New Drug Updates Cardiology Potpourri

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Disclosure

• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

• I will be discussing non-FDA approved indications

Objectives

• Describe newly approved and/or emerging pharmacotherapy agents for the management of pulmonary, cardiovascular, and endocrine disorders
• Discuss guideline updates, therapy changes, and/or clinical evidence surrounding the drugs discussed
• Evaluate risks, benefits, and safety concerns of new pharmacotherapy agents for pulmonary, cardiovascular, and endocrine disorders
• Recognize clinical indications of pharmacotherapy agents discussed
• Identify brand/generic and pertinent side effects of new pharmacotherapy agents utilized to treat pulmonary, cardiovascular, and endocrine disorders

Edoxaban

not FDA approved

• Oral Factor Xa inhibitor
• Linear kinetics
• Absorption not affected by food
• Onset 0.5-1hr
• Metabolism
  • Hydrolysis (major) & CYP3A4 (<4%)
  • Elimination (73% as parent drug)
  • Urine 35%
  • Feces 65%

ENGAGE AF-TIMI 48

• Edoxaban compared to warfarin (INR 2.0-3.0) in patients with AFib and CHADS2 >2
• Randomized, Double-blind, Double-dummy, Intention-to-treat, International, Non-inferior trial
  • N= 21,105
  • Median follow-up 2.8yrs
  • Edoxaban 30 or 60mg daily
• Primary endpoint stroke or systemic embolism
• Safety outcome major bleeding

Inclusion:

• Age ≥ 18y/o
• AFib
• CHADS2 > 2

Exclusion:

• Reversible AFib
• CrCl < 30ml/min
• High bleed risk
• Dual antiplatelet therapy
• Mitral stenosis (moderate - severe)
• Other indications for anticoagulation
• ACS
• Coronary revasc.
• CVA past 30 days
### Dose Reduction

- Edoxaban dose reduced 50%
- CrCl 30-50mL/min
- Weight ≤60kg
- Concomitant strong P-glycoprotein
  - Verapamil, quinidine, or dronedarone

60mg ➔ 30mg
30mg ➔ 15mg

### Efficacy Outcomes

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>MITT</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 30mg</td>
<td>1.6% (0.87-1.31)</td>
<td>Non-inferior (p&lt;0.005)</td>
</tr>
<tr>
<td>Edoxaban 60mg</td>
<td>1.18% (0.63-0.99)</td>
<td>Superior (p=0.02)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.5%</td>
<td></td>
</tr>
</tbody>
</table>

- ITT population no significant reductions
- Major efficacy driver was significant reduction of hemorrhagic strokes

### Safety Outcomes

<table>
<thead>
<tr>
<th>Major Bleed</th>
<th>Edoxaban 30mg</th>
<th>Edoxaban 60mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.61% [0.41-0.55]</td>
<td>Significant (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.75% [0.71-0.91]</td>
<td>Significant (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.43%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Edoxaban (high) significant reductions:
  - Critical organ/area bleeds (108 vs. 211)
  - Intracranial bleeds (61 vs. 132)
- Edoxaban (high) significant increased GI bleed
  - 232 vs. 190
- Net benefit significant for both edoxaban doses

### Edoxaban 60 vs. 30mg

- How robust is the data for 30mg dose?
  - Non-inferior to warfarin
  - Numerically higher ischemic strokes and systemic emboli
  - Inferior to 60mg dose
  - Significant reduction of major/minor bleeds compared to warfarin

<table>
<thead>
<tr>
<th>Dose</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 60mg</td>
<td>236</td>
<td>P&lt;0.001</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>Edoxaban 30mg</td>
<td>333</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>235</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

### Bottom line

- **Pro**
  - Fixed dosing
  - Less monitoring
  - Renal dose studied
  - Less bleeding compared to warfarin
  - Few drug interactions

- **Cons**
  - Limited evidence
  - Cost
  - No reversal agent

- As effective as warfarin
- Statistically less major and non-major bleeds
- Net clinical benefit favored edoxaban group

### Atrial Fibrillation Comparison

<table>
<thead>
<tr>
<th>Pivotal AFib Trial</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Superior</td>
<td>Not Inferior</td>
<td>Superior</td>
<td>Superior</td>
<td></td>
</tr>
<tr>
<td>CHADS2</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Mean Warfarin TTR</td>
<td>64%</td>
<td>55%</td>
<td>62.2%</td>
<td>64.9%</td>
<td></td>
</tr>
<tr>
<td>Dosing Interval</td>
<td>Daily</td>
<td>BID</td>
<td>Daily</td>
<td>BID</td>
<td></td>
</tr>
<tr>
<td>Half life (t1/2)</td>
<td>40</td>
<td>12-17</td>
<td>4-9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Rapid</td>
<td></td>
</tr>
<tr>
<td>Peak Effect</td>
<td>5-7dys</td>
<td>1-2hrs</td>
<td>2-4hrs</td>
<td>3hrs</td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Reversal</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Renal Dose</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>++</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

Giugliano. NEJM 369;22:2093-2104.
Antiplatelet Combinations

• Common suspect: AFib or mech valve pt on life-long anticoagulation that requires coronary intervention
  • ACCF/AHA 2013 STEMI = Class I LOE C
  • ESC 2013 STEMI = Class I LOE C
  • ACCF/AHA/HRS 2011 AFib = IIb LOE B
  • CHEST 9 AFib= CHADS2, based rec 2C
• Recs: INR target 2-2.5, low potency P2Y12 inhib, low dose aspirin, shortest duration, BMS
  • Evidence lacking to support decisions

Inclusion:

• Indication for long term anticoagulation
• PCI indication
• Age 18-80y/o

Exclusion:

• Hx Intracranial bleed
• Cardiogenic shock
• CI to aspirin, clopidogrel
• Peptic ulcer past 6mo
• Platelet <50K
• TIMI major bleed last 12mo
• Pregnancy

Patient population is a mix of urgent and planned PCI

WOEST

• Patients on warfarin undergoing PCI, use clopidogrel alone
  • N=573
  • 1 year follow-up
• Open-label, randomized, intention to treat, control trial in Europe
  • Groups:
    • Warfarin plus clopidogrel 300-600mg load then 75mg daily
    • As above plus Aspirin 80-100mg daily
    • Target INR 2.0 for all

Results

<table>
<thead>
<tr>
<th></th>
<th>TIMI Major + Minor</th>
<th>GUSTO Severe</th>
<th>BARC 1</th>
<th>BARC 2</th>
<th>BARC 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (Triple)</td>
<td>44.4% 5.6% 31.1%</td>
<td>3.5% 12.3%</td>
<td>6.5%</td>
<td>8.2%</td>
<td>6.5%</td>
</tr>
<tr>
<td>No aspirin (Dual)</td>
<td>19.4% 3.2% 14%</td>
<td>1.4% 5.4%</td>
<td>15.8%</td>
<td>20.8%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Significance</td>
<td>S NS S NS S NS</td>
<td>S S S NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001 &lt;0.001</td>
<td>0.003 0.004</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

Outcomes

• Primary Outcome
  • Any bleed (TIMI, GUSTO, BARC)
• Secondary
  • Composite of any death, MI, CVA, target-vessel revascularization, & stent thrombosis
• Duration
  • At least 1 month for bare metal stents
  • At least 1 year for drug eluting
• Pros
  • Prospective data
  • Limited inclusion criteria

• Cons
  • Open-label
  • Urgent and planned PCI
  • Various PCI indications
  • High bleeding rate
  • Self-reported bleeds
  • Not powered for secondary endpoints
  • Warfarin TTR not done
  • Multiple medications to control
  • Multiple co-morbidities
  • Potent antiplatelets / NOAC

**Bottom Line**

- Starting point for prospective evaluation
  - Major/Severe bleeding not reduced
  - Secondary outcomes not answered with confidence (underpowered)
  - Can there be an excess of stent thrombosis?

**Future Research**

- STENT Technology
  - Bio-absorbable stents
  - Improved Drug-eluting stents
    - Non-inferior DAPT 3 months vs. 12 mo
      - Clopidogrel 75mg daily plus Aspirin 100-200mg daily

**Inclusion:**

- Age ≥ 18y/o
- Non-pregnant

**Exclusion:**

- Taking NSAIDS or antiplatelet medications
- Coagulation disorders
- Renal impairment
- Hepatic impairment
- HIV, Hepatitis B & C
- Abnormal lab values

Not an ACS study

**Morphine Drug Interactions**

- Opiates delay gastric emptying which delays drug absorption
- Morphine may delay clopidogrel biotransformation
- Double-blind, block randomized, placebo-controlled, cross-over trial
  - 14 day washout period
  - N=24
- Clopidogrel 600mg loading dose followed by morphine 5mg IV or placebo
Results

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Pharmacodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_max</td>
<td>C_max</td>
</tr>
<tr>
<td>Min</td>
<td>mg/mL</td>
</tr>
<tr>
<td>Morphine</td>
<td>105</td>
</tr>
<tr>
<td>Placebo</td>
<td>83</td>
</tr>
</tbody>
</table>

Significant: Yes Yes Yes Yes

Pharmacokinetics

<table>
<thead>
<tr>
<th>VASP (Median Platelet Reactivity Units %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Morphine + Clopidogrel</td>
</tr>
</tbody>
</table>

Significant between treatments: No

• Poor clopidogrel metabolizers (CYP2C19) had significantly lower C_max & AUC

Inclusion:
- STEMI w/in 12hrs symptom onset
- ≤ 18y/o
- Bleeding or bleeding diathesis
- Previous TIA/CVA
- p2Y12 inhib w/in 7 days
- Hematologic deviation
- Life expectancy < 1yr
- Severe hepatic disease
- Severe renal disease

Exclusion:
- Double DM
- ½ Dyslipidemia
- ½ Previous MI or PCI
- No LD timing differences between the groups
- 36% ED
- 64% on table

What About New Agents?

<table>
<thead>
<tr>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>600mg</td>
<td>60mg</td>
<td>180mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prodrug (steps)</th>
<th>Onset</th>
<th>IPA Peak (hrs)</th>
<th>t½ (hrs)</th>
<th>Time for platelet aggreg. return to baseline</th>
<th>Major CYP 450 enzy</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (2)</td>
<td>2 hrs</td>
<td>30-37% (6)</td>
<td>9 / 23</td>
<td>~ 5 days</td>
<td>3A4, 2C19, 1A2, 2B6</td>
<td>50% renal</td>
</tr>
<tr>
<td>Prasugrel 60mg</td>
<td>0.5 hr</td>
<td>79-84% (4)</td>
<td>48 / 75</td>
<td>~ 7 days</td>
<td>3A4, 2B6</td>
<td>70% renal</td>
</tr>
<tr>
<td>Ticagrelor 180mg</td>
<td>0.5 hr</td>
<td>88% (2)</td>
<td>41 / 80</td>
<td>~ 5 days</td>
<td>3A4, 3A5</td>
<td>26% renal</td>
</tr>
<tr>
<td>IPA% - 0.5 / 1hr</td>
<td>7</td>
<td>7</td>
<td>7-9</td>
<td></td>
<td></td>
<td>27% feces</td>
</tr>
<tr>
<td>Excretion</td>
<td>46% feces</td>
<td>70% renal</td>
<td>58% feces</td>
<td></td>
<td></td>
<td>58% feces</td>
</tr>
</tbody>
</table>

RAPID

- Prasugrel and ticagrelor platelet inhibition during STEMI
- Randomized, 2-arm, prospective non-inferiority study
  - N=50
  - Prasugrel 60mg
  - Ticagrelor 180mg
- Primary Outcome:
  - Residual platelet activity (VerifyNow) 2hrs post LD

Demographics

- Prasugrel:
  - Double DM
  - ½ Dyslipidemia
  - ½ Previous MI or PCI
- No LD timing differences between the groups
  - 36% ED
  - 64% on table

Protocol

- Concomitant medications
  - Aspirin
  - Bivalirudin
  - Heparin discouraged
  - No GPIIb/IIIa inhib

Outcome

- Prasugrel non-inferior to ticagrelor
- Independent variable for HRPR at 2hrs = Morphine use and baseline PRU

Population

- Inclusion
  - DM type 2
  - Established CV dz or
- Multiple risk factors

<table>
<thead>
<tr>
<th>Baseline Demographic Sample</th>
<th>Saxagliptin (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established atherosclerotic dz</td>
<td>78.4</td>
<td>78.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81.2</td>
<td>82.4</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>71.2</td>
<td>71.2</td>
</tr>
<tr>
<td>Prior MI</td>
<td>38</td>
<td>57.6</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>12.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Prior coronary revasc.</td>
<td>43.1</td>
<td>43.3</td>
</tr>
</tbody>
</table>

Bottom Line

- Pharmacokinetic variances exist between patient types
- Morphine may reduce P2Y12 antagonist bioavailability
  - NSTEMI guideline warning
  - No mortality benefit for ACS
- Morphine role lacking for ACS in an intervention driven environment
  - Door to balloon time< 60min
  - Anticoagulant + oral p2Y12 inhibitor

Results

- NS primary composite outcome
- CHF hospitalization worsened by saxagliptin
  - Mechanism unknown, peripheral edema?

DPP-IV CHF Risk?

- Primary outcome = composite of CV death, MI, or ischemic CVA
  - N=16,492
  - 2 year follow-up
- Multi-center, randomized, double-blind, placebo controlled, International, phase 4 trial
- Groups:
  - Saxagliptin (Onglyza*) 2.5-5mg daily
  - Placebo

Bottom Line

- Many Cons remaining to be answered:
  - Too short of treatment to see CV outcome benefits
  - Benefits mitigated by:
    - Statins
    - Antiplatelet agents
    - BP control
    - Additional hypoglycemic agent allowed
- Nonetheless add HF worsening to your evaluation of patients on the medication
Questions?
New Drug Updates
Cardiology Potpourri

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