Heart Failure:
An Update on Pharmacological Therapy

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Disclosures

• I, Stacie L. Penkova, PharmD, MHSA, BCPS, do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

• Special thanks to Hillary Hardwick for assisting me in compiling and condensing the material for this and my other presentations you will see today.
Objectives

• Define the classes of recommendations and levels of evidence of treatments represented in this guideline.

• Discuss the pharmacology of ACE inhibitors, ARBs, Entresto™ and Corlanor®.

• Review the 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure.
Yancy, CW, et al.
Heart Failure Focused Update on Pharmacological Therapy

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the International Society for Heart and Lung Transplantation

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Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated August 2015)

<table>
<thead>
<tr>
<th>Class (Strength) of Recommendation</th>
<th>Level (Quality) of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Strong)</td>
<td>Level A</td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk</td>
<td>High-quality evidence from more than 1 RCT</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td></td>
<td>RCTs or more RCTs corroborated by high-quality registry studies</td>
</tr>
<tr>
<td>Class IIa (Moderate)</td>
<td>Level B (Randomized)</td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk</td>
<td>Moderate-quality evidence from 1 or more RCTs</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td>Class IIb (Weak)</td>
<td>Level B-M (Nonrandomized)</td>
</tr>
<tr>
<td>Benefit = Risk</td>
<td>Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td>Class III: No Benefit (Moderate)</td>
<td>Level C (Limited Data)</td>
</tr>
<tr>
<td>Benefit = Risk</td>
<td>Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td>Class III: Harm (Strong)</td>
<td>Level C-ED (Expert Opinion)</td>
</tr>
<tr>
<td>Risk &gt;&gt; Benefit</td>
<td>Consensus of expert opinion based on clinical experience</td>
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CIR and CIE are determined independently (any CIR may be paired with any CIE). A recommendation with CIR C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are valuable, they may be very clear clinical scenarios that a particular test or therapy is useful or effective.  
* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental diagnostic information). 
* For comparability of effectiveness recommendations (CIR A and B only), studies that support the use of comparator would should involve direct comparisons of the treatments or strategies being evaluated. 
* The method of assessing quality is outlined, including the application of standardized, widely used, and previously validated evidence-guiding tools, and for systematic reviews, the incorporation of an Evidence Review Committee.

CIR indicates Class of Recommendation; ED, expert opinion; LD, limited data; LE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.
ACE Inhibitors

- Benazepril (Lotensin)
- Captopril (Capoten)
- Enalapril (Vasotec)
- Fosinopril (Monopril)
- Lisinopril (Prinivil, Zestril)
- Moexipril (Univasc)
- Perindopril (Aceon)
- Quinapril (Accupril)
- Ramipril (Altace)
- Trandolapril (Mavik)

- Inhibit the conversion of angiotensin–I to angiotensin–II.
- Angiotensin–II is a potent vasoconstrictor and promotes the production of aldosterone.
- Aldosterone promotes sodium and water retention.
- By inhibiting the production of angiotensin–II, ACE-inhibitors cause vasodilation and indirectly inhibit fluid volume increases that result from the actions of aldosterone.
ARBs

- Azilsartan (Edarbi)
- Candesartan (Atacand)
- Irbesartan (Avapro)
- Losartan (Cozaar)
- Telmisartan (Micardis)
- Valsartan (Diovan)

- By blocking the binding of angiotensin-II to the angiotensin-II receptor, these agents inhibit the vasoconstriction effects of angiotensin-II and prevent the angiotensin-II-mediated release of aldosterone.

- Aldosterone promotes sodium and water retention.

- By inhibiting the production of aldosterone, ARBs indirectly inhibit fluid volume increases that result from the actions of aldosterone.
• Valsartan/Sacubitril (Entresto)
• Neprilysin is a neutral endopeptidase that degrades some vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.
• Inhibition of neprilysin by LBQ657, the active metabolite of sacubitril, increases the levels of these peptides, decreasing vasoconstriction, sodium retention, and maladaptive remodeling.
How Supplied

• Entresto comes as film-coated, unscored, ovaloid-shaped tablets containing sacubitril/valsartan 24/26 mg, 49/51 mg, and 97/103 mg.

• Note that tablets are not proportionately the same (i.e., two 24/26 mg tablets does not equal one 49/51 mg tablet).

• And, also be aware that in some references you’ll see the 24/26 mg tablet referred to as 50 mg, the 49/51 mg tablet as 100 mg, and the 97/103 tablet as 200 mg.

• Tablets are supplied in bottles of 60 (i.e., a one-month supply) at a cost of $375 (WAC) or 180 for $1125 and blister packages of 100 for $625 (WAC).

• Tablets should be protected from moisture and stored in their original container.
Dosage

• Starting dose for Entresto is 49/51 mg twice daily.
• The dose should be increased every two to four weeks, as tolerated, to a target dose of 97/103 mg twice daily as maintenance.
• A reduced starting dose of 24/26 mg twice daily should be given to patients if they have not had previous therapy with an ACEI or an ARB, been on only low-dose ACEI or ARB, have severe renal impairment (eGFR <30 mL/min/1.73m2), or have moderate hepatic impairment.
• If a patient is switching from an ACEI to Entresto, they should wait 36 hours from the last dose before giving the first dose of Entresto.
  • Overlapping these two medications can increase the risk of angioedema.
• It is important to note that the 103 mg of valsartan in Entresto’s target dose is equivalent to 160 mg of valsartan in Diovan due to the fact that they are different salts.
Contraindications & Precautions

• Entresto is contraindicated in patients with a history of angioedema with a previous ACEI or ARB, concomitant use of an ACEI, and concomitant use with aliskiren in patients with diabetes.

• Patients on Entresto should be closely monitored for signs and symptoms of angioedema and hypotension. Renal function and serum potassium levels should be monitored periodically.

• Entresto is not recommended in patients with severe hepatic impairment.
**SN I\(_f\) Inhibitor**

- Ivabradine (Corlanor)
- Blocks the hyperpolarization–activated cyclic nucleotide–gated (HCN) channel responsible for the cardiac pacemaker I\(_f\) ‘funny’ current, which regulates heart rate.
- In clinical electrophysiology studies, the cardiac effects were most pronounced in the sinoatrial (SA) node, but prolongation of the AH interval has occurred on the surface ECG, as has PR interval prolongation.
- There was no effect on ventricular repolarization and no effects on myocardial contractility.
How Supplied

• Corlanor comes as 5 mg (oval) and 7.5 mg (triangular) salmon-colored, film-coated tablets, both available in bottles of 60 and 180.

• Cost for Corlanor is $375 (WAC) per month for both 5 mg and 7.5 mg twice daily dosing.
Dosage

- Corlanor should be started at a dose of 5 mg twice daily, given with meals.
- After two weeks, if heart rate is greater than 60 beats per minute, the dose should be increased to 7.5 mg twice daily.
- After two weeks, if heart rate is less than 50 beats per minute, the dose should be decreased to 2.5 mg twice daily.
- Patients at risk of hemodynamic compromise, such as those with a history of heart conduction defects, sinus node dysfunction, or ventricular dyssynchrony, should be started at a dose of 2.5 mg twice daily.
Contraindications & Precautions

- Use of Corlanor in patients with any of the following conditions is contraindicated:
  - Acute decompensated heart failure
  - Hypotension <90/50 mmHg
  - Sick sinus syndrome, sinoatrial block, or 3rd degree AV block in patients without pacemakers
  - Resting HR <60
  - Severe hepatic impairment
  - Heart rate completely maintained by pacemaker
  - Patients taking a strong CYP3A4 inhibitor
- Corlanor should be used with caution in patients with bradycardia and cardiac conduction disturbances.
- Of note, patients with sustained atrial fibrillation or flutter are not considered good candidates for Corlanor, as their heart rhythm is not directed by the sinoatrial node but rather originates in the atria where Corlanor has no known effects.
Recommendations for Renin–Angiotensin System Inhibition With ACEIs or ARBs or ARNI

The clinical strategy of inhibition of the renin–angiotensin system with Angiotensin–converting enzyme (ACE) inhibitors OR Angiotensin receptor blockers (ARBs) OR ARNI (an ARB combined with an inhibitor of neprilysin) in conjunction with evidence–based beta blockers and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF (HF with reduced ejection fraction also known as systolic heart failure) to reduce morbidity and mortality.

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<tr>
<th>Class (Strength) of Recommendation</th>
<th>Level (Quality) of Evidence</th>
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<tbody>
<tr>
<td>Class I (Strong): Benefit &gt;&gt;&gt; Risk</td>
<td>ACEIs: A (High-Quality)</td>
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<td></td>
<td>ARBs: A (High-Quality)</td>
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<td>ARNI: B-R (Moderate Quality)</td>
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Recommendations for Renin–Angiotensin System Inhibition With ACEIs or ARBs or ARNI

• The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality.

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<tbody>
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<td>Class I (Strong): Benefit &gt;&gt;&gt; Risk</td>
<td>B-R (Moderate-Quality)</td>
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Recommendations for Renin–Angiotensin System Inhibition With ACEIs or ARBs or ARNI

- The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema.

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<tbody>
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<td>A (High-Quality)</td>
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Recommendations for Renin–Angiotensin System Inhibition With ACEIs or ARBs or ARNI

- In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.

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<td>B-R (Moderate-Quality)</td>
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Recommendations for Renin–Angiotensin System Inhibition With ACEIs or ARBs or ARNI

- ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.

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<tr>
<td>Class III (Harm): Risk &gt; Benefit</td>
<td>B-R (Moderate-Quality)</td>
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- ARNI should not be administered to patients with a history of angioedema.

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<tbody>
<tr>
<td>Class III (Harm): Risk &gt; Benefit</td>
<td>C-EO (Expert Opinion)</td>
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Recommendation for Ivabradine

- Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II–III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.

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</thead>
<tbody>
<tr>
<td>Class Iia (Moderate): Benefit &gt;&gt; Risk</td>
<td>B-R (Moderate Evidence)</td>
</tr>
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