New Developments in Antiplatelet Therapy

29 April 2004        Seoul, Korea

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Atherothrombosis: a progressive process

1. Normal
2. Fatty streak
3. Fibrous plaque
4. Atherosclerotic plaque

Plaque rupture/fissure & thrombosis

- Myocardial infarction
- Ischemic stroke
- Critical leg ischemia
- Cardiovascular death

Clinically silent
- Angina
- Transient ischemic attack
- Claudication/PAD

Increasing age
Modes of Action of Clopidogrel & ASA


COX (cyclo-oxygenase)
ADP (adenosine diphosphate)
TXA₂ (thromboxane A₂)
Antithrombotic Trialists’ Collaboration: Efficacy of Antiplatelet Therapy on Vascular Events

<table>
<thead>
<tr>
<th>Category</th>
<th>% odds reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Acute stroke</td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Prior stroke/transient ischemic attack</td>
<td></td>
</tr>
<tr>
<td>Other high risk</td>
<td></td>
</tr>
<tr>
<td>• CAD (e.g. unstable angina, heart failure)</td>
<td></td>
</tr>
<tr>
<td>• PAD (e.g. intermittent claudication)</td>
<td></td>
</tr>
<tr>
<td>• Risk of embolism (e.g. atrial fibrillation)</td>
<td></td>
</tr>
<tr>
<td>• Other (e.g. diabetes)</td>
<td></td>
</tr>
<tr>
<td>All trials</td>
<td>22% ±2</td>
</tr>
</tbody>
</table>

*Vascular events = myocardial infarction, stroke or vascular death

Data on 135,000 patients in 287 trials

CAPRIE: Long-Term Benefit of Clopidogrel Compared with ASA

Cumulative Event Rate
(Myocardial Infarction, Ischemic Stroke or Vascular Death)

ASA: 8.7%*

Overall relative risk reduction

Clopidogrel

*p = 0.043  n = 19,185

*ITT analysis

CAPRIE: Benefit of Clopidogrel over ASA in the Reduction of Myocardial Infarction¹

Cumulative event rate (%)

Months of follow-up

ASA 3.6%

Clopidogrel 2.9%

\( p = 0.008 \)  \( n = 19,185 \)

* ITT analysis

1. Cannon C. *Am J Cardiol.* 2002; 90; 760-762
## CAPRIE: Favorable Safety for Clopidogrel Compared with ASA*

<table>
<thead>
<tr>
<th>Adverse experiences†</th>
<th>ASA (n = 9,586)</th>
<th>Clopidogrel (n = 9,599)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea (severe)¹</td>
<td>0.11%</td>
<td>0.23%</td>
<td>NS</td>
</tr>
<tr>
<td>Gastritis²</td>
<td>1.32%</td>
<td>0.75%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gastrointestinal ulcer²</td>
<td>1.15%</td>
<td>0.68%</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage (severe)¹</td>
<td>0.71%</td>
<td>0.49%</td>
<td>&lt; 0.05</td>
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<tr>
<td>Intracranial hemorrhage¹</td>
<td>0.49%</td>
<td>0.35%</td>
<td>NS</td>
</tr>
<tr>
<td>Rash (severe)¹</td>
<td>0.10%</td>
<td>0.26%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Neutropenia²</td>
<td>0.17%</td>
<td>0.10%</td>
<td>NS</td>
</tr>
</tbody>
</table>

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*Patients with ASA intolerance were excluded
†Clinically severe or resulting in early drug discontinuation

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Synergistic Action of Clopidogrel on top of ASA in Thrombus Formation

Experimental model

- Clopidogrel (10 mg/kg)
- ASA (10 mg/kg)
- Clopidogrel plus ASA (10 mg/kg plus 10 mg/kg)
- Placebo

Blood flow (% decrease)

Time (minutes)

A Loading Dose of Clopidogrel Provides Rapid and Full Effect by 3 Hours

Healthy Volunteers

Mean inhibition (%)

Time (hours)

Clopidogrel 75 mg

Clopidogrel 300 mg

(*p < 0.002 vs clopidogrel 75 mg)

CURE: Early and Long-Term Benefits of Clopidogrel\textsuperscript{1,2}

Cumulative Events
(Myocardial Infarction, Stroke, or Cardiovascular Death)

![Graph showing cumulative hazard rate over months of follow-up for Placebo* (n = 6,303) and Clopidogrel* (n = 6,259).]

- Placebo*: 20% Relative risk reduction, \( p = 0.00009 \)

*On top of standard therapy (including ASA)

CV Death/MI/Stroke/Severe Ischemia Within 24 hrs of Randomization

Clopidogrel

Clopidogrel

Placebo

Placebo

RR= 0.66        P=0.002

Yusuf, ACC March 2001

Cumulative Hazard Rates

Hours after Randomization
### CURE: Consistent Benefit Independent of Patient History

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Percent events</th>
<th></th>
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<th></th>
<th></th>
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<th></th>
<th></th>
<th>Clopidogrel better</th>
<th>Placebo better</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Clopidogrel*</td>
<td>Placebo*</td>
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<td>Overall</td>
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<td>Non-Q-W MI</td>
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<td>Unstable angina</td>
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</tbody>
</table>

*On top of standard therapy (including ASA)*

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CURE: Consistent Benefit on Top of Various Standard Therapies

<table>
<thead>
<tr>
<th>Concomitant medication/therapy</th>
<th>N</th>
<th>Clopidogrel (%)</th>
<th>Placebo (%)</th>
<th>Clopidogrel better</th>
<th>Placebo better</th>
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<tbody>
<tr>
<td>Heparin/LMWH</td>
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<td>951</td>
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<td>11611</td>
<td>9.7</td>
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<td>ASA</td>
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<td>&lt; 100 mg</td>
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<td>100–200 mg</td>
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<td>&gt; 200 mg</td>
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<td>10.8</td>
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<td>Yes</td>
<td>823</td>
<td>15.7</td>
<td>19.2</td>
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<td>Beta-blocker</td>
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<td>No</td>
<td>2032</td>
<td>9.9</td>
<td>12.0</td>
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<td>10530</td>
<td>9.2</td>
<td>11.3</td>
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<td>ACEI</td>
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<td>4813</td>
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<td>8.1</td>
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<td>7749</td>
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<td>Lipid-lowering</td>
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<td>13.1</td>
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<td>Yes</td>
<td>8101</td>
<td>8.4</td>
<td>10.5</td>
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<td>PTCA/CABG</td>
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<td>No</td>
<td>7977</td>
<td>8.1</td>
<td>10.0</td>
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<tr>
<td>Yes</td>
<td>4585</td>
<td>11.4</td>
<td>13.8</td>
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</tbody>
</table>

*On top of standard therapy (including ASA)

CURE: Effects of Clopidogrel Stratified by TIMI Risk Score at 12 Months$^{1,2}$

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>ARR*</th>
<th>RRR†</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>1.6</td>
<td>29%</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.6</td>
<td>15%</td>
</tr>
<tr>
<td>High</td>
<td>4.8</td>
<td>27%</td>
</tr>
</tbody>
</table>

**MI, stroke or vascular death (%)**

- **Placebo**
  - Low risk: 5.7
  - Moderate risk: 11.4
  - High risk: 20.7

- **Clopidogrel**
  - Low risk: 4.1
  - Moderate risk: 9.8
  - High risk: 15.9

$p = 0.003$


*Absolute risk reduction
†Relative risk reduction
## CURE: Bleeding Episodes

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo* (n = 6,303)</th>
<th>Clopidogrel* (n = 6,259)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding¹</td>
<td>2.7%</td>
<td>3.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>• Life-threatening</td>
<td>1.8%</td>
<td>2.2%</td>
<td>NS</td>
</tr>
<tr>
<td>• Other major bleeding</td>
<td>0.9%</td>
<td>1.5%</td>
<td>0.002</td>
</tr>
<tr>
<td>Transfusions of ≥ 2 units of blood¹</td>
<td>2.2%</td>
<td>2.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>Minor bleeding¹</td>
<td>2.4%</td>
<td>5.1%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Major bleeding by TIMI definition²</td>
<td>1.2%</td>
<td>1.1%</td>
<td>0.70</td>
</tr>
<tr>
<td>Major bleeding by GUSTO definition³</td>
<td>1.1%</td>
<td>1.2%</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*On top of standard therapy (including ASA)

CURE: Relation Between Safety and ASA Dosage


*On top of standard therapy (including ASA)

One of the Largest Clinical Trial Programs Ever Developed
More than 100,000 patients in studies with clopidogrel

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Maximum follow-up</th>
<th>Number of patients</th>
<th>Status of study (data expected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE²</td>
<td>Ischemic stroke, MI or PAD</td>
<td>36 months</td>
<td>19,185</td>
<td>Published (Lancet, 1996)</td>
</tr>
<tr>
<td>CLASSICS³</td>
<td>Coronary stenting</td>
<td>12 months</td>
<td>1,020</td>
<td>Published (Circulation, 2000)</td>
</tr>
<tr>
<td>CREDO⁴</td>
<td>PCI</td>
<td>12 months</td>
<td>2,116</td>
<td>Published (JAMA, 2002)</td>
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<tr>
<td>CURE⁵</td>
<td>Unstable angina or NQWMI</td>
<td>12 months</td>
<td>12,562</td>
<td>Published (N Engl J Med, 2001)</td>
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<tr>
<td>PCI-CURE*⁶</td>
<td>CURE patients undergoing PCI</td>
<td>12 months</td>
<td>2,658</td>
<td>Published (Lancet, 2001)</td>
</tr>
<tr>
<td>ACTIVE</td>
<td>Atrial fibrillation</td>
<td>48 months</td>
<td>~14,000</td>
<td>Ongoing (2007)</td>
</tr>
<tr>
<td>CARESS</td>
<td>Carotid stenosis with MES</td>
<td>10 days</td>
<td>~100</td>
<td>Completed (2004)</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>Coronary, cerebrovascular, PAD, or major risk factors</td>
<td>42 months</td>
<td>~15,200</td>
<td>Ongoing (2005/6)</td>
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<tr>
<td>COMMIT</td>
<td>Acute MI</td>
<td>4 weeks</td>
<td>~45,000</td>
<td>Ongoing (2005)</td>
</tr>
<tr>
<td>CLARITY</td>
<td>Acute MI (angiography)</td>
<td>4 weeks</td>
<td>3,000</td>
<td>Ongoing (2005)</td>
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<tr>
<td>MATCH</td>
<td>TIA or ischemic stroke</td>
<td>18 months</td>
<td>7,601</td>
<td>Completed (2004)</td>
</tr>
</tbody>
</table>


* PCI-CURE is a substudy of the CURE study
Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance
CHARISMA: Inclusion Criteria

Patients aged 45 years and older

with

at least 1 of the following:

1) 2 major or 1 major and 2 minor or 3 minor risk factors
   and/or

2) documented cerebrovascular disease
   and/or

3) documented coronary artery disease
   and/or

4) documented symptomatic peripheral arterial disease (PAD)
CHARISMA: Study Design

Patients aged 45 years or older at high-risk of atherothrombotic event

Randomization (R) n = 15,200

Event driven trial

Clopidogrel 75mg daily (n = 7,600)

Placebo 1 tab daily (n = 7,600)

All patients receive low-dose ASA (75-162 mg daily) as background therapy
COMMIT Trial
(PCS-2)
Clopidogrel Metoprolol Myocardial Infarction Trial
COMMIT

Study Design

Patients with suspected AMI* < 24 hours

Aspirin 162 mg po qd

Clopidogrel 75 mg po qd

Clopidogrel Placebo

Metoprolol 200mg CR po qd

Metoprolol Placebo

Metoprolol 200mg CR po qd

Metoprolol Placebo

1⁰ endpoint = death/death or MI

CR = controlled release

N = 45,000-48,000

* typical ECG changes
ACTIVE

Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events
ACTIVE : 3 Nested Trials

- **ACTIVE-W**
  - *Noninferiority* trial: clopidogrel + ASA vs. adjusted dose (INR 2.0-3.0) oral anticoagulation (OAC) [N=6500]
  - Open-label PROBE design

- **ACTIVE-A**
  - *Superiority* trial: clopidogrel vs. placebo on a background of standard care including ASA 75-100 mg (double-blind) [N=7500]

  Common 1° outcome = VD, MI, stroke, or peripheral embolism

- **ACTIVE-I**
  - Factorial design: irbesartan (150 mg with forced titration to 300 mg) vs. placebo [N≈10,000]
  - 1° outcome = VD, MI, or stroke
ACTIVE : Inclusion Criteria

- Evidence of Atrial Fibrillation:
  - Documented chronic AF or recurrent intermittent AF, and
  - No current plan to achieve sinus rhythm

- High risk of vascular events (any of):
  - Age $\geq 75$ years
  - On treatment for systemic hypertension
  - Prior stroke, non-CNS systemic embolus or TIA
  - Left ventricular dysfunction, with left ventricular EF $<45$
  - Age 65 to 74 years, and one of the following:
    - Diabetes mellitus requiring treatment
    - Coronary artery disease (coronary angiographic evidence or positive perfusion study)
    - Peripheral arterial disease
Evidence of AF
Evidence of High Risk of Vascular Events
No exclusion criteria for ACTIVE

Exclusion criteria for ACTIVE-W

Eligible for ACTIVE-W
(C+A* vs OAC - INR 2.0-3.0)

Eligible for ACTIVE-A
(C+A* vs placebo+A)

No exclusion criteria for ACTIVE-I

Eligible for ACTIVE-I
(Irbesartan vs placebo-I)

Partial Factorial Design

Mean Follow-up 3 years

*C = clopidogrel 75 mg once a day
A = ASA 75-100 mg once a day (recommended)
New Developments in Antiplatelet Therapy

29 April 2004                Seoul, Korea

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