New Medications in Chronic Heart Failure: How Should they be Incorporated into Practice?

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October 24, 2015
Outline

• Review the two new medications for systolic heart failure

• Present the studies that support FDA approval

• Review indications, dosing, side effects, warnings

• Discuss cost, insurance and clinical considerations & controversies
Drugs that inhibit the renin-angiotensin system have modest effects on survival.

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RÂLES and EMPHASIS-HF

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>% Decrease in Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin receptor blocker</td>
<td>10%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>20%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>30%</td>
</tr>
<tr>
<td>Mineralocorticoid receptor</td>
<td>40%</td>
</tr>
</tbody>
</table>
Cases

1. Mr. X is a 63 yo males, 15 year history of HFrEF (LVEF 32%) despite GDMT and ICD, NYHA class I
   – What do you do next?

2. What if Mr. X has NYHA class II-III symptom?

3. Mrs. Y has never been hospitalized, has been on GDMT for 7 months, average HR is 75, she is NYHA class II, getting ready for ICD implantation for persistent LVEF < 35%
   – What do you do next?
Clinical Trials Supporting 2 New Drugs for Systolic Heart Failure
A Comparison of Angiotensin Receptor-Neprilysin Inhibition (ARNI) With ACE Inhibition in the Long-Term Treatment of Chronic Heart Failure With a Reduced Ejection Fraction
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

Endogenous vasoactive peptides
(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin inhibition

- Neprilysin
- Inactive metabolites
- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention
Mechanisms of Progression in Heart Failure

Myocardial or vascular stress or injury

- Increased activity or response to maladaptive mechanisms
  - Angiotensin receptor blocker

- Decreased activity or response to adaptive mechanisms
  - Inhibition of neprilysin

Evolution and progression of heart failure
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

Aim of the PARADIGM-HF Trial

LCZ696 400 mg daily  ↔  Enalapril 20 mg daily

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE
NYHA class II-IV heart failure

LV ejection fraction ≤ 40% → 35%

BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months

Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks

Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists

Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization
PARADIGM-HF: Study Design

Randomization

Single-blind run-in period

- Enalapril 10 mg BID
- LCZ696 200 mg BID
- 2 weeks
- 1-2 weeks
- 2-4 weeks

Double-blind period

- LCZ696 200 mg BID
- Enalapril 10 mg BID
- (1:1 randomization)
10,521 patients screened at 1043 centers in 47 countries

Did not fulfill criteria for randomization (n=2079)

Randomized erroneously or at sites closed due to GCP violations (n=43)

8399 patients randomized for ITT analysis

LCZ696 (n=4187)

At last visit
375 mg daily
11 lost to follow-up

Enalapril (n=4212)

median 27 months of follow-up

At last visit
18.9 mg daily
9 lost to follow-up
<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>16.5%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>Enalapril (n=4212)</th>
<th>LCZ696 (n=4187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1117</td>
<td>914</td>
</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>540</td>
<td></td>
<td></td>
</tr>
<tr>
<td>720</td>
<td></td>
<td></td>
</tr>
<tr>
<td>900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1080</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1260</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR = 0.80 (0.73-0.87)

P = 0.0000002

Number needed to treat = 21
### Kaplan-Meier Estimate of Cumulative Rates (%)

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>Kaplan-Meier Estimate of Cumulative Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enalapril (n=4212)</td>
</tr>
<tr>
<td></td>
<td>LCZ696 (n=4187)</td>
</tr>
<tr>
<td></td>
<td>Patients at Risk</td>
</tr>
<tr>
<td></td>
<td>LCZ696</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
</tr>
</tbody>
</table>

**HR = 0.80 (0.71-0.89)**

**P = 0.00004**

**Number need to treat = 32**

PARADIGM-HF: Cardiovascular Death
PARADIGM-HF: All-Cause Mortality

**HR = 0.84 (0.76-0.93)  P<0.0001**

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Days After Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696</td>
<td>4187 4056 3891 3282 2478 1716 1005 280</td>
</tr>
<tr>
<td>Enalapril</td>
<td>4212 4051 3860 3231 2410 1726 994 279</td>
</tr>
</tbody>
</table>
## PARADIGM-HF: Effect of LCZ696 vs Enalapril on Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Treatment effect</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KCCQ clinical summary score at 8 months</strong></td>
<td>– 2.99 ± 0.36</td>
<td>– 4.63 ± 0.36</td>
<td>1.64 (0.63, 2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>New onset atrial fibrillation</strong></td>
<td>84/2670 (3.2%)</td>
<td>83/2638 (3.2%)</td>
<td>Hazard ratio 0.97 (0.72,1.31)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Protocol-defined decline in renal function</strong></td>
<td>94/4187 (2.3%)</td>
<td>108/4212 (2.6%)</td>
<td>Hazard ratio 0.86 (0.65, 1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
### PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>388</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discontinuation for adverse event</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angioedema (adjudicated)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications, no hospitalization</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>
In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

**LCZ696 was more effective than enalapril in . . .**

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

**LCZ696 was better tolerated than enalapril . . .**

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema
Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
Indication: Sacubitril/valsartan

- To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II–IV) and reduced ejection fraction.

- Usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.
Prescribing and Monitoring: Sacubitril/valsartan

- **Starting dose:**
  - 49/51 mg sacubitril/valsartan twice daily
  - Double dose after 2-4 weeks, as tolerated
  - Target dose 97/103 mg twice daily

- **When to reduce the dose:**
  - To 24/26 mg twice daily for:
    - Not taking ACEi or ARB, or previously on low doses of these
    - Severe renal impairment (GFR < 30)
    - Moderate hepatic impairment (Child-Pugh B)
Adverse Events: Sacubitril/valsartan

• Side effects/adverse reactions compared to enalapril
  – hypotension (18%, 12%)
  – hyperkalemia (12%, 14%)
  – cough (9%, 13%)
  – dizziness (6%, 5%)
  – renal failure/acute renal failure (5%, 5%)
Contraindications: Sacubitril/valsartan

• Contraindicated:
  – concomitant use of ACEi
    • Needs 36 hours off ACEi before starting
  – in patients on aliskiren
  – in pregnant females (no information about use in lactation)
  – in patients with prior angioedema with ACEI/ARB

• Drug Interactions:
  – ACEi
  – Potassium sparing diuretics
  – NSAIDS, COX-2’s
  – Lithium
Warnings: Sacubitril/valsartan

- If pregnancy is suspected, discontinue the drug
- Angioedema
- Hypotension
- Impaired renal function
- Hyperkalemia

Topics for patient education
What is Ivabradine (Corlanor)?

• New class of heart medications
  – hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers
• Approved by the FDA April 2015
  – After SHIFT trial

Sympathetic neurons to the SA node increases the frequency of action potentials. cAMP augments the opening of funny channels and T-type Ca$^{++}$ channels which increases the slope of spontaneous depolarization. The frequency of action potentials increase and increases the heart rate.
How was Ivabradine Studied?

**SHIFT**

**S**ystolic **H**eart failure treatment with the **I**f inhibitor ivabradine **T**rial

About the SHIFT Trial

• N=6558 patients
  • with stable NYHA class II-IV,
  • systolic HF patients with HR > 70 bpm
  • hospitalized within the prior year, yet stable
• on GDMT--ACEi/ARB, beta blocker, aldosterone antagonist for 4 weeks

ivabradine  placebo
Results of SHIFT Trial

Ivabradine vs. Placebo

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOSPITALIZED- WORSENING HF</td>
<td>20.2</td>
<td>15.6</td>
</tr>
<tr>
<td>CARDIVASCULAR DEATH</td>
<td>8.9</td>
<td>8.5</td>
</tr>
</tbody>
</table>

An important study finding was little if any benefit was noted in patients on target doses of beta blockers.
Mean heart rate reduction

70% of patients on ivabradine 7.5 mg bid

Heart rate (bpm)

Placebo

Ivabradine

Decreased HR without affecting contractility

Incidence of selected adverse events (n = 6492)

<table>
<thead>
<tr>
<th>Event</th>
<th>Ivabradine N=3232, n (%)</th>
<th>Placebo N=3260, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>1450 (45%)</td>
<td>1553 (48%)</td>
<td>0.025</td>
</tr>
<tr>
<td>All adverse events</td>
<td>2439 (75%)</td>
<td>2423 (74%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3%)</td>
<td>17 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>17 (1%)</td>
<td>7 (&lt;1%)</td>
<td>0.042</td>
</tr>
</tbody>
</table>
Indications: Ivabradine

- HFrEF, maximized on usual GDMT
- Stable, yet with continued HF symptoms
- In normal sinus rhythm
- LVEF < 35%
- Heart rate > 70 bpm

**NOT intended to replace beta blockers**

It *may be considered* in beta blocker intolerant patients, after other GDMT is maximized
Prescribing and Monitoring: Ivabradine

- Starting dose is 5 mg oral twice daily
  - then if the heart rate is > 60 after two weeks consider increasing the dose to 7.5 mg twice daily
  - If the HR is < 50 either decrease to 2.5 mg twice daily or discontinue

- BOTH providers and patients should monitor HR trend
  - especially with concomitant use of beta blockers, digoxin, amiodarone, verapamil or diltiazem
  - Target HR 50-60 bpm
Adverse Events: Ivabradine

- Bradycardia
- Hypertension
- Atrial fibrillation
- Temporary brightness in field of vision

Topics for patient education
Contraindications: Ivabradine

- Acute decompensated HF
- Blood pressure < 90/50 mm Hg & resting HR < 60 bpm before treatment
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functional pacemaker is present
- Pacemaker dependence
- Severe hepatic impairment
Warnings: Ivabradine

• Don’t use in
  – Pregnant or lactating patients
  – Patients with atrial arrhythmias and/or:
    • Sick sinus syndrome, sinoatrial block
    • 2nd or 3rd degree AV block
  – To attempt to reduce HF readmissions
  – In acute decompensated HF
  – If hypotensive (< 90/50)
  – Resting HF < 60 before starting

• Drug interactions (cytochrome P450 based medications)
  – azole antifungals, macrolide antibiotics, HIV protease inhibitors, diltiazem, verapamil, and grapefruit juice, St. John’s wort, rifampicin, barbiturates, phenytoin
Costs & Insurance Considerations
# Local Snapshot of Costs

<table>
<thead>
<tr>
<th>#60 tablets</th>
<th>Entresto</th>
<th>Corlanor</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24/26</td>
<td>$517.50</td>
<td>5 → $517.50</td>
</tr>
<tr>
<td>49/51</td>
<td>$517.50</td>
<td>7.5 → $517.50</td>
</tr>
<tr>
<td>97/103</td>
<td>$517.50</td>
<td></td>
</tr>
<tr>
<td>Costco</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24/26</td>
<td>$444.92</td>
<td>5 → N/A</td>
</tr>
<tr>
<td>49/51</td>
<td>$444.92</td>
<td>7.5 → N/A</td>
</tr>
<tr>
<td>97/103</td>
<td>$444.92</td>
<td></td>
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<tr>
<td>Walmart</td>
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<td></td>
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<tr>
<td>24/26</td>
<td>$426.00</td>
<td>5 → $426.00</td>
</tr>
<tr>
<td>49/51</td>
<td>$428.25</td>
<td>7.5 → $426.00</td>
</tr>
<tr>
<td>97/103</td>
<td>$426.00</td>
<td></td>
</tr>
<tr>
<td><strong>SelectHealth</strong></td>
<td><strong>OptumRx- Medicare part D plan</strong></td>
<td></td>
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<tr>
<td>-----------------</td>
<td>----------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| **Entresto**- Requires Prior authorization  
With High Deductible plan- after met Deductible/Out-of-Pocket for the year, policy would cover 100% of charge  
**Estimated cost for 1 pill per day - for 30 days - $200.00 – for any dose**  
If the policy goes by tier levels – this is a **tier 3 drug** – and the patient would be responsible for **50% of the costs**  
If it were a policy with **co-pays** – the policy are all so different there is no way to know what all of those co-pays might be | **Entresto**-  
Tier 4 drug – 30 day supply **$250.00** –  
90 day mail order **$625.00** – (2 tablets per day limit) |
| **Ivabradine**:  
Coverage Requirement: Fail two qualifying therapies  
co-pays on this medication mirror Entresto’s co-pays | **Ivabradine**  
Tier 4 drug – 30 day supply **$250.00** –  
90 day mail order **$625.00** – (2 tablets per day limit) |
Two ways your patients may save on their out-of-pocket costs

Enrollment Form for Entresto Central Patient Support Program

FAX: 1-844-263-5644; PHONE: 1-888-Entresto (368-7378)
Please complete all fields to minimize delays. Please include copies of both sides of the insurance card.

1. Patient and Insurance Information – PATIENT SIGNATURE REQUIRED

First Name ___________________________ Last Name ___________________________ Primary Insurance ___________________________

Pay as little as a $10 co-pay a month for ENTRESTO™*
$10 CO-PAY CARD*
For eligible commercially insured patients
Cases & Controversies

1. Mr. X is a 63 yo males, 15 year history of HFrEF (LVEF 32%), on GDMT & ICD, NYHA class I
   – What do you do?

2. What if Mr. X has NYHA class II-III symptoms?
   – What do you do?

3. Mrs. Y has never been hospitalized, has been on GDMT for 7 months, average HR is 75, she is NYHA class II, getting ready for ICD implantation for persistent LVEF < 35%
   – What do you do? Start drug before or after, or at all?
Other treatments with less-certain benefits in patients with symptomatic (NYHA class II–IV) systolic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended to reduce the risk of HF hospitalization and the risk of premature death in patients with an EF ≤40% and unable to tolerate an ACE inhibitor because of cough (patients should also receive a beta-blocker and an MRA).</td>
<td>I</td>
<td>A</td>
<td>108, 109</td>
</tr>
<tr>
<td>Recommended to reduce the risk of HF hospitalization in patients with an EF ≤40% and persisting symptoms (NYHA class II–IV) despite treatment with an ACE inhibitor and a beta-blocker who are unable to tolerate an MRA.</td>
<td>I</td>
<td>A</td>
<td>110, 111</td>
</tr>
<tr>
<td><strong>Ivabradine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35%, a heart rate remaining ≥70 b.p.m., and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).</td>
<td>IIa</td>
<td>B</td>
<td>112</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35% and a heart rate ≥70 b.p.m. who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤45% who are unable to tolerate a beta-blocker (ivabradine is an alternative in patients with a heart rate ≥70 b.p.m.). Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).</td>
<td>IIb</td>
<td>B</td>
<td>113</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients with an EF ≤45% and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker, ACE inhibitor (or ARB), and an MRA (or ARB).</td>
<td>IIb</td>
<td>B</td>
<td>113</td>
</tr>
<tr>
<td><strong>H-ISDN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May be considered as an alternative to an ACE inhibitor or ARB, if neither is tolerated, to reduce the risk of HF hospitalization and risk of premature death in patients with an EF ≤45% and dilated LV (or EF ≤35%). Patients should also receive a beta-blocker and an MRA.</td>
<td>IIb</td>
<td>B</td>
<td>114, 115</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization and risk of premature death in patients with an EF ≤45% and dilated LV (or EF ≤35%) and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker, ACE inhibitor (or ARB), and an MRA (or ARB).</td>
<td>IIb</td>
<td>B</td>
<td>116</td>
</tr>
<tr>
<td>An n-3 PUFA preparation may be considered to reduce the risk of death and the risk of cardiovascular hospitalization in patients treated with an ACE inhibitor (or ARB), beta-blocker, and an MRA (or ARB).</td>
<td>IIb</td>
<td>B</td>
<td>117</td>
</tr>
</tbody>
</table>
How do we Integrate these Drugs into HF Practice?

• So new, these drugs are not yet in the HF guidelines
• Both may be considered a “niche drugs”

• **Take away:**
  - Not for HfrEF med naïve patients
  - They should be considered in patients on GDMT
  - These are only for use in HFrEF
  - Consider how future studies may answer other questions
  - Consider the cost issues
"Be not the first nor the last to use a new drug. Let others use it and await their problems and their solutions."
Ivabradine (Corlanor), a Novel Drug for Chronic Systolic Heart Failure\textsuperscript{1,2,3}

Ivabradine (name brand of Corlanor) is a new drug approved by the FDA in April 2015 that works on spontaneous pacemaker activity in the sinoatrial node. Technically, this drug is a hyperpolarization-activated cyclic nucleotide-gated channel blocker. It lowers heart rate without lowering blood pressure or affecting myocardial contractility.

- Ivabradine’s FDA approval comes after the SHIFT Trial\textsuperscript{1,2,3} that studied ivabradine compared to placebo in 6558 patients with stable NYHA class II-IV, systolic HF patients with HR > 70 bpm, who were hospitalized within the prior year yet stable on GDMT--ACEi/ARB, beta blocker, aldosterone antagonist for 4 weeks.
  - When ivabradine was added to GDMT, it showed a reduced risk of combined endpoint of hospitalization for worsening HF or cardiovascular death (hazard ratio: 0.82, 95% confidence interval: 0.75, 0.90, p < 0.0001) with a treatment effect on reducing readmissions, but not mortality.
  - An important study finding was little if any benefit was noted in patients on target doses of beta blockers.
Pharmacists: Receiving CE Credit

- CE provided by the California Society of Health-System Pharmacists
- Log-in to http://ihc.cshep.wceea.education (First time only: create account)
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