No Conflicts to Declare

What medication do you add to Aspirin in Acute Coronary Syndrome?
A. Cox-2 Inhibitor
B. ADP Receptor Inhibitor
C. 2C19 Antagonist
D. P2Y12 Inhibitor

Clopidogrel, Prasugrel, Ticagrelor and Platelets ...
Oh, My!

Platelets ... Acute Coronary Syndromes
SC: 23rd Nationally for CHD deaths
US Annual incidence: 610,000 new 325,000 recurrent

It’s the Platelets!
Aspirin: Main therapy PLUS antiplatelet
est. 560,000 Stents a year
Acute Coronary Syndrome: Treatment causes Platelet activation

Platelet Inhibition: the other drugs
- ADP binds to P2Y12 receptor
- G-protein activation

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P2Y12 Receptor Antagonists
- Thienopyridines: Clopidogrel 75 mg, Prasugrel 10 mg, Ticlopidine 250 mg bid
- Nonthienopyridines:
  - Cyclo-pentyl-triazolo-pyrimidines: Ticagrelor 90 mg bid
Indication for Ticagrelor (Brilinta®)

- Indication is for ACS: to reduce rate of thrombotic cardiovascular events in patients with ACS.
- Clinical trial: administered **BEFORE** PCI
- Duration of therapy: at least 12 months*

**Clinical trial:** administered **BEFORE** PCI

**Duration of therapy:** at least 12 months*

*2011ACCF/AHA focused Update of guidelines for UA/NSTEMI. JACC; 57 (18)

FDA Approved Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>ACS/NST EMI</th>
<th>STEMI</th>
<th>CVA</th>
<th>Previous MI</th>
<th>PAD</th>
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</thead>
<tbody>
<tr>
<td>Plavix® (clopidogrel)</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>Effient® (Prasugrel)</td>
<td>YES, but only PCI</td>
<td>YES, but only PCI</td>
<td>Contraindicated</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Brilinta® (Ticagrelor)</td>
<td>YES</td>
<td>YES</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Pharmacokinetics

- Active Metabolite!
- Metabolism: CYP3A4/5, equipotent metabolite (1/3 concentration of ticagrelor)
- > 99% bound to protein, time. Excretion: hepatic through biliary excretion. <1% renal
- Clinical Implications: Interaction with other 3A4 inhibitors and inducers
  - Ketoconazole (632%), Diltiazem (174%), Rifampin, Simvastatin (60%), Atorvastatin (56%)
- Peak plasma concentration: 1.3 to 2 hours
- Mean 1½ life is 7 hours for ticagrelor and 9 hours for the active metabolite
  But does this explain the delayed offset and the recommendation to avoid surgery for 5 days?

Platelet Inhibition

- *Faster* inhibition should translate to reducing clinical endpoints (MACE)
- Antiplatelet Resistance: Do not confuse with recurrence of cardiac events
  - Describes Ex Vivo magnitude of platelet inhibition achieved in a treated population
  - NO universal definition!
  - GRAVITAS: Platelet Reactivity Units 230 changed to 208

Pharmacodynamics

\[
\%IPA = \frac{PA_{pre-dose} - PA_{post-dose}}{PA_{predose}}
\]

- Rate of onset measured % inhibition of platelet aggregation
- Onset faster than Clopidogrel and Prasugrel
- Offset faster **“Reversibly”**
- Switching from clopidogrel/prasugrel will temporarily increase %IPA
### Pleiotrophic Effects

- Blocks nonplatelet P2Y12 on vascular smooth muscle
- Increases adenosine concentration
- Inhibits uptake by erythrocytes
- Vasodilation
- Source for potential side effects
- Bradycardia
- Dyspnea
- Serum Creatinine and Uric Acid (mean 0.7 not gout)

*Arterioscler Thromb Vasc Bio 2003;23:357-362

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### Posology

- Ticagrelor 180 mg
- Prasugrel 60 mg
- Clopidogrel 300 mg

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### Kaplan-Meier Curves

**PCI CURE (n=2685)**
- Clopidogrel vs. Ticlopidine
- CV death, MI, revascularization
- ARR 1.9%


**TRITON (N= 13,608)**
- Non-Fatal MI
- ARR 2.2%


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### Kaplan-Meier Curves

**CURE (N= 12,562)**
- Nonfatal MI
- ARR 2.1%

Kaplan-Meier Curves
- PLATO (N=18,624)
- Death from Vascular Causes, MI, or CVA
- ARR 1.9%


- NO Difference with KMC with Ticagrelor UNTIL 30 days!
  Difference was CV death and MI; no difference for Stroke
- Plavix Loading Dose
  79.1%: 300 mg plavix load
  19.6%: 600+ mg plavix
- Despite immediate onset and greater platelet inhibition

Possible Causes: Vasodilation from P2Y12, Adenosine, Interaction with Statins?

When Can I Cut?!?!
- Ticagrelor: 5 days!!
- Clopidogrel: 5 - 7 Days
- Prasugrel: 7 days

Platelet Function Test: < 20%

Bleeding
- Transfusion of platelets for bleeding:
  - Ticagrelor: may not work since ticagrelor may inhibit the transfused platelets.
  - Plavix: effectiveness reduced if within 4 hours of loading dose or 2 hours of maintenance
  - Prasugrel: reduced 6 hours of loading and 4 hours maintenance

Side Effects
- Dyspnea
  - Ticagrelor 13.8%, Aspirin, Clopidogrel 7.8%, Prasugrel
  - No worsening of COPD, bronchospasms, Heart Failure, Pulmonary function tests
- Uric Acid increase 0.7 mg/dl
- No difference in either group for incidence of gout
- Gynecomastia (3:1000)

Rates of Bleeding in PLATO

Lancet 2010;375:363-45
Time to Major Bleeding in planned Invasive strategy

Decline therapy
- Current/require anticoagulation
- AFib, previous CVA
- Active bleeding, or increased risk
- Fibrinolytic therapy
- Moderate to Severe Hepatic impairment
- eGFR less than 30
- Bradycardia

<table>
<thead>
<tr>
<th>Region</th>
<th>Triptal (mg)</th>
<th>Clopidogrel (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Europe</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Asia</td>
<td>100</td>
<td>75</td>
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Brilinta prescribing information

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS
- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).
Aspirin interaction?

- "no clear pathophysiological, pharmacodynamic or pharmacokinetic explanation for an ASA-ticagrelor interaction was discernible in the data submitted."
- Dr. Robert Fiorentino, FDA
- Based on Sub-group Analysis
- North American phenomenon (9.7%)
- Canada (401) US (1,413) 7.5%

Summary

- Novel Antiplatelet Inhibitor - Active Metabolite
- P2Y12 in Vascular Smooth Muscle
- Adenosine
- Faster onset and more IPA
- Reversibly
- No worries ... interactions with PPI or CYP2C19 ...
- no increased bleeding like Prasugrel
- Better survival rates than ASA and Clopidogrel

Dark Side?

- North American Anomaly/Aspirin
- Faster IPA = Earlier benefit?
- Higher rate of fatal intracranial bleed
- Major bleeding; treatment VERY limited
- Twice a day Dosing, Co$t ($7.24, $6.08, $5.78)
- Drug interactions: Diltiazem
- Bradycardia
- Dyspnea, Serum Creatinine, Uric Acid

What Does the Future Hold?

- PEGASUS-TIMI 54: Post (1-3 years) MI

ACS

62 yo female with STEMI Inferior Wall.
PMH: HTN, Dyslipidemia
VS BP 135/72 HR 58 RR 20

Which Antiplatelet would you use with Aspirin?

A. Clopidogrel
B. Prasugrel
C. Ticagrelor (Aspirin 81 mg daily)
You Decide!

THE END