Monitoring Persistent Platelet Reactivity in Patients with Unprotected Left Main Stenting

Impact of Platelet Function Monitoring and Optimization of Dual Antiplatelet Therapy in Patients With Unprotected Left Main Disease Treated by Percutaneous Coronary Intervention: The ALMA Registry

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Dr. Jean-Guillaume DILLINGER has conflict of interest with:

* MSD
* Astra Zeneca
* BMS
* Shering plough
* Servier medical
* Lilly – Daishi Sankyo
* Abbott vascular
* Terumo
* Cordis
* Medtronic
Background

Long-Term Safety and Efficacy of Percutaneous Coronary Intervention With Stenting and Coronary Artery Bypass Surgery for Multivessel Coronary Artery Disease

A Meta-Analysis With 5-Year Patient-Level Data From the ARTS, ERACI-II, MASS-II, and SoS Trials

Death at 5 years

Death/Stroke/MI at 5 years

High Residual Platelet Reactivity After Clopidogrel Loading and Long-Term Clinical Outcome After Drug-Eluting Stenting for Unprotected Left Main Coronary Disease

Cardiac Survival (%)

- Low residual platelet reactivity (LRPR)
- High residual platelet reactivity (HRPR)

No at risk
- Low residual platelet reactivity: 175
- High residual platelet reactivity: 40

Time (years)

- 0: 118
- 1: 69
- 2: 15
- 3: 7

p = 0.005

92.0 ± 3.1

71.7 ± 10.4

Objective and Design

• **Objective**
  - to determine the rate and potential clinical impact of persistent platelet reactivity (PPR) under dual antiplatelet therapy in patients treated by angioplasty for unprotected left main disease (ULMD).

• **Inclusion criteria:**
  - patients with stable or unstable angina and/or documented ischemia
  - ≥50% de novo stenosis of ULMD

• **Exclusion criteria:**
  - Acute coronary syndrome with ST elevation
  - Cardiogenic shock or out hospital cardiac arrest
  - Impossibility to perform aggregation assessment or to use DAPT
Flow-chart

294 Unprotected left main disease (ULMD) January 2007- December 2010

- 33 ULMD with medical treatment
- 142 ULMD with PCI
- 119 ULMD with bypass surgery
- 17 ULMD with emergency PCI
- 125 ULMD with PCI

ALMA prospective registry

ALMA 1 period
64 ULMD with PCI
January 2007 – December 2008

ALMA 2 period
Systematic platelet aggregation monitoring
61 ULMD with PCI
January 2009 – December 2010

Follow-up at 1 Year: MACCE
death, stroke, myocardial infarction, and repeat revascularization
Methods

Basal antithrombotic therapy in ALMA-1

• Aspirin: non-enteric coated lysine acetylsalicylate, 75-250mg/j
• Clopidogrel 75 mg/day with a loading dose of 300 to 600 mg
  In patients weighing >80 kg or with type 2 diabetes, 150 mg/day was administered for the first month after PCI followed by 75mg/day.

Basal antithrombotic therapy in ALMA-2

• Aspirin: non-enteric coated lysine acetylsalicylate, 75-250mg/j
• Use of Clopidogrel was similar in ALMA-2 until PPR measurement
• From January 2010, prasugrel in the case of acute coronary syndrome
• Aspirin or clopidogrel at least 48 hours before PPR assessment
Platelet persistent reactivity (PPR) assessment

PPR for aspirin and treatment adaptation

• Aspirin-PPR = *aggregation intensity (MAI) ≥20%* measured by aggregometry (LTA-AA).

⇒ aspirin was given twice a day: 75mg morning and 75mg evening

PPR for clopidogrel and treatment adaptation

• Clopidogrel-PPR = *MAI ≥67% measured by LTA-ADP and VASP index ≥50%*

⇒ increase clopidogrel to 150mg/day and, from January 2010, to switch to prasugrel 10 mg/day

Dual antiplatelet therapy (DAPT) for at least 1 month in the case of a bare metal stent (BMS) and 12 months in the case of a DES or acute coronary syndrome.
Time dependance of aspirin biological efficacy

Maximal intensity LTA with 0.5 mg/ml AA (%)

- Intensity <20% after 24h
- Intensity ≥20% after 24h
- TBX2 >2.45ng/ml at 24 h

Time after last aspirin intake (h):

Aspirin twice a day and biological efficacy

Light transmission aggregometry - LTA-AA 0.5mg/ml

## Results

<table>
<thead>
<tr>
<th></th>
<th>ALMA-1 (n=64)</th>
<th>ALMA-2 (n=61)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, (mean±SD)</strong></td>
<td>71±13</td>
<td>68±12</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Men, % (n)</strong></td>
<td>68.8 (44)</td>
<td>81.9 (50)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>31.3 (20)</td>
<td>42.6 (26)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Prior myocardial infarction, % (n)</strong></td>
<td>14.0 (9)</td>
<td>13.1 (8)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Prior angioplasty, % (n)</strong></td>
<td>32.8 (21)</td>
<td>39.3 (24)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>NSTEMI, % (n)</strong></td>
<td>39.0 (25)</td>
<td>34.4 (21)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>LVEF, %, mean±SD</strong></td>
<td>55±10</td>
<td>53±10</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Additive EuroSCORE, mean±SD</strong></td>
<td>5.3±3.2</td>
<td>5.1±3.9</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>SYNTAX Score, mean±SD</strong></td>
<td>23.2±10.2</td>
<td>22.3±8.3</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Aspirin dose, mg, mean±SD</strong></td>
<td>176±66</td>
<td>159±56*</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Clopidogrel, % (n)</strong></td>
<td>100 (64)</td>
<td>84 (51)*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Prasugrel, % (n)</strong></td>
<td>NA</td>
<td>16 (10) *</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Radial approach, % (n)</strong></td>
<td>70.3 (45)</td>
<td>93.4 (57)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Drug Eluting Stent, % (n)</strong></td>
<td>62.5 (40)</td>
<td>78.6 (48)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Bare Metal Stent, % (n)</strong></td>
<td>37.5 (24)</td>
<td>21.3 (13)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Glycoprotein IIb/IIIa inhibitor, % (n)</strong></td>
<td>46.8 (30)</td>
<td>26.2 (16)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Lesion treated per patients, mean±SD</strong></td>
<td>2.3±1.3</td>
<td>2.1±1.1</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Total stent length, mm, mean±SD</strong></td>
<td>47±37</td>
<td>48±37</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Complete revascularization, % (n)</strong></td>
<td>53.1 (34)</td>
<td>57.3 (35)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

* Before platelet reactivity assessment in ALMA-2
Adaptation of DAPT

- Aspirin N=61
  - 28% of Aspirin related PPR
  - Aspirin Twice a day N=17

- Clopidogrel N=40
  - 30% of Clopidogrel related PPR
  - Clopidogrel HD N=16
    - N=8
    - N=6

- Clopidogrel HD N=11
  - 27% of Clopidogrel HD related PPR
  - Prasugrel N=10
    - 10% of Prasugrel related PPR
  - Prasugrel N=19
Results

A

Freedom from event (%)

MACCE

p=0.04

Time (months)

0 3 6 9 12

B

Freedom from event (%)

Cardiovascular death / stent thrombosis

p=0.02

Time (months)

0 3 6 9 12
### MACCE at 1 year

<table>
<thead>
<tr>
<th>Event</th>
<th>ALMA-1 (n=64)</th>
<th>ALMA-2 (n=61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE, % (n)</td>
<td>20.8 (13)</td>
<td>8.2 (5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiovascular death, % (n)</td>
<td>6.2 (4)</td>
<td>0 (0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stent thrombosis, % (n)</td>
<td>4.7 (3)</td>
<td>0 (0)</td>
<td>0.08</td>
</tr>
<tr>
<td>CV Death or Stent thrombosis, % (n)</td>
<td>8.3 (5)</td>
<td>0 (0)</td>
<td>0.02</td>
</tr>
<tr>
<td>MI, % (n)</td>
<td>7.8 (5)</td>
<td>3.3 (2)</td>
<td>0.24</td>
</tr>
<tr>
<td>CVA, % (n)</td>
<td>1.6 (1)</td>
<td>1.6 (1)</td>
<td>0.93</td>
</tr>
<tr>
<td>Death/MI/CVA, % (n)</td>
<td>10.3 (6)</td>
<td>4.9 (3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Revascularization, % (n)</td>
<td>13.1 (8)</td>
<td>6.6 (4)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Results are presented as percentages from Kaplan-Meier analysis and numbers of event. *P* values are from log-rank test.

MACCE indicates major cardiac and cerebrovascular events; CV, cardiovascular; MI, myocardial infarction; CVA, cerebrovascular accident.
# Multivariate baseline predictors of one-year MACCE

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Coefficient</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet reactivity monitoring</td>
<td>-1.61</td>
<td>0.20 (0.05-0.82)</td>
<td>0.03</td>
</tr>
<tr>
<td>Radial access</td>
<td>-1.25</td>
<td>0.29 (0.09-0.84)</td>
<td>0.04</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>0.06</td>
<td>1.06 (1.00-1.14)</td>
<td>0.08</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>0.31</td>
<td>1.37 (1.09-1.72)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Cox proportional-hazards regression. Data with p<0.10 are presented.
Limitations

ALMA registry

• Small cohort (n=125)
• Not randomized registry with 2 different periods
• 2nd generation of DES (OR=0.92; [0.36-2.35]; p=0.78)
• Prasugrel in 31% of patients in ALMA-2 (OR=0.63; [0.21-1.82]; p=0.39)

Aggregations tests and cut-off

• Light transmission aggregometry: the gold standard
• Use of aspirin twice not evaluated clinically
• No measurement of PPR after DAPT adaptation.
In this real-life study,

• PPR for aspirin or clopidogrel is frequent in patients referred for ULMD angioplasty.

• Monitoring PPR and the optimization of DAPT appears to significantly decrease the rate of acute events such as cardiovascular death and ST.

• Further prospective studies are required.
Merci de votre attention!
Aggregation tests results in the population (n=51) before left main PCI according to antiplatelet treatment.
Impaired suppression of platelet cyclooxygenase-1
Inadequate dose of aspirin

Drug interactions
- Concurrent intake of NSAIDs, preventing access of aspirin to the COX-1 binding site

Increased turnover of platelets
- Immature platelets unexposed to aspirin during the 24-h dose interval

Genetic polymorphisms
- Polymorphisms of COX-1

Bypass of aspirin’s inhibition of platelet cyclooxygenase-1 (aspirin bypass)
Alternative sources of thromboxane production
- Non-platelet sources of thromboxane biosynthesis (e.g., monocyte COX-2)

Increased turnover of platelets
- Immature platelets containing measurable levels of COX-2

Genetic polymorphisms
- Polymorphisms of COX-2
Concept de « Time dependence » de l’efficacité de l’aspirine

- Durée de l’aspirine courte (≈ 2 h)
- Les nouvelles plaquettes sanguines après cette période ne sont pas acetylées jusqu’à la nouvelle prise d’aspirine
- Chez les volontaires sains, 12-15% de nouvelles plaquettes en 24 heures sans possibilité de déclencher une agrégation significative.
- En cas de turnover plaquettaire accéléré, >20% de nouvelles plaquettes capables de déclencher une agrégation significative.
- Augmenter non pas la dose mais la fréquence d’aspirine pourrait avoir un impact en cas de turnover plaquettaire accéléré

![Diagramme montrant la différence entre les plaquettes acetylées et non acetylées.]

- Healthy volunteers (12-15% de nouvelles plaquettes en 24 h sans possibilité de déclencher une agrégation significative)
- Patients with high platelet turnover (>20% de nouvelles plaquettes capables de déclencher une agrégation significative)
Figure 2: Percentage of patients with a significant serum TXB2 synthesis against time after the last aspirin administration in the 24-h variation study. Significant TXB2 synthesis is >2.45 ng/ml. Study performed on the last 47 patients.
Facteurs prédicteurs

Table 2: Relative risk of aspirin resistance 24 h after last aspirin ingestion in the overall population (univariate analysis).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen &gt;4 g/l *</td>
<td>2.94 [1.81 – 4.76]</td>
</tr>
<tr>
<td>Platelets count &gt;270.10^9/l *</td>
<td>2.15 [1.34 – 3.44]</td>
</tr>
<tr>
<td>hsCRP &gt;8.5 mg/l *</td>
<td>1.88 [1.12 – 3.17]</td>
</tr>
<tr>
<td>&lt;5 years previous or current smoking</td>
<td>1.87 [1.17 – 2.98]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.68 [1.06 – 2.65]</td>
</tr>
</tbody>
</table>

Odds ratio of resistance*: Median value observed in the study population. HsCRP: high sensitive CRP. CI, confidence interval.

Aspirin twice a day and biological efficacy

LTA-AA 0.5mg/ml

Patients resistant who became sensitive with change of treatment

Thrombocytémie et aspirine en deux prises

Agrégation optique par transmission - LTA-AA 0.5mg/ml

B