Updated Guidelines for Heart Failure Medications

John Tran, MD
UCLA Family Medicine
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Disclosures

- None

Learning Objectives

- Review guidelines for heart failure medications
- Understand guideline-directed medical therapy
- Encourage culturally sensitive and patient-centered care

Introduction

- Heart Failure Categorization
  - Heart Failure with Reduced Ejection Fraction (HFrEF):
    - Ejection Fraction ≤ 40%
  - Heart Failure with Mid-Range Ejection Fraction (HFmrEF)
    - Ejection Fraction 41% - 49%
  - Heart Failure with Preserved Ejection Fraction (HFpEF)
    - Ejection Fraction ≥ 50%

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013; 128:1810.

Introduction

- Heart Failure Categorization
  - **Heart Failure with Reduced Ejection Fraction (HFrEF):**
    - **Ejection Fraction ≤ 40%**
  - Heart Failure with Mid-Range Ejection Fraction (HFmrEF)
    - Ejection Fraction 41% - 49%
  - Heart Failure with Preserved Ejection Fraction (HFpEF)
    - Ejection Fraction ≥ 50%

Introduction

- Many medications with mortality benefits for patients with heart failure with **reduced ejection fraction (HFrEF)**
- Many opportunities to improve patient outcomes that are being missed for patients with **HFrEF**
- Eligible patients
  - 1) never receive therapies or
  - 2) receive them too late

Greene SJ, Butler J, Fonarow GC. Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure—Optimizing Therapy With the Need for Speed. JAMA Cardiol. Published online March 31, 2021. doi:10.1001/jamacardio.2021.0496

Greene SJ, Fonarow GC, DeVore AD, et al. Titration of medical therapy for heart failure with reduced ejection fraction. J Am Coll Cardiol. 2019;73(19):2365-2383. doi:10.1016/j.jacc.2019.02.015

Common Questions – To Be Answered

Common Questions – To Be Answered

- Does race or ethnicity play a role in heart failure?
- For patients with heart failure, do I start ACEis/ARBs, Beta-blockers, aldosterone antagonists, or the newer ARNIs first?
- Is it necessary to achieve target or maximally tolerated doses of other medications before adding another medication with known mortality benefit?

Heart Failure with **Reduced** Ejection Fraction

Guidelines

- 2013 ACCF/AHA Guideline for the Management of Heart Failure
- 2014 DHS Expected Best Practices via eConsult
- 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure
- 2020 JAMA Heart Failure With Reduced Ejection Fraction: A Review
- 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment
  - Comprehensive and definitive Heart failure (HF) guideline under development by the American College of Cardiology

HFrEF Medications with Mortality Benefit

- Angiotensin-Converting Enzyme Inhibitors (ACEi)/Angiotensin II Receptor Blockers (ARB)
- Angiotensin Receptor-Neprilysin Inhibitors (ARNI)
- Beta Blockers
- Mineralocorticoid Receptor Antagonists
- Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)
- Vasodilators

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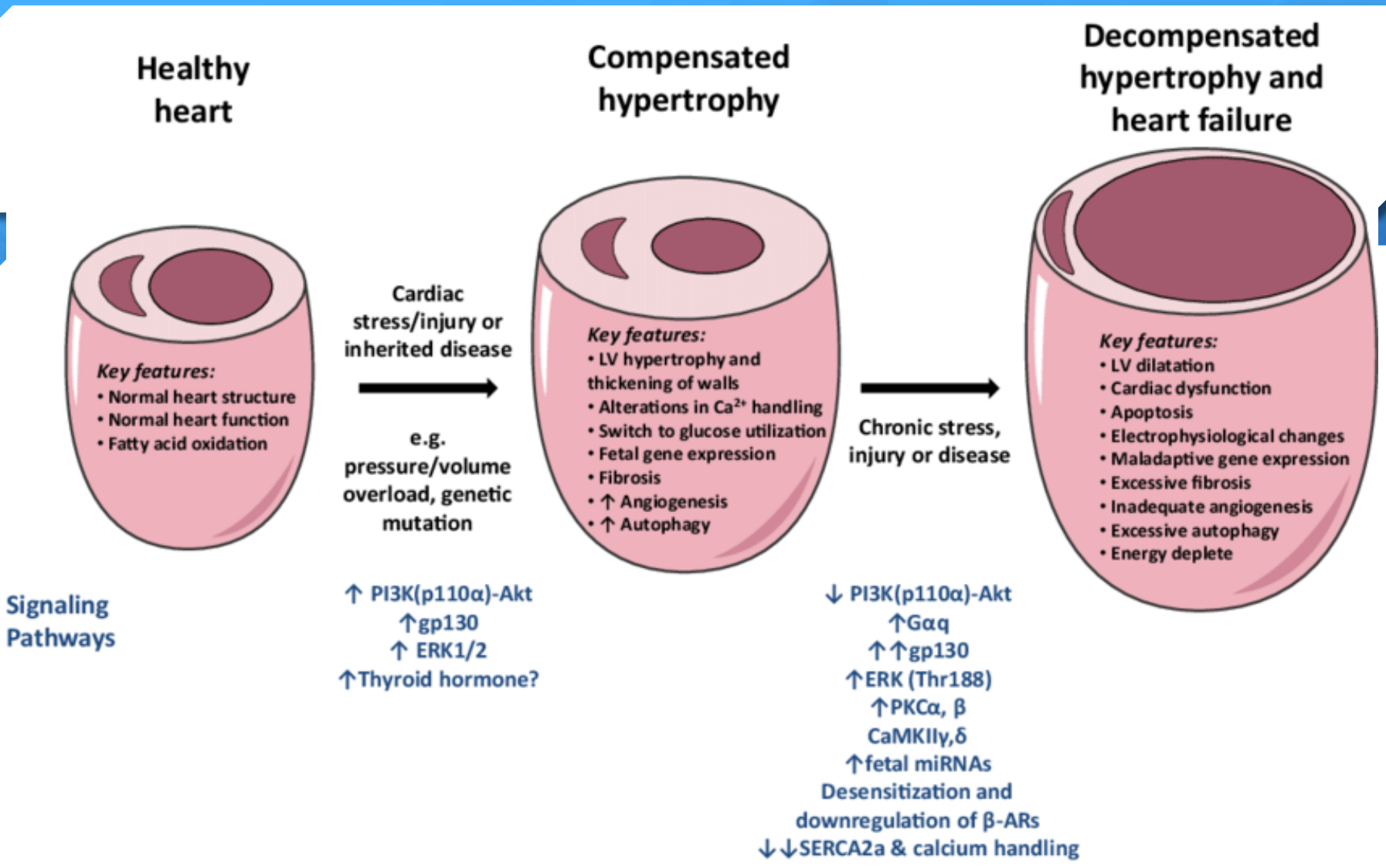
Heart Failure Pathophysiology

- Pathophysiology:
  - **Maladaptive** response to heart failure during which the renin-angiotensin-aldosterone system (RAAS) is activated
  - RAAS activation leads to vasoconstriction, hypertension, increased aldosterone levels, increased sympathetic tone, and eventually cardiac remodeling

Angiotensin-Converting Enzyme Inhibitors/Angiotensin II Receptor Blockers

- Mechanism of action
  - Inhibits the renin-angiotensin-aldosterone system (RAAS)
  - Reduce ventricular remodeling after myocardial damage

Tham, Yow Keat & Bernardo, Bianca & Ooi, Jenny & Weeks, Kate & Mcmullen, Julie. (2015). Pathophysiology of cardiac hypertrophy and heart failure: Signaling pathways and novel therapeutic targets. Archives of toxicology. 89. 10.1007/s00204-015-1477-x.



Tham, Yow Keat & Bernardo, Bianca & Ooi, Jenny & Weeks, Kate & Mcmullen, Julie. (2015). Pathophysiology of cardiac hypertrophy and heart failure: Signaling pathways and novel therapeutic targets. Archives of toxicology. 89. 10.1007/s00204-015-1477-x.

Angiotensin-Converting Enzyme Inhibitors/Angiotensin II Receptor Blockers

- Mechanism of action
  - Reduce ventricular remodeling after myocardial damage
- Caution:
  - Low blood pressure (SBP < 80)
  - CKD (Cr > 3)
  - Hyperkalemia (K > 5.5)

Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart Failure With Reduced Ejection Fraction: A Review. JAMA. 2020 Aug 4;324(5):488-504. doi: 10.1001/jama.2020.10262. Erratum in: JAMA. 2020 Nov 24;324(20):2107. PMID: 32749493.

Angiotensin-Converting Enzyme Inhibitors/Angiotensin II Receptor Blockers

- ACEi
  - Captopril
    - SAVE (NEJM 1992)
  - Ramipril
    - AIRE (J Cardiovasc Pharmacol 1991)
  - Enalapril
    - SOLVD (NEJM 1991)
- ARB
  - Candesartan
    - CHARM (Circulation 2004)
  - Losartan
    - OPTIMAL (Lancet 2002)
  - Valsartan
    - Val-HeFT (NEJM 2001)

HFrEF Medications with Mortality Benefit

- Angiotensin-Converting Enzyme Inhibitors (ACEi)/Angiotensin II Receptor Blockers (ARB)
- **Angiotensin Receptor-Neprilysin Inhibitors (ARNI)**
- Beta Blockers
- Mineralocorticoid Receptor Antagonists
- Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)
- Vasodilators

Heart Failure Pathophysiology

- Pathophysiology:
  - **Maladaptive** responses to heart failure
    - Renin-angiotensin-aldosterone system (RAAS) is activated
    - Neprilysin is an endopeptidase that degrades natriuretic peptides (BNP and NT-pro BNP).
  - **Favorable** response to heart failure
    - Natriuretic peptide system works antagonistically to the RAAS
      - Compensatory mechanism that leads to vasodilation, natriuresis and diuresis, lowers blood pressure (BP), lowers sympathetic tone, and reduces aldosterone levels

Nicolas D, Kerndt CC, Reed M. Sacubitril/Valsartan. [Updated 2020 Dec 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

- Mechanism of Action
  - Inhibition of neprilysin, which prolongs favorable effects of natriuretic peptides
  - Inhibits the renin-angiotensin-aldosterone system (RAAS)

Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart Failure With Reduced Ejection Fraction: A Review. JAMA. 2020 Aug 4;324(5):488-504. doi: 10.1001/jama.2020.10262. Erratum in: JAMA. 2020 Nov 24;324(20):2107. PMID: 32749493.

Natriuretic Peptide Physiology

Straight Healthcare. "Neprilysin Inhibitors (Entresto)." Neprilysin Inhibitors (Entresto®), 2021, www.straighthealthcare.com/neprilysin-inhibitors.html#moa.

Atrial Natriuretic Peptide (ANP)
Secreted by the atria in response to atrial distension

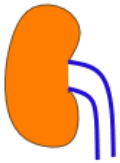
B-type Natriuretic Peptide (BNP)
Secreted by the ventricles in response to distension from volume overload

C-type Natriuretic Peptide (CNP)
Secreted by vascular endothelial cells in response to inflammatory mediators

Sacubitril (Entresto®)
Inhibits neprilysin and blocks ANP, BNP, and CNP metabolism

Neprilysin
Metabolizes ANP, BNP and CNP

ANP
BNP
CNP



ANP and BNP stimulate sodium and fluid excretion

ANP and BNP promote myocardial relaxation and inhibit hypertrophy and fibrosis

ANP and BNP suppress sympathetic outflow

ANP, BNP, and CNP stimulate vasodilation

Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

- Mechanism of Action
  - Inhibition of neprilysin, which prolongs favorable effects of natriuretic peptides
- Caution
  - Angioedema
  - Same contraindications for ARBs
  - For eGFR < 30, reduce starting dose to 24/26 mg twice daily
- Population
  - In EF < 35

Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart Failure With Reduced Ejection Fraction: A Review. JAMA. 2020 Aug 4;324(5):488-504. doi: 10.1001/jama.2020.10262. Erratum in: JAMA. 2020 Nov 24;324(20):2107. PMID: 32749493.

Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

- Sacubitril/Valsartan (Entresto)
  - PARADIGM-HF (NEJM 2014)
  - PIONEER-HF (NEJM 2018)

Clinical Pearl

- Initiation of an ARNI/ACEI/ARB is often better tolerated when the patient is still congested ("wet")
- Beta-blockers are better tolerated when the patient is less congested ("dry") with an adequate resting heart rate

HFrEF Medications with Mortality Benefit

- Angiotensin-Converting Enzyme Inhibitors (ACEi)/Angiotensin II Receptor Blockers (ARB)
- Angiotensin Receptor-Neprilysin Inhibitors (ARNI)
- **Beta Blockers**
- Mineralocorticoid Receptor Antagonists
- Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)
- Vasodilators

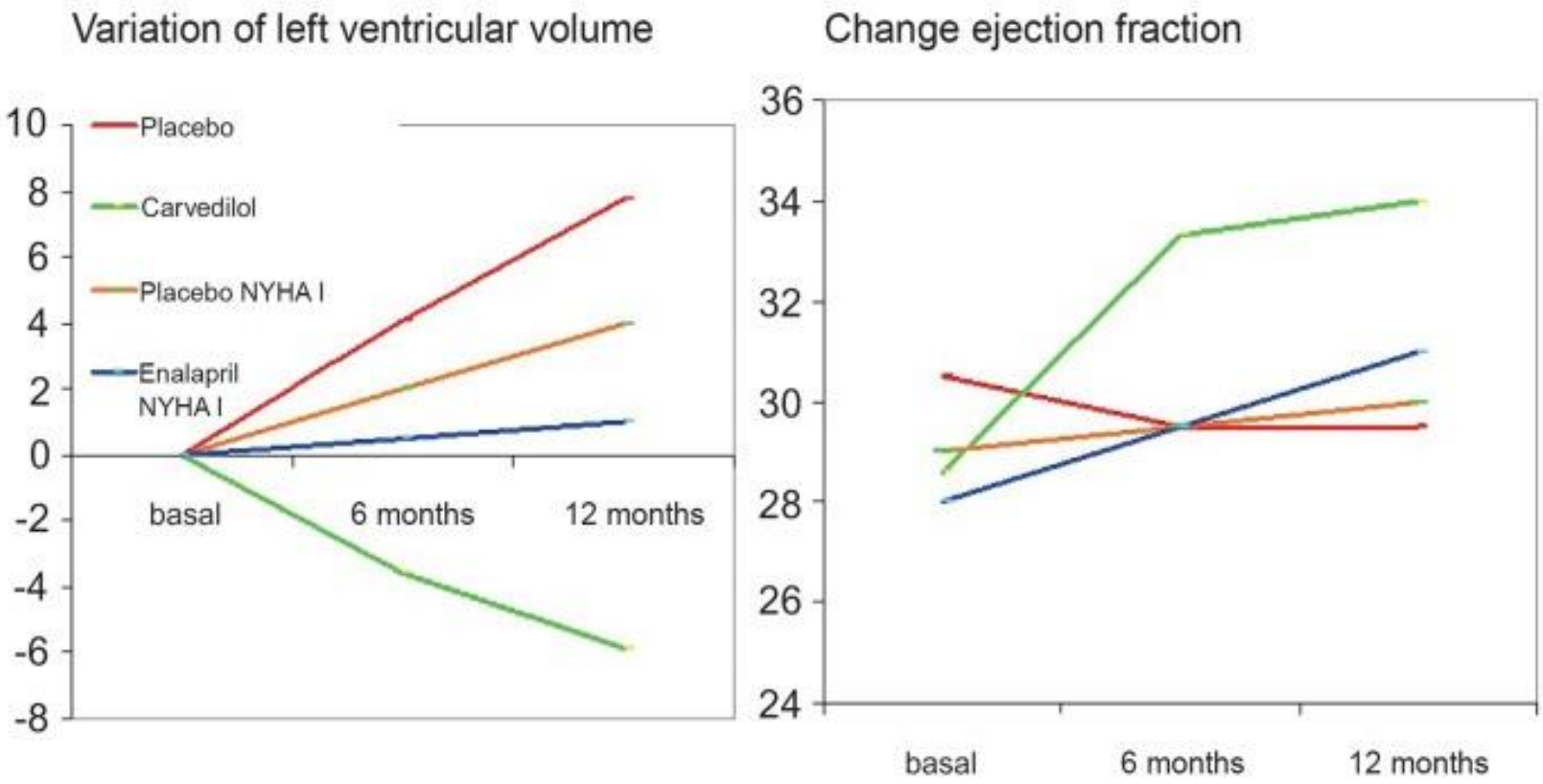
Beta Blockers

- Mechanism of Action
  - Slows and **reverses** the progression of ventricular remodeling

ACE inhibitors prevent cardiac dilation and beta-blockers reverse it.

Coh JN et al JACC 2000; 35: 569-82

Ventricular remodeling - role of drugs



Reis Filho, José Rosino de Araújo Rocha et al. "Reverse Cardiac Remodeling: A Marker of Better Prognosis in Heart Failure." Arquivos brasileiros de cardiologia vol. 104,6 (2015): 502-6. doi:10.5935/abc.20150025

Beta Blockers

- Mechanism of Action
  - Slows and reverses the progression of ventricular remodeling
- Caution
  - Symptomatic bradycardia
  - Advanced heart failure and low cardiac output
  - High-grade atrioventricular block
  - Hypotension
- Population
  - In EF < 35

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Beta Blockers

- Bisoprolol
  - CIBIS II (Lancet 1999)
- Metoprolol succinate
  - MERIT (Lancet 1999)
- Carvedilol
  - COPERNICUS (Circulation 2002)
  - COMET (Lancet 2003)

HFrEF Medications with Mortality Benefit

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- Beta Blockers
- **Mineralocorticoid Receptor Antagonists**
- Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)
- Vasodilators

Mineralocorticoid Receptor Antagonists

- Mechanism of Action
  - Inhibits the renin-angiotensin-aldosterone system (RAAS)
  - Reduce ventricular remodeling after myocardial damage

Mineralocorticoid Receptor Antagonists

- Mechanism of Action
  - Reduce ventricular remodeling after myocardial damage
- Caution
  - Cr > 2.5 (or eGFR < 30)
  - K > 5
- Population
  - In EF < 35 and NYHA class II to IV symptoms

Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart Failure With Reduced Ejection Fraction: A Review. JAMA. 2020 Aug 4;324(5):488-504. doi: 10.1001/jama.2020.10262. Erratum in: JAMA. 2020 Nov 24;324(20):2107. PMID: 32749493.

Mineralocorticoid Receptor Antagonists

- Spironolactone
  - RALES (NEJM 1999)
- Eplerenone
  - EPHESUS (NEJM 2003)
  - EMPHASIS-HF (NEJM 2011)

HFrEF Medications with Mortality Benefit

- Angiotensin-Converting Enzyme Inhibitors (ACEi)/Angiotensin II Receptor Blockers (ARB)
- Angiotensin Receptor-Neprilysin Inhibitors (ARNI)
- Beta Blockers
- Mineralocorticoid Receptor Antagonists
- **Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)**
- Vasodilators

Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)

- Mechanism of Action
  - Inhibiting SGLT2 in the proximal convoluted tubule to prevent reabsorption of glucose
  - Mechanism for mortality benefit remains unknown
    - Not solely due to effects of natriuresis, osmotic diuresis, weight loss, and blood pressure reduction
    - Theories including beneficial effects on myocardial metabolism, fibrosis, inflammation, vascular function, and ion transport

Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)

- Mechanism of Action
  - Mechanism for mortality benefit remains unknown
- Caution
  - eGFR < 30 (< 20 for empagliflozin)
  - T1DM, T2DM with prior DKA
  - Frequent UTI/GU yeast infection
- Population
  - EF ≤ 40%, regardless of diabetic status

Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart Failure With Reduced Ejection Fraction: A Review. JAMA. 2020 Aug 4;324(5):488-504. doi: 10.1001/jama.2020.10262. Erratum in: JAMA. 2020 Nov 24;324(20):2107. PMID: 32749493.

Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)

- Currently awaiting trials for HFpEF
- Anticipated to be endorsed by the 2021 American College of Cardiology guidelines

Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)

- Dapagliflozin
  - DAPA-HF trial (NEJM 2019)
- Empagliflozin
  - EMPEROR-Reduced trial (NEJM 2020)
- Canagliflozin
  - CREDENCE trial (NEJM 2019)

HFrEF Medications with Mortality Benefit

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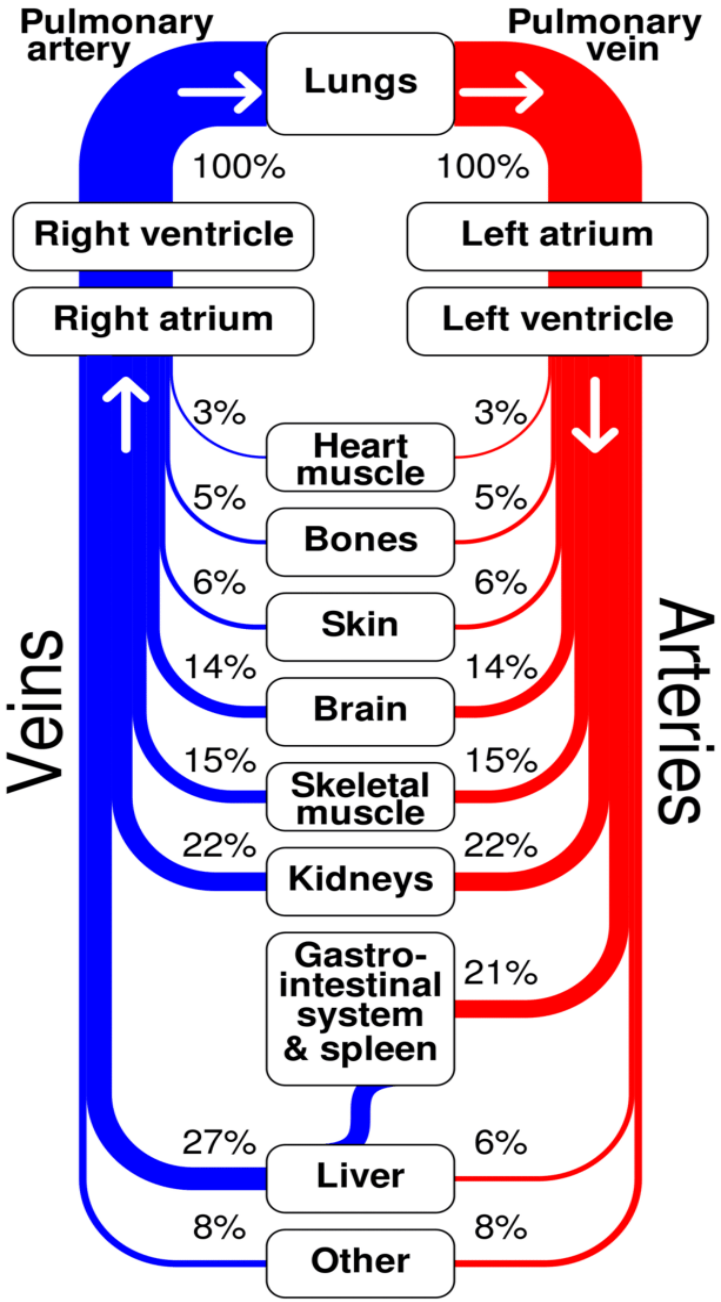
- Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)
- **Vasodilators**

Vasodilators

- Mechanism of Action
  - Vasodilation through increased nitric oxide signaling
  - Reduce the intra-cardiac filling pressures which will in turn reduce the maladaptive cardiac remodeling process

Al-Mohammad, Abdallah. "Hydralazine and nitrates in the treatment of heart failure with reduced ejection fraction." ESC heart failure vol. 6,4 (2019): 878-883. doi:10.1002/ehf2.12459

Isosorbide dinitrate



Hydralazine

Vasodilators

- Mechanism of Action
  - Reduce the intra-cardiac filling pressures which will in turn reduce the maladaptive cardiac remodeling process
- Caution
  - Concomitant use of PDE-5 inhibitors or soluble guanulate cyclase stimulators
- Population
  - In Black population with EF < 35, after treatment with ACEi/ARB/ARNI/BB/MRA

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Vasodilators

- Isosorbide dinitrate (Isordil) + Hydralazine
  - A-HeFT (NEJM 2004)
  - Isosorbide mononitrate (Imdur) extended release may be used as an alternative to Isordil
    - Not in the 2017 HF guidelines update

HFrEF Medications with Mortality Benefit

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- Angiotensin Receptor-Neprilysin Inhibitors (ARNI)
- Beta Blockers
- Mineralocorticoid Receptor Antagonists
- Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)
- Vasodilators

Versus

HFrEF Medications with Morbidity Benefit but no Mortality Benefit

- Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers
  - Ivabradine
- Oral Soluble Guanulate Cyclase Stimulator
  - Vericiguat

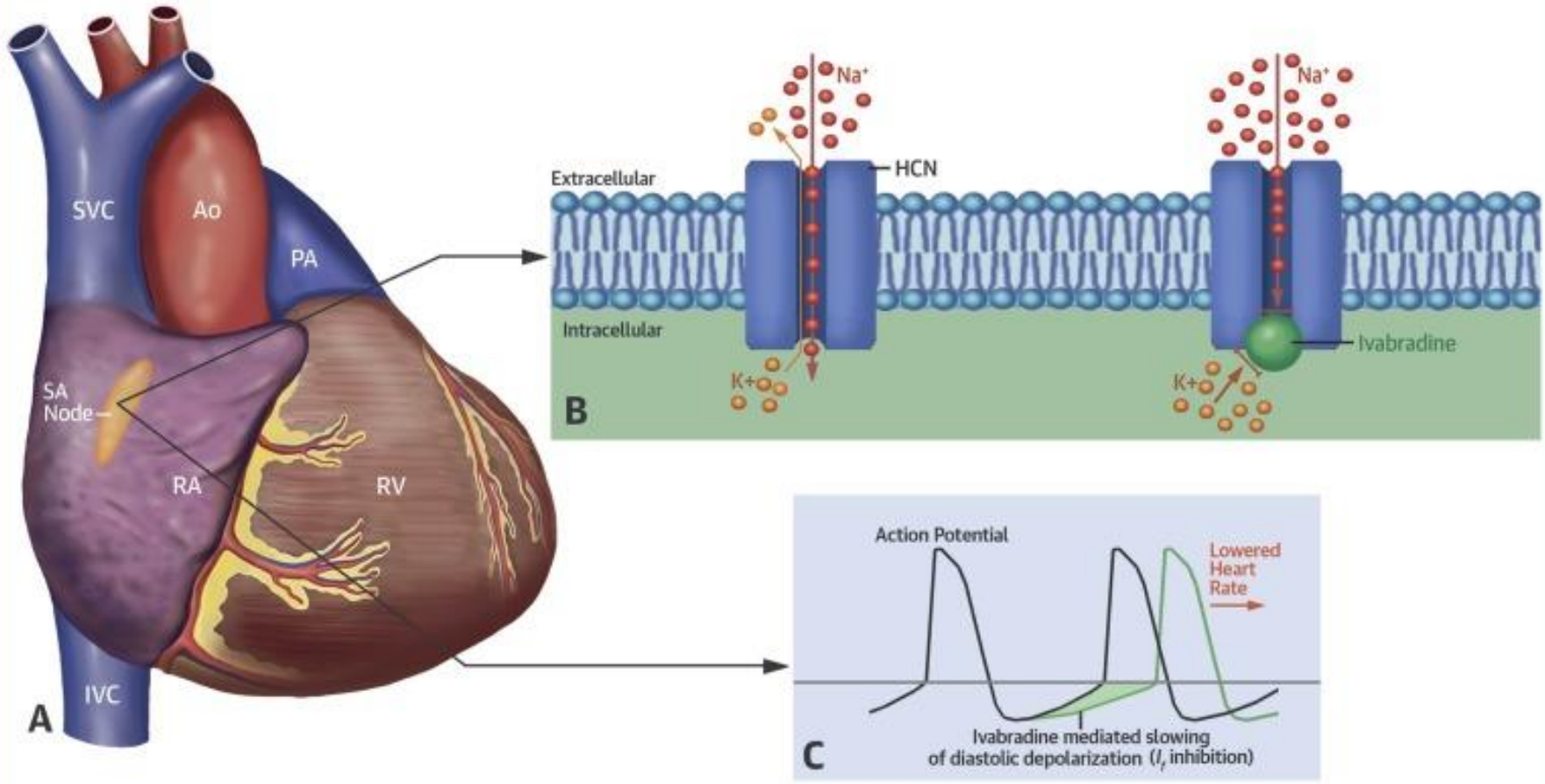
HFrEF Medications with Morbidity Benefit but no Mortality Benefit

- **Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers**
  - **Ivabradine**
- Oral Soluble Guanulate Cyclase Stimulator
  - Vericiguat

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers

- Mechanism of Action
  - Blocks funny channel current
    - Which inhibits pacemaker activity in the sinoatrial node
    - Which leads to slower heart rate
  - Does not affect blood pressure, myocardial contractility, or intracardiac conduction

CENTRAL ILLUSTRATION: Mechanism of Action of Ivabradine



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

Jacob S. Koruth, Anuradha Lala, Sean Pinney, Vivek Y. Reddy, Srinivas R. Dukkipati, The Clinical Use of Ivabradine, Journal of the American College of Cardiology, Volume 70, Issue 14, 2017, p 1777-1784

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers

- Mechanism of Action
  - inhibits pacemaker activity in the sinoatrial node which leads to slower heart rate
- Caution
  - Bradycardia, advanced heart block, severe liver dysfunction
- Population
  - EF ≤ 35, NYHA II or III, sinus heart rate ≥ 70 bpm, and on maximally tolerated beta-blocker

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Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers

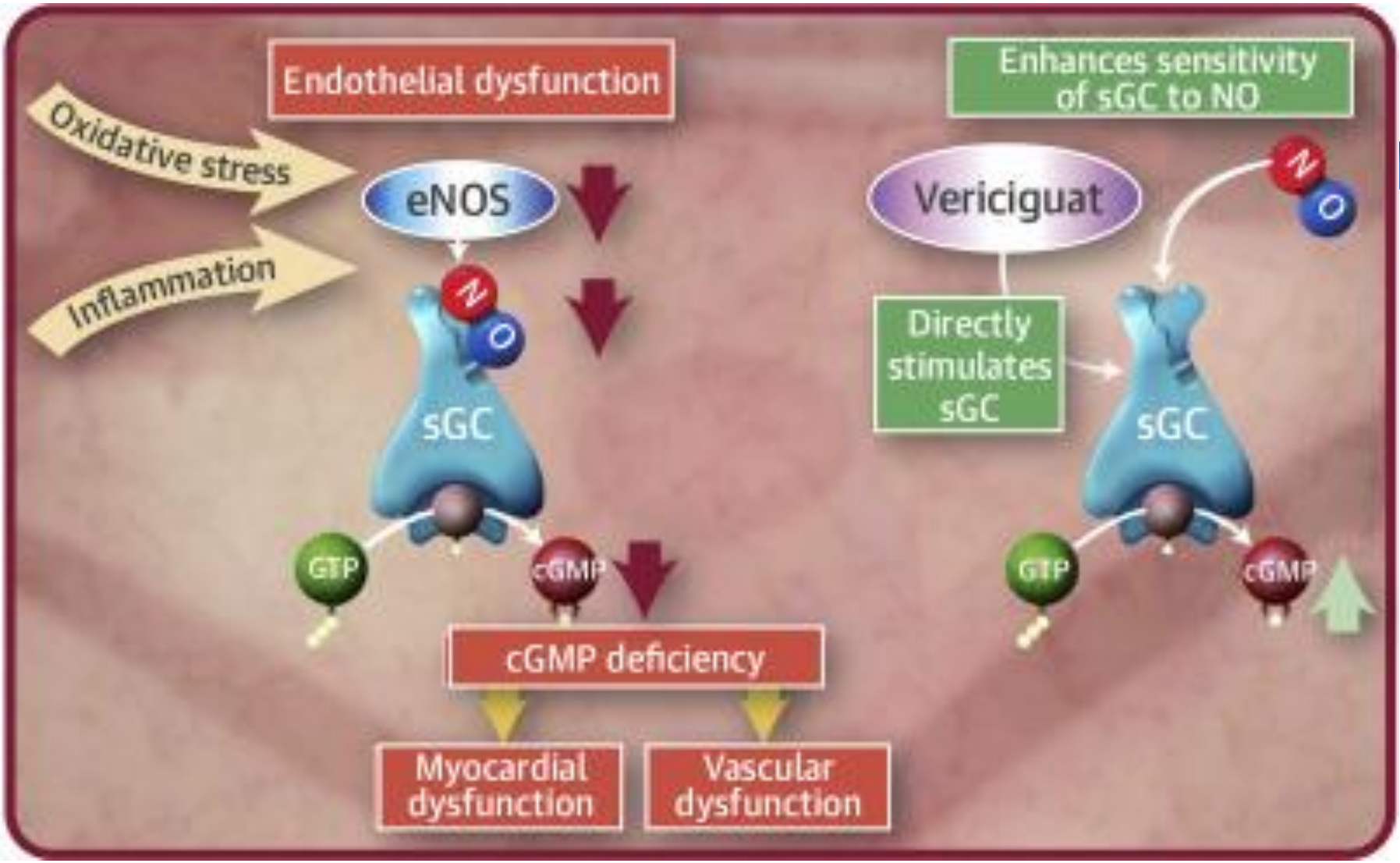
- Ivabradine
  - SHIFT (Lancet 2010)

HFrEF Medications with Morbidity Benefit but no Mortality Benefit

- Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers
  - Ivabradine
- **Oral Soluble Guanulate Cyclase (sGC) Stimulator**
  - **Vericiguat**

Oral Soluble Guanulate Cyclase (sGC) Stimulator

- Mechanism of Action
  - Increases cycle guanosine monophosphate (cGMP) activity
    - Regulates protective cardiovascular actions such as vasodilation



Paul W. Armstrong et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator: The VICTORIA Trial, JACC: Heart Failure,Volume 6, Issue 2,2018, p 96-104

Oral Soluble Guanulate Cyclase (sGC) Stimulator

- Mechanism of Action
  - Regulates protective cardiovascular actions such as vasodilation
- Caution
  - Nitrate or PDE inhibitor use given risk of hypotension
- Population
  - EF < 45 % and NYHA Class II to IV HF

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Oral Soluble Guanulate Cyclase (sGC) Stimulator

- Vericiguat
  - VICTORIA (NEJM 2020)

Guideline-Directed Medical Therapy

- How do we use these medications?
  - JAMA 2020 method

JAMA

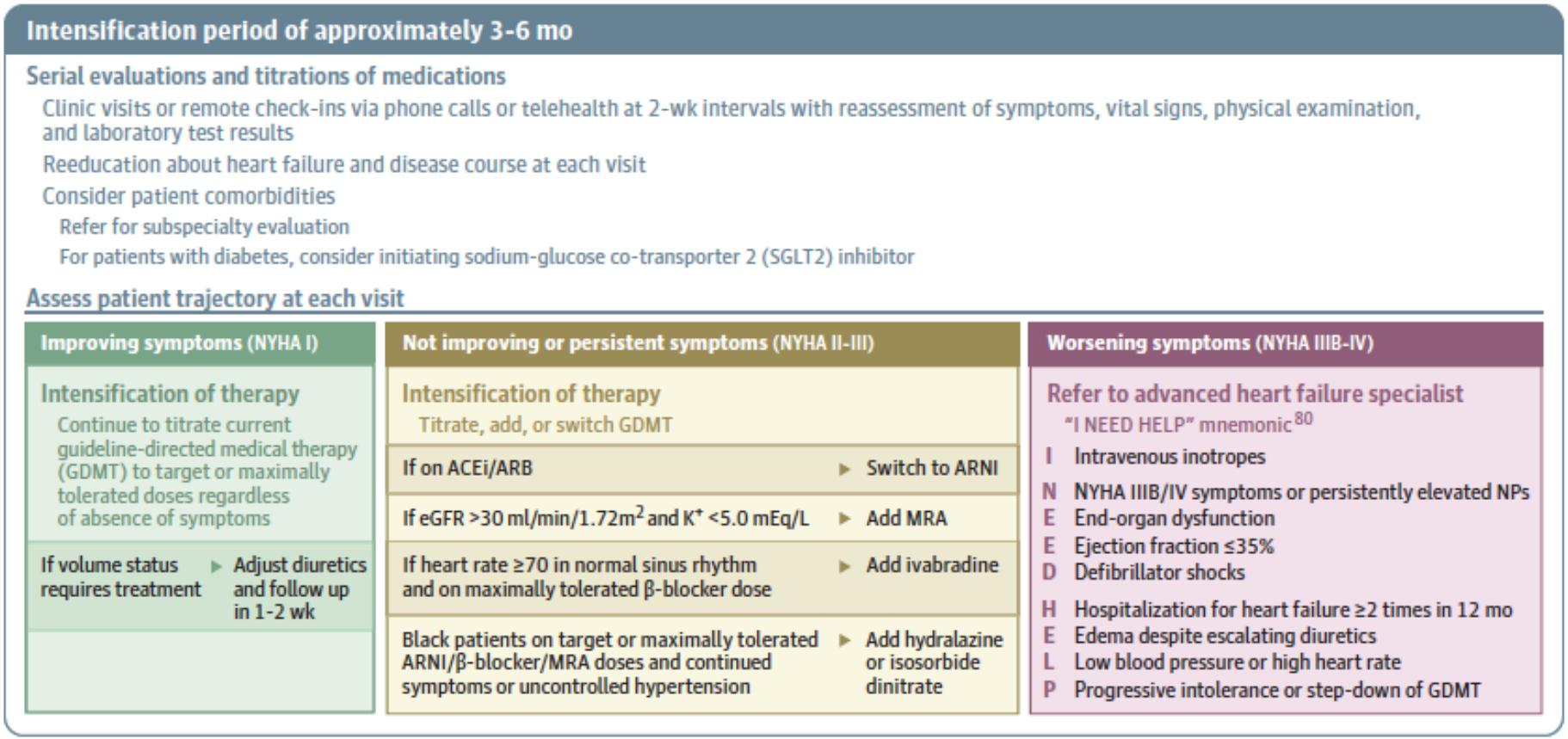
  - JACC 2021 method

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

American Medical Association Approach to Guideline-Directed Medical Therapy

Guideline-Directed Medical Therapy

Figure. Suggested Management of HFrEF: Intensification and Stabilization Periods



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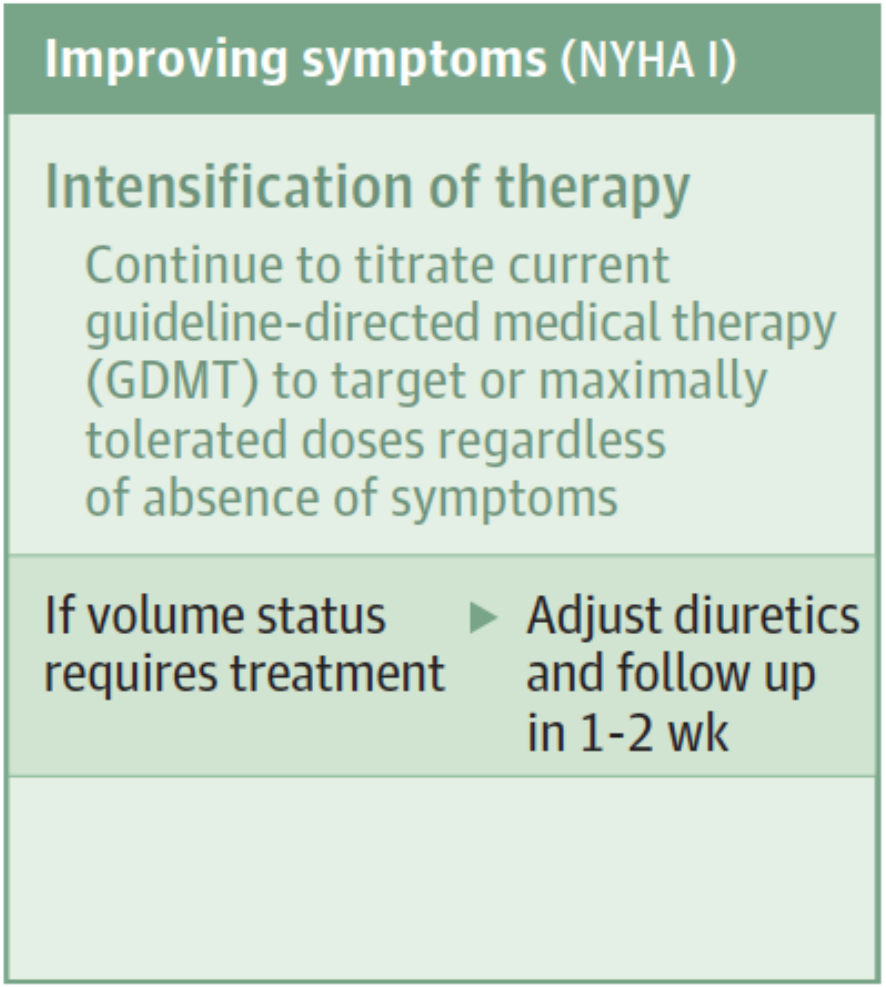
Guideline-Directed Medical Therapy



Guideline-Directed Medical Therapy

Not improving or persistent symptoms (NYHA II-III)	
Intensification of therapy Titrate, add, or switch GDMT	
If on ACEi/ARB	▶ Switch to ARNI
If eGFR >30 ml/min/1.72m^2 and K^+ <5.0 mEq/L	▶ Add MRA
If heart rate ≥70 in normal sinus rhythm and on maximally tolerated β-blocker dose	▶ Add ivabradine
Black patients on target or maximally tolerated ARNI/β-blocker/MRA doses and continued symptoms or uncontrolled hypertension	▶ Add hydralazine or isosorbide dinitrate

Guideline-Directed Medical Therapy

Worsening symptoms (NYHA IIIB-IV)

Refer to advanced heart failure specialist

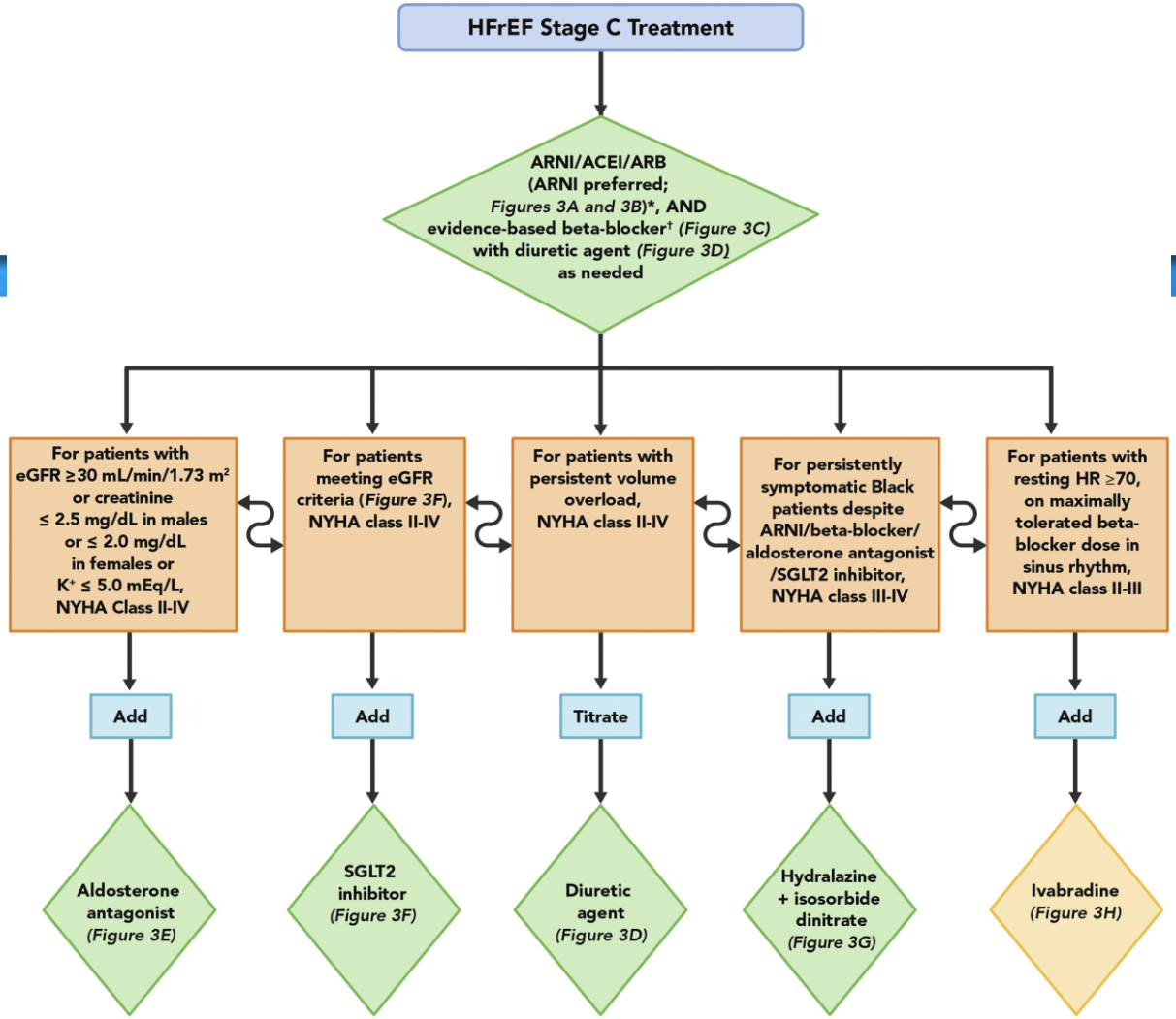
"I NEED HELP" mnemonic [80]

- **I** Intravenous inotropes
- **N** NYHA IIIB/IV symptoms or persistently elevated NPs
- **E** End-organ dysfunction
- **E** Ejection fraction ≤35%
- **D** Defibrillator shocks
- **H** Hospitalization for heart failure ≥2 times in 12 mo
- **E** Edema despite escalating diuretics
- **L** Low blood pressure or high heart rate
- **P** Progressive intolerance or step-down of GDMT

Guideline-Directed Medical Therapy

- Assess response to every change in therapy, especially at stabilization period after 3-6 months

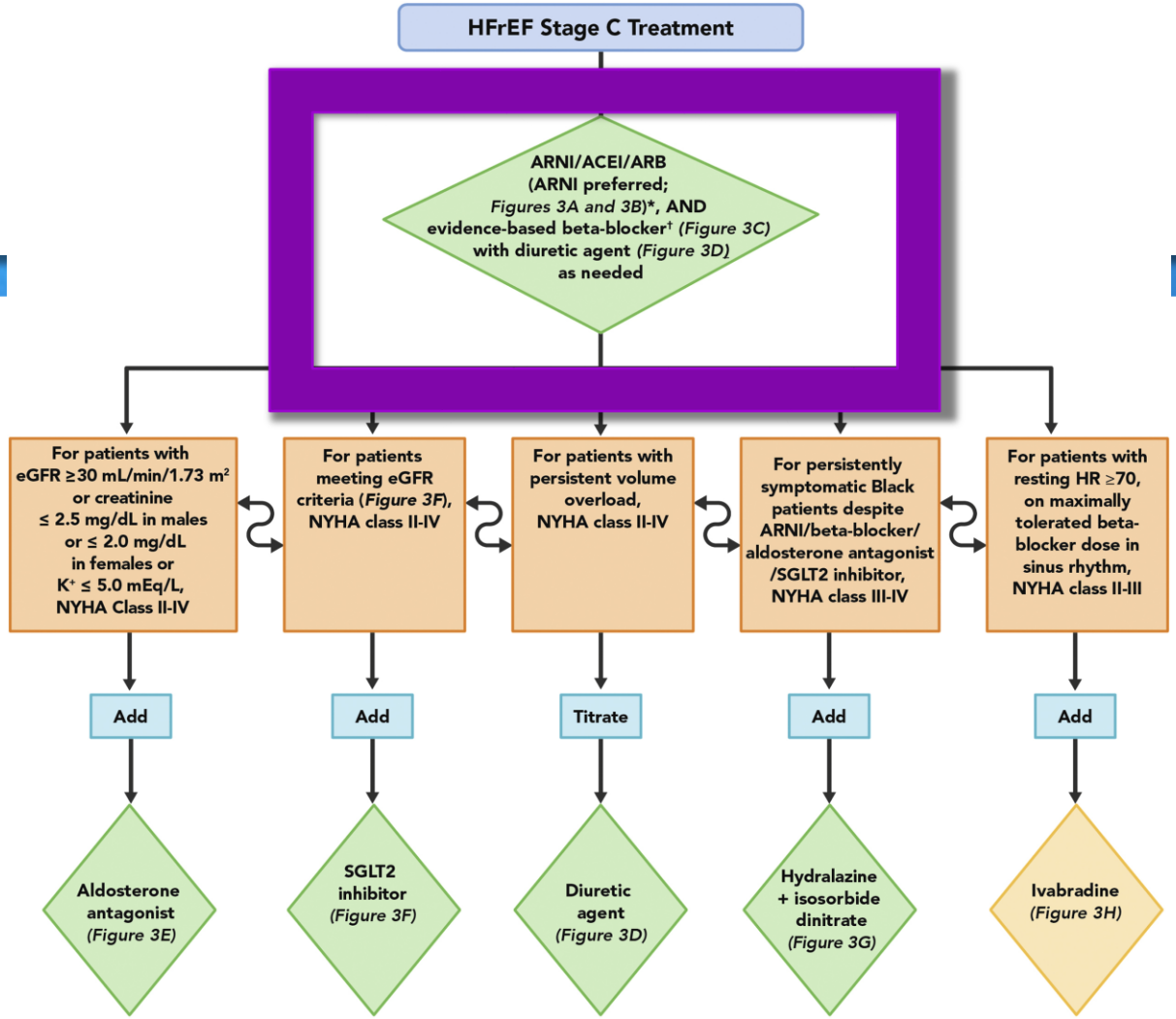
American College of Cardiology Approach to Guideline-Directed Medical Therapy



*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.

†Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K^+ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.



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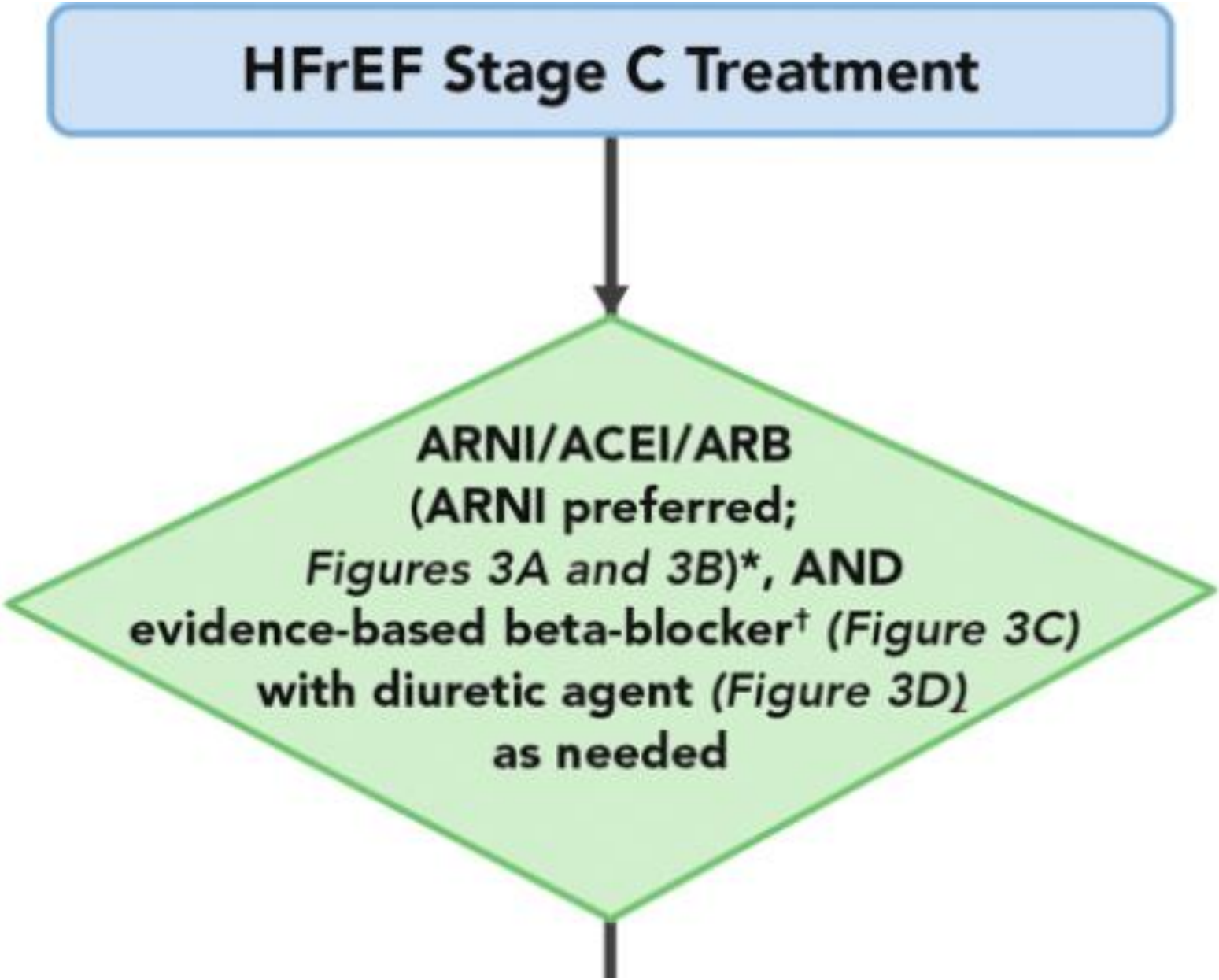
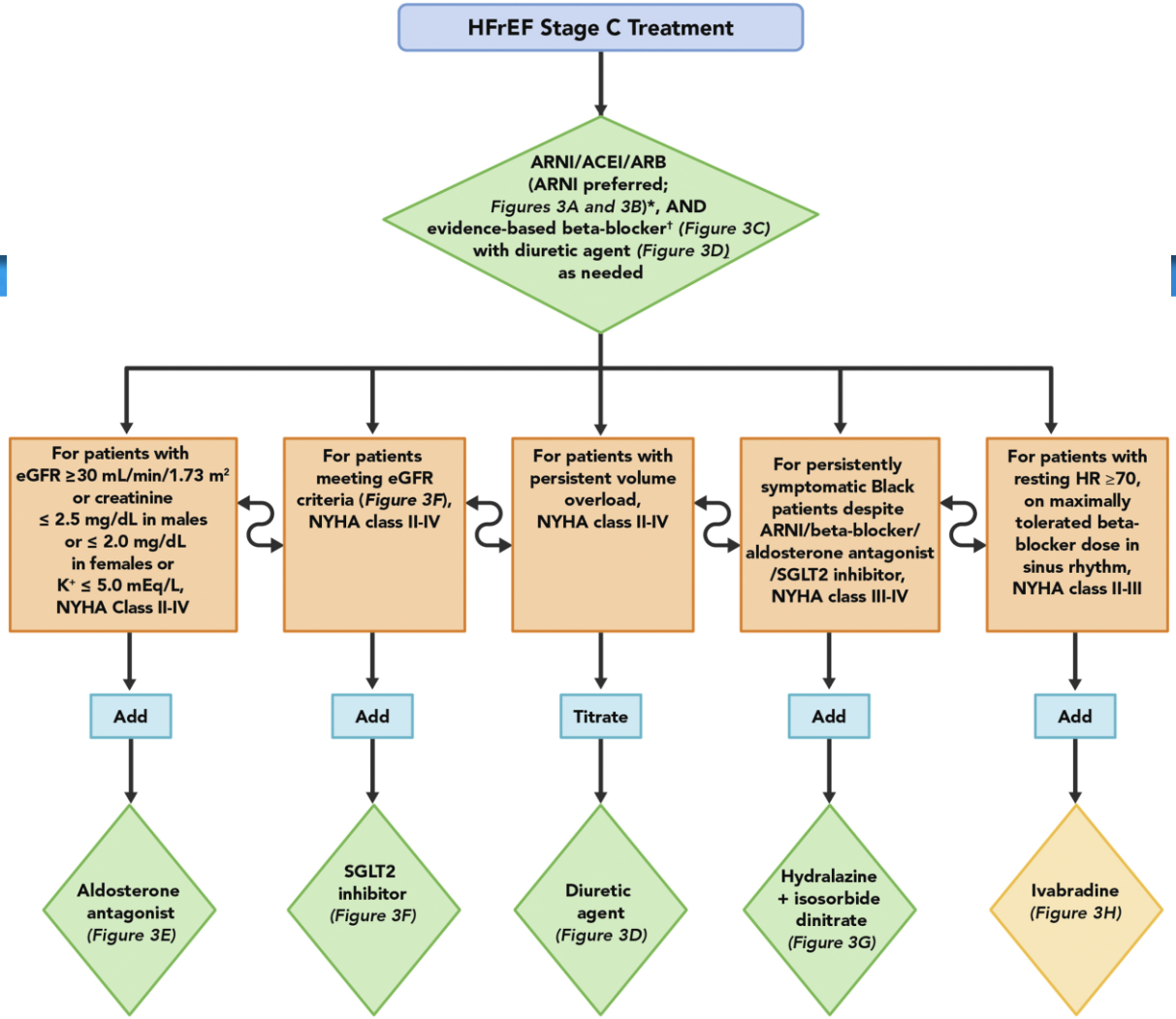
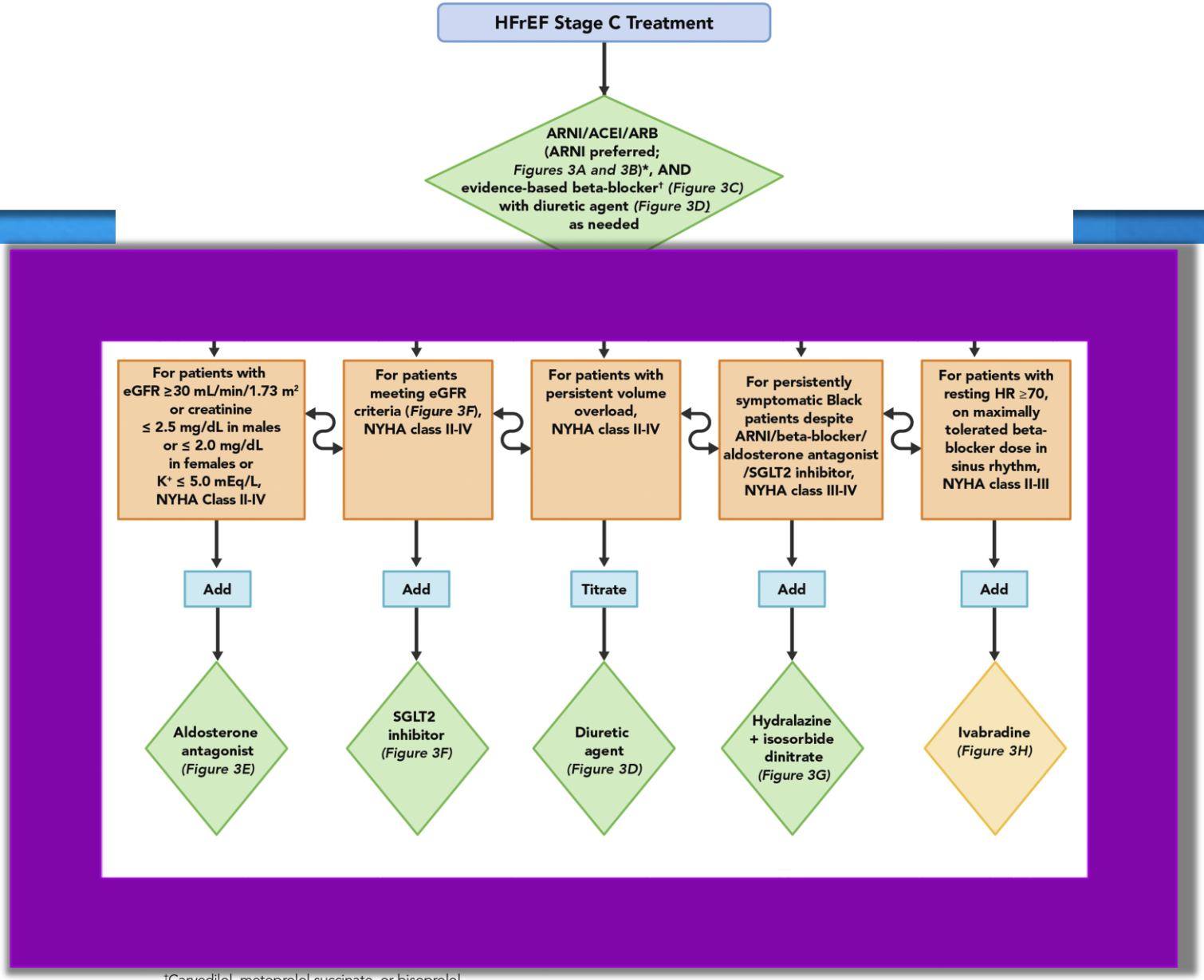

HFrEF Stage C Treatment
ARNI/ACEI/ARB
(ARNI preferred;
Figures 3A and 3B)*, AND
evidence-based beta-blocker† (Figure 3C)
with diuretic agent (Figure 3D)
as needed



*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.

†Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K^+ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.



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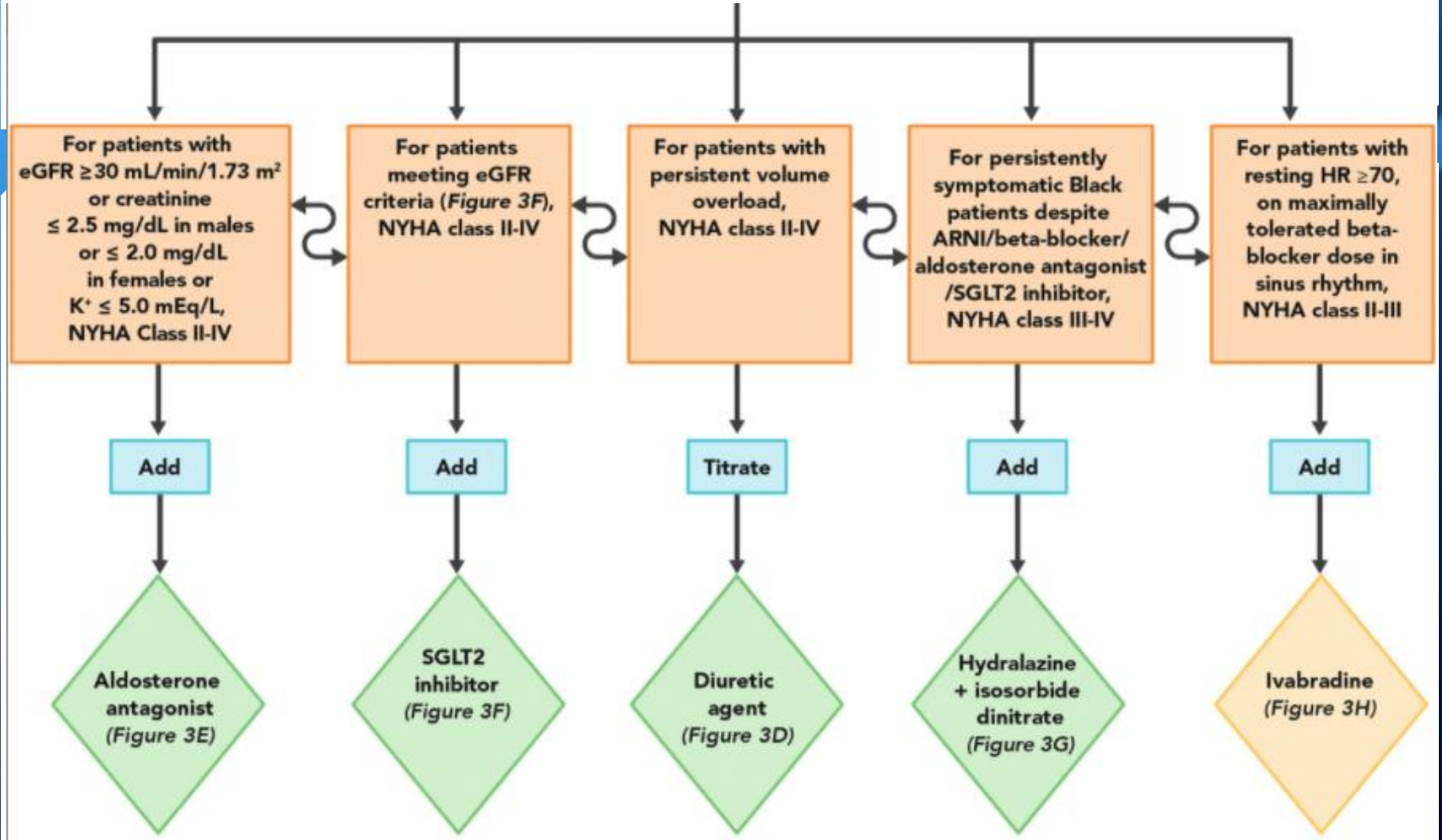
For patients with eGFR ≥30 mL/min/1.73 m² or creatinine ≤ 2.5 mg/dL in males or ≤ 2.0 mg/dL in females or K⁺ ≤ 5.0 mEq/L, NYHA Class II-IV
For patients meeting eGFR criteria (Figure 3F), NYHA class II-IV
For patients with persistent volume overload, NYHA class II-IV
For persistently symptomatic Black patients despite ARNI/beta-blocker/ aldosterone antagonist /SGLT2 inhibitor, NYHA class III-IV
For patients with resting HR ≥70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III
Add
Add
Titrate
Add
Add
Aldosterone antagonist (Figure 3E)
SGLT2 inhibitor (Figure 3F)
Diuretic agent (Figure 3D)
Hydralazine + isosorbide dinitrate (Figure 3G)
Ivabradine (Figure 3H)

Nonadherence to Guideline-Directed Medical Therapy

- After stabilization, with documented improvement in LVEF and decreased cardiac remodeling, heart failure can relapse following treatment withdrawal

Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2019; 393:61.

Optimization – Why do we need it?

- All HFrEF patients have high risk of complications
  - Quadruple therapy reduce risk of death by 73% over 2 years
  - 5-year survival rate after hospitalization for HFrEF is 25%
- Consider intensifying medications at every visit (if feasible) for "stable HFrEF patients"
  - Key word: consider
- Goal:
  - Achieve optimal titration with gradual titration or addition of new meds over more prolonged periods of time.

Greene SJ, Butler J, Fonarow GC. Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure—Optimizing Therapy With the Need for Speed. JAMA Cardiol. Published online March 31, 2021. doi:10.1001/jamacardio.2021.0496

Table 3. Starting and Target Doses of Guideline-Directed Medical Therapy for Heart Failure With Reduced Ejection Fraction

	Starting dose[a]	Target dose[a]
β-Blockers		
Bisoprolol	1.25 mg	10 mg
Metoprolol succinate	12.5-25 mg	200 mg
Carvedilol	3.125 mg 2 times/d	25 mg 2 times/d (weight <85 kg) or 50 mg 2 times/d (weight >85 kg
Angiotensin-converting enzyme inhibitors		
Captopril	6.25 mg 3 times/d	50 mg 3 times/d
Ramipril	1.25 mg	10 mg
Enalapril	2.5 mg 2 times/d	10-20 mg
Lisinopril	2.5-5 mg	20-40 mg
Angiotensin receptor blocker		
Candesartan	4-8 mg	32 mg
Losartan	25-50 mg	150 mg
Valsartan	40 mg 2 times/d	160 mg 2 times/d

Angiotensin receptor-neprilysin inhibitor		
Sacubitril/valsartan	24/26 mg-49/51 mg 2 times/d	97/103 mg 2 times/d
Mineralocorticoid receptor antagonists		
Eplerenone	25 mg 2 times/d	50 mg 2 times/d
Spironolactone	12.5-25 mg	25-50 mg
Vasodilators		
Hydralazine	25 mg 3 times/d	75 mg 3 times/d
Isosorbide dinitrate	20 mg 3 times/d	40 mg 3 times/d
Fixed-dose hydralazine/isosorbide dinitrate	20/37.5 mg (1 tablet) 3 times/d	Two tablets 3 times/d
Ivabradine	2.5-5 mg 2 times/d	Titrate to heart rate 50-60/min Max dose 7.5 mg 2 times/d

Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart Failure With Reduced Ejection Fraction: A Review. JAMA. 2020 Aug 4;324(5):488-504. doi: 10.1001/jama.2020.10262. Erratum in: JAMA. 2020 Nov 24;324(20):2107. PMID: 32749493.

Common Questions - Revisited

Common Questions

- Question:
  - Does race or ethnicity play a role in heart failure?

Common Questions - Answered

- Question:
  - Does race or ethnicity play a role in heart failure?
- Answer: Yes
  - Black patients
    - Have a greater risk of heart failure-related hospitalization and mortality
      - Consider SGLT2 inhibitor in pre-HF stage to reduce the onset of the disease in black patients with known diabetes.
    - Are consistently underrepresented in clinical trials for heart failure
      - ARNIs, SGLT2 inhibitors, and ivabradine were tested in clinical trial populations with few or no black patients

Maddox et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment. J Am Coll Cardiol. 2021 Feb, 77 (6) 772–810

Common Questions

- Question:
  - Start ARNI/ACEI/ARB or Beta-Blocker first?

Common Questions - Answered

- Question:
  - Start ARNI/ACEI/ARB or Beta-Blocker first?
- Answer:
  - Either will suffice
    - However, remember that beta-blocker has a bigger impact on reversing cardiac modeling
  - Can consider starting at the same time
  - Both classes of agent should be up-titrated to the maximum tolerated or target doses every 2 weeks

Common Questions

- Question:
  - Which is preferred for patients with heart failure? ARNI or ACEi/ARBs?

Common Questions - Answered

- Question:
  - Which is preferred for patients with heart failure? ARNI or ACEi/ARBs?
- Answer:
  - ARNI is preferred over ACEi/ARB except for contraindications or inaccessibility
  - Directly initiating an ARNI, rather than a pretreatment period ACEI or ARB, is a safe and effective strategy

Maddox et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment. J Am Coll Cardiol. 2021 Feb, 77 (6) 772–810

Common Questions

- Question:
  - Should heart failure patients receive aldosterone antagonists or ARNIs first?

Common Questions - Answered

- Question:
  - Should heart failure patients receive aldosterone antagonists or ARNIs first?
- Answer:
  - Lack of treatment with an aldosterone antagonist should not delay initiating or switching a patient to an ARNI.
    - No existing data to suggest an aldosterone antagonist is mandatory before ARNI therapy

Maddox et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment. J Am Coll Cardiol. 2021 Feb, 77 (6) 772–810

Common Questions

- Question:
  - Is it necessary to achieve target or maximally tolerated doses of other drugs before adding more?

Common Questions - Answered

- Question:
  - Is it necessary to achieve target or maximally tolerated doses of other drugs before adding more?
- Answer:
  - Data is lacking.
  - Two sides of the argument
    - Argument 1: "uptitrate medications to target doses"
    - Argument 2: "add more medications before target dose is achieved"

Argument 1: Uptitrate meds

- "Uptitrate medications to target doses"
  - J Am Coll Cardiol 2012:
    - Use of lower doses of GDMT has been associated with poorer patient outcomes
    - Titration to highest possible doses is crucial

Argument 2: Add more meds

- "Add more medications before target dose is achieved"
  - JAMA 2021:
    - While every effort should be made to achieve target or maximally tolerated dosages, lower dosages confer benefit
  - J Am Coll Cardiol 2021:
    - Although data are lacking, it is logical to assume that below-target doses of multiple classes of GDMT are likely more effective in reducing risk than large doses of 1 or 2 agents.

Greene SJ, Butler J, Fonarow GC. Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure—Optimizing Therapy With the Need for Speed. JAMA Cardiol. Published online March 31, 2021. doi:10.1001/jamacardio.2021.0496

Argument 2: Add more meds

- J Am Coll Cardiol 2021:
  - It is NOT necessary to achieve target or maximally tolerated doses of other drugs before adding aldosterone antagonists
    - In the RALES (NEJM 1999) trial, they used spironolactone 25 mg (uptitrated to 50 mg), which is typically below those that might influence blood pressure
    - For hypertension, spironolactone is uptitrated to 100 mg

Barriers to Intensification of Therapy

- Physician level
  - Lack of knowledge, lower level of comfort
- Patient level
  - Social determinants of health
- System-level
  - Cost

Barriers to Intensification of Therapy – Physician Level

- Conundrum of inpatient physicians deferring these meds until the outpatient setting
  - Statistics:
    - Deferring initiation of lifesaving medication to the outpatient setting carries a > 75% chance therapy will not be started within the next year
- Simultaneous or rapid sequence initiation of quadruple therapy seeks to break clinical inertia and treats HFrEF with the urgency it deserves

Greene SJ, Butler J, Fonarow GC. Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure—Optimizing Therapy With the Need for Speed. JAMA Cardiol. Published online March 31, 2021. doi:10.1001/jamacardio.2021.0496

Barriers to Intensification of Therapy – Patient Level

- Social Determinants of Health
- Lack of Insurance
- Difficulty of Instructions
  - A washout period of 36 hours is necessary when transitioning from ACE inhibitor to ARNI to avoid angioedema
- Patients in clinical practice are typically older, compared to patients in clinical trials
  - They are more susceptible to hypotension

Barriers to Intensification of Therapy – System Level

- Los Angeles County Lack of Access
- Cost
  - 30-day ARNI supply costs Medicare beneficiaries an average of $57 (per Medpage)
  - 30-day valsartan, carvedilol, and furosemide each cost around $2 to $5, on average (per Medpage)

Conclusion

- Delaying therapy can lead to preventable deaths and hospitalizations
- Consider titrating or adding new medications at every visit (if feasible) for "stable HFrEF patients"
- Take into consideration social determinants of health before adding new medications

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