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%

Introduction

- Heart Failure Categorization
  - Heart Failure with Reduced Ejection Fraction (HFrEF):
    - Ejection Fraction $\leq$ 40%
  - Heart Failure with Mid-Range Ejection Fraction (HFmrEF)
    - Ejection Fraction 41% - 49%
  - Heart Failure with Preserved Ejection Fraction (HFpEF)
    - Ejection Fraction $\geq$ 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

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-Nephrilysin Inhibitors (ARNI)
- Beta Blockers
- Mineralocorticoid Receptor Antagonists
- Sodium-Dependent Glucose Cotransporter Inhibitors (SGLT2i)
- Vasodilators
HFrEF Medications with Mortality Benefit

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

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)

# Angiotensin-Converting Enzyme Inhibitors/Angiotensin II Receptor Blockers

<table>
<thead>
<tr>
<th>ACEi</th>
<th>ARB</th>
</tr>
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<tbody>
<tr>
<td>Captopril</td>
<td>Candesartan</td>
</tr>
<tr>
<td>SAVE (NEJM 1992)</td>
<td>CHARM (Circulation 2004)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Losartan</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Valsartan</td>
</tr>
<tr>
<td>SOLVD (NEJM 1991)</td>
<td>Val-HeFT (NEJM 2001)</td>
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</tbody>
</table>
HFrEF Medications with Mortality Benefit

- Angiotensin-Converting Enzyme Inhibitors (ACEi)/Angiotensin II Receptor Blockers (ARB)
- Angiotensin Receptor-Nepri lysin 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-Nephrilysin Inhibitors (ARNI)

Mechanism of Action

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

Natriuretic Peptide Physiology

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 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-Nephrilysin Inhibitors (ARNI)

**Mechanism of Action**
- Inhibition of nephrilysin, 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

Angiotensin Receptor-Nephrilysin 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-Nephrilysin 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

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

Beta Blockers

- Bisoprolol
  - CIBIS II (Lancet 1999)

- Metoprolol succinate
  - MERIT (Lancet 1999)

- Carvedilol
  - COPERNICUS (Circulation 2002)
  - COMET (Lancet 2003)
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
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

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

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

- Angiotensin-Converting Enzyme Inhibitors (ACEi)/Angiotensin II Receptor Blockers (ARB)
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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

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

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

- Angiotensin-Converting Enzyme Inhibitors (ACEi)/Angiotensin II Receptor Blockers (ARB)
- Angiotensin Receptor-Nephrilysin Inhibitors (ARNI)
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- 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
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

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
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

Oral Soluble Guanulate Cyclase (sGC) Stimulator

- Vericiguat
  - VICTORIA (NEJM 2020)
Guideline-Directed Medical Therapy

- How do we use these medications?
  - JAMA 2020 method
  - JACC 2021 method
American Medical Association Approach to Guideline-Directed Medical Therapy
# Guideline-Directed Medical Therapy

**Figure. Suggested Management of HFrEF: Intensification and Stabilization Periods**

<table>
<thead>
<tr>
<th>Intensification period of approximately 3-6 mo</th>
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<tbody>
<tr>
<td><strong>Serial evaluations and titrations of medications</strong></td>
</tr>
<tr>
<td>Clinic visits or remote check-ins via phone calls or telehealth at 2-wk intervals with reassessment of symptoms, vital signs, physical examination, and laboratory test results</td>
</tr>
<tr>
<td>Reeducation about heart failure and disease course at each visit</td>
</tr>
<tr>
<td>Consider patient comorbidities</td>
</tr>
<tr>
<td>Refer for subspecialty evaluation</td>
</tr>
<tr>
<td>For patients with diabetes, consider initiating sodium-glucose co-transporter 2 (SGLT2) inhibitor</td>
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**Assess patient trajectory at each visit**

### Improving symptoms (NYHA I)
- **Intensification of therapy**
  - Continue to titrate current guideline-directed medical therapy (GDMT) to target or maximally tolerated doses regardless of absence of symptoms
  - If on ACEi/ARB
    - Adjust diuretics and follow up in 1-2 wk
  - If volume status requires treatment
    - Adjust diuretics and follow up in 1-2 wk

### 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/1.72m² 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 orisosorbide dinitrate

### Worsening symptoms (NYHA IIIB-IV)
- **Refer to advanced heart failure specialist**
  - “I NEED HELP” mnemonic
    - I: Intravenous inotropes
    - N: NYHA IIIb/IV symptoms or persistently elevated NPs
    - E: End-organ dysfunction
    - J: 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

Improving symptoms (NYHA I)

Intensification of therapy
Continue to titrate current guideline-directed medical therapy (GDMT) to target or maximally tolerated doses regardless of absence of symptoms

If volume status requires treatment ▶ Adjust diuretics and follow up in 1-2 wk
Guideline-Directed Medical Therapy

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<td><strong>Intensification of therapy</strong></td>
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### Guideline-Directed Medical Therapy

#### Worsening symptoms (NYHA IIIB-IV)

Refer to advanced heart failure specialist

**“I NEED HELP” mnemonic**

- **I**: Intravenous inotropes
- **N**: NYHA IIIB/IV symptoms or persistently elevated NPs
- **E**: End-organ dysfunction
- **E**: Ejection fraction $\leq 35\%$
- **D**: Defibrillator shocks
- **H**: Hospitalization for heart failure $\geq 2$ 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
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

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
Add
Aldosterone antagonist (Figure 3E)

For patients meeting eGFR criteria (Figure 3F), NYHA class II-IV
Add
SGLT2 inhibitor (Figure 3F)

For patients with persistent volume overload, NYHA class II-IV
Titrage
Diuretic agent (Figure 3D)

For persistently symptomatic Black patients despite ARNI/beta-blocker/aldosterone antagonist/SGLT2 inhibitor, NYHA class III-IV
Add
Hydralazine + isosorbide dinitrate (Figure 3G)

For patients with resting HR ≥ 70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III
Add
Ivabradine (Figure 3H)

*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.
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:

- Add Aldosterone antagonist (Figure 3E)

For patients meeting eGFR criteria (Figure 3F), NYHA class II-IV:

- Add SGLT2 inhibitor (Figure 3F)

For patients with persistent volume overload, NYHA class II-IV:

- Titrare Diuretic agent (Figure 3D)

For persistently symptomatic Black patients despite ARNI/beta-blocker/aldosterone antagonist/SGLT2 inhibitor, NYHA class III-IV:

- Add Hydralazine + isosorbide dinitrate (Figure 3G)

For patients with resting HR ≥ 70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III:

- Add Ivabradine (Figure 3H)

*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.
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
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

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Add

Aldosterone antagonist (Figure 3E)

For patients meeting eGFR criteria (Figure 3F), NYHA class II-IV

Add

SGLT2 inhibitor (Figure 3F)

For patients with persistent volume overload, NYHA class II-IV

Titrate

Diuretic agent (Figure 3D)

For persistently symptomatic Black patients despite ARNI/beta-blocker/aldosterone antagonist /SGLT2 inhibitor, NYHA class III-IV

Add

Hydralazine + isosorbide dinitrate (Figure 3G)

For patients with resting HR ≥ 70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III

Add

Ivabradine (Figure 3H)

*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; HF/EF = heart failure with reduced ejection fraction; HR = heart rate; K⁺ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.
**HFrEF Stage C Treatment**

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

**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**

Add

Aldosterone antagonist (Figure 3E)

**For patients meeting eGFR criteria (Figure 3F), NYHA class II-IV**

Add

SGLT2 inhibitor (Figure 3F)

**For patients with persistent volume overload, NYHA class II-IV**

Titrator

Diuretic agent (Figure 3D)

**For persistently symptomatic Black patients despite ARNI/beta-blocker/aldosterone antagonist/SGLT2 inhibitor, NYHA class III-IV**

Add

Hydralazine + isosorbide dinitrate (Figure 3G)

**For patients with resting HR ≥ 70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III**

Add

Ivabradine (Figure 3H)

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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

- Add Aldosterone antagonist (Figure 3E)

For patients meeting eGFR criteria (Figure 3F), NYHA class II-IV

- Add SGLT2 inhibitor (Figure 3F)

For patients with persistent volume overload, NYHA class II-IV

- Titrate Diuretic agent (Figure 3D)

For persistently symptomatic Black patients despite ARNI/beta-blocker/aldosterone antagonist/SGLT2 inhibitor, NYHA class III-IV

- Add Hydralazine + isosorbide dinitrate (Figure 3G)

For patients with resting HR ≥ 70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III

- Add 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.
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.

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<table>
<thead>
<tr>
<th></th>
<th>Starting dose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Target dose&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5-25 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg 2 times/d</td>
<td>25 mg 2 times/d (weight &lt;85 kg) or 50 mg 2 times/d (weight &gt;85 kg)</td>
</tr>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3 times/d</td>
<td>50 mg 3 times/d</td>
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<tr>
<td>Ramipril</td>
<td>1.25 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg 2 times/d</td>
<td>10-20 mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5 mg</td>
<td>20-40 mg</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blocker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4-8 mg</td>
<td>32 mg</td>
</tr>
<tr>
<td>Losartan</td>
<td>25-50 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg 2 times/d</td>
<td>160 mg 2 times/d</td>
</tr>
<tr>
<td>Angiotensin receptor–neprilysin inhibitor</td>
<td></td>
<td></td>
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<tr>
<td>-----------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24/26 mg-49/51 mg 2 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97/103 mg 2 times/d</td>
<td></td>
<td></td>
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<tr>
<td>Mineralocorticoid receptor antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg 2 times/d</td>
<td></td>
<td></td>
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<tr>
<td>50 mg 2 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.5-25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg 3 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 mg 3 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg 3 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 mg 3 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed-dose hydralazine/isosorbide dinitrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/37.5 mg (1 tablet) 3 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two tablets 3 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5-5 mg 2 times/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titrate to heart rate 50-60/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose 7.5 mg 2 times/d</td>
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</tbody>
</table>

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

Common Questions

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

Common Questions

Question:
- Should heart failure patients receive aldosterone antagonists or ARNIs first?
**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.
Common Questions

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


