New Solutions for Old Problems: Novel Therapeutic Options for Hyperlipidemia and Heart Failure

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Objectives

• Review ivabradine and sacubitril/valsartan as options for chronic heart failure as compared to the current standard treatment
• Discuss the role of PCSK9 enzymes in lipid metabolism
• Discuss the role of PCSK9 inhibitors in the management of hypercholesterolemia
FDA 2015

Heart Failure
• Corlanor (Ivabradine): April
• Entresto (Sacubitril/Valsartan): July

Hypercholesterolemia
• Alirocumab (Praluent): July
• Evolocumab (Repatha) August
Epidemiology

Heart Failure
- 5.1 million Americans with clinically manifest heart failure
  - >650,000 new cases diagnosed annually
  - 20% risk ≥ 40 years old
- >1 million hospitalizations annually
- Mortality
  - 50% within 5 years of diagnosis

Hyperlipidemia
- 31.9 million American adults have total cholesterol levels ≥ 240 mg/dL with a 13.8% prevalence rate
- CVD accounts for almost 50% of all deaths in the US

Heart Failure Guidelines

HFrEF Stage C
NYHA Class I - IV

Digoxin: Reduces hospitalizations (Class IIa, Level of evidence B)

If volume overloaded, NYHA class II-IV
Add Loop diuretics

ACEi or ARB and BB

If persistently symptomatic AA, NYHA class III-IV
Add Hydral-nitrates

NYHA class II-IV (If CrCl >30 ml/min and K <5 mEq)
Add Aldosterone Antagonist

Ivabradine: Corlanor® & Sacubitril/Valsartan: Entresto®
Ivabradine: MOA

Sinus node
The pacemaker of the heart

Ivabradine selectively inhibits the If current in the sinus node

Na$^+$

K$^+$

If-channel

Ivabradine

0 mv

-40 mv

-70 mv

Heart rate reduction

Ivabradine reduces the slow diastolic depolarization phase

Heart Rate Matters

50 bpm

70 bpm

100 bpm

> 19% increase in risk of all-cause mortality in patients with left ventricular dysfunction (LVEF ≤ 40%)

> 25% increase in risk of composite outcome of CV death or hospitalization for worsening HF in patients with left ventricular dysfunction (LVEF ≤ 40%)

Sacubitril/valsartan: MOA

Study Designs

SHIFT Trial
- Ivabradine vs Placebo
- Inclusion
  - EF ≤ 35%
  - HR > 70 bpm in SR
  - Current symptoms
  - Prior HF hospitalization
- Exclusion
  - Afib
  - Pacer dependent
  - Low BP
- CV death or hospitalization for HF

Paradigm Trial
- Sacubitril/Valsartan vs Placebo
- Inclusion
  - EF ≤ 35%
  - Current symptoms
  - Prior HF hospitalization or ↑BNP
- Exclusion
  - GFR < 30 ml/min
  - K > 5.2 mmol/L
  - Hx angioedema
  - Low BP
- CV death or hospitalization for HF

Patient Populations

SHIFT
- 60 yo, 76% male
- FC II/III
- Baseline Meds
  - Beta-blocker: 89%
    - Only 25% target dose
    - 56% on > 50% target
    - Low BP, fatigue
  - ACEi or ARB: > 90%
  - Diuretic: 84%
  - Aldosterone Antag: 60%
  - Cardiac Glycoside: 22%

PARADIGM
- 64 yo, 79% male
- FC II >> FC III
- Baseline Meds
  - Beta-blocker: 93%
  - Pre trial ACEi: 78%
  - Pre trial ARB: 22%
  - Diuretic: 80%
  - Aldosterone Antag: 54%

PARADIGM-HF Patient screening

- Enalapril 10 mg BID x 2 weeks
- Sacubitril/valsartan 200 mg BID x 4-6 weeks
  - ~12% of patients withdrew because of adverse events
  - Cough
  - Hyperkalemia
  - Renal dysfunction
  - Hypotension

SHIFT Heart Rate Results

Study Results

Zannad, F et al. NEJM 2011; 364: 11-21
**Significant Adverse Events**

**Ivabradine**
- 4% ↑ symptomatic brady
- 5% ↑ Asympt brady
- 1% ↑ New Afib
- 2% ↑ Phosphenes
  - Visual changes/Bright lights

*All < 10%*

**Sacubutril/Valsartan**
- 5% ↑ Symptomatic hypotension
- 1.2% ↓ Cr ≥ 2.5 mg/dl
- 1.3% ↓ K > 6.0 mmol/L
- 3% ↓ Cough
- No diff angioedema
  - *Pl states increased incidence in blacks*

Ivabradine Clinical Considerations

**Approved indication**
- Stable, symptomatic chronic heart failure with EF < 35%, in sinus rhythm, resting HR > 70 bpm and on maximum tolerated beta blocker

**Dosage**
- Start 5 mg BID with meals, after 2 weeks, adjust dose to maintain HR between 50 – 60 bpm
- Maximum dose: 7.5 mg BID

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>Dose adjustment</th>
</tr>
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<tbody>
<tr>
<td>&gt;60 bpm</td>
<td>Increased by 2.5 mg BID</td>
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<tr>
<td>50-60 bpm</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>&lt;50 bpm or bradycardia signs</td>
<td>Decrease by 2.5 mg BID, if current dose is 2.5 mg BID, discontinue therapy</td>
</tr>
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</table>

Monitoring: Afib, visual changes
Cost: $15.00/day or $465.00/month
# Sacubitril/valsartan

## Clinical Considerations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing</th>
<th>Safety</th>
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</table>
| - Reduce the risk of CV death and HF hospitalization in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction | - Start at 49/51 mg (100 mg) BID  
- Double the dose after 2 to 4 weeks to target maintenance dose of 97/103 mg (200 mg) BID | - Switching between ACEis and sacubitril/valsartan  
- Wait 36 hours  
- Take ACEi from patient  
- Ensure old Rx is d/c at the retail pharmacy  
- Monitoring parameters  
  - K and SCr  
  - Blood pressure |

Cost: $15/day : $465/month
Potential Place in Therapy

HFrEF Stage C
NYHA Class I - IV

- ACEi or ARB and BB
- If volume overloaded, NYHA class II-IV
- If persistently symptomatic AA, NYHA class III-IV

- Persistently symptomatic on target dose
- NYHA class II-IV (If CrCl >30 ml/min and K <5 mEq)

- Switch
- Sacubitril/valsartan
- If EF <35%, HR >70, without Afib and persistently symptomatic

Add
- Loop diuretics
- Hydral-nitrates
- Aldosterone Antagonist
- Ivabradine

Hyperlipidemia Guidelines

2013 ACC/AHA blood cholesterol guidelines:
• Introduction of treatment groups instead of specific lipid goals
• Four treatment groups identified:
  • Clinical ASCVD
  • Primary elevation of LDL-C ≥ 190 mg/dL
  • 40 - 75 y/o with diabetes and LDL-C 70 - 189 mg/dL
  • 40 - 75 y/o with LDL-C 70 - 189 mg/dL and 10 year ASCVD risk ≥7.5%
• Moderate to High Dose Statin therapy recommended as first line

2015 NLA Recommendations:
• Identify highest ASCVD risk category that applies to patient
• If very-high risk, begin with mod-high intensity statin
  • LDL goal < 70 and non HDL goal < 100
• In remaining patients count number of major risk factors
  • LDL goal < 100 and non HDL goal < 130

MECHNISMS OF ACTION

- Proprotein convertase subtilisin/kexin 9 (PCSK9) causes lysosomal degradation of hepatocyte LDL-C receptors and decreased clearance of LDL-C

- Monoclonal antibodies bind to PCSK9 protein to promote LDL-C receptor recycling

<table>
<thead>
<tr>
<th><strong>FDA approved indication</strong></th>
<th><strong>Alirocumab</strong></th>
<th><strong>Evolocumab</strong></th>
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<tbody>
<tr>
<td>Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with:</td>
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<tr>
<td></td>
<td>Heterozygous familial hypercholesterolemia</td>
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<td>Clinical atherosclerotic CVD requiring additional LDL-C lowering</td>
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<tr>
<td></td>
<td></td>
<td>Homozygous familial hypercholesterolemia in combination with other LLT</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>75 mg SC every 2 weeks (Max 150 mg SC every 2 weeks)</td>
<td>140 mg SC every 2 weeks 420 mg SC every month (3 injections)</td>
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<tr>
<td><strong>Product</strong></td>
<td>Available as a single dose pre-filled pen and syringe</td>
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<tr>
<td><strong>Cost</strong></td>
<td>&gt; $14,000/year</td>
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LLT = Lipid lowering therapies (e.g. statins, ezetimibe and LDL apheresis)

PRALUENT Prescribing Information. Sanofi/Regeneron Pharmaceuticals, 2015
REPATHA Prescribing Information. Amgen Pharmaceuticals, 2015
Alirocumab LDL RESULTS

HeFH population

Non-HeFH population

Evolocumab LDL RESULTS

Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels.

Adverse effects

Common (occurring in ≥ 3% of patients)
- Upper respiratory tract infections (e.g. nasopharyngitis, sinusitis)
- Bronchitis
- Influenza
- Nausea and diarrhea
- Injection site reactions
- Musculoskeletal pain (e.g. arthralgia, myalgia, back pain)
- Urinary tract infection

Serious
- Allergic reactions (rash, urticaria, erythema, eczema)
- Neurocognitive events
Role in hypercholesterolemia management?

- Efficacy
- Safety
- Patient access
EFFICACY

Cardiovascular benefit

- Significant reduction in LDL-C levels as monotherapy or adjunct to statin therapy
- Lack of cardiovascular morbidity/mortality data

Sustainability of effects

- Studies show sustained reduction in lipid levels for up to 78 weeks
- Free PCSK9 concentrations returned to baseline when alirocumab and evolocumab concentrations decreased below limit of quantitation
- Neutralizing antibodies reported in 1.2% of patients who received alirocumab
SAFETY

Adverse effects
• Common adverse effects are relatively mild
• Concerns for neurocognitive adverse effects
• Absence of required lab monitoring
• Limited long term safety data

Administration /Storage
• Self administered subcutaneous injection versus oral tablets
• Special storage requirements (refrigerated prefilled pens and syringes)
• Injection Training required
Cost/insurance coverage

• May be cost effective for:
  • Patients receiving LDL apheresis- average cost of $2,500 per treatment
  • Patients who have significant CVD history requiring frequent hospitalization
• Insurance Coverage evolving

Distribution

• Specialty medication
• Limited pharmacy distribution - Alirocumab
Current PLACE IN Therapy?

Possible treatment groups:

Patients with primary hypercholesterolemia (e.g. FH) or mixed dyslipidemia who are not adequately controlled on maximally tolerated statin or have contraindications to statin use (primary prevention)

Clinical ASCVD history on appropriate statin therapy (secondary prevention) needing additional lowering of LDL

- Not ready for “prime time” d/t lack of outcomes data
- Prioritize patients based on highest risk
  - Patients still in need of large LDL reduction (50-60%)
    - Other agents provide 10-30%
  - Recurrent events/revascularizations
  - Multiple additional CV risk factors
  - LDL 50-100 with ACS (consider ezetimibe): IMPROVE IT Study
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University of Illinois PGY2 Ambulatory Care Residents