Welcome to the Duke University Hospital Department of Pharmacy 2014 Spring Symposium!

Continuing Education Information

• ACPE:
  – Pharmacists: 00851-0000-14-013-L01-P
  – Technicians: 00851-0000-14-013-L01-T

• CME:
  – LA_JA_140513_1

Hypertension Management: An Update on JNC8

Rachel Rogers, PharmD
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Durham, NC

Disclosure Statement

These individuals have the following to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation:

Rachel Rogers, PharmD: Nothing to disclose

Objectives

Compare major updates to the hypertension guidelines to historical goals and treatment of patients as outlined by JNC 7

Summarize evidence supporting the recommendations for changes in treatment goals and initial pharmacologic therapy in the updated guidelines
Case

HP is a 64 year old black male with a history of DM type I controlled with insulin who presents to clinic with a chief complaint of persistent headaches.

Medications:
- Aspirin 81 mg po daily
- Insulin glargine 28 units SubQ HS
- Insulin aspart 3 units SubQ with meals
- Atorvastatin 10 mg po at bedtime

Vitals

<table>
<thead>
<tr>
<th>HR</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>164/97</td>
</tr>
<tr>
<td>RR 17</td>
<td>Temp 37°C</td>
</tr>
</tbody>
</table>

Pertinent Labs

<table>
<thead>
<tr>
<th>K</th>
<th>SCr 1.4 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>160 mg/dL</td>
</tr>
<tr>
<td>CrCl</td>
<td>~44 mL/min</td>
</tr>
</tbody>
</table>

How should the blood pressure be managed for this 64 year old, gentleman with diabetes and chronic kidney disease (CKD)?

- A. Start Hydrochlorothiazide 12.5 mg po daily with a goal BP <130/80
- B. Start Lisinopril 10 mg po daily with a goal BP of <140/90
- C. Start Lisinopril 10 mg po daily with a goal BP of <130/80
- D. Do nothing

Hypertension

One of the most preventable contributors to disease and death

Decreases in blood pressure reduce adverse health outcomes

Blood Pressure Level (mmHg)

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>OR 80-89</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>&gt;140</td>
<td>OR &gt;90</td>
</tr>
<tr>
<td>Stage I Hypertension</td>
<td>140-159</td>
<td>OR 90-99</td>
</tr>
<tr>
<td>Stage II Hypertension</td>
<td>≥160</td>
<td>OR ≥100</td>
</tr>
</tbody>
</table>

Updating JNC 7

In adults with hypertension:

- Does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
- Does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
- Do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

Literature Search

Included Patients

- ≥18 years with HTN
- Subgroups:
  - Diabetes
  - Coronary/Peripheral Artery Disease
  - Heart Failure
  - Previous Stroke
  - Chronic Kidney Disease/proteinuria
  - Older adults – men and women
  - Racial and Ethnic Groups
  - Smokers
**Literature Search**

**Excluded Studies**
- <100 patients
- Follow-up period of less than one year

**Study Outcomes**
- Overall mortality, cardiovascular disease (CVD)/chronic kidney disease (CKD)-related mortality
- Myocardial infarction, heart failure, hospitalization for heart failure, stroke
- Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty, and coronary stent placement), other revascularization (includes carotid, renal, and lower extremity revascularization)

**Other Considerations**
- **Randomized Controlled Trials**
  - Less bias
  - Gold standard for determining efficacy
- **Recommendations**
  - Centered around the top three questions

**Recommendation Grading**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong (high certainty of substantial net benefit)</td>
</tr>
<tr>
<td>B</td>
<td>Moderate (moderate certainty of moderate/substantial net benefit; high certainty of moderate net benefit)</td>
</tr>
<tr>
<td>C</td>
<td>Weak (at least moderate certainty of small net benefit)</td>
</tr>
<tr>
<td>D</td>
<td>Against (at least moderate certainty of no or negative net benefit)</td>
</tr>
<tr>
<td>E</td>
<td>Expert Opinion (“There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.”)</td>
</tr>
<tr>
<td>N</td>
<td>No recommendations for or against (“There is insufficient evidence or evidence in unclear or conflicting.”)</td>
</tr>
</tbody>
</table>

**Recommendations**

**Recommendation 1**
- **General population (≥60 years)**, pharmacologic treatment to goal:
  - SBP <150 mmHg and DBP <90 mmHg (Grade A)
  - Corollary recommendation
  - Treated SBP <140 without adverse effects, no adjustment needed (Grade E)

**Recommendation 2**
- **General population (<60 years)**, pharmacologic treatment to DBP <90 mmHg
  - Ages 30–59 (Grade A)
  - Ages 18–29 (Grade E)

**Recommendation 3**
- **General population (<60 years)**, pharmacologic treatment to SBP <140 mmHg (Grade E)

**Recommendation 4**
- **Population ≥18 years with CKD**, pharmacologic treatment at goal:
  - SBP <140 mmHg and DBP <90 mmHg (Grade E)

**Recommendation 5**
- **Population ≥18 years with diabetes**, pharmacologic treatment at goal:
  - SBP <140 mmHg and DBP <90 mmHg (Grade E)
Recommendation 6
- General non-black population, including those with diabetes, initial treatment:
  - Thiazide-type diuretic, calcium channel blocker (CCB), angiotensin converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) (Grade B)

Recommendation 7
- General black population, including those with diabetes, initial treatment:
  - Thiazide-type diuretic or CCB (Grade B, Grade C for blacks with diabetes)

Recommendation 8
- Population ≥18 years with CKD and HTN, initial/add-on treatment:
  - Angiotensin converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) (Grade B)
  - Applies to all CKD patients with HTN regardless of race or diabetes

Recommendation 9
- BP not at goal in one month:
  - Increase dose of initial drug or add second drug
  - May add and titrate third drug – not ACE/ARB together
  - If uncontrolled due to contraindication/max therapy – use alternate antihypertensive drug and may refer to hypertension specialist (Grade E)

Comparison of Current Recommendations with JNC 7 Guidelines

<table>
<thead>
<tr>
<th>Topic</th>
<th>JNC 7</th>
<th>JNC 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodology</td>
<td>• Non-systematic literature review by expert committee including a range of study designs</td>
<td>• Critical questions and review criteria defined by expert committee</td>
</tr>
<tr>
<td></td>
<td>• Recommendations based on consensus</td>
<td>• Initial systematic review by methodologists restricted to RCT evidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Subsequent review of RCT evidence and recommendations by the committee according to a standardized protocol</td>
</tr>
</tbody>
</table>

Definitions
- Defined HTN and pre-HTN
- Definitions of HTN and pre-HTN not addressed, but thresholds for pharmacologic treatment defined

Comparison of Current Recommendations with JNC 7 Guidelines

<table>
<thead>
<tr>
<th>Topic</th>
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<th>JNC 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Goals</td>
<td>Separate treatment goals for &quot;uncomplicated&quot; HTN and for subsets with various comorbid conditions (Diabetes, CKD)</td>
<td>Similar treatment goals defined for all hypertensive populations except where evidence review supports different goals for a particular subgroup</td>
</tr>
<tr>
<td>Lifestyle Recommendations</td>
<td>Recommended lifestyle modifications based on literature review and expert opinion</td>
<td>Recommends lifestyle modifications, by endorsing the evidence-based recommendations of the Lifestyle Work Group</td>
</tr>
</tbody>
</table>

Comparison of Current Recommendations with JNC 7 Guidelines

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<tr>
<td>Drug Therapy</td>
<td>• Recommended 6 classes to be considered as initial therapy, but recommended thiazide-type diuretics for most patients</td>
<td>• Recommends selection among four specific medication classes and doses based on RCT evidence</td>
</tr>
<tr>
<td></td>
<td>• Specified particular antihypertensive medication classes for patients with compelling indications</td>
<td>• Recommends specific medication classes based on evidence review for racial, CKD, and diabetic subgroups</td>
</tr>
<tr>
<td></td>
<td>• Includes table of oral antihypertensive drugs including names and usual dose ranges</td>
<td>• Table of drugs and doses used in the outcome trials reviewed by Committee but are not necessarily meant to exclude use of other agents</td>
</tr>
</tbody>
</table>

Review Process Prior to Publication
- Reviewed by the National High Blood Pressure Education Program Coordination Committee
- Reviewed by 20 experts including those affiliated with professional and public organization and federal agencies. No official sponsorship.
Main Differences

- Only RCTs included for review
- Similar BP goals for all patients
  - Decreased BP goal for 60-79 years old
- No specific first-line preference
- Only specified medication classes for diabetes, CKD, and race

Treatment Algorithm

Evidence supporting a systolic blood pressure goal of less than 150 mmHg in patients aged 60 years or older: the minority view

- Wright et al.
  - Increasing target may reduce intensity of treatment in high-risk CVD population
  - Evidence supporting increase to 150 mmHg was insufficient and inconsistent
  - Higher goal may reverse decrease in CVD observed over past ten years

Other Organizations

- American Society of Hypertension/International Society of Hypertension (ASH/ISH) Hypertension Guidelines
  - Most patients: <140/90 mmHg (including 60-79 years old)
  - Non-black patients start with ACEI/ARB
  - Non-black patients ≥60 years: CCB or thiazide

Other Organizations

- American Diabetes Association (ADA)
  - Patients with Diabetes:
    - <140/80 mmHg
    - <130/80 mmHg in those who can tolerate the lower goal
Conclusions

- Updated guidelines to JNC 7
  - Recommend more agents as first line
  - Increased the BP goal for patients ≥60 years
  - Removed compelling indications
    - Same goal for patients with or without diabetes or CKD
  - Pushback from healthcare providers
    - Not enough evidence to support lowered BP goal for patients 60–79 years old
    - Other organizations provide BP goals

Case

- HP is a 64 year old black male with a history of DM type 1 controlled with insulin who presents to clinic with a chief complaint of persistent headaches.

Vitals

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<td>CrCl ~44 mL/min</td>
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Case / Self-Assessment Question #1

- According to the update guidelines, how should the blood pressure be managed for this 64 year old diabetic gentleman, with chronic kidney disease?
  - A. Start Hydrochlorothiazide 12.5 mg po daily with a goal BP <130/80
  - B. Start Lisinopril 10 mg po daily with a goal BP of <140/90
  - C. Start Lisinopril 10 mg po daily with a goal BP of <130/80
  - D. Do nothing

Self-Assessment Question #2

- JNC 8 guidelines recommended a higher blood pressure goal for which subset of patients?
  - A. <50 years old
  - B. Patients with diabetes
  - C. ≥60 years old
  - D. All patients have the same blood pressure goal

New Pharmacologic Agents

Cathy Vaughan, PharmD
Sarah White, PharmD
Clinical Pharmacists, Center for Medication Policy
Duke University Hospital
May 13, 2014

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Cathy Vaughan, PharmD: Nothing to disclose
Sarah White, PharmD: Residency stipend funded through GlaxoSmithKline

Objectives

- Identify newly approved medications which offer pharmacotherapeutic advances
- Discuss clinical applications for each agent and compare with standard medications
- Identify important drug-drug interactions, adverse effects, and other safety issues
- List patient counseling information and monitoring parameters for each new medication

Hydrocodone Extended-Release Capsules [Zohydro ER - Zogenix]

- First single-entity extended-release hydrocodone product
- FDA Indication: For the management of severe pain requiring daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- More potent than hydrocodone combination products
  - Available strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg
  - Initial dose for opioid naïve patients: 10 mg every 12 hours
  - Titrate in 10 mg increments every 3-7 days as needed
  - Renal impairment/Severe hepatic impairment: Initiate with lowest dose

Clinical Trial: Design

- Randomized, double-blind, placebo-controlled, multicenter trial that included opioid-experienced subjects with moderate to severe chronic low back pain

  Open-label conversion and titration phase
  (≤ 6 wks)  
  [N = 510]

  12-week double-blind treatment phase
  [N = 302]

  Hydrocodone ER every 12h (equi-analgesic dose of pre-study opioid medication)
  - Increased by 10 mg per 12h dose, once every 3-7 days until stable dose achieved, or max dose 100 mg every 12h
  - Subjects randomized to stabilized dose of hydrocodone ER 20 mg-100 mg q 12h or placebo
  - Hydrocodone 5mg/APAP 500mg < 2 doses (2 tabs) per day as rescue medication

Clinical Trial: Results

The percentage of subjects in each group who demonstrated improvement in their Numeric Rating Scale (NRS) pain score at 2 weeks of blinded use, as compared to Blinded Study, is shown in Figure 1. The figure is comparable, so that subjects whose change from baseline is the greatest improvement is the largest. A difference of 50% in the proportion of subjects with an improvement defined as subjects with NRS of 2 or less was observed between the treatments. Treatment with Zohydro ER demonstrated a significantly greater improvement in pain relief compared to placebo (41.3% vs. 31.1%).

CONTROVERSIAL

"New pain pill’s approval: Genuinely frightening”

"Zohydro: America's Deadliest New Drug?*

"Is the super potent new opiate painkiller Zohydro just too dangerous?"
**Boxed Warning**

- Risk of addiction, abuse, and misuse, which can lead to overdose and death
- Serious, life-threatening, or fatal respiratory depression may occur
- Accidental consumption, especially in children, can result in fatal overdose
- For pregnant patients who require opioid therapy, infants may require treatment for neonatal opioid withdrawal syndrome
- Consuming alcohol with hydrocodone ER can result in fatal plasma hydrocodone levels

**Hydrocodone Extended-Release Capsules**

**Contraindications**
- Significant respiratory depression
- Acute or severe bronchial asthma or hypercarbia
- Known or suspected paralytic ileus

**Warnings/Precautions**
- Use in elderly, cachectic, debilitated patients
- Respiratory depression more likely to occur due to altered pharmacokinetics or clearance
- Patients with chronic pulmonary disease
- Monitor for respiratory depression, particularly when initiating therapy and titrating dose
- Hypotensive effect
  - May cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients

**Drug Interactions**
- CYP3A4 inhibitors/inducers – Increased or decreased hydrocodone plasma concentrations
- CNS depressants – Concomitant use may cause profound sedation, respiratory depression, and death
- MAOIs – Concomitant use may increase the effect of either the MAOI or hydrocodone
- Anticholinergics – Concomitant use may increase the risk of urinary retention or severe constipation

**Common Adverse Effects**
- Constipation, nausea, vomiting, somnolence, fatigue, headache, dizziness, dry mouth, pruritis

**Patient Counseling/Monitoring**

**Counseling Points:**
- Take medication as prescribed. Do not stop taking or change dose without talking to provider.
- Do not crush or chew; swallow whole
- Do not drink alcohol
- Proper storage and disposal

**Monitoring:**
- Liver and renal function at baseline and periodically during therapy
- Pain control

**Oxycodone/Acetaminophen Extended-Release Tablets**

**Boxed Warning and other warnings/precautions similar to other opioids**

**Drug Interactions**
- CNS depressants, MAOIs, Anticholinergics
- CYP3A4 inhibitors and inducers

**Most common AEs:** nausea, dizziness, headache, vomiting, constipation and somnolence
**Patient Counseling/Monitoring**

**Counseling Points:**
- Take medication as prescribed. Do not stop taking or change dose without talking to provider.
- Do not crush or chew; swallow whole
- Caution when using with acetaminophen or other acetaminophen containing products
- Proper storage and disposal

**Monitoring:**
- Pain control

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**Pulmonary Hypertension: New Therapies**

**Macitentan tablets**
[Opsumit]

**Riociguat tablets**
[Adempas]

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**PH: Definition and Classification**

- Type of high blood pressure that affects the arteries in the lungs
  - Sustained elevation of the mean pulmonary artery pressure (mPAP) of ≥25 mm Hg at rest

**Clinical Classification of PH**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Pulmonary arterial hypertension (PAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td>- atrial/ventricular heart disorders or valvular heart disorders</td>
</tr>
<tr>
<td>Group 3</td>
<td>PH due to lung diseases and/or hypoxemia</td>
</tr>
<tr>
<td></td>
<td>- COPD, interstitial lung disease</td>
</tr>
<tr>
<td>Group 4</td>
<td>PH due to chronic thrombotic or embolic disorders</td>
</tr>
<tr>
<td>Group 5</td>
<td>PH with unclear multifactorial mechanisms</td>
</tr>
<tr>
<td></td>
<td>- Tumors, sarcoidosis</td>
</tr>
</tbody>
</table>

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**PAH: Epidemiology**

- A rare disease with an estimated prevalence of 15-50 cases per million
- Idiopathic PAH has an annual incidence of 1-2 cases per million and is more common in women than in men
- Mean age at diagnosis is ~ 45 years

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**Treatment Algorithm**

- **Macitentan Tablets [Opsumit - Actelion]**
  - Endothelin Receptor Antagonist (ERA) indicated for treatment of PAH to delay disease progression
  - MOA: Prevents binding of ET-1 to both ET₂ and ET₅ receptors. Exhibits high affinity and sustained occupancy of the ET receptors.
  - Dose: 10 mg daily
  - **SERAPHIN**
    - Long-term treatment study with a primary endpoint of morbidity and mortality

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*All Rights Reserved, Duke Medicine 2007*
Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

NEJM 2013;369(9):809-818

Primary Objective

- To assess whether long-term treatment with macitentan reduces morbidity and mortality among patients with PAH

Macitentan: Pivotal Study

Study Design

- Multi-center, randomized, double-blind, placebo controlled phase 3 trial
- Total of 742 patients enrolled

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitentan 3 mg daily</td>
<td>250</td>
</tr>
<tr>
<td>Macitentan 10 mg daily</td>
<td>242</td>
</tr>
<tr>
<td>Placebo daily</td>
<td>250</td>
</tr>
</tbody>
</table>

Inclusion Criteria

- >/= 12 years of age
- Dx of idiopathic or heritable PAH or PAH related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV, or drug use or toxin exposure
- 6-minute walk distance >/= 50 m
- WHO functional class II, III or IV

Exclusion Criteria

- Patients receiving IV or SC prostanoids
- Concomitant tx with PDE-5 inhibitors, oral/inhaled prostanoids, CCB's, or L-arginine allowed if stable dose >/= 3 months prior to randomization

Baseline Characteristics (N=742)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex (N, %)</td>
<td>556 (75.5%)</td>
</tr>
<tr>
<td>Race (N, %)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>403 (54.5%)</td>
</tr>
<tr>
<td>Asian</td>
<td>205 (27.7%)</td>
</tr>
<tr>
<td>Time from diagnosis of PAH (yr)</td>
<td>2.7 ± 4.1</td>
</tr>
<tr>
<td>PAH Classification (N, %)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>404 (55%)</td>
</tr>
<tr>
<td>Associated with connective tissue disease</td>
<td>224 (30.3%)</td>
</tr>
<tr>
<td>Associated with congenital shunts</td>
<td>62 (8.4%)</td>
</tr>
<tr>
<td>6-minute walk distance</td>
<td>360 ± 100.2</td>
</tr>
<tr>
<td>WHO functional class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>387 (52.4%)</td>
</tr>
<tr>
<td>III</td>
<td>337 (45.5%)</td>
</tr>
<tr>
<td>Receipt of background treatment for PAH (N, %)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>471 (63.7%)</td>
</tr>
<tr>
<td>No</td>
<td>271 (36.3%)</td>
</tr>
<tr>
<td>PDE-5 Inhibitor</td>
<td>454 (61.4%)</td>
</tr>
<tr>
<td>Oral or inhaled prostanoid</td>
<td>96 (13.2%)</td>
</tr>
</tbody>
</table>

Primary Endpoint

- Time from the initiation of treatment to the first occurrence of a composite endpoint of death, lung transplant, treatment initiation with IV or SC prostanoids, or worsening of PAH
- Worsening of PAH – All 3 of following had to occur: ↓ 6-minute walk distance >/= 15% of baseline, worsening of PAH symptoms, and need for additional PAH treatment
Macitentan: Pivotal Study

Secondary Endpoints

- Change from baseline to month 6 in 6-minute walk distance
- Percentage of patients with an improvement in WHO functional class at month 6, death due to PAH or hospitalization for PAH up to treatment end, and death from any cause up to treatment end and up to study end

Pivotal Study: Additional Results

- 6-minute walk distance at month 6
  - Placebo = ↓ mean of 9.4 m
  - Macitentan 3 mg = ↑ mean of 7.4 m (p=0.01)
  - Macitentan 10 mg = ↑ mean of 12.5 m (p=0.008)

- Improvement in WHO functional class at month 6
  - Placebo = 13% of patients
  - Macitentan 3 mg = 20% of patients (p=0.04)
  - Macitentan 10 mg = 22% of patients (p=0.006)

Pivotal Study: Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (N,%):</th>
<th>Macitentan 3mg (N,%):</th>
<th>Macitentan 10mg (N,%):</th>
<th>3mg vs Placebo (HR, p-value):</th>
<th>10mg vs Placebo (HR, p-value):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event related to PAH or death as first event</td>
<td>116 (46.4)</td>
<td>95 (36.6)</td>
<td>76 (31.4)</td>
<td>0.70 (0.01)</td>
<td>0.55 (&lt;0.001)</td>
</tr>
<tr>
<td>Decreasing in WHO</td>
<td>69 (26.8)</td>
<td>72 (28.8)</td>
<td>59 (24.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>11 (4.4)</td>
<td>21 (8.4)</td>
<td>10 (4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostanoid initiation</td>
<td>6 (2.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung transplant</td>
<td>0</td>
<td>1 (0.4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All events</td>
<td>116 (46.4)</td>
<td>95 (36.6)</td>
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<td>Death due to PAH or hospitalization for PAH as first event</td>
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<td>Hospitalizations for PAH</td>
<td>79 (31.6)</td>
<td>56 (22.4)</td>
<td>46 (19.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to PAH</td>
<td>5 (2.0)</td>
<td>9 (3.6)</td>
<td>5 (2.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pivotal Study: Safety Results

- Nasopharyngitis, headache, and anemia
  - AE’s experienced by a higher percentage of patients in both macitentan groups compared to placebo

- Incidence of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 3 x ULN was similar across 3 groups

Boxed Warning and REMS

WARNING: EMBRYO-FETAL TOXICITY

- Do not administer macitentan to a pregnant female because it may cause fetal harm
- Females of reproductive potential: exclude pregnancy before start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for 1 month after treatment by using acceptable methods of contraception.

- For all female patients, macitentan is only available through a restricted program called the Opsumit REMS

Macitentan Tablets

Other Warnings/Precautions

- Hepatotoxicity and liver failure
  - Based on data with other ERAs
  - Obtain baseline liver enzymes and monitor periodically during treatment

- Decreased hemoglobin
  - Measure prior to therapy initiation and periodically during treatment

- Decreased sperm count
  - Based on data with other ERAs

DI’s: Metabolized by CYP3A4
### Macitentan: Cost

<table>
<thead>
<tr>
<th>Endothelin Receptor Antagonist</th>
<th>Cost Per Month of Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan 62.5 mg and 125 mg</td>
<td>$8,000</td>
</tr>
<tr>
<td>Ambrisentan 5 mg and 10 mg tablets</td>
<td>$7,738</td>
</tr>
<tr>
<td>Macitentan 10 mg tablets</td>
<td>$8,208</td>
</tr>
</tbody>
</table>

*Cost as of [date] from [source].

### Patient Counseling/Monitoring

**Counseling Points:**
- Female patients: Risk of fetal harm and REMS Program requirements
- Male patients: Potential for ↓ sperm count reduction
- Signs and symptoms of hepatotoxicity
- Mailed to patient’s home via a specialty pharmacy

**Monitoring:**
- Pregnancy test prior to initiating therapy and monthly during treatment
- Liver function tests and hemoglobin prior to initiating therapy and periodically during therapy

### Riociguat Tablets [Adempas - Bayer]

New Class • Soluble Guanylate Cyclase (sGC) Stimulators

FDA approved for treatment of 2 forms of PH:
- PAH to improve exercise capacity, improve WHO functional class and to delay clinical worsening
- Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class

### Riociguat: Mechanism of Action

\[
\text{sGC} \rightarrow \text{NO} \rightarrow \text{cGMP}
\]

### CHEST-1

**Primary Objective**
- To assess the efficacy and safety of riociguat in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were considered by experienced surgeons to be ineligible for surgery or who had persistent or recurrent PH after pulmonary endarterectomy
Study Design
• Multi-center, randomized, double-blind, placebo-controlled 16-week study
• Total of 261 patients enrolled

Riociguat
[Dose range 0.5 mg – 2.5 mg]  • N = 173
Placebo  • N = 88

Inclusion Criteria
• 18 – 80 years of age
• Inoperable CTEPH or persistent/recurrent PH following surgery
• 6-minute walk distance of 150-450 m
• PVR > 300 and mPAP ≥ 25 mm Hg

Exclusion Criteria
• Received an ERA, prostacyclin analogue, PDE-5 inhibitor, or NO within 3 months before study entry

Primary Endpoint
• Change from baseline to the end of week 16 in the distance walked in 6 minutes

Secondary Endpoints
• Change from baseline to end of week 16 in the following: pulmonary vascular resistance, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, WHO functional class, Borg dyspnea score, EuroQol questionnaire score, and Living with PH (LPH) questionnaire score

Baseline Characteristics (N=261)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>172 (66%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59 ± 14</td>
</tr>
<tr>
<td>Race (N, %)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>185 (71%)</td>
</tr>
<tr>
<td>Asian</td>
<td>57 (22%)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>Chronic thromboembolic pulmonary hypertension (N, %)</td>
<td>189 (72%)</td>
</tr>
<tr>
<td>Inoperable</td>
<td>72 (28%)</td>
</tr>
<tr>
<td>6-minute walk distance</td>
<td>347 ± 80</td>
</tr>
<tr>
<td>WHO functional class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>II</td>
<td>90 (35%)</td>
</tr>
<tr>
<td>III</td>
<td>107 (44%)</td>
</tr>
<tr>
<td>IV</td>
<td>10 (4%)</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (N=88)</th>
<th>Riociguat (N=173)</th>
<th>LSMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-minute walk distance (m)</td>
<td>356 ± 75</td>
<td>342 ± 80</td>
<td>34 ± 79</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>779 ± 401</td>
<td>791 ± 418</td>
<td>22 ± 274</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1706 ± 2567</td>
<td>1508 ± 2338</td>
<td>76 ± 1447</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>Moved to lower class 15%</td>
<td>33%</td>
<td>Stayed in same class 62%</td>
</tr>
<tr>
<td>Borg dyspnea score</td>
<td>4.0 ± 2.3</td>
<td>3.4 ± 2.2</td>
<td>0.6 ± 2.2</td>
</tr>
<tr>
<td>EQ-5D score</td>
<td>0.66 ± 0.25</td>
<td>0.64 ± 0.24</td>
<td>0.08 ± 0.34</td>
</tr>
<tr>
<td>LPH score</td>
<td>41 ± 23</td>
<td>41 ± 22</td>
<td>-2 ± 19</td>
</tr>
</tbody>
</table>
**CHEST-1: Safety Results**

**Most Common Adverse Events (>10%)**
- Headache, dizziness, dyspepsia, peripheral edema, nasopharyngitis, nausea, vomiting, diarrhea

**Drug-Related Serious Adverse Events (N, % incidence)**
- Syncope: 3 patients (2%)
- Gastritis and Acute renal failure: 1 patient each (1%)

**Riociguat Tablets**

- **Dose:**
  - Initially, 1 mg three times daily
  - ↑ by 0.5 mg at >/= 2-week intervals as tolerated to a maximum of 2.5 mg three times daily
  - Consider starting dose of 0.5 mg three times daily for patients unable to tolerate hypotensive effect

- **Dose Adjustment:**
  - Concomitant use with strong CYP and P-gp/BCRP inhibitors - consider lower starting dose
  - Smokers - consider titrating to doses > 2.5 mg three times daily
  - Antacids - separate administration by ≥ 1 hour

**Patient Counseling/Monitoring**

- **Counseling Points:**
  - Female patients: Risk of fetal harm and REMS Program requirements
  - Signs and symptoms of low blood pressure
  - Signs and symptoms of bleeding
  - Mailed to patient’s home via a specialty pharmacy

- **Monitoring:**
  - Pregnancy test prior to initiating therapy and monthly during treatment
  - Blood pressure during initiation of therapy

**Newly Approved Chronic Obstructive Pulmonary Disease (COPD) Agents**

- Fluticasone furoate / Vilanterol [Breo Ellipta]
- Umeclidinium / Vilanterol [Anoro Ellipta]

**COPD Statistics**

- Nearly 134,000 deaths in 2009 (3rd highest in USA)
- 12.7 million adults estimated to have diagnosis in 2011
  - 24 million have evidence of impaired lung function
- Responsible for over 700,000 hospital discharges in 2010
- Primary risk factor: Smoking (causes 85-90% COPD deaths)
- Cost to nation in 2010 was estimated at nearly $50 billion

American Lung Association. Chronic Obstructive Pulmonary Disease (COPD) Fact Sheet.
Diagnosis and Severity

- **Diagnosis**: Spirometry is the gold standard
  - Post-bronchodilator FEV\textsubscript{1}/FVC ratio <0.70 is indicative of airflow limitation
- **Severity**: Based on exacerbation risk and symptoms
  - **Group A**: Low risk, less symptoms
  - **Group B**: Low risk, more symptoms
  - **Group C**: High risk, less symptoms
  - **Group D**: High risk, more symptoms

Pharmacologic Management of COPD

- **SABAs**
- Short-acting anticholinergics
- Combination SABAs and short-acting anticholinergics
- Methylxanthines
- **LABAs**
- Long-acting anticholinergics
- **ICS**
- Systemic corticosteroids
- Combination LABA and ICS
- Combination LABA and long-acting anticholinergics

Mechanism of Action

- **Combination LABA/ICS**
- **Fluticasone furoate**: ICS component
  - Activity on cells (mast cells, eosinophils)
  - Mediators (histamine, cytokines)
  - Inhibition of pro-inflammatory transcription factors
- **Vilanterol**: LABA component
  - Beta\textsubscript{2}: Predominant number of adrenergic receptors in bronchial smooth muscle
  - Stimulates enzyme causing increased production of a molecule producing relaxation of bronchial smooth muscle

Dosing and Administration

- **Product available in one strength**
- **Dose**: 1 inhalation once daily
  - Fluticasone furoate: 100 mcg
  - Vilanterol: 25 mcg
- **Renal impairment**: No adjustment required
- **Hepatic impairment**: Use with caution in moderate or severe impairment, monitor for corticosteroid side effects
Warnings

- **Boxed Warning: Asthma-Related Death**
  - Based on a placebo-controlled trial with salmeterol
  - This is a class effect for all LABA-containing agents

- **Other Warnings Include:**
  - Do not initiate in acutely deteriorating COPD
  - *Candida albicans* of mouth and pharynx
  - Increased risk of pneumonia
  - Concerns related to ICS component
  - Concerns related to LABA component

Comparison vs. Vilanterol for Prevention of Moderate-Severe Exacerbations

**Study Design**

- 2 randomized, double-blind, 52-week studies
- Patients randomized (1:1:1:1 ratio) to vilanterol 25 mcg or fluticasone/vilanterol (50 mcg/25 mcg; 100 mcg/25 mcg; or 200 mcg/25 mcg)

**Subjects**

- (N = 3255)
  - Both studies: Yearly rate of moderate and severe COPD exacerbations

**Primary Endpoint**

- Adults 40 years and older
- Diagnosis of COPD
- FEV₁/FVC ratio of 0.7 or less
- At least a 10 pack-year smoking history
- At least 1 moderate or severe exacerbation in the past year

Results of Exacerbations Trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean Annual Rate (Exacerbations/Yr.)</th>
<th>Ratio vs. Vilanterol</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone 100 mcg/ vilanterol 25 mcg</td>
<td>403</td>
<td>0.9</td>
<td>0.79</td>
<td>(0.64, 0.79)</td>
</tr>
<tr>
<td>Vilanterol 25 mcg</td>
<td>409</td>
<td>1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone 100 mcg/ vilanterol 25 mcg</td>
<td>403</td>
<td>0.7</td>
<td>0.66</td>
<td>(0.54, 0.81)</td>
</tr>
<tr>
<td>Vilanterol 25 mcg</td>
<td>409</td>
<td>1.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Future Directions and Cost

- Exacerbations study versus fluticasone furoate in asthma
- Studies comparing to fluticasone propionate / salmeterol
  - COPD subjects
    - No significant difference in spirometry at 12 weeks
  - Asthmatics (adults and adolescents)
    - No significant differences in spirometry measures at 24 weeks
- Survival study currently underway in COPD patients
- Cost: ~$290 for one 30-dose inhaler

Patient Counseling

1. Open inhaler cover to reveal mouthpiece until “click” is heard.
2. Exhale fully before administering dose.
3. Inhale medicine by taking one long, deep breath from mouth.
4. Remove inhaler and hold breath for 3-4 seconds afterwards.
5. Breathe out slowly and gently.
6. After inhaler is used, rinse mouth with water and spit out.
7. Close the inhaler. Store at room temperature.
8. Discard after opening the foil tray after 6 weeks or when dose counter is “0”.

Umeclidinium / Vilanterol [Anoro Ellipta - GlaxoSmithKline]

- FDA approved December 2013
- Indication: Maintenance treatment of airflow obstruction in patients with COPD
- NOT indicated for:
  - Acute relief of bronchospasm
  - Treatment of asthma
Mechanism of Action

• Combination long-acting anticholinergic and LABA

• Umeclidinium: long-acting anticholinergic component
  – Long-acting antimuscarinic agent
  – Competitively inhibits the M3 receptor in smooth muscle
  – Prevention of cholinergic-induced bronchoconstriction

• Vilanterol: LABA component (see previous slide)

• First long-acting anticholinergic / LABA combination product approved in the United States

Dosing and Administration

• Product available in one strength

• Dose: 1 inhalation once daily
  – Umeclidinium: 62.5 mg
  – Vilanterol: 25 mcg

• Renal Impairment: No adjustment necessary

• Hepatic Impairment: No adjustment provided in manufacturer labeling

Warnings

• Boxed Warning: Asthma-Related Death
  – Due to vilanterol component in combination product

• Other Warnings Include:
  – Do not initiate in acutely deteriorating COPD
  – Worsening of narrow-angle glaucoma
  – Worsening of urinary retention
  – Use with caution in patients with bladder-neck obstruction or hyperplasia of the prostate
  – Concerns related to LABA component

Comparison vs. Vilanterol or Umeclidinium

Study Design

• Randomized, double-blind, 24-week study
• Given (3:3:3:2) umeclidinium 62.5 mcg/vilanterol 25 mcg; umeclidinium 62.5 mcg; vilanterol 25 mcg; or placebo

Subjects

(N = 1532)

• Adults 40 years and older
• Diagnosis of COPD
• FEV1/FVC ratio of 0.7 or less
• At least a 10 pack-year smoking history

Primary Endpoint

• Change from baseline in trough (predose) FEV1 after 24 weeks of treatment

Study Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Trough FEV1, (mL) at Day 169</th>
<th>Difference From:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (95% CI)</td>
<td>280</td>
<td></td>
<td>Umeclidinium</td>
</tr>
<tr>
<td>n = 280</td>
<td></td>
<td>167 (128, 207)</td>
<td>52 (17, 87)</td>
</tr>
<tr>
<td>Vilanterol 25 mcg (95% CI)</td>
<td></td>
<td>95 (60, 130)</td>
<td></td>
</tr>
<tr>
<td>n = 421</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umeclidinium 62.5 mcg/Vilanterol 25 mcg</td>
<td>413</td>
<td>167 (128, 207)</td>
<td>52 (17, 87)</td>
</tr>
</tbody>
</table>

Patient Counseling

1) Open inhaler cover to reveal mouthpiece until “click” is heard.
2) Exhale fully before administering dose.
3) Inhale medicine by taking one long, deep breath from mouth.
4) Remove inhaler and hold breath for 3-4 seconds afterwards.
5) Breathe out slowly and gently.
6) Close the inhaler. Store at room temperature.
7) Discard after opening the foil tray after 6 weeks or when dose counter is “0”.
Future Directions and Cost

- As of now, no published outcomes data
- Similar study published using umeclidinium 125 mcg/vilanterol 25 mcg as the combination dose
  - Similar results to previously-reviewed study
- Comparison studies have been conducted with
  - Once-daily tiotropium
  - Twice daily fluticasone propionate/salmeterol
- Cost: ~$300 for one 30-dose inhaler

Newly Approved Agents for Treatment of Hepatitis C Virus (HCV)

- Simeprevir [Olysio]
- Sofosbuvir [Sovaldi]

Disease State Information

- Most common blood-borne infection (United States and throughout world)
- Leading cause of chronic liver disease, hepatocellular carcinoma (HCC), and liver transplantation
- Six different genotypes (GT) throughout world
  - (GT1 most prevalent in United States)
- Estimated that 5 million Americans currently have HCV
  - Nearly 2 million are undiagnosed

Outcomes Definitions

- Rapid Virological Response (RVR) = Absence of detectable HCV 4 weeks after treatment
- End of Treatment Response (ETR) = Absence of detectable HCV RNA at end of recommended treatment period
- Sustained Virologic Response (SVR) = Plasma HCV RNA <25 units/mL at follow-up after treatment has ended
- Sustained Treatment Response (STR) = Absence of HCV RNA in serum 6 months after a full treatment course has ended

Therapy Before Protease Inhibitors

- Standard Therapy: Peginterferon (Peg-IFN) + Ribavirin (RBV)
  - GT1 and GT4: 48-week duration
  - GT2 and GT3: 24-week duration
  - GT5 and GT6: Insufficient data for recommendation
- Treatment Concerns:
  - Low SVR, long duration of therapy, tolerability
  - Boxed Warnings:
    - RBV: Hemolytic anemia and teratogenicity
    - Peg-IFN: Neuropsychiatric disorders, autoimmune disease exacerbation, aggravation of infectious or ischemic disorders
Previously Approved Protease Inhibitors

• Boceprevir [Victrelis - Merck]
  - Indication: Adults with HCV GT1 in compensated liver disease with Peg-IFN and RBV (treatment naïve or experienced)
  - Dose: 800 mg by mouth 3 times daily (with meal or snack)
  - CI: Use with CYP3A4/5 inducers or drugs highly dependent on CYP3A4/5 for clearance

• Telaprevir [Incivek - Vertex]
  - Indication: Adults with HCV GT1 in compensated liver disease with Peg-IFN and RBV (treatment naïve or experienced)
  - Dose: 1125 mg by mouth twice daily (with non-low fat food)
  - CI: Use with strong CYP3A inducers or drugs highly dependent on CYP3A for clearance
  - Boxed Warning: Serious skin reactions (SJS, DRESS, TEN)

Simeprevir [Olysio - Janssen]

• FDA Approved November 2013
• Indication: Treatment of adults with chronic HCV GT1 in compensated liver disease with Peg-IFN and RBV
• Not Recommended As:
  - Monotherapy for HCV treatment
  - For HCV with NS3 Q80K polymorphism
  • Screening patients prior to treatment strongly recommended

Dosing and Administration

• Product available in one strength (150 mg capsule)
• Dose: 150 mg with food once daily
• Renal impairment: No adjustment required
  – Need to still consider RBV component of therapy
• Hepatic impairment: No recommendation made for patients with moderate to severe hepatic impairment
  – Peg-IFN and RBV contraindicated in decompensated cirrhosis

Warnings

• Boxed Warnings: None
• Contraindications: All associated with Peg-IFN and RBV
• Other Warnings Include:
  – Embryo-fetal toxicity due to RBV component
  – Photosensitivity (presents as an exaggerated sunburn)
  – Rash (most prevalent during first 4 weeks of treatment)
  – Allergy (contains a sulfonamide moiety)

Adverse Reactions and Drug-Drug Interactions

• Common Adverse Reactions:
  – Rash (including photosensitivity): 28%
  – Pruritus: 22%
  – Nausea: 22%
  – Myalgia: 16%
  – Dyspnea: 12%

• Drug-Drug Interactions:
  – Mild inhibitor of intestinal CYP3A4 (not hepatic)
  – Primarily metabolized by CYP3A4
  – Co-administration with moderate or strong CYP3A4 inducers or inhibitors not recommended
QUEST

HCV viral load

Two separate studies

Common side effects (when taken with other agents):
- Tiredness/Headache/Difficulty sleeping
- Nausea

Cost: $66360 for a 12-week therapy course

Liver function, renal function, skin rash/photosensitivity

Monitor for:
- Liver function, renal function, skin rash/photosensitivity
- HCV viral load

Future Directions and Cost

- Simeprevir and Sofosbuvir combination therapy
  - Peg-IFN and RBV-free regimen
  - GT1 patients (treatment-naive and experienced)
    - Two separate studies
      - Patients without and with cirrhosis
  - As ribavirin-free regimens become options, will need to ascertain dosing

- Overall SVR

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Simeprevir + Peg-IFN + RBV</th>
<th>Placebo + Peg-IFN + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 521, % (n/N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall SVR-12</td>
<td>80 (419/521)</td>
<td>50 (132/264)</td>
</tr>
<tr>
<td>GT 1a</td>
<td>75 (191/191)</td>
<td>47 (62/131)</td>
</tr>
<tr>
<td>Without Q80K</td>
<td>84 (138/165)</td>
<td>43 (36/83)</td>
</tr>
<tr>
<td>With Q80K*</td>
<td>58 (49/84)</td>
<td>52 (23/44)</td>
</tr>
<tr>
<td>GT 1b</td>
<td>85 (226/267)</td>
<td>53 (70/133)</td>
</tr>
</tbody>
</table>

*Difference did not reach statistical significance in pooled analysis of QUEST trials

Breakdown of QUEST-1 and QUEST-2

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Simeprevir + Peg-IFN + RBV</th>
<th>Placebo + Peg-IFN + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 264, % (n/N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall SVR-12</td>
<td>79 (206/260)</td>
<td>37 (49/133)</td>
</tr>
<tr>
<td>GT 1a</td>
<td>70 (78/111)</td>
<td>28 (15/54)</td>
</tr>
<tr>
<td>Without Q80K</td>
<td>78 (62/79)</td>
<td>26 (9/34)</td>
</tr>
<tr>
<td>With Q80K*</td>
<td>47 (14/30)</td>
<td>30 (6/20)</td>
</tr>
<tr>
<td>GT 1b</td>
<td>86 (128/149)</td>
<td>43 (34/79)</td>
</tr>
</tbody>
</table>

*Difference did not reach statistical significance in PROMISE trial

PROMISE Results

Patient Counseling and Monitoring

- Take once daily with food
- Taken with ribavirin; contraindicated in pregnancy and male partners of pregnant patients
- Many drug-drug interactions; be sure medication list health care provider has is current
- Common side effects (when taken with other agents):
  - Tiredness/Headache/Difficulty sleeping
  - Nausea
  - Anemia
- Monitor for:
  - Liver function, renal function, skin rash/photosensitivity
  - HCV viral load

QUEST-1 and QUEST-2 Results

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Simeprevir + Peg-IFN + RBV</th>
<th>Placebo + Peg-IFN + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 264, % (n/N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall SVR-12</td>
<td>12 (86/79)</td>
<td>20 (14/70)</td>
</tr>
</tbody>
</table>

QUEST-1

Simeprevir Trial

- Randomized
- Placebo-controlled
- Double-blind
- RGT criteria applied for Peg-IFN/RBV therapy duration
  - Treatment-naive
  - HCV GT1 infection
  - Stratified by GT subtype
  - Simeprevir or placebo (2:1) for 12 weeks with 24 or 46 weeks of Peg-IFN + RBV

QUEST-2

- Randomized
- Placebo-controlled
- Double-blind
- RGT criteria applied for Peg-IFN/RBV therapy duration
  - Treatment-naive
  - HCV GT1 infection
  - Stratified by GT subtype
  - Simeprevir or placebo (2:1) for 12 weeks with 24 or 46 weeks of Peg-IFN + RBV

PROMISE

- Randomized
- Placebo-controlled
- Double-blind
- RGT criteria applied for Peg-IFN/RBV therapy duration
  - Treatment-experienced
  - HCV GT1 infection
  - Stratified by GT subtype
  - Simeprevir or placebo (2:1) for 12 weeks with 24 or 46 weeks of Peg-IFN + RBV

Study Design

Randomized RGT criteria applied for Peg-IFN/RBV therapy duration

Double blind controlled

IFN/RBV therapy duration

Population

HCV GT1 infection

Stratified by GT subtype

Simeprevir or placebo (2:1)

# Subjects

299

Primary Endpoint

SVR-12
Sofosbuvir [Sovaldi – Gilead]

- FDA Approved December 2013
- Indications:
  - Chronic HCV infection (GT 1, 2, 3, or 4)
  - HCC patients awaiting transplant
  - Patients with HCV/HIV-1 co-infection
- Not Recommended As:
  - Monotherapy for HCV treatment
- Available in one strength (400 mg capsule)
- Dose: 400 mg once daily with or without food*
- Chronic HCV infection (GT 1, 2, 3, or 4)
- Patients with HCV/HIV
- Regimen duration based on indication for use

Dosing Based on Indication

- Chronic HCV or HCV/HIV-1 co-infection
  - GT 1 or GT4: Sofosbuvir + Peg-IFN + RBV for 12 weeks
  - Sofosbuvir + RBV for 24 weeks is also an option
  - GT 2: Sofosbuvir + RBV for 12 weeks
  - GT3: Sofosbuvir + RBV for 24 weeks
- HCC patients awaiting liver transplant
  - Sofosbuvir + RBV for 48 weeks or until transplant (whichever comes first)

Warnings

- Boxed Warnings: None
- Contraindications: All associated with Peg-IFN and RBV
- Other Warnings Include:
  - Embryo-fetal toxicity due to RBV component
  - Use with potent P-glycoprotein inducers may decrease sofosbuvir plasma concentrations

Adverse Reactions and Drug-Drug Interactions

- Common Adverse Reactions (≥20%):
  - Fatigue
  - Headache
  - Nausea
  - Insomnia
  - Anemia
- Drug-Drug Interactions:
  - Substrate of P-glycoprotein
  - Co-administration with P-glycoprotein inducers not recommended
    - St. John’s Wort
    - Rifampin
    - Carbamazepine

Sofosbuvir Trial | Study Design | Population | # Subjects | Primary Endpoint
--- | --- | --- | --- | ---
NEUTRINO | Open | Active-control (12 wks or 16 wks) | 223 | SVR 12
FUSION | Open | Active-control (12 wks or 16 wks) | 221 | SVR 12
VALENCE | Open | Active-control (12 wks or 16 wks) | 223 | SVR 12
PHOTON-1 | Open | Active-control (12 wks or 16 wks) | 223 | SVR 12

* Dose: 400 mg once daily with or without food
NEUTRINO Results (SVR-12 Endpoint)

Lawitz E, et al. Treatment with sofosbuvir + peginterferon + ribavirin for 12 weeks achieves 90% SVR12 in treatment-naïve genotype 1, 4, 5, and 6 HCV-infected patients: The NEUTRINO study. Poster session presented at the 48th Annual European Association for the Study of the Liver Meeting; 2013 Apr 24-28; Amsterdam, The Netherlands.

FISSION Results (SVR-12)

Gane E, et al. Phase 3 randomized controlled trial of all-oral treatment with sofosbuvir + ribavirin for 12 weeks compared to 24 weeks of PEG + ribavirin in treatment-naïve GT 2/3 HCV-infected patients (FISSION). Poster session presented at the 48th Annual European Association for the Study of the Liver Meeting; 2013 Apr 24-28; Amsterdam, The Netherlands.

POSITRON Results (SVR-12)

Jacobson IM, et al. Treatment with sofosbuvir + ribavirin for 12 weeks achieves SVR12 of 78% in GT 2/3 interferon-ineligible, intolerant, or unwilling patients: Results of the phase 3 POSITRON trial. Poster session presented at the 48th Annual European Association for the Study of the Liver Meeting; 2013 Apr 24-28; Amsterdam, The Netherlands.

Patient Counseling and Monitoring

- May be taken with or without food (different from protease inhibitors)
- Taken with ribavirin: contraindicated in pregnancy and male partners of pregnant patients
- Common side effects (when taken with other agents):
  - Tiredness/Headache/Difficulty sleeping
  - Nausea
  - Anemia
- Monitor:
  - Renal function
  - Liver function
  - Viral load

Future Directions and Cost

- Sofosbuvir and Ledipasvir fixed-dose combination
  - Ledipasvir is an NS5A inhibitor
  - Submitted to FDA in February for HCV GT1
  - Treatment duration of 8-12 weeks
- Sofosbuvir and Daclatasvir: (currently under investigation)
  - Includes multiple GTs and patients who failed treatment with boceprevir or telaprevir
- Cost: ~$1000 per capsule ($84000 for 12-week course)

Self-Assessment Question 1

How often is hydrocodone extended-release dosed?

a. Once daily
b. Every 12 hours as needed for pain
c. Every 12 hours
d. Every 8 hours
Self-Assessment Question 2

Why do macitentan and riociguat have REMS Programs? They both have the potential for:

a. Liver toxicity
b. Teratogenicity
c. Renal toxicity
d. Cardiotoxicity

Self-Assessment Question 3

What is the mechanism of action for umeclidinium/vilanterol?

a. Inhaled corticosteroid / long-acting anticholinergic
b. Long-acting anticholinergic / long-acting beta₂ agonist
c. Long-acting beta₂ agonist / methylxanthine
d. Methylxanthine / inhaled corticosteroid

Self-Assessment Question 4

What is the labeled daily dose for sofosbuvir?

a. 150 mg by mouth once daily
b. 800 mg by mouth three times daily
c. 750 mg by mouth three times daily
d. 400 mg by mouth once daily

New Pharmacologic Agents

Cathy Vaughan, PharmD
Sarah White, PharmD
Clinical Pharmacists, Center for Medication Policy
Duke University Hospital
May 13, 2014

Continuing Education Information

• ACPE:
  – Pharmacists: 00851-0000-14-013-L01-P
  – Technicians: 00851-0000-14-013-L01-T

• CME:
  – LA_JA_140513_1

Updates in Anticoagulation:
Edoxaban and Human Prothrombin Complex Concentrate
Doug Raiff, PharmD, BCPS: Clinical Pharmacist, Center for Medication Policy
May 13, 2014
Disclosure Statement

• These individuals have the following to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation:

Doug Raiff, PharmD, BCPS: Nothing to Disclose

Learning Objectives

• Compare and contrast the mechanism of action of edoxaban with other novel oral anticoagulants

• Given a patient weight and INR, provide an appropriate dose of human prothrombin complex concentrate

What is Edoxaban Used For?

• Submitted to the Food and Drug Administration as a New Drug Application (NDA) in January 2014

• NDA is for the following indications:
  - Decrease risk of stroke/systemic embolism in patients with non-valvular atrial fibrillation (AF)
  - Venous thromboembolism (VTE) treatment and recurrence prevention

• If approved, would be the fourth oral anticoagulant approved since 2010

How Does Edoxaban Work?

| Anticoagulant | Dabigatran | Rivaroxaban | Apixaban | Edoxaban*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Direct Thrombin Inhibitor</td>
<td>Factor Xa Inhibitor</td>
<td>Factor Xa Inhibitor</td>
<td>Factor Xa Inhibitor*</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>↓ risk of stroke and systemic embolism in non-valvular AF</td>
<td>↓ risk of stroke and systemic embolism in non-valvular AF</td>
<td>↓ risk of stroke and systemic embolism in non-valvular AF</td>
<td>↓ risk of stroke and systemic embolism in non-valvular AF</td>
</tr>
<tr>
<td>↓ VTE treatment and recurrence prevention</td>
<td>↓ VTE treatment and recurrence prevention</td>
<td>↓ VTE prophylaxis in hip or knee replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing Frequency</td>
<td>Twice daily (both labeled indications)</td>
<td>↑ AF: Once daily</td>
<td>↓ AF: Once daily</td>
<td>↓ AF: Twice daily (for 21 days), once daily thereafter</td>
</tr>
<tr>
<td>Hip/Knee: Once daily</td>
<td>Hip/Knee: Once daily</td>
<td>↓ VTE prophylaxis in hip or knee replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>*P-gp (glycoprotein)</td>
<td>+Combined P-gp/CYP3A4</td>
<td>+Comb. P-gp/CYP3A4</td>
<td>+Strong P-gp</td>
</tr>
</tbody>
</table>

*Currently under FDA review for both proposed indications.
More Edoxaban Information

- **Pharmacokinetics:**
  - Peak concentrations observed 1-2 hrs post-dose
  - Mean elimination half-life of 9 to 10.5 hours
  - ~50% of absorbed drug eliminated via renal excretion

- **P-gp drug-drug interactions caused ↑ edoaxaban exposure**
  - Dronedaron: 84.5%
  - Quinidine: 76.7%
  - Verapamil: 52.7%
  - Amiodarone: 39.8%

- In the pivotal trials, edoaxaban was administered with or without food

Further Information On ENGAGE AF-TIMI 48

- **Edoaxaban 30 mg and 60 mg dosing ↓ 50% if:**
  - Estimated CrCl 30-50 mL/min
  - Body weight ≤60 kg
  - Concomitant use of verapamil or quinidine (P-gp inhibitors)

- **Definitions of Major Bleeding:**
  - Decrease in hemoglobin ≥2 g/dL
  - Required ≥2 units of blood
  - Occurred in a critical site or contributed to death

- **Non-Inferiority Analysis:**
  - Upper limit of 97.5% CI for primary outcome HR was 1.38

ENGAGE AF-TIMI 48 Study

- **Study Design**
  - Randomized, double-blind, non-inferiority study
  - Patients randomized (1:1:1 ratio) to edoaxaban 60 mg daily, 30 mg daily, or warfarin
  - Median follow-up: 2.8 years

- **Patients**
  - N = 21026

- **Primary Endpoints**
  - Co-primary:
    - Stroke / systemic embolism (% patients/year)
    - Annualized rate of major bleeding

ENGAGE AF-TIMI 48 Study: Efficacy Outcomes

- **Non-inferiority analysis (mITT)**
  - Warfarin: 1.5% per year
  - High-dose (HD) edoaxaban
    - 1.18% per year; HR: 0.79
    - 95% CI: (0.63; 0.99; p < 0.001)
  - Low-dose (LD) edoaxaban
    - 1.61% per year; HR: 1.07
    - 95% CI: (0.87; 1.31; p = 0.005)

ENGAGE AF-TIMI 48 Study: Other Outcomes

- **Major Bleeding Events**
  - Warfarin: 3.43% per year
  - HD edoaxaban
    - 2.75% per year; HR: 0.8
    - 95% CI: (0.71; 0.91; p < 0.001)
  - LD edoaxaban
    - 3.81% per year; HR: 0.98
    - 95% CI: (0.84; 1.15; p < 0.001)

- **Primary Net Clinical Outcome**
  - Warfarin: 8.11% per year
  - HD edoaxaban: 7.26%; (p < 0.001)
  - LD edoaxaban: 6.79%; (p < 0.001)

*Defined by International Society on Thrombosis and Hemostasis*
Further Information on Hokusai-VTE

- Patients received 30 mg daily if ≥1 of the following:
  - CrCl of 30-50 mL/min
  - Body weight ≤60 kg
  - Concomitant treatment with potent P-glycoprotein inhibitors

- Definitions of major bleeding: Same as Edoxaban AF trial
  - Clinically relevant non-major bleeding: Overt bleeding linked to:
    - Need for medical intervention or contact with physician
    - Interruption of the study drug or impairment in activities of daily living

- Non-Inferiority Analysis:
  - Upper limit of 95% CI for primary outcome HR was 1.5

**Hokusai-VTE Trial: Efficacy Outcome**

- Recurrent VTE:
  - Warfarin: 3.2%
  - Edoxaban: 3.5%; HR: 0.89 (95% CI: 0.71-1.13; p < 0.001)
  - No difference with patients who received edoxaban 30 mg
  - PE Patients with Right Ventricular Dysfunction:
    - Warfarin: 6.2%
    - Edoxaban: 3.3%; HR: 0.52 (95% CI: 0.28-0.58)

**Hokusai-VTE Trial: Safety Data**

- Clinically Relevant Bleeding*:
  - Warfarin: 10.3%
  - Edoxaban: 8.5%; HR: 0.81 (95% CI: 0.71-0.94; p = 0.004)

- Major Bleeding*:
  - Warfarin: 1.6%
  - Edoxaban: 1.4%; HR: 0.84 (95% CI: 0.59-1.21; p = 0.36)

- Decreased clinically relevant bleeding also seen at 30 mg dose

*Superiority analysis conducted for bleeding endpoints

**Cost Considerations**

- Cost of Therapy/Month (Patient with Normal Renal Function):
  - Atrial Fibrillation
    - Dabigatran: $350
    - Rivaroxaban: $318
    - Apixaban: $318
  - VTE Treatment/Recurrence Prevention
    - Dabigatran: $350
    - Rivaroxaban: $445 (first 21 days); $318 per month afterwards
  - VTE Prophylaxis Post-Hip or Knee Replacement
    - Rivaroxaban: $400.75 (35 days); $137.40 (12 days)
    - Apixaban: $371.70 (35 days); $127.44 (12 days)

**Summary**

- Edoxaban is another addition to the options for non-warfarin oral anticoagulation
- The pivotal trials have shown edoxaban to be non-inferior to warfarin for the following:
  - Prevention of stroke/systemic embolism in non-valvular AF
  - VTE treatment and prevention of recurrence
- Comparative safety data to warfarin (at both higher and lower doses) are favorable so far

**Human Prothrombin Complex Concentrate [Kcentra]**
Bleeding Issues Associated with Warfarin

- In United States, annual rate of major hemorrhage in warfarin-treated patients range from 1.3% to 3.4%
- Determinants of bleeding:
  - Patient characteristics
    - Age
    - Comorbid conditions
    - Pharmacogenetic factors
  - Intensity of anticoagulation
  - Use of other drugs interfering with hemostasis
  - Length of anticoagulation

What do the Guidelines Recommend

- 2012 CHEST Guideline Recommendations
- Besides vitamin K, these agents are mentioned:
  - Prothrombin complex concentrate
  - Fresh frozen plasma
  - Recombinant factor VIIa
- Vitamin K antagonist (VKA)-associated major bleeding
  - Rapid reversal of anticoagulation using 4F-PCC recommended over plasma (Grade 2C)
  - Additional use of vitamin K 5-10 mg given by slow IV injection recommended (Grade 2C)

Revisiting the Coagulation Cascade...

Human Prothrombin Complex Concentrate (PCC) [Kcentra – CSL Behring]

- Non-activated, 4-factor (4F) PCC was approved by the FDA in April 2013
  - Urgent reversal of coagulation factor deficiency induced by warfarin (VKA) treatment in adults with acute major bleeding
- Previously approved in Europe in January 2008 [Beriplex]
- Additional indication in December 2013
  - Urgent VKA reversal in adults with a need for urgent surgery or invasive procedure

Dosing and Administration Considerations

- Dosing is based on two factors:
  - Patient Weight (Total Body Weight)
    - Capped at 100 kg
  - INR
    - Three INR ranges correspond with a weight-based dose
- Product is dosed in Factor IX units
  - Nominal potency is 500 units per vial (25 units/mL)
    - Ranges from 400-620 units per vial (20-31 units/mL)
    - Actual potency (Factor IX units) stated on each vial
    - Contents of multiple vials may be pooled

Dosing and Administration Considerations

- Administration rate
  - 3 units/kg/min (0.12 mL/kg/min)
    - Up to 210 units/min (8.4 mL/min)
- Vitamin K must be administered concurrently
  - To maintain factor levels once PCC effects diminish
    - In study, patients received slow IV vitamin K (typically 5-10 mg)
- Contains heparin
  - Do not administer to patients with history of heparin-induced thrombocytopenia
**Boxed Warning: Thromboembolic Events**

- Patients on VKAs have disease states which predispose them to thromboembolic risks.
- Fatal and nonfatal venous and arterial thrombotic events have been reported with this agent.
- Not studied in subjects with the following during the previous 3 months:
  - Thromboembolic event
  - Myocardial infarction
  - Disseminated intravascular coagulation
  - Cerebral vascular accident or transient ischemic attack
  - Unstable angina
  - Severe peripheral vascular disease

**4F-PCC vs. Plasma for VKA Reversal in Major Bleeding**

**Study Design**
- Phase IIIb, multicenter, open-label, non-inferiority trial
- Received either PCC or plasma (1:1 ratio); followed 45 days

**Patient Population (N = 202)**
- Included:
  - ≥18 years old; INR ≥2 within the past 3 hours; experienced acute major bleeding event
- Key Exclusion:
  - Expected surgery in ≤24 hrs; TEE within 3 months; UFH/LMWH within the past 24 hrs/expected in next 24 hrs

**Co-Primary Endpoints**
- Hemostatic efficacy over 24 hours from beginning of infusion
- Rapid INR reduction (≤1.3 within 30 minutes after end of infusion)

**4F-PCC vs. Plasma for VKA Reversal in Major Bleeding: Hemostatic Efficacy**

<table>
<thead>
<tr>
<th>Primary Rating</th>
<th>4F-PCC (%) (n = 98)</th>
<th>Plasma (%) (n = 104)</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>44 (44.9)</td>
<td>45 (43.3)</td>
<td>-</td>
</tr>
<tr>
<td>Good</td>
<td>27 (27.6)</td>
<td>23 (22.1)</td>
<td>-</td>
</tr>
<tr>
<td>Poor / None</td>
<td>27 (27.6)</td>
<td>36 (34.6)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Hemostatic rating assessed by a blinded Endpoint Adjudication Board
*4F-PCC noninferior to plasma (P = 0.0045 for noninferiority)

**4F-PCC vs. Plasma for VKA Reversal in Major Bleeding: Safety Data**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>4F-PCC (%) (n = 103)</th>
<th>Plasma (%) (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Event</td>
<td>32 (31.1)</td>
<td>26 (23.9)</td>
</tr>
<tr>
<td>Thromboembolic AE</td>
<td>8 (7.8)</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Fluid Overload</td>
<td>5 (4.9)</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 30</td>
<td>6 (5.8)</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Day 45</td>
<td>10 (9.7)</td>
<td>5 (4.6)</td>
</tr>
</tbody>
</table>
**Study Design**
- Randomized, open-label, non-inferiority study
- Patients randomized (1:1 ratio) to receive either PCC or plasma
- Follow-up for SAEs: 45 days post-treatment

**Patients (N = 168)**
- Included: Age >18; surgery required within 24 hrs; INR ≥2 within previous 3 hours
- Key Exclusion: TEE within 3 months; IV vitamin K and D/C warfarin sufficient; reversal of VKA does not solve coagulopathy; UFH or LMWH within 24 hrs

**Primary Endpoints**
- Co-primary:
  - Effective perioperative hemostasis
  - Rapid INR reduction (INR ≤1.3 at 30 minutes post-infusion )

**Dosing Information**

<table>
<thead>
<tr>
<th>Baseline INR</th>
<th>PCC Dose (units/kg)</th>
<th>Plasma (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;4</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>4 to 6</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50</td>
<td>15</td>
</tr>
</tbody>
</table>

*Dose in units of Factor IX

**Effective Hemostasis Definition (Co-Primary Endpoint):**
- Actual blood loss not exceeding predicted blood loss by 50 mL or by 30% if the difference was >50 mL
- Hemostasis considered “normal” or “mildly abnormal”
- No administration of non-study coagulation products

**Baseline INR**

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>Treatment Group</th>
<th>Difference 4F-PCC minus plasma, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>49 (55.7)</td>
<td>53 (60.2)</td>
</tr>
<tr>
<td>Any Serious Adverse Event</td>
<td>22 (25)</td>
<td>23 (26.1)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (3.4)</td>
<td>8 (9.1)</td>
</tr>
<tr>
<td>Thromboembolic Event</td>
<td>6 (6.6)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Serious Thromboembolic Event</td>
<td>3 (3.4)</td>
<td>6 (6.8)</td>
</tr>
<tr>
<td>Fluid Overload</td>
<td>3 (3.4)</td>
<td>11 (12.5)</td>
</tr>
<tr>
<td>Serious Fluid Overload</td>
<td>1 (1.1)</td>
<td>2 (2.3)</td>
</tr>
</tbody>
</table>

**Results: VKA Reversal for Surgical Procedure**

**Safety Outcomes (ITT Analysis at Day 45)**

**Summary**
- 4F-PCC is a newer option to urgently reverse the effects of warfarin in patients:
  - Experiencing acute major bleeding
  - Requiring urgent warfarin reversal for surgery
- Dosing is based on two components:
  - Body weight
  - INR
- Cost of the product: ~ $1090 per 500-unit vial
Assessment Question #1
• Which of the following factors in the coagulation cascade does edoxaban inhibit?
  A. IX
  B. IIa
  C. Xa
  D. VII

Assessment Question #2
• MD is a 64 yo female who weighs 60 kg. She has currently taking warfarin 5 mg daily. After a fall, she is brought to the ED, and a CT scan reveals an intracranial hemorrhage. Her INR is 3.8. What is the appropriate dose (in units) of prothrombin complex concentrate for MD?
  A. 1200 units
  B. 1500 units
  C. 2100 units
  D. 3000 units

Updates in Anticoagulation: Edoxaban and Human Prothrombin Complex Concentrate
Doug Raiff, PharmD, BCPS: Clinical Pharmacist, Center for Medication Policy
May 13, 2014

Managing the Unmanageable: Monitoring and reversing new oral anticoagulants
Kimberly Hodulik, PharmD, CACP
Duke Hospital Anticoagulation Services

Disclosure Statement
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  Kimberly Hodulik, PharmD, CACP: Nothing to disclose

Objectives
• Review measurement of anticoagulant effect of novel oral anticoagulants (NOACs)
• Discuss management of bleeding complications from NOAC therapy
**Background**

- Dabigatran, rivaroxaban and apixaban are approved agents for prevention and treatment of thromboembolism.
- Difficult to determine degree of anticoagulant effect.
- No therapies exist to specifically reverse anticoagulant effect of these agents.

**Case of ACK**

- ACK is a 42 yo male who presents to ED with 7-10 day hx of headaches. Pain 7-10/10, no falls.
- PMH: Diabetes, GERD, HTN, paraplegia, PE 2008
- Meds:
  - Rivaroxaban 20 mg po daily
  - Cyclobenzaprine 10 mg po tid prn
  - Gabapentin 300 mg po tid
  - Insulin aspart tidac
  - Lisinopril 40 mg po daily
  - Simvastatin 20 mg po qhs

**Management Considerations**

- Drug dose and interval
- Kinetics of drug
- Renal function
- Other medications
- Performance of available coagulation test(s) for specific drug
- Reversal options

**Pharmacokinetics and Dynamics**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak plasma concentration</td>
<td>1-3 hours</td>
<td>2-4 hours</td>
<td>1-3 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>7-17 hours</td>
<td>7-17 hours</td>
<td>8-14 hours</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>80-85%</td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>90-95%</td>
<td>87%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>P-glycoprotein</td>
<td>P-glycoprotein CYP3A4 CYP2J2</td>
<td>P-glycoprotein CYP3A4</td>
</tr>
</tbody>
</table>

**Mechanisms of Action**

[Diagram showing mechanisms of action]
Measuring Dabigatran

Dabigatran Assay

- Measures drug concentration
- Range: 0.1 mcg/mL - 0.4 mcg/mL
- Normal: <0.04 mcg/mL
- Available at Duke Hospital
- Turnaround time 1-1.5 hours
- Not to be used for routine management

Factor Xa Inhibitors - aPTT and PT

Factor Xa Inhibitors- Anti-factor Xa Assay

Recommended Coagulation Labs- Duke

- Dabigatran
  - Thrombin clot time (TT): Quick turnaround time
  - Dabigatran assay
- Rivaroxaban/ Apixaban
  - Anti-Xa LMWH assay
  - Anti-Xa rivaroxaban assay in future

Case of ACK

Head CT findings
1. Right frontoparietal temporal subdural hematoma containing acute, subacute and chronic blood products
2. There is mass effect on adjacent brain parenchyma, right lateral ventricle and 3rd ventricle. Component of blood in right lateral ventricle difficult to totally exclude
3. Midline shift from right to left
Reversal of Anticoagulant Effect

- FFP?
- rFVIIa?
- PCC?
- aPCC?
- DDAVP?
- Some other confusing, expensive acronym?

Prothrombin Complex Concentrates (PCC)

- No high-quality evidence supporting use
- Conflicting results in decreasing bleeding in animals
- Rivaroxaban- Normalized PT in healthy volunteers
- Dabigatran
  - Did not improve aPTT, ecarin clotting time (ECT) or TT in healthy volunteers
  - Did not manage massive bleeding in small case series
- Consider thrombotic risk to patients

Activated Prothrombin Complex Concentrate (APCC)

- High-quality clinical data are lacking
- Dabigatran and rivaroxaban
  - Anticoagulant effect reversed in animals
  - Reversal effect on coagulation tests shown in vitro
- Dabigatran
  - Case report in patient with ablation-induced pericardial tamponade
  - Increased thrombin generation ex-vivo
- Consider risk to patients- Thrombosis, DIC

Recombinant Factor VIIa

- No clinical studies evaluating use
- Did not lessen bleeding in animal models with dabigatran or rivaroxaban
- Dabigatran- failed to control bleeding in 3 of 4 case reports
- Associated with increased risk of arterial thrombotic events vs. placebo (5.5% vs 3.2%)

Plasma

- Reports fail to demonstrate efficacy
- Consider risks
  - Volume overload
  - Transfusion-related acute lung injury
  - Allergic reaction
  - Infection

Other Measures

- Activated charcoal if within 1-2 hours of ingestion
- DDAVP to stimulate von Willebrand factor release
- Hemodialysis
  - Use for dabigatran associated bleeding
  - Consider bleeding risk in obtaining central line
Bleeding Management Strategy

**RISK STRATIFY**

- **Minor bleeding**
  - Local hemostasis
  - Consider hold or discontinue anticoagulant
  - Consider hold or discontinue antiplatelet agents

- **Moderate bleeding**
  - Hold anticoagulants & antiplatelet agents
  - Mechanical compression or low-dose anticoagulant if high thrombotic risk
  - Monitor hemodynamic status, volume replacement, identify source of bleeding
  - RBC transfusion for anemia
  - Consider platelets for patients receiving antiplatelet therapy

- **Severe bleeding**
  - Hemodynamic support
  - Consider 4-factor PCC (25 unit/kg) or aPCC (25 unit/kg)
  - Oral charcoal for ingestion within 2 hours
  - Consider hemodialysis for dabigatran removal

Bleeding Management Strategy- Future

- aDabi-Fab- Humanized monoclonal antibody fragment against dabigatran
- Recombinant andexanet alpha- Inactive factor Xa derivatives

Assessment Question #1

For emergent assessment of a critically bleeding patient who is on dabigatran therapy, one should recommend which laboratory test?

a. Low molecular weight heparin level (LMWH)

b. Thrombin Clot Time (TT)

c. Activated Partial Thromboplastin Time (aPTT)

d. Dabigatran Level
Assessment Question #2

Factor replacement has been proven as an effective therapy for reversal of patients receiving target-specific oral anticoagulants in high-quality clinical trials.

a. True
b. False

Questions?

Managing the Unmanageable: Monitoring and reversing new oral anticoagulants

Kimberly Hodulik, PharmD, CACP
Duke Hospital Anticoagulation Services

2013 ACC/AHA Lipid Guidelines: Review and Critique

Lindsey Burgess, PharmD, BCPS
Michelle Cefaretti, PharmD
May 13, 2014

Disclosure Statement

These individuals have the following to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation:

    Lindsey Burgess, PharmD, BCPS: Nothing to disclose
    Michelle Cefaretti, PharmD: Nothing to disclose

Objectives

• Compare the components of the Pooled Cohort Equation to those of the Framingham Risk Assessment
• Analyze the benefits and limitations of the 2013 ACC/AHA recommendations for lipid management
Previous Guidelines for Lipid Management

- 10-year risk calculated using Framingham Risk Assessment
- ATPIII provided guidelines for treatment
  - Primary goal → low-density lipoprotein (LDL)
    - Goals based on CHD risk factors and 10-year risk
  - Secondary goal → non-high-density lipoprotein (HDL)
  - Statins considered first line treatment

Abandoning LDL Targets

- Improvement in atherosclerotic cardiovascular disease (ASCVD) events noted with maximum tolerated statin therapy
- No specific LDL goal has been shown to further reduce ASCVD outcomes in RCTs
  - If patients are already managed on statins with unknown baseline, an LDL target of <100 mg/dL may be appropriate

Abandoning LDL Goals

- Nonstatin therapy in addition to statins to further reduce LDL has not been shown to be beneficial in reducing ASCVD events
  - AIM-HIGH - the addition of niacin to statins to further reduce LDL to 40-80 mg/dL in patients with low HDL and high triglycerides did not further reduce ASCVD risk
  - ACCORD - fenofibrate not beneficial in patients with DM

Pooled Cohort Equation

- Comprehensive multivariable risk equation used to estimate 10-year ASCVD
- Utilized in white and black men and women age 40-79 without clinical ASCVD
- External validation studies completed using data from available cohorts
### Clinical CVD Definition
- Secondary prevention following:
  - Acute coronary syndromes
  - A history of myocardial infarction
  - Stable or unstable angina
  - Coronary or other arterial revascularization
  - Stroke
  - Temporary ischemic attack
  - Peripheral arterial disease presumed to be of atherosclerotic origin

### New Recommendations
- Level of intensity based on concomitant disease states
  - Moderate-intensity statin therapy
    - Reduces LDL by 30-50%
  - High-intensity statin therapy
    - Reduces LDL by ≥50%

### Lifestyle Management
- Lifestyle modifications are the foundation for ASCVD reduction
  - Heart healthy diet
  - Regular exercise
  - Tobacco cessation
  - Maintain healthy weight

### New Recommendations
- Statin Therapy
  - Clinical ASCVD
    - LDL ≥130 mg/dL
    - DM & 40-75yo
      - 10-year ASCVD Risk ≥7.5%
  - 2.75yo
    - Moderate-intensity statin
    - Risk ≤7.5%
  - 5yo
    - High-intensity statin
    - Moderate or High-intensity statin
    - Risk ≥7.5%
A Focus on Older Adults

- Those >75 years old
  - Evaluate the ASCVD risk-reduction benefits
  - Adverse drug events
  - Drug-drug interactions
  - Patient preferences
    - Medication burden
    - Life expectancy

Statin Intensity Groups

<table>
<thead>
<tr>
<th>High-intensity Statin Therapy</th>
<th>Moderate-intensity Statin Therapy</th>
<th>Low-intensity Statin Therapy</th>
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</thead>
<tbody>
<tr>
<td>Atorvastatin 80 mg (40mg)</td>
<td>Atorvastatin 10 mg (20mg)</td>
<td>Pravastatin 10-20 mg</td>
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<tr>
<td>Rosuvastatin 20 mg (40mg)</td>
<td>Rosuvastatin 10 mg (5mg)</td>
<td>Lovastatin 20 mg</td>
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<tr>
<td>Simvastatin 20-40 mg</td>
<td>Simvastatin 10 mg</td>
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</tr>
<tr>
<td>Pravastatin 40 mg (80mg)</td>
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</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Fluvastatin 10 mg</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 40 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin XL 80 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitavastatin 2-4 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nonstatin Recommendations

- Avoid niacin if transaminases >2-3x ULN, hyperglycemia, acute gout, GI sx or abdominal pain occurs, new onset AFib or weight-loss occur
- Fenofibrate may be added to low or moderate statin therapy when TGs are >500 mg/dL
  - Avoid gemfibrozil with concomitant statin therapy
- Omega fatty acids may be used when TGs are >500 mg/dL
- Avoid BAS when triglycerides are ≥300 mg/dL

Unclear Risk Factors

- LDL >160 mg/dL
- CAC score ≥300 Agatston or ≥75% for age, sex, ethnicity
- Genetic hyperlipidemia
- Elevated lifetime risk of ASCVD
- Ankle-brachial index <0.9
- High-sensitivity CRP ≥2mg/L
- FH premature ASCVD <55yo (M) or <65yo (F)

Not Covered in the New Guidelines

- Treatment of hypertriglyceridemia
- Use of non-HDL in treatment decision making
- Using noninvasive imaging for refining risk estimates to guide treatment decisions
- Defining the optimal age for initiating statin therapy to reduce lifetime risk of ASCVD
- Heart failure and hemodialysis
- Long-term effects of statins
- Role of pharmacogenetic testing

Guideline Critique – Pros

- Simplified approach for managing hypercholesterolemia
- Eliminates need to monitor LDL routinely
- Acknowledges that more than CVD risk should be taken into account for those >75 years old
- Supports the concept that initiation of treatment should involve a conversation between the physician and patient
Guideline Critique - Cons

- Calculator requires computer or phone app
- Risk calculator has not been prospectively tested and may overestimate risk
- Calculator only takes into account white and African American race
- Guidelines only include RCTs published before 2011
- 6 out of 15 panelists reported conflicts of interest with statin manufacturers
- 20 out of 46 recommendations are based “E” or Expert Opinion

How Guidelines Have Been Incorporated Into Practice

- Sample Case:
  - 52 year old male with BMI of 25
  - Family history of blindness due to T2DM
  - Recent increase in running to 3 miles daily
  - Smokes ½ PPD
  - TC 180mg/dL, TG 150mg/dL, HDL 35mg/dL, LDL 115mg/dL, BP 130/85

Recommendations

- ATPIII: Framingham Risk = 13%
  - Goal LDL < 130mg/dL
  - Would not recommend statin therapy
- Pooled Cohort Equation: 10.9%
  - Would recommend moderate or high intensity statin

Treatment Option #1: Do Not Start Statin

- 10-year ASCVD risk could improve dramatically with lifestyle modifications
  - Quit smoking -> 5.4%
  - Increased HDL from quitting smoking -> 5.1%
- Concern for developing T2DM and statins may increase blood sugars
- Based on current lab values, may not have been eligible for statin trials

Treatment Option #2: Start Statin and Monitor LDL

- Three risk factors for ASCD
  - Male, smoker, low HDL
- Lipid panel is consistent with metabolic syndrome
- Recommend aggressive lifestyle modification with low-to-moderate statin
- Continue to monitor lipid panel, glucose and A1C

Treatment Option #3: Start Statin and Do Not Monitor LDL

- If patient did not quit smoking, statin would be needed to decrease his risk of an event
- If lifestyle modifications are made, the benefit is not immediate
- Poor lifestyle decisions were likely made ~30 years ago and the damage to the arteries may already be present
- Monitoring could be used to assess adherence but is not needed to determine efficacy of treatment
Self Assessment Question #1

What risk factor has been added to the Pooled Cohort Equation?

A. Congestive Heart Failure  
B. Family History  
C. Race  
D. Weight

Self Assessment Question #2

- What lipid-lowering therapy would you recommend for the following individual?
  - 84 yo F with a prior history of CVA and an LDL of 190 mg/dL?
  
A. Atorvastatin 80 mg po daily  
B. Pravastatin 40 mg po daily  
C. Zetia 10 mg po daily  
D. Consider patient goals and preferences before prescribing therapy

2013 ACC/AHA Lipid Guidelines: Review and Critique

Lindsey Burgess, PharmD, BCPS  
Michelle Cefaretti, PharmD  
May 13, 2014

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