Mechanism of Plaque Rupture/Clot Formation and Drugs Considerations

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CRITICAL TOPICS IN SAVING LIVES IN NORTH CAROLINA
May 1, 2013
No Diclosures
Sequence of Atherosclerotic Changes

- Adaptive intimal thickening
- Intimal xanthoma
- Pathologic intimal thickening
- Fibroatheroma
- Thin-cap fibroatheroma

Virmani, Renu
Vulnerable Plaque

Thin Cap Fibro-Atheroma (TCFA)
- Presence of large necrotic core
- Thin fibrous cap (< 65 μm)
- Cap infiltrated by macrophages and lymphocytes
- Type I collagen with few or absent SMCs in cap

Virmani, Renu
PATHOGENESIS OF PLAQUE RUPTURE

Plaque Rupture
- Discontinuous fibrous cap
- Underlying necrotic core
- Luminal thrombus

Virmani, Renu
Causes of Coronary Thrombosis

Rupture

Erosion

Calcified nodule

Clinical and Morphologic Difference in Plaques Associated with Luminal Thrombi

Plaque rupture
- 75% thrombi
- M>F, Older
- Eccentric = concentric
- Greater % stenosis
- Macs, T cells rich

Plaque erosion
- 15-20% thrombi
- M=F, younger
- Usually eccentric
- Lesser % stenosis
- SMC rich

Calcified nodule
- 2-5% thrombi
- M>F, Older
- Usually eccentric
- Stenosis variable
- Ca++ rich

STEMI
# Antithrombotic Therapy

## Antiplatelet Therapy

- Aspirin
- Platelet P2Y12 Receptor Blockers
  - Clopidogrel (Plavix)
  - Ticlopidine (Ticlid)
  - Prasugrel (Effient)
  - Ticagrelor (Brilinta)
- GP IIb/IIIa Inhibitors
  - Abciximab (Reopro)
  - Tirofiban (Aggrastat)
  - Eptifibatide (Integritin)
- PAR-1 Antagonists

## Anticoagulant Therapy

- Heparin
- Low Molecular Weight Heparins
  - Enoxaparin (Lovenox)
  - Dalteparin (Fragmin)
- Synthetic Heparin Pentasaccharide
  - Fondaparinux (Arixtra)
- Direct Thrombin Inhibitors
  - Bivalirudin (Angiomax)
- Anti Xa Inhibitors
  - Rivaroxaban (Xarelto)
Site of Action of Antiplatelet Agents

Shear, PCI Plaque Rupture → Collagen vWF → Initial Activation

Platelet → ADP → Clopidogrel Prasugrel Ticagrelor

TxA2 → TP → Fibrinogen

Thrombin → Amplification → Abciximab Eptifibatide

Aspirin → PAR-1 → GPIIb/IIIa Activation

Platelet-Fibrin Clot Formation
Pathways of Coagulation

- Bivalirudin
- Fondaparinux
- Heparin
- Antithrombin

Additional LMWH effects:
- ↑ TFPI release
- ↓ VWF release

Platelet activation

*Inactivated by APC; protein C is activated when thrombin binds thrombomodulin.*
Case

- 50 year old male with history of hypertension, hypercholesterolemia, gout, hiatal hernia, tobacco abuse

- Presents with acute onset of substernal chest pain at 12:00 midnight radiating to left arm, jaw and ear with associated SOB and diaphoresis
- ABNORMAL ECG -

Unconfirmed diagnosis

Rate 81  Sinus rhythm  
PR 189  Interoposterior infarct, acute (RCA)
QRSd 85  Probable RV involvement, suggest recording right precordial leads
QT 385  >>> Acute MI <<<
QTc 447

Axes
P 73
QRS 79
T 108
ACC/AHA Guideline Recommendations for the Use of Aspirin

A daily dose of aspirin (initial dose of 162 to 325 mg orally; maintenance dose of 75 to 162 mg) should be given indefinitely after STEMI to all patients without a true aspirin allergy.

Anti-Platelet Therapy

<table>
<thead>
<tr>
<th>Category of trial</th>
<th>N of trials</th>
<th>MI, Stroke, or Vascular Death</th>
<th>Adjusted controls</th>
<th>Odds ratio &amp; CI (Antiplatelet: Control)</th>
<th>% odds reduction (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>11</td>
<td>1330/9677 (13.7%)</td>
<td>1693/9914 (17.1%)</td>
<td>Antiplatelet therapy better</td>
<td>25%</td>
</tr>
<tr>
<td>Acute MI</td>
<td>9</td>
<td>992/9388 (10.6%)</td>
<td>1348/9385 (14.4%)</td>
<td>Antiplatelet therapy better</td>
<td>29%</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>18</td>
<td>1076/5837 (18.4%)</td>
<td>1301/5870 (22.2%)</td>
<td>Antiplatelet therapy worse</td>
<td>22%</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>7</td>
<td>182/1991 (9.1%)</td>
<td>285/2027 (14.1%)</td>
<td>Antiplatelet therapy worse</td>
<td>45%</td>
</tr>
</tbody>
</table>

## Dose-dependence and Aspirin Efficacy

### Aspirin Dose

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th># Trials</th>
<th>OR* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500–1500 mg</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>160–325 mg</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>75–150 mg</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
</tr>
</tbody>
</table>

*ASA Better*   *ASA Worse*

Study Design

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)
✓ Planned Early (<24 h) Invasive Management with intended PCI

Randomized to receive (2 X 2 factorial):
- CLOPIDOGREL: Double-dose vs Standard dose
- ASA: High Dose (300-325 mg/d) vs Low dose (75-100 mg/d)

Angio 24,769 (99%)
- PCI 17,232 (70%)
- No PCI 7,855 (30%)
  - No Sig. CAD 3,616
  - CABG 1,809
  - CAD 2,430

Efficacy Outcomes:
- CV Death, MI or stroke at day 30
- Stent Thrombosis at day 30
ASA Dose Comparison
Primary Outcome and Bleeding

<table>
<thead>
<tr>
<th></th>
<th>ASA 75-100 mg</th>
<th>ASA 300-325 mg</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death/MI/Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (2N=17,232)</td>
<td>4.2</td>
<td>4.1</td>
<td>0.98</td>
<td>0.84-1.13</td>
<td>0.76</td>
</tr>
<tr>
<td>No PCI (2N=7855)</td>
<td>4.7</td>
<td>4.4</td>
<td>0.92</td>
<td>0.75-1.14</td>
<td>0.44</td>
</tr>
<tr>
<td>Overall (2N=25,087)</td>
<td>4.4</td>
<td>4.2</td>
<td>0.96</td>
<td>0.85-1.08</td>
<td>0.47</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>1.9</td>
<td>0.91</td>
<td>0.73-1.12</td>
<td>0.37</td>
</tr>
<tr>
<td>TIMI Major Bleed</td>
<td>1.03</td>
<td>0.97</td>
<td>0.94</td>
<td>0.73-1.21</td>
<td>0.71</td>
</tr>
<tr>
<td>CURRENT Major Bleed</td>
<td>2.3</td>
<td>2.3</td>
<td>0.99</td>
<td>0.84-1.17</td>
<td>0.90</td>
</tr>
<tr>
<td>CURRENT Severe Bleed</td>
<td>1.7</td>
<td>1.7</td>
<td>1.00</td>
<td>0.83-1.21</td>
<td>1.00</td>
</tr>
</tbody>
</table>

GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

No other significant differences between ASA dose groups
Antithrombotic Therapy

**Antiplatelet Therapy**

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Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset ≤12 hours

- UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)
- Bivalirudin monotherapy (± provisional GP IIb/IIIa)

CABG – Primary PCI – Medical Rx

- Paclitaxel-eluting TAXUS stent
- Bare metal EXPRESS stent

Clinical Follow up

Stone GW et al
NEJM 2008;358:2218-30 &
NEJM 2009;360:1946-1459
Three-Year Major Bleeding

* Intracranial intraocular, retroperitoneal, access site bleed requiring intervention/surgery, hematoma ≥5 cm, hgb ↓ ≥3g/dL with or ≥4g/dL w/o overt source; reoperation for bleeding; or blood product transfusion
Three-Year Reinfarction

- Bivalirudin alone (n=1800)
- Heparin + GPIIb/IIIa (n=1802)

Reinfarction (%)

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0%</td>
<td>1.1%</td>
<td>2.2%</td>
<td>3.2%</td>
<td>4.3%</td>
<td>5.2%</td>
<td>6.2%</td>
<td>7.2%</td>
<td>8.2%</td>
<td>9.2%</td>
<td>10.2%</td>
<td>11.2%</td>
<td>12.2%</td>
</tr>
</tbody>
</table>

3-yr HR [95%CI] = 0.76 [0.59, 0.92]  
P = 0.04
Three-Year All-Cause Mortality

Bivalirudin alone (n=1800)
Heparin + GPIIb/IIIa (n=1802)

All-Cause Mortality (\%) vs Months

3-yr HR [95%CI] = 0.75 [0.58, 0.97]
P = 0.03
Three-Year Stent Thrombosis (ARC Definite/Probable)

**Bivalirudin alone (n=1611)**

Stent Thrombosis (%)

- Months: 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36
- Stent Thrombosis: 3.5%

**Heparin + GPIIb/IIIa (n=1591)**

Stent Thrombosis (%)

- Months: 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36
- Stent Thrombosis: 5.1%

**HR [95%CI]**

- Bivalirudin alone: 1.16 [0.79, 1.71] (p=0.45)
- Heparin + GPIIb/IIIa: 0.89 [0.65, 1.23] (p=0.49)
THROMBECTOMY

Mechanical

Aspiration

Rheolytic thrombectomy (AngioJet)
AngioJet Rheolytic Thrombectomy
AiMI Trial: Study Design

Transmural anterior MI or large inferior MI undergoing emergent PCI within 12 hours of symptom onset.

- Rheolytic Thrombectomy using the Possis Angiojet XMI device
  n=240

- Primary PCI Control
  n=240

Primary Endpoint: Final infarct size at 14-28 days, as measured by Tc-99m sestamibi SPECT imaging

Secondary Endpoint: ST segment resolution, post-procedure TIMI flow, corrected TIMI frame count, TIMI myocardial perfusion grade, MACE (death, new Q wave MI, stroke, target lesion revascularization), ejection fraction and procedural complications
AiMI Trial: 30 Day Endpoints

Rate of MACE in Patients Undergoing Thrombectomy

- **Angiojet**: 6.7%
- **Primary PCI**: 1.7%

*p=0.01*

Rate of Mortality in Patients Undergoing Thrombectomy

- **Angiojet**: 4.6%
- **Primary PCI**: 0.8%

*p=0.01*

*J Am Coll Cardiol 2006;48:244–52*
JETSTENT Study Design

Pts with STEMI admitted within 12 hours from symptom onset

- Lysis
- Stroke < 30 days
- Surgery < 6 weeks
- Pre-stented IRA

After angiography and IRA wiring: thrombus grade 3 to 5
Randomization 1:1

N = 500

Direct Stenting (DS)

Rheolytic Thrombectomy + DS
Aspiration Catheter
TAPAS: Study Design

1,071 STEMI Patients Randomized

535 to Thrombus Aspiration
- 33 – No PCI
- 502 – Primary PCI
  - 295 - TA followed by direct stenting
  - 153 - TA with addit. balloon dilation
  - 54 - crossover to conventional PCI

530 Complete Follow-Up at 1 year

536 to Conventional PCI
- 33 – No PCI
- 503 – Primary PCI
  - 485 - balloon dilation then stenting
  - 12 – standard PCI with additional TA
  - 6 - crossover to TA

530 Complete Follow-Up at 1 year

Svilaas T et al. Am Heart J 2006
Primary endpoint: Myocardial blush grade

Svilaas T et al. NEJM 2008;358:557 - FZ 2008-8
ST-segment elevation resolution

P < 0.001

Patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Thrombus aspiration</th>
<th>Conventional PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30%</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>30-70%</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>&gt; 70%</td>
<td>57</td>
<td>44</td>
</tr>
</tbody>
</table>

Svilaas T et al. NEJM 2008;358-557 - FZ 2008-9
Mortality or non-fatal MI at 1 year

Svilaas T et al. NEJM 2008;358:557 - FZ 2008-9
Meta-analysis of Thrombectomy on Mortality

30 Studies, 6415 patients, weighted mean FU of 5 months

Mortality (%)

Aspiration

Mechanical Thrombectomy

- Device
  - Aspiration: 2.7%
  - Mechanical Thrombectomy: 4.4%

- PCI Alone
  - Aspiration: 2.8%
  - Mechanical Thrombectomy: 5.3%

Bavry AA et al, Eur Heart J 2008; 29: 2989-3001
A loading dose of P2Y$_{12}$ antagonist is recommended for STEMI patients for whom PCI is planned (given as early as possible).

### Possible regimens

- **Clopidogrel 600 mg**
  - If prior fibrinolytic Rx, then 300 mg

- **Prasugrel 60 mg**
  - Contraindicated in pts with prior TIA/CVA: Class III LOE: B; Generally not recommended in pts ≥75 y of age; Consider using a 5 mg maintenance dose in pts weighing <60 kg

- **Ticagrelor 180 mg**
  - Maintenance aspirin 81mg PO Daily

---

Ticagrelor: An oral reversible P2Y$_{12}$ antagonist

- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y$_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel

- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Hold 5 days prior to surgical procedures
Onset of platelet inhibition

Time (hours)

IPA %

Loading
Dose

Ticagrelor (n=54)
180mg

Clopidogrel (n=50)
600mg

Placebo (n=12)

(Gurbel PA et al. Circulation, 2009)
PLATO Trial - Study Design

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

**NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)**
Clopidogrel-treated or -naive;
randomised within 24 hours of index event (N=18,624)

**Clopidogrel**
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

**Ticagrelor**
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure
PLATO Trial—Primary Endpoint: CV death, MI or stroke

HR: 0.84 (95% CI = 0.75–0.94), p=0.0025

<table>
<thead>
<tr>
<th>Days after randomization</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.65</td>
<td>9.02</td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>360</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

K-M estimated rate (% per year)

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6,676</td>
<td>6,732</td>
</tr>
<tr>
<td>60</td>
<td>6,129</td>
<td>6,236</td>
</tr>
<tr>
<td>120</td>
<td>6,034</td>
<td>6,134</td>
</tr>
<tr>
<td>180</td>
<td>5,881</td>
<td>5,972</td>
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<tr>
<td>240</td>
<td>4,815</td>
<td>4,889</td>
</tr>
<tr>
<td>300</td>
<td>3,680</td>
<td>3,735</td>
</tr>
<tr>
<td>360</td>
<td>2,965</td>
<td>3,048</td>
</tr>
</tbody>
</table>

PLATO Trial

Myocardial infarction

Cardiovascular death

<table>
<thead>
<tr>
<th>Days after randomization</th>
<th>No. at risk</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cumulative incidence (%)</td>
<td>Cumulative incidence (%)</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Ticagrelor</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>6.010</td>
<td>3.4</td>
</tr>
<tr>
<td>60</td>
<td>6.010</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>6.010</td>
<td>3.4</td>
<td></td>
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<td>180</td>
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<tr>
<td>360</td>
<td>6.010</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

HR 0.80 (95% CI = 0.69–0.92), p=0.002

HR 0.82 (95% CI = 0.68–0.98), p=0.025

PLATO Trial:
Definite Stent Thrombosis

Event Rate

0.000 0.005 0.010 0.015 0.020 0.025 0.030

0 60 120 180 240 300 360

Time from PCI / Randomization (Days)

Clopidogrel 1.93 %

Ticagrelor 1.37 %

HR 0.67, 95% CI (0.50 – 0.90)
P=0.009

### Geographic Regions

**CV Death, MI, Stroke**

<table>
<thead>
<tr>
<th>Geographic region</th>
<th>Total patients</th>
<th>KM at month 12</th>
<th>Interaction p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tic</td>
<td>Clop</td>
</tr>
<tr>
<td>Asia / Australia</td>
<td>1714</td>
<td>11.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Central America / South America</td>
<td>1237</td>
<td>15.2</td>
<td>17.9</td>
</tr>
<tr>
<td>Europe / Middle East / Africa</td>
<td>13859</td>
<td>8.8</td>
<td>11.0</td>
</tr>
<tr>
<td>North America</td>
<td>1814</td>
<td>11.9</td>
<td>9.6</td>
</tr>
</tbody>
</table>

**Comparison:**
- Ticagrelor better
- Clopidogrel better

**Interaction p-values:**
- 0.01
## Interaction of Treatment Effect with ASA Dose

<table>
<thead>
<tr>
<th>ASA Dose (mg)</th>
<th>Ticagrelor</th>
<th></th>
<th>Clopidogrel</th>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>E</td>
<td>N</td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>≥300</td>
<td>464</td>
<td>68</td>
<td>492</td>
<td>50</td>
<td>1.45 (1.01, 2.09)</td>
</tr>
<tr>
<td>&gt;100 – &lt;300</td>
<td>525</td>
<td>64</td>
<td>527</td>
<td>65</td>
<td>0.99 (0.70, 1.40)</td>
</tr>
<tr>
<td>≤100</td>
<td>7733</td>
<td>565</td>
<td>7706</td>
<td>723</td>
<td>0.77 (0.69, 0.86)</td>
</tr>
</tbody>
</table>

χ²=16.1
p=0.00006

- Ticagrelor Better
- Clopidogrel Better
Similar Effect of ASA Maintenance Dose In Both U.S. and Non-U.S.

<table>
<thead>
<tr>
<th>Region</th>
<th>ASA Dose (mg)</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>E</td>
<td>N</td>
</tr>
<tr>
<td>US</td>
<td>≥300</td>
<td>324</td>
<td>40</td>
<td>352</td>
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<td></td>
<td>&gt;100 - &lt;300</td>
<td>22</td>
<td>2</td>
<td>16</td>
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<tr>
<td></td>
<td>≤100</td>
<td>284</td>
<td>19</td>
<td>263</td>
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<tr>
<td>Non-US</td>
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<td>140</td>
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<td>140</td>
</tr>
<tr>
<td></td>
<td>&gt;100 - &lt;300</td>
<td>503</td>
<td>62</td>
<td>511</td>
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<tr>
<td></td>
<td>≤100</td>
<td>7449</td>
<td>546</td>
<td>7443</td>
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</tbody>
</table>
PLATO Trial: Interaction Between Treatment Effect and ASA Maintenance Dose

ASA Low (>300mg): HR (95% CI) = 0.79 (0.71, 0.88)
ASA High (≥300mg): HR (95% CI) = 1.45 (1.01, 2.09)

Mahaffey KW et al. Circulation 2011;124:544-54
ONSET/OFFSET: Pharmacodynamics in Stable CAD Patients

- Loading Dose: 180 mg, 600 mg
- Last Maintenance Dose: 90 mg bid, 75 mg qd

IPA % over time:
- Ticagrelor (n=54)
- Clopidogrel (n=50)

Time (Hours):
- Onset
- Maintenance
- Offset

Gurbel P, Circ 2009
Summary of Ticagrelor

- **Advantages**
  - Rapid onset on action
  - Better clinical outcomes than clopidogrel
  - Can be given to all patients
  - Shorter offset of effect

- **Disadvantages**
  - Trial data from North American patients
  - Requires ASA 81mg Daily
  - Twice a day dosing
  - Associated with dyspnea and pauses
Prasugrel:
An oral irreversible P2Y\textsubscript{12} antagonist

- **Not direct acting**
  - Prodrug; does require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y\textsubscript{12} receptor
  - Greater inhibition of platelet aggregation than clopidogrel

- **Irreversibly bound**
  - Longer offset of effect than clopidogrel
  - Hold 7 to 10 days prior to surgical procedures
TRITON TIMI 38-Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,608

Double-blind

Clopidogrel
300 mg LD/75 mg MD

Prasugrel
60 mg LD/ 10 mg MD

Median duration of therapy – 12 months
TRITON-TIMI 38: Balance of Efficacy and Safety

CV Death/MI/Stroke

Time (Days)

Endpoint (%)

N=13,608

Clopidogrel 12.1

HR=0.81 (CI=0.73-0.90)

P=0.0004

Prasugrel 9.9

138 events

Non-CABG Bleeds

TIMI Major

1.8

Clopidogrel

2.4

Prasugrel

35 events

HR=1.32 (1.03-1.68)

P=0.03

Stent Thrombosis (ARC Definite + Probable)

Any Stent at Index PCI
N = 12,844

Prasugrel

NNT = 77

Clopidogrel

P < 0.0001

Days

Endpoint (%)
TRITON TIMI 38 Trial: Outcomes in Patients with Diabetes
Death, MI or Stroke at 1 year

A

DM
HR 0.70 (0.58-0.85), P<0.001

No DM
HR 0.86 (0.76-0.98), P = 0.02

PInteraction = 0.09

Wiviott, Circ 2008
Summary of Prasugrel

- **Advantages**
  - Rapid onset on action
  - Better clinical outcomes than clopidogrel
  - Once a day dosing regimen
  - Improved efficacy in diabetic patients

- **Disadvantages**
  - Black Box warning: History of TIA/CVA, Age >75 and Weight <60kg
  - Longer offset of effect
  - More life threatening bleeds
Antithrombotic Therapy in STEMI Patients: 2013

- Aspirin 325mg load on arrival then 81mg Daily indefinitely
- Atorvastatin 80mg PO
- IV Bivalirudin per protocol
- Aspiration Thrombectomy as indicated
- Ticagrelor 180mg load then 90mg BID for 12 months or Prasugrel 60mg load then 10mg Daily for 12 months