ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

Approach to Heart Failure in 2018: What Do the Recent Guidelines Tell Us?

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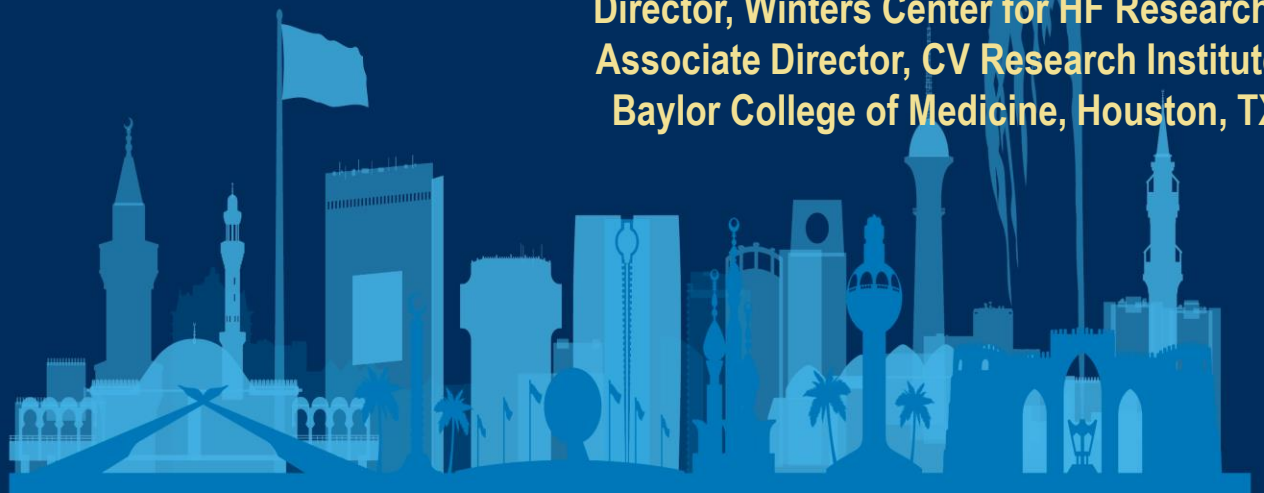
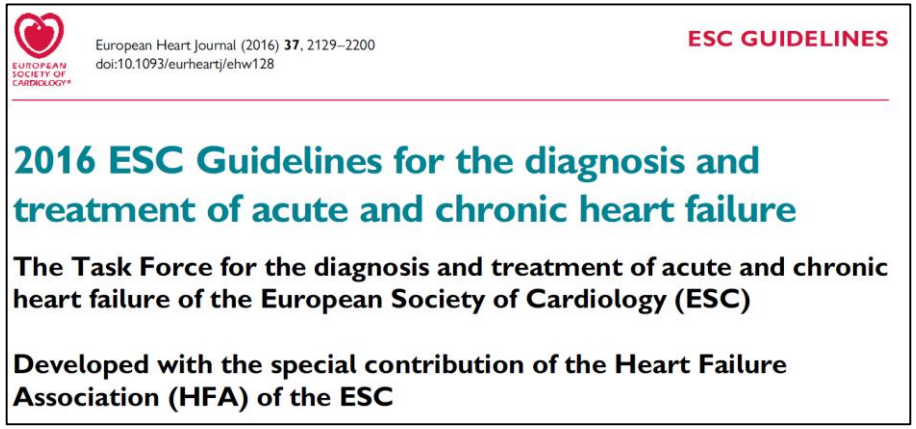
Professor of Medicine
Medical Care Line Executive,
DeBakey VA Medical Center,
Director, Winters Center for HF Research,
Associate Director, CV Research Institute
Baylor College of Medicine, Houston, TX



Outline

- Guidelines for HFrEF
  - New Therapies: ARNI,Ivabradine
  - HTN
  - Anemia
  - Sleep Apnea
- HFpEF
- HFmEF
- Diabetes
- **Biomarkers**

HF Guidelines: AHA/ACC/HFSA and ESC



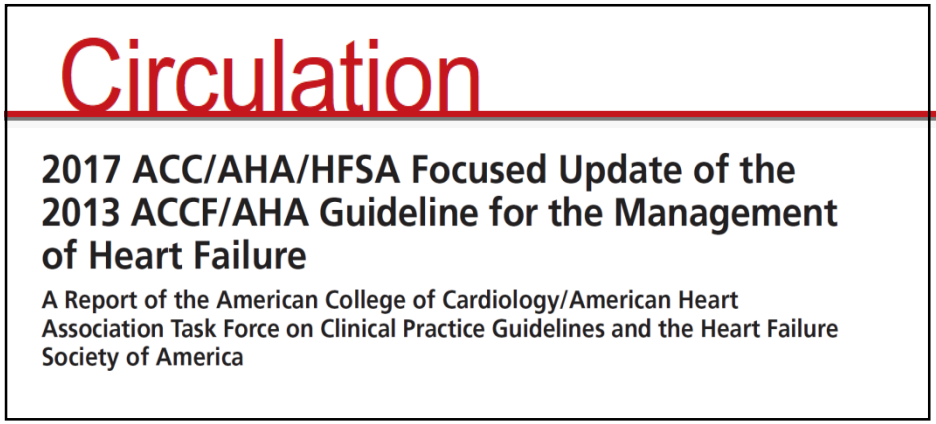
European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

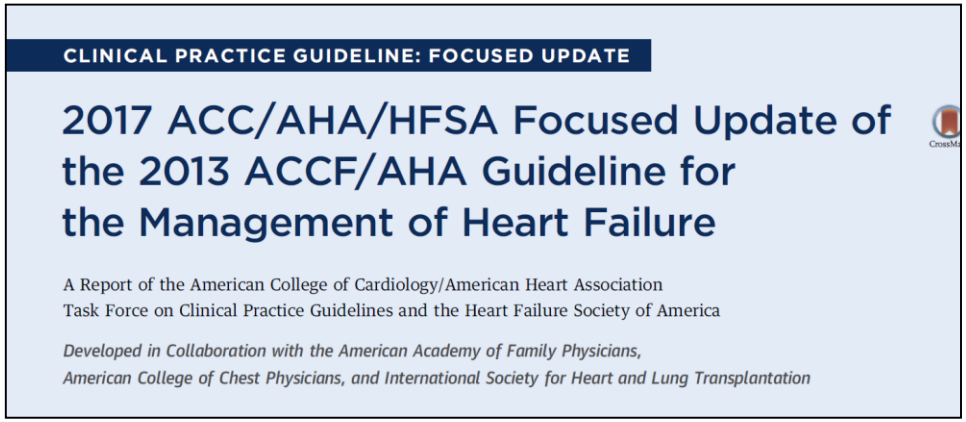
Developed with the special contribution of the Heart Failure Association (HFA) of the ESC



Circulation

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



CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

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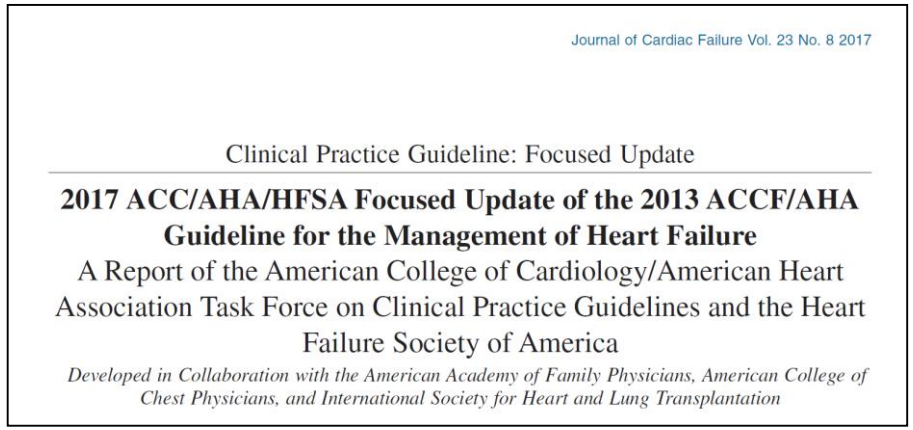

Journal of Cardiac Failure Vol. 23 No. 8 2017

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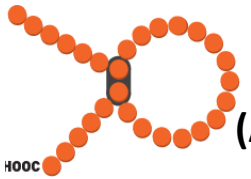
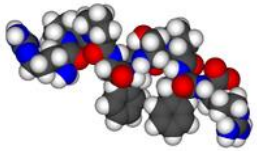
Heart Failure

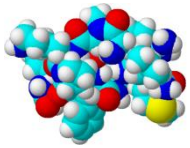
Neprilysin Inhibition and ARNI



Natriuretic peptides (ANP,BNP,CNP)



Bradykinin



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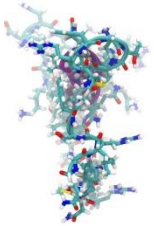
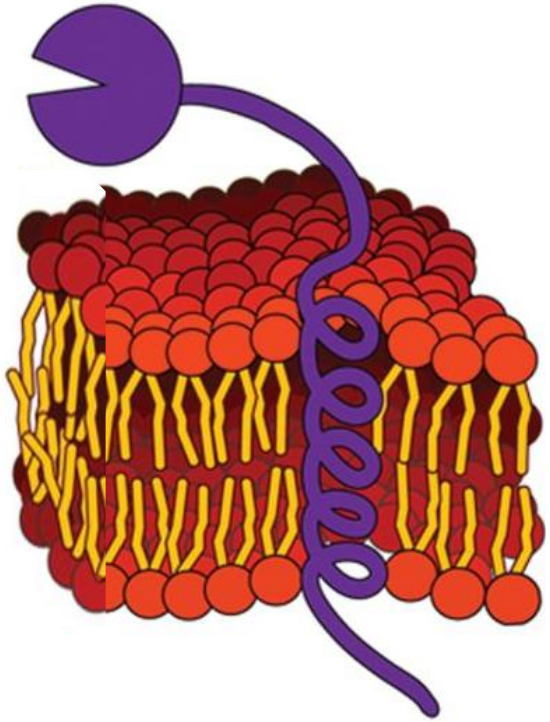


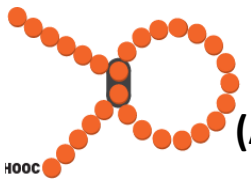
Adrenomedullin



NEPRILYSIN

NEP is a zinc dependent membrane endopeptidase

cleaves peptides containing up to 40–50 amino acids



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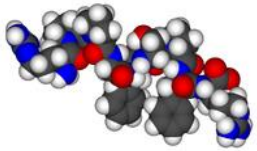

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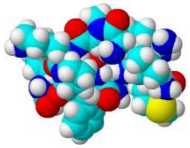

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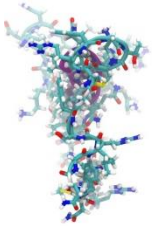

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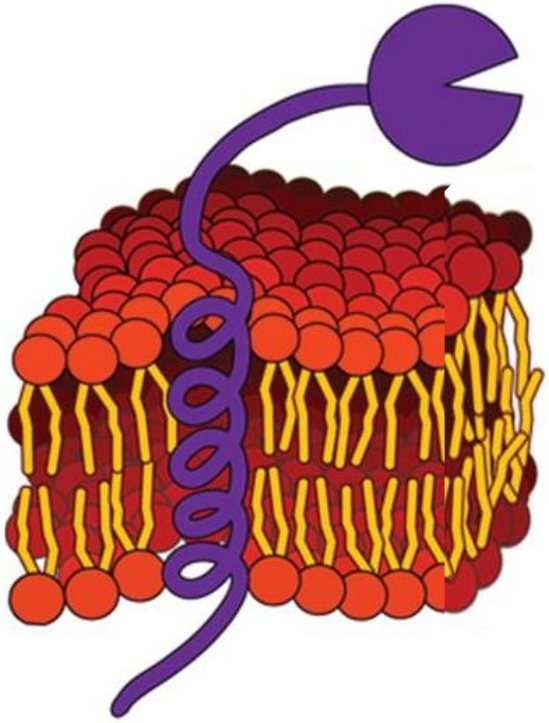

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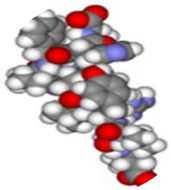
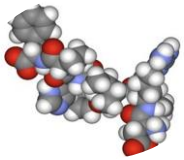
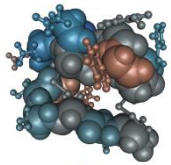


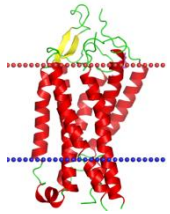
Angiotensin I



Angiotensin II



Endothelin I



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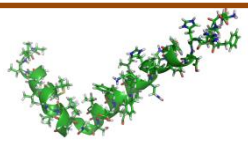
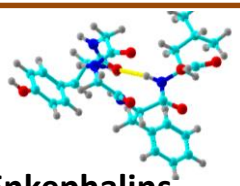
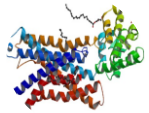


Amyloid β Peptide



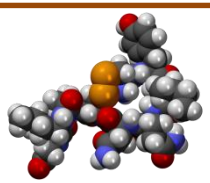
Enkephalins, Endomorphins



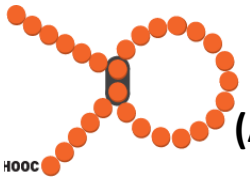
Corticotropin

Neuropeptide Y

Gastrin, Cholecystokinin-8, Somatostatin, Glucagon, VIP



Oxytocin



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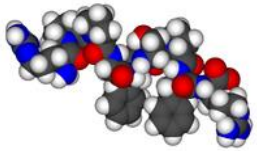

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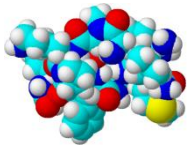

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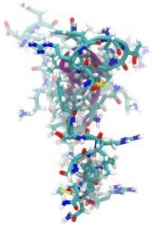

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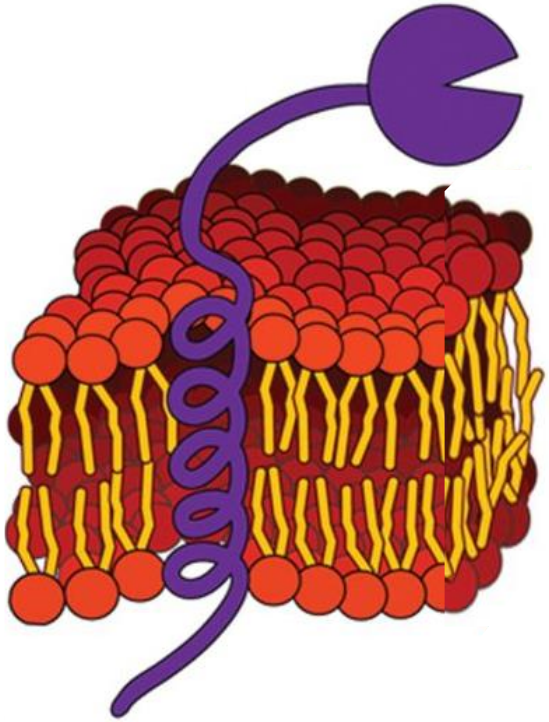

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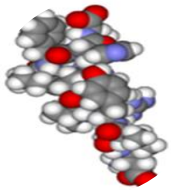

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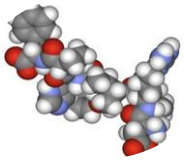

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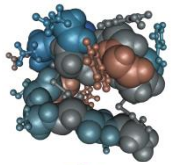

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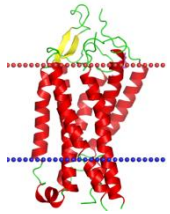

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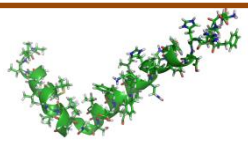

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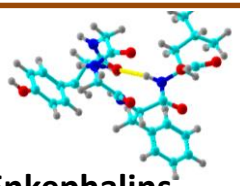

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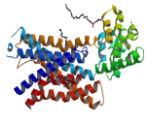

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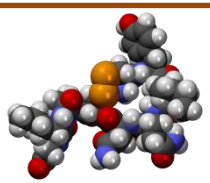

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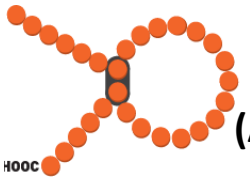

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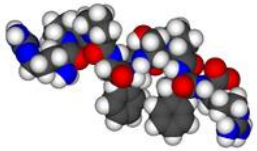

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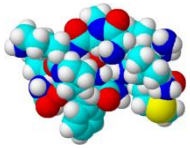

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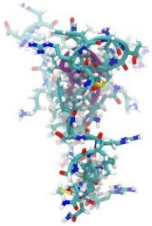

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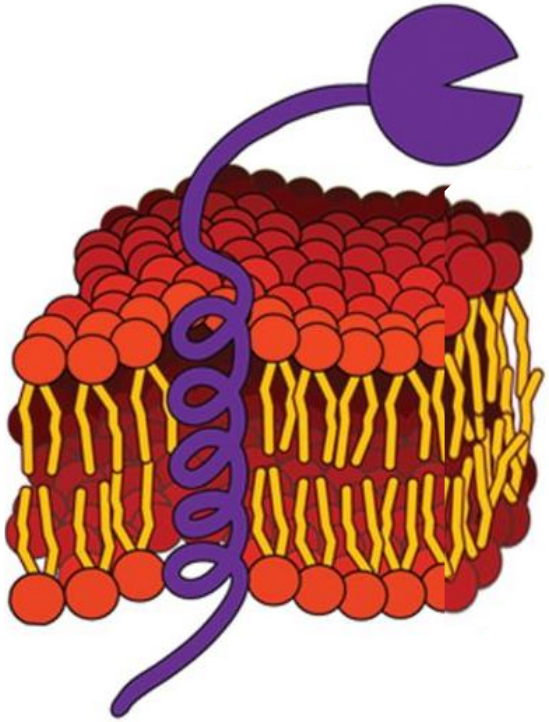

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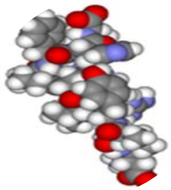

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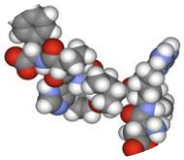

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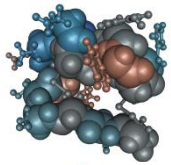

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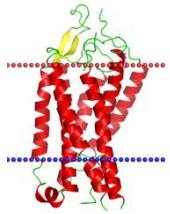

Neurotensin

✓

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X

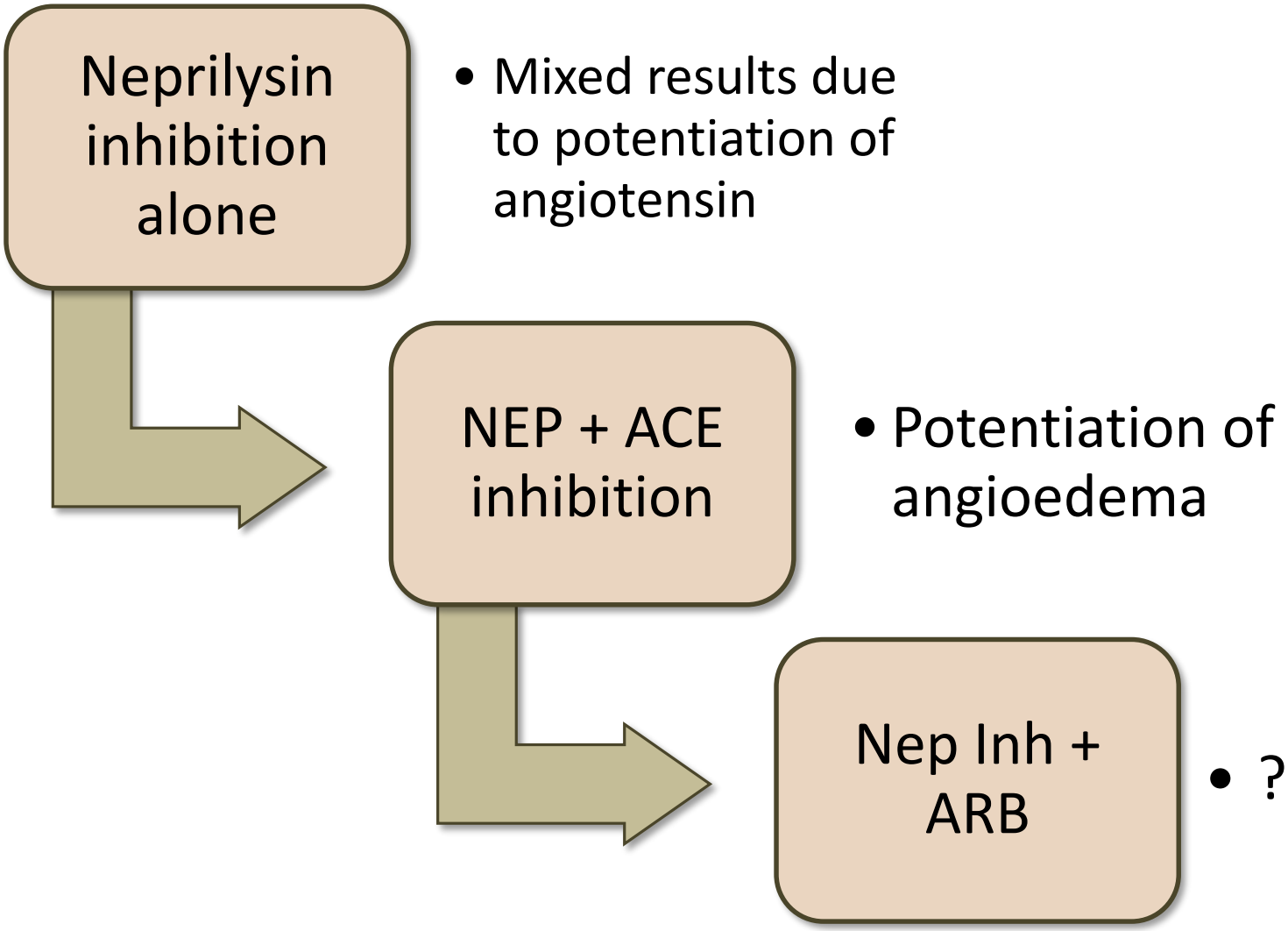
Balance of NEP Inhibition

Reduced breakdown of ANP, BNP, CNP,
Vasodilation , ↓ Fibrosis, ↓Hypertrophy

Reduced breakdown of angiotensin II, (endothelin I) Vasoconstriction, ↑ Fibrosis, ↑ Hypertrophy

The antihypertensive effects may be offset by an increased activity of the RAAS and sympathetic nervous system and/or by downregulation of ANP receptors.

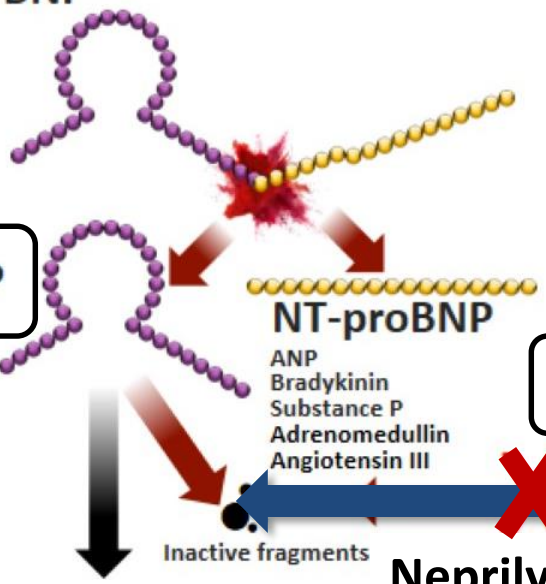
Corti R, et al. Vasopeptidase inhibitors: a new therapeutic concept in cardiovascular disease? Circulation. 2001;104:1856–1862.


Neprilysin inhibition alone
• Mixed results due to potentiation of angiotensin
NEP + ACE inhibition
• Potentiation of angioedema
Nep Inh + ARB
• ?

Mechanisms of Action of ARNI

Natriuretic Peptides

Pro-BNP



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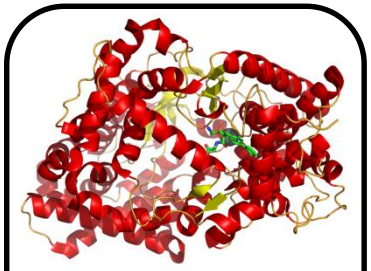


LCZ696

Sacubitril

Valsartan

Renin Angiotensin System

Angiotensinogen

↓

Angiotensin I

↓

Angiotensin II

↓

AT_1 Receptor

↑ PRA, plasma renin

↓ BP, Vasodilation
↓ Fibrosis
↓ Hypertrophy

***NT-proBNP not a neprilysin substrate**

Vardeny O. et al. Clin. Pharmacol Ther 2013; 94:445-448

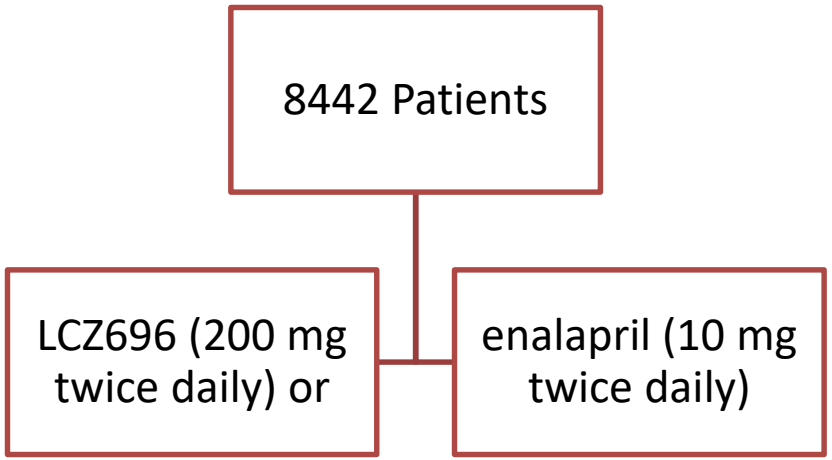
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

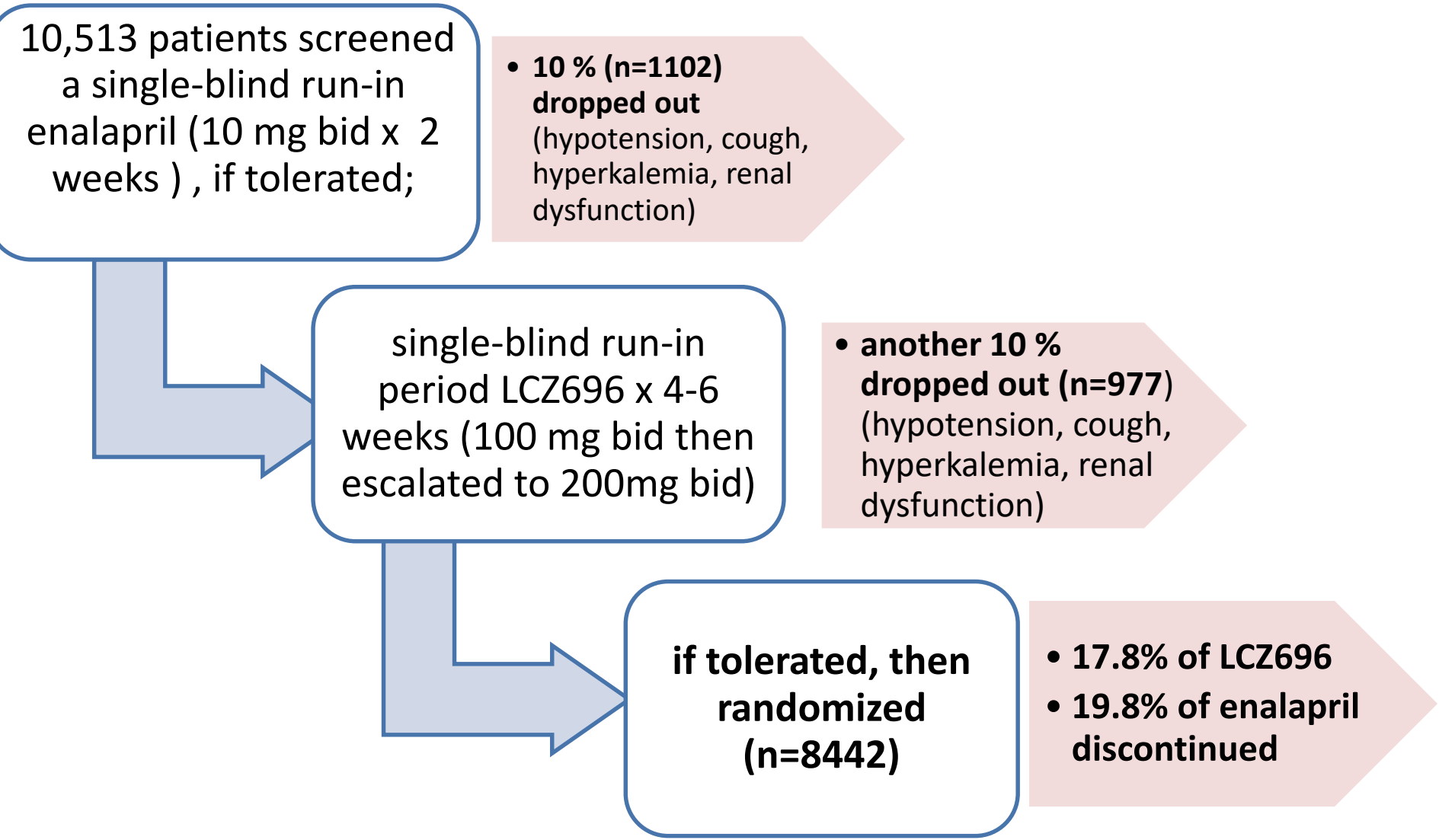
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

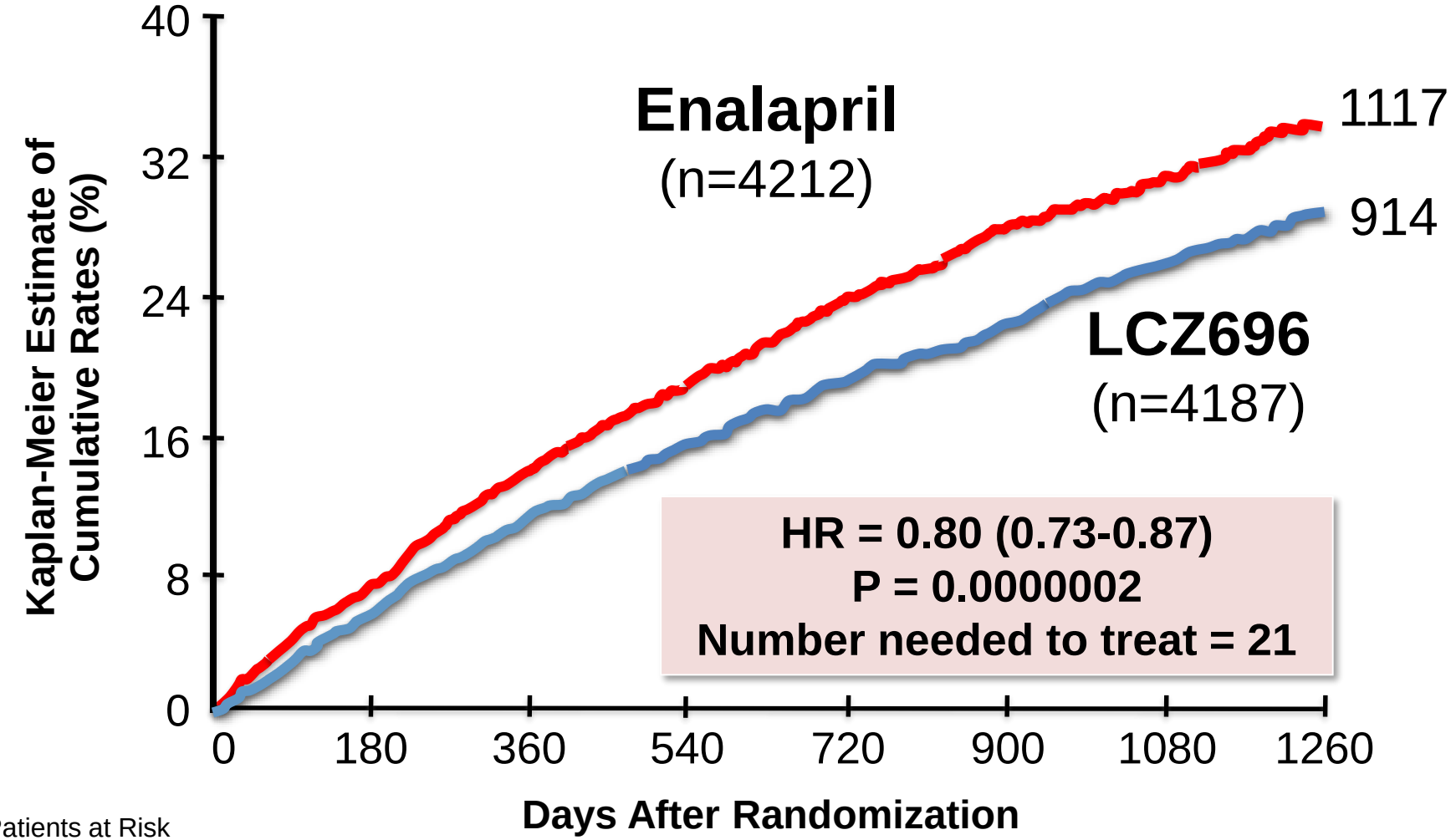
- NYHA class II-IV (<1 % NYHA IV)
- LVEF ≤ 40% then ≤35%:
- BNP ≥ 150 (or NT-proBNP ≥ 600)
- β-blockers , MRA,
- **ACEi of ARB ≅enalapril 10 mg/d ≥4 wks**
- SBP ≥ 95 mm Hg, eGFR ≥ 30, K ≤ 5.4 mEq/L



Run-In Before Randomization



PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)

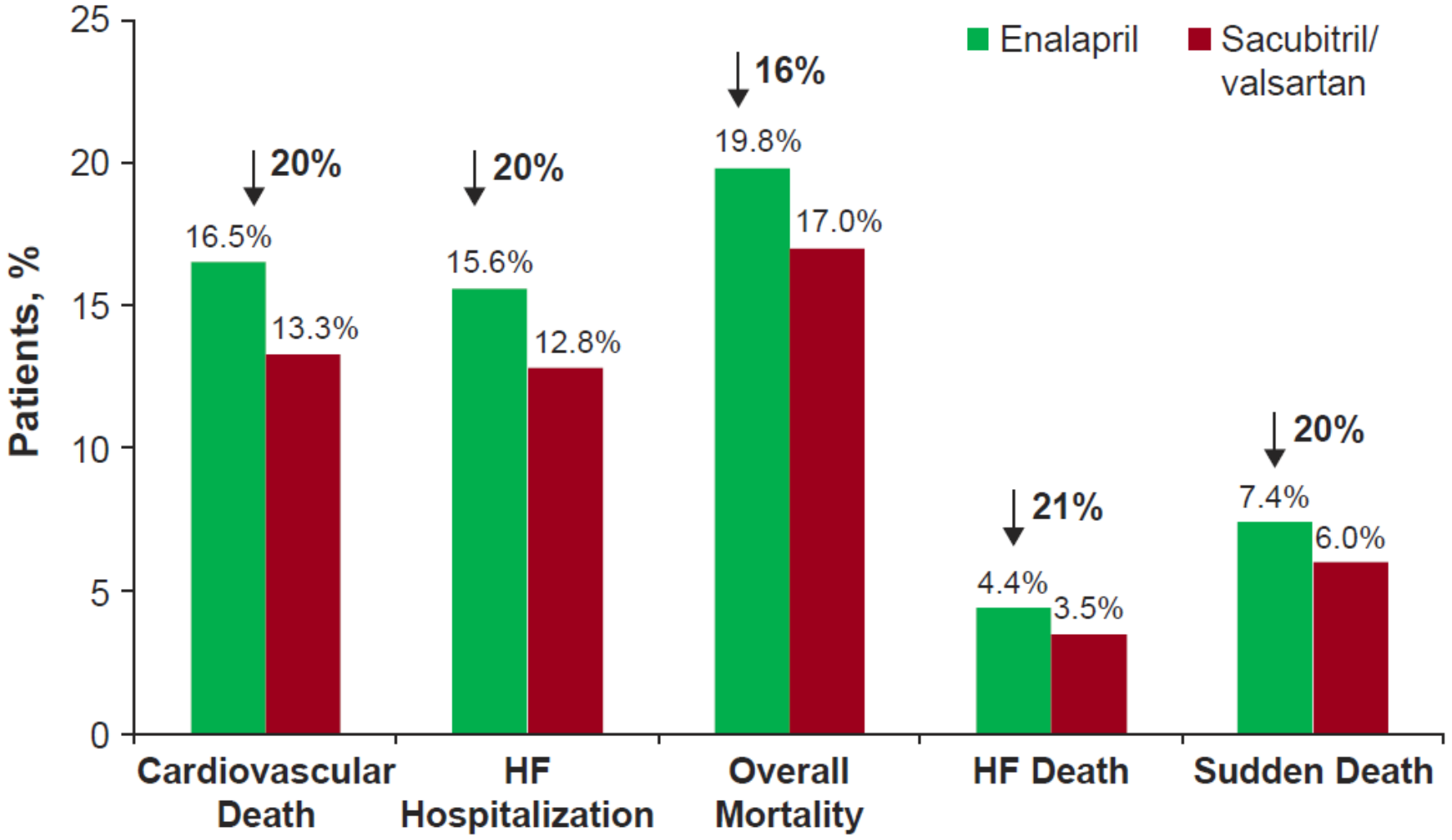


Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

McMurray J. et al. New Engl J Med. 2014; 371 (11): 993-1004

PARADIGM-HF: Other Key Endpoints



1. McMurray JJ et al. *N Engl J Med*. 2014;371:993-1004. 2. Desai AS et al. *Eur Heart J.* 2015;36:1990-1997.

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588 (14%)	388 (9.2%)	< 0.001
Serum potassium > 6.0 mmol/l	181 (4.3%)	236 (5.6%)	0.007
Serum creatinine ≥ 2.5 mg/dl	139 (3.3%)	188 (4.5%)	0.007
Cough	474 (11.3%)	601 (14.3%)	< 0.001
Discontinuation for adverse event	449	516	0.02
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16 (0.3%)	9 (0.2%)	NS
Hospitalized; no airway compromise	3 (0.1%)	1 (<0.1%)	NS
Airway compromise	0	0	----

Angioedema in OVERTURE 0.5 %, OCTAVE 0.68 %

New Studies with ARNI

NAME	TITLE	Primary End Point
PARAGON-HF	Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in **HFpEF**	CV death and HF hospitalizations
TITRATION	Safety and Tolerability of Initiating LCZ696 in Heart Failure Patients 200 mg twice daily (bid) over 3 weeks vs 6 weeks)	Hypotension, Renal Dysfunction, Hyperkalemia and Angioedema
PARABLE	ARNI in **Asymptomatic Patients** With Elevated Natriuretic Peptide and Elevated Left Atrial Volume	impact on LV diastolic function
PIONEER	comParIson Of Sacubitril/valsartaN Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an **Acute Heart Failure Episode**	Change from baseline in NT-proBNP (hypotension, hyperkalemia, angioedema)
PARASAIL	Description of Tolerability of LCZ696 (Sacubitril / Valsartan) in Heart Failure With Reduced Ejection Fraction (HFrEF) Treated in Real Life Setting (PARASAIL) in CANADA	% Pts tolerated LCZ696 at the dose of 97.2 mg sacubitril / 102.8 mg valsartan bid at month 6

Source: ClinicalTrials.gov

2017 ACC/AHA/HFSA Update: Recommendations for Stage C HF*r*EF

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI		
COR	**LOE**	**Recommendations**
I	**ACE: A** **ARB: A** **ARNI: B-R**	The clinical strategy of inhibition of the renin-angiotensin system with **ACE inhibitors** *(LOE:A)*, **OR ARBs** *(LOE: A)*, **OR ARNI** *(Level of Evidence: B-R)* in conjunction with evidence based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HF*r* EF to reduce morbidity and mortality

Yancy C. et al. J Am Coll Cardiol. 2017 Aug 8;70(6):776-803, Circulation. 2017;136:e137-e161, J Card Fail. 2017 Aug;23(8):628-651.

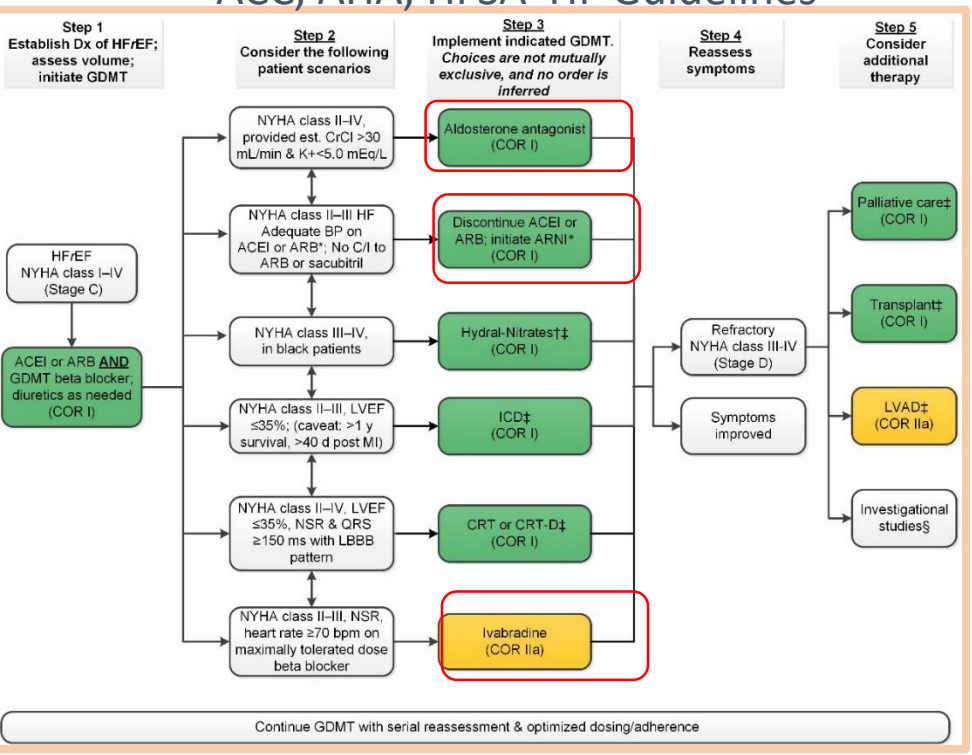
2017 ACC/AHA/HFSA Update: Recommendations for Stage C HF*r*EF

Recommendations for Renin-Angiotensin System Inhibition With ACE-I or ARB or ARNI		
COR	**LOE**	**Recommendations**
I	**ACE: A**	The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFr EF to reduce morbidity and mortality
I	**ARB: A**	The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HF*r* E F who ~~are intolerant to ACE inhibitors because of cough or angioedema~~
I	**ARNI: B-R**	In patients with chronic symptomatic HF*r* E F NYHA class II or III who tolerate an ACE inhibitor or ARB, **replacement by an ARNI is** recommended to further reduce morbidity and mortality
III: Harm	**B-R**	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor
III: Harm	**C-EO**	ARNI should not be administered to patients with a history of angioedema

Yancy C. et al. J Am Coll Cardiol. 2017 Aug 8;70(6):776-803, Circulation. 2017;136:e137-e161, J Card Fail. 2017 Aug;23(8):628-651.

Treatment of HFrEF Stage C and D

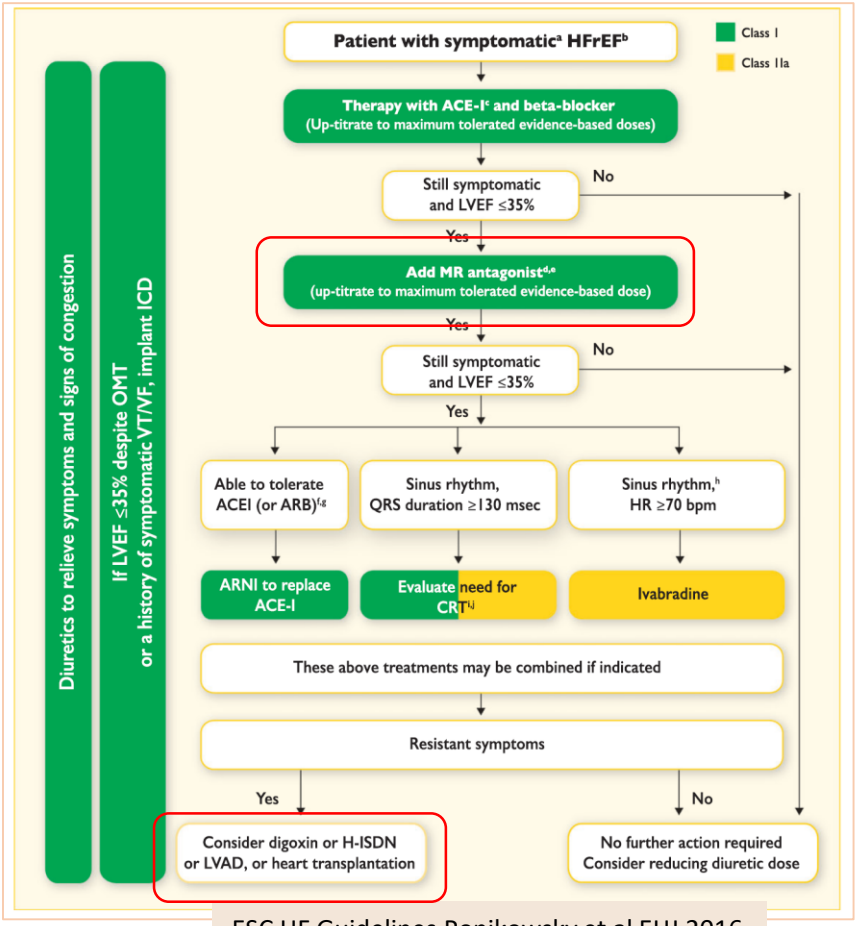
ACC, AHA, HFSA HF Guidelines



† The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored.

AHA/ACC/HFSA HF Guidelines. Yancy C. et al. Circulation/ JACC/JCF 2017

ESC Guidelines

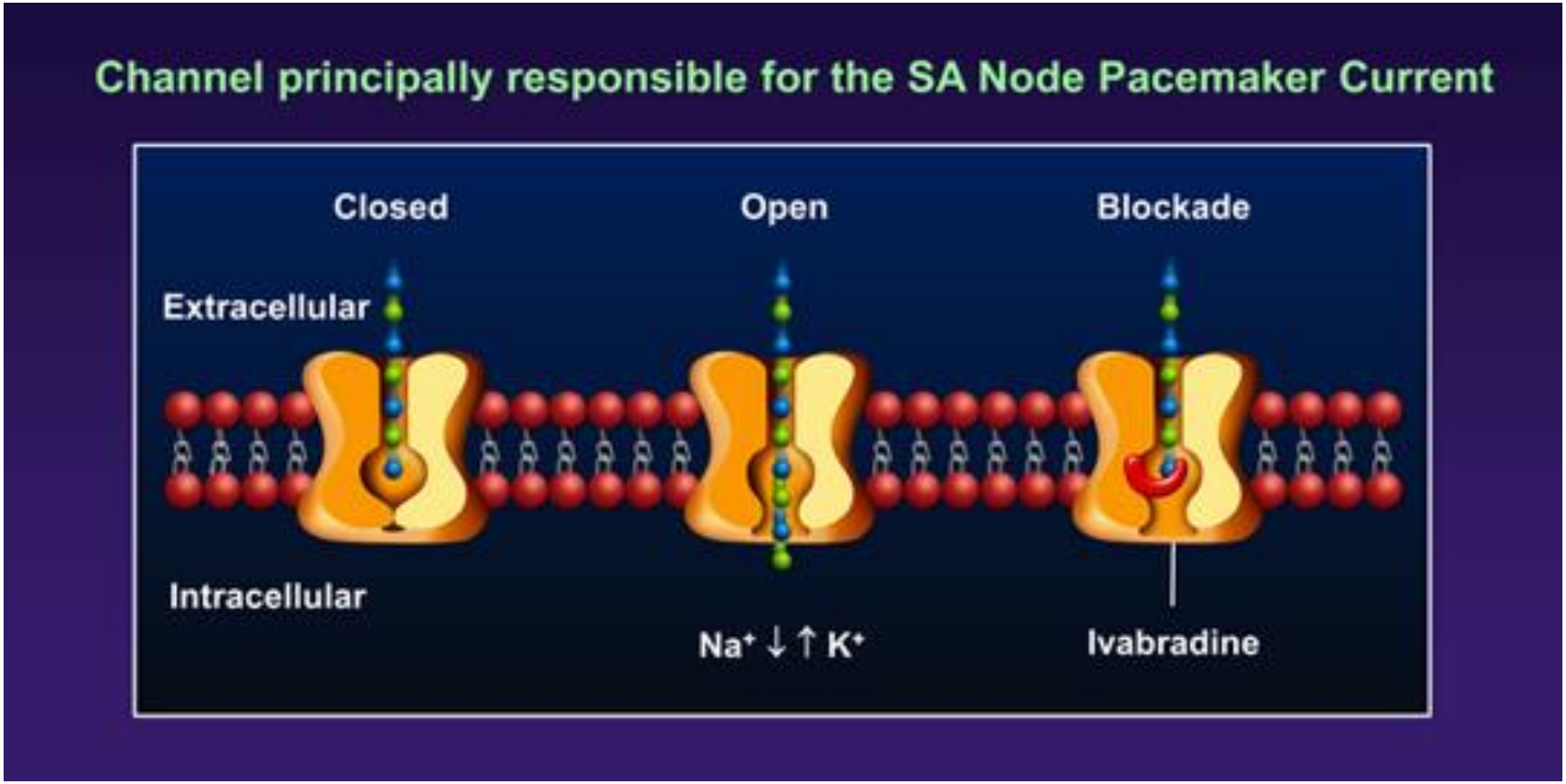


ESC HF Guidelines.Ponikowsky et al EHJ 2016

Heart Failure

Ivabradine

Ivabradine : Specific and Selective Inhibitor of the I_f Ion Channel



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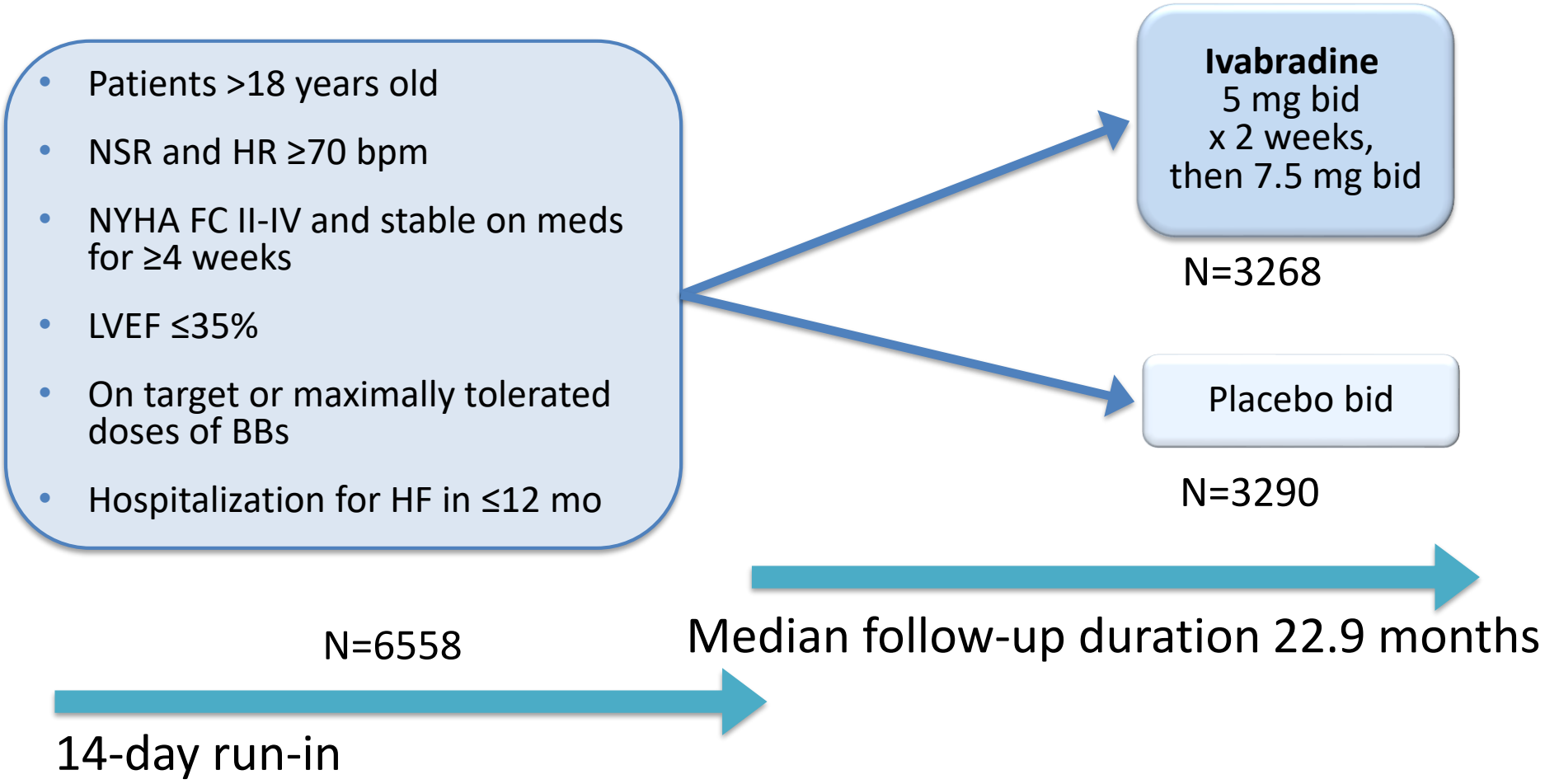
I_f ion channel (the funny current) is highly expressed in spontaneously active cardiac regions, such as the sinoatrial node, the AV node and the Purkinje fibers. The funny current is a mixed Na/ K current that activates upon hyperpolarization at voltages in the diastolic range

Di Francesco D, Camm JA. Drugs 2004; 64: 1757-1765

SHIFT Study Design



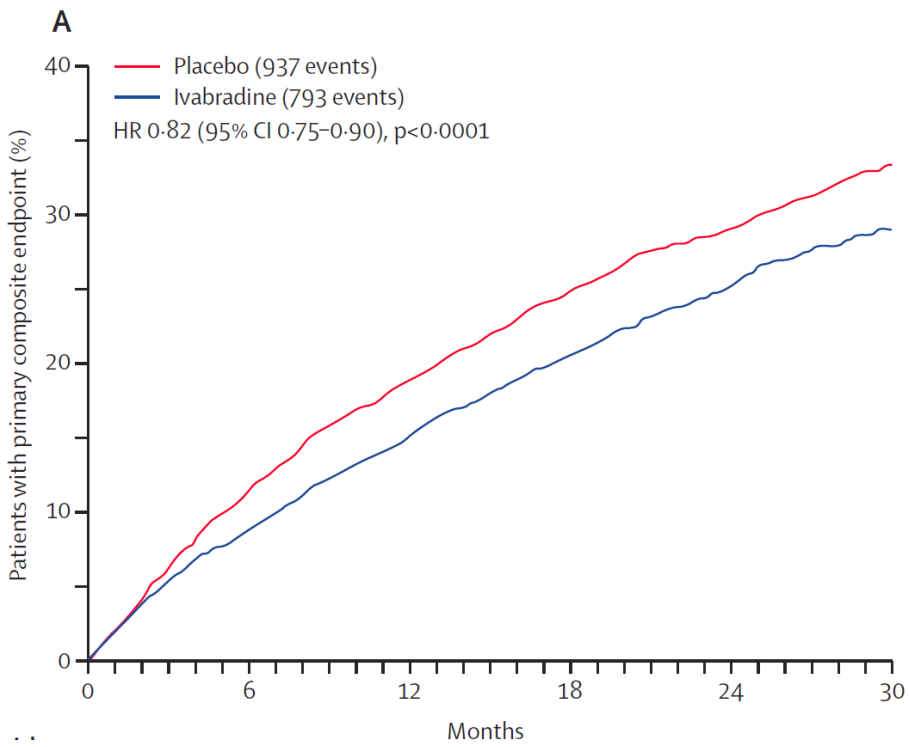
BB, beta-blocker; bpm, beats per minute; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; meds, medications; mo, months; NSR, normal sinus rhythm; NYHA FC, New York Heart Association functional classification.

Swedberg K, et al. *Lancet*. 2010;376(9744):875-885.

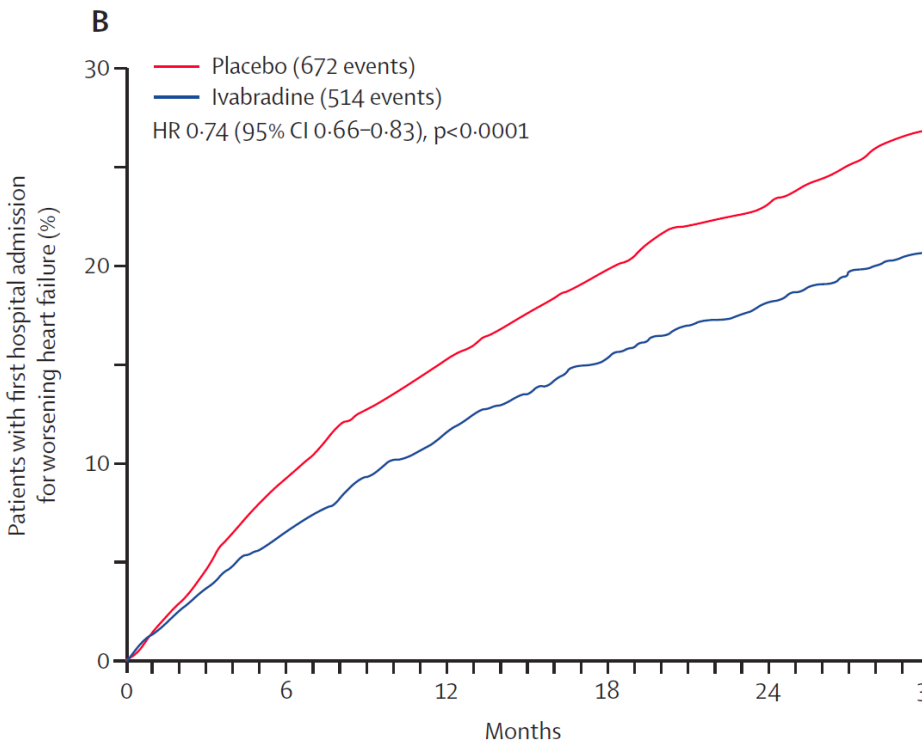
Heart Rate Modulation with Ivabradine-

The Systolic HF treatment with the If inhibitor Ivabradine Trial SHIFT Trial

CV Mortality & HF Hospitalization



HF Hospitalization



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NYHA II–IV, EF < 35%, SR rate of ≥70 b.p.m.
background therapy β-blocker (90%), and an MRA (60%)

Only 26% of patients were on full-dose β-locker

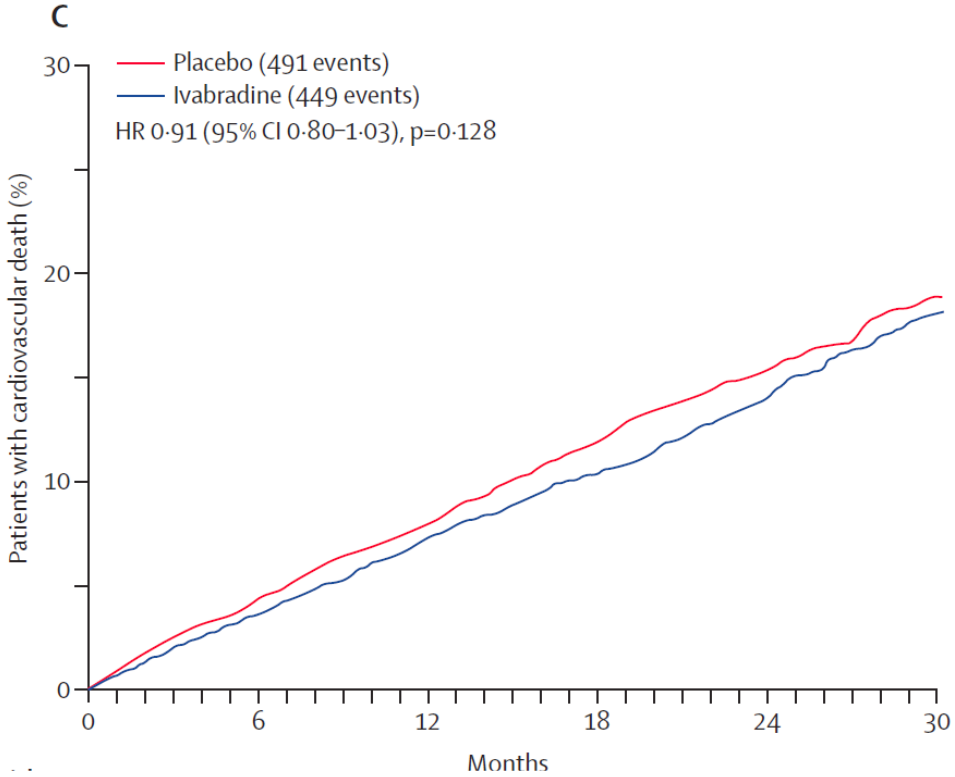
Swedberg et al. Lancet 2010. 376:875-85

Heart Rate Modulation with Ivabradine-

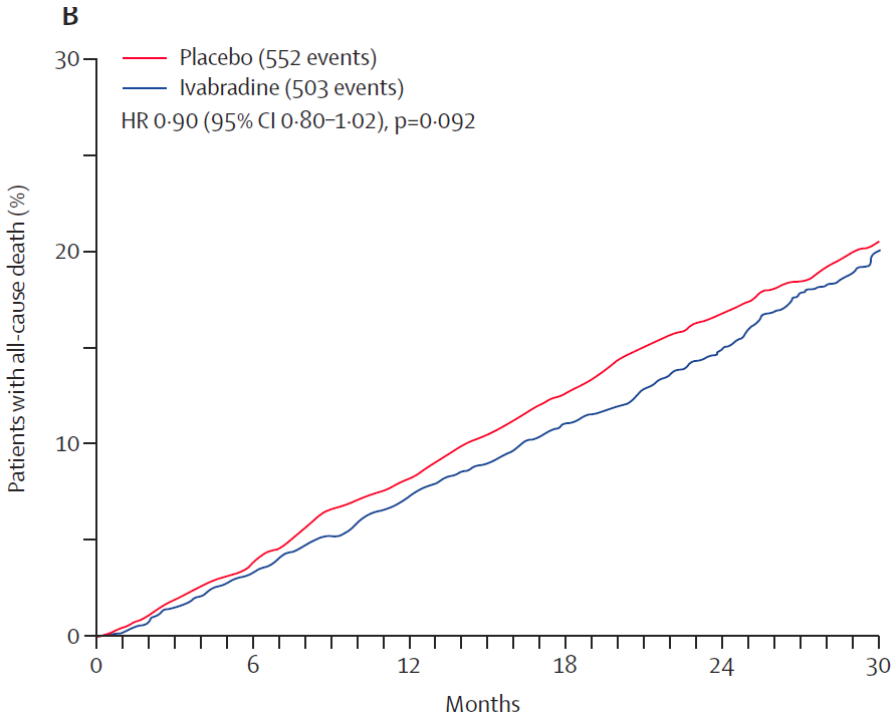
The Systolic HF treatment with the If inhibitor ivabradine Trial SHIFT Trial

No significant reduction in all cause or CV mortality

CV Mortality



All cause mortality



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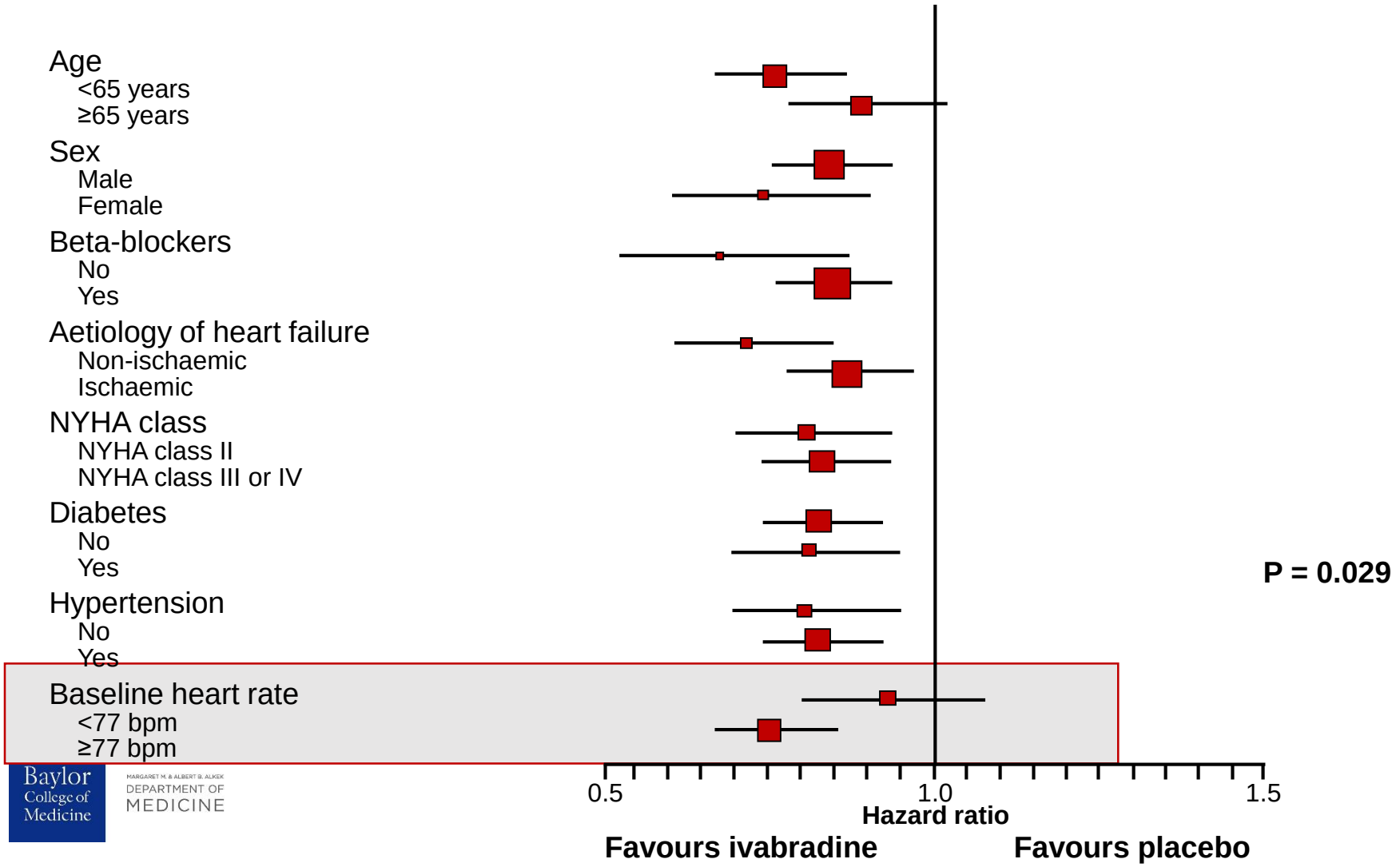
Swedberg et al. Lancet 2010. 376:875-85

Effect of ivabradine in prespecified subgroups



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Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Incidence of selected adverse events

	Patients with an event		
	Ivabradine N=3232, n (%)	Placebo N=3260, n (%)	*p* value
All serious adverse events	**1450** (45%)	**1553** (48%)	**0.025**
All adverse events	2439 (75%)	2423 (74%)	0.303
Symptomatic bradycardia	150 (5%)	32 (1%)	<0.0001
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0.0001
Atrial fibrillation	306 (9%)	251 (8%)	0.012
Phosphenes	89 (3%)	17 (1%)	<0.0001
Blurred vision	17 (1%)	7 (<1%)	0.042

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Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Indications for Use: Ivabradine (FDA)

- To reduce hospitalization risk for worsening HF in patients with stable, symptomatic chronic HF with LVEF ≤35% in sinus rhythm with resting HR of ≥70 bpm or higher[1,2]
  - **AND** on maximally tolerated doses of beta-blockers
  - **OR** have a contraindication to beta-blocker use
- Contraindications:
  - Acute decompensated HF
  - BP <90/50 mm Hg
  - Sick sinus syndrome
  - Sinoatrial or third-degree AV block*
  - Resting HR <60 bpm prior to treatment
  - Severe hepatic impairment
  - Pacemaker dependence
- Most common (≥1%) adverse events:
  - Bradycardia, HTN, AF, and temporary vision disturbances

*Unless a functioning demand pacemaker is present.

AF, atrial fibrillation; AV, atrioventricular; BP, blood pressure; HTN, hypertension.

1. Swedberg K, et al. *Lancet.* 2010;376(9744):875-885.
2. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products [drug label]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206143Orig1s000lbl.pdf. Revised April 2015. Accessed August 31, 2016.

2017 ACC/AHA/HFSA Update: Recommendations for Stage C HF*r*EF

Recommendations for Ivabradine		
COR	**LOE**	**Recommendations**
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.

2016 ESC HF Guidelines

I*f*-channel inhibitor			
Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B	180
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C	181

Yancy C. et al. Circulation. 2017;136:e137-e161

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EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

10 Principles for Successful Treatment of Heart Failure

2017 ACCF/AHA Heart Failure Guidelines

How to implement GDMT...

I. Initiate & Switch
Treatment algorithm for guideline-directed medical therapy including novel therapies (*Figure 2* and *3*)

II. Titration
Target doses of select guideline-directed heart failure therapy (*Tables 1, 2, 3, 4, 5*)

Considerations for monitoring

How to address challenges with...

III. Referral
Triggers for referral to HF specialist (*Table 6*)

IV. Care Coordination
Essential skills for a HF team (*Table 7*)

Infrastructure for team-based HF care (*Table 8*)

V. Adherence
Causes of non-adherence (*Table 9*)

Interventions for adherence (*Table 10, 11*)

VI. Specific Patient Cohorts
Evidence based recommendations and assessment of risk for special cohorts: African Americans; older adults; frail (*Table 12*)

VII. Cost of Care
Strategies to reduce cost (*Table 13*)

Helpful information for completion of prior authorization forms (*Table 14*)

How to manage...

VIII. Increasing Complexity
Ten pathophysiologic targets in HFrEF and treatments (*Table 15*)

Ten principles and actions to guide optimal therapy

IX. Comorbidities
Common cardiac and non-cardiac comorbidities with suggested actions (*Table 16*)

X. Palliative/Hospice Care
Seven principles and actions to consider regarding palliative care

Yancy et al. *J Am Coll Cardiol*. 2018 Jan 16;71(2):201-230.

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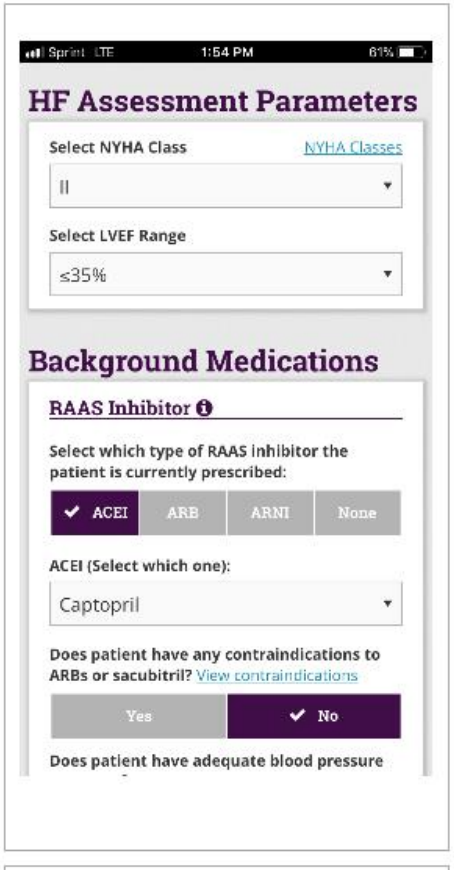
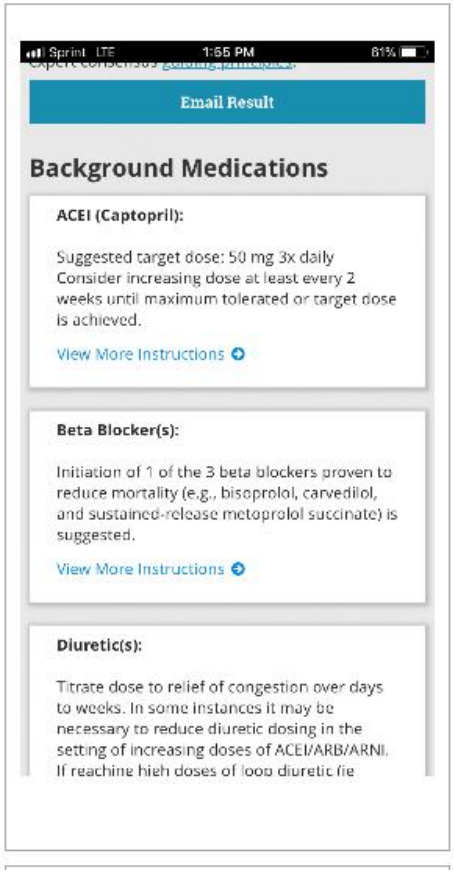
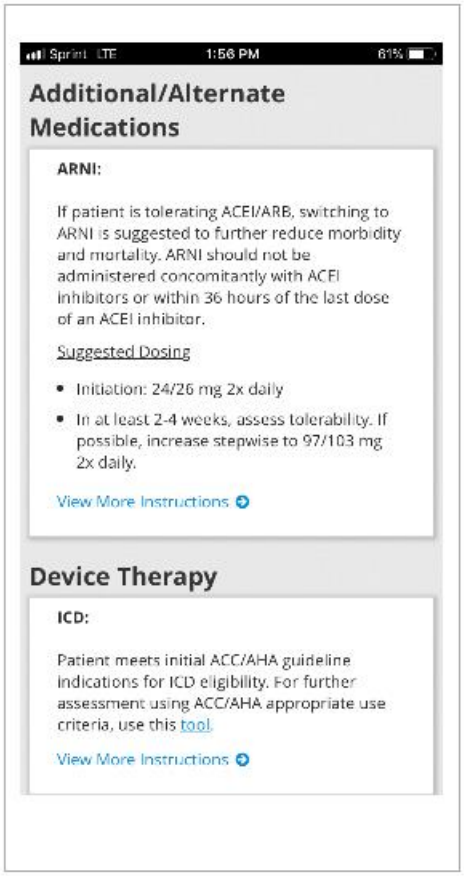
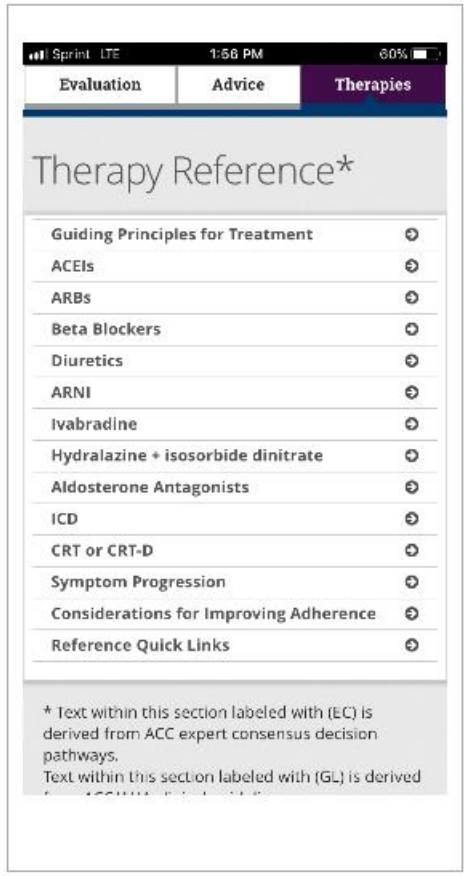
Treat HF APP









- 2017 ACC Expert Consensus Decision Pathway for Optimization of HF Treatment,
- 2017 ACC/ AHA/HFSA Focused Update of HF Guidelines
- 2013 ACCF/AHA Guideline for the Management of Heart Failure.

http://tools.acc.org/TreatHF/#!/content/evaluate

Heart Failure

HF-pEF

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations
I	C	Diuretics should be used for relief of symptoms due to volume overload
I	B	Systolic and diastolic BP should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity
IIa	C	Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia having an adverse effect on symptomatic HF*p*EF despite GDMT.
IIa	C	Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF.
IIa	C	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control BP in patients with HF*p*EF.

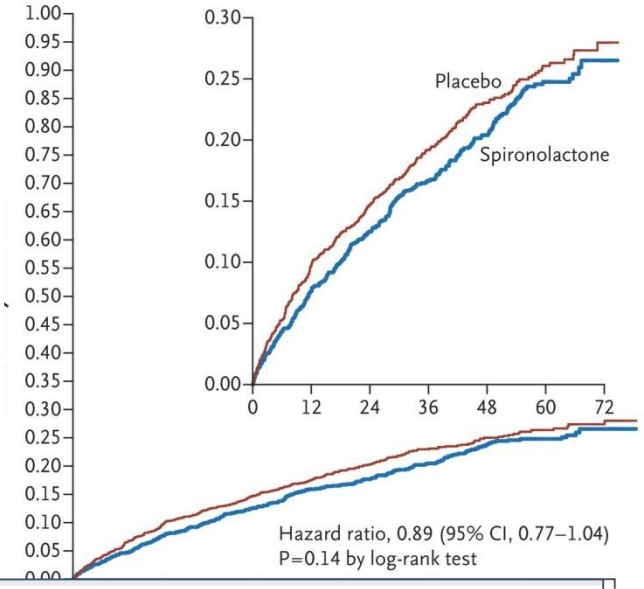
Clyde W. Yancy et al. Circulation. 2017;136:e137-e161

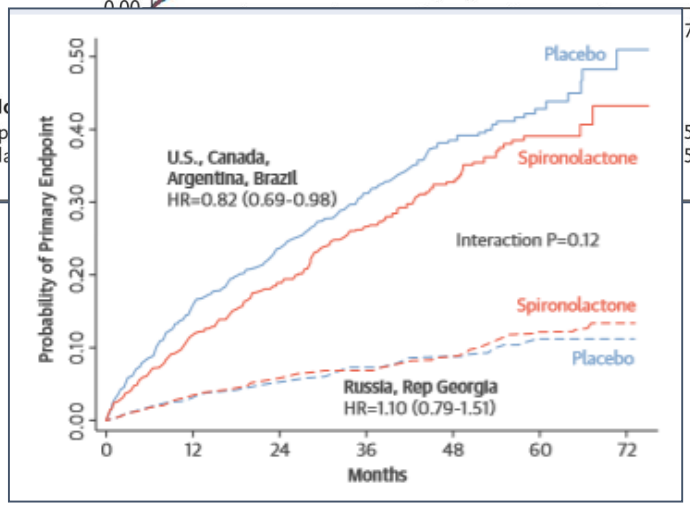
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 10, 2014 VOL. 370 NO. 15

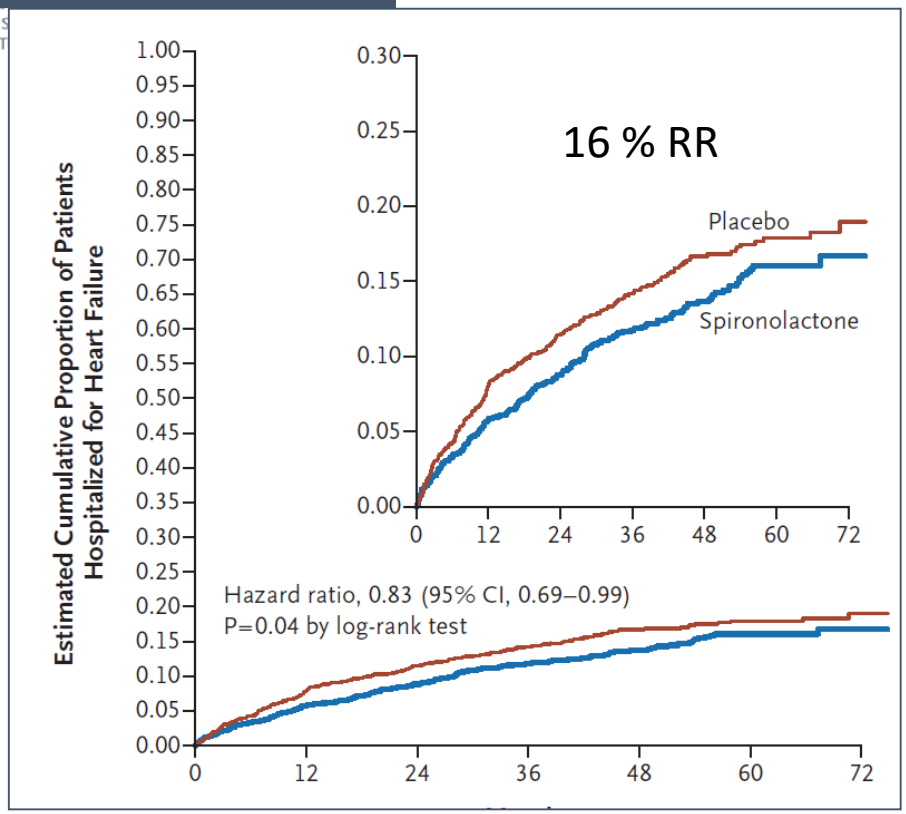
Spironolactone for Heart Failure with Preserved Ejection Fraction

TOPCAT

combined endpoint of death, aborted cardiac death







JACC; Volume 66, Issue 24, December 2015

Pharmacological Treatment for Stage C HF With Preserved EF

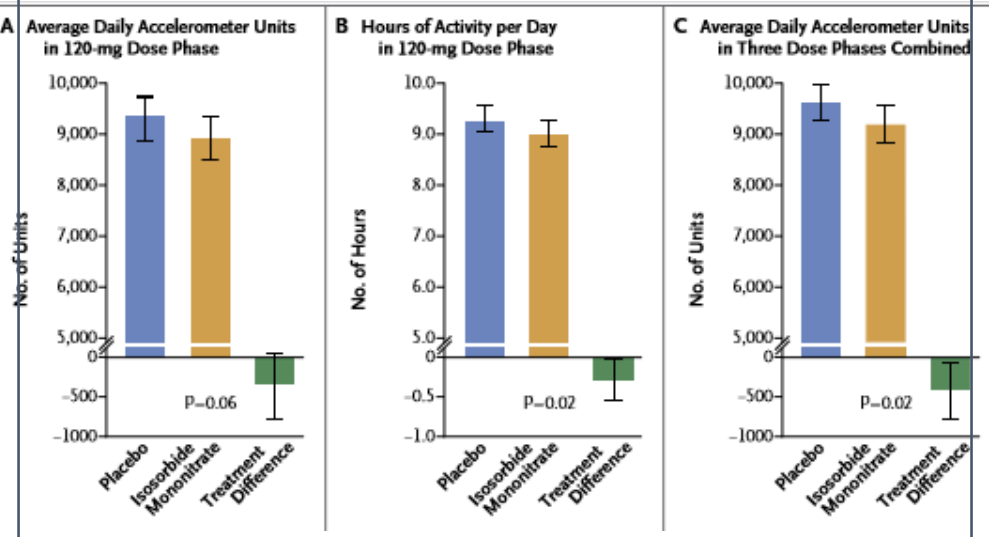
COR	LOE	Recommendations
IIb	B-R	In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP or Hfadm/year, eGFR >30 mL/min, creatinine <2.5 mg/dL, K <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D.,

NEAT-HF



- 110 patients with HFEF ≥50% randomized to either isosorbide mononitrate or placebo
- no beneficial effects on activity levels, QoL, exercise tolerance, or NT-proBNP levels.

ONLINE FIRST

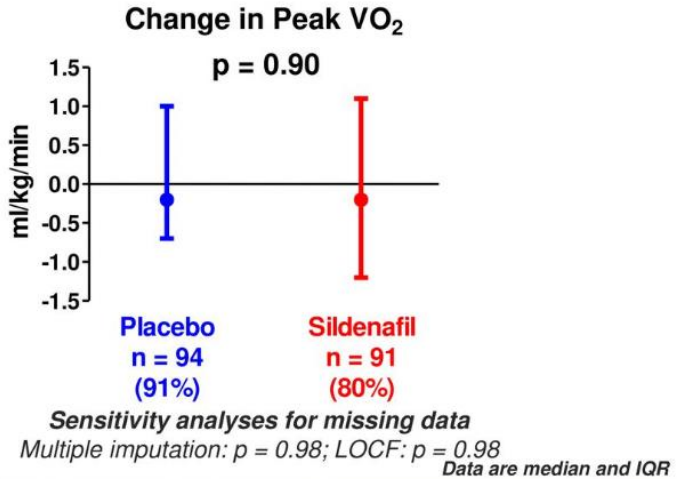
Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction

A Randomized Clinical Trial

RELAX-HF

Results: Primary Endpoint

HEART FAILURE NETWORK



- PDE-5 inh augments the NO by upregulating cGMP
- Randomized 216 patients with HFEF ≥50% on and pVo2 <60% to sildenafil or placebo.
- No improvement in O2 consumption or exercise tolerance

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations
IIb	B	The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF.
III: No Benefit	B-R	Routine use of nitrates or PDE-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective.

Clyde W. Yancy et al. Circulation. 2017;136:e137-e161

Heart Failure

Mid-Range LVEF

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GWTG-HF data linked to Medicare data, ~ 40 k pts,

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https://doi.org/10.1016/j.jacc.2017.08.074

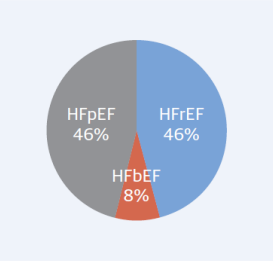
Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction

5-Year Outcomes

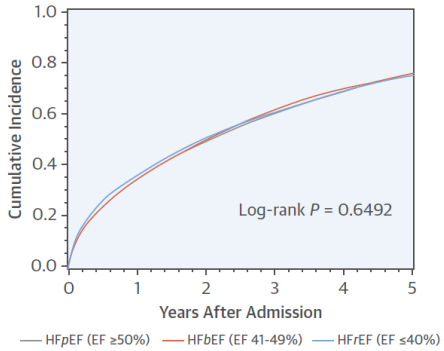
Kevin S. Shah, MD,[a] Haolin Xu, MS,[b,c] Roland A. Matsouaka, PhD,[b,c] Deepak L. Bhatt, MD, MPH,[d]

CENTRAL ILLUSTRATION 5-Year Outcomes in Patients Hospitalized With HF With Preserved, Borderline, and Reduced EF

Heart Failure



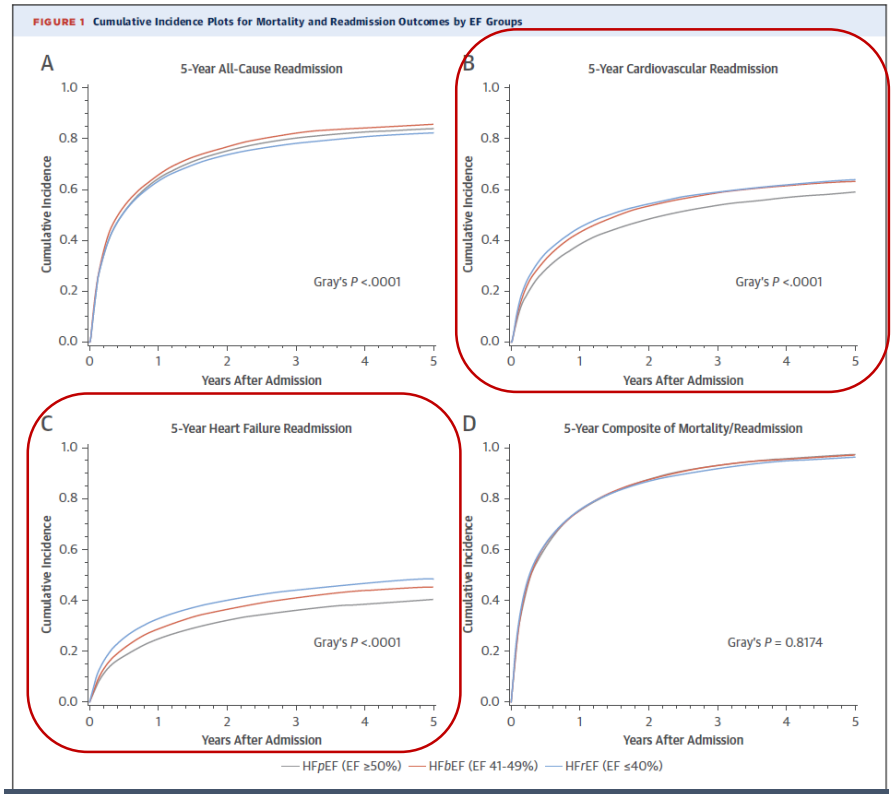
5-Year Mortality



Outcomes – 5-Year Event Rates (%)					
	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3

Mortality

FIGURE 1 Cumulative Incidence Plots for Mortality and Readmission Outcomes by EF Groups



Hospitalization

All 3 groups had **similar 5-year mortality** (HFrEF 75.3% vs. HFpEF 75.7%; HFbEF 75.7%)
CVH and HFH higher in HFrEF and HFbEF compared with those with HFpEF

ESC European Society of Cardiology
European Heart Journal (2018) 39, 26–35
doi:10.1093/eurheartj/ehx564

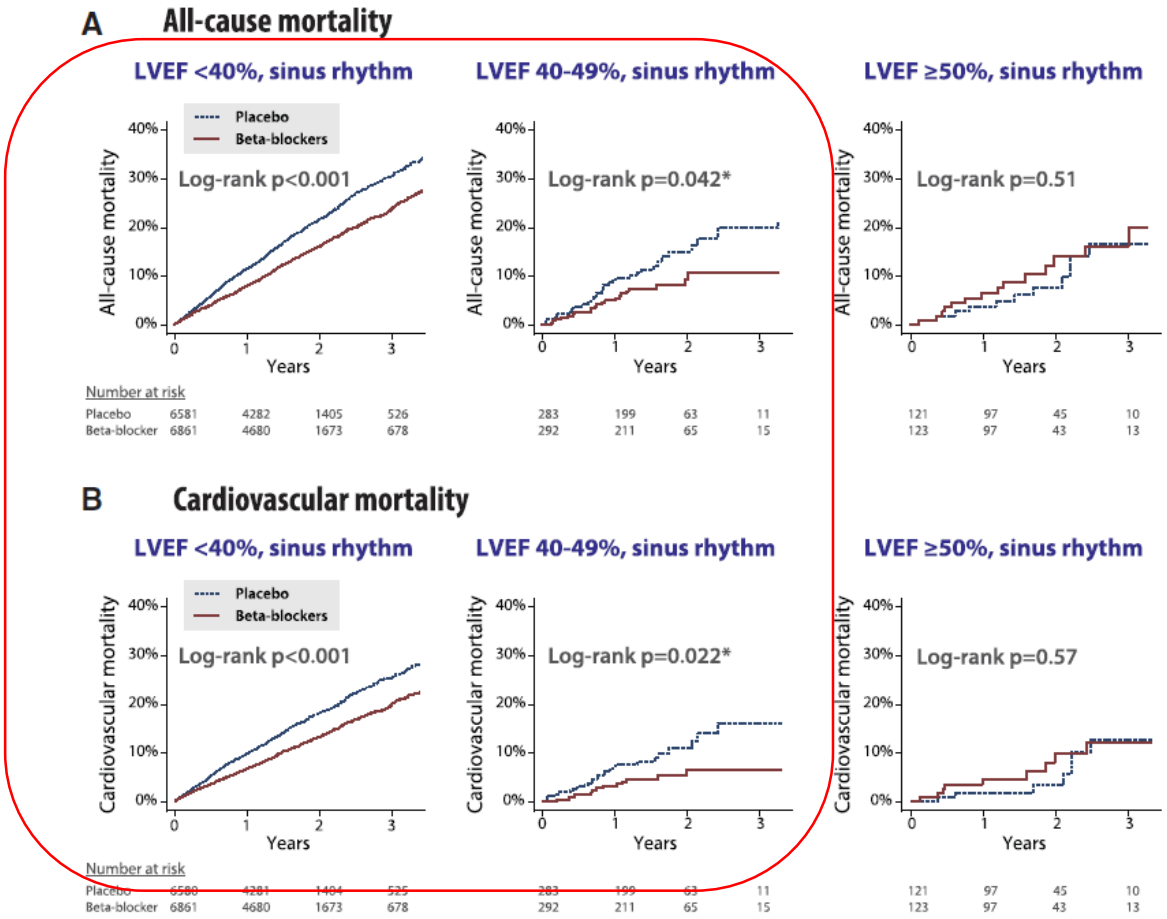
FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials

John G.F. Cleland[1], Karina V. Bunting[2], Marcus D. Flather[3], Douglas G. Altman[4], Jane Holmes[4], Andrew J.S. Coats[5], Luis Manzano[6], John J.V. McMurray[7], Frank Ruschitzka[8], Dirk J. van Veldhuisen[9], Thomas G. von Lueder[10,11], Michael Böhm[12], Bert Andersson[13], John Kjekshus[14], Milton Packer[15], Alan S. Rigby[16], Giuseppe Rosano[17,18], Hans Wedel[19], Åke Hjalmarson[13], John Wikstrand[20], and Dipak Kotecha[2,11]*; on behalf of the Beta-blockers in Heart Failure Collaborative Group

- The Beta-blockers in Heart Failure Collaborative Group (BBmeta-HF) pool individual patient data from 11 major HF RCTs : :Australia/New Zealand Heart Failure Study (ANZ), BEST, CAPRICORN, CHRISTMAS, CIBIC I , CIBIS II, COPERNICUS, MDC, MERIT-HF, SENIORS, U.S.Carvedilol HF Program (US-HF)
- to determine efficacy of beta blockers in mid range and preserved EF and also atrial fibrillation patients
- Though guidelines suggest to treat mid-range EF as HF-PEF, in practice most of these patients are treated as HFrEF
- 14262 patients in sinus rhythm, 3050 patients in atrial fibrillation
- Pts with **baseline LVEF** and ECG that showing either sinus rhythm or AF/atrial flutter included

Treat HFmEF like HFrEF



Recommendations for treatment of patients w failure with preserved ejection fraction and hea with mid-range ejection fraction

Recommendations	Class [a]	Level [b]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B

β-blockers improve outcomes for all pts with HF any reduced EF and in SR.
Most robust for LVEF<40%, but similar benefit in LVEF 40–49 %

Heart Failure

Hypertension

Hypertension Management in HF

ACC, AHA, HFSA HF Guidelines

COR	LOE	Recommendations
I	B-R	In patients at increased risk, **stage A HF**, the optimal BP in those with HTN should be **<130/80 mm Hg**.
I	C-EO	Patients with **HF*r*EF and HTN** should be prescribed GDMT titrated to attain **SBP < 130 mm Hg**.
I	C-LD	Patients with **HF*p*EF** & persistent HTN after management of volume overload should be prescribed GDMT to attain **SBP<130 mm Hg**

Yancy C. et al. J Am Coll Cardiol. 2017 Aug 8;70(6):776-803, Circulation. 2017;136:e137-e161, J Card Fail. 2017 Aug;23(8):628-651.

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

COR	LOE	Recommendations for BP Goal for Patients With Hypertension
I	SBP: B-R[SR]	For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher a BP target of less than 130/80 mm Hg is recommended.
	DBP: C-EO	
IIb	SBP: B-NR	For adults with confirmed hypertension, without additional markers of increased CVD risk, a BP target of less than 130/80 mm Hg may be reasonable.
	DBP: C-EO	

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Heart Failure

Anemia

Stages of Iron Deficiency

	Stage I Prelatent	Stage II Latent	Stage III Anemia
BM Iron	↓	Absent	Absent
Ferritin	↓	<12 ug/L	<12 ug/L
Hb	Normal	Normal	↓
MCV	Normal	Normal	↓
Symptoms	+/-	+/-	+

FAIR-HF

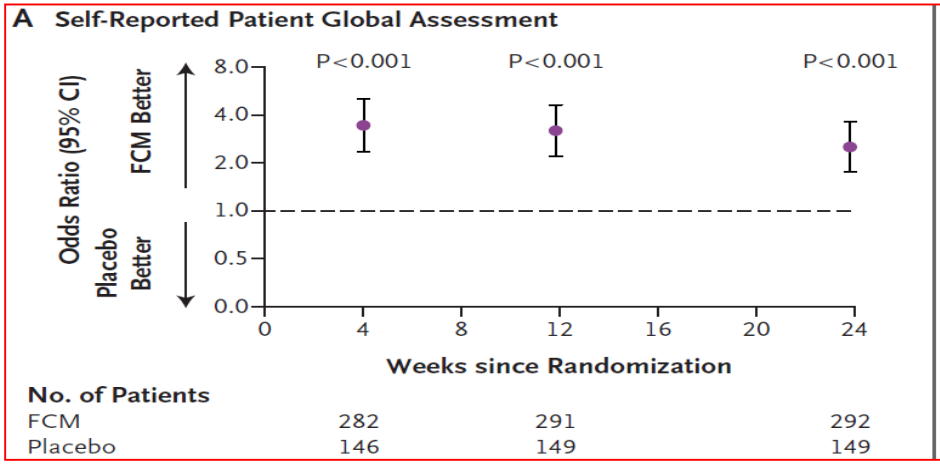
ORIGINAL ARTICLE

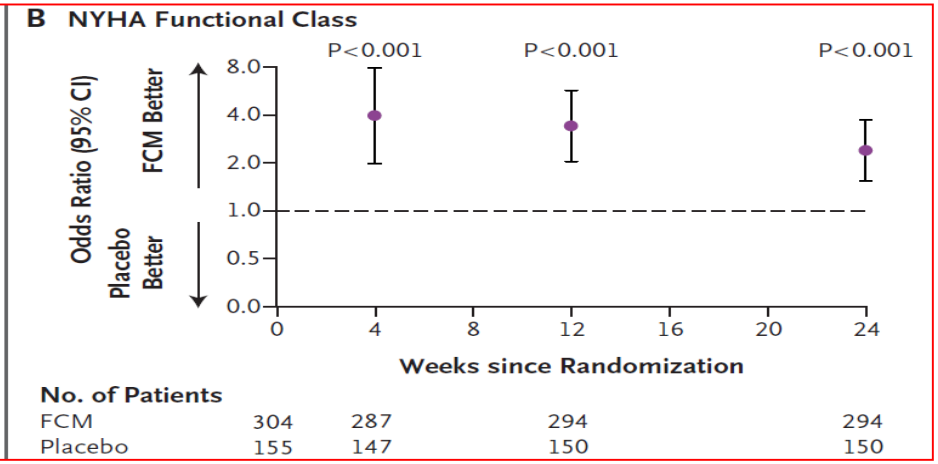
Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

- 459 patients NYHA II –III, LVEF < 40 % ,
- iron deficiency (ferritin level <100 µg / L or 100 - 300 µg /L, if the transferrin saturation was <20%), and a Hb 9.5 to 13.5 g /dL.

for the FAIR-HF Trial Investigators†

- 200 mg of IV ferric carboxy maltose or saline (placebo) for 24 weeks





- 50% reported being much or moderately improved vs 28% of placebo
- Improvements in 6 MWT and QOL with FCM
- Death, adverse events, and SAEs similar

N Engl J Med 2009;361:2436-48.

CONFIRM-HF

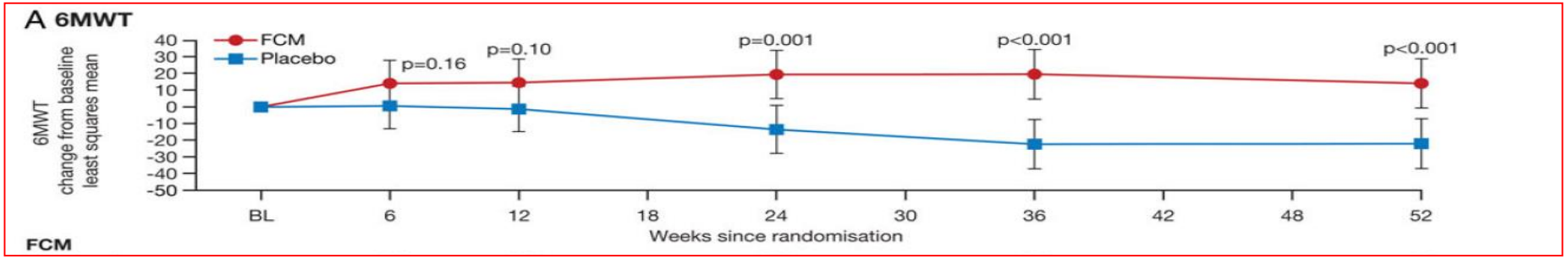
European Heart Journal (2015) **36**, 657–668
doi:10.1093/eurheartj/ehu385

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],

- **304 patients NYHA II –III, LVEF ≤ 45 % , elevated natriuretic peptides**
- **iron deficiency (ferritin level <100 µg / L or or 100 - 300 µg /L, if the transf saturation <20%).**

- **200 mg of IV ferric carboxy maltose or**
- **saline (placebo) for 52 weeks**



Primary End-Point

FCM prolonged 6MWT distance at 6 mo (difference FCM vs. placebo: 33 ± 11 m, P = 0.002)

Ponikowski P. et al . Eur Heart J. 2015 Mar 14;36(11):657-68.

META-ANALYSIS-Anker 2018

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.823

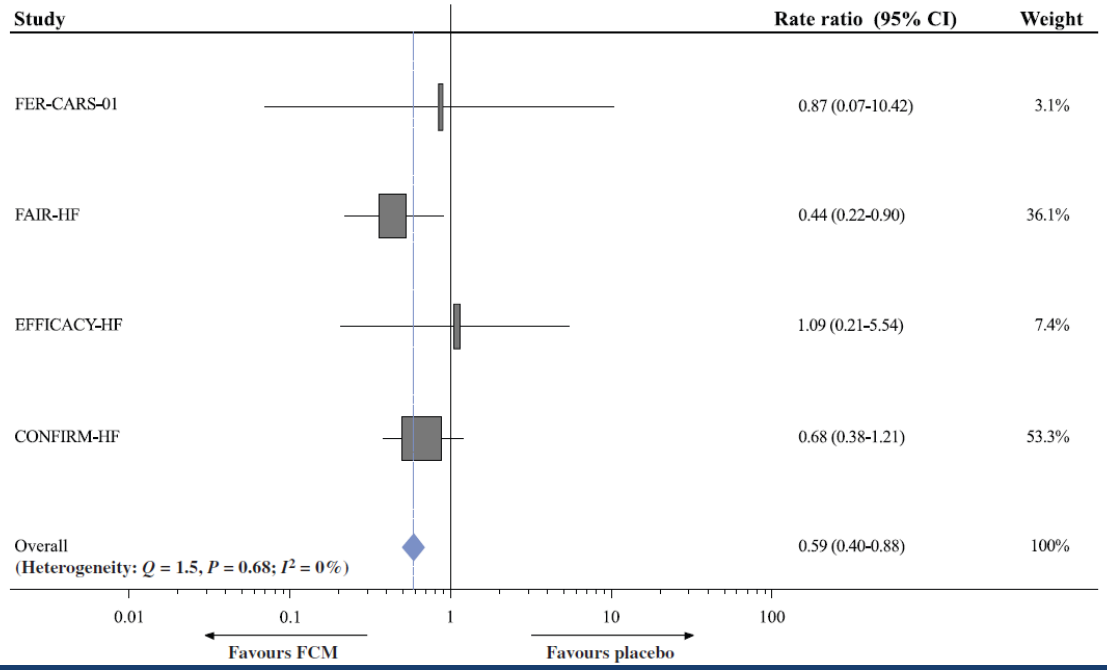
Individual patient data from 4 RCTs of FCM vs placebo in patients with systolic HF & iron def

4 Studies 839 pts: FER-CARS-01 FAIR-HF EFFICACY-HF, CONFIRM-HF

Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis

Stefan D. Anker[1]*, Bridget-Anne Kirwan[2,3], Dirk J. van Veldhuisen[4], Gerasimos Filippatos[5], Josep Comin-Colet[6], Frank Ruschitzka[7],

CV Mortality and CV Hospitalizations



IV iron associated with

- ↓ CV mortality & CV hosp (RR: 0.59; *p*=0.009)
- ↓ CV mortality & HFH (RR 0.53, p = 0.011)
- All cause mortality and recurrent CV Hosp (RR 0.6, p = 0.009)
- No increase in adverse events

Anker S. BA, at al. Eur J Heart Fail.2018;20:125-133

No efficacy with oral iron in HF in clinical trials

ORAL IRON

- Convenient, vailable and inexpensive, but oral iron is not absorbed well
- Elevated hepcidin prevents iron absorption
- Tolerability and compliance with of oral iron is low due to GI side effects

IRON-OUT HF

- largest phase 2 , double blind RCT
- 225 patients with NYHA class II-IV HF with HFrEF
- Hb 9-15 g/dL (men) or 9-13.5 g/dL women) and ID (ferritin 15-100 ug/L or 100-299 ug/L with TSAT <20%)
- oral iron polysaccharide 150 mg twice daily or placebo

At 16 weeks, **there was no significant difference in**

- primary end point : change in peak VO2 from baseline,
- Or secondary endpoints : 6MWD, NT-proBNP levels or KCCQ score
- oral iron increased TSAT, ferritin and hepcidin, and reduced soluble transferrin receptor levels

Lewis GD, et al. IRONOUT HF Randomized Clinical Trial. JAMA. 2017;317:1958-1966

Possible Explanations for Failure of Oral Iron in HF

- Inadequate repletion of iron stores with oral iron despite large doses

STUDY	Total Iron Dose	TSAT increase	Ferritin Increase
ORAL IRON-OUT	33.6 gm	3 %	11 ug/L
IV FAIR-HF	2 gm	11.3 %	259.5 ug/L

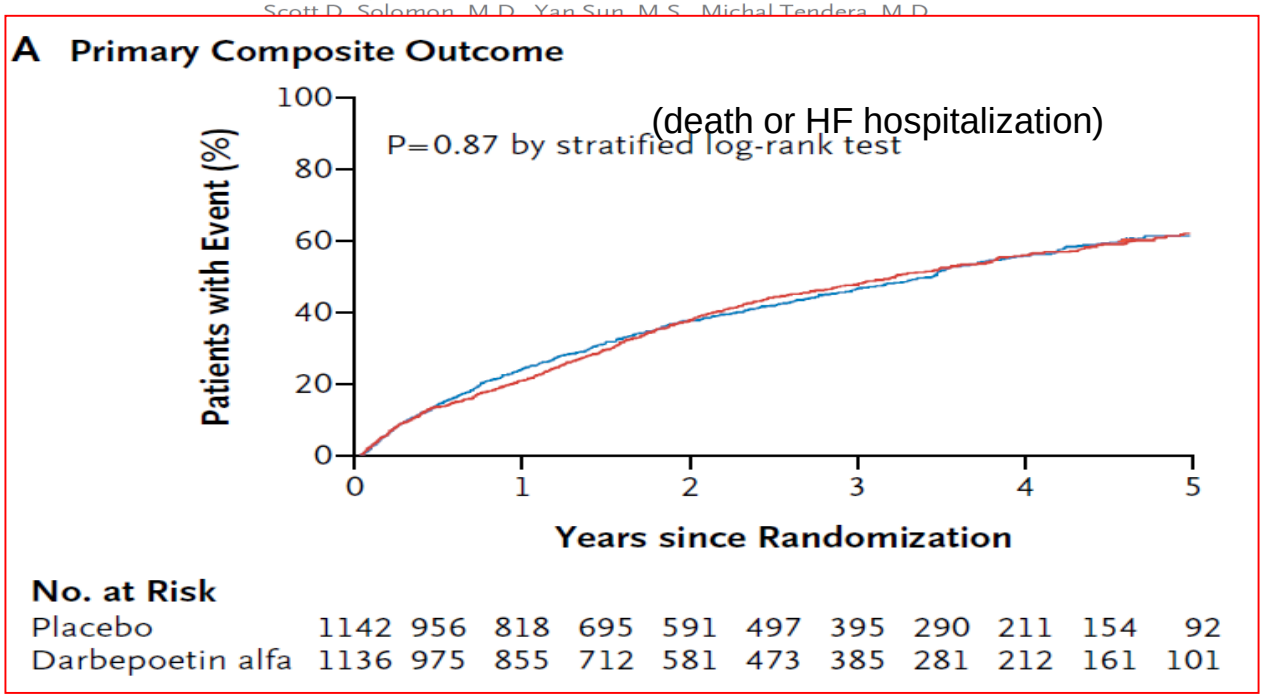
- Higher hepcidin levels associated with less improvement in TSAT and ferritin
- Higher hepcidin levels inhibit duodenal iron absorption

The NEW ENGLAND JOURNAL of MEDICINE

RED-HF TRIAL

Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure

Karl Swedberg, M.D., Ph.D., James B. Young, M.D., Inder S. Anand, M.D.,
Sunfa Cheng, M.D., Akshay S. Desai, M.D., Rafael Diaz, M.D.,
Aldo P. Maggioni, M.D., John J.V. McMurray, M.D.,
Christopher O'Connor, M.D., Marc A. Pfeffer, M.D., Ph.D.,
Scott D. Solomon, M.D., Yan Sun, M.S., Michal Tendera, M.D.



N Engl J Med **2013**; 368:1210-1219

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Anemia

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%), IV iron replacement might be reasonable to improve functional status and QoL.
III: No Benefit	B-R	In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality.

Clyde W. Yancy et al. Circulation. 2017;136:e137-e161

Heart Failure

Sleep Anemia

Sleep Disorders

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.
IIb	B-R	In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.
III: Harm	B-R	In patients with NYHA class II–IV HF*r*EF and central sleep apnea, adaptive servo-ventilation causes harm.

Clyde W. Yancy et al. Circulation. 2017;136:e137-e161

Heart Failure

Diabetes / Metabolic Syndrome

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AHA / ACCF 2013 HF Guidelines Stage A

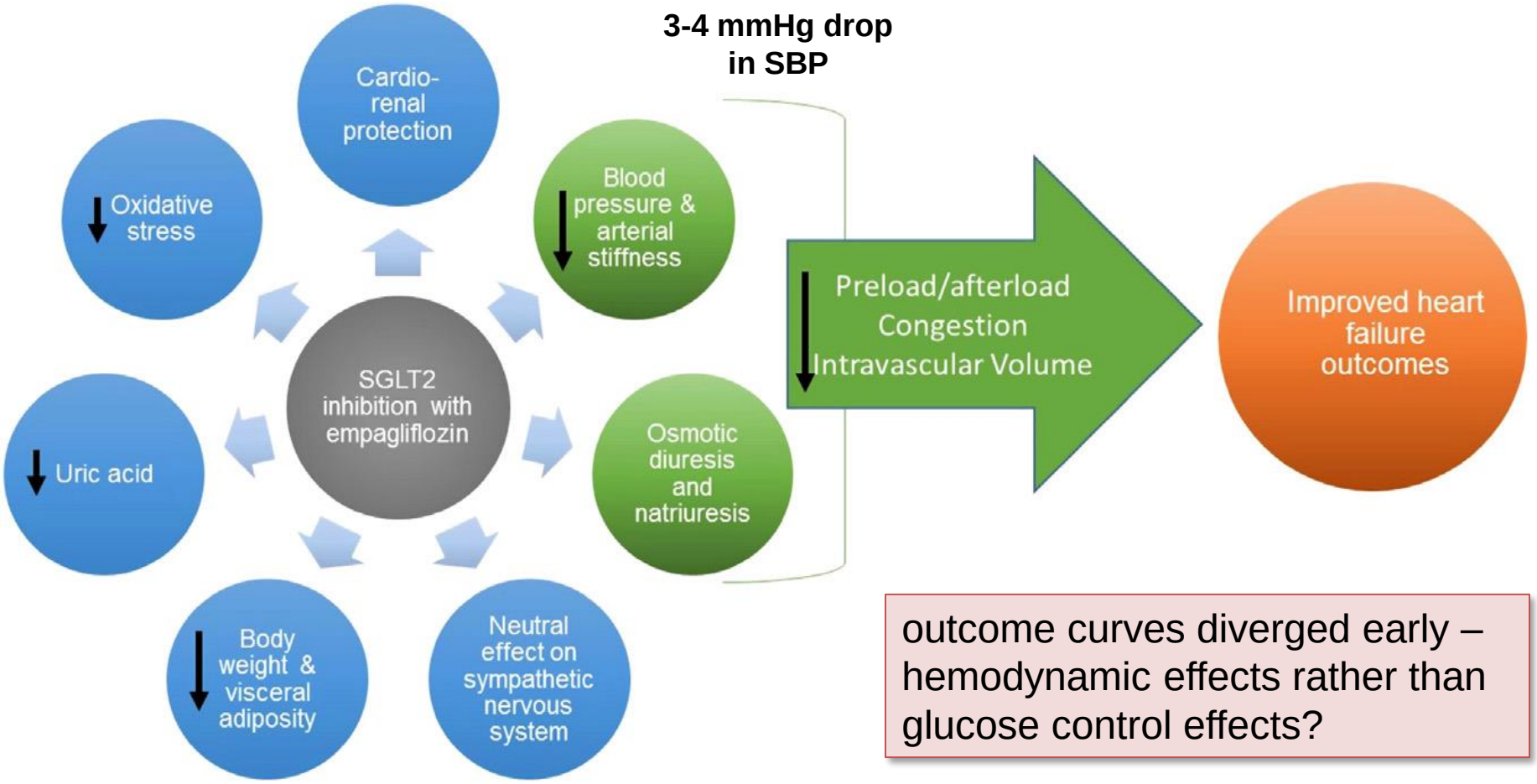
Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.

Yancy CW, Jessup M et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure, Circulation; 2013 Oct 15;128

Glucose Lowering Agents in DM and HF

Glucose Lowering Agents	Incident HF Risk in High CV risk Patients	Outcomes in Established HF Patients
Sulfanylurea	Not increased	No large scale RCT
Insulin	Possibly increased (residual confounding)	No large scale RCT
Metformin	Not increased	**Reduced HFH** / all cause mortality in population based retrospective cohorts, No large scale RCT
DPP4 inh (increase GLP-1)	Increased HF with saxagliptin (SAVOR-TIMI 53), no signal with others (TECOS, EXAMINE Trials)	Not studied
GLP-1 Agonists	No effect HF, Reduced CVD (LEADER, SUSTAIN trials)	Post ADHF discharge increased trend for HFH+ Mortality with liraglutide (FIGHT- NIH Trial)
SGLT2i	**Reduced HFH, CVD, MACE (EMPA-REG, CANVAS Trials)**	Ongoing

Potential Mechanisms of Empagliflozin for Benefit in HF Outcomes

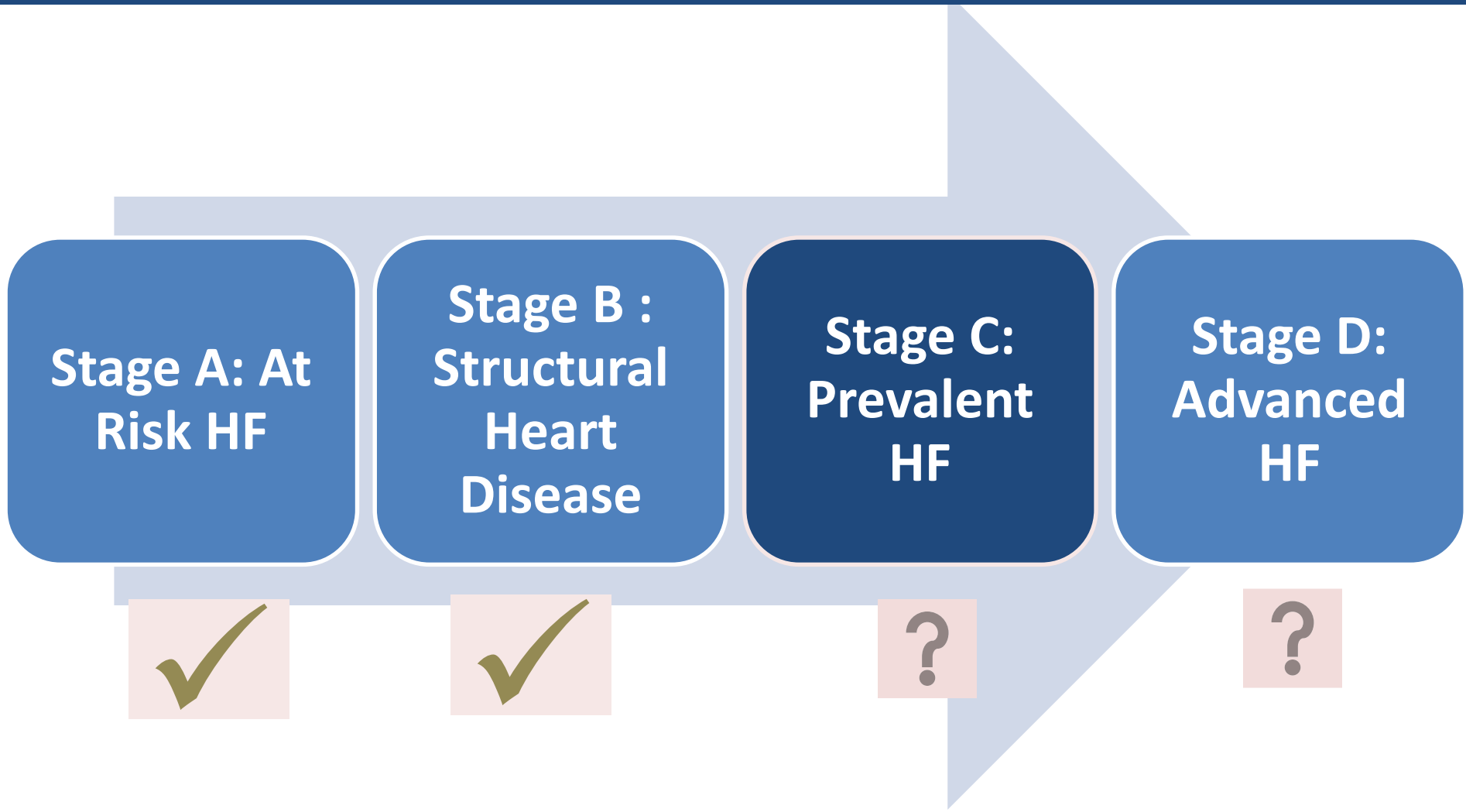


outcome curves diverged early – hemodynamic effects rather than glucose control effects?

myocardial fuel/energetics hypothesis:?, increase blood β-hydroxybutyrate a "superfuel" oxidized by the heart in preference to fatty acids and glucose, ? increase mechanical efficiency, prevent pro-hypertrophic transcription pathways.

From Pham D. et al. Trends in Cardiovascular Medicine Aug 4, 2016, Ferrannini et al., 2016; Mudaliar et al., 2016, Tahara et al.,2014, Aubert et al., 2016

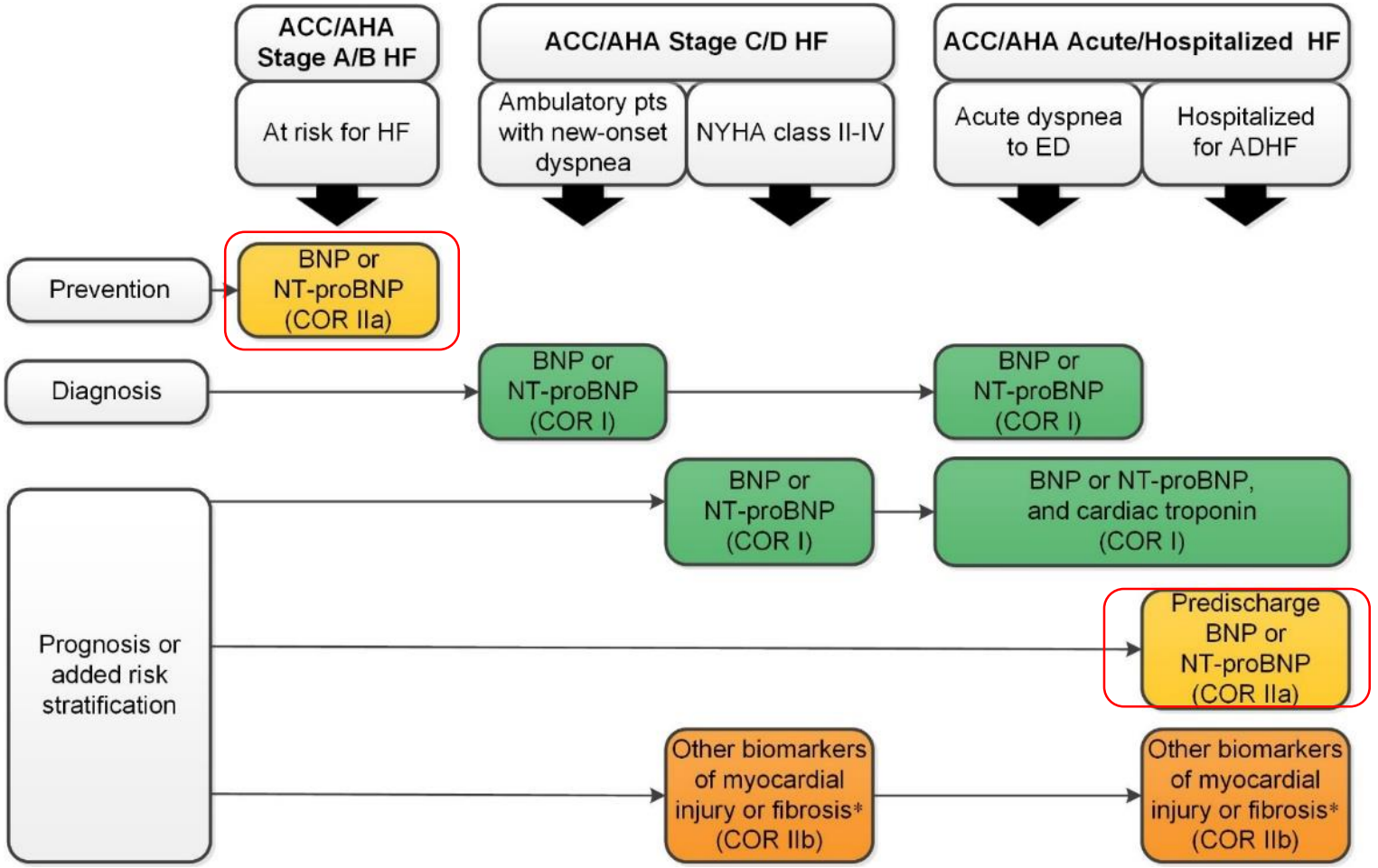
Primary and Secondary Prevention of HF with SGLT2i



Heart Failure

Biomarkers

2017 ACC/AHA/HFSA Update: Biomarkers Indications for Use



Yancy C. et al. J Am Coll Cardiol. 2017 Aug 8;70(6):776-803, Circulation. 2017;136:e137-e161, J Card Fail. 2017 Aug;23(8):628-651.

Biomarkers for Prevention of HF (Stage A/B)

COR	LOE	Recommendation
IIa	B-R	For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.

- Yancy C. et al. Circulation. 2017;136:e137-e161
- Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA. 2013;310:66-74.
- Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol. 2013;62:1365-72.

Biomarkers

Biomarkers for Diagnosis, Prognosis

COR	LOE	Recommendation
I	A	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF.
I	A	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.
I	A	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF.
IIa	B-NR	During a hospitalization for HF, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis.
IIb	B-NR	In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification.

GUIDE-IT

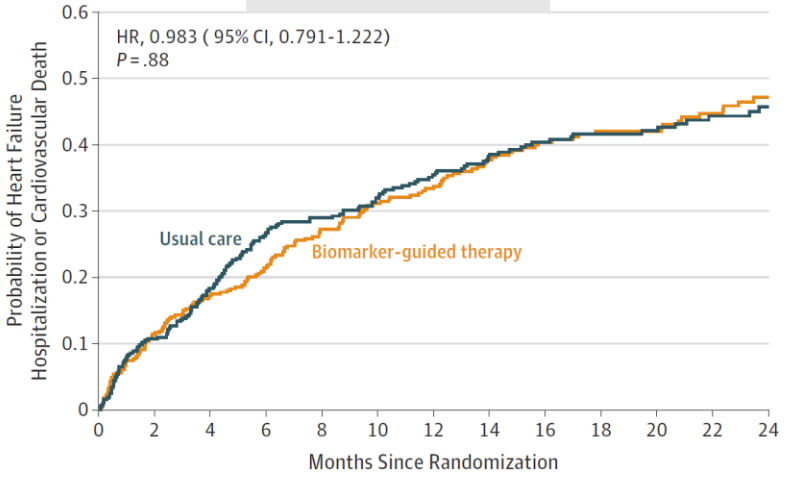
JAMA | Original Investigation

Effect of Natriuretic Peptide–Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction

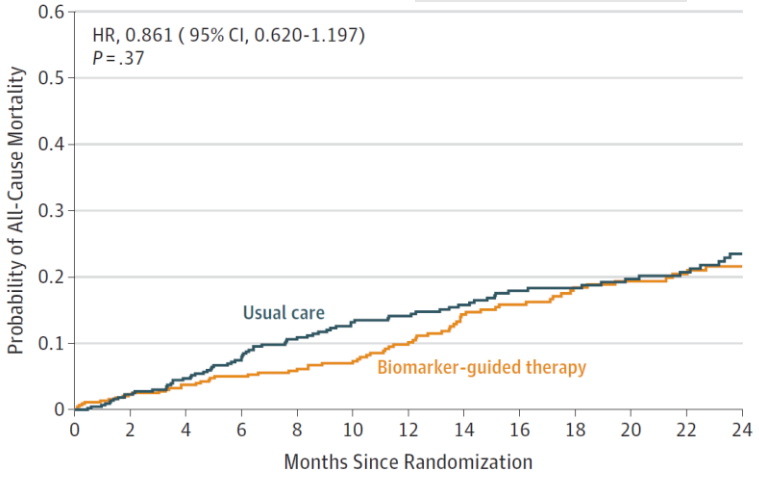
A Randomized Clinical Trial

G. Michael Felker, MD, MHS; Kevin J. Anstrom, PhD; Kirkwood F. Adams, MD; Justin A. Ezekowitz, MBBCh, MSc; Mona Fiuzat, PhD; Nancy Houston-Miller, RN, BSN; James L. Januzzi Jr, MD; Daniel B. Mark, MD, MPH; Ileana L. Piña, MD, MPH; Gayle Passmore, PMP; David J. Whellan, MD, MHS; Hongqiu Yang, PhD; Lawton S. Cooper, MD, MPH; Eric S. Leifer, PhD; Patrice Desvigne-Nickens, MD; Christopher M. O'Connor, MD

HFH or CVD



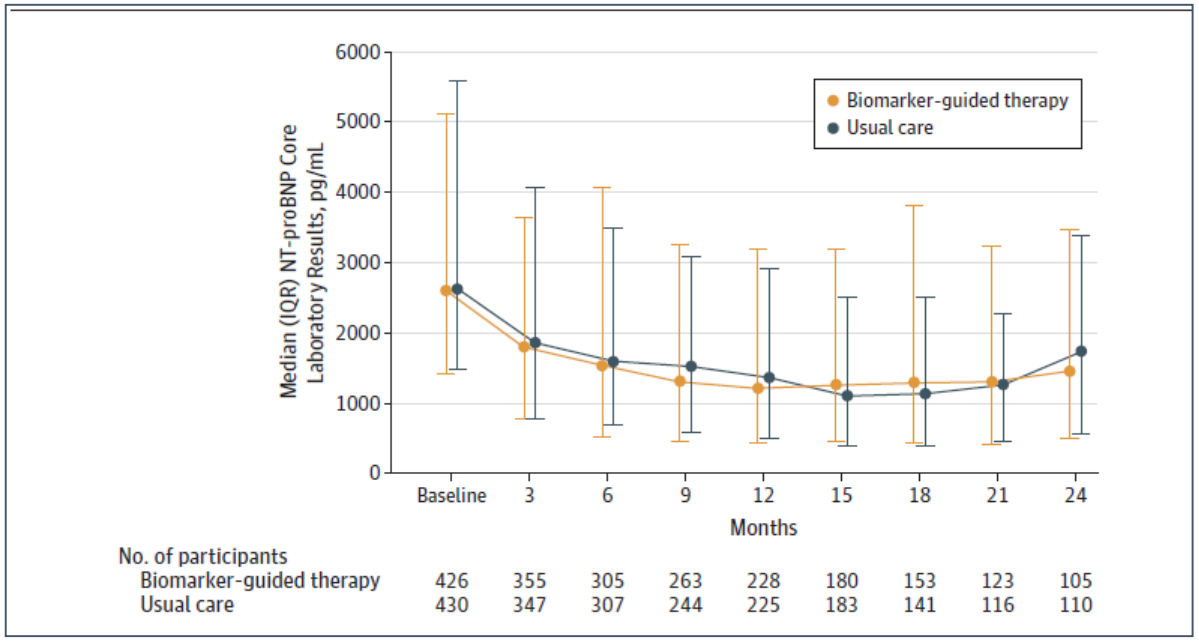
Mortality



- 894 of 1100 enrolled
- HFrEF prior HFH, NT-proBNP >2000 or BNP>400
- Target NT-proBNP < 1000 pg/mL

	NT-ProBNP-Guided Group	Usual Care Group	Effect (95% CI)	*P* Value
Mortality, No. (%)	66 (15)	77 (17)	HR, 0.86 (0.62-1.20)	.37
CV mortality, No. (%)	53 (12)	57 (13)	HR, 0.94 (0.65-1.37)	.75
Non-CV mortality, No. (%)	13 (3)	20 (5)	HR, 0.66 (0.33-1.32)	.24
First HF hospitalization, No. (%)	147 (33)	141 (32)	HR, 1.04 (0.82-1.31)	.76
Total HF hospitalizations, No.	350	277	HR, 1.29 (0.97-1.72)	.08[a]
Days alive and not hospitalized for CV reasons, mean (SD), d	581 (14.4)	562 (15.1)	Mean difference, 19.26 (−21.58 to 60.10)	.36[b]

Change in NT-proBNP



	NP Guided	Usual	p
Achieved target NT-proBNP < 1000 pg/mL	46 %	40 %	0.21

Similar NP levels can be achieved with empirical adjustment in HFrEF medications

Circulation

HOME ABOUT THIS JOURNAL ALL ISSUES SUBJECTS BROWSE FEATURES RESOURCES

ORIGINAL RESEARCH ARTICLE

NT-proBNP-Guided Therapy in Acute Decompensated Heart Failure: The PRIMA II Randomized Controlled Trial

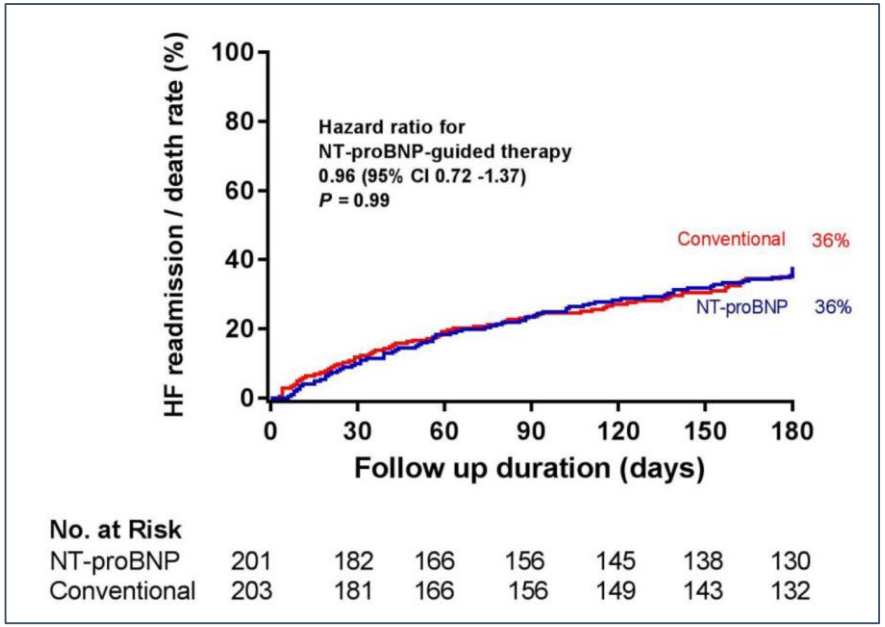
Susan Stienen, Khibar Salah, Arno H. Moons, Adrianus L. Bakx, Petra van Pol, Mikael Kortz, João Pedro Ferreira, Irene Marques, Jutta M. Schroeder-Tanka, Jan T. Keijer, Antoni Bayés-Genis, Jan G.P. Tijssen, Yigal M. Pinto, Wouter E. Kok

ADHF patients with NT-proBNP levels of > 1700

After achieving clinical stability, 405 pts randomized

Treatment to achieve 30% reduction in NT-proBNP

Conventional Treatment



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https://doi.org/10.1161/CIRCULATIONAHA.117.029882
December 14, 2017

NP Guided therapy in Guidelines

"Because of the **absence of clear and consistent evidence for improvement in mortality and CV outcomes**, there are insufficient data to inform specific guideline recommendations related to NP-guided therapy or serial measurements of BNP or NT-proBNP levels for the purpose of reducing hospitalization or deaths"

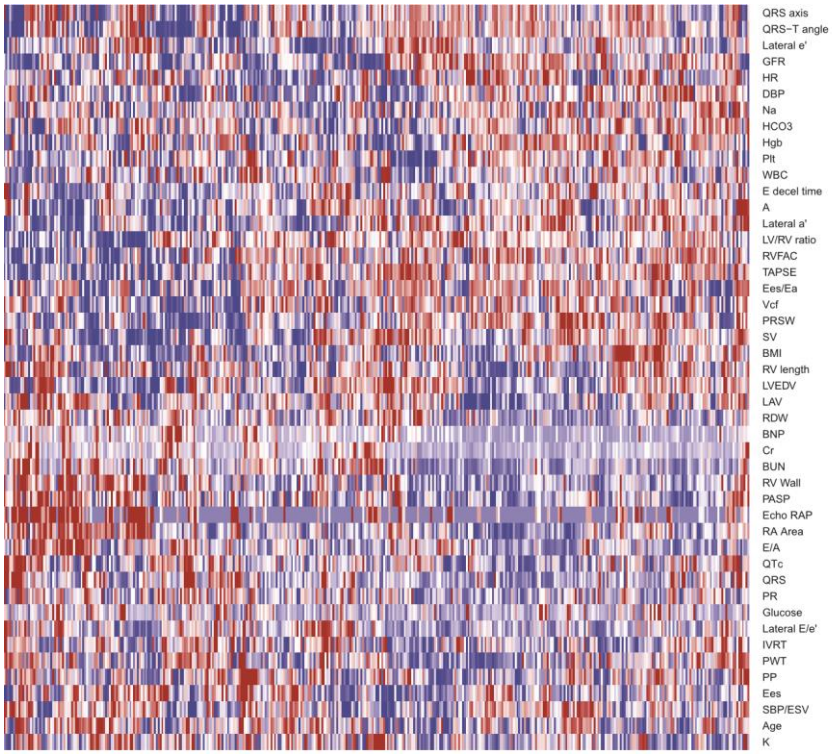
Clyde W. Yancy et al. Circulation. 2017;136:e137-e161

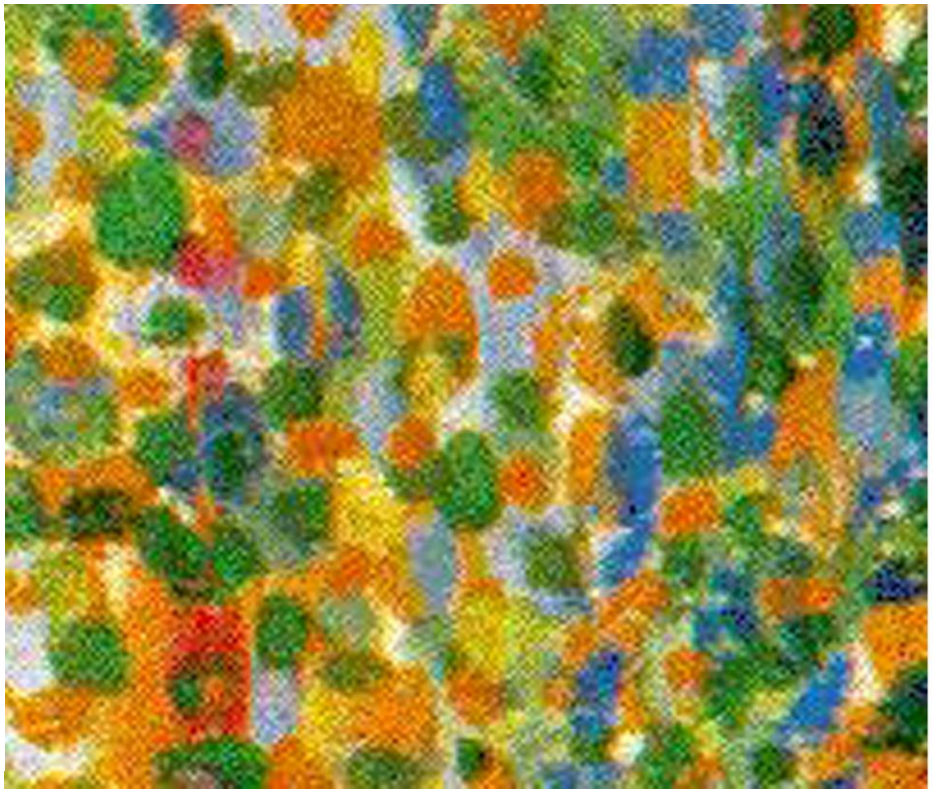
Individualization

- It is not ONE magical marker

(example: rise in creatinine with successful decongestion not associated bad outcomes)

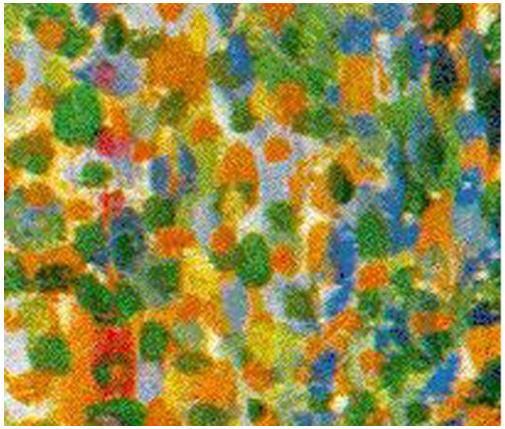
It is the ART of what we do with many markers

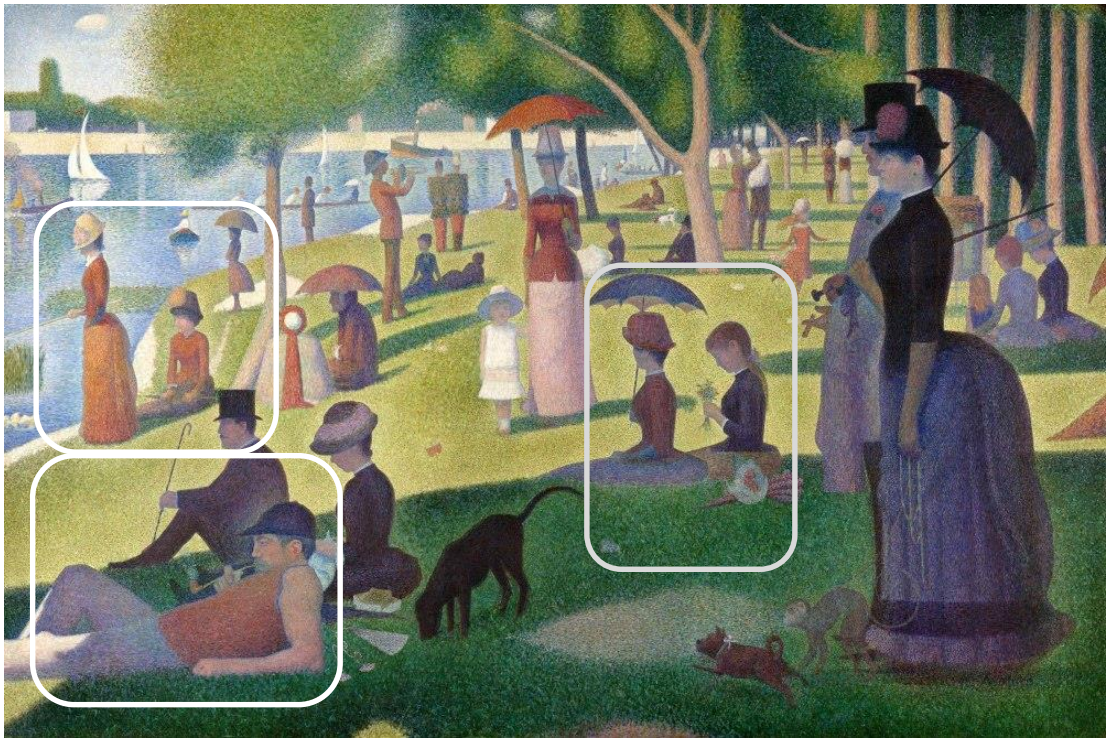




Unidirectional Heat Map Analysis of Potential Markers /Biomarkers: Phenomapping

stretch, fibrosis, injury, cytokines/ proinflammatory neurohormones, cGMP, genetics, metabolomics, miRNA ?





Georges Seurat, “A Sunday Afternoon on the Island of La Grande Jatte”

- It is the ART of what we do with many markers representing multiple pathway targets, in relation to each other and journey of each organism
- Role of AI Technology ?

Heart Failure Stage C Treatment According to Pheno-groups

Stage II HFrEF stable	Stage III frequent hosp /congestion	Stage III with LV+RV failure	Stage III HFrEF HTN	Stage II-III HFrEF and DM	Tachycardia / Injury Pattern
Maximize GDMT ACEi, BB, then switch to ARNI	ACEi, BB, MRA, diuretics	ACEI, BB, MRA, diuretics	ACEI/ARB, BB, switch to ARNI, HYD+ISDN for MRA	ACEI/ARB, BB, switch to ARNI, SGLT2i	BB, ACEI

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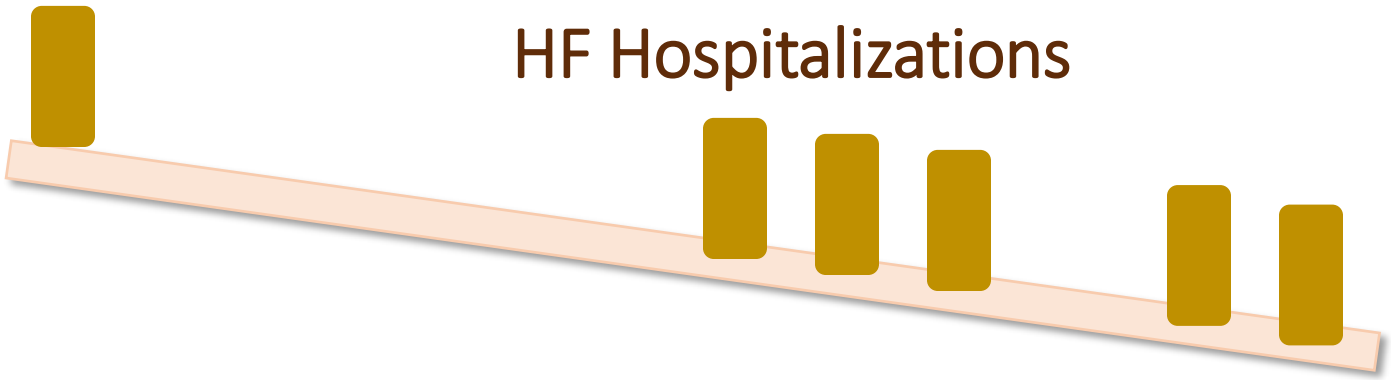
Anticipatory Management in Journey of the Patient-Stage C➔Stage D



- Decongestion, maintaining QOL
- Treatment and prevention of precipitating factors
- Guideline driven medical treatment –
- Disease modifying approaches such as CRT
- Consideration for advanced care such as transplant /VAD
- Palliative Care, Decision making strategies, End of Life

Heart Failure

Stage C/D Treatment Strategies Need to be Individualized for

- Patient's severity of illness and trajectory
- Responsiveness to therapy
- Goals of care
- Comorbidities and side effect profile
- Tolerability
- Phenogroups

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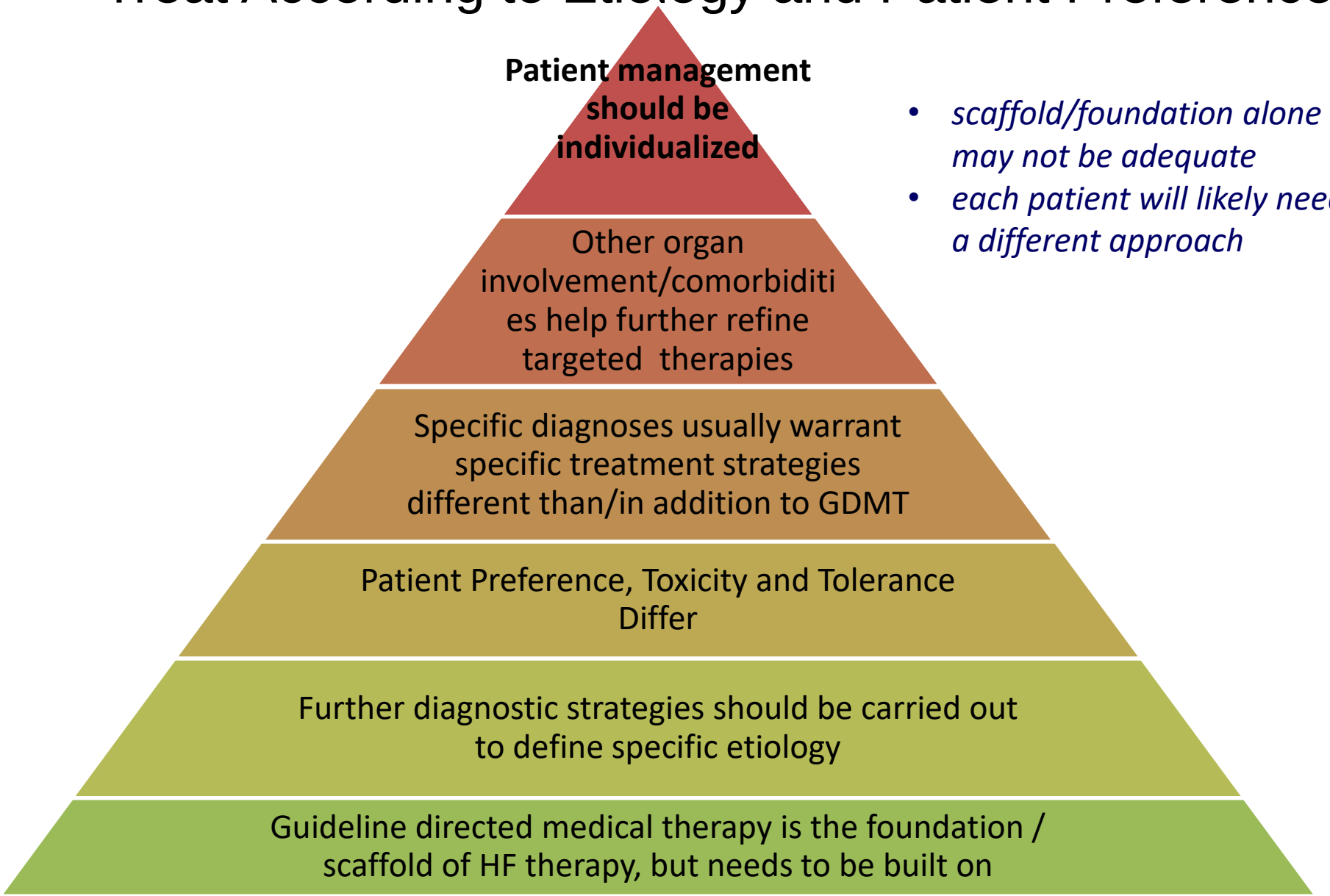
Individualized / Precision Medicine in HF
Treat According to Etiology and Patient Preference



- *scaffold/foundation alone may not be adequate*
- *each patient will likely need a different approach*