

Pharmacologic Therapy for Systolic Failure (HFrEF):

What's new in the guidelines?

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Cooper Medical School of Rowan University

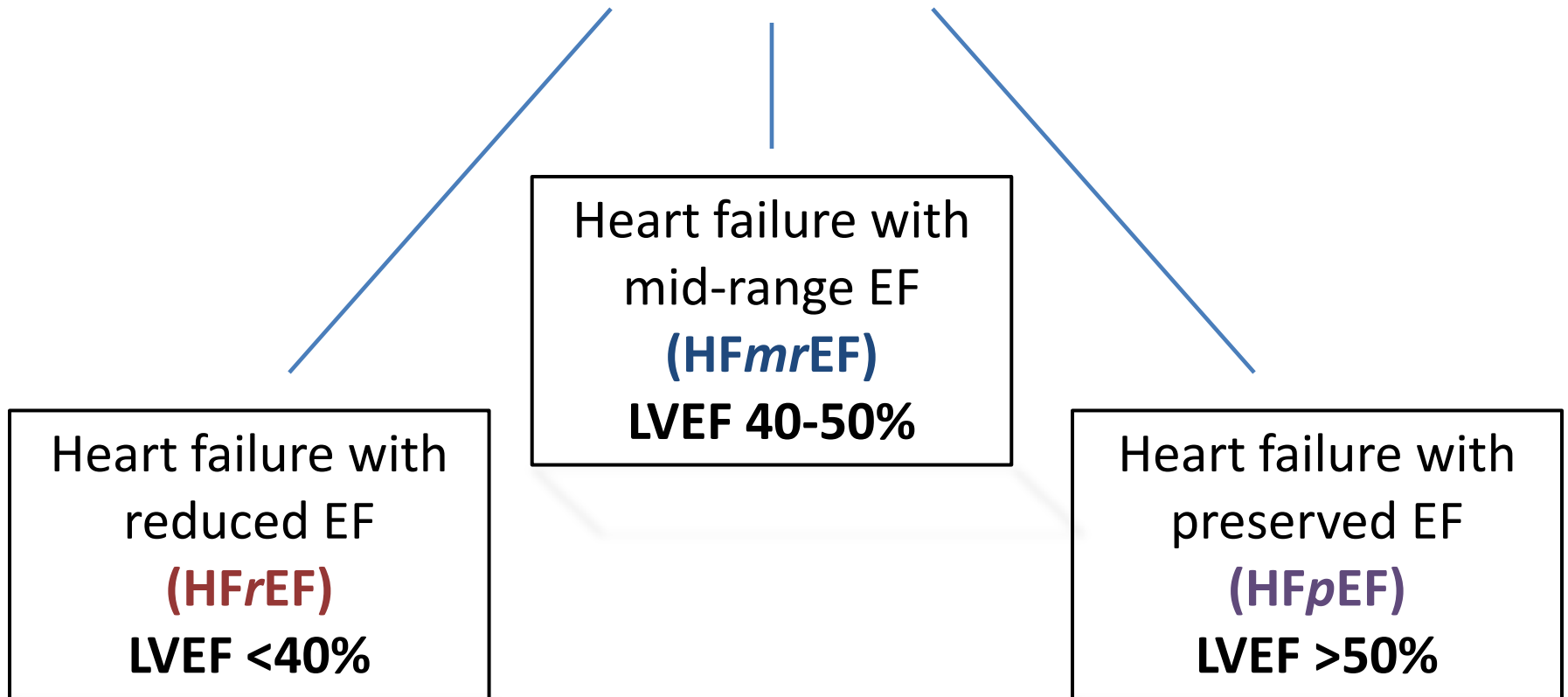
Outline

- Heart failure classification
- Goals of Therapy in heart failure
- Guideline-Directed Medical therapy for HFrEF
 - 2017 Update (Newer targets)
 - Natriuretic peptide System
 - Heart rate (HR) Inhibition

- No disclosures

Nomenclature

Heart Failure



CENTRAL ILLUSTRATION: Characterization of HFpEF, HFmrEF, and HFrEF

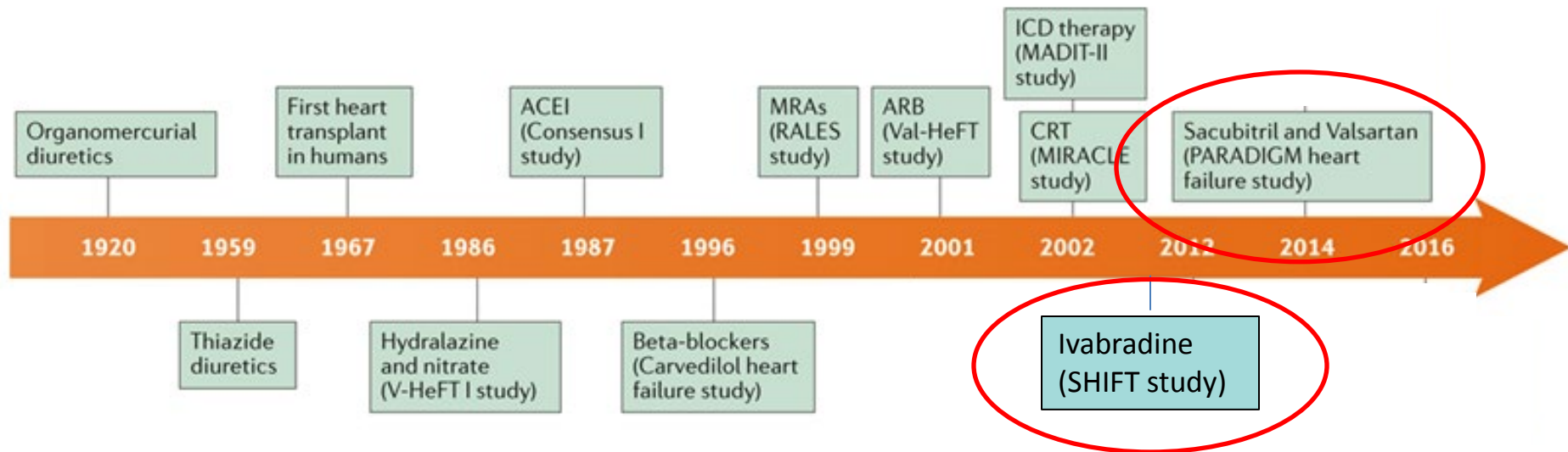
Heart Failure		Characteristics			Outcomes		Guideline-Directed Medical Therapies				
		Older Age	Male Sex	CAD	Morbidity	Mortality	ACEI	ARB	ARNI	BB	MRA
	HFpEF (LVEF>50%)	+++	+	++	++	++	X	✓ (IIB)	?	X	✓ (IIB)
	HFmrEF (LVEF40-50%)	++	++	+++	++/+++	++	?	✓ (IIB)	?	?	✓ (IIB)
	HFrEF (LVEF<40%)	+	+++	+++	+++	+++	✓ (I)	✓ (I)	✓ (I)	✓ (I)	✓ (I)


Hsu, J.J. et al. J Am Coll Cardiol HF. 2017;5(11):763-71.

Goals of Therapy in Heart Failure

- Improve symptoms
- Reduce hospitalizations
- Slow or reverse myocardial dysfunction
- **Reduce mortality**

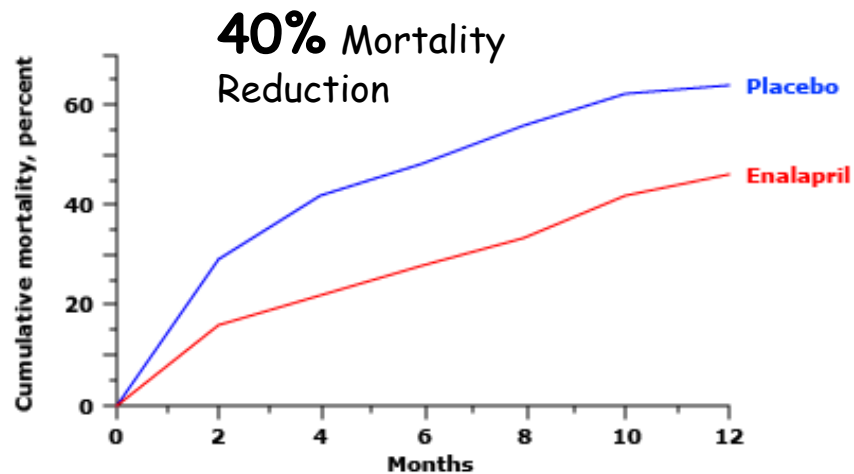
Heart Failure Therapy Timeline



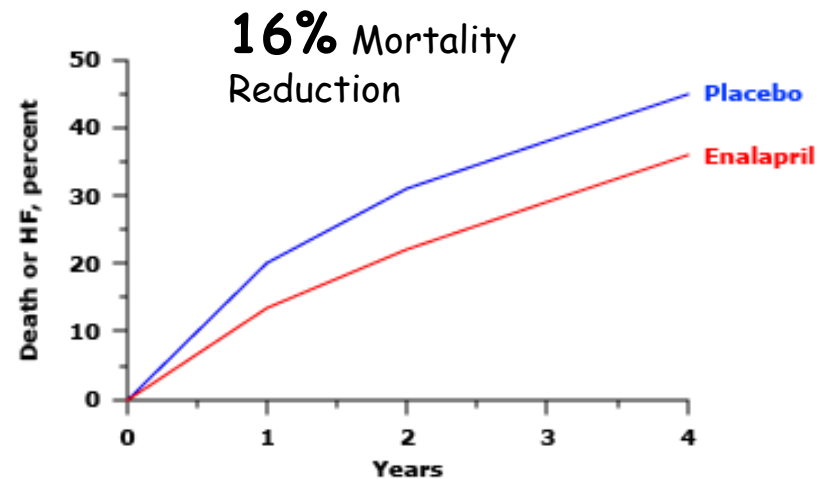


Evidence-Based Therapy: HF/rEF

ACEi in LV dysfunction



CONSENSUS - 1987

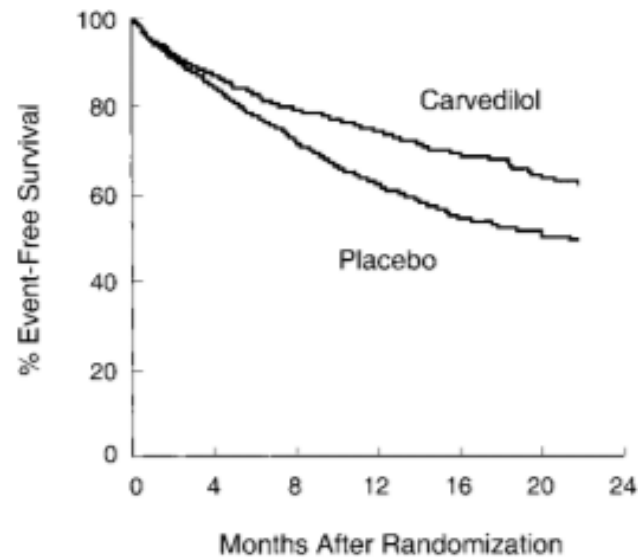


SOLVD Trial - 1992

N Engl J Med. 1987;316(23):1429
N Engl J Med. 1991;325(5):293.



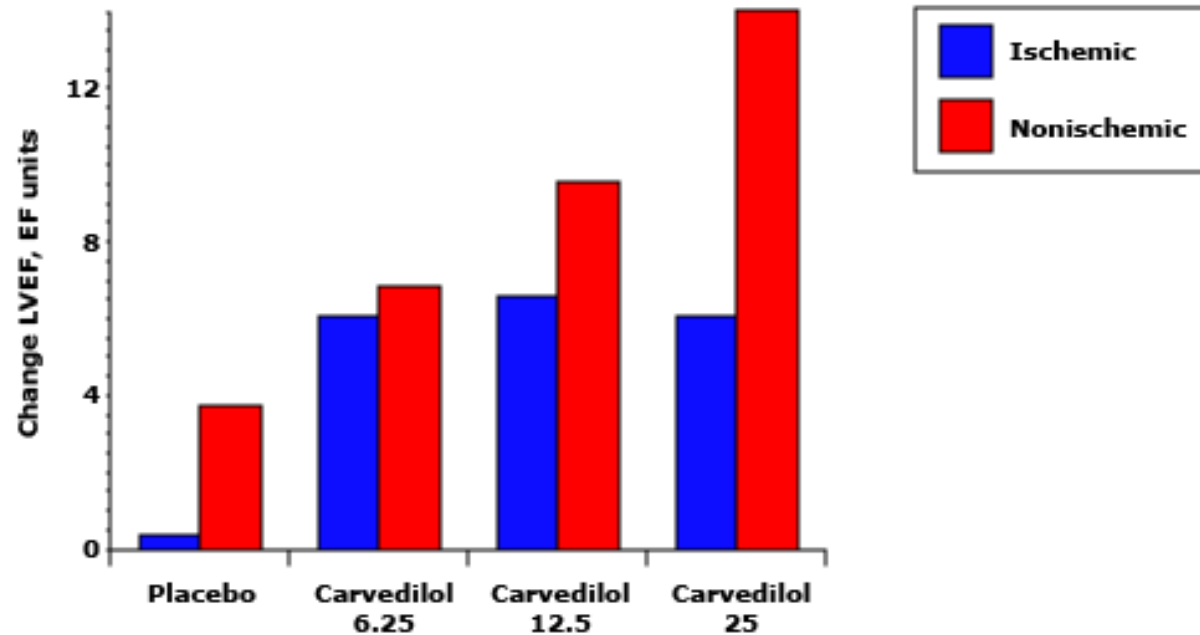
Carvedilol in Chronic Heart Failure



COPERNICUS - 2002

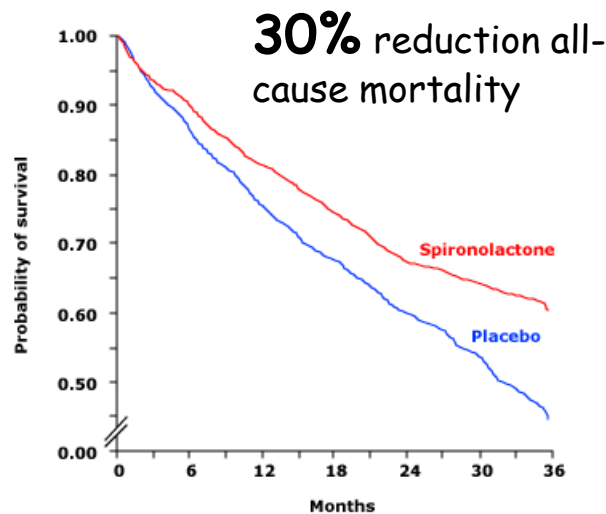
31% reduction in combined risk of death or HF hospitalization

Dose-related increase in LVEF with carvedilol in non-ischemic cardiomyopathy

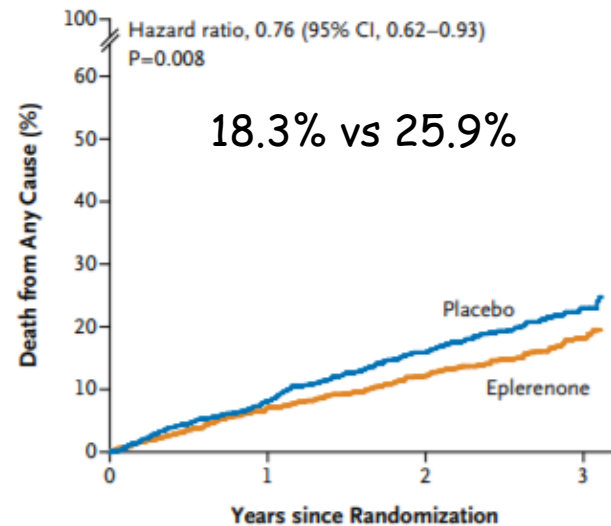


Bristow MR, Gilbert EM, Abraham WT, et al. *Circulation* 1996; 94:2807.

Mineralocorticoid receptor antagonists in HFrEF



RALES - 1999
NYHA class III or IV, LVEF \leq 35%



EMPHASIS-HF - 2011
NYHA class II, LVEF \leq 35%

Other Medications

- Hydralazine/ Isosorbide dinitrate
(V-HeFT, A-HeFT trials)




- Digoxin



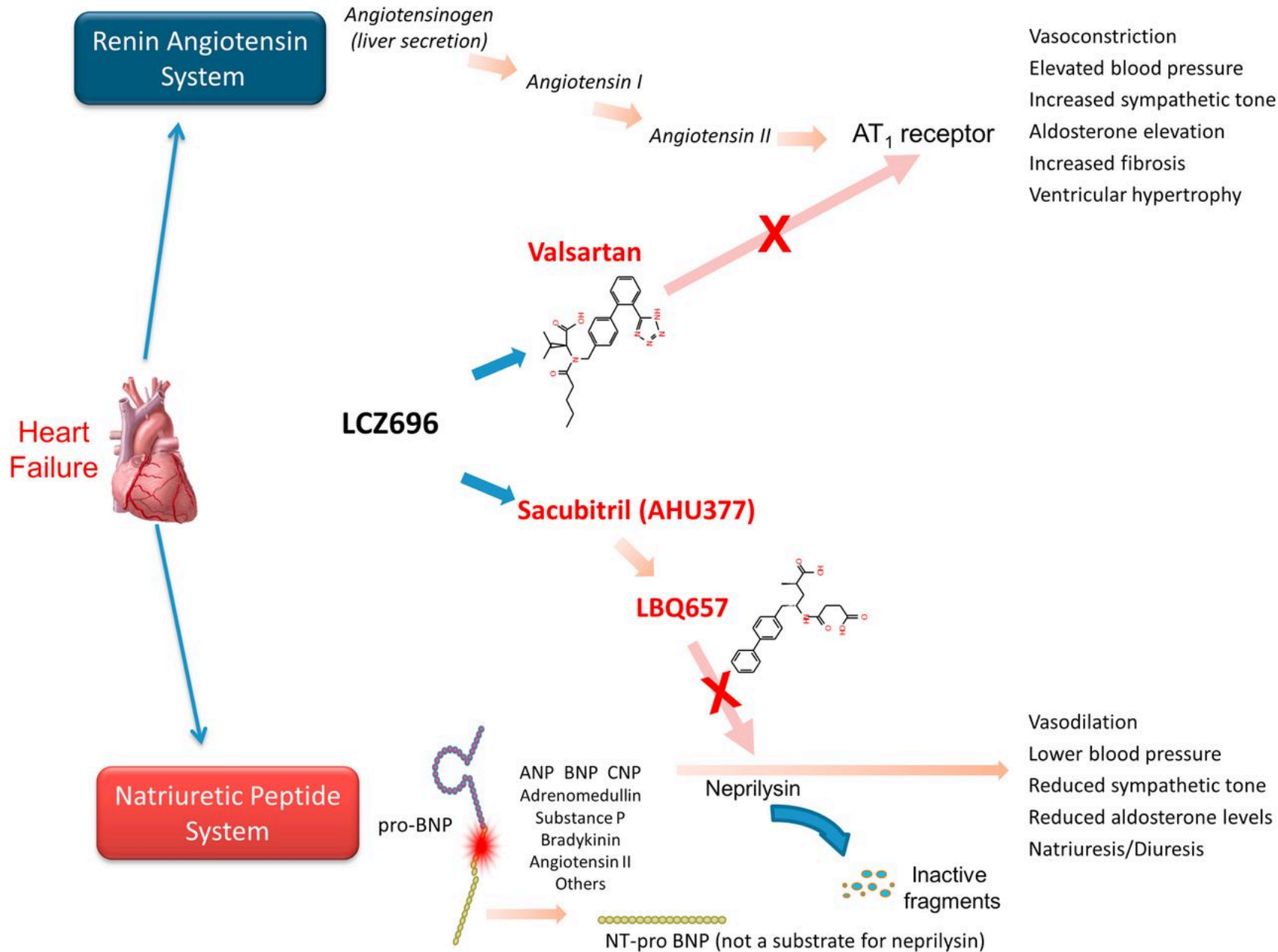
- Diuretics

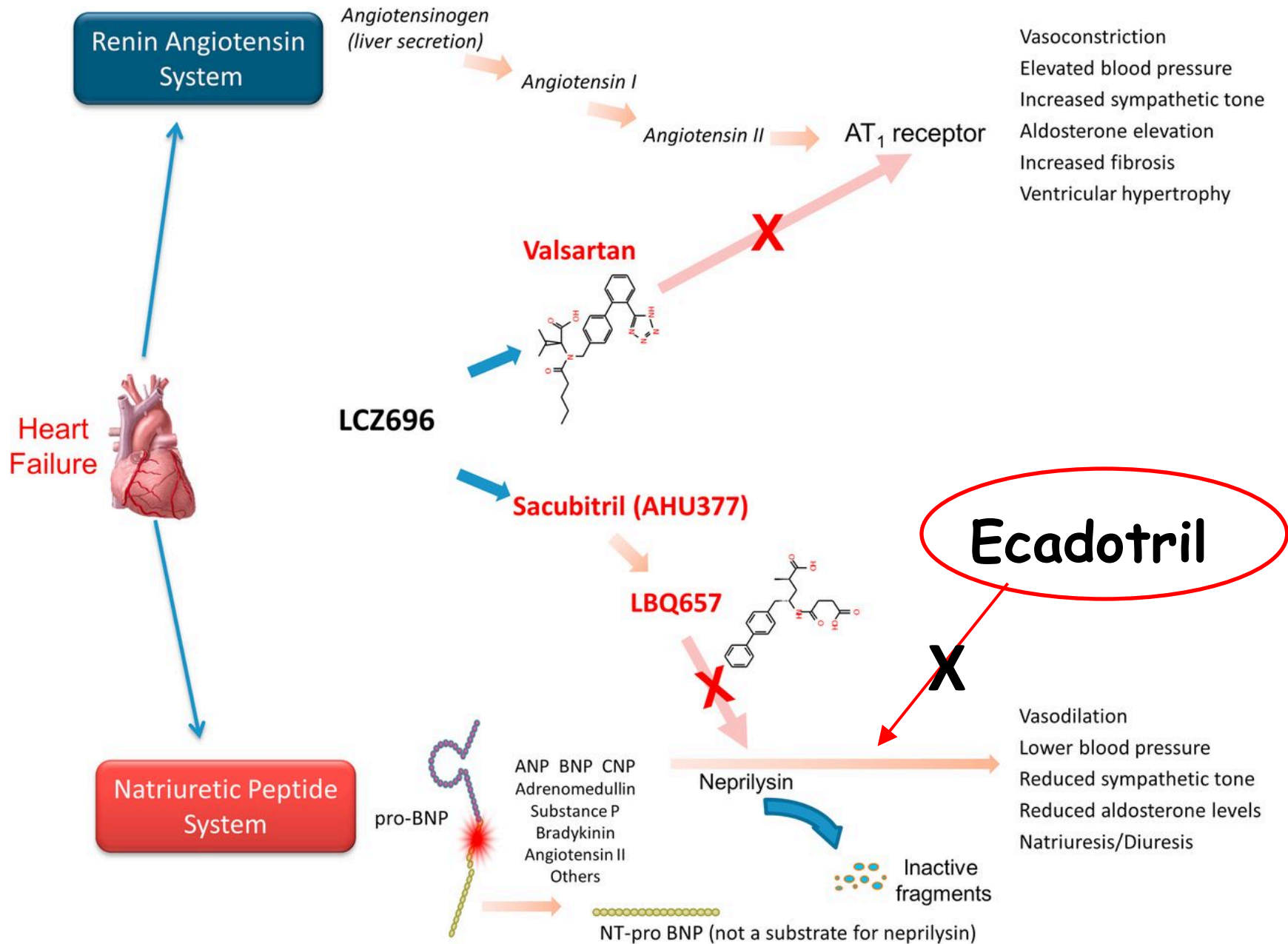


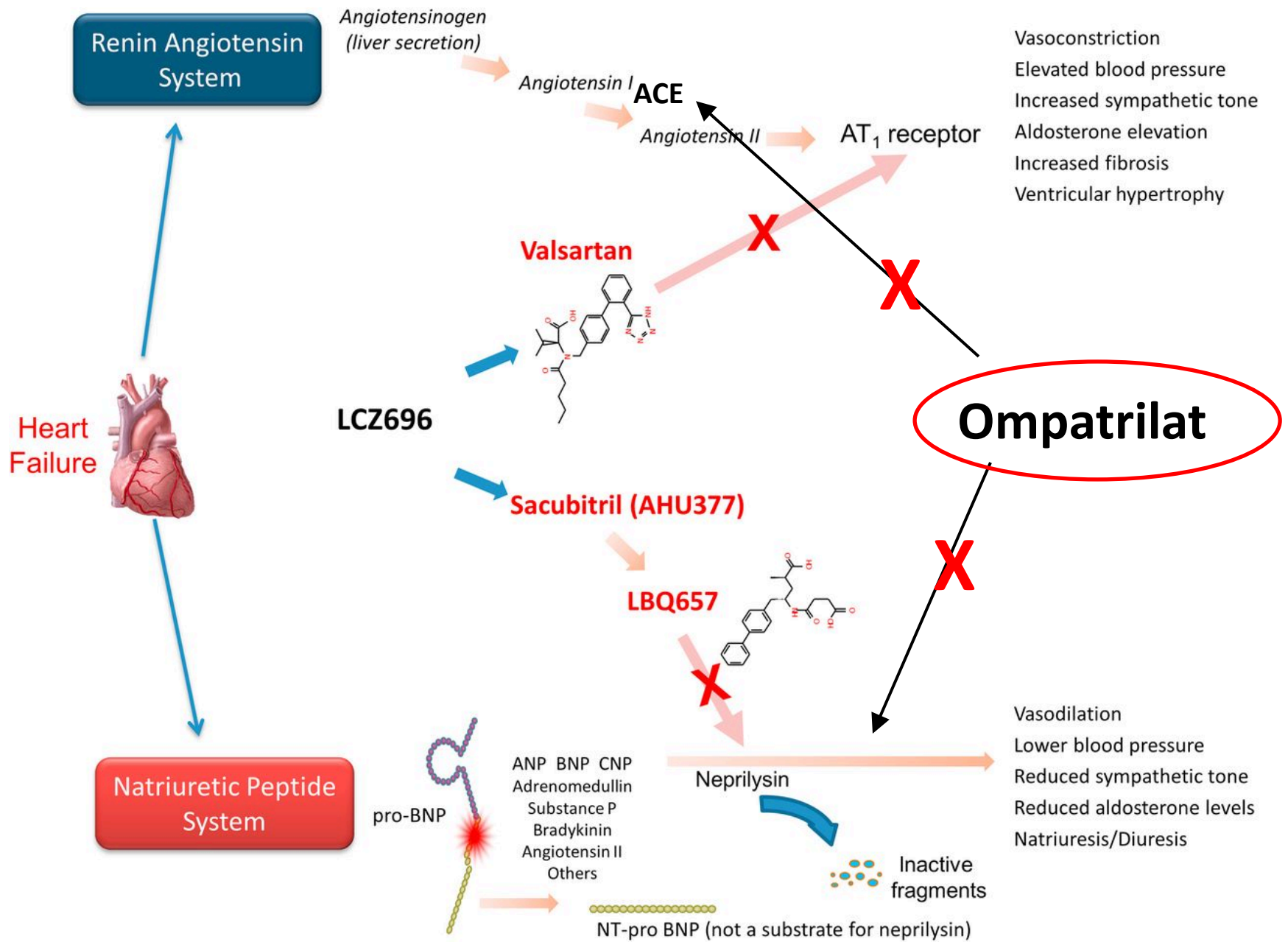


Newer Heart Failure Therapies

Target: Natriuretic peptides







Renin Angiotensin System

Angiotensinogen (liver secretion)

Angiotensin I

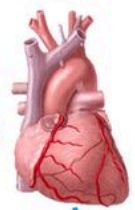
ACE

Angiotensin II

AT₁ receptor

- Vasoconstriction
- Elevated blood pressure
- Increased sympathetic tone
- Aldosterone elevation
- Increased fibrosis
- Ventricular hypertrophy

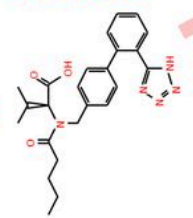
Heart Failure



Natriuretic Peptide System

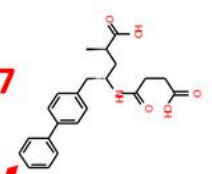
LCZ696

Valsartan

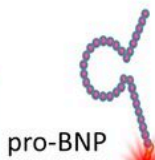


Sacubitril (AHU377)

LBQ657



Ompatrilat



- ANP
- BNP
- CNP
- Adrenomedullin
- Substance P
- Bradykinin
- Angiotensin II
- Others

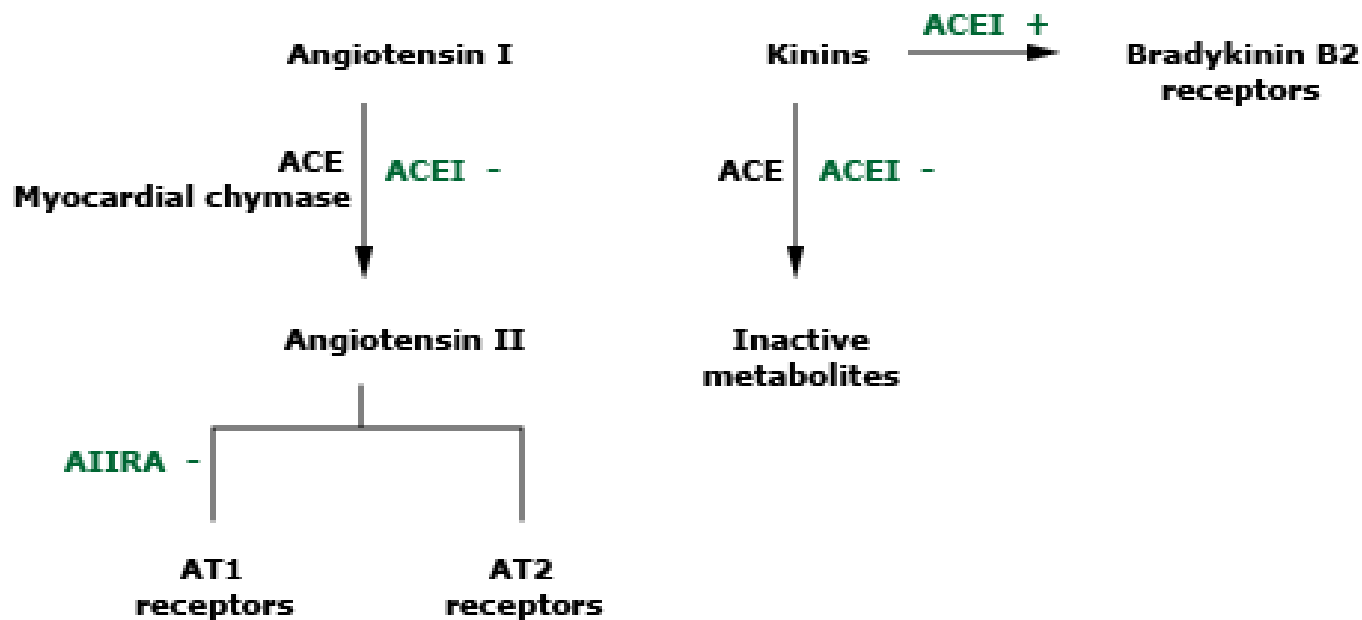
Neprilysin

Inactive fragments

NT-pro-BNP (not a substrate for neprilysin)

- Vasodilation
- Lower blood pressure
- Reduced sympathetic tone
- Reduced aldosterone levels
- Natriuresis/Diuresis

Comparison of the actions of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers



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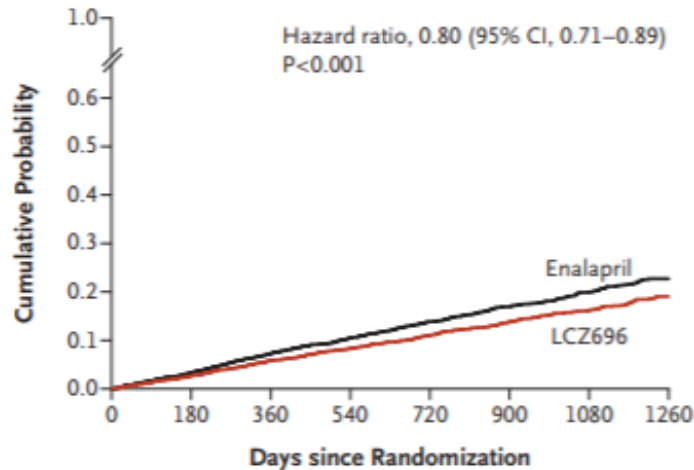
Angiotensin–Neprilysin Inhibition versus Enalapril
in Heart Failure

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*

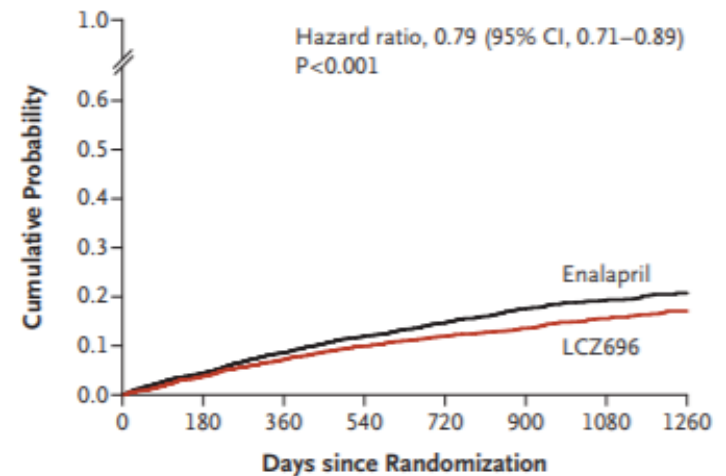
- **Over 8000 Patients**
- **Randomized to sacubitril-valsartan or Enalapril**
- **NYHA class II-IV, LVEF \leq 40%**

PARADIGM-HF: Results

B Death from Cardiovascular Causes



C Hospitalization for Heart Failure



21.8% vs 26.5% (20% RRR)
NNT 21



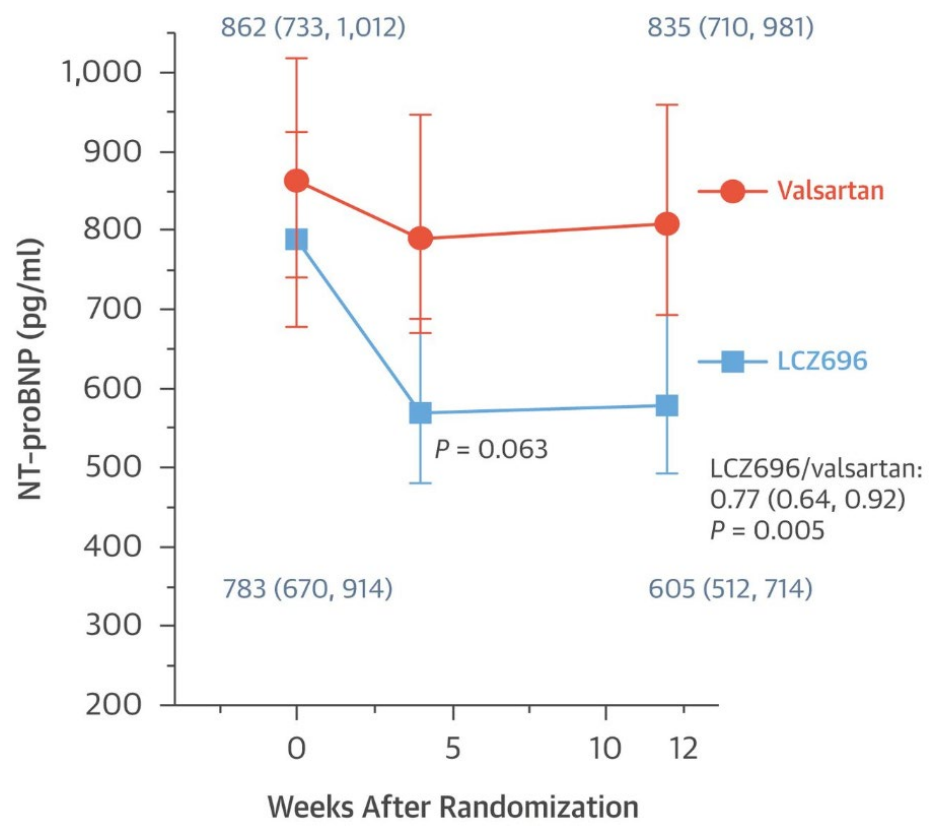
Impact on natriuretic peptide levels

- ARNI therapy leads to an elevation of B-type natriuretic peptide (BNP) levels
- N-terminal proBNP (NT-proBNP) is not degraded by neprilysin



The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fracTion (PARAMOUNT) Investigators*





Sacubitril-Valsartan: Adverse Effects

- Hypotension (18% vs 12%)
- Hyperkalemia
- Cough
- Dizziness
- Renal Failure
- Angioedema

Contraindications to Sacubitril-Valsartan

- History of angioedema
- Patients who are pregnant
- Concurrent use with ACEi/ ARB/ Aliskiren
- Use caution in patients with liver failure



Dosing: Sacubitril-Valsartan

- ARNI should be started at least 36 hours after the last dose of ACE inhibitor to minimize the risk of angioedema.
- Three doses
 - 24/26 mg twice daily
 - 45/91 mg twice daily
 - 97/103 mg twice daily



2017 ACC/AHA Focused Update of Heart Failure Guidelines

I

ARNI: B-R


In patients with chronic symptomatic HF_rEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended

Sacubitril-Valsartan in HF_pEF?

- PARAGON-HF
 - ~4800 Patients
 - NYHA Class II-IV
 - Completion date: May, 2019

Newer Heart Failure Therapies

Target: Heart rate



Heart Rate as a Target of HF Therapy:

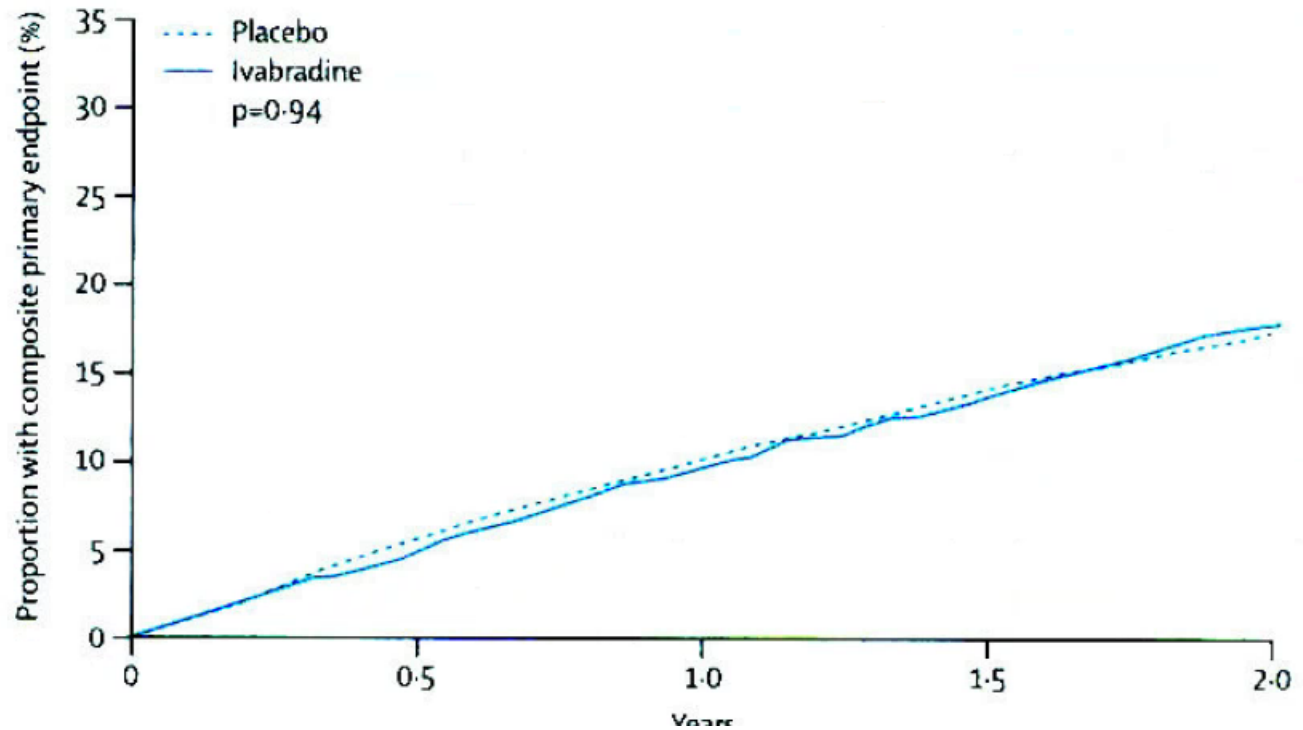
- Elevated heart rate in HFrEF:
 - Associated with worse CV outcomes
 - Reflects activation of the sympathetic nervous system
- Detrimental effects of elevated heart rate:
 - Increased myocardial oxygen consumption and shear stress
 - Reduced myocardial perfusion
- Is heart rate a determinant of prognosis or simply a marker of sympathetic activation?



Heart rate lowering drugs:

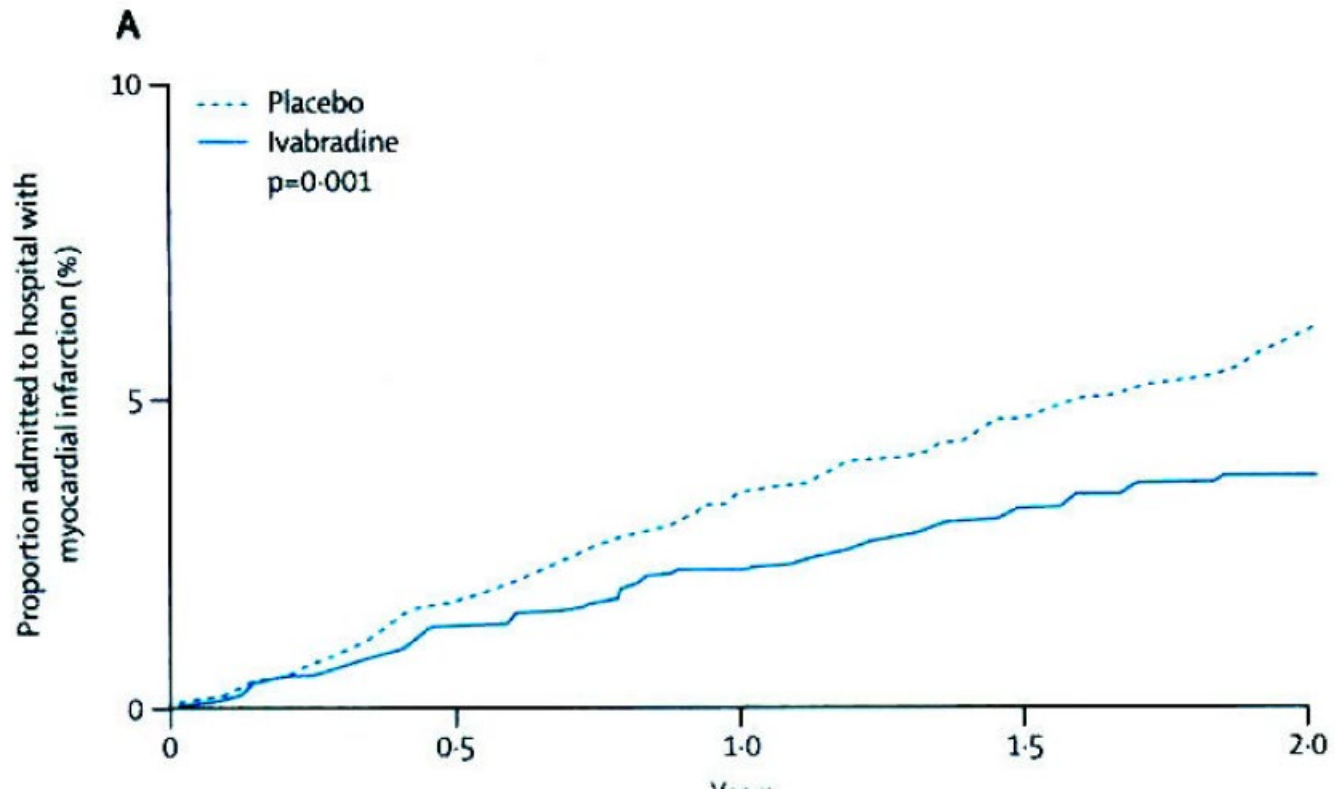
- **Beta blockers**
 - Carvedilol, metoprolol succinate, bisoprolol decrease all-cause mortality
 - Unwanted side effects: hypotension, decreased inotropy
- **Digoxin**
 - Anti-sympathetic and pro-sympathetic effects
 - Reduces risk of hospitalization in HFrEF
- **Diltiazem, verapamil**
 - Negative inotropic effects and reduce heart rate
 - No benefit in HFrEF

Ivabradine: BEAUTIFUL Trial

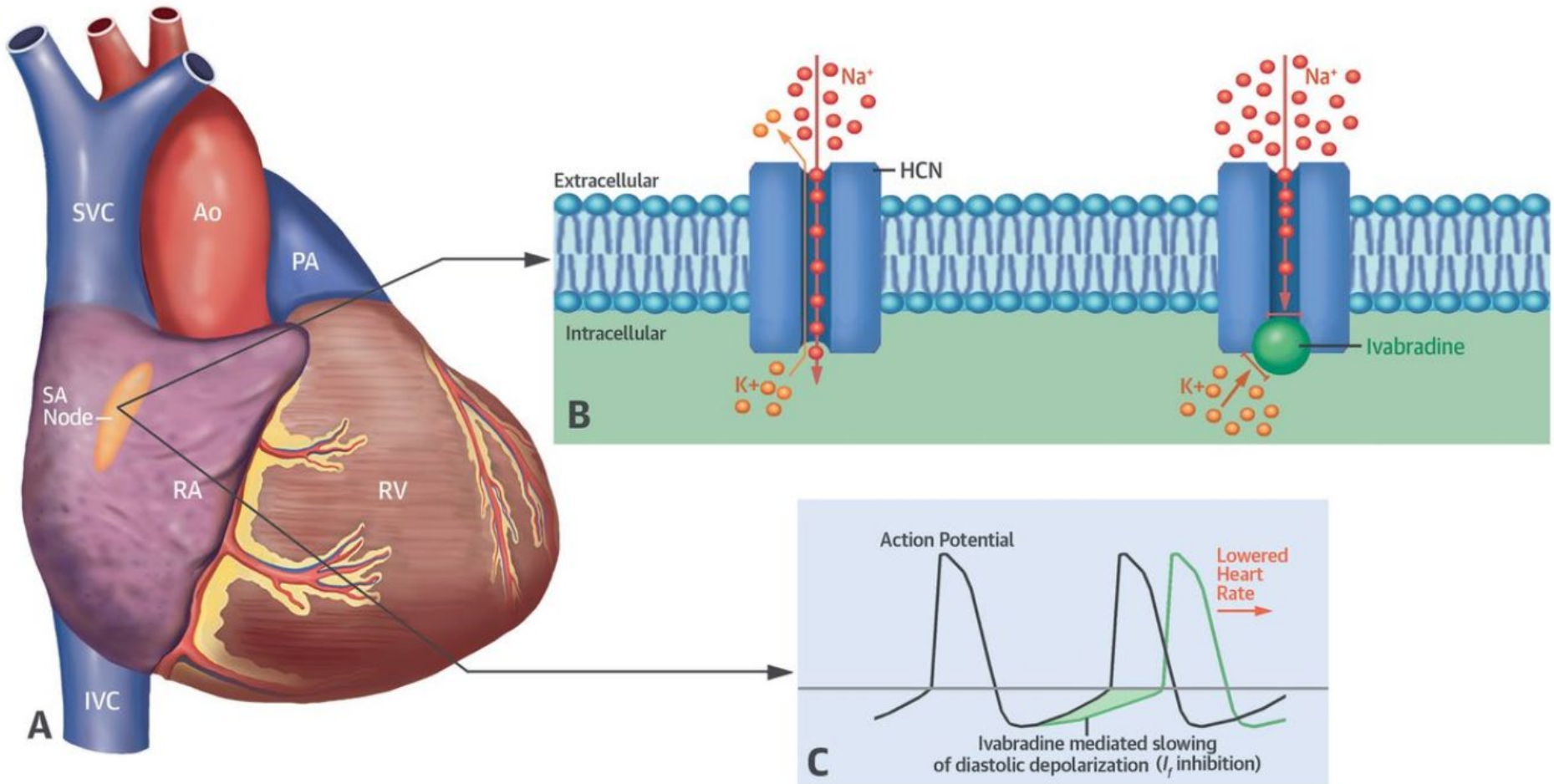


Fox K, et al. Lancet. 2008 Sep 6;372(9641):807-16

Ivabradine: BEAUTIFUL Trial



CENTRAL ILLUSTRATION: Mechanism of Action of Ivabradine



Koruth, J.S. et al. J Am Coll Cardiol. 2017;70(14):1777-84.



Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

- 6500 Patients randomized to Ivabradine vs Placebo
 - Symptomatic HF, LVEF \leq 35%
 - Sinus rhythm, HR \geq 70 bpm
- Admitted to hospital for HF within previous year
- On medical therapy for HF, including beta blocker



Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

- **Primary endpoint:** composite of cardiovascular death or hospital admission for worsening heart failure

Ivabradine: SHIFT Trial

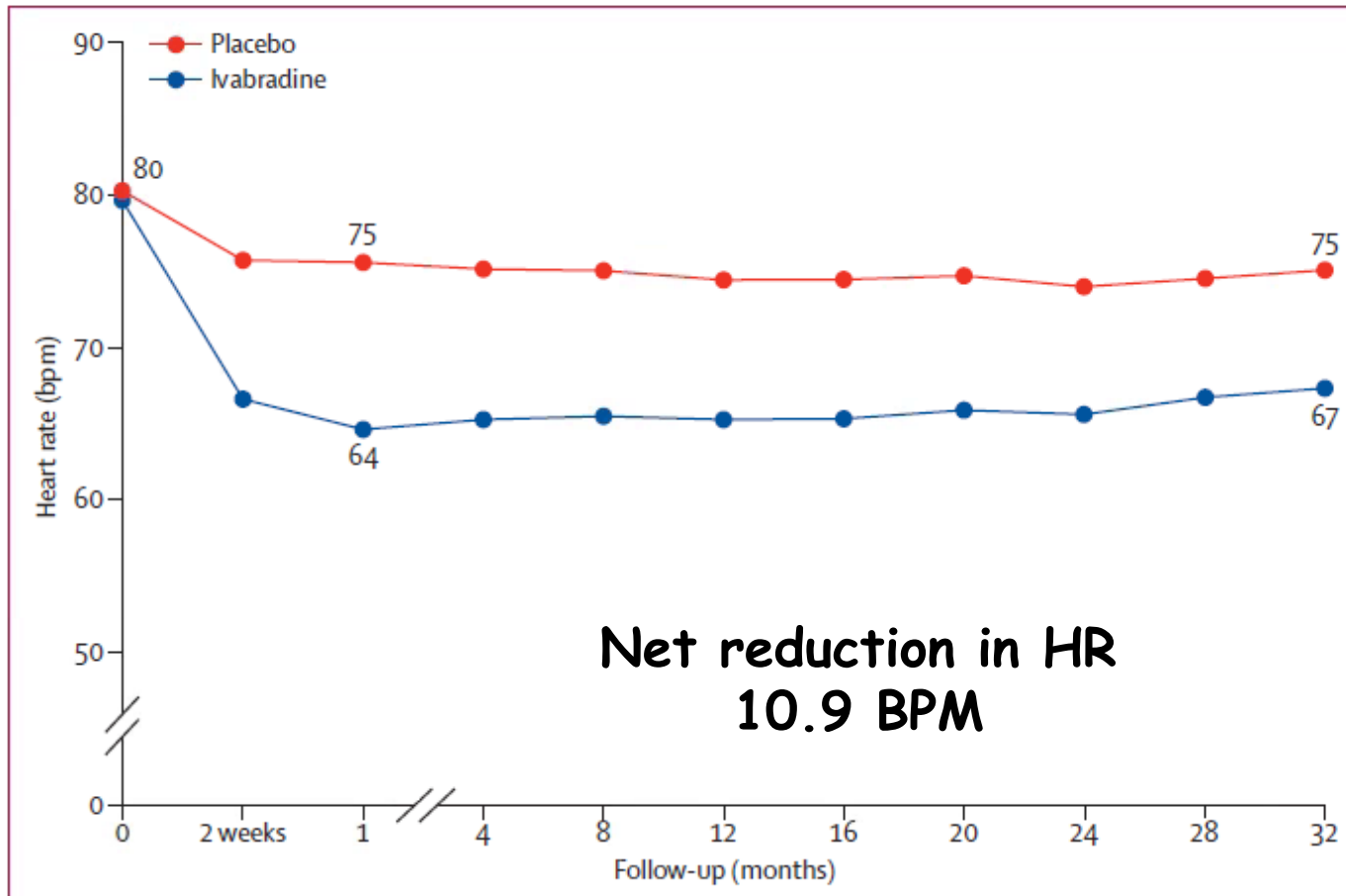
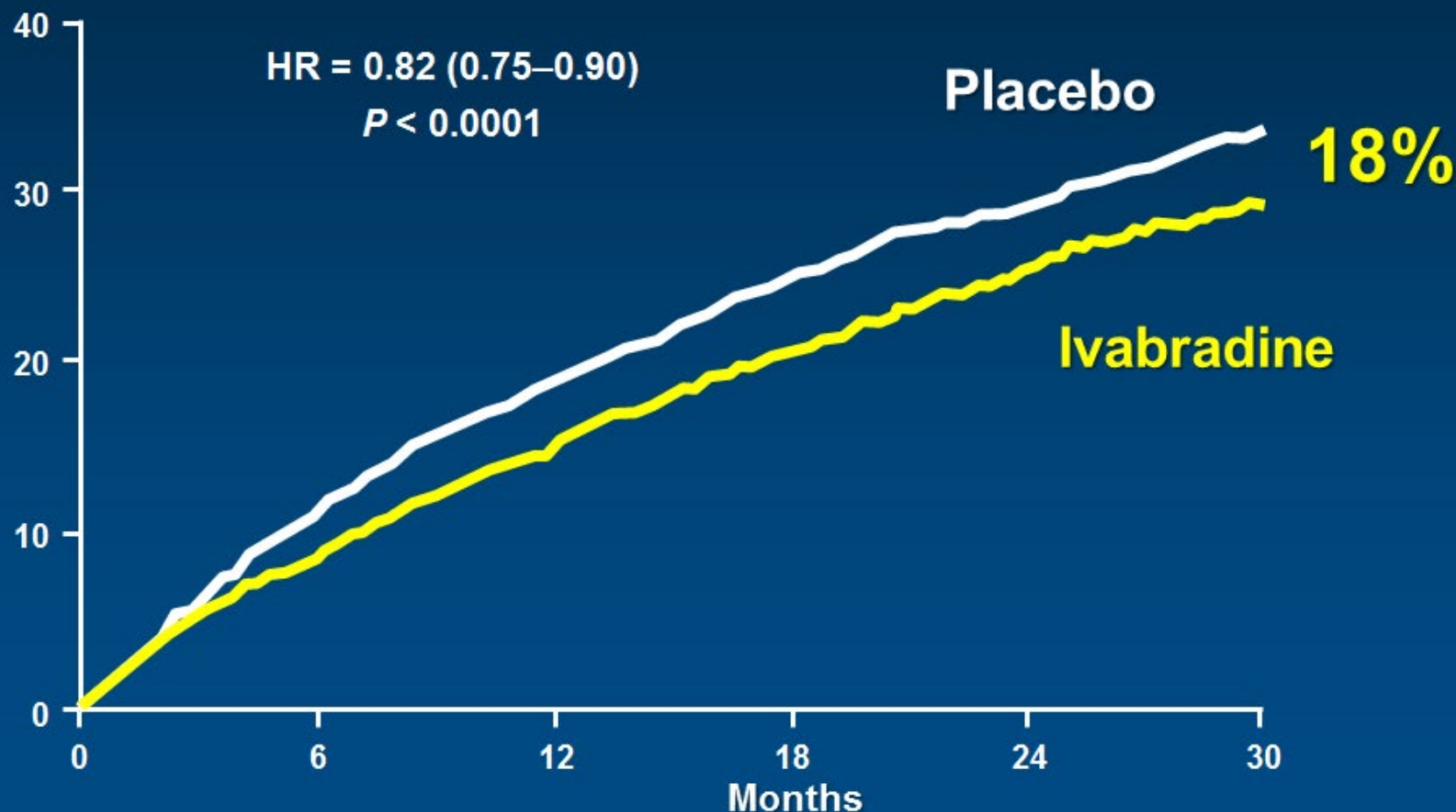


Figure 2: Mean heart rate during the study in the total study population, by allocation groups

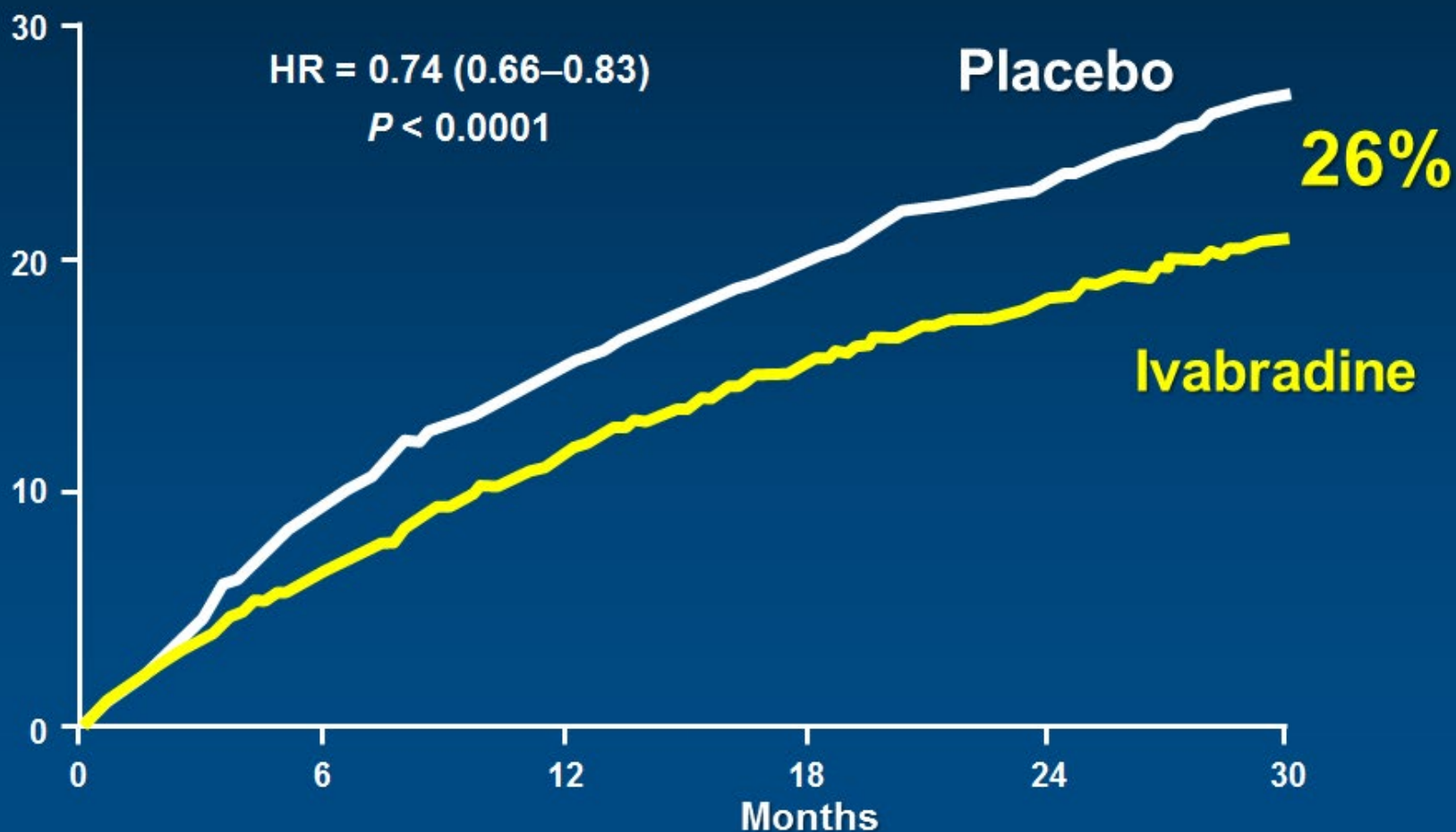


Primary composite endpoint (CV death or hospital admission for worsening HF)

Cumulative frequency (%)

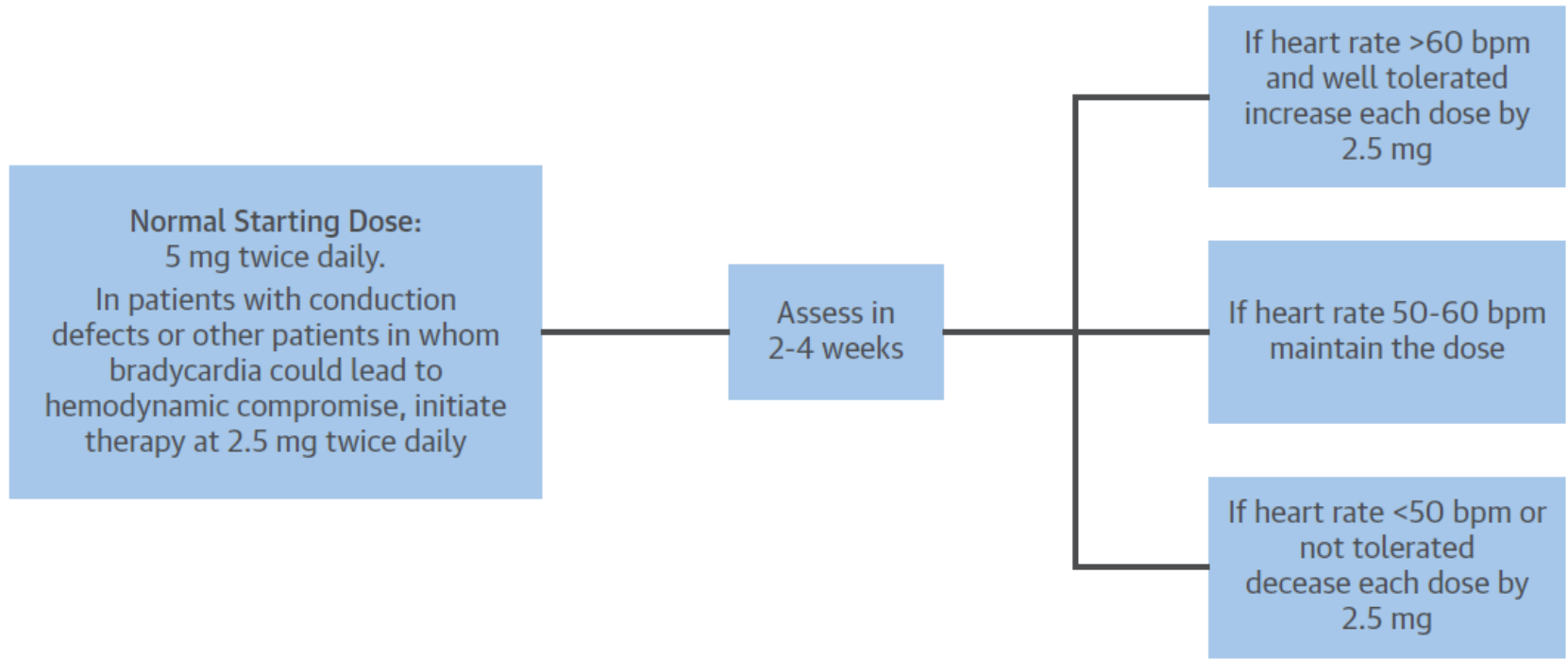


Cumulative frequency (%)



Ivabradine: FDA approval 2015

FIGURE 2 Dosing Approach for Ivabradine



Ivabradine: Adverse effects

- Symptomatic and asymptomatic bradycardia
- Visual disturbance (phosphenes)

Ivabradine - Drug interactions

TABLE 2 Drugs to Avoid With Ivabradine

Ivabradine use is avoided/contraindicated with moderate to strong CYP3A4 inhibitors, as they can result in toxicity.

Nondihydropyridine calcium antagonists	Diltiazem, verapamil
Macrolide antibiotics	e.g., clarithromycin, telithromycin
Antiretroviral drugs	Nelfinavir
Antifungal agents	e.g., ketoconazole, itraconazole
Others	Grapefruit juice, nefazodone

Ivabradine use should be avoided with inducers of CYP3A4, as they can lower efficacy

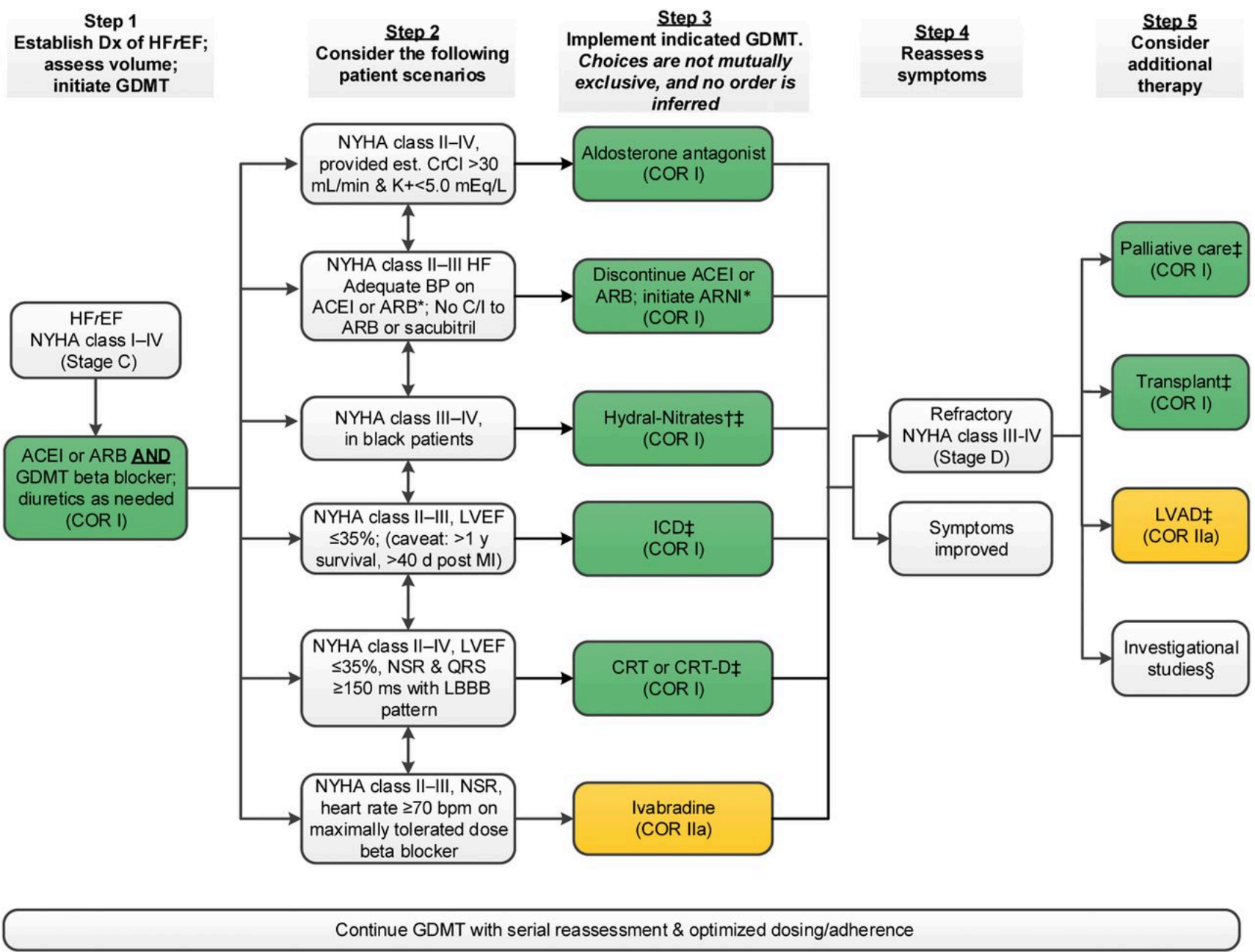
St. John's wort, rifampicin, barbiturates, and phenytoin

2017 ACC/AHA Focused Update of Heart Failure Guidelines

Ia

B-R

Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF \leq 35%) who are receiving GDEM, including a beta blocker and who are in sinus rhythm with a HR of \geq 70 bpm



Questions?

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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*

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