Effect of upstream clopidogrel treatment in patients with ST-segment elevation myocardial infarction undergoing primary PCI

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Definition of upstream treatment

- Ambulance
- Referral hospital
- Medical emergency departement
- Cardiac ICU

= ie prior to arrival at the PCI lab
Important trials evaluating treatment benefit of clopidogrel administration in STEMI patients

Fibrinolysis (upstream treatment not evaluated)

- COMMIT Chen et al Lancet 2005

Primary PCI (Upstream clopidogrel vs procedural clopidogrel)

- Fefer et al (n= 383) Am J Cardiol 2009
  Reduced composite endpoint of death, re-infarction, stent thrombosis and heart failure (33.7% vs 21.7%)

- Lev et al (n= 292) Am J Cardiol 2008
  Improved TIMI grade 3
  Reduced rate of reinfarctions at 30 days (0 vs 3.2%, p = 0.04)
  Reduced rate of stent thrombosis at 6 months (0 vs 3.9%, p = 0.02).

Post hoc analysis of HORIZONS-AMI (n= 3 311) Dengas et al JACC 2009

Vlaar et al (meta-analysis) Circulation 2008
Post hoc analysis of HORIZONS-AMI

- Evaluation of 600 mg vs 300 mg loading dose of clopidogrel in STEMI patients undergoing PCI.
- Total of 3,311 patients included.
- Unadjusted lower mortality at 30 days (3.1% vs 2.0%).
- Unadjusted lower rate of reinfarction at 30 days (2.6% vs 1.4%).
- Unadjusted lower rate of major bleeding at 30 days (9.4% vs 6.1%)

Dengas et al JACC 2009
Post hoc analysis of HORIZONS-AMI

• Loading dose of clopidogrel not randomized, left to the physicians discretion.

• Several differences in baseline variables, most notably Killips class II-IV at presentation (11.5% in 300 mg group vs 6.9% in 600 mg group).

• After adjustment for baseline variables only a statistically significant reduction in 30 days MACE was reported.

Dengas et al JACC 2009
Meta-analysis of upstream clopidogrel in STEMI-patients

- 26 pooled randomized trials
- 8429 patients

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>TIMI grade 2/3 flow</td>
<td>1.53</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.52</td>
</tr>
<tr>
<td>Death/reinfarction</td>
<td>0.50</td>
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</tbody>
</table>

OR is for the occurrence of TIMI grade 2/3 flow, mortality, and death/reinfarction for pretreatment with clopidogrel.

Vastly different trial designs, PCI strategies and pharmacological therapies
Current ESC and AHA/ACC guidelines

**ESC - 2008**

“Although clopidogrel is less studied in patients with STEMI treated with primary PCI, there is abundant evidence on its usefulness as an adjunctive antiplatelet therapy on top of aspirin in patients undergoing PCI. Based on these data, clopidogrel should be given as soon as possible to all patients with STEMI undergoing PCI.”

Class I, Level of Evidence C

**AHA/ACC - 2009**

“A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI.”

Class I, Level of Evidence C
Effect of upstream clopidogrel treatment in patients with ST-segment elevation myocardial infarction undergoing primary PCI.

Primary endpoint: Combined composite endpoint of 1-year death/reinfarction.

Secondary endpoints: Death
Reinfarction
Stent thrombosis.
Methods - Databases

• The Swedish Coronary Angiography and Angioplasty Register (SCAAR) was used to identify patients according to inclusion criteria (N= 13 847).

• Data on death were obtained from the Swedish national population register.

• Data regarding previous medical history and patient follow up were obtained from the Swedish Hospital Discharge Register.

• Data regarding discharge medications obtained from RIKS-HIA.

Follow-up of events until 31 December 2008.
Inclusion/exclusion criteria and statistical methods

- STEMI patients undergoing primary PCI between 2003 and 2008 included.
- All patients required to have received aspirin upstream.
- Patients with prior coronary angiography excluded.
- Patients with concomitant warfarin medication excluded.
- Crude event rates presented by Kaplan-Meier curves.
- Cox proportional hazards models with propensity scoring methods to adjust for baseline variables.
## Baseline characteristics

<table>
<thead>
<tr>
<th>Total = 13 847</th>
<th>Upstream Clopidogrel treatment</th>
<th>No upstream clopidogrel treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.8 yrs</td>
<td>67.0 yrs</td>
</tr>
<tr>
<td>Male sex</td>
<td>70.9%</td>
<td>68.4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35.1%</td>
<td>36.6%</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>40.1%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>25.9%</td>
<td>25.5%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>34.0%</td>
<td>31.9%</td>
</tr>
<tr>
<td>Upstream heparin treatment</td>
<td>24.8%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Upstream LMWH</td>
<td>21.3%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Upstream GpIIb/IIIa-inhibitor</td>
<td>12.6%</td>
<td>14.6%</td>
</tr>
<tr>
<td>GpIIb/IIIa-inhibitor during procedure</td>
<td>68.3%</td>
<td>67.8%</td>
</tr>
<tr>
<td>Previous Statin treatment</td>
<td>10.8%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Previous ACE inhibitor treatment</td>
<td>9.4%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Previous Betablocker treatment</td>
<td>20.8%</td>
<td>25.4%</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>3.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>5.3%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Previous kidney failure</td>
<td>0.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Previous COPD</td>
<td>5.6%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Previous dementia</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>2.2%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4.4%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Previous diabetes</td>
<td>14.4%</td>
<td>15.2%</td>
</tr>
<tr>
<td>Previous cancer</td>
<td>2.5%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Treated vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>40.2%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>44.5%</td>
<td>44.3%</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>14.3%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Left main stem</td>
<td>1.0%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
• Unadjusted absolute risk reduction of 4.1%
• After adjustment with propensity scoring, significant relative risk reduction at one year (HR 0.83 95% CI = 0.73 - 0.95).
• Unadjusted absolute risk reduction of 2.5%.
• Significant propensity adjusted relative risk reduction at 30 days (HR 0.77 95% CI 0.60-0.99).
• Significant propensity adjusted relative risk reduction at one year (HR 0.79 95% CI 0.65-0.96)
Reinfarction

- Unadjusted absolute risk reduction of 1.8% at one year.
- Non-significant adjusted risk reduction at 30 days (HR 0.95 95% CI 0.74-1.21).
- Non-significant adjusted risk reduction at one year (HR 0.87 95% CI 0.73-1.04).
Discharge rates of clopidogrel and aspirin

<table>
<thead>
<tr>
<th></th>
<th>No upstream clopidogrel</th>
<th>Upstream clopidogrel</th>
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<tbody>
<tr>
<td>Aspirin at discharge</td>
<td>93.2%</td>
<td>95.5%</td>
</tr>
<tr>
<td>Clopidogrel at discharge</td>
<td>89.2%</td>
<td>93.8%</td>
</tr>
</tbody>
</table>

- High degree of clopidogrel and aspirin at discharge.
- New cox-regression analysis with propensity scoring where only patients on dual anti-platelet therapy upon discharge were included.
- Similar propensity score adjusted risk reductions for composite endpoint of death/MI (HR 0.86 95% CI: 0.74-1.00).
- Similar propensity score adjusted risk reductions for one year mortality (HR 0.79 95% CI: 0.61-1.01).
Subgroups analysis – year of procedure

Consistent trends in mortality reduction over time.
- Interaction GPIIb/IIIa-inhibitors.
- Underweight patients.
Stent thrombosis?

- No effect on stent thrombosis.

- Hazard ratio of 1.04 (95% CI 0.58-1.89) for the clopidogrel upstream group.

- Angiographically verified stent thrombosis.
Limitations

• Register study.
• Exact dose of upstream clopidogrel not known (300 – 600 mg).
• Differences in baseline variables pertaining to upstream LMWH/Heparin.

Advantages

• Large sample size (n= 13 847).
• Solid follow up.
• Baseline correction using propensity scoring methods.
Conclusions

• Upstream treatment of clopidogrel in STEMI patients undergoing primary PCI reduces one year composite endpoint of death/myocardial reinfarction.

• Upstream treatment of clopidogrel in STEMI patients undergoing primary PCI reduces total mortality both short-term (30-day) as well as long-term mortality (1 year).

• Patients already having received GpIIb/IIIa-blockers upstream as well as patients under 60 kg are neutral in treatment benefit.