Role of Clopidogrel in Acute Coronary Syndromes

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ACS Treatment Strategies

Reperfusion/Revascularization Therapy

- Thrombolyis
- PCI (with/without stenting)
- CABG
- Medical therapy

Antithrombotic Cotherapy

- ASA
- UFH
- LMWH
- Penta.
- DTI
- GP IIb/IIIa
- ADP antagonist

Acute and Long-term Medical Therapy

- Nitrates
- BBs
- ACEIs
- ARBs
- CCBs
- Statins
- APT

PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; ASA = aspirin; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; Penta. = pentasaccharide; DTI = direct thrombin inhibitors; GP IIb/IIIa = glycoprotein IIb/IIIa inhibitors; ADP antagonist = adenosinediphosphate antagonist; BBs = beta blockers; ACEI = angiotensin converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CCBs = calcium channel blockers; APT = antiplatelet therapy
Both are prodrugs that depend on metabolites for their effects. Their metabolites block platelet P2Y12 receptor. Polymorphism within P2Y12 gene is responsible for Clopidogrel resistance in some patients.
ADP receptor subtypes

**Antagonist**
- A3P5P
- Cangrelor
- Clopidogrel

**Receptor subtype**
- P2X1
- P2Y1
- P2Y12

**Molecular structure**
- Intrinsic ion channel
  - [Na⁺ and Ca²⁺]↑
- GPCR  
  - G₀  
    - ↑ PLC/IP
    - ↑[Ca²⁺]
- GPCR  
  - G₁  
    - ↓AC
    - ↓Cyclic AMP

**Second messenger**
- [Na⁺ and Ca²⁺]↑
- ↑ PLC/IP
- ↑[Ca²⁺]
- ↓AC
- ↓Cyclic AMP

**Functional response**
- Shape change
- Aggregation
- Transient aggregation
- Sustained aggregation
- Secretion
Clopidogrel 75 mg - once daily
Pharmacokinetics / Pharmacodynamics

• ADP receptor antagonist
• Rapidly absorbed (oral), unaffected by food
• 1 h to peak plasma concentration
• Rapid and extensive hepatic metabolism
• Once-daily dosing at 75 mg
  – Significant inhibition of platelet aggregation within 2 hours
  – Maximum inhibition of ADP-induced platelet aggregation (40-60%) at steady-state (between 3 and 7 days)
  – Bleeding time increases up to twice baseline value

Coukell and Markham. Drugs 1997;54(5):745-750
Clopidogrel:
No Significant interactions with concomitant medications other than anticoagulants, antithrombotic agents, antithombolytic agents and NSAIDs

- No significant clinical interactions with frequently prescribed concomitant medications without evidence of clinically significant adverse interaction:
  - ACE inhibitors
  - anti-epileptic therapy
  - calcium antagonists
  - coronary vasodilators
  - peripheral vasodilators
  - anti-diabetic therapy
  - beta-blocking agents
  - cholesterol reducers
  - diuretics

**CAPRIE Study: Methodology**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Multicenter, prospective, randomized, blinded</th>
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<tbody>
<tr>
<td>Study population</td>
<td>19,185 patients with atherosclerotic vascular disease</td>
</tr>
</tbody>
</table>
| Qualifying conditions        | Ischemic stroke ($\geq$1 week and $\leq$6 months)  
                            | Myocardial infarction (MI) ($\leq$35 days)  
                            | Established peripheral arterial disease |
| Study drugs                  | Clopidogrel 75 mg once daily  
                            | Aspirin 325 mg once daily |
| Primary end point            | MI, ischemic stroke, or vascular death |
| Treatment duration           | Up to 3 years (mean 1.6 years) |
| Investigational sites        | 384 in 16 countries |

**Clopidogrel:**
Reduction of fatal and non-fatal MI outcome

**Event rate per year**

<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.6%</td>
<td>2.9%</td>
</tr>
<tr>
<td>1</td>
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<td>36</td>
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</tbody>
</table>

*For overall population of the CAPRIE study. Combined endpoint 8.7% (p=0.043), 7.6% relative risk reduction (RRR) for vascular death, 5.2% RRR for ischemic stroke.*

**Combined endpoint (MI, ischemic stroke, and vascular death)**

Based on the CAPRIE trial and Antiplatelet Trialists’ Collaboration meta-analysis, aspirin can be expected to prevent 19 ischemic events* for every 1,000 patients treated per year. In contrast, clopidogrel can be expected to prevent 24 ischemic events* for every 1,000 patients treated per year, a 26% difference.


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### CAPRIE Study:
Clinical Evidence of Efficacy of Clopidogrel

**Clopidogrel prevents 26% more atherothrombotic events* than aspirin**

*Combined endpoint (MI, ischemic stroke, and vascular death)

**Based on the CAPRIE trial and Antiplatelet Trialists’ Collaboration meta-analysis, aspirin can be expected to prevent 19 ischemic events* for every 1,000 patients treated per year. In contrast, clopidogrel can be expected to prevent 24 ischemic events* for every 1,000 patients treated per year, a 26% difference.

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**Graph:**
- **Aspirin**
  - 19 events prevented/year/1,000 patients
- **Clopidogrel**
  - 24 events prevented/year/1,000 patients

**26%** increase in efficacy with clopidogrel compared to aspirin.
# Events Prevented by Cardiovascular Pharmacotherapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Population</th>
<th>End Point</th>
<th>Mean No. of Events Prevented per 1,000 Patients per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel(^{1,2})</td>
<td>Atherosclerotic</td>
<td>IS, MI, vascular death</td>
<td>24</td>
</tr>
<tr>
<td>Aspirin(^{1,2})</td>
<td>Atherosclerotic</td>
<td>IS, MI, vascular death</td>
<td>19</td>
</tr>
<tr>
<td>Antihypertensive Drugs(^3)*</td>
<td>Hypertension (&gt;60 yrs)</td>
<td>Fatal or non-fatal stroke, MI, CHD death</td>
<td>8</td>
</tr>
<tr>
<td>ACE inhibitors(^4)**</td>
<td>Acute MI + LV dysfunction</td>
<td>MI, vascular death</td>
<td>18</td>
</tr>
</tbody>
</table>

The purpose of this table is not to compare efficacy, but to provide a rough estimate of different kinds of protection.

\(^{1}\)CAPRIE Steering Committee. Lancet 1996;348:1329-1339.  
Clopidogrel: Safety profile vs. aspirin

- Indigestion/nausea/vomiting
- Rash
- Diarrhoea
- Gastrointestinal bleeding
- Gastrointestinal ulcers
- Intracranial haemorrhage
- Neutropenia (< 1200/mm³)

% of patients with events

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (325 mg/day)</th>
<th>Clopidogrel (75 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigestion</td>
<td>17.59*</td>
<td>15.01</td>
</tr>
<tr>
<td>Rash</td>
<td>4.61</td>
<td>6.02*</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3.36</td>
<td>4.46*</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2.66*</td>
<td>1.99</td>
</tr>
<tr>
<td>Gastrointestinal ulcers</td>
<td>1.15*</td>
<td>0.68</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>0.49</td>
<td>0.35</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.17</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*p < 0.05

CREDO Objectives
(Clopidogrel for the Reduction of Events During Observation)

Objectives

- To evaluate the **long term efficacy** of prolonged (1 year) therapy with clopidogrel 75mg vs placebo in patients on top of standard therapy (including ASA)

- To evaluate the effect of **pretreatment** with a clopidogrel 300 mg loading dose on the composite of death (all-cause), MI (Q- or non-Q-wave), or UTVR at **Day 28**, in patients who underwent PCI

- To evaluate the safety of clopidogrel, specifically the frequency of major bleeding events and early discontinuation of study drug


UTVR= Urgent Target Vessel Revascularization
Long-term Benefits of Clopidogrel in PCI Patients

COMBINED ENDPOINT OCCURRENCE (%)

MONTHS FROM RANDOMIZATION

1 year results (MI, Stroke, or Death)

- 27% RRR
- \( p = 0.02 \)

8.5% Placebo**
11.5% Clopidogrel*

* On top of standard therapy including ASA
# All patients received clopidogrel post PCI up to day 28
### Timing of Loading Dose - 28 Days

#### Events (%)

<table>
<thead>
<tr>
<th></th>
<th>PT-Clopidogrel*</th>
<th>No-PT Clopidogrel*</th>
<th>n</th>
<th>PT-Clopidogrel Better</th>
<th>No-PT Clopidogrel Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 hrs</td>
<td>7.9</td>
<td>7.0</td>
<td>893</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 to 24 hr</td>
<td>5.8</td>
<td>9.4</td>
<td>851</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall CREDO Results**

- **RRR -13.4**
  - *p=NS*
- **RRR 38.6**
  - *p=0.05*
- **RRR 18.5**
  - *p=0.23*

*On top of standard therapy including ASA, PT= Pretreatment*

Duration of Clopidogrel Post Stent Implantation

• Among patients who undergo PCI, the 2005 ACC/AHA/SCAI guidelines recommend:
  • Clopidogrel therapy (in addition to aspirin) for at least one month after bare metal stent implantation
  • Because of delayed endothelial coverage of the stent struts a minimum of three or six months for the sirolimus- and paclitaxel-eluting stents, respectively, and ideally up to twelve months in those who are not at high risk for bleeding
  • The purpose of prolonged Clopidogrel therapy is to minimize the risk of stent thrombosis
Duration of Clopidogrel Post Stent Implantation

- The probable importance of continuing Clopidogrel therapy beyond the minimum periods recommended by the guidelines for drug-eluting stents was illustrated in an angioscopy study of 37 consecutive stented lesions (15 sirolimus stents and 22 bare metal stents).

- There were two main findings:
  - Neointimal coverage was complete in only two of the 15 sirolimus stents.
  - Three had essentially no coverage.
In contrast, neointimal coverage was complete in all 22 bare metal stents.

Thrombi were present in eight stented segments, none of which was seen on angiography.

Thrombi were more common with incomplete neointimal coverage (5 of 13 versus 3 of 24 stents with complete neointimal coverage).
For optimal cost effectiveness and long-term benefit, DES may be restricted to:

- small vessels
- stents <3mm
- bypass grafts
- restenotic lesions
• Objectives

- **Primary**: 
  - Evaluation of the acute & long-term efficacy of Clopidogrel on top of standard therapy (including ASA 75 - 325 mg. / day) vs. standard therapy alone (including ASA 75 - 325 mg. / day) in preventing ischaemic complications (heart attack, stroke & vascular death) in patients with ACS without ST segment elevation.
  1- First Primary: Composite of Vascular death, nonfatal MI or stroke
  2- Second Primary: First Primary Outcome or refractory ischaemia
    (The percentages of patients with in-hospital refractory or severe ischaemia, heart failure & need for revascularization were also evaluated).

- **Secondary**: 
  - Evaluate the safety of Clopidogrel in patients with ACS who are receiving ASA therapy.
Randomized, double-blind, placebo-controlled, multi-center & international (482 centers in 28 countries) trial

**Patients:**
- 12,562 patients with ACS without ST segment elevation
- Assigned within 24 hr. after the onset of symptoms

**Study Drugs:**
- **Clopidogrel**: Loading dose of 300 mg. (immediately) followed by 75 mg od on top of the standard therapy (6,259 patients)
- **Placebo**: on top of the standard therapy (6,303 patients)
CURE: Results

Primary End Point (MI / Stroke / CV Death)

The curves began to diverge within hours and continued to diverge over the course of 12 months.

Placebo + ASA*

Clopidogrel + ASA*

20% RRR

* In combination with standard therapy

p < 0.001
Clopidogrel for all ACS patients?

- If low bleed risk, yes. May not want to start on admission if CABG likely

- Up to one year post-PCI, may be longer!

- In non-revascularized patients it seems like a reasonable addition to ASA
Conclusion

• Clopidogrel is beneficial both early and long-term in patients with ACS

• The benefits are consistently observed in various subgroups examined in addition to other established therapies