Two New Agents in the Management of Heart Failure:
Corlanor and Entresto

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Objectives:
At the conclusion of this activity, the attendee should be able to describe:

• Indications for use
• Mechanism of action
• Dosing, Titration & Monitoring
• Adverse reactions
• Contraindications
• Precautions
• Financial assistance
Corlanor

Approved in April 2015 – First new chronic HF agent approved by the FDA in a decade

In May 2016, update to 2013 clinical guidelines – ivabradine received Class IIA recommendation

2016 Update to Clinical Guidelines for HF Management

- The ACC/AHA/HFSA guideline update gives a Class IIA recommendation (Level of Evidence: B-R) for use of ivabradine to reduce HF hospitalization in patients with:
  - Symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%)
  - Receiving GDMT including a beta blocker at maximum tolerated dose
  - NSR with a HR > of 70 bpm at rest.
Applying Classification of Recommendations & Level of Evidence

SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial)

• Randomized double blind placebo controlled
• 6505 chronic heart failure patients in sinus rhythm with:
  • a recent heart failure hospitalization
  • EF ≤35%
  • HR ≥70 bpm
  • On optimal GDMT

• Results: 18% reduction in cardiovascular mortality or heart failure hospitalization for worsening heart failure.
• This beneficial effect was mainly driven by significant 26% reductions in heart failure deaths and heart failure hospitalizations for worsening heart failure.

Indications and Usage

To reduce hospitalization in chronic HF patients with:

• Stable, symptomatic chronic heart failure NYHA II-IV
• LVEF ≤35%
• Sinus rhythm with resting heart rate 70+ bpm
• Either on maximally tolerated beta-blockers or have a contraindication to them
Mechanism of Action

• Binds to channels in the SA node known as funny current If channels.
• First in class to selectively & specifically inhibit hyperpolarization-activated cyclic nucleotide (HCN) gated (If current) channel within the SA node that lowers HR which results in HR reduction with no effect on ventricular repolarization & no effects on myocardial contractility.
• It causes a dose dependent reduction in HR. Size of the effect is dependent on the baseline HR.
• Ivabradine also inhibits the retinal current (I_h), partial inhibition of I_h may underlie the luminous phenomena (phosphenes) experienced by patients.

Dosing & Titration

<table>
<thead>
<tr>
<th>Corlanor, twice-daily dosing with meals</th>
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<tbody>
<tr>
<td><strong>RECOMMENDED STARTING DOSE</strong></td>
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<td>5 mg 2x/day</td>
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Monitor heart rate & cardiac rhythm

<table>
<thead>
<tr>
<th>AFTER INITIAL DOSE KEEPING HEART RATE IN RANGE</th>
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<tr>
<td>&lt; 60 bpm</td>
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<tr>
<td>60-90 bpm</td>
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<td>&gt; 90 bpm</td>
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Does not require washout period of SED
Twice a day dosing with food:
- Recommended starting dose 5mg BID
- For pts with conduction defects or bradycardia 2.5mg BID
- Uptitrate q2 weeks to max dose of 7.5mg BID
  - HR>60, increase dose by 2.5mg to max of 7.5mg BID
  - HR 50-60, maintain dose
  - HR <50 or symptoms of bradycardia, decrease dose by 2.5mg BID
    or d/c if dose is 2.5mg BID

Dosing in Specific Populations
- **Mod to Severe Renal Impairment** – (Cr CL 15 to 60 mL/min)
  - No dose adjustment dosage
- **Mild or Moderate Hepatic Impairment**
  - Child-Pugh class A or B – No dosage adjustment
- **Severe Hepatic Impairment** – Use is contraindicated

**Adverse Reactions**

Most common adverse events:
- Bradycardia 10%
- Hypertension 8.9%
- Atrial fibrillation 8.3%
- Luminous phenomena (Phosphenes) 2.8%

**Contraindications**

- Acute decompensated heart failure
- Blood pressure less than 90/50 mmHg
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present
- Resting heart rate < 60 bpm
- Severe hepatic impairment
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker) Should be set at < 60
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitor
- Patients with sustained Afib/flutter not considered good candidates for Corlanor as their heart rhythm is not directed by the SA node but rather originates in the atria where Corlanor has no known effects
- Pregnancy
Warnings & Precautions

- Increased risk of AF. Discontinue if AF develops.
- Monitor for bradycardia, sinus arrest, and heart block.
  Risk factors for bradycardia:
  - sinus node dysfunction
  - conduction defects (e.g., 1st or 2nd degree AV block, bundle branch block)
  - ventricular dyssynchrony
  - Use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, amiodarone).
- Concurrent use of verapamil or diltiazem should be avoided.
- Avoid use in patients with 2nd degree AV block, unless a functioning demand pacemaker is present.

Drug Interactions

- Avoid concomitant use of moderate CYP3A4 inhibitors and inducers, which can increase or decrease ivabradine plasma concentrations and lead to complications.
- Bradycardia risk increases with use of meds that slow heart rate (digoxin, amiodarone, beta blockers).

Use in Specific Populations

- May cause fetal toxicity - Category D. Patients started on Corlanor, especially during the first trimester, should be followed closely for destabilization of their congestive heart failure that could result from heart rate slowing.
- Advise females of childbearing age to use effective contraception.
- Breastfeeding is not recommended.
- Safety and effectiveness in pediatric patients have not been established.
Summary

• First in class Hyperpolarizing-activated Cyclic Nucleotide (HCN) channel blocker that lowers heart rate, indicated for stable chronic HFrEF & HR > 70
• Use in pts who are already on maximally medically tolerated doses of BB’s or are unable to use BB’s
• Reduces HR without reducing heart contractibility (no negative inotropic effects)
• No clinical benefit in the treatment of AF

*This drug has been used in Europe for years
2016 Update to Clinical Guidelines for HF Management

The ACC/AHA/HFSA guideline update gives a Class I recommendation for the clinical strategy of inhibition of the RAAS system with:

- ACE-I's (Level of Evidence: A)
- or ARB's (Level of Evidence: A)
- or ARNI's (Level of Evidence: B-R)

In conjunction with evidence-based BB's & aldosterone antagonists in selected patients with chronic heart failure with reduced ejection fraction (HFrEF) to reduce morbidity and mortality.

The recommendation for ARNI is based on the PARADIGM trial, which reported a 20% reduction in the composite endpoint of cardiovascular death or HF hospitalization—this composite endpoint of cardiovascular death or HF hospitalization was consistent across subgroups.

The ACC/AHA/HFSA guideline update gives a Class I recommendation (Level of Evidence: B-R) to replace an ACE-I or ARB by an ARNI in selected patients with chronic symptomatic HF rEF (NYHA class II/III) with an adequate blood pressure who are already tolerating a reasonable dose of ACE-I or ARB.

Applying Classification of Recommendations & Level of Evidence

PARADIGM-HF trial

- Multinational, randomized, double-blind trial
- Comparing ENTRESTO & enalapril
- 8,442 adult patients with symptomatic chronic heart failure (NYHA class II-IV) & systolic dysfunction (LVEF <40%)

Results:

- 20% reduction in the rate of death or hospitalization for heart failure
- 16% reduction in the rate of all-cause death compared to enalapril at 3 years of follow up.
Indications and Usage

**Indications:**
- To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with:
  - chronic heart failure (NYHA Class II-IV)
  - reduced EF ≤40%
- administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or ARB

Mechanism of Action

Contains sacubitril (a neprilysin inhibitor) and an angiotensin receptor blocker, valsartan.

**Sacubitril:** (the first in a new class of Neprilysin inhibitors):
- inhibits the enzyme neprilysin from breaking down peptides that lower blood pressure, hence increasing peptide levels
- which means more vasodilatation and sodium loss plus less cardiac and vascular hypertrophy and remodeling
- helps to improve many of the pathophysiological abnormalities of heart failure

**Valsartan:**
- selectively blocks the angiotensin II type-I receptor and inhibits release of angiotensin II-dependent aldosterone
- this action is needed in addition to Sacubitril since inhibiting neprilysin is accompanied by the activation of the renin-angiotensin system possibly because angiotensin itself may be a substrate for neprilysin

The cardiovascular and renal effects of ENTRESTO in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides and the simultaneous inhibition of the effects of angiotensin II by valsartan so both Sacubitril and Valsartan will work in tandem.
Entresto Dosing & Titration Guide

Dosing

Dosing initial:
- Previous ACE-I or ARB – 49/51mg BID
- No ACE-I/ARB or low doses – 24/26mg BID

Renal impairment:
- Mild-Moderate – (GFR >30) No dose adjustment
- Severe – (GFR <30) 24mg/26mg BID (initial)

Hepatic impairment:
- Mild - No adjustment
- Moderate – (Child Pugh - B) 25mg/26mg BID initial
- Severe – (Child Pugh - C) Not recommended

Monitoring Parameters

Efficacy Monitoring:
- Blood pressure at each visit & dose titration

Dosing Target:
- Titrate after 2-4 wks to 97/103mg BID as tolerated by the pt

Toxicity Monitoring-Baseline then 7-10 days after dose increase
- Serum Electrolytes (K+)
- Serum Creatinine
- Cannot use BNP as a guide for effectiveness of treatment. Use NT ProBNP
- Entresto does not clear through dialysis
### Contraindications

- Hypersensitivity to any component
- History of angioedema related to previous ACE inhibitor or ARB therapy
- Concomitant use of ACE inhibitors or ARB's. Increased risk of angioedema
- Concomitant use of Aliskiren (Tekturna) – dual RAAS blockade
- Pregnancy
- Effectiveness in pediatric patients has not been established

### Drug Interactions

- NSAIDs, including COX-2 inhibitors, with ENTRESTO may result in worsening of renal function, including possible acute renal failure in the elderly, volume-depleted or those with compromised renal function.
- Increased lithium toxicity reported with the use of ARB's
- Potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to hyperkalemia

### Adverse Reactions

- Clinically significant adverse reactions which occur at a frequency of at least 5% include:
  - Angioedema     0.5%
  - Hypotension    18%
  - Impaired Renal Function  6%
  - Hyperkalemia    12%
  - Cough          9%
• Entresto is not indicated for diastolic heart failure patients

• There is an ongoing study to assess the efficacy of Entresto in this group, PARAGON-HF, scheduled to run 2013-2019

Summary
• Entresto inhibits Neprilysin & Angiotensin receptors
• Indicated to reduce the risk of cardiovascular death & hospitalization for heart failure pts with chronic HF (NYHA II-IV) & reduced EF
• Initial dose based on receipt of ACE-I or ARB therapy prior to initiation, renal or hepatic impairment
• There is a 36 hour washout period after the last dose of ACE-I or ARB
• Avoid use in combination with an ACE-I or ARB in pts with a hx of angioedema
• Most common side effect is hypotension
• Potential drug interaction with CYP3A4 inhibitors/inducers

Interesting Commentary
• Neprilysin contributes to the degradation of beta-amyloid plaque in the brain and the eye, so the concern is that inhibition of neprilysin might then lead to an increased risk for Alzheimer’s disease and age-related macular degeneration.

• The macular degeneration issue is new and has not been raised in the cardiology community until now, as a possible role for beta-amyloid in macular degeneration was only recently discovered.
Stages, Phenotypes & Treatment of HF

Heart Failure Therapy

ACE-I, ARB, ARNI  
Loop Diuretic (for volume control)

Beta Blocker

Optimize ACE-I, ARB, ARNI & Beta Blocker doses

Aldosterone Antagonist if GFR >30 & K+ >5

Hydralazine/Isosorbide Dinitrate

Add Digoxin and/or Iverapine  
Use hydralazine for pt with NYHA III on maximally tolerated doses of BB

Refer to Cardiology for consideration of Advanced Therapies

* In pts with chronic asymptomatic HFrEF, titrate to a class III or IV who tolerate an ACE-I or ARB, replacement by an ARNI is recommended to further reduce mortality & morbidity.

African Americans with moderate to severe symptoms
Financial Assistance

Corlanor:
- Wholesale cost of $375 per month or $4500 per year.
- Corlanor savings card: a $20 copay may pay up to $250 toward Rx cost.
- Corlanor Ready - 844-660-7126
- Insurance Verification and Prior Authorization Assistance
- Comprehensive Coverage Support

Entresto:
- Wholesale cost of $375 per month or $4500 per year.
- Free 30-day trial offer with card available for all patients.
- $10 Co-pay support program for those with commercial insurance pays up to $100 per month.
- Enrollment form for Entresto Central Patient Support Program

For both:
- Patient Assistance Programs
  Coverage is approved for the year. www.panfoundation.org

Questions???

Thank you for your attention!!!