NEW DRUGS IN CARDIOLOGY

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OBJECTIVES

- Identify recent FDA approvals in cardiology
- Describe the impact of recent FDA approvals on current practice
- Design a treatment plan utilizing new medications

PRESENTATION OUTLINE

- Hyperlipidemia Medications
  - PCSK9 inhibitors
  - Pipeline agents
- Heart Failure Medications
  - Iverolirine (Conlar)
  - Sacubitril/valsartan (Entresto)
- Antidotes
  - Idarucizumab (Praxbind)
  - Andexanet Alfa
  - Other Pipeline agents

PCSK9 AND HYPERCHOLESTEROLEMIA

- PCSK9
  - Discovery reported in 2003 and 2004
  - PCSK9 missense/LOF mutations - ARIC study
  - African Americans: 28% less LDL-C, 88% lower risk of developing CVD
  - Whites with less severe mutation: 15% reduction in LDL-C; 47% reduced risk of CVD
  - PCSK9 - mediated cholesterol effects revealed
  - GOF mutations lead to less LDL-R degradation
  - LOF mutations lead to increase LDL-R available to remove LDL-C

### PCSK9 INHIBITORS

<table>
<thead>
<tr>
<th>Name</th>
<th>Drug Company</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab (Praluent)</td>
<td>Renergon/Sanofi</td>
<td>Approved July 2015</td>
</tr>
<tr>
<td>Evolocumab (Repatha)</td>
<td>Amgen</td>
<td>Approved August 2015</td>
</tr>
<tr>
<td>Bococumab</td>
<td>Pfizer</td>
<td>Phase III trial</td>
</tr>
</tbody>
</table>

### ALIROCUMAB (PRALUENT)

- **Indication**
  - Heterozygous familial hypercholesterolemia
  - Adjunct to diet and maximally tolerated statin therapy
  - Clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-cholesterol
- **Dose**
  - 75 mg subcutaneously every 2 weeks
  - Titrated to a maximum dose of 150 mg subcutaneously every 2 weeks

- **Adverse Reactions**
  - Diarrhea (5%)
  - Increased serum transaminases (2%)
  - Hypersensitivity reactions
  - Influenza (6%)
  - Injection site reactions (7%)
  - Myalgia (4%)
  - Muscle spasms (3%)
  - Cough (3%)

- **Administration**
  - Warm to room temperature for 30 to 40 minutes prior to use
  - Do NOT use if it has been at room temperature for 24 hours or longer
  - Administer by subcutaneous injection into the thigh, abdomen, or upper arm
  - Rotate injection site with each injection
  - Do NOT inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections
  - Do NOT co-administer with other injectable drugs at the same injection site

- **Dosage**
  - No dosage adjustments
  - Renal impairment
  - Hepatic impairment
  - Storage
    - Store at 2°C to 8°C (36°F to 46°F) in the outer carton to protect from light
    - Do not freeze
    - Do not expose to extreme heat
    - Do not shake
EVOLOCUMAB (REPATHA) INDICATIONS

- Primary hyperlipidemia
  - Heterozygous familial hypercholesterolemia (HeFH)
  - Adjunct to diet and maximally tolerated statin therapy
  - Clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of LDL
  - Homozygous familial hypercholesterolemia (HoFH)
  - Adjunct to diet and other LDL-lowering therapies

EVOLOCUMAB (REPATHA) DOSING

- Primary Hyperlipidemia
  - 140 mg SUBQ every 2 weeks
  - 420 mg SUBQ monthly
- Homozygous familial hypercholesterolemia (HoFH)
  - 420 mg SUBQ monthly
- Renal Impairment
  - No adjustment in mild to moderate
  - Not studied in severe
- Hepatic Impairment
  - No adjustment in mild to moderate
  - Not studied in severe

Repatha (evolocumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; August 2015.
EVOLOCUMAB (REPATHA) ADVERSE REACTIONS

- Nasopharyngitis (6% – 11%)
- Hypertension (3%)
- Dizziness (4%)
- Fatigue (2%)
- Gastroenteritis (3% - 6%)
- Nausea (2%)
- UTI (5%)
- Influenza (8 – 9%)
- Injection site reaction (6%)
- Myalgia (4%)
- Upper respiratory tract infection (9%)
- Sinusitis (4%)
- Skin rash (1%)


EVOLOCUMAB (REPATHA) ADMINISTRATION

- Administer by subcutaneous injection into the thigh, abdomen, or upper arm
- Rotate injection site with each injection
- Do NOT inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections
- Do NOT co-administer with other injectable drugs at the same injection site
- Dose of 420 mg
- 3 injections of 140 mg consecutively within 30 minutes


EVOLOCUMAB (REPATHA) STORAGE

- Refrigerator
- Warm to room temperature for 30 to 40 minutes prior to use
- Room Temperature in original carton
- Must be used within 30 days


DESCARTES: TREATMENT EMERGENT ADVERSE EVENTS

<table>
<thead>
<tr>
<th></th>
<th>Placebo  N = 302</th>
<th>Evolocumab  N = 599</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Treatment Emergent Adverse Event</td>
<td>224 (74.2)</td>
<td>448 (74.8)</td>
</tr>
<tr>
<td>Serious</td>
<td>13 (4.3)</td>
<td>33 (5.5)</td>
</tr>
<tr>
<td>Adjudicated events</td>
<td>2 (0.7)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Leading to discontinuation of study drug</td>
<td>3 (1)</td>
<td>13 (2.2)</td>
</tr>
</tbody>
</table>

BLOCCOCIZUMAB PHASE III ONGOING

- The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects
- Study Arms
  - Bococizumab 150mg subcutaneously every 2 weeks
  - Placebo subcutaneously every 2 weeks
- Primary Endpoint
  - Time from randomization to first occurrence of a major cardiovascular event
  - Composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization
  - Time frame: 58 months

STUDY ARMS

- Bococizumab 150mg subcutaneously every 2 weeks
- Placebo subcutaneously every 2 weeks

PRIMARY ENDPOINT

- Time from randomization to first occurrence of a major cardiovascular event
- Composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization
- Time frame: 58 months

Guidelines to Manage Dyslipidemia

| 2013 ACC/AHA Guidelines
d | 2011 ESC/EAS Guidelines |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Recommendations</td>
</tr>
<tr>
<td>Lipoproteins and triglycerides</td>
<td>LDL-C ≤ 70 mg/dL, or ≥ 50% reduction in LDL-C</td>
</tr>
<tr>
<td>Apheresis</td>
<td>LDL-C ≤ 40 mg/dL, or ≥ 50% reduction in LDL-C</td>
</tr>
<tr>
<td>Statins</td>
<td>Low risk, high-intensity statins</td>
</tr>
<tr>
<td></td>
<td>High risk, high-intensity statins</td>
</tr>
<tr>
<td></td>
<td>Medium risk, moderate-intensity statins</td>
</tr>
<tr>
<td></td>
<td>Low risk, moderate-intensity statins</td>
</tr>
</tbody>
</table>

IMPROVE-IT

Table 1: Primary, Secondary, and Individual End Points

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Severance Median (mg/dL)</th>
<th>Severance Median (mmol/L)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>140 (91)</td>
<td>100 (6.2)</td>
<td>1.1 (0.93-1.28)</td>
<td>0.30</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>130 (65)</td>
<td>100 (6.2)</td>
<td>1.0 (0.84-1.20)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>130 (65)</td>
<td>100 (6.2)</td>
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</tr>
</tbody>
</table>
PCSK9 CV OUTCOMES TRIALS

- FOURIER
  - Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (Evolocumab)
    - Estimated enrollment: 22,500 patients
- ODYSSEY Program
  - Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab
    - Estimated enrollment: 18,000 patients
- SPIRE-1/SPIRE-2
  - The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects
    - Estimated enrollment: 18,300 patients

PCSK9 INHIBITORS

- Cost
  - Evolocumab (Repatha) 140 mg: $650.77 per dose
  - 140 mg every 2 weeks: annual cost $16,920.02
  - 480 mg monthly: annual cost $23,427.77
  - Alirocumab (Praluent) 75 mg/150mg: $672 per dose
  - Every 2 weeks administration: annual cost $17,472

PIPELINE CHOLESTEROL LOWERING AGENTS

- BEMPEDOCIC ACID (ETC-1002)
  - Orally available
  - Inhibits ACL, enzyme that supplies substrate for cholesterol and fatty acid synthesis in the liver
  - Enrolling in Phase III trial

- ANACETRAPIB
  - CETP-inhibitor
  - 3 previous CETP-inhibitors have failed in trials
  - Phase III trial
  - Concludes Jan. 2017

HOW LOW IS TOO LOW?

- No clear data in human studies
- JUPITER trial
  - Rosuvastatin treated patients
    - Median LDL-C: 59 mg/dL
  - IMPROVE-IT trial
    - Median LDL-C: 53.7 mg/dL

HEART FAILURE NEW MEDICATIONS

**IVABRADINE**

**Indication**
- Reduce risk of hospitalization for worsening heart failure (HF)
- LVEF less than 35%
- Resting heart rate above 70 bpm
- Taking maximally tolerated doses of beta blockers or contraindicated to beta blockers

**Dosage**
- 5 mg twice daily with meals
- 2.5 mg twice daily with meals
- Or patients with concern of bradycardia
- Titrate up in 2 weeks for resting heart rate of 50-60 bpm
- Maximum dose of 7.5 mg twice daily

**Adverse Reactions**
- Bradycardia
- Hypertension
- Atrial Fibrillation
- Heart block

**Contraindications**
- Acute decompensated HF
- BP less than 90/50 mmHg
- Sick sinus syndrome, sinoatrial block, or third-degree AV block
- Resting HR less than 60 bpm
- Severe hepatic impairment
- Pacemaker dependence
- Concomitant use with strong CYP 3A4 inhibitors

**SHIFT STUDY**

<table>
<thead>
<tr>
<th>Indication group</th>
<th>Placebo group</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>70% (24%)</td>
<td>87% (29%)</td>
<td>1.04 (0.96-1.12)</td>
</tr>
<tr>
<td>Morbidity endpoints</td>
<td>55% (16%)</td>
<td>52% (16%)</td>
<td>1.01 (0.94-1.08)</td>
</tr>
<tr>
<td>Cardiac deatly</td>
<td>4.9% (04%)</td>
<td>8.9% (14%)</td>
<td>1.67 (0.87-3.25)</td>
</tr>
<tr>
<td>Non-fatal death</td>
<td>3.2% (2%)</td>
<td>3.0% (2%)</td>
<td>1.07 (0.60-1.94)</td>
</tr>
<tr>
<td>Office visits</td>
<td>12% (9%)</td>
<td>16% (12%)</td>
<td>1.32 (0.92-1.93)</td>
</tr>
</tbody>
</table>

Table 1: Effects of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure (the SHIFT Study). Eur Heart J. 2012;33(22):2813-2820.
HF GUIDELINES UPDATE

<table>
<thead>
<tr>
<th>COR</th>
<th>LCE</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF &lt;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</td>
</tr>
</tbody>
</table>

2016 ANNUAL MEETING

Corlandor (ivabradine) [prescribing information]. Thousand Oaks, CA: Amgen Inc; April 2015.

SACUBITRIL/VALSARTAN

- **Indication**
  - Reduce the risk of cardiovascular death and hospitalizations in patients with chronic Heart Failure (HF) and reduced ejection fraction

- **Dosing**
  - Starting dose of 49/51 mg twice daily
  - Target maintenance dose of 97/103 mg twice daily
  - Increase to 2 to 4 weeks
  - Reduce starting dose to 24/25 mg twice daily
  - Not currently taking ACEi/ARB or low doses
  - eGFR less than 30ml/min/1.73m²
  - Moderate hepatic impairment

- **Contraindications**
  - Hypersensitivity to sacubitril or valsartan
  - History of angioedema related to previous ACE inhibitor or ARB therapy
  - Concomitant use or use within 36 hours of ACE inhibitors
  - Concomitant use of aliskiren in patients with diabetes

- **Black Box Warning**
  - Pregnancy
  - Can cause injury and death to the developing fetus
  - When pregnancy is detected, discontinue sacubitril/valsartan as soon as possible

2016 ANNUAL MEETING

SACUBITRIL/VALSARTAN (ENTRESTO)

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  - Reduce the risk of cardiovascular death and hospitalizations in patients with chronic Heart Failure (HF) and reduced ejection fraction

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- **Black Box Warning**
  - Pregnancy
  - Can cause injury and death to the developing fetus
  - When pregnancy is detected, discontinue sacubitril/valsartan as soon as possible
SACUBITRIL/VALSARTAN (ENTRESTO)

- Adverse Reactions
  - Hypotension (18%)
  - Hyperkalemia (12%)
  - Increase serum creatinine (up to 16%)
  - Renal failure (5%)
  - Cough (9%)
  - Angioedema (black patients: 2%; others: <1%)
  - Dizziness (6%)

2016 ANNUAL MEETING
Entresto (sacubitril/valsartan) [prescribing information]. East Hanover, NJ: Novartis; August 2015.

PARADIGM-HF


HF GUIDELINES UPDATE

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFREF to reduce mortality and morbidity</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>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</td>
</tr>
<tr>
<td>1</td>
<td>B-R</td>
<td>In patients with chronic symptomatic HFREF NYHA class II or III who tolerate ACE inhibitors or ARBs, replacement by an ARNI is recommended to further reduce morbidity and mortality</td>
</tr>
</tbody>
</table>

ANTIDOTES

New Oral Anticoagulants | Classification | Reversal Agent Available |
------------------------|---------------|--------------------------|
Rivaroxaban             | Factor Xa Inhibitor | No                       |
Apixiban                | Factor Xa Inhibitor | No                       |
Edoxaban                | Factor Xa Inhibitor | No                       |
Dabigatran              | Direct Thrombin Inhibitor | Yes                  |
**IDARUCIZUMAB (PRAXBIND)**

- **Indication**
  - Reversal of the anticoagulant effects of dabigatran
  - Emergency surgery/urgent procedures
  - Life-threatening or uncontrolled bleeding

- **Dosing**
  - 5 grams
  - Administered as 2 doses of 2.5 g no more than 15 minutes apart
  - No adjustments for renal or hepatic impairment

- **Mechanism of action**
  - Humanized monoclonal antibody fragment (Fab)
  - Binds to dabigatran and its acyl glucuronide metabolites neutralizing their anticoagulant effect
  - Almost 350 times greater affinity than the binding affinity of dabigatran to thrombin

- **Administration**
  - Intravenously administer the dose of 5 grams (2 vials containing 2.5 g each)
  - Two consecutive infusions
  - Bolus injection consecutively
  - Once removed from vial
  - Administration should begin within 1 hour
  - Do not mix with other medicinal products
  - Aseptic technique
  - Flush IV line with normal saline prior to infusion

- **Cost**
  - 5 gram dose: $4,200

- **Resume anticoagulant**
  - Dabigatran can be re-initiated 24 hours after idarucizumab administration

- **Warnings/Precautions**
  - Re-evaluation of coagulation parameters
  - Hypersensitivity reactions
  - Thromboembolic risk
  - Hereditary fructose intolerance

- **Adverse Reactions**
  - Delirium (7%)
  - Headache (5%)
  - Hypokalemia (7%)
  - Constipation (7%)
  - Hypersensitivity
  - Pneumonia (6%)
  - Fever (6%)

**REVERSE-AD**

Prospective cohort study to determine safety and ability to reverse anticoagulant affects of patients receiving dabigatran with:

- **Group A**
  - Overt, uncontrollable or life-threatening bleeding

- **Group B**
  - Required surgery or other invasive procedure that could not be delayed for at least 8 hours

**REVERSE-AD**

Interim analysis results

![Graph](image1)

**REVERSE-AD**

• Interim analysis results of primary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median maximum percentage reversal</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>dTT normalization</td>
<td>98%</td>
<td>93%</td>
</tr>
<tr>
<td>ECT normalization</td>
<td>89%</td>
<td>88%</td>
</tr>
</tbody>
</table>

![Graph](image2)

**REVERSE-AD**

• Interim analysis results of secondary (clinical) outcomes

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median investigator-reported time to cessation of bleeding</td>
<td>11.4 hours</td>
<td>—</td>
</tr>
<tr>
<td>Normal intra-operative hemostasis</td>
<td>—</td>
<td>92%</td>
</tr>
</tbody>
</table>

![Graph](image3)

**ANDEXANET ALFA**

• Novel agent currently in Phase III trials
• Reversal of factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
• Mechanism of Action
  - Recombinant modified human factor Xa decoy protein
  - Binds and sequesters factor Xa inhibitors
  - Decoy of factor Xa molecule
  - Bind with high affinity to anti-factor Xa

![Graph](image4)
Andexanet Alfa

- Phase III trial ongoing
- Prospective, open label study of andexanet alfa in patients receiving a factor Xa inhibitor who have acute major bleeding
- Primary outcome
  - Demonstrate the decrease in anti-fXa activity following andexanet treatment
  - Evaluate hemostatic efficacy of andexanet in patients receiving a fXa inhibitor who have acute major bleeding and reduced fXa activity
- Secondary outcome
  - Assess the relationship between decrease in anti-fXa activity and achievement of hemostatic efficacy in patients receiving a fXa inhibitor who have acute major bleeding and reduced fXa activity

Per977 (Ciraparantag)

- Currently in Phase II clinical trials
- Broad spectrum reversal agent
  - Low molecular weight heparin
  - Unfractionated heparin
  - Edoxaban
  - Dabigatran
  - Rivaroxaban
  - Apixiban
- Single IV bolus

Summary

- Idarucizumab
  - Approved for reversal of dabigatran
- Andexanet alfa
  - Currently in phase III trials
  - Reversal agent for rivaroxaban and apixiban
- PER977
  - Currently in phase II trials
  - Broad spectrum reversal agent
QUESTIONS??

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