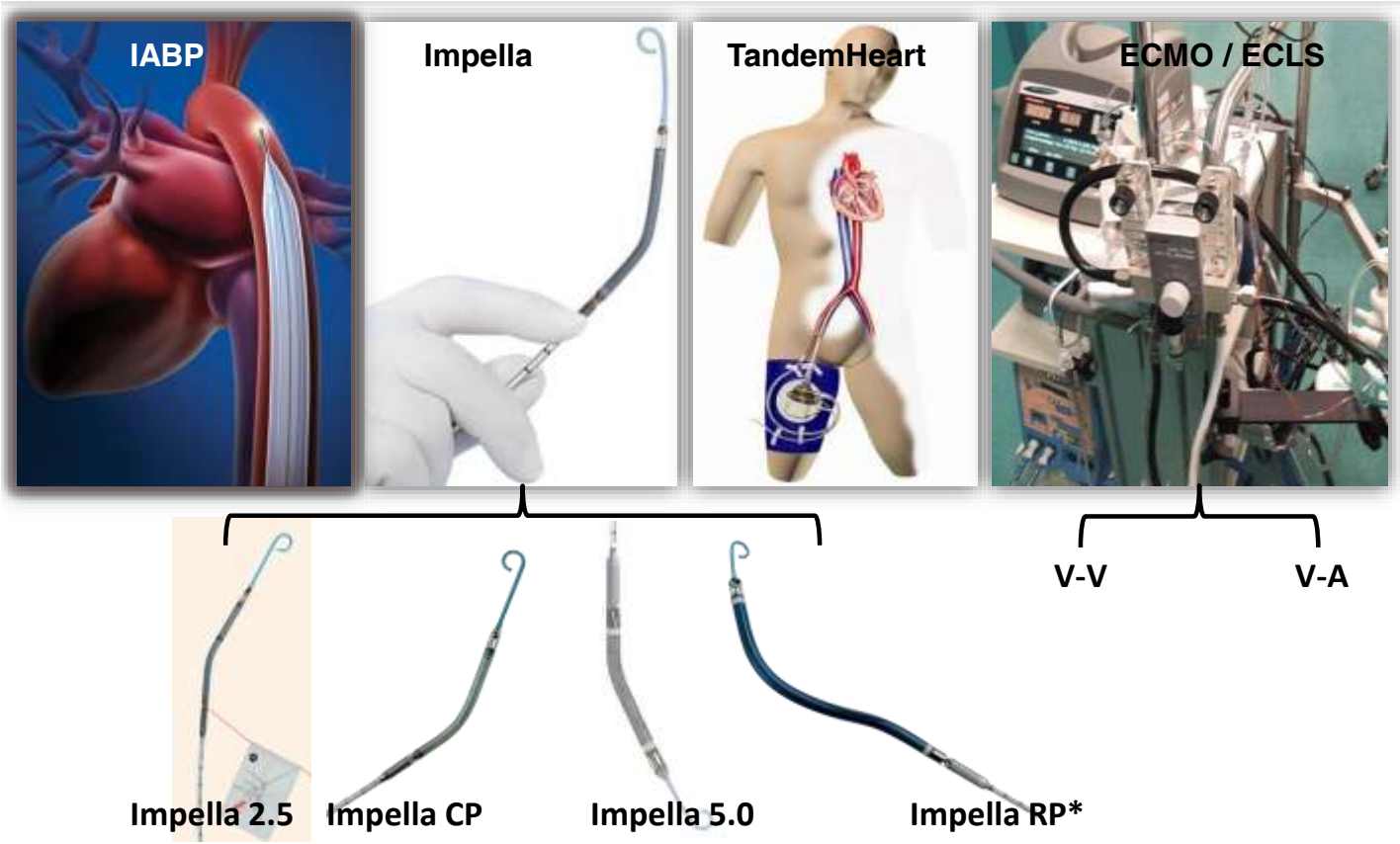
JACC 2017;70(6):776-803.
J Card Fail 2017;23(8):628-51.

Survival Among End-Stage Heart Failure Patients Discharged on Continuous Inotropes

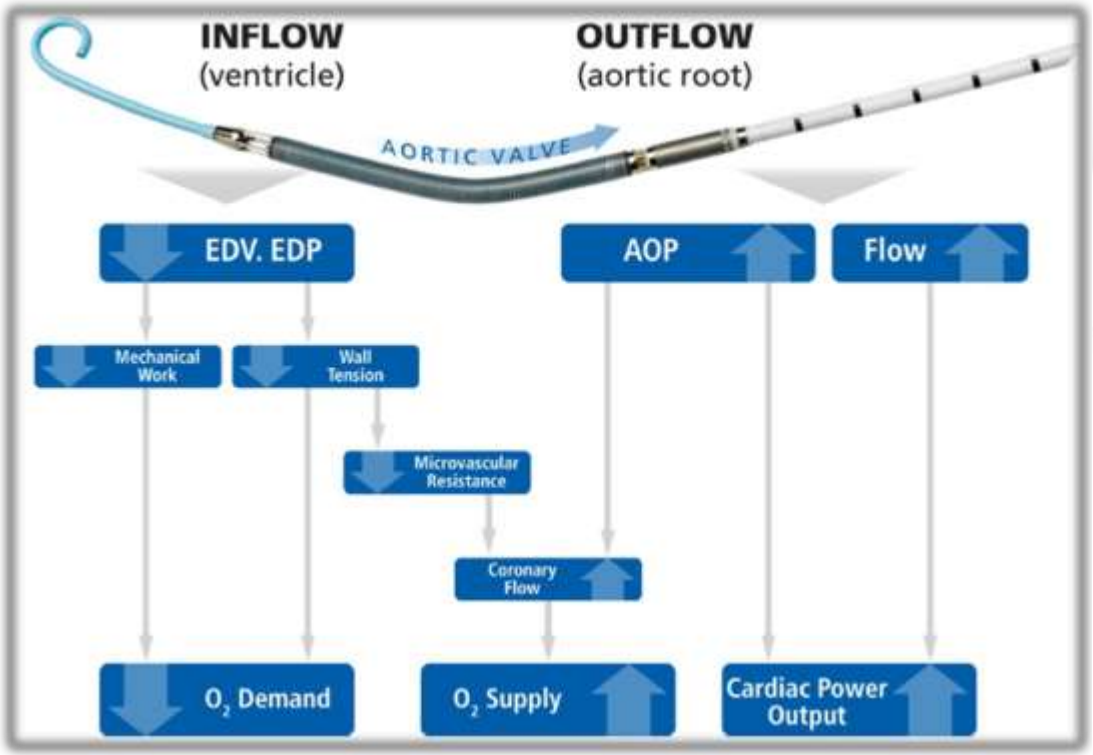
"The high mortality in both the inotrope groups warrants clinicians to carefully consider all options and priorities for further care."



Gorodeski et al. *Circ Heart Fail.*2009; 2: 320-324


IABP
Impella
TandemHeart
ECMO / ECLS
V-V
V-A
Impella 2.5
Impella CP
Impella 5.0
Impella RP*

Physiologic Impact of Impella

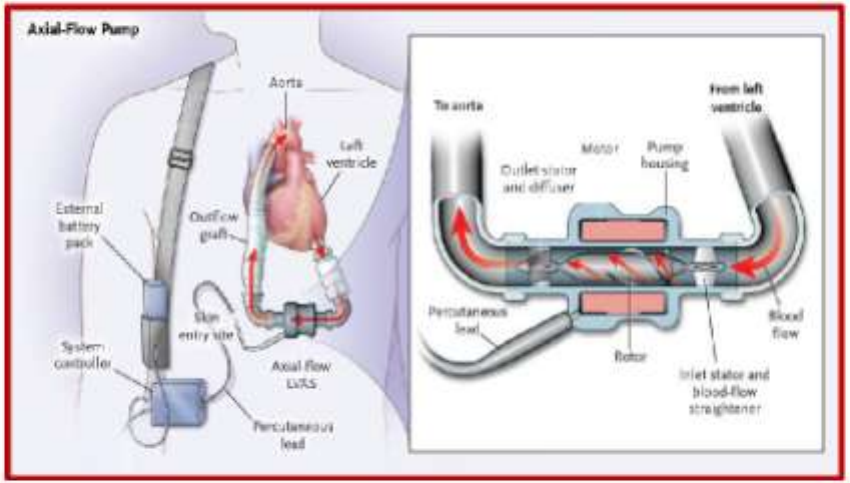


Impella 5.0L Axillary

- 58 yo CAD, MR, TR, EF 15% pre transplant, IABP
- PA 77/50 (59) PCW 40
  - TPG 19 CO 4 PVR 5
  - +3 TR Mod RV dysfunc
- Impella 5 R axillary art
- POD 2 RA 8 PA 40/24 (30) PCW 18 TPG 12 CO 6 PVR 2
- POD 7 HM3 LVAD

Background

- Continuous-flow Left Ventricular Assist Systems (LVAS) improve survival and quality of life in patients with advanced heart failure refractory to medical therapy[1]



The HeartMate II LVAS is a mechanical bearing axial continuous-flow blood pump;
An LVAS approved for *both* Bridge-To-Transplant (BTT) and Destination Therapy (DT) patients

MOMENTUM 3

[1]Slaughter et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device. *N Engl J Med*. 2009;361(23):2241-2251.

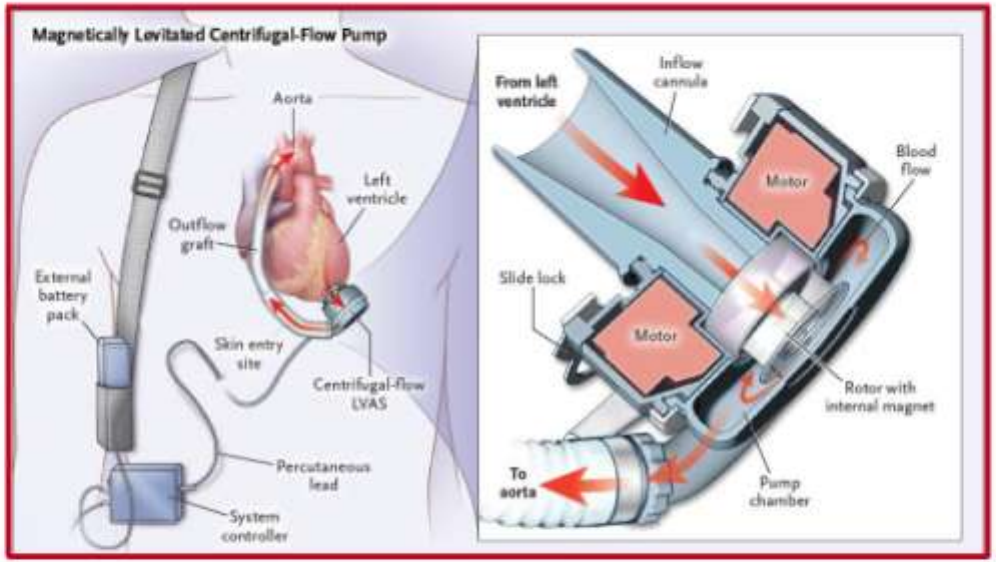
Background

- LVAS, such as the HeartMate II, are associated with significant risk of pump thrombosis requiring pump exchange, limiting long-term durability

- Other major adverse events of concern with LVAS devices include stroke, bleeding and device related infection[1]

[1]Slaughter et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device. *N Engl J Med*. 2009;361(23):2241-2251.

HeartMate 3 LVAS

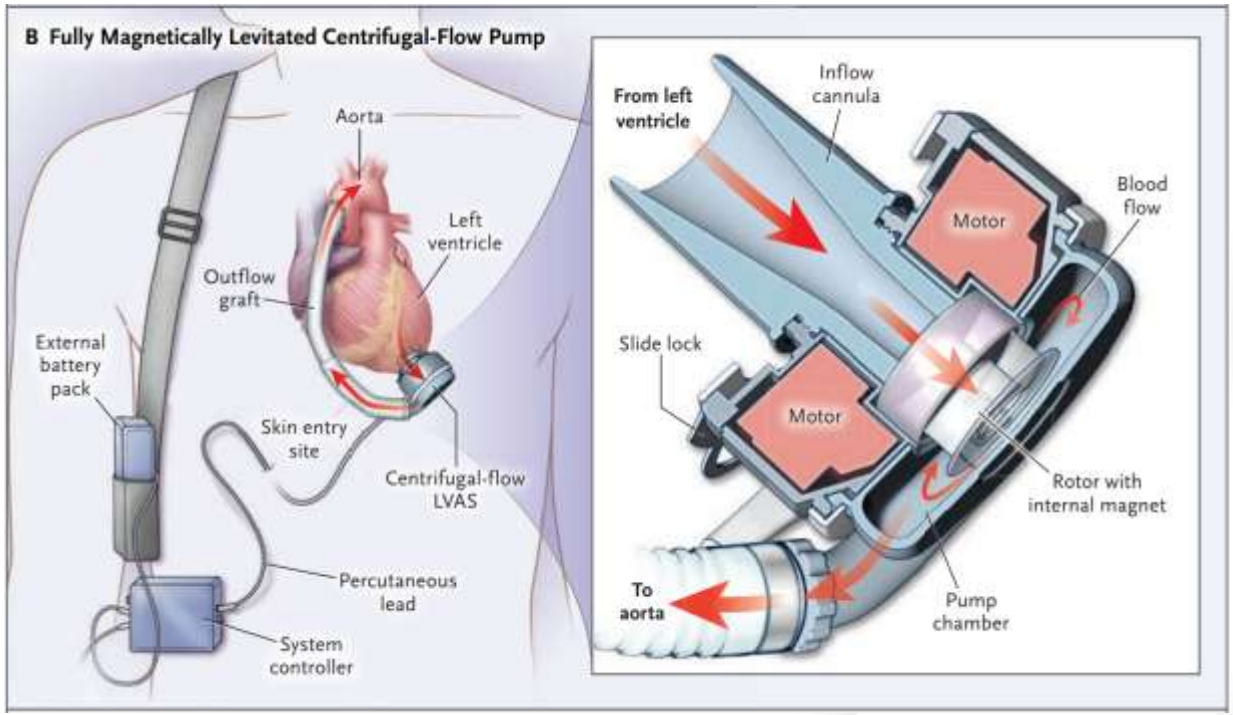


- **Wide** blood-flow passages to reduce shear stress
- **Frictionless** with absence of mechanical bearings
- **Intrinsic Pulse** designed to reduce stasis and avert thrombosis

Mehra et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* 2017;376(5):440-50.
Bourque et al. Design Rationale and Preclinical Evaluation of the HeartMate 3 Left Ventricular Assist System for Hemocompatibility. *ASAIO J* 2016;62(4):375-83

Heart Mate3 LVAD
Pulsatility

HeartMate 3
Approved by FDA August 28, 2017
Short Term Use



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

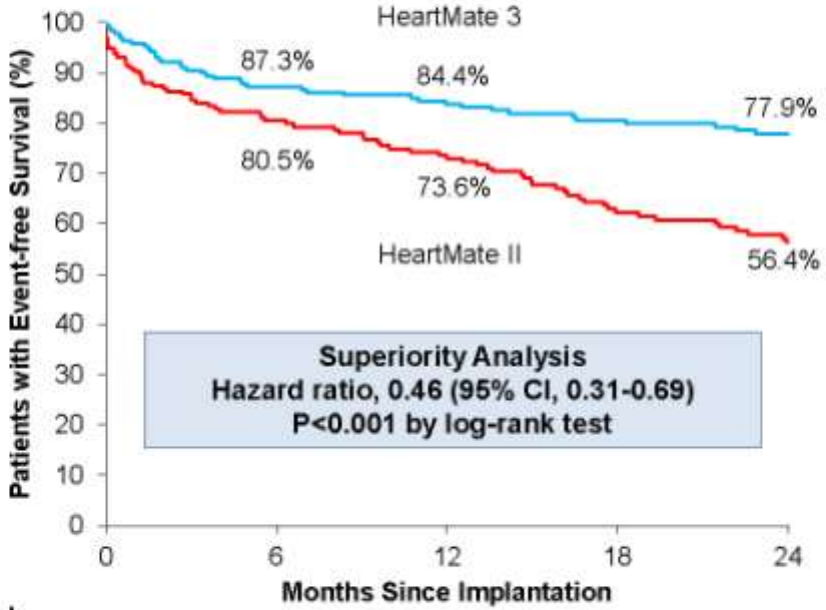
Two-Year Outcomes of a Magnetically Levitated Cardiac Pump in Heart Failure

M.R. Mehra, D.J. Goldstein, N. Uriel, J.C. Cleveland, Jr., M. Yuzefpolskaya, C. Salerno, M.N. Walsh, C.A. Milano, C.B. Patel, G.A. Ewald, A. Itoh, D. Dean, A. Krishnamoorthy, W.G. Cotts, A.J. Tatooles, U.P. Jorde, B.A. Bruckner, J.D. Estep, V. Jeevanandam, G. Sayer, D. Horstmanshof, J.W. Long, S. Gulati, E.R. Skipper, J.B. O'Connell, G. Heatley, P. Sood, and Y. Naka, for the MOMENTUM 3 Investigators*

Available now on www.nejm.org

Primary End Point Analysis (ITT)

Survival at 2 years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device

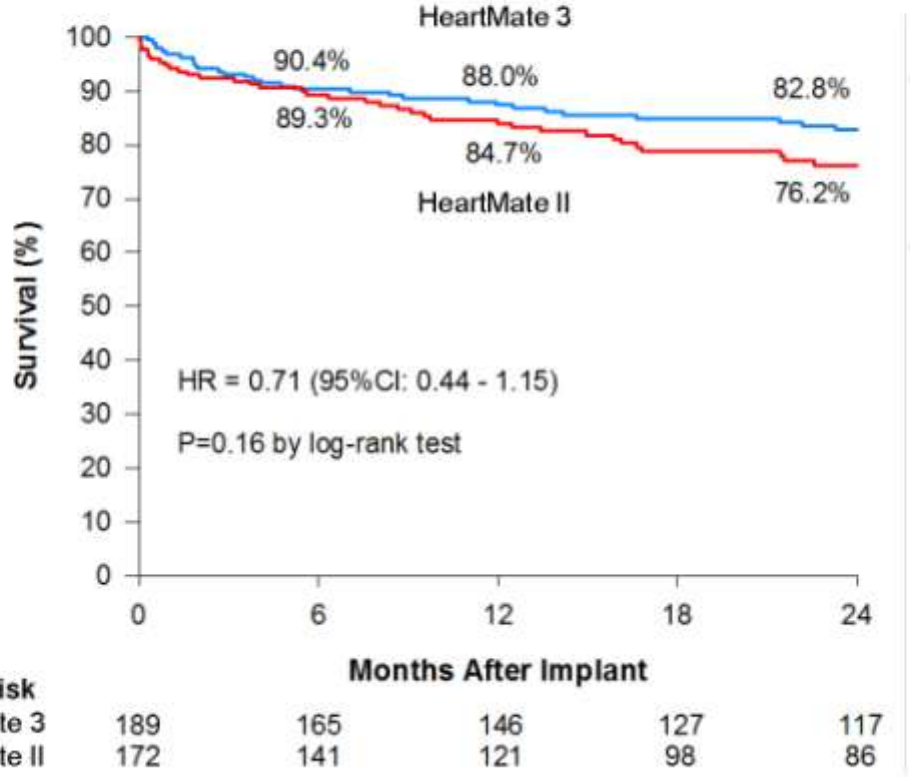


No. at Risk					
HeartMate 3	190	161	141	122	111
HeartMate II	176	134	114	90	75

MOMENTUM 3

mRS denotes modified Rankin Score; CI, confidence interval

Primary Endpoint Component 1
Overall Survival

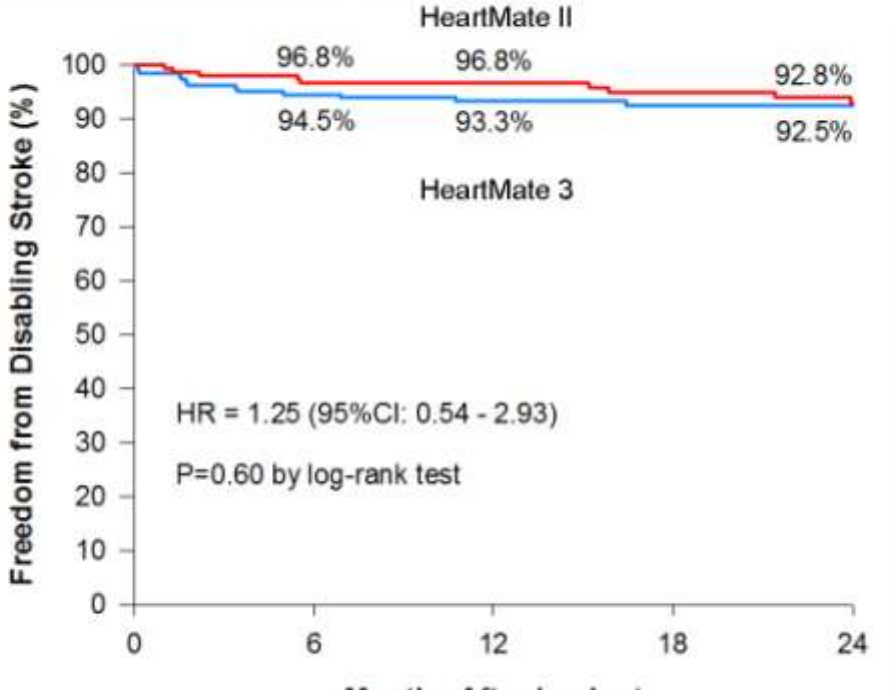


No. at Risk					
HeartMate 3	189	165	146	127	117
HeartMate II	172	141	121	98	86

Survival similar
To heart transplant

HR denotes hazard ratio; CI, confidence interval

Primary Endpoint Component 2
Freedom from Disabling Stroke



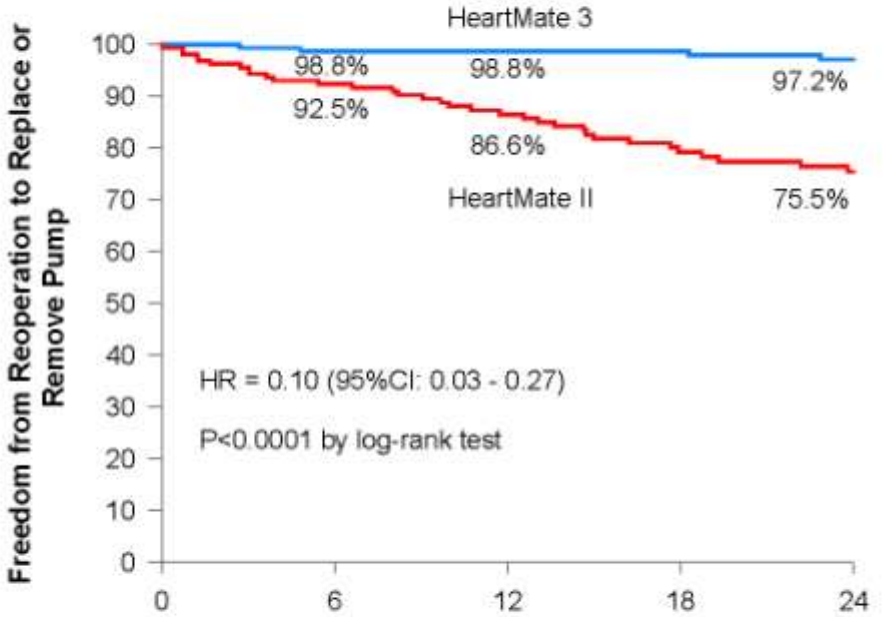
No. at Risk					
HeartMate 3	189	162	142	123	114
HeartMate II	172	139	121	97	84

MOMENTUM 3

HR denotes hazard ratio; CI, confidence interval

Primary Endpoint Component 3

Freedom from Reoperation to Replace or Remove Pump



No. at Risk

HeartMate 3	189	164	145	126	114
HeartMate II	172	135	114	90	76

- There was a **ten-fold** difference in the reoperation rate between HeartMate II and HeartMate 3
- HeartMate 3 reoperations were due to infection (1), electrical fault (1), and outflow-graft twist (1)
- **2/3rd** of HeartMate II reoperations were due to "pump thrombosis or severe hemolysis"

HR denotes hazard ratio, CI, confidence interval

Key Adverse Events

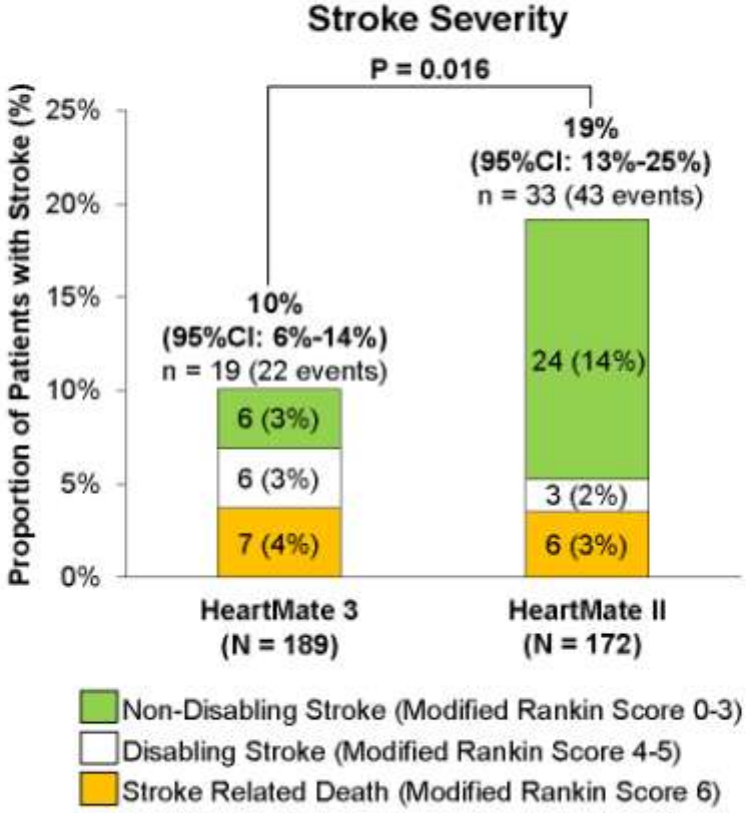
Pump Thrombosis, Neurological Events, Bleeding

	HeartMate 3 (n=189)		HeartMate II (n=172)			
	n (%)	no. of Events	n (%)	no. of Events	HR (95% CI)	P Value*
* Suspected or confirmed pump thrombosis	2 (1.1)	2	27 (15.7)	33	0.06 (0.01-0.26)	<0.001
Resulting in reoperation	0 (0)	0	21 (12.2)	25	NA	<0.001
Any stroke	19 (10.1)	22	33 (19.2)	43	0.47 (0.27-0.84)	0.02
Ischemic stroke	12 (6.3)	14	23 (13.4)	26	0.44 (0.22-0.88)	0.03
Hemorrhagic stroke	8 (4.2)	8	16 (9.3)	17	0.42 (0.18-0.98)	0.06
Other neurologic event†	22 (11.6)	25	15 (8.7)	16	1.27 (0.66-2.45)	0.39
Bleeding	81 (42.9)	187	90 (52.3)	206	0.71 (0.53-0.96)	0.07
Bleeding that led to surgery	23 (12.2)	29	30 (17.4)	34	0.66 (0.38-1.13)	0.18
* * Gastrointestinal bleeding	51 (27.0)	107	47 (27.3)	100	0.92 (0.62-1.37)	1.00

HR denotes hazard ratio; CI, confidence interval

*P values were calculated with the use of Fisher's exact test. †Includes transient ischemic attacks and neurologic events other than stroke

Key Adverse Events
Stroke



Two HeartMate 3 subjects and 9 HeartMate II subjects had >1 stroke. The score for the most severe stoke is shown. 1.6% of HeartMate 3 subjects (n = 3) and 5.2% of HeartMate II subjects (n = 9) had a modified Rankin score of 0 at 60 days post-stroke. CI denotes confidence interval.

Conclusions

- The HeartMate 3 LVAS is **clinically superior** when compared to the HeartMate II axial-flow pump, at 2-years

- These benefits were primarily driven by a **lower reoperation rate** in the HeartMate 3 arm
  - largely due to excess device malfunctions resulting from **pump thrombosis** in the HeartMate II LVAS

- Importantly, we observed a markedly **lower rate of stroke** with the HeartMate 3 LVAS

Thank You

starlir@ccf.org

@rcstarling

Cleveland Clinic Heart and Vascular Institute