An Evidence-Based Review of HFrEF

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WELCOME BACK!

SAVE THE DATE!

Tuesday November 21st: A patient focused approach to the management of pharmacotherapy for geriatrics presented by Jason Chenard RPh

December: Management of Patients with Addictions presented by Josh Noyce PA

Presentation Outline

- **Learning Objectives**
- Heart Failure 101
- Clinical Drug Review Case Presentation
  - New Onset Acute Decompensated HFrEF Patient
    - ACE-I/ARB and Beta Blockers
  - Outpatient Follow-up
    - Mineralocorticoid Receptor Antagonist
      - (MRA) (eplerenone or spironolactone)
    - Angiotensin Receptor-Neprilysin Inhibitor (ARNI)
      - (Sacubitril/Valsartan combination or *Entresto ™)*
    - Additional Rate Controlling Medications
      - Ivabradine
      - Digoxin

Learning Objectives

- Review the pathophysiology of chronic HF with reduced ejection fraction (HFrEF)
- Discuss primary literature for all recommended therapies for patients with HFrEF
- Review a case based approach to transitioning stable HF patients to:
  - ACE Inhibitors and ARBs
  - Beta-Blockers
  - Mineralocorticoid Receptor Antagonists (MRAs)
  - Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)
  - Digoxin

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Heart Failure in Canada

600,000 **people are affected** by heart failure in Canada today

10 billion

spent annually on **hospital costs** associated with heart failure

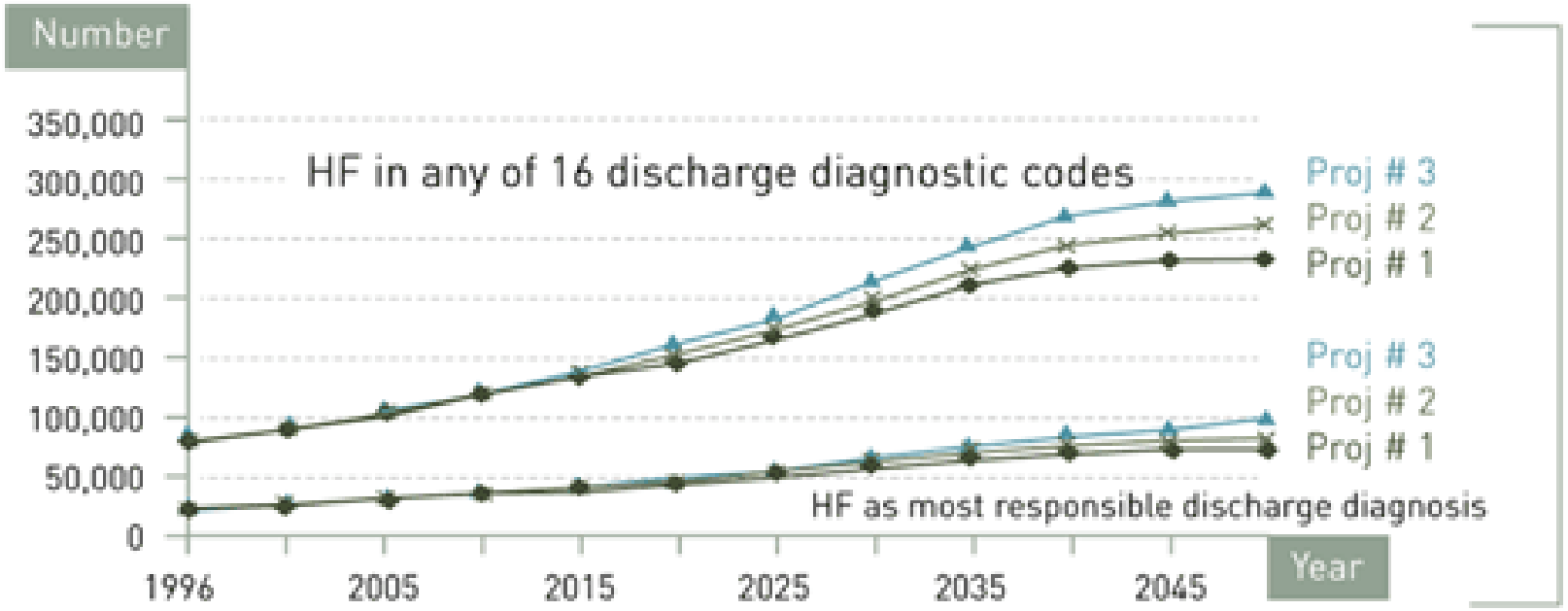
No. **1**

driver for unplanned **hospital admission**

Annual deaths from heart failure in Canada exceed the combined total of BREAST + COLON + PROSTATE CANCER

Heart Failure on the Rise

Projected number of incident hospitalizations for HF patients, using high, medium and low population growth projections in Canada 1996-2050



Johansen et al. Can J Cardiol 2003;19(4):430-5.

Heart Failure Prognosis

- The overall 5-year survival is approximately 50% for all patients with a diagnosis of HF, with mortality increasing with symptom severity.

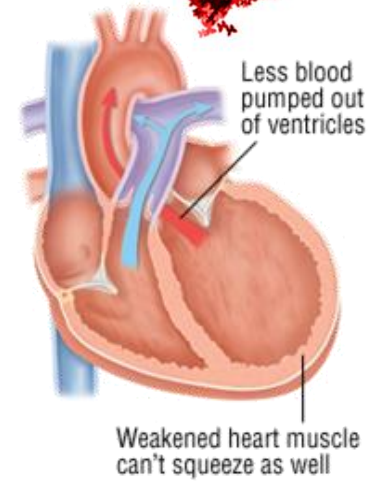
- Factors affecting the prognosis of patients with HF include:
  - Age, gender, LVEF, renal function, natriuretic peptide plasma concentrations, diabetes, metabolic syndrome, extent of underlying coronary artery disease, blood pressure (BP), HF etiology, and drug or device therapy

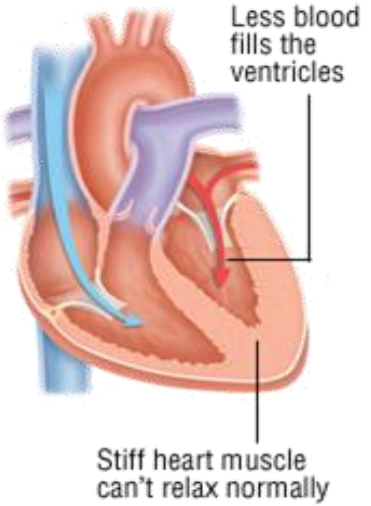
Heart Failure Definition

- **Heart failure (HF):**
  - Is a progressive clinical syndrome that can result from any abnormality in cardiac structure or function that impairs the ability of the ventricle to fill with or eject blood.
  - May be caused by an abnormality in systolic function, diastolic function, or both. It may be right-sided, left-sided, or both.
  - The final common pathway for numerous cardiac disorders including those affecting the pericardium, heart valves, and myocardium.

**Historically, this disorder was commonly referred to as congestive HF; the preferred nomenclature is now HF since a patient may have the clinical syndrome of HF without having symptoms of congestion.*

HF "*reduced*" EF vs HF "*preserved*" EF



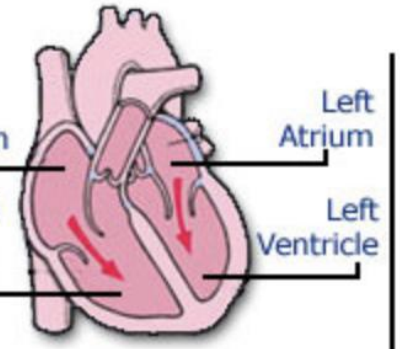


- HFrEF – (systolic) diminished ability to eject blood due to decreased ventricular contractility
  = **<u>Increased afterload</u>**
  - Enlarged ventricles fill with blood normally, but only pump out <u>≤</u>40%
  - i.e. pumping problem
  - Often due to CAD (70%), MI, faulty valves, arrhythmias

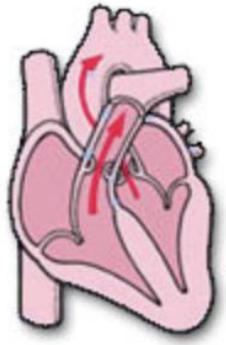
- HFpEF – (diastolic)
  = **<u>impaired ventricular relaxation</u>**
  - Restriction in ventricular filling due to increased ventricular wall stiffness still pump out ≥ 50%
  - i.e. Filling Problem
  - Often due to hypertension, stenosis

HF "*reduced*" EF vs HF "*preserved*" EF

Normal

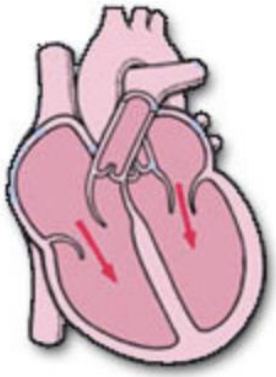


The Ventricles fill normally with blood

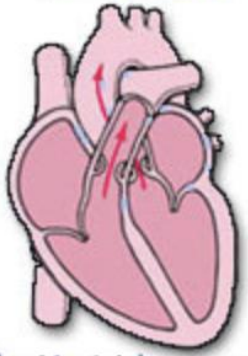


The Ventricles pump out about 60% of the blood

Systolic Dysfunction

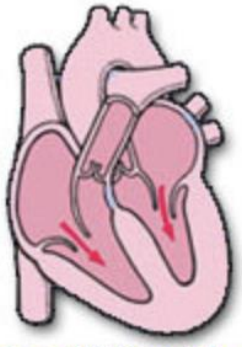


The enlarged Ventricles fill with blood

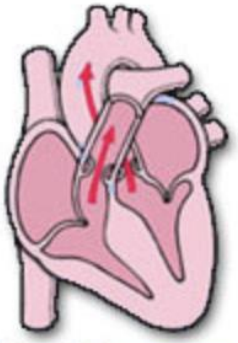


The Ventricles pump out less than 40 to 50% of the blood

Diastolic Dysfunction

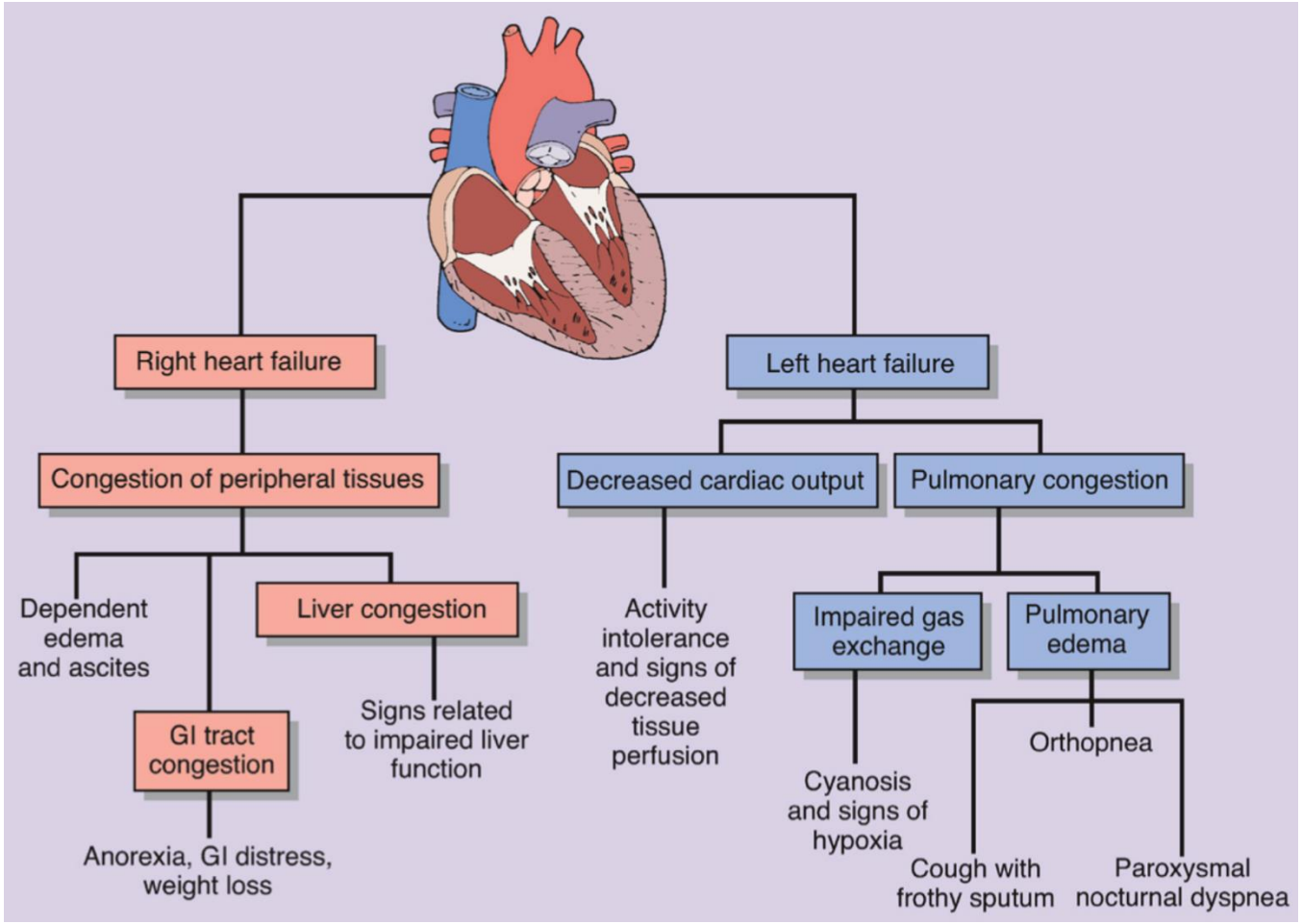


The stiff Ventricles fill with less blood than usual

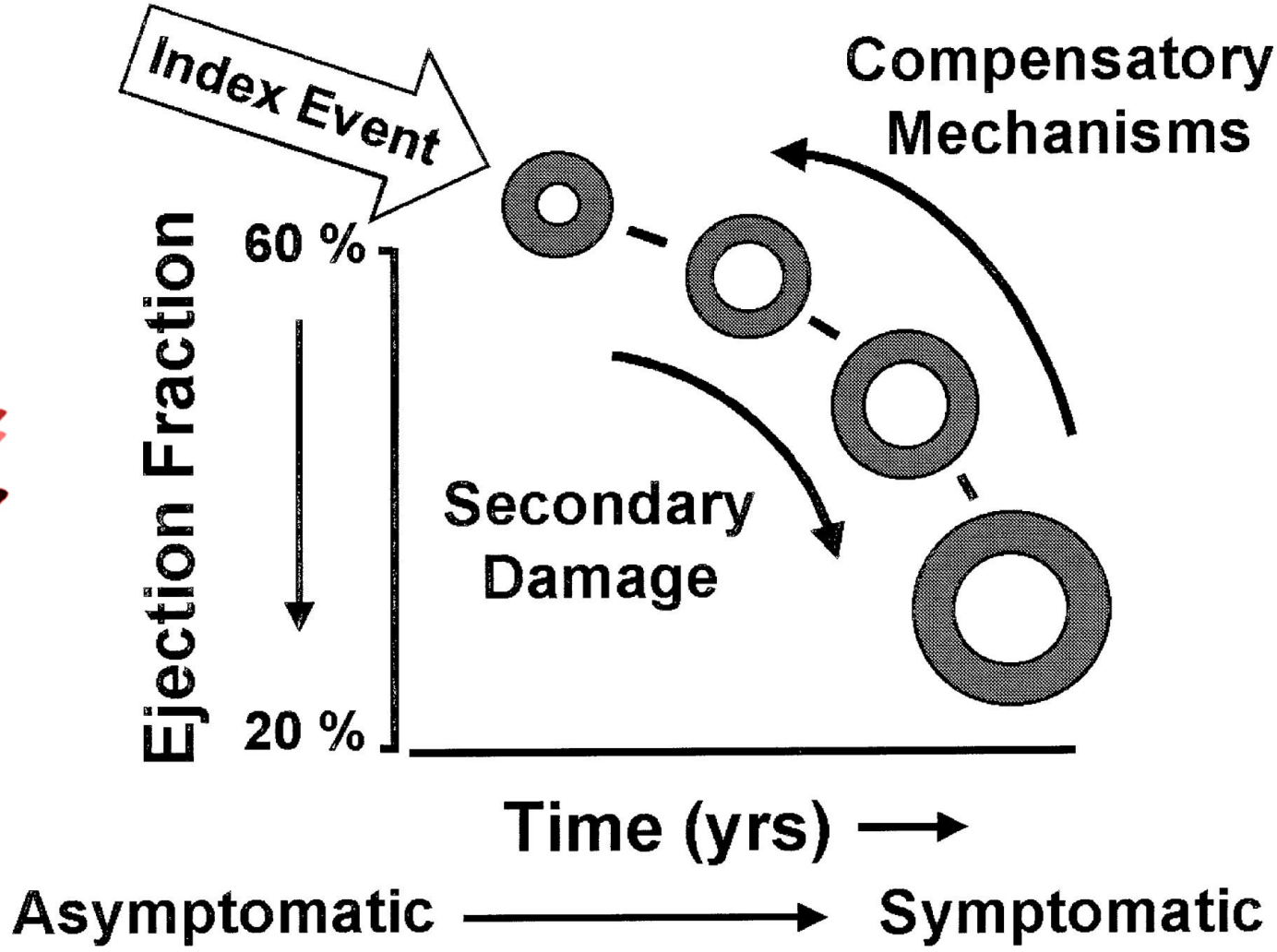


The Ventricles pump out about 60% of the blood but the amount may be lower than normal

Left Side vs Right Side HF

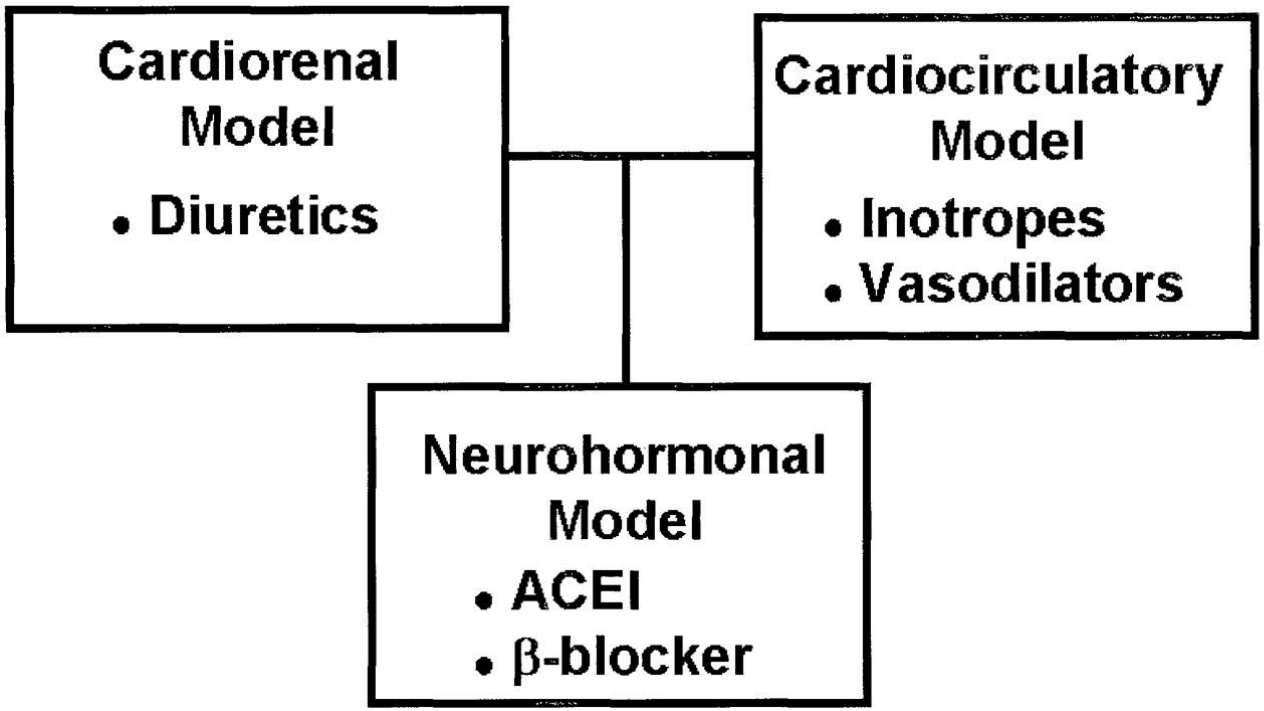


Pathogenesis of Heart Failure



American Heart Association.

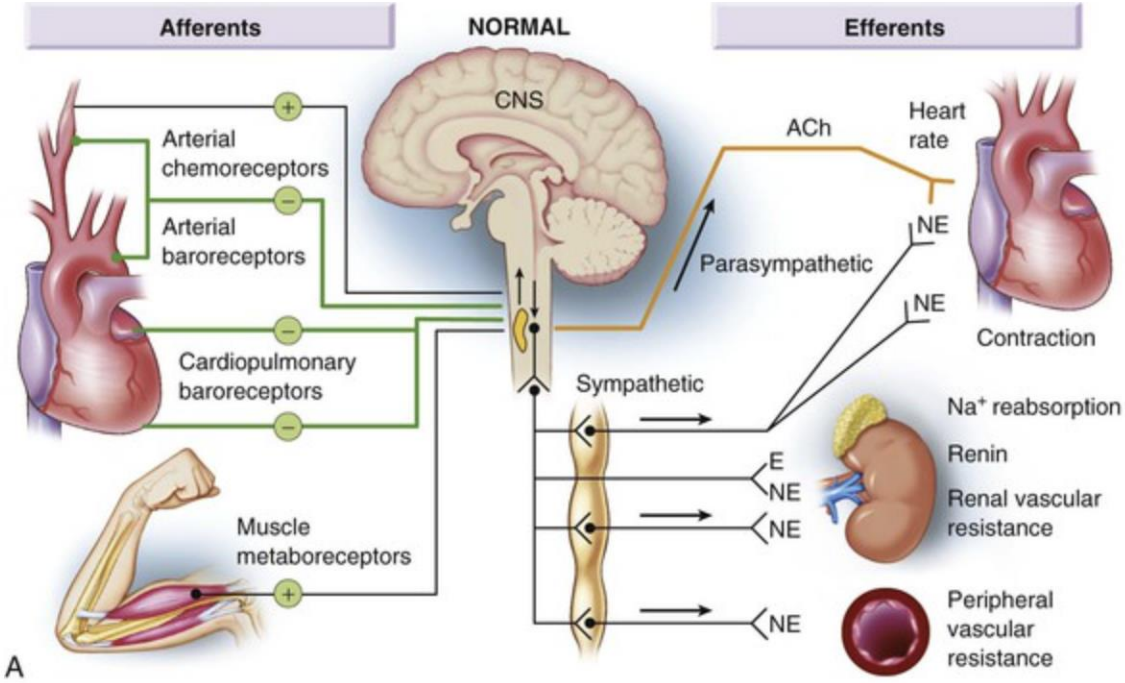
Paradigms of Heart Failure

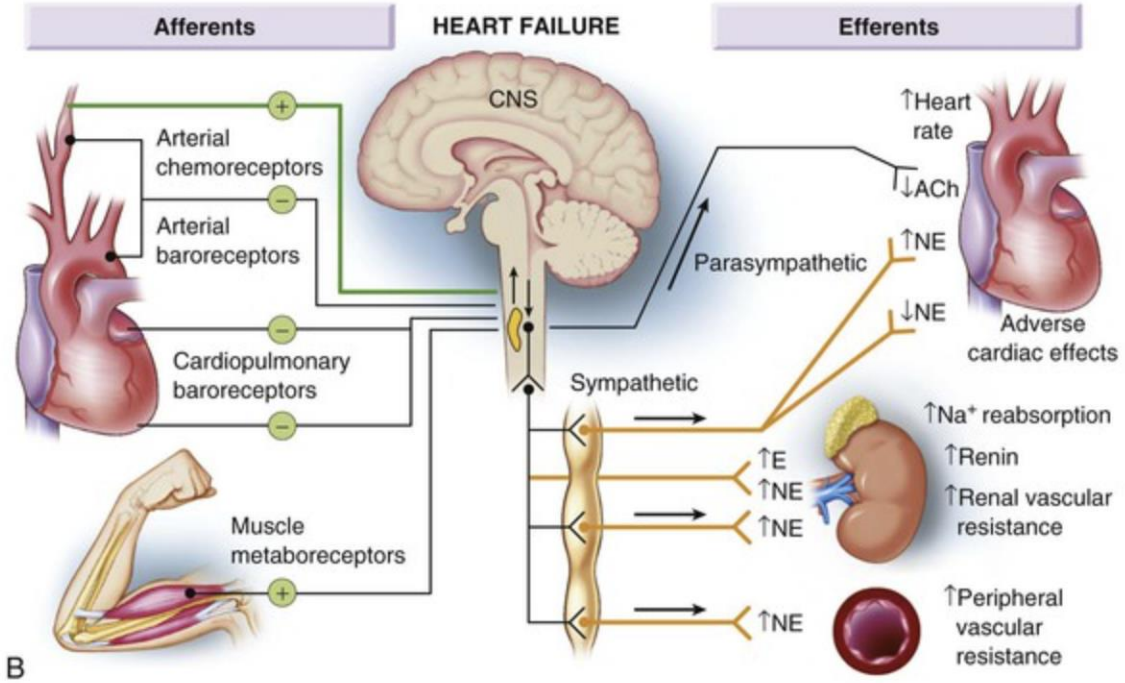


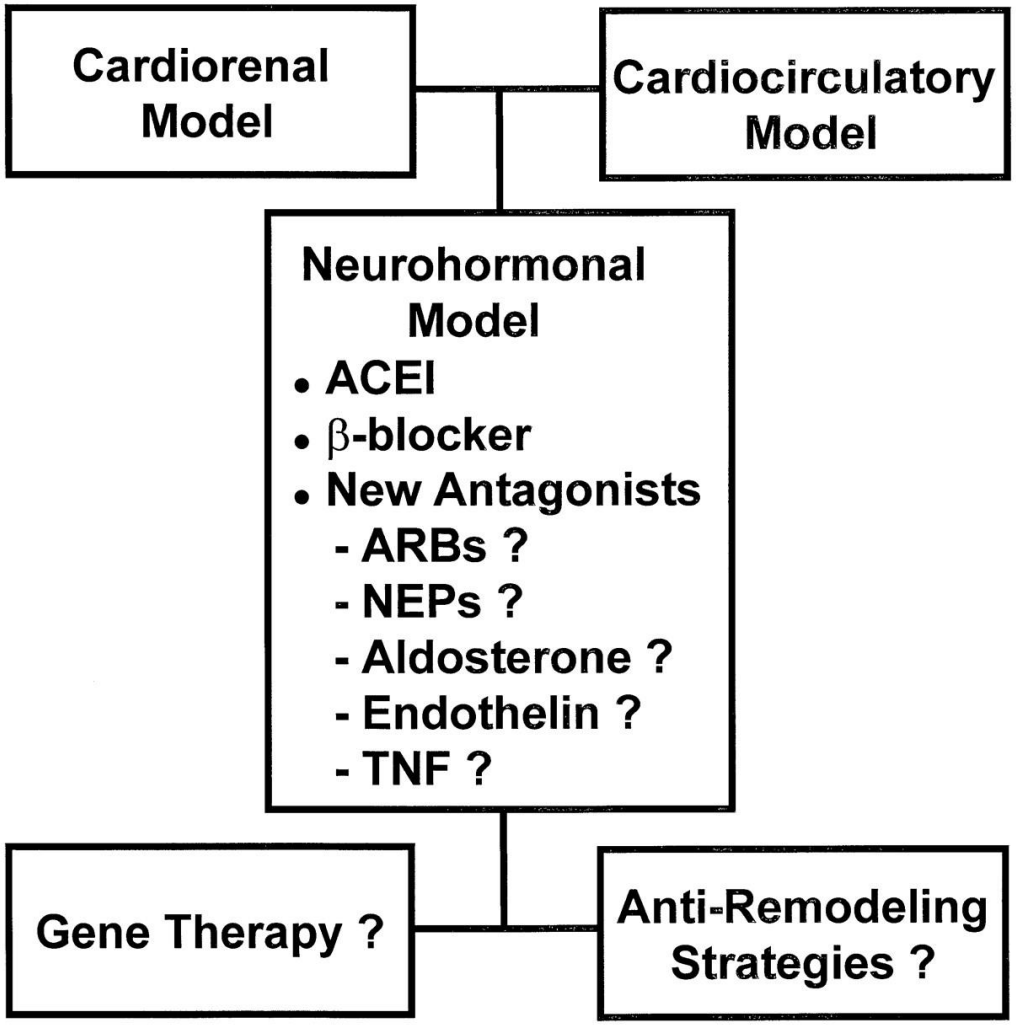
Symptom Relief

Prevention of Disease Progression

American Heart Association.


Afferents
NORMAL
Efferents
CNS
Arterial chemoreceptors
Arterial baroreceptors
Cardiopulmonary baroreceptors
Muscle metaboreceptors
ACh
Heart rate
Parasympathetic
NE
NE
Contraction
Sympathetic
Na+ reabsorption
Renin
Renal vascular resistance
E
NE
NE
NE
Peripheral vascular resistance
A


Afferents
HEART FAILURE
Efferents
CNS
Arterial chemoreceptors
Arterial baroreceptors
Cardiopulmonary baroreceptors
Muscle metaboreceptors
↑Heart rate
↓ACh
Parasympathetic
↑NE
↓NE
Adverse cardiac effects
Sympathetic
↑Na+ reabsorption
↑Renin
↑Renal vascular resistance
↑E
↑NE
↑NE
↑NE
↑Peripheral vascular resistance
B



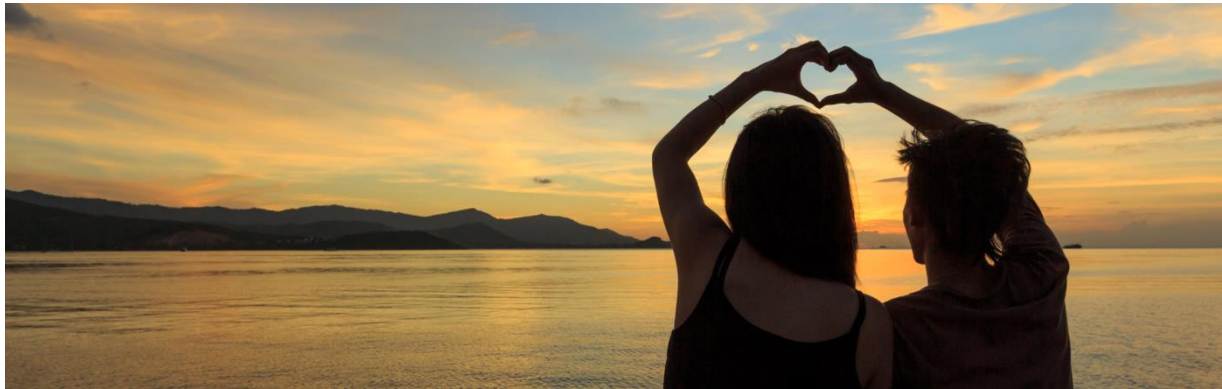
Symptom Relief

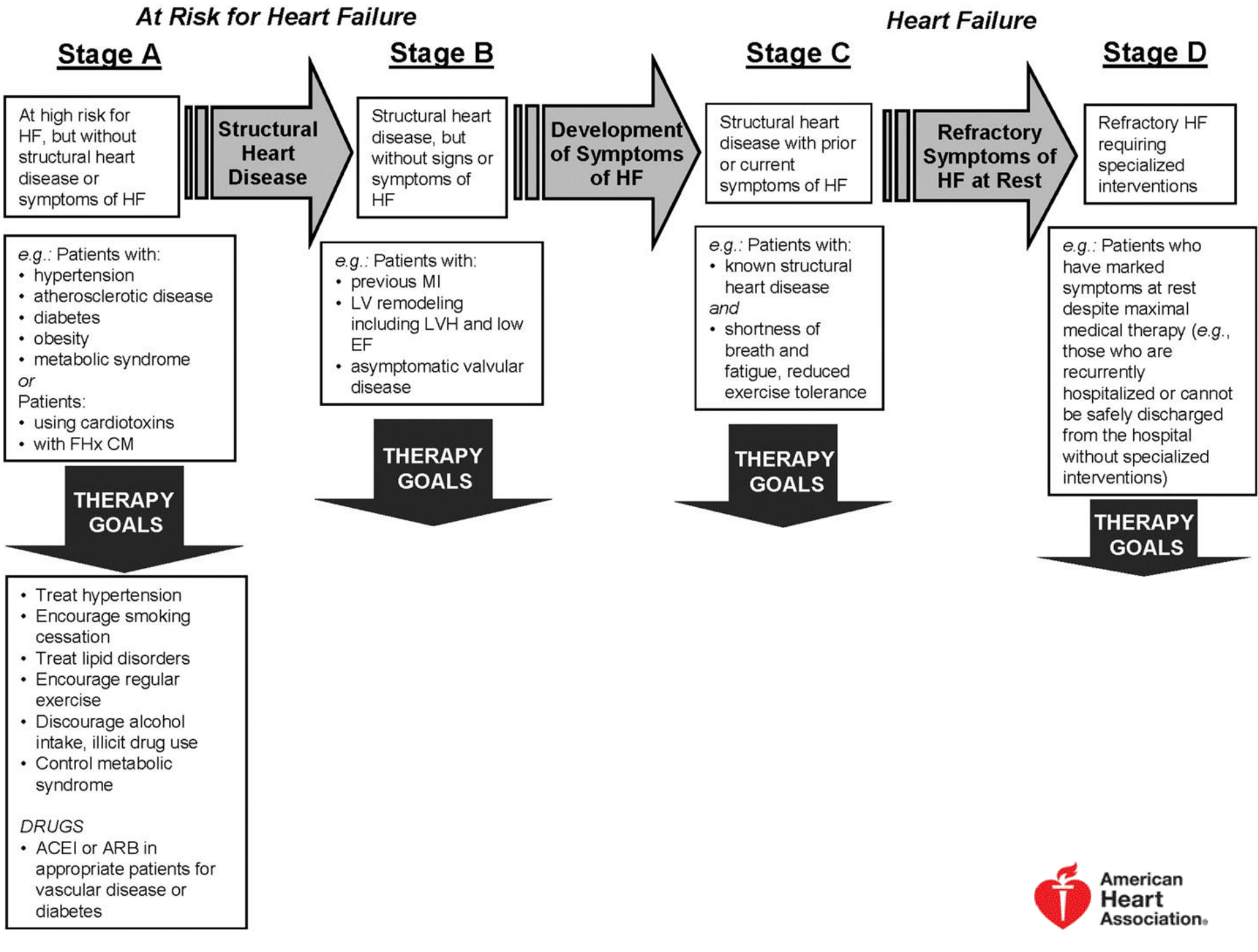
Prevention of Disease Progression

Reversal of Heart Failure Phenotype ?

Goals of Therapy

- Improve the patient's quality of life
- Relieve or reduce symptoms
- Prevent or minimize hospitalizations
- Slow progression of the disease
- Prolong survival




At Risk for Heart Failure
Heart Failure
Stage A
Stage B
Stage C
Stage D
At high risk for HF, but without structural heart disease or symptoms of HF
Structural Heart Disease
Structural heart disease, but without signs or symptoms of HF
Development of Symptoms of HF
Structural heart disease with prior or current symptoms of HF
Refractory Symptoms of HF at Rest
Refractory HF requiring specialized interventions
e.g.: Patients with:
• hypertension
• atherosclerotic disease
• diabetes
• obesity
• metabolic syndrome
or
Patients:
• using cardiotoxins
• with FHx CM
e.g.: Patients with:
• previous MI
• LV remodeling including LVH and low EF
• asymptomatic valvular disease
e.g.: Patients with:
• known structural heart disease
and
• shortness of breath and fatigue, reduced exercise tolerance
e.g.: Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)
THERAPY GOALS
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THERAPY GOALS
• Treat hypertension
• Encourage smoking cessation
• Treat lipid disorders
• Encourage regular exercise
• Discourage alcohol intake, illicit drug use
• Control metabolic syndrome
DRUGS
• ACEI or ARB in appropriate patients for vascular disease or diabetes
American Heart Association.

New York Heart Association (NYHA)

Functional Classification

Class	:	Patient Symptoms
I		No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.
II		Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III		Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV		Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

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Patient JD Presents in the GPs office

JD presented to his GPs office with symptoms of SOB

- 47 year old male
- Referred from community
- No hx of MI, father deceased at 53 from MI
- Never smoked, occasional alcohol, no drugs
- SOB x 3 months that started with cough
- Improved over a couple of months and then returned
  - GP started him on furosemide orally

Patient JD Presents to HSN's ED

JD Admitted to HSN with Progressive Fatigue/Dyspnea

- Now→NYHA II-III
- Fatigued
- Poor appetite→ 83 kg
- 2 pillow orthopnea, no PND, no S3 or S4, no JVP, no peripheral edema
- VS → 133/88 sitting, 125/86 standing, HR 70 (normal sinus rhythm), RR 16, SATS 99% R/A

Patient JD Presents to HSN's ED

- **Labs**:
  - WBC 8.0
  - HgB 169
  - Hct 0.054
  - Plts 263

- **Chemistry**:
  - Na+ 140
  - K+ 3.7
  - Cl 103
  - Urea 5.8,
  - SrCr 108, eGFR >60
  - NT Pro BNP – 5111
  - Iron normal

- **Investigations**:
  - Echo – EF – 22%
  - Grade IV LV
  - RVSP 53 (moderate TR, hypocontractile RV, LA dilated, LVH)
  - Chest X rays: bilateral haziness
  - Auscultation: pulmonary rales/crackles

- **Medications**:
  - Furosemide 40 mg IV once
  - (HOLD) Furosemide 40 mg PO BID
  - Escitalopram 5 mg po daily
  - Acetaminophen 500 po QID PRN

Patient JD Presents to HSN's ED

Day 2 of Admission:

- Patient is approaching being clinically "euvolemic"
  - Crackles resolved, chest x-ray clear
- Orthopnea improved to 1 pillow
- Poor appetite improved
- Fatigue and dyspnea on exertion marginally improved
- Still no paroxysmal nocturnal dyspnea, no S3 or S4, no JVP, no peripheral edema
- VS →*128/83 sitting, 117/89 standing*, NSR 70 , RR 16, SATS 99% R/A

Patient JD Presents to HSN's ED

Day 3, Discharge Planning Started….

- Only new medication was furosemide IV instead of PO, which has helped us achieve "euvolemia"
- What is the pharmacotherapy approach and goals to Chronic management of stable HFrEF?
  - Reduce Mortality
  - Prevent Hospitalization
  - Improved Symptoms
  - Improve Exercise Capacity

Medications:

- Furosemide 40 mg IV BID
- (HOLD) Furosemide 40 mg PO BID
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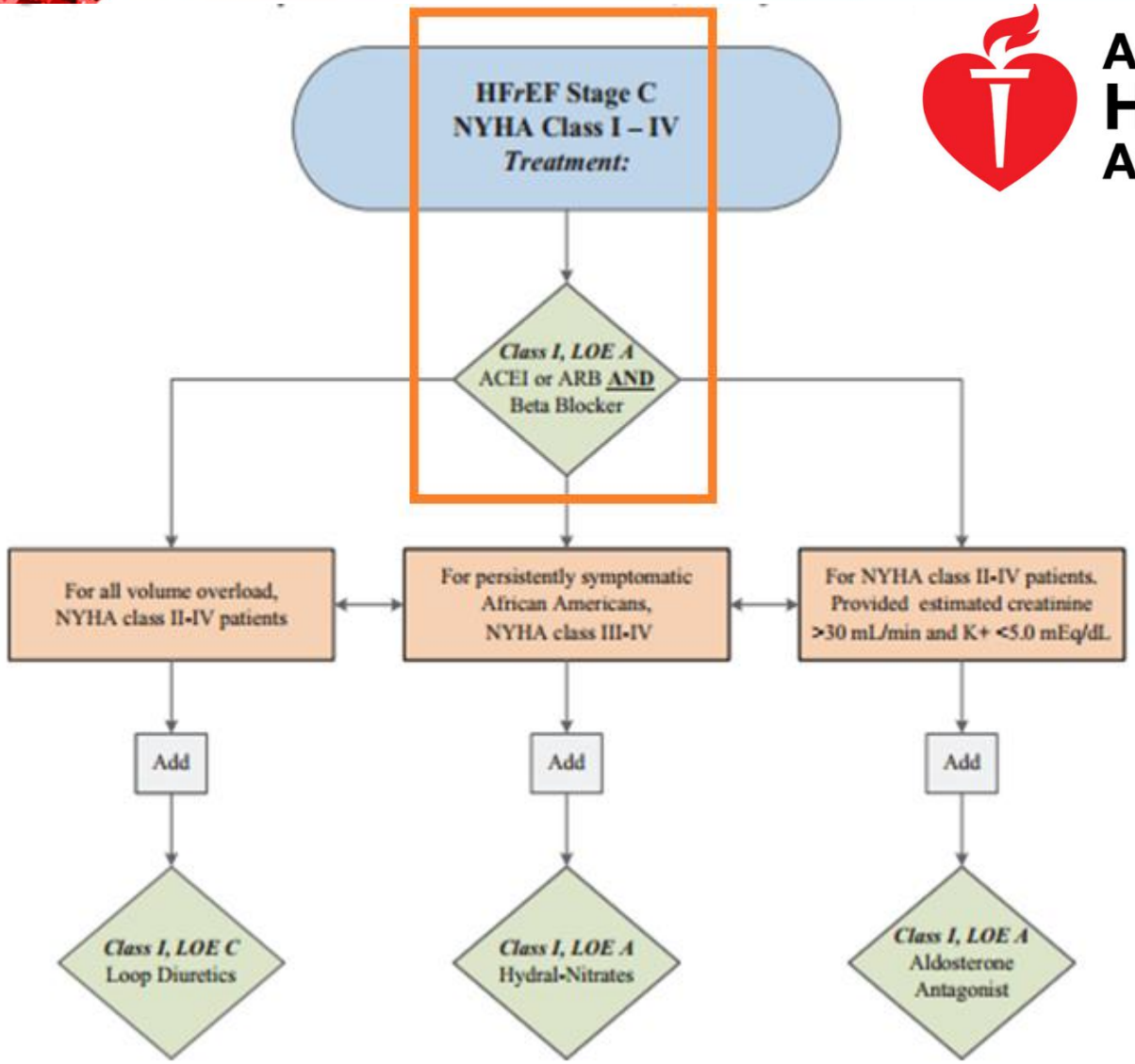
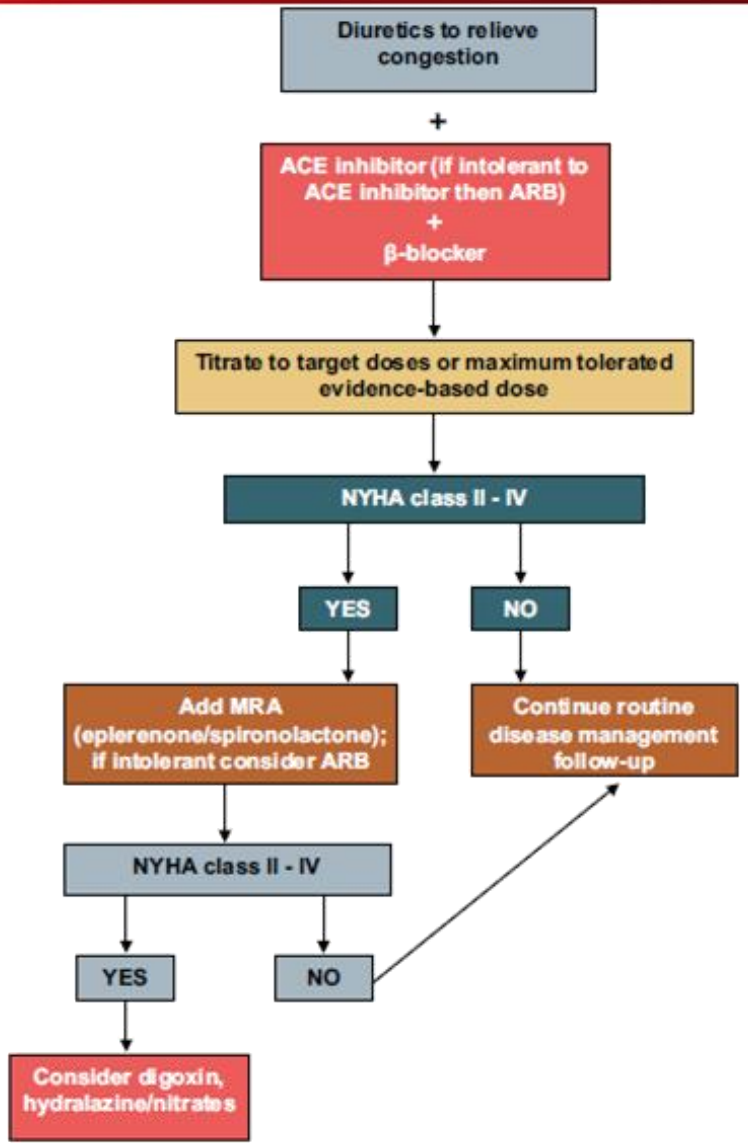
2013 American Heart Association

American Heart Association®



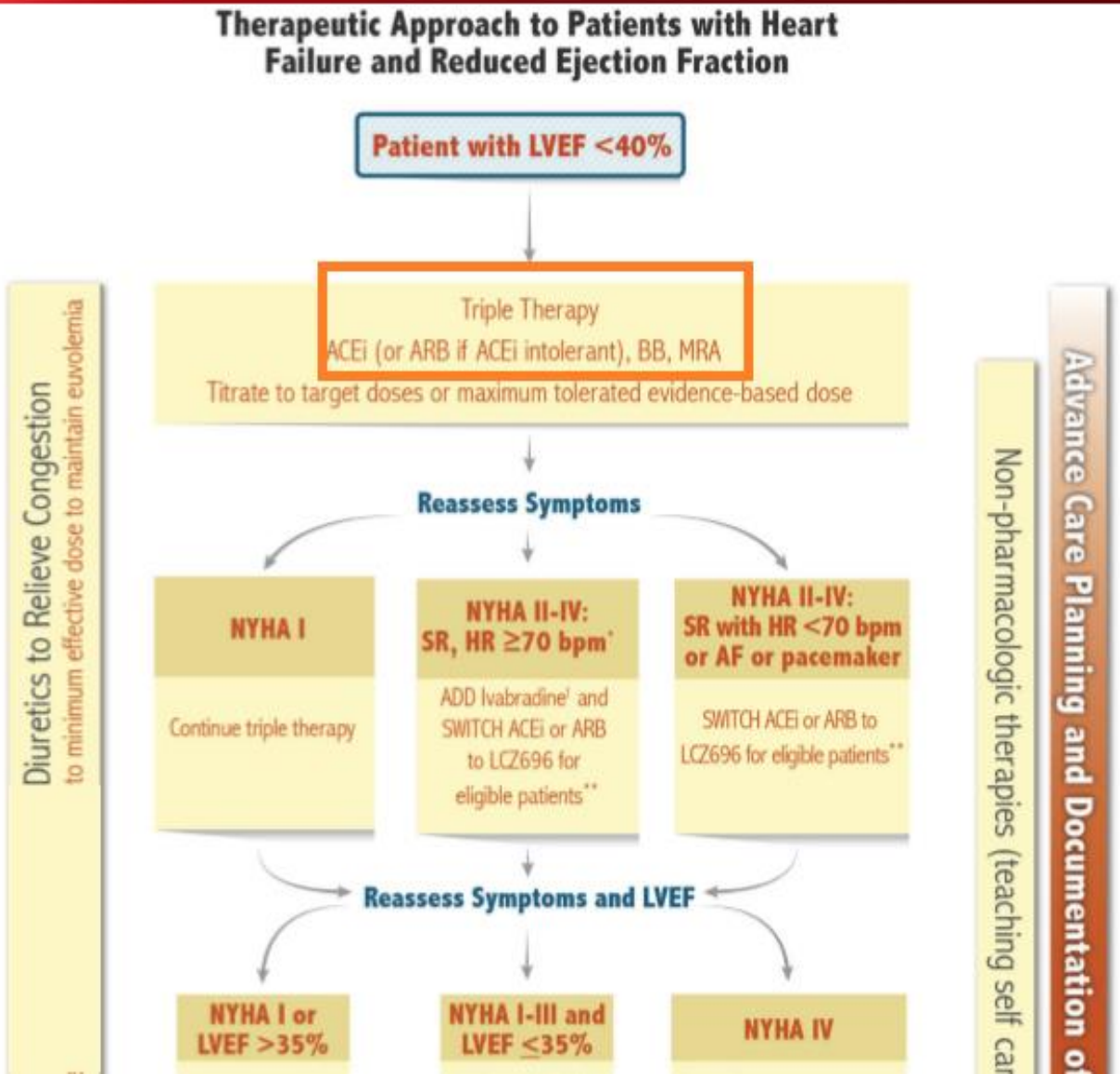
2012 Canadian Cardiovascular Society

Canadian Cardiovascular Society



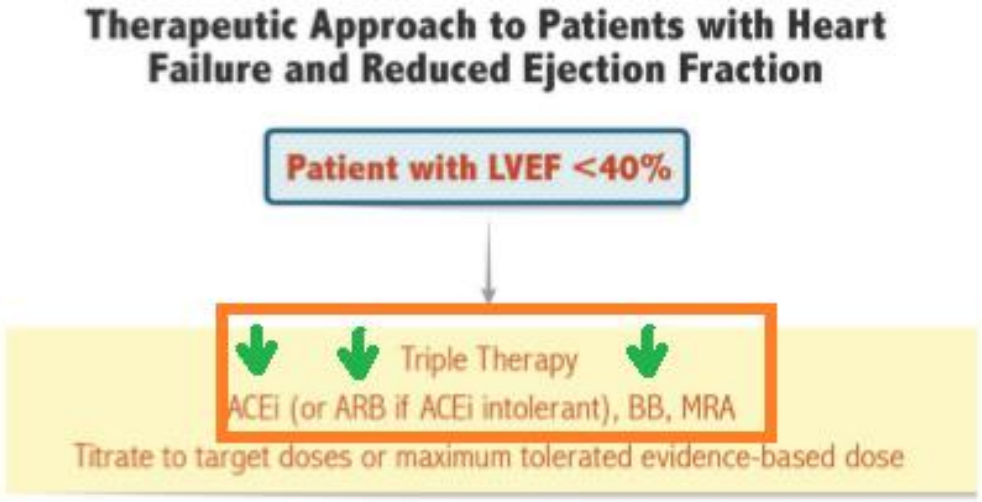
2016 Canadian Cardiovascular Society

Canadian Cardiovascular Society



Start an ACE-I and Beta Blocker

Canadian Cardiovascular Society



CCS Guidelines Recommend:

- Triple therapy should take 4-6 months to initiate and titrate
- Titration of ONLY ACE-I and Beta-Blocker (BB) should take 4 months

Which to Start First: ACE-I or BB?

- Contraindications or short terms risks are the key factors in this decision

Comparison of Renin-Angiotensin System Inhibitors (ACE-I and ARBs) in HFrEF

- CCS recommends, **indicated** in all patients with HFrEF, ***unless*** there is a short-term safety risk
  - **Contraindicated if….**
    - Bilateral renal artery stenosis
    - Pregnancy
    - History of angioedema or past hypersensitivity to ACE-I or ARB (ACE-I have cross sensitivity for ACE only..)
- **Adverse Effects:** renal insufficiency/srcr elevation, cough, hypotension, hyperkalemia
- ***Use Caution in patients with…***
  - CrCl < 30 mL/min
  - Elevated levels of serum potassium (> 5.0 mEq)
  - Low blood pressure (< SBP 90-100mmhg) and/or symptomatic hypotension

Comparison of Renin-Angiotensin System Inhibitors (ACE-I and ARBs) in HFrEF

Canadian Cardiovascular Society

American Heart Association

- ACE-I **VS** ARB in HFrEF?
  - 2016 Canadian guidelines ACE-I > ARB
    - Meta-analysis of ACE-I showed substantial reductions in mortality, HF hospitalization, and MI…(CHEP 2016)
  - 2016 AHA guidelines ACE-I = ARB
  - Differences in RCT endpoints and outcomes

- Safety: ARB > ACE-I
  - Cough or angioedema relative intolerance
  - 1 to 20% of ACE-I patients experience, an "ACE Cough"

Comparison of Renin-Angiotensin System Inhibitors (ACE-I and ARBs) in HFrEF

Agent	Outcomes	Statistically Significant
Enalapril	**CONSENSUS and SOLVED trial**: (Enalapril vs. Placebo) **Limitation:** Duration?	**All-Cause Mortality** ***NNT* 6 over 6 months**
Lisinopril	**ATLAS Trial:** (High dose Lisinopril vs. Low dose) **Limitation:** no placebo control	**Composite Death + Hospitalization** ***NNT* 8.3 over 4 years**
Ramipril	**AIREX Trial**: (Ramipril vs. Placebo) **Limitations:** patient population acute MI early HF	**All-Cause Mortality** ***NNT* 8.7 over 4.9 years**
Trandolapril	**TRACE Trial:** (Trandolapril vs. Placebo) **Limitation:** patient population acute MI early HF	**All-Cause Mortality** ***NNT* 13.4 over 1 year**
Captopril	**SAVED Trial:** (Captopril vs. Placebo) **Limitations**: ?	**All-Cause Mortality** ***NNT* 20 over 3.5 years**

Comparison of Renin-Angiotensin System Inhibitors (ACE-I and ARBs) in HFrEF

Agent	Outcomes	Statistically Significant
Candesartan	**CHARM-Alternative trail** (Candesartan vs. Placebo) **Limitations:** ACE Intolerant, βB patients only 25%)	**CV Death or Hospitalization** ***NNT* 14.2 over 2.75 years**
Losartan	**HEAL trial** (High dose losartan vs. Low dose) **Limitations:** Only ACEI intolerant, no placebo	**Composite Death + Hospitalization** ***NNT* 33 over 4.7 years**
Valsartan	**ValHeFT:** (Valsartan vs. Placebo) **Limitations:** Benefit mostly from HF Admissions	**Composite Death + Hospitalization** ***NNT* 8.7 over 4.9 years**
Fosinopril	**FEST Trial** (Fosinopril vs. Placebo) **Limitations**: exercise was only significant endpoint	**Exercise Tolerance** **Max Bike time by 15 sec**
Perindopril	**PEP-CHF Trial:** (Perindopril vs. Placebo) **Limitation:** no statistical significant benefit	**Composite Death + Hospitalization** **NS**
Quinapril	**QUIET Trial** (Quinapril versus placebo) **Limitation:** pEF only and NS for composite endpoint	**Composite** **Ischemic Death or Hospitalization** **NS**

2013 AHA Evidence Based Dosing

Table 15. Drugs Commonly Used for Stage C HF*r*EF

Drug	Mean Doses Achieved in Clinical Trials	Initial Daily Dose(s)
ACE inhibitors		
Captopril	122.7 mg/d[422]	6.25 mg 3 times
Enalapril	16.6 mg/d[413]	2.5 mg twice
Fosinopril	N/A	5 to 10 mg once
Lisinopril	32.5 to 35.0 mg/d[445]	2.5 to 5 mg once
Perindopril	N/A	2 mg once
Quinapril	N/A	5 mg twice
Ramipril	N/A	1.25 to 2.5 mg once
Trandolapril	N/A	1 mg once
ARBs		
Candesartan	24 mg/d[420]	4 to 8 mg once
Losartan	129 mg/d[421]	25 to 50 mg once
Valsartan	254 mg/d[108]	20 to 40 mg twice

American Heart Association®

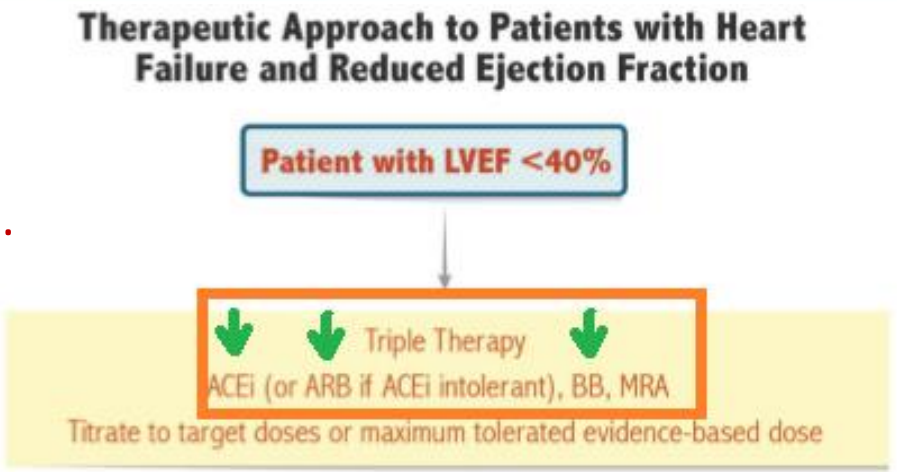
Plan and Follow-up for JD

Plan / Follow-up:

- Enalapril was titrated to 5 mg po bid before discharge on day 7
  - JD had one hypotensive event during initiation although was normotensive (117/80 mmHg)

- BP, renal function, serum potassium, and HR were normal at discharge and should be assessed within 1-2 weeks of initiation of therapy.

Follow-up for JD 2 Weeks Later



JD presents in the community 2 weeks later…

JD is stable and with minor improvements in symptoms of fatigue/dyspnea

JD is tolerating his enalapril 5 mg po bid (no hypotension)

Labs: CrCl 78 mL/min, BUN 3.9, K^+ 4.2 **BP:** 124/86 sitting, 119/85 standing

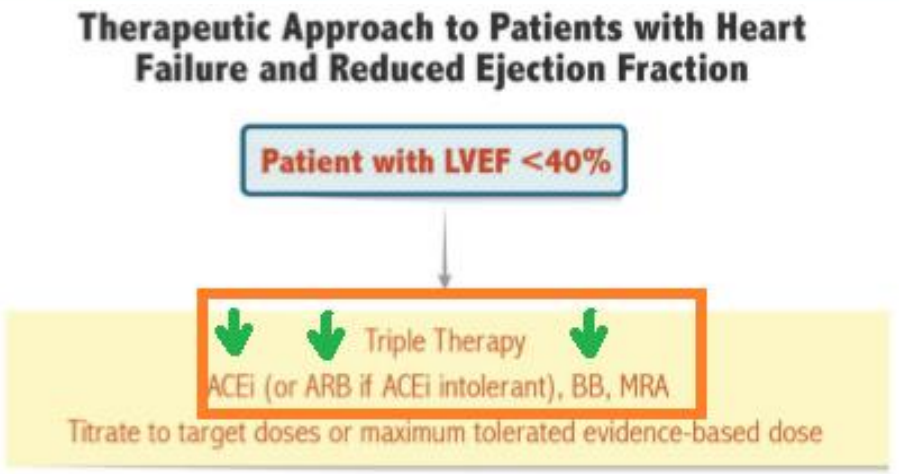
What do we do next? (A or B)

A) **Finish titrating ACE-I to EBM dose of enalapril 20 mg po bid**

B) **Start a Beta-Blocker at a low dose?**

Follow-up for JD 2 Weeks Later

Canadian Cardiovascular Society



Start a Beta Blocker at a low dose!

- *Comparative effects of low and high doses of the angiotensin converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure.* ATLAS Study Group. Circulation. 1999

- BB + Low dose ACE-I > High dose ACE for mortality and symptoms of HF

Abrupt Discontinuation of Therapy

Canadian Journal of Cardiology 32 (2016) 296–310

Special Article

The Canadian Cardiovascular Society Heart Failure Companion: Bridging Guidelines to Your Practice

Jonathan G. Howlett, MD, FRCPC,[a] Michael Chan, MBBS, FRCPC, FACC,[b]
Justin A. Ezekowitz, MBBCh, MSc, FRCPC,[c] Karen Harkness, RN, PhD,[d]

withdrawal of chronic ACEi/β-blocker therapy for patients with dilated cardiomyopathy (ischemic or non-ischemic) whose LVEF improved with triple therapy will result in a 60%-80% likelihood of recurrence of low LVEF, usually with symptoms.[39] As such, withdrawal of these medications should only be considered after consultation with a physician experienced and competent in the treatment of HF.

Comparison of Beta-Blockers in HFrEF

- CCS recommends, indicated in all patients with HFrEF, ***unless*** there is a short-term safety risk.

- **Contraindicated if…**
  - Cardiogenic shock
  - Severe reactive airway disease
  - 2/3rd degree HB (without BiV pacing)
  - Decompensated cardiac failure

- **Use with Caution/Adverse Effects:**

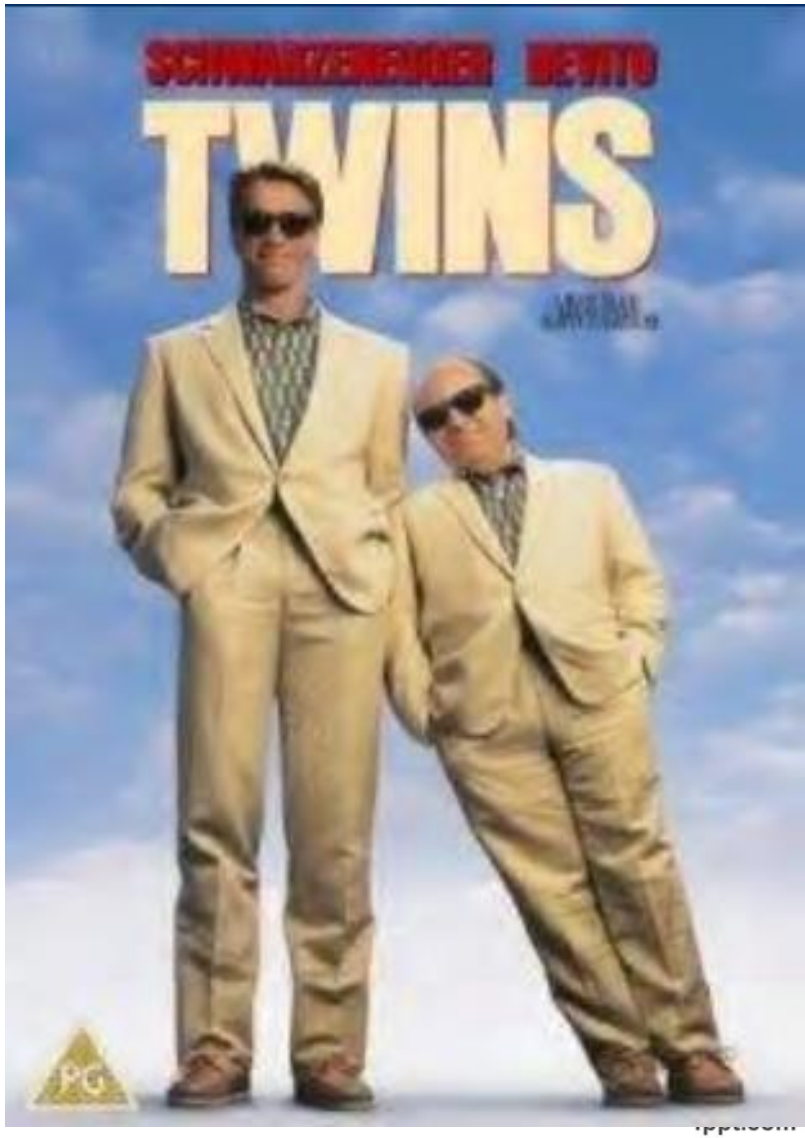
  Bronchoconstriction, Fatigue, Sexual dysfunction, Arthralgia
  - *Hypotension NNH20 (do not use with SBP less than 90)*
  - *Bradycardia NNH 13 (do not use in HR less than 50)*
  - *Dizziness NNH 8*

Which is the best Beta Blocker in HFrEF?

7.3.2.4. Beta Blockers: Recommendation

Class I

1. **Use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HF*r*EF, unless contraindicated, to reduce morbidity and mortality.[346,416–419,448] *(Level of Evidence: A)***



Comparison of Beta-Blockers in HFrEF

Agent	Outcomes	Statistically Significant
Carvedilol	**COPERNICUS Trail** (Carvedilol vs. Placebo) **Limitations:** terminated early	**All-Cause Death or Hospitalization** ***NNT* 15 over 10 months**
	U.S. Carvedilol Heart Failure (Carvedilol vs. Placebo) **Limitations:** 2 week run in period	**All-Cause Death** ***NNT* 18 over 6 months**
Bisoprolol	**CIBIS II Trial:** (Bisoprolol vs placebo) **Limitations:** terminated early	**All-Cause Death** ***NNT* 18 over 1.3 years**

2013 AHA Evidence Based Dosing

Table 15. Drugs Commonly Used for Stage C HF*r*EF

Drug	Mean Doses Achieved in Clinical Trials	Initial Daily Dose(s)
Beta blockers		
Bisoprolol	8.6 mg/d[117]	1.25 mg once
Carvedilol	37 mg/d[447]	3.125 mg twice
Carvedilol CR	N/A	10 mg once
Metoprolol succinate extenc (metoprolol CR/XL)	159 mg/d[448]	12.5 to 25 mg once

Plan and Follow-up for JD

- Bisoprolol was titrated to 1.25 mg PO daily with no adverse effects (no hypotension, no bradycardia)
  - Titrating the dose of a beta-blocker should be delayed until any observed adverse effects with lower doses have disappeared.
  - Clinicians may minimize the risk of hypotension by administering the beta-blocker and ACE-I at different times during the day.
  - Hypotensive symptoms may also resolve after a decrease in the dose of diuretics in patients who are volume depleted.
    - Diuretics are needed to prevent the exacerbation of fluid retention that can accompany the initiation of beta-blocker

Follow- up for JD 3 months later

JD presents in the community 3 months later…

JD is stable with noticeable improvements in symptoms of fatigue/ dyspnea

JD is tolerating his bisoprolol/ enalapril well (no hypotension)

Labs: CrCl 72 mL/min, BUN 4.1, K^+ 4.3

BP: 120/86 sitting, 119/85 standing

Medications:

- Furosemide 40 mg PO BID
- Enalapril 10 mg PO bid
- Escitalopram 5 mg PO daily
- Acetaminophen 500 PO QID PRN
- Bisoprolol 5 mg PO daily

Presentation Outline

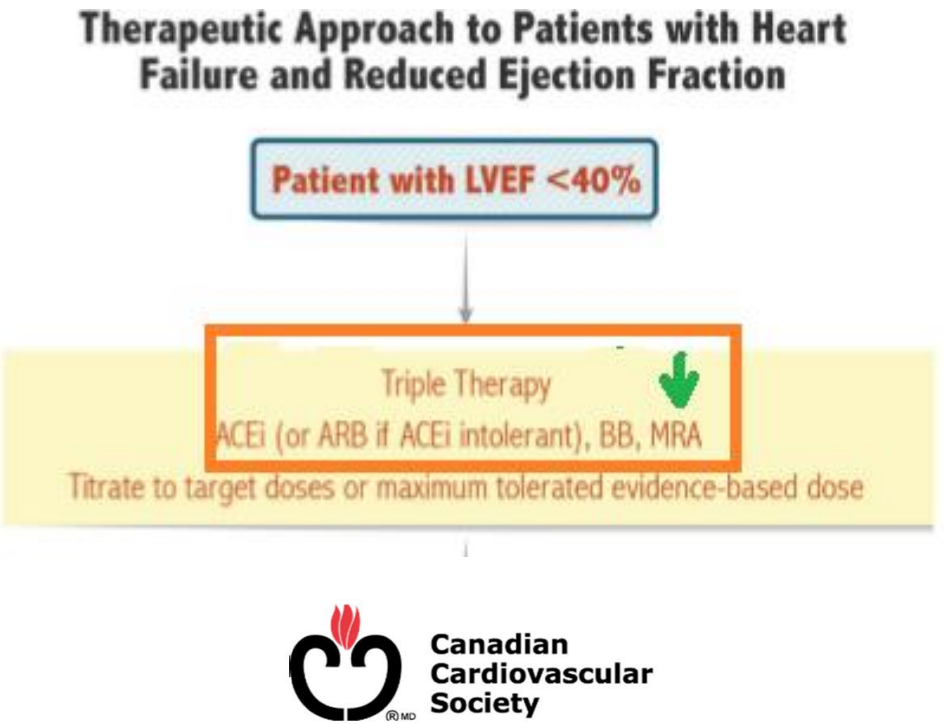
- Learning Objectives
- Heart Failure 101
- Clinical Drug Review Case Presentation
  - ➢ New Onset Acute Decompensated HFrEF Patient
    - ❑ACE-I/ARB and Beta Blockers
  - ➢ Outpatient Follow-up
    - ❑**Mineralocorticoid Receptor Antagonist**
      - ❑ **(MRA) (eplerenone or spironolactone)**
    - ❑Angiotensin Receptor-Neprilysin Inhibitor (ARNI)
      - ❑ (Sacubitril/Valsartan combination or *Entresto ™)*
    - ❑Additional Rate Controlling Medications
      - ❑ Ivabradine
      - ❑ Digoxin

Start a Mineralocorticoid Receptor Antagonist

Recommended by CCS:

- Often added after ACE-I is titrated as per EBM (for hyperkalemia reasons)

- MRAs:
  - Spironolactone
  - Eplerenone (Inspra)



Comparison of Mineralocorticoid Receptor Antagonists in HFrEF

- CCS recommends, indicated in all patients with HFrEF, ***unless*** there is a short-term safety risk

- **Contraindicated if**…
  - Elevated levels of serum potassium (> 5.0 mEq/L)
  - Serum creatinine > 220 mmol/L
  - Acute renal dysfunction

- **Not Recommended/Caution in** CrCl < 30 mL/min

- **Adverse Effects**:
  - Hyperkalemia (serious NNH 62)
  - Hyponatremia
  - Gynecomastia (10% spironolactone > 1% eplerenone)

Comparison of Mineralocorticoid Receptor Antagonists in HFrEF

Agent	Outcomes	Statistically Significant
Eplerenone	**EMPHASUS-HF:** (eplerenone vs. Placebo) **Limitations:** NYHA II patient	**All-Cause Death or Hospitalization** ***NNT* 13 over 1.75 years**
	EPHESUS(eplerenone vs. Placebo) **Limitations:** Post MI patients	**All-Cause Death** ***NNT* 43 over 1.3 years**
Spironolactone	**RALES:** (spironolactone vs placebo) **Limitations:** predated widespread BB use	**All-Cause Death** ***NNT* 9 over 2 years**

2013 AHA Evidence Based Dosing

Drug	Mean Doses Achieved in Clinical Trials	Initial Daily Dose(s)
Aldosterone antagonists		
Spironolactone	26 mg/d[425]	12.5 to 25.0 mg once
Eplerenone	42.6 mg/d[448]	25 mg once

American Heart Association®

Plan and Follow-up

- Spironolactone 12.5 mg PO daily initiated, titrate to 25 mg po daily gradually
- Follow-up on SrCr, K^+, BUN every 1-2 weeks after initiation
- The development of K^+levels > 5.2-5 mEq/L should generally trigger discontinuation or dose reduction

Follow-up for JD 6 Months

JD presents to HF clinic 6 months later…

JD is stable with minor improvements in symptoms of fatigue/ dyspnea.

JD is tolerating his enalapril, spironolactone, bisoprolol well (no hypotension)

Labs: CrCl 85 mL/min, BUN 4.0, K^+ 4.5

BP: 118/84 sitting, 116/83 standing

Medications:

- Furosemide 20 mg PO daily
- Escitalopram 5 mg po daily
- Acetaminophen 500 po QID PRN
- Enalapril 10 mg po bid
- Spironolactone 25 mg po daily
- Bisoprolol 10 mg po daily

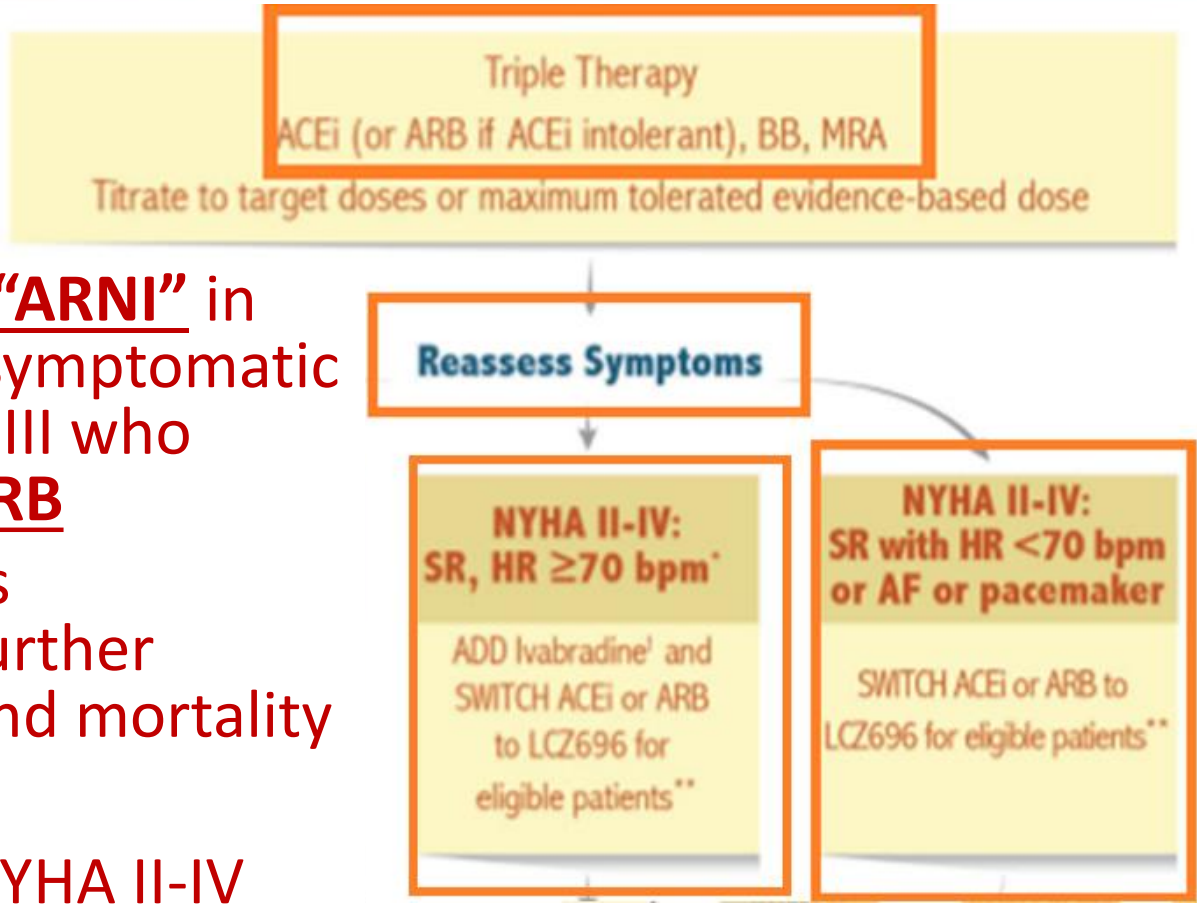
Presentation Outline

- Learning Objectives
- Heart Failure 101
- Clinical Drug Review Case Presentation
  - ➢ New Onset Acute Decompensated HFrEF Patient
    - ❑ACE-I/ARB and Beta Blockers
  - ➢ Outpatient Follow-up
    - ❑**Mineralocorticoid Receptor Antagonist**
      - ❑ **(MRA) (eplerenone or spironolactone)**
    - ❑**Angiotensin Receptor-Neprilysin Inhibitor (ARNI)**
      - ❑ **(Sacubitril/Valsartan combination or *Entresto* ™)**
    - ❑Additional Rate Controlling Medications
      - ❑ Ivabradine
      - ❑ Digoxin

Start an Angiotensin Receptor-Neprilysin Inhibitor

- AHA Recommends an **"ARNI"** in patients with chronic symptomatic HFrEF NYHA class II or III who **tolerate an ACE-I or ARB**
  - *Switch to an ARNI* is recommended to further reduce morbidity and mortality

- CCS Recommends in NYHA II-IV HFrEF after stable on triple therapy (ACE-I, BB, MRA)



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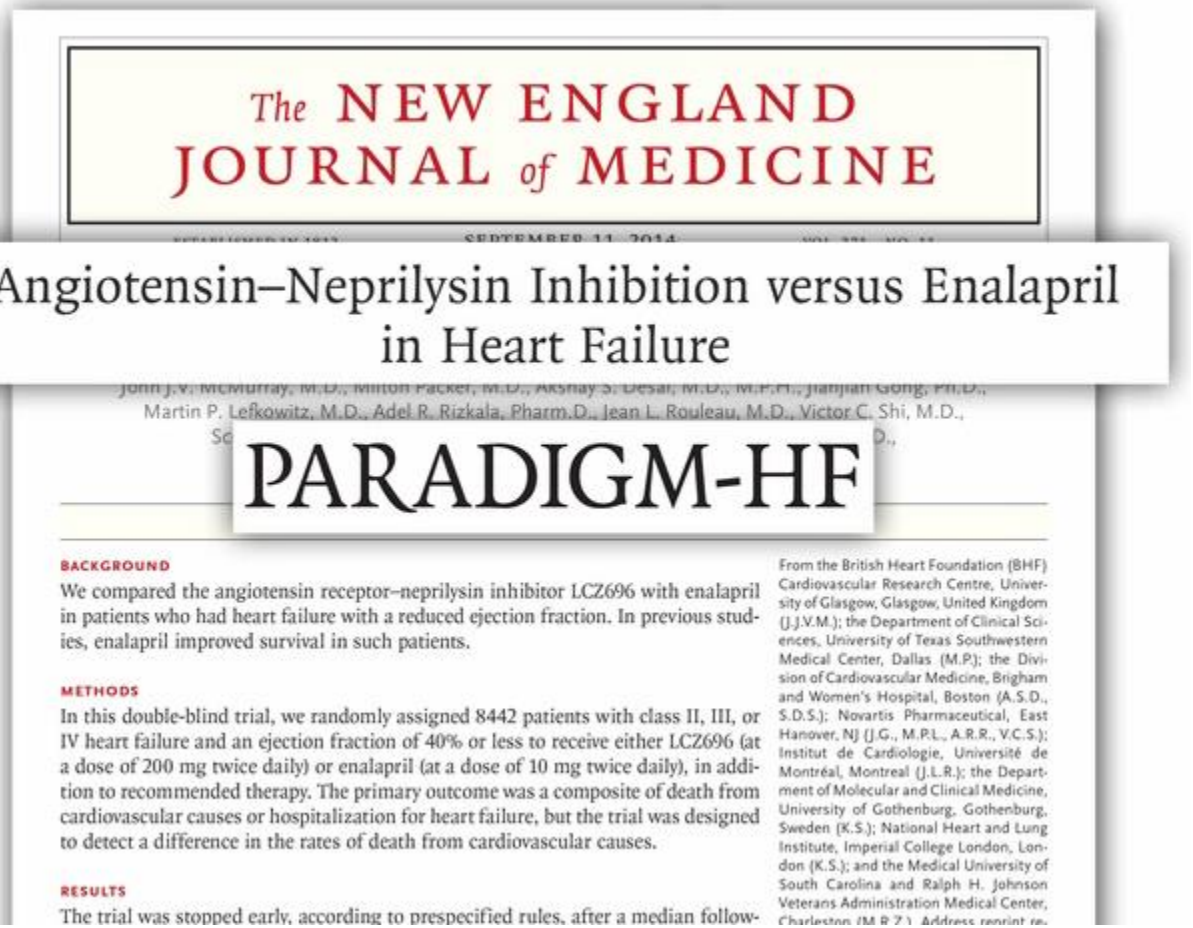
American Heart Association®

I	ARNI: B-R	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 (19).

PARADIGM-HF



The NEW ENGLAND JOURNAL of MEDICINE

SEPTEMBER 11, 2014

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., So... D.,

PARADIGM-HF

BACKGROUND

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-

From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceutical, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Administration Medical Center, Charleston (M.R.Z.). Address reprint re-

The New England Journal of Medicine, 2014 371(11); 993-1004

PARADIGM-HF

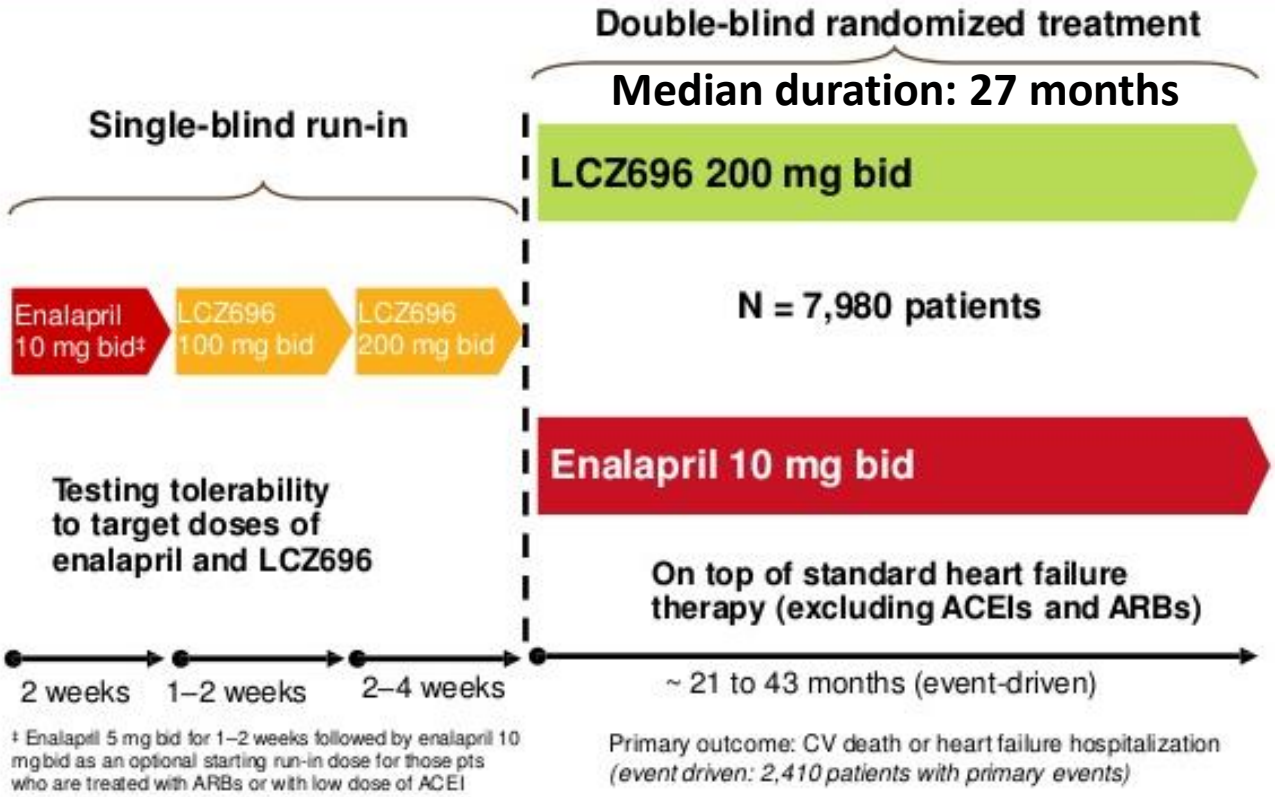
- **Study Inclusion Criteria:**
  - 18 years or older
  - NYHA II, III, or IV symptoms (very few in class IV ~ 0.7%)
  - LVEF </= 40%
  - Hospitalized for heart failure in the last 12 months or BNP >/= 150 pg/mL or NT-proBNP >/= 600 pg/mL
  - Taking a stable dose of an ACE-I or an ARB equivalent to at least 10 mg of Enalapril daily for 4 weeks
    - Ramapril 5 mg daily
    - Captopril 100 mg daily
    - Perindopril 4 mg daily
    - Trandolapril 2 mg daily
    - Fosinopril 20 mg daily
    - Irbesartan 150 mg daily
    - Losartan 50 mg daily
    - Telmisartan 40 mg daily
    - Candesartan 16 mg daily

PARADIGM-HF

- **Study Exclusion Criteria:**
  - History of hypersensitivity to ACE-I or ARBs
  - History of angioedema or previous history of intolerance in titrating to target doses
  - Current acute decompensated heart failure
  - Symptomatic hypotension and/or SBP < 100 mmHg at screening or < 95 mmHg at randomization
  - eGFR < 30 ml/min/1.73m2 or > 25% decline prior to randomization
  - K^+ > 5.2 or > 5.4 at randomization
  - ACS, stroke, TIA, major CV surgery, PCI, angioplasty, or ICD implantation within last 3 months
  - Coronary or carotid artery disease likely to require intervention within the next 6 months

PARADIGM-HF

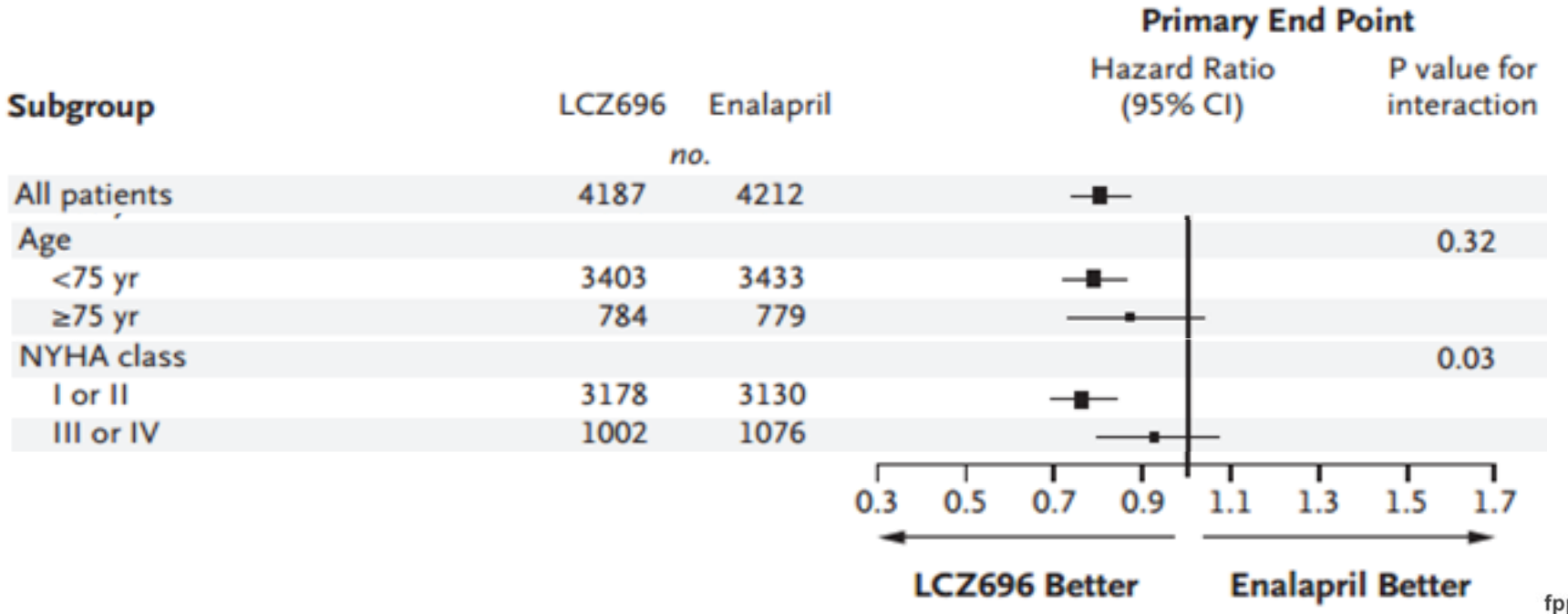
PARADIGM-HF: Study Design



PARADIGM-HF

Study Results:

- CV death or hospitalization for HF
- Sacubitril/Valsartan: 914 (21.8%) vs Enalapril: 1117 (26.5%)
- ARR ↓4.7%; NNT = 21 over 2.25 years



PARADIGM-HF

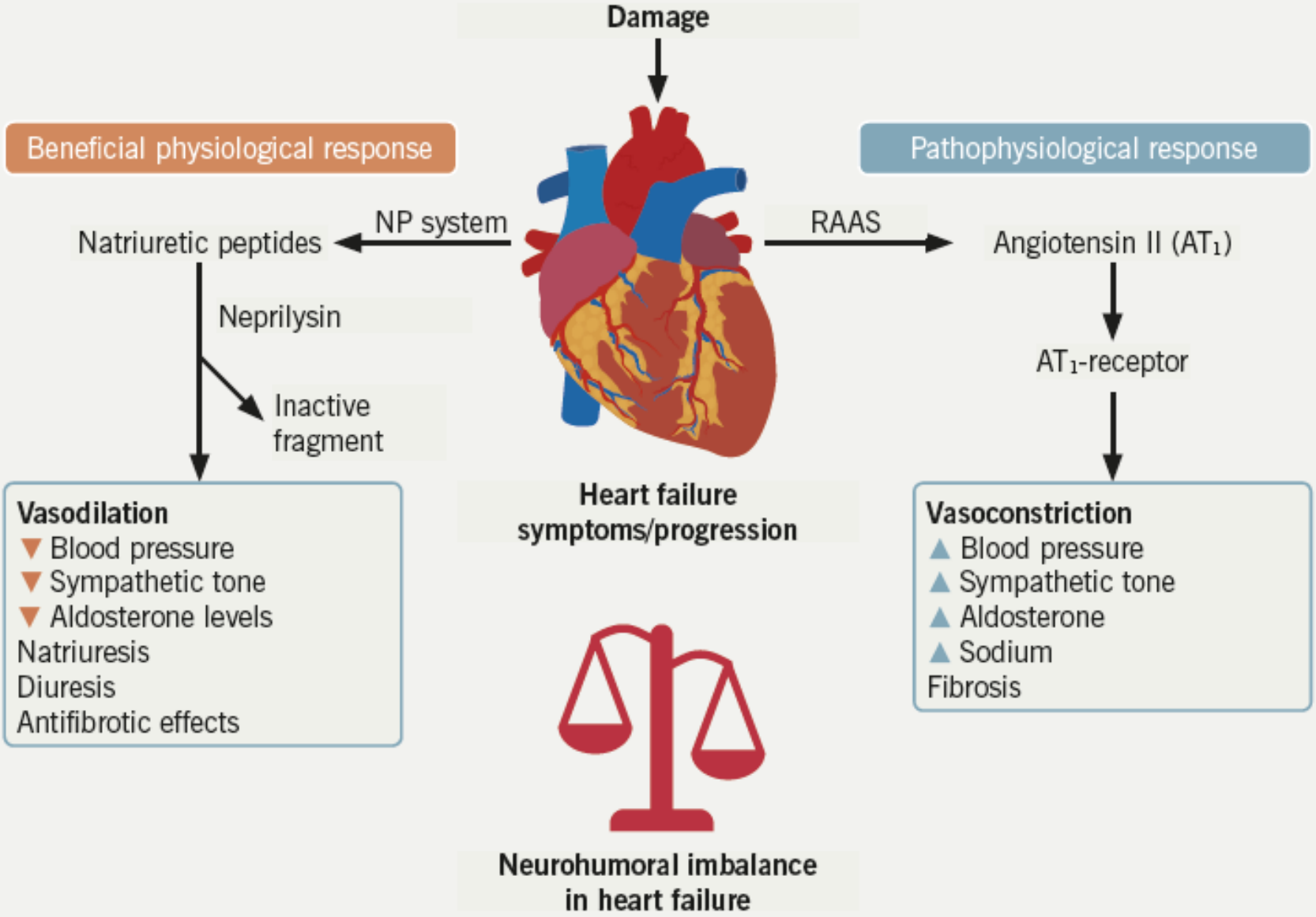
- **Secondary End-Points:**
  - CV Death
    - ARR ↓3.2%; NNT = 32
  - 1st Hospitalization for Heart Failure
    - ARR ↓2.8%; NNT = 36
  - All-Cause Mortality
    - ARR ↓2.8%; NNT = 35

PARADIGM-HF

- **Adverse Effects**
  - Symptomatic Hypotension
    - **↑4.8% NNH = 24**
    - Sacubitril/Valsartan: 558 (14.0%) vs Enalapril: 388 (9.2%)
  - Elevated SCr ≥ 221 micromol/L
    - **↓1.2%; NNT = 87**
    - Sacubitril/Valsartan: 139 (3.3%) vs Enalapril: 188 (4.5%)
  - Elevated K^+ > 6.0 mmol/L
    - **ARR ↓1.3%; NNT = 78**
    - Sacubitril/Valsartan: 181 (4.3%) vs Enalapril: 236 (5.6%)

Health Canada Approved Indication

- Indicated for the treatment of HFrEF (LVEF < 40%):
  - In patients with NYHA Class II or III (to reduce the incidence of cardiovascular death and hospitalization due to heart failure);
  - In place of an ACE-I or ARB; *SWITCHES ONLY*
  - In combination with other heart failure therapies (e.g. beta-blockers, diuretics);
  - Initiated and titrated by a physician experienced in the treatment of heart failure.



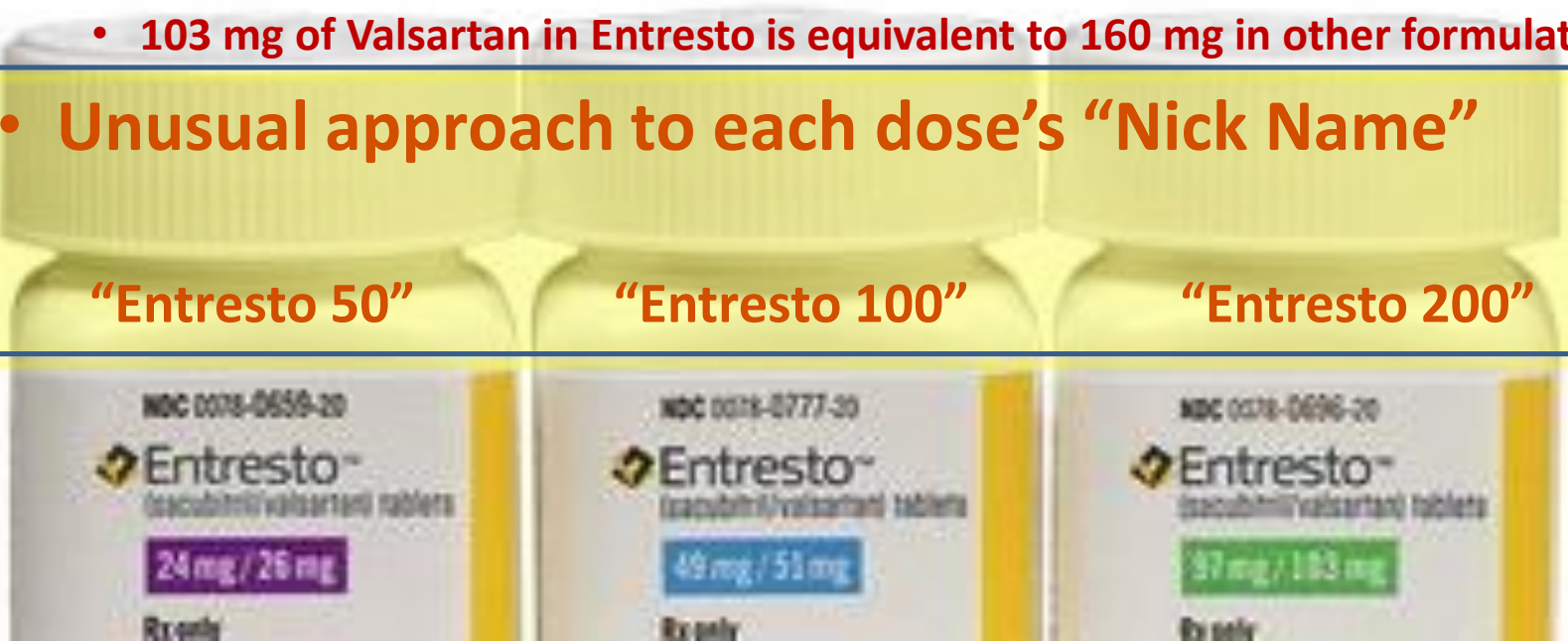
Adapted from Langenickel TH, Dole WP. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discovery Today: Therapeutic Strategies* 2012;9:e131–e139.

Key: NP = natriuretic peptide; RAAS = renin-angiotensin-aldosterone-system

Names/Doses/Equivalent Valsartan

- **Bioavailability of Valsartan in Entresto is greater than that of Valsartan in other formulations**
  - **26 mg of Valsartan in Entresto is equivalent to 40 mg in other formulation**
  - **51 mg of Valsartan in Entresto is equivalent to 80 mg in other formulation**
  - **103 mg of Valsartan in Entresto is equivalent to 160 mg in other formulations**
- **Unusual approach to each dose's "Nick Name"**

"Entresto 50" **"Entresto 100"** **"Entresto 200"**



Contraindications

- Recent symptomatic hypotension
- Concomitant use with an **ACE-I** or within 36 hours of use
- Known history of angioedema related to previous ACE-I or ARB therapy or history of hereditary or idiopathic angioedema
- Concomitant use with Aliskiren-containing drugs in patients with diabetes or renal impairment
- Hyperkalemia > 5.2
- Renal Artery stenosis or Creatinine clearance < 30 mL/min

How to Switch to Entresto

Angiotensin-converting enzyme inhibitor (ACEi)	Patients receiving a **total daily dose of >10 mg of enalapril** or therapeutically equivalent doses of another ACEi, for example[2]: • Lisinopril >10 mg • Ramipril >5 mg	**Stop ACEi 36 hours before starting ENTRESTO**	Start ENTRESTO at the recommended dose of 49/51 mg twice daily	**Double the dose of ENTRESTO after 2 to 4 weeks, as tolerated by the patient, to reach the target maintenance dose of 97/103 mg twice daily**
	Patients receiving a **total daily dose of ≤10 mg of enalapril** or therapeutically equivalent doses of another ACEi, for example[2]: • Lisinopril ≤10 mg • Ramipril ≤5 mg	**Stop ACEi 36 hours before starting ENTRESTO**	Start ENTRESTO at the recommended dose of 24/26 mg twice daily Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient	
Angiotensin II receptor blocker (ARB)	Patients receiving a **total daily dose of >160 mg of valsartan** or therapeutically equivalent doses of another ARB, for example[2]: • Losartan >50 mg • Olmesartan >10 mg	Start ENTRESTO at the recommended dose of 49/51 mg twice daily		
	Patients receiving a **total daily dose of ≤160 mg of valsartan** or therapeutically equivalent doses of another ARB, for example[2]: • Losartan ≤50 mg • Olmesartan ≤10 mg	Start ENTRESTO at the recommended dose of 24/26 mg twice daily	Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient	
Not on ACEi or ARB	Not currently taking ACEis or ARBs	Start ENTRESTO at the recommended dose of 24/26 mg twice daily	Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient	

- **ENTRESTO is contraindicated with concomitant use of an ACE inhibitor. If switching from an ACE inhibitor to ENTRESTO, allow a washout period of 36 hours between administration of the 2 drugs**
- **Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker valsartan**

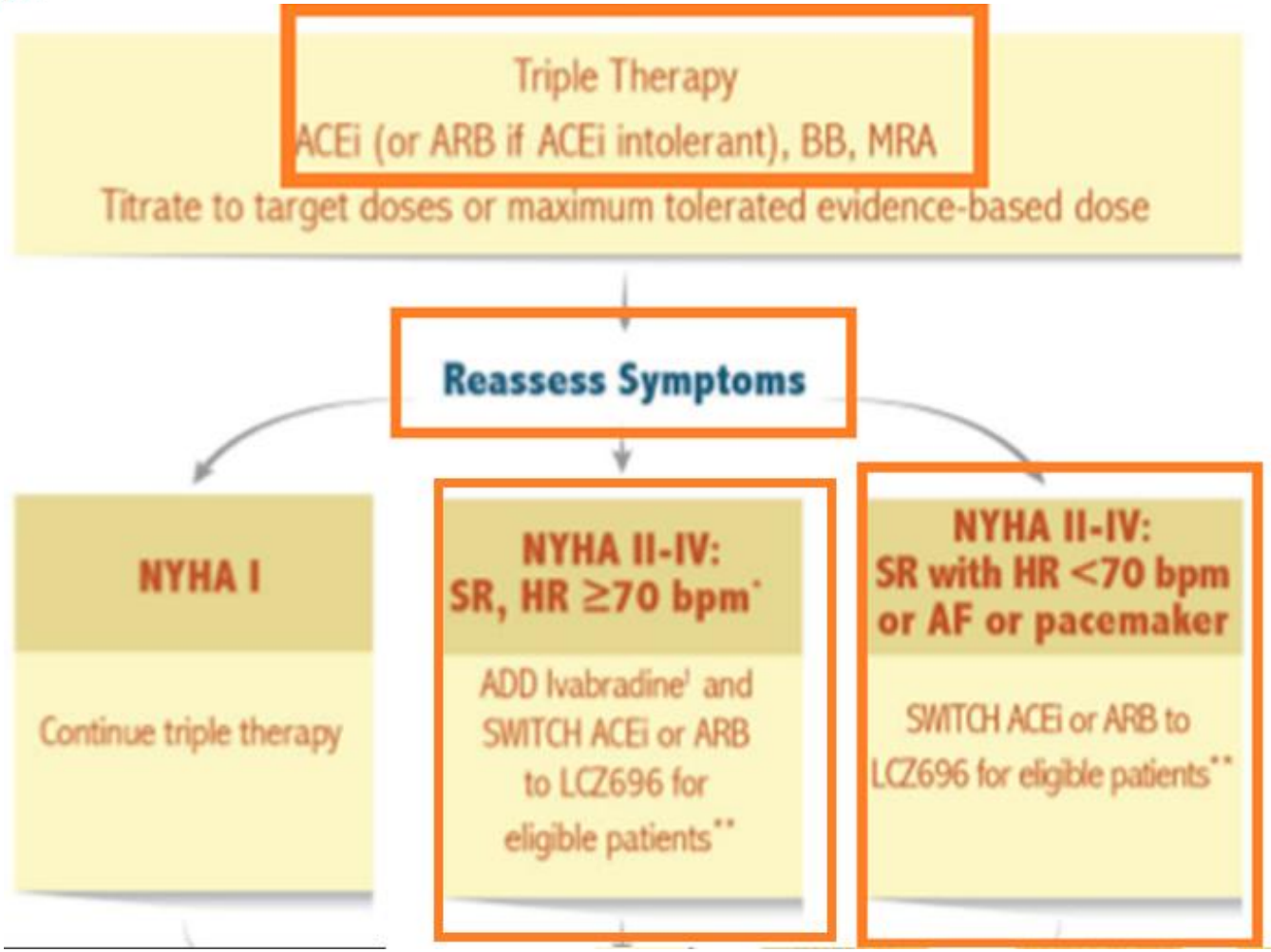
Plan and Follow-up

- Stop ACE-I for 36 hours before initiating
- Sacubitril/Valsartan 49/51 mg PO BID (double the dose after 2-4 weeks if tolerable to target maintenance dose of 97/103 mg)
- Titration might take several weeks to months depending on disease severity
- Follow-up on hypotension SrCr, K^+, BUN Q 3-7 days after initiation

Presentation Outline

- Learning Objectives
- Heart Failure 101
- Clinical Drug Review Case Presentation
  - ➢ New Onset Acute Decompensated HFrEF Patient
    - ❑ACE-I/ARB and Beta Blockers
  - ➢ Outpatient Follow-up
    - ❑Mineralocorticoid Receptor Antagonist
      - ❑ (MRA) (eplerenone or spironolactone)
    - ❑Angiotensin Receptor-Neprilysin Inhibitor (ARNI)
      - ❑ (Sacubitril/Valsartan combination or *Entresto ™)*
    - **❑Additional Rate Controlling Medications**
      - **❑ Ivabradine**
      - **❑ Digoxin**

Ivabradine



2017 CCS HF Guidelines

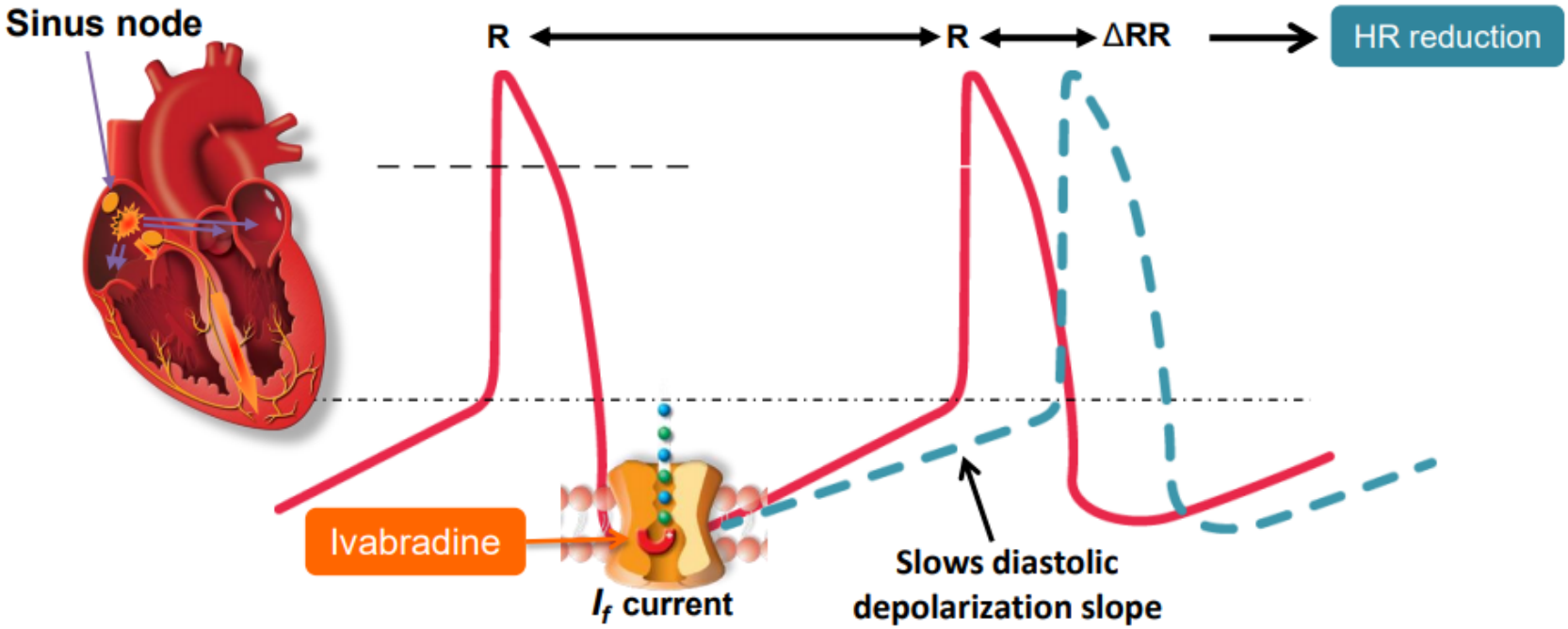
2017 Recommendation

Ivabradine

- **Recommendation:** We recommend that ivabradine be considered in patients with HFrEF, symptomatic despite treatment with appropriate doses of GDMT, with a resting HR > 70 bpm, in sinus rhythm and a prior HF hospitalization within 12 months, for the prevention of CV death and HF hospitalization (Strong Recommendation, Moderate Quality Evidence).
- **Values and preferences:** High value is placed on the improvement of CV death and HF hospitalizations as adjunctive therapy to standard HF treatments in a selected HF population. The health economic implications are unknown. **Differing criteria** for HR eligibility have been approved by various regulatory authorities ranging from 70 to 77 bpm with the trial entry criteria of 70 bpm (FDA HR >70 bpm; Health Canada HR > 77 bpm)

Ivabradine MOA

If **is the main current of diastolic depolarization that leads to the generation of a new potential action**



Ivabradine

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**

Summary

Background Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure.

Methods Patients were eligible for participation in this randomised, double-blind, placebo-controlled, parallel-group study if they had symptomatic heart failure and a left-ventricular ejection fraction of 35% or lower, were in sinus rhythm with heart rate 70 beats per min or higher, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a β blocker if tolerated. Patients were randomly assigned by computer-generated allocation schedule to ivabradine titrated to a maximum of 7·5 mg twice daily or matching placebo. Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure. Analysis was by intention to treat. This trial is registered, number ISRCTN70429960.

Findings 6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). Data were available for analysis for 3241 patients in the ivabradine group and 3264 patients allocated placebo. Median follow-up was 22·9 (IQR 18–28) months. 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0·82, 95% CI 0·75–0·90, p<0·0001). The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo *vs* 514 [16%] ivabradine; HR 0·74, 0·66–0·83; p<0·0001) and deaths due to heart failure (151 [5%] *vs* 113 [3%]; HR 0·74, 0·58–0·94, p=0·014). Fewer serious adverse events

Published Online August 29, 2010 DOI:10.1016/S0140-6736(10)61198-1

See Online/Article DOI:10.1016/S0140-6736(10)61259-7

See Online/Comment DOI:10.1016/S0140-6736(10)61314-1

*Investigators listed at end of paper

Department of Emergency and Cardiovascular Medicine, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden (Prof K Swedberg MD); Department of Cardiology, University Pierre et Marie Curie Paris VI, La Pitié-Salpétrière Hospital, Paris, France

SHIFT Trial

Study Inclusion Criteria:

- Age 18+ years
- Stable symptomatic HF for at least 4 weeks
- LVEF 35% or lower
- HF hospitalization in the last 12 months
- Normal sinus rhythm with HR 70+ bpm (12-lead EKG after 5 min of rest on 2 consecutive visits)

Study Exclusion Criteria:

- HF etiology of congenital heart disease or primary severe valvular disease
- MI in last 2 months
- Implantable pacemaker that's pacing >40% of the day
- AF/flutter
- Symptomatic hypotension
- Drugs: diltiazem or verapamil, class I antiarrhythmics, or strong CYP 3A4 inhibitors

SHIFT Trial Patient Characteristics

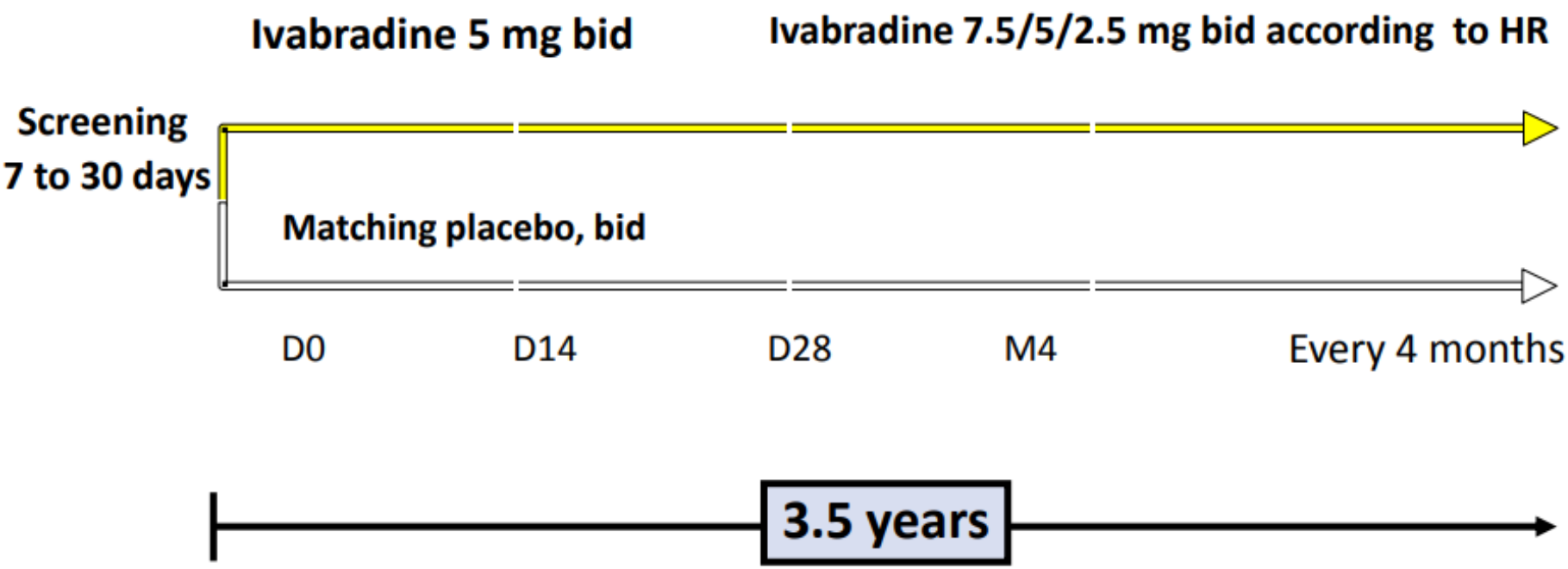
- Age 60 years, Male 76%
- Duration of HF 3.5 years
- HF etiology: Ischemic 68%
- NYHA class: II (~50%), III (~50%)
- PMHx:
  - MI 56%
  - HTN 67%
  - Diabetes 30%
- BP 122/76 mm Hg, HR 80 bpm, LVEF 29%, eGFR 75 mL/min*1.73 m^2
- Medications:
  - Beta-blocker ~90% (26% on target dose, 56% on at least 1/2 target dose)
  - ACE-I ~80%, ARB 14%
  - Mineralocorticoid antagonist ~60%
  - Diuretic 84%
  - Digoxin 22%

SHIFT Trial Methods

- Versus placebo…
- Initial dose of 5 mg PO BID
- After 14 days:
  - If HR >60 bpm, increased to 7.5 mg PO BID
  - If HR 50-60 bpm, kept on 5 mg PO BID
  - If HR <50 bpm or symptomatic bradycardia, dose reduced to 2.5 mg PO BID
- At each subsequent follow-up, above algorithm used to titrate between 2.5-7.5 mg PO BID

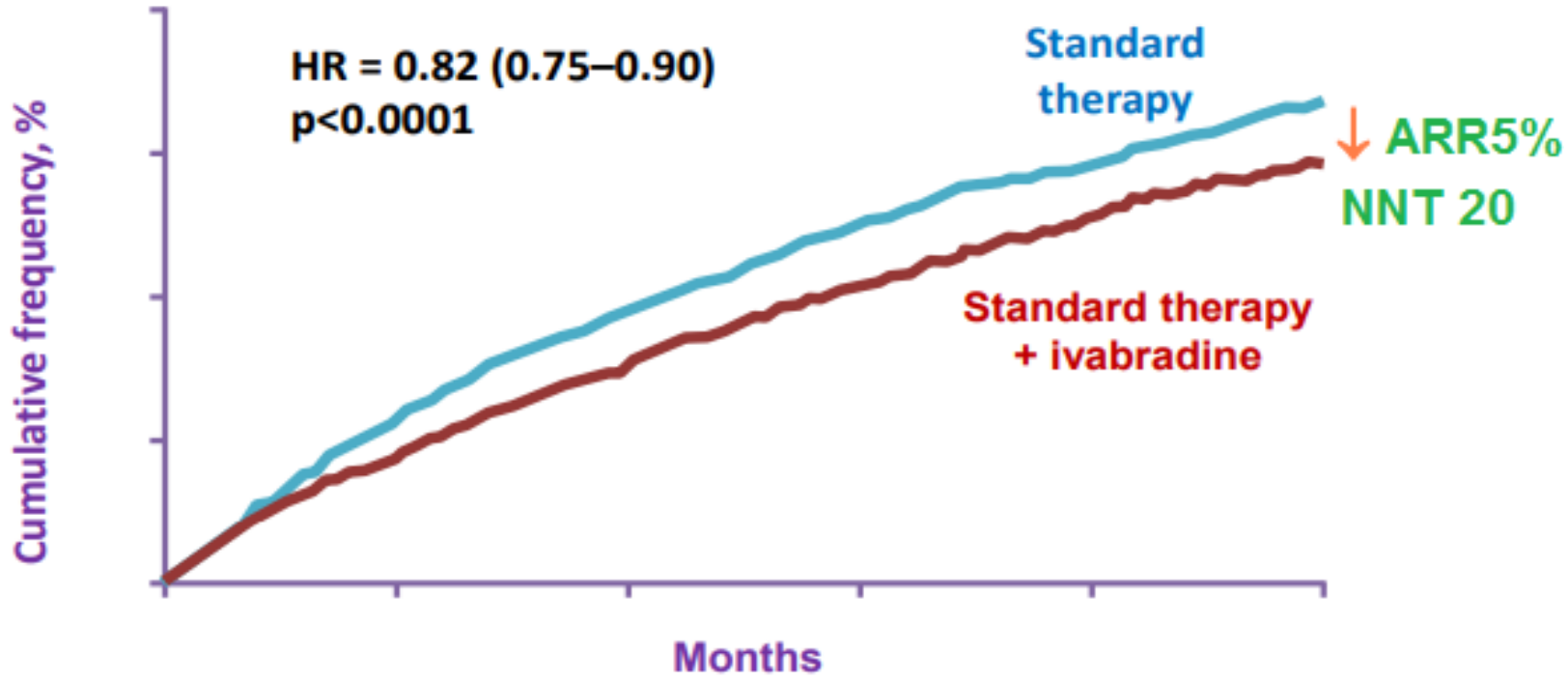
SHIFT Trial Methods

Sinus rhythm, HR ≥70 bpm, LVEF ≤35%



SHIFT Trial Results

CV mortality and HF hospitalization benefits (primary endpoint)



Placebo	3 264	2 868	2 489	2 061	1 089	439
Ivabradine	3 241	2 928	2 600	2 173	1 191	447

SHIFT Trial Results

An Average of 1.9 years…

- **Heart Rate**
  - 67 vs 75 bpm

- **Primary outcome** (CV death or hospital admission for HF):
  - 24% vs 29%, NNT 20
    - Subgroup analyses demonstrated a significant interaction between baseline HR 77 bpm or greater versus less than 77 bpm and effect on the primary outcome. Greater relative benefit was seen in patients with a higher baseline HR.

- **Adverse Effects**
  - Serious adverse events: Ivabradine 45%, placebo 48% (p=0.025)
    - Symptomatic bradycardia: 5% vs 1%, NNH 25
    - Asymptomatic bradycardia: 6% vs 1%, NNH 20
    - Atrial fibrillation: 9% vs 8%, NNH 100
    - Blurred vision: 1% vs <1%, NNH 100
    - Phosphenes: 3% vs 1%, NNH 50

SHIFT Trial Summary

Bottom-line:

In patients with HFrEF and a resting heart rate >70 bpm, despite maximally-tolerated beta-blocker therapy, ivabradine reduced the risk of hospital admissions (NNT 25), mainly by reducing HF-related hospitalization, over ~2 years.

Swedberg K, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. Lancet 2010;376:875-85

Health Canada Indication

INDICATIONS AND CLINICAL USE

LANCORA™ (ivabradine) is indicated for the treatment of stable chronic heart failure with reduced left ventricular ejection fraction (≤ 35%) in adult patients with NYHA Classes II or III who are in sinus rhythm with a resting heart rate ≥ 77 beats per minute, to reduce the incidence of cardiovascular mortality and hospitalisations for worsening heart failure. LANCORA™ should be administered in combination with standard chronic heart failure therapies (see CLINICAL TRIALS).

Monograph Dosing/Titration

Table 3 Dose titration according to resting heart rate achieved after initiation of treatment

Serial Heart Rate Measurements	Dose Adjustment
> 60 bpm	Increase dose by 2.5 mg twice daily (maximum dose 7.5 mg BID)
50-60 bpm	Maintain dose
< 50 bpm or signs and symptoms of bradycardia**	Decrease dose by 2.5 mg twice daily; if current dose is 2.5 mg twice daily, discontinue therapy

**Such as dizziness, fatigue or hypotension; bpm: beats per minute

Treatment must be discontinued if the patient, despite receiving the lowest LANCORA™ dose (2.5 mg BID), has a resting heart rate below 50 bpm or experiences signs or symptoms of bradycardia (see WARNINGS AND PRECAUTIONS).

Monograph Dosing/Titration

……Start with 2.5 mg po bid

Concomitant use of CYP3A4 inducers: LANCORA™ use may be initiated at the usual recommended dose of 5 mg twice daily and may be titrated upward to a maximum dose of 7.5 mg twice daily (Table 3). Caution should be exercised if treatment with a CYP3A4 inducer needs to be interrupted after LANCORA™ had been titrated. Close heart rate monitoring is recommended and LANCORA™ dosing may need to be reduced. Concomitant use of St John's Wort, which is known to induce CYP3A4, should be avoided (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Patients with arrhythmias: In patients with a history of conduction defects, or other patients in whom bradycardia could lead to hemodynamic compromise, initiate therapy at 2.5 mg of LANCORA™ twice daily before increasing the dose based on heart rate (Table 3) (see WARNINGS AND PRECAUTIONS).

Geriatrics (≥ 75 years of age): In patients aged 75 years and older, a lower starting dose of 2.5 mg of LANCORA™ twice daily is recommended (i.e. one half 5 mg tablet twice daily) (see WARNINGS AND PRECAUTIONS). Up-titration may follow depending on the therapeutic response (Table 3).

Ivabradine Contraindications

- Resting heart rate below 70 bpm prior to treatment
- Unstable or acute heart failure
- Patients with existing prolonged QT interval
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension
- Severe hepatic impairment
- Sick sinus syndrome /Sino-atrial block /3rd degree AV block
- Pacemaker dependence
- Concomitant use of strong Inhibitors of P450 3A4
- Concomitant use of verapamil or diltiazem

Plan and Follow-up

JD presents in the community 3 months later…

JD is stable with **optimized beta-blocker dose** and a rest HR of 79 bpm

- Start at 5 mg po bid (titrate according to HR)
- Administer with food, tablet can be split/crush
- Monitor:
  - New onset AFIB, Amidarone initiation
  - Minimal effect on BP, bradycardia, hypokalemia, QTc, HR!

Medications:

- Furosemide 40 mg PO BID
- Valsartan/Sacubitril 49/51 mg po bid
- Escitalopram 5 mg PO daily
- Acetaminophen 500 PO QID PRN
- Bisoprolol 10 mg PO daily
- Spironolactone 25 mg PO daily
- Ivadrabine 5 mg PO BID

AFIB/Amiodarone Follow-up

Atrial Fibrillation

In patients treated with LANCORA™ the risk of developing atrial fibrillation is increased (see ADVERSE REACTIONS). It is recommended to regularly monitor patients for the occurrence of atrial fibrillation, which should include ECG monitoring if clinically indicated. Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur. Discontinue treatment with LANCORA™ if atrial fibrillation occurs.

Atrial fibrillation appears more common in ivabradine-treated patients concomitantly treated with amiodarone, although the mechanism involved remains unclear. Concomitant use of LANCORA™ and amiodarone should be avoided. If the combination is deemed necessary, close cardiac monitoring is required (see DRUG INTERACTIONS).

Another option… Digoxin Therapy

Mechanism of Action

1. Increases cardiac contractility
2. Slows heart rate

Positive Effects on the Heart

- Increased EF
- Increased CO
- Neutral effect on BP
- Lower Pulmonary wedge pressure

↑Ca

Toxicities: Proarrythmic properties, AV block

Metabolism and Elimination

- Reduction within stomach to metabolites that contribute to toxic effects
- Renally eliminated (P-gp) (50-70% unchanged)

Toxicities Cont.

- Lethargy
- Confusion
- GI (anorexia, NVD, abdominal pain)
- Visual Disturbances

The Digoxin Controversy

Early Studies:

The Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED)

The Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE)

Population: chronic HF pts (mild-moderate symptoms) stabilized on diuretics +dig (RADIANCE also stabilized on ACE)

Intervention(s): switch digoxin therapy to placebo

Comparator: continue stabilized digoxin

Outcomes favored digoxin therapy

Discontinuation of digoxin resulted in…

- Reduced maximal exercise capacity
- Worsening of HF status
- Increased incidence of treatment failure

The Digoxin Controversy

The Digitalis Investigation Group Study [DIG]

Randomized 1:1, double-blind, placebo controlled

P- 6800 chronic HF pts NYHA class 2-3, w/ EF≤45%

I- digoxin

C-placebo

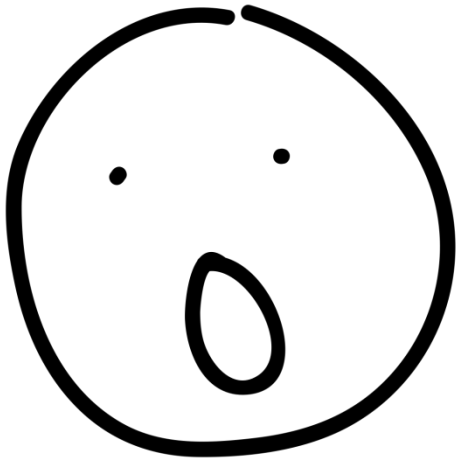
O- all-cause mortality

Results: In comparison to placebo…

- 13% relative risk reduction in hospitalization rates
- 28% relative risk reduction in worsening HF
- Trend towards decrease in mortality (P=0.06)
- Increased death rate due to other cardiac causes (P=0.04)

Scrutiny of the DIG Trial :

- High Doses of Digoxin
- Pre-trial digoxin therapy
- Pre-beta blocker era



2017 CCS HF Recommendations on Digoxin

Recommendation 37: We suggest digoxin be considered in patients with HFrEF in sinus rhythm who continue to have moderate to severe symptoms, despite appropriate doses of GDMT to relieve symptoms and reduce hospitalizations (Weak Recommendation, Moderate Quality Evidence).

Recommendation 80: We recommend the addition of digoxin in patients with HFrEF and chronic AF and poor control of ventricular rate and/or persistent symptoms despite optimally tolerated beta-blocker therapy, or when beta-blockers cannot be used (Strong Recommendation, Low Quality Evidence).

Recommendation 124: We recommend that digoxin should be avoided in patients with acute renal injury and in patients with chronic, severe renal insufficiency (GFR < 30). In mild to moderate, stable renal insufficiency, digoxin should be used judiciously, at a low dose. As renal function declines, digoxin usage should be re-assessed to avoid development of digoxin toxicity (Strong Recommendation, Low Quality Evidence).

Digoxin Take Home

- Digoxin may give rEF HF symptomatic relief
- Niche tool (rEF symptoms, AF, borderline BP)
- Patient already on digoxin and stable? Use a low dose, don't D/C
- Be cognizant of use when such factors are present:
  - hypokalemia, dehydration, renal fxn decline, lower body weight
  - Drugs: verapamil, amiodarone, macrolides, azoles, cyclosporine

Summary

- Getting patients on triple therapy: ACE-I, Beta-Blocker and MRA should take 4-6 months
- 3x therapy is indicated in all HFrEF due to reduced mortality risks; the main guiding principle is short term safety risks
- In select patients with HFrEF, Sacubitril/Valsartan provides substantial mortality benefits;
- Ivabradine is a safe and effective rate controlling therapy for patient's optimized on beta-blockers without atrial fibrillation

THANK YOU FOR COMING!

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