“Διαχείριση των Οξέων Στεφανιαίων Συνδρόμων: Ο ρόλος των αντιαιμοπεταλιακών και η θέλτιστη διάρκεια της διπλής αντιαιμοπεταλιακής αγωγής”

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Thrombotic events

Bleeding Risk

DAPT duration
To disclaimer:
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Ο ομιλητής έχει λάβει οικονομική ενίσχυση με μορφή honoraria και Research Grants από
ASTRAZENECA
TERUMO DIAGNOSTICS
BIOTRONIK
Orbus Neich
ELPEN
The role of platelets in atherothrombosis
Most PLTs never undergo firm adhesion to the endothelium.
This changes after plaque rupture or erosion.

Sub-endothelial layers are exposed

or in uncovered stent struts
Platelet activation and adhesion begins
Rolling at high shear

Collagen / vW / vitronectin/ laminin, fibronectin
Collagen / vW / vitronectin/ laminin, fibronectin
Collagen / vW / vitronectin / laminin, fibronectin
Collagen / vW / vitronectin/ laminin, fibronectin
Collagen / vW / vitronectin / laminin, fibronectin
Collagen / vW / vitronectin/ laminin, fibronectin
Collagen / vW / vitronectin / lamin / fibronectin
Collagen / vW / vitronectin / laminin / vitronectin
Collagen / vW / vitronectin / laminin, fibronectin
Collagen / vW / vitronectin/ laminin / vitronectin

GP Ib/V/IX
ADP RECEPTORS P2Y12R AND P2Y1R

- Dense granule release from adjacent PLTs
- P2Y12R
- ADP
- P2Y1R
- Gi
- cAMP
- Ca++
- GPⅡb/Ⅲa inactive
- GPⅡb/Ⅲa active
- Pro-Coagulation
- TXA2 generation
- Enhancement of TXA2/TH PLT activation
- thick platelet
- giant granule release
- alpha granule release
- (P-selectin expression)
- PLT recruitment
- Pro-Coagulation
Non-infarct related coronary artery

Single Hit

Unable to proceed to NETosis

Infarct related coronary artery

Vessel occlusion (STEMI)

Resting platelet

Activated platelet

Inflammatory stimuli

Neutrophil

Tissue Factor (TF)

Occlusive Thrombus

Plaque rupture/vascular TF
Antiplatelets in acute coronary syndromes
Inhibition of platelet function and clinical outcomes (CVD prevention by ASPIRIN)

<table>
<thead>
<tr>
<th>Event</th>
<th>6 primary prevention trials</th>
<th>16 secondary prevention trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event ($\chi^2 = 4.7; p=0.03$)</td>
<td>Male: 635 (0.57)</td>
<td>Male: 880 (4.70)</td>
</tr>
<tr>
<td></td>
<td>Female: 299 (0.14)</td>
<td>Female: 115 (2.59)</td>
</tr>
<tr>
<td></td>
<td>Total: 934 (0.28)</td>
<td>Total: 995 (4.30)</td>
</tr>
<tr>
<td>Ischaemic stroke ($\chi^2 = 3.3; p=0.08$)</td>
<td>Male: 141 (0.15)</td>
<td>Male: 95 (0.51)</td>
</tr>
<tr>
<td></td>
<td>Female: 176 (0.05)</td>
<td>Female: 45 (1.04)</td>
</tr>
<tr>
<td></td>
<td>Total: 317 (0.11)</td>
<td>Total: 140 (0.61)</td>
</tr>
<tr>
<td>Serious vascular event* ($\chi^2 = 0.0; p=0.9$)</td>
<td>Male: 1063 (0.95)</td>
<td>Male: 1255 (6.88)</td>
</tr>
<tr>
<td></td>
<td>Female: 608 (0.28)</td>
<td>Female: 259 (5.88)</td>
</tr>
<tr>
<td></td>
<td>Total: 1671 (0.51)</td>
<td>Total: 1505 (6.69)</td>
</tr>
</tbody>
</table>

99% CI or $\Rightarrow$ 95% CI

*Significant events
The combination of aspirin and clopidogrel was superior to aspirin alone in preventing vascular events in cardiac patients with **unstable angina**.
or in those requiring percutaneous coronary intervention (PCI)..

JAMA, 2002
Limitations of clopidogrel therapy

- Variable platelet-inhibition response
- Slow onset of action (Pro-drug)
  - Irreversibly binds to platelet P2Y_{12} receptors

New antiplatelet agents
Ticagrelor: important characteristics

- Direct acting; does not require metabolic activation
  - A rapid onset of inhibitory effect
  - Greater and more consistent platelet inhibition than clopidogrel
    - Less variability in individual response
- Reversibly binds to the P2Y$_{12}$ receptor

PLATO – study design

ACS on aspirin randomized
(N=18,624)

Clopidogrel
300 mg / 75 mg

Ticagrelor
180 mg / 90 mg x 2

12 mo

Efficacy Endpoints: CVD, MI or stroke
Total mortality, MI or stroke
Death from any cause

Safety Endpoints: Total major bleeding

PLATO: efficacy endpoint:

(composite of CV death, MI or stroke)

Cumulative incidence (%)

Months after randomization

Clopidogrel

Ticagrelor

(HR, 0.84; 95% CI, 0.77-0.92; P<0.001)

PLATO: primary safety endpoint

K-M estimated rate (% per year)

Days from first IP dose

- Ticagrelor: 11.6%
- Clopidogrel: 11.2%

(HR 1.04; 95% CI, 0.95-1.13; P=0.43)

P=NS
### PLATO primary efficacy endpoint and incidence of stent thrombosis:

<table>
<thead>
<tr>
<th>Patients with intent for invasive treatment*</th>
<th>Ticagrelor (n=6732)</th>
<th>Clopidogrel (n=6676)</th>
<th>HR for ticagrelor (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Definite</strong></td>
<td>71 (1.3)</td>
<td>106 (1.9)</td>
<td>0.67 (0.50-0.91)</td>
<td><strong>0.0091</strong></td>
</tr>
<tr>
<td><strong>Probable + Definite</strong></td>
<td>118 (2.1)</td>
<td>158 (2.8)</td>
<td>0.75 (0.59-0.95)</td>
<td><strong>0.0167</strong></td>
</tr>
<tr>
<td><strong>Possible + Probable + Definite</strong></td>
<td>155 (2.8)</td>
<td>202 (3.6)</td>
<td>0.77 (0.62-0.95)</td>
<td><strong>0.0131</strong></td>
</tr>
</tbody>
</table>

*Intent for invasive or medical management declared prior to randomization.

Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

TRITON–TIMI 38

**Primary Efficacy End Point**

- Clopidogrel: 12.1 events
- Prasugrel: 9.9 events
  - Hazard ratio: 0.81
  - 95% CI: 0.73–0.90
  - P < 0.001
  - ↓ 138 Events

**Key Safety End Point**

- Clopidogrel: 2.4 events
- Prasugrel: 1.8 events
  - Hazard ratio: 1.32
  - 95% CI: 1.03–1.68
  - P = 0.03
  - ↑ 35 Events
<table>
<thead>
<tr>
<th>End Point</th>
<th>Prasugrel (N=6741)</th>
<th>Clopidogrel (N=6716)</th>
<th>Hazard Ratio for Prasugrel (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG-related TIMI major bleeding (key safety end point)</td>
<td>146 (2.4)</td>
<td>111 (1.8)</td>
<td>1.32 (1.03–1.68)</td>
<td>0.03</td>
</tr>
<tr>
<td>Related to instrumentation</td>
<td>45 (0.7)</td>
<td>38 (0.6)</td>
<td>1.18 (0.77–1.82)</td>
<td>0.45</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>92 (1.6)</td>
<td>61 (1.1)</td>
<td>1.51 (1.09–2.08)</td>
<td>0.01</td>
</tr>
<tr>
<td>Related to trauma</td>
<td>9 (0.2)</td>
<td>12 (0.2)</td>
<td>0.75 (0.32–1.78)</td>
<td>0.51</td>
</tr>
<tr>
<td>Life-threatening†</td>
<td>85 (1.4)</td>
<td>56 (0.9)</td>
<td>1.52 (1.08–2.13)</td>
<td>0.01</td>
</tr>
<tr>
<td>Related to instrumentation</td>
<td>28 (0.5)</td>
<td>18 (0.3)</td>
<td>1.55 (0.86–2.81)</td>
<td>0.14</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>50 (0.9)</td>
<td>28 (0.5)</td>
<td>1.78 (1.12–2.83)</td>
<td>0.01</td>
</tr>
<tr>
<td>Related to trauma</td>
<td>7 (0.1)</td>
<td>10 (0.2)</td>
<td>0.70 (0.27–1.84)</td>
<td>0.47</td>
</tr>
<tr>
<td>Fatal‡</td>
<td>21 (0.4)</td>
<td>5 (0.1)</td>
<td>4.19 (1.58–11.11)</td>
<td>0.002</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>64 (1.1)</td>
<td>51 (0.9)</td>
<td>1.25 (0.87–1.81)</td>
<td>0.23</td>
</tr>
<tr>
<td>Intracranial</td>
<td>19 (0.3)</td>
<td>17 (0.3)</td>
<td>1.12 (0.58–2.15)</td>
<td>0.74</td>
</tr>
<tr>
<td>Major or minor TIMI bleeding</td>
<td>303 (5.0)</td>
<td>231 (3.8)</td>
<td>1.31 (1.11–1.56)</td>
<td>0.002</td>
</tr>
<tr>
<td>Bleeding requiring transfusion§</td>
<td>244 (4.0)</td>
<td>182 (3.0)</td>
<td>1.34 (1.11–1.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG-related TIMI major bleeding¶</td>
<td>24 (13.4)</td>
<td>6 (3.2)</td>
<td>4.73 (1.90–11.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Prasugrel vs. Clopidogrel

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Prasugrel Events</th>
<th>Prasugrel Total</th>
<th>Clopidogrel Events</th>
<th>Clopidogrel Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUMBO</td>
<td>3</td>
<td>650</td>
<td>2</td>
<td>254</td>
<td>1.9%</td>
<td>0.58 [0.10, 3.52]</td>
</tr>
<tr>
<td>TRITON TIMI-38</td>
<td>146</td>
<td>6741</td>
<td>111</td>
<td>6716</td>
<td>98.1%</td>
<td>1.32 [1.03, 1.69]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>7391</strong></td>
<td><strong>6970</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.30 [1.01, 1.66]</strong></td>
</tr>
</tbody>
</table>

Total events: 149 \(\pm 113\)

Heterogeneity: \(\tau^2 = 0.00; \chi^2 = 0.77, \text{df} = 1 (P = 0.38); I^2 = 0\%

Test for overall effect: \(Z = 2.07 (P = 0.04)\)

### Ticagrelor vs. Clopidogrel

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ticagrelor Events</th>
<th>Ticagrelor Total</th>
<th>Clopidogrel Events</th>
<th>Clopidogrel Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISPERSE-2</td>
<td>46</td>
<td>657</td>
<td>26</td>
<td>327</td>
<td>28.7%</td>
<td>0.87 [0.53, 1.44]</td>
</tr>
<tr>
<td>PLATO</td>
<td>221</td>
<td>9235</td>
<td>177</td>
<td>9186</td>
<td>71.3%</td>
<td>1.25 [1.02, 1.52]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>9892</strong></td>
<td><strong>9513</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.13 [0.82, 1.55]</strong></td>
</tr>
</tbody>
</table>

Total events: 267 \(\pm 203\)

Heterogeneity: \(\tau^2 = 0.03; \chi^2 = 1.70, \text{df} = 1 (P = 0.19); I^2 = 41\%

Test for overall effect: \(Z = 0.73 (P = 0.47)\)
Effectiveness vs Bleeding Risk in Antiplatelet Regiments

When increased protection is needed?
High risk stents
55y F/ Unstable Angina / SLE
71y F/ Inferior MI / Prior Lysis

Low risk stents..
Low risk stents..
Low risk stents... in High risk patients...

- (Generally outnumber stenotic plaques)
Initial Culprit Lesion vs New Atherosclerotic Plaque Recurrent Events

- Culprit lesion-related events 12.9%
- Non-culprit lesion-related events 11.6%
- Indeterminate events 2.7%

ACS, acute coronary syndrome; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; PROSPECT, Providing Regional Observations to Study Predictors of Events in the Coronary Tree.
Πολλαπλές πλάκες

Αγγειακή φλεγμονή

Υπολειπόμενη αντιδραστικότητα αιμοπεταλίων

Οξύ στεφανιαίο σύνδρομο

ΣΤΕΦΑΝΙΟΓΡΑΦΙΑ
1 in 5 patients post-MI, will suffer an MI, stroke or death within 3 years

APOLLO 4-country analysis : Adjusted Incidence*

**MI/stroke/all-cause death**

<table>
<thead>
<tr>
<th>Country</th>
<th>Adjusted Risk (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>19.8 (19.4–20.2)</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>18.2 (17.6–18.9)</td>
<td></td>
</tr>
<tr>
<td>England</td>
<td>21.3 (18.2–24.2)</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>16.7 (14.3–19.2)</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up (years)
67y F, inf MI / prior Lysis / 2010
67y F, inf MI / prior Lysis / 2010
67→70y F, Unstable angina/2013
67→70y F, Unstable angina/ 2013
67→ 70y → 72y F, Unstable angina/ 2015
67→ 70y → 72y F, Unstable angina/ 2015
ACS (patient reaction overtime..)

Plaque reaction → Platelet reaction → Vessel reaction

Extended antiplatelet protection..?
Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Long term high risk patients ➔ Ticagrelor in long term use

April 2017 - no intervention

65y F, Inf MI
Potent antiplatelet drugs (accelerated nature of atherosclerosis)
47 y Male/ inf MI / shock
High Risk Stents in High Risk Patient
High Risk Stents in High Risk Patient
PEGASUS-TIMI 54: Inclusion Criteria

• Age ≥50 years old
• History of MI + high risk

PEGASUS-TIMI 54: Major Exclusion Criteria

- Μη ανοχή του φαρμάκου (παρενέργειες)
- Bleeding disorder, history of ischaemic stroke or intracranial bleeding, central nervous system tumour or intracranial vascular abnormality
- Gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days
- High risk of bradycardic events
- Severe hepatic or renal disease

Primary Endpoint

21,162 patients with MI 1-3 years prior and treated with low-dose aspirin

Median follow-up 33 months

- Placebo (9.0%)
- Ticagrelor 90 (7.8%)
- Ticagrelor 60 (7.8%)

CV Death, MI, or Stroke (%)

- Ticagrelor 90 mg
  HR 0.85 (95% CI 0.75 – 0.96)
  P=0.008

- Ticagrelor 60 mg
  HR 0.84 (95% CI 0.74 – 0.95)
  P=0.004

Bonaca MP et al. and Sabatine MS. *NEJM* 2015;372:1791-800
High risk stents in Low risk patients (Location)
Low risk stents in High risk patients (Recurrent events)
High risk stents in High risk patients (Location & events)
Long term use
48 y  BMI>50

Osteomyelitis / DVT Right Foot
IVC filter
On Anticoagulants
Unstable Angina
High risk stent (Location) – long term use in high Bleeding Risk patient
PEGASUS-TIMI 54: Major Exclusion Criteria

- Planned use of anticoagulant therapy during the study period
- Bleeding disorder, history of ischaemic stroke or intracranial bleeding, central nervous system tumour or intracranial vascular abnormality
- Gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days
- High risk of bradycardic events
- Severe hepatic or renal disease

Θητότητα μετά από θρόμβωση του stent

ASA
Clopidogrel
Rivaroxaban

3m
Clopidogrel
Rivaroxaban

6m
?
Rivaroxaban
Conclusions

**ACS**

Patient Risk Assessment (accelerated atherosclerosis)
Stent Risk Assessment (localization)
Thrombotic Risk Assessment (Recurrent events)

Bleeding Risk Assessment (mainly use of antiCoagulants)

Potency of antiplatelet agent
Duration of antiplatelet agent

*Maintenance antithrombotic strategy after ST-elevation myocardial infarction*

In high ischaemic-risk patients who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to 3 years. The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation.