Proton Pump Inhibitors In Patients Treated With Aspirin And Clopidogrel

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No potential conflict of interest
Background

- Clopidogrel is a potent antiplatelet agent (through P2Y12 adenosine diphosphate receptor inhibition)
- Treatment with clopidogrel in addition to ASA has been proven to reduce cardiovascular events after coronary stenting and following the whole spectrum of acute coronary syndrome (ACS):
Background

- Clopidogrel is a prodrug converted to its metabolite by cytochrome P-450 isoenzymes (mainly CYP219)
- Numerous drugs are known to inhibit P-450 isoenzymes, such as proton pump inhibitors (PPIs)
- Mechanistic studies first suggested that PPIs might reduce the antiplatelet effect of clopidogrel, raising the question about the clinical significance of PPI – clopidogrel interaction
Recent published studies showed that the addition of a PPI to clopidogrel in ACS patients significantly increased the risk of recurrent cardiovascular events:


Conflicting reports and expert opinions exist about the PPI-clopidogrel interaction and mainly its clinical significance.
Aims

- Evaluate the prescription of a PPI in addition to ASA and clopidogrel in ACS patients
- Compare the clinical characteristics and therapeutic strategies of patients medicated or not with a PPI
- Determine if the addition of a PPI to ASA and clopidogrel was associated with a worst prognosis
Methods

- Retrospective study - a total of 959 patients admitted with ACS and discharged with ASA and clopidogrel, from January 2004 to April 2008, were reviewed – we chose to analyze patients on ASA and clopidogrel as they represented the majority of ACS patients as well as the more relevant clinical scenario.

- Patients were classified in two groups according to the association or not of a PPI to ASA and clopidogrel.
Methods

- All PPIs were considered except pantoprazole
  - Although pantoprazole can be metabolized by CYP219 isoenzyme, it preferentially uses other routes
- The prescription and clinical records were used to define exposure to PPI during dual antiplatelet therapy
Results

- 959 patients on ASA and clopidogrel
  - 59 without information
  - 29 on Pantoprazole
  - 297 on PPI
  - 574 not on PPI
Results
Baseline characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>61.1 ± 13.2 years</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>1</td>
<td>65.7 ± 13.2 years</td>
<td></td>
</tr>
</tbody>
</table>
Results
Baseline characteristics

* $p < 0.05$
Results
Baseline characteristics

* $p < 0.05$
## Results

### At presentation

<table>
<thead>
<tr>
<th></th>
<th>With PPI n=297</th>
<th>Without PPI n=574</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>36.7%</td>
<td>36.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Killip Class &gt; 1</td>
<td>24.1%</td>
<td>15.3%</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean SBP (mmHg ±SD)</td>
<td>138 ± 27</td>
<td>140 ± 27</td>
<td>NS</td>
</tr>
<tr>
<td>Mean HR (bpm ±SD)</td>
<td>76 ± 18</td>
<td>75 ± 19</td>
<td>NS</td>
</tr>
</tbody>
</table>
Results

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>PPI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin at admission</td>
<td>14.1 ± 1.8 g/dl</td>
<td>13.7 ± 2.1 g/dl</td>
<td>0.001</td>
</tr>
</tbody>
</table>

p = 0.001
Results

In-hospital medical treatment

*Considering only STEMI patients

*Reperfusion Therapy*

Beta Blocker

ACE Inhibitor

Statin

With PPI

Without PPI

*Considering only STEMI patients*
Results

* Defined as three-vessel or left main disease
Results

ACS with ST elevation

ACS without ST elevation

Coronary Angiography

PCI

With PPI

Without PPI

With PPI

Without PPI
Results
Medical treatment at discharge

<table>
<thead>
<tr>
<th></th>
<th>With PPI</th>
<th>Without PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Blocker</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Statin</td>
<td>100%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Independent predictors of PPI prescription

Age >60

OR (95%CI)
1.9 (1.2 - 2.92)

Haemoglobin at admission

0.8 (0.71 - 0.9)
Results
Six-month follow-up

Composite Endpoint* with and without PPI

* Defined as all-cause mortality or rehospitalization for ACS
Results
Multivariate analysis
Composite Endpoint

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (1.03 – 1.09)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>2.57 (1.3 – 5.01)</td>
</tr>
<tr>
<td>Haemoglobin at admission</td>
<td>0.84 (0.72 – 0.97)</td>
</tr>
<tr>
<td>Killip Class &gt;1</td>
<td>1.9 (1.1 – 3.27)</td>
</tr>
<tr>
<td>PPI use</td>
<td>0.8 (0.47 – 1.33)</td>
</tr>
</tbody>
</table>
Results
Six-month follow-up Stratification

ACS with ST elevation

ACS without ST elevation

PCI

No PCI
Results
Multivariate analysis
Composite Endpoint/Stratification

ACS with ST elevation
- PPI use

ACS without ST elevation
- PPI use

PCI
- PPI use

No PCI
- PPI use
Conclusions

- Patients on PPI were older, more often had renal insufficiency and less often had smoking history and history of previous revascularization; they more often presented with Killip class >1 and lower haemoglobin at admission.

- There were no differences regarding in-hospital or discharge medical treatment, invasive procedure and coronary revascularization.

- Independent and positive predictors of PPI prescription were older age and lower haemoglobin at admission.
Conclusions

- PPI prescription in addition to aspirin and clopidogrel was not associated with a worst prognosis in patients with ACS, even after adjustment for potential confounding factors.
Limitations

- This was an observational and nonrandomized study, and as such, both identified and unidentified confounders may have influenced the results.
- Prescription and clinical records might be incomplete.
- Therapeutic compliance was not assessed (namely ASA, clopidogrel, and PPI).
- The number of patients assessed may have been insufficient.
Limitations

- Randomized trials would be the preferential way to obtain definite conclusions about the clinical relevance of PPI-clopidogrel interaction
Thank you!