Clopidogrel in Cardiovascular Disease

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Cleveland, Ohio
Platelet ADP Receptors

- **Platelet ADP Receptors**
- **Thienopyridines**
  - AR-C69931MX
  - Inhibition of adenylate cyclase
  - Intracellular Ca\(^{2+}\) mobilization
  - Secretion
  - Sustained aggregation
  - Shape change
- **ADP**
  - Ca\(^{2+}\) influx
  - Shape change
  - Aggregation
  - Rapid Ca\(^{2+}\) influx
- **Acetylsalicylic Acid (ASA)**
- **Intracellular Ca\(^{2+}\) levels**
  - Rapid Ca\(^{2+}\) influx
  - Shape change
  - Aggregation
- **Adenylyl Cyclase (AC)**
  - Inhibition of adenylate cyclase
- **Phospholipase C (PLC)**
  - Intracellular Ca\(^{2+}\) mobilization
  - Shape change
  - Transient aggregation
Randomized, double-blind trial
- Clopidogrel 75 mg qd vs Aspirin 325 mg qd
- 19,185 patients, followed for 1 to 3 yrs (mean 1.91 yrs)
- Entry with MI, stroke, or PVD

Ticlopidine in Stenting

Randomized Trials

Death, MI, CABG, or TVR (%)

- Aspirin
- Aspirin + Ticlopidine
- Aspirin + Warfarin

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aspirin</th>
<th>Aspirin + Ticlopidine</th>
<th>Aspirin + Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall</td>
<td>3.9</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>ISAR</td>
<td>1.6</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>STARS</td>
<td>3.6</td>
<td>0.6</td>
<td>2.4</td>
</tr>
<tr>
<td>MATTIS</td>
<td>5.6</td>
<td>11.0</td>
<td>8.3</td>
</tr>
<tr>
<td>FANTASTIC</td>
<td>5.7</td>
<td>11.0</td>
<td>8.3</td>
</tr>
</tbody>
</table>

- Hall: n = 226, p = 0.1
- ISAR: n = 517, p = 0.01
- STARS: n = 1652, p < 0.001
- MATTIS: n = 350, p = 0.07
- FANTASTIC: n = 485, p = 0.37
Clopidogrel in Non-ST Elevation ACS

CURE Trial

**Endpoint at Mean 9 Month F/U (%)**

- **Composite**: Placebo (n = 6303) = 11.47, Clopidogrel (n = 6259) = 9.28
- **CV Death**: Placebo (n = 6303) = 5.49, Clopidogrel (n = 6259) = 5.06
- **MI**: Placebo (n = 6303) = 6.68, Clopidogrel (n = 6259) = 5.19
- **Stroke**: Placebo (n = 6303) = 1.40, Clopidogrel (n = 6259) = 1.20

**% of Patients**

- **Major**: Placebo = 2.7, Clopidogrel = 3.6
- **Life-Threat**: Placebo = 1.8, Clopidogrel = 2.1
- **Tx 2U**: Placebo = 2.2, Clopidogrel = 2.8

CURE Investigators. NEJM 2001;345:494.
Clopidogrel in CAD

- When should it be started
- What else is needed
- When should it be stopped
- The future
Ticlopidine and Stenting

Pretreatment - Cleveland Clinic Experience


<table>
<thead>
<tr>
<th>Days of Ticlopidine Pretreatment</th>
<th>CK &gt; 210 IU/L (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28.8</td>
</tr>
<tr>
<td>1-2</td>
<td>16.7</td>
</tr>
<tr>
<td>&gt;3</td>
<td>11.2</td>
</tr>
</tbody>
</table>

N = 175
p = 0.024
Clopidogrel in Non-ST Elevation ACS
Death, MI, Urgent Revascularization

Cumulative Hazard Rates

- Placebo, N = 1345
- Clopidogrel, N = 1313

RR 0.70, p = 0.03
Death or MI 4.4 vs. 2.9%, RR 0.66, p = 0.04

> 80% of pts received open label clopidogrel for 30 days post PCI

Platelet Inhibition - Pre-PCI Clopidogrel

**PRONTO Trial**

100 pts randomized: clopidogrel load (3-24 hrs prior) or no load

CREDO Trial

Clopidogrel PreRx and Prolonged Rx in PCI

N = 2116 Patients (6/99 - 4/01): Planned PCI
All patients received aspirin

Randomization

- Clopidogrel 300 mg
  - 3-24 Hrs Prior to PCI -> Placebo
- Clopidogrel 75 mg qd
  - PCI to Day 28 -> Clopidogrel 75 mg qd
- Clopidogrel 75 mg qd
  - Day 29 to Day 365 -> Placebo

- 28 Day Endpoint: Death, MI, Urgent TVR •
- 1 Year Endpoint: Death, MI, Stroke •
CREDO Trial

28-Day Endpoint

Events at 28 Days (%)

- Composite
  - No Pretreatment (n = 915): 8.3%
  - Pretreatment (n = 900): 6.8%
  - RRR: 18.5% (p = 0.23)

- Death
  - No Pretreatment (n = 915): 0.4%
  - Pretreatment (n = 900): 0.0%

- MI
  - No Pretreatment (n = 915): 6.6%
  - Pretreatment (n = 900): 5.8%

- Urg TVR
  - No Pretreatment (n = 915): 1.3%
  - Pretreatment (n = 900): 1.0%

Steinhubl et al. JAMA 2002;288:2411.
CREDO Trial

28-Day Endpoint by Pretreatment Duration

Steinhubl et al. JAMA 2002;288:2411.
CREDO Trial

Loading Dose Timing and Risk of MACE

Log Odds of Death, MI or UTVR at 28 Days

Placebo

Clopidogrel

P = 0.020 for treatment / timing interaction

Courtesy of S. Steinhubl, MD
Activated CD40L and CD62P Expression during PCI

79 pts in prospective non-randomized study of pretreatment (dose >24 hrs pre-PCI) vs no pretreatment

Clopidogrel Loading

Before Administration

Clopidogrel Loading Dose

Ticlopidine 2x 500mg, then 250 BID
Clopidogrel 300 mg, then 75 mg QD
Clopidogrel 600 mg, then 75 mg BID

% of 20 µM ADP-induced aggregation

Time after Administration (hours)

# CURE - CABG and Bleeding

## Major Bleeding within 7 Days after CABG

<table>
<thead>
<tr>
<th>Last Study Rx Dose Before CABG</th>
<th>Clopidogrel + ASA</th>
<th>Placebo + ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5 days (n = 910)</td>
<td>4.4%</td>
<td>5.3%</td>
</tr>
<tr>
<td>&lt; 5 days (n = 912)</td>
<td>9.6%*</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

*P = 0.06

Clopidogrel in CAD

◊ **When should it be started**

◊ **What else is needed**

◊ **When should it be stopped**

◊ **The future**
Clopidogrel Pretreatment

Benefit Independent of GP IIb/IIIa Inhibition

GPIIb/IIIa Inhibitor

- Yes
- No

Pretreatment

- Better
- No Pretreatment

0.4 0.6 0.8 1.0 1.2

Courtesy of Steve Steinhubl, M.D.
ISAR - REACT

Abciximab vs Placebo with Clopidogrel Pre-Rx

Exclusions:
- ACS with ST Δ’s or ↑ Tn
- DM with insulin Rx
- SVG PCI
- Occlusion, thrombus
- EF < 30%
- Hemodynamic instability

30 Day Event Rate (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 1080)</th>
<th>Abciximab (n = 1079)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comp</td>
<td>4.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Death</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>QMI</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>NQMI</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>UTVR</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

All p = N.S.

ADP P2Y$_{12}$ Receptor Inhibition

Synergy with Thrombin or Factor Xa Inhibition

Arterial Thrombosis in the FeCl$_3$-injury model

<table>
<thead>
<tr>
<th>Genotype</th>
<th>WT</th>
<th>P2Y$_{12}^{+/+}$</th>
<th>WT Biv.</th>
<th>WT C921-78</th>
<th>P2Y$_{12}^{+/-}$ Biv.</th>
<th>P2Y$_{12}^{+/-}$ C921-78</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16.1±2</td>
<td>24.7±3</td>
<td>33.9±3</td>
<td>35.8±4</td>
<td>&gt; 50</td>
<td>&gt; 50</td>
</tr>
</tbody>
</table>

0. Mean time for Occlusion (min)

Clopidogrel in CAD

- When should it be started
- What else is needed
- When should it be stopped
- The future
IMPACT II: Long-Term Ischemic Events

6 Month Death, MI or Urgent Revasc

% Composite Endpoint

Days

Placebo
Eptifibatide 135/0.75
Eptifibatide 135/0.50

P = NS

CURE Trial

MACE (CV Death, MI or Stroke): 31 Days - 1 Year

- **Relative risk 0.82**
- **95% CI 0.70-0.95**
- **P=0.009**

CURE Investigators. NEJM 2001;345:494.
CREDO Trial

1-Year Outcome

Death, MI, or Stroke (%)

Days from Randomization

Placebo (n = 1063)
Clopidogrel (n = 1053)

RRR = 26.9% (3.9% - 44.4%)

p = 0.02

Steinhubl et al. JAMA 2002;288:2411.
Clopidogrel and Brachytherapy

6-Months vs 1-Year of Clopidogrel Therapy


Event-Free Survival

% of Patients

Clopidogrel 12 Mo (WRIST 12)*

Clopidogrel 6 Mo (WRIST PLUS)*

P=0.013
Clopidogrel - Prevention

Secondary or High-Risk Primary Prevention

Patients aged 45 years or older

Considered to be at high-risk of atherothrombotic event

n = 15,607

Double-blind treatment up to 1,040 primary efficacy events*

ASA 75–162 mg once daily

Clopidogrel 75 mg once daily

Placebo 1 tab once daily

ASA 75–162 mg once daily

1 month visit

3 month visit

42 month or final visit

R = Randomization

* event driven trial

Clopidogrel in CAD

- When should it be started
- What else is needed
- When should it be stopped
- The future
# Ongoing Trials (> 85,000 Patients)

<table>
<thead>
<tr>
<th>Trial</th>
<th># Patients</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTIVE</td>
<td>14,000</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>ARCH</td>
<td>1500</td>
<td>Aortic arch atheroma</td>
</tr>
<tr>
<td>CAMPER</td>
<td>2000</td>
<td>Peripheral arterial intervention</td>
</tr>
<tr>
<td>CASPAR</td>
<td>1460</td>
<td>Peripheral artery bypass surgery</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>15,200</td>
<td>2° and high-risk 1° prevention</td>
</tr>
<tr>
<td>CLARITY</td>
<td>2200</td>
<td>Acute STEMI</td>
</tr>
<tr>
<td>COMMIT</td>
<td>40,000</td>
<td>Acute STEMI</td>
</tr>
<tr>
<td>MATCH</td>
<td>7600</td>
<td>High-risk stroke or TIA</td>
</tr>
<tr>
<td>WATCH</td>
<td>1587</td>
<td>Heart failure</td>
</tr>
</tbody>
</table>

Cangrelor (AR-C69931MX)

Parenteral ADP-P_{2}Y_{12} Inhibitor

◊ ATP analog; molecular weight <1000 daltons
◊ Plasma half-life 5-9 minutes
◊ Return of normal platelet function within 20 minutes
92 patients undergoing elective stenting. Clopidogrel 300 mg at time of stent, then 75 mg daily. LTA with 5\(\mu\)M ADP and 20 \(\mu\)M ADP at baseline, 2 hrs, 24 hrs, day 5 and 30. Non-responders with < 10% change.

Gurbel P. Circulation 107:2908-13, 2003
Adequate ADP-receptor blockade prior to PCI associated with ↓ MACE, with and without GPIIb/IIIa antagonists.

Long-term therapy significantly reduces the risk of atherothrombotic events after PCI.

Variability of response may be important factor

New parenteral agents may enhance pretreatment and outcomes