Impact of inflammatory markers on platelet function and cardiovascular outcome in patients undergoing coronary intervention

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I, Tobias Geisler DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Procedure related factors:
- bifurcational stenting
- stent length
- remaining dissection
- small stent diameter
- stent malapposition

Patient related factors:
- Adherence to antiplatelet therapy
- Diabetes
- Acute coronary syndromes, myocardial infarction
- Low left ventricular ejection fraction
- Renal failure

Pharmacological factors:
- Platelet responsiveness to antiplatelet therapy
- Drug-drug interaction via common CYP450 pathways (PPI’s, Ca-channel blockers?, statins?)
- Genetic polymorphisms influencing metabolism of thienopyridines

Multiple and diverse factors contributing to stent thrombosis
Residual platelet aggregation is a predictor of early stent thrombosis

Geisler T, et al, Eur Heart J 2010
Multiple and diverse factors contributing to stent thrombosis

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Inflammation?
Baseline CRP is an independent risk factor for stent thrombosis

Impact of elevated CRP on Hazard Ratios
-mutivariable adjusted-

Stent thrombosis
Definite or probable
Definite
Any
Clinical outcomes
Death
MI
Death or MI
TVR

Park et al., Circulation 2009
Crosslink between platelet activation/aggregability and inflammatory markers

Interaction between platelets and monocytes/macrophages

- Thrombosis
- Proteolysis
- Chemotaxis
- CRP

- Tissue factor
- uPA/uPAR
- MCP-1
- PSGL-1
- P-selectin

- Differentiation to macrophages
- Activation
- Adhesion
- IL-6
- TNF-α
- Mac-1
- VLA-4
- Endothelial ligands of Mac-1: α₅β₃/laminin, GPⅡb/Ⅲa, or JAM-3

Direct effects of CRP on monocyte-platelet aggregate formation and agonist induced platelet aggregation

Danenberg HD, Eur J Haemat 2007

Fiedel BA, Blood 1985

Gawaz M, J Clin Invest 2005
AIMS

To evaluate

Association of inflammatory markers with platelet response to dual antiplatelet therapy in a pilot PCI-collective.

Association of baseline CRP-levels with residual platelet function and long-term outcome (major events and stent thrombosis) after PCI in a large consecutive cohort.
STUDY DESIGN – pilot study

- Inflammatory markers CRP, IL-6, RANTES, MCP-1 by Multiplex cytokine assay
- Platelet function analysis (ADP+AA induced MEA) before and ≥ 6h after 600mg Clopidogrel loading dose → Clopidogrel 75mg/d + ASA 100mg/d

- Response to Clopidogrel: inhibition of ADP induced PA (pre-post LD)
- Response to AA: residual AA induced Aggregation
Influence of baseline inflammatory markers on platelet responses to clopidogrel and ASA

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Influence of baseline inflammatory markers on platelet responses to clopidogrel and ASA

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* p<0.05 compared to >=10 %
consecutive monocentre registry  
{n= 903 patients STENT

Baseline CRP levels, Platelet function analysis (ADP-LTA) \( \geq 6h \) after 600mg Clopidogrel loading dose \( \rightarrow \) Clopidogrel 75mg/d. + ASA 100mg/d

Follow-Up Mean 344 days (telephone interview, review of patients´ records)

Myocardial infarction and Death or Stent thrombosis  
(SAT/LAT; ARC criteria: definite, probable, possible)
## RESULTS

(Patients‘ Characteristics)

<table>
<thead>
<tr>
<th></th>
<th>Low to moderate CRP (≤ 0.72 mg/dl) N=452</th>
<th>High CRP (&gt; 0.72 mg/dl) N=451</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female (%)</td>
<td>102 (22.6)</td>
<td>128 (28.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Age / years, mean ± Std.-Deviation</td>
<td>67.1± 11.1</td>
<td>69.7± 10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipoproteinemia (%)</td>
<td>300 (67.4)</td>
<td>256 (57.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Severe left ventricular dysfunction %</td>
<td>44 (9.8)</td>
<td>76 (16.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute coronary syndromes %</td>
<td>180 (43.9)</td>
<td>297 (69.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of Diuretics</td>
<td>209 (49.2)</td>
<td>235 (54.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Use of ACE-Inhibitors %</td>
<td>318 (74.6)</td>
<td>346 (80.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of AT1-Blockers (%)</td>
<td>69 (16.2)</td>
<td>48 (11.2)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Influence of baseline CRP on residual platelet aggregation

Mean residual platelet aggregation (Final ADP20µMol/L-induced PA)

Baseline CRP levels

- **1st quartile** (≤0.19mg/dl)
- **2nd quartile** (>0.19-0.72mg/dl)
- **3rd quartile** (>0.72-2.4mg/dl)
- **4th quartile** (>2.4mg/dl)

*p=0.04*  
4th vs. 1st quartile

Error bars: 95% confidence interval of the mean

n=903
# RESULTS

*(Multivariate Survival Analysis)*

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>Hazard ratio</th>
<th>95% Confidence Interval</th>
<th>Sig.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
</tr>
<tr>
<td>Baseline CRP levels</td>
<td>1.05</td>
<td>1.00</td>
<td>1.09</td>
</tr>
<tr>
<td>RPA</td>
<td>1.02</td>
<td>1.01</td>
<td>1.03</td>
</tr>
<tr>
<td>LV- Dysfunction</td>
<td>1.20</td>
<td>1.02</td>
<td>1.59</td>
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<tr>
<td>Age</td>
<td>1.01</td>
<td>0.98</td>
<td>1.03</td>
</tr>
<tr>
<td>Gender</td>
<td>1.09</td>
<td>0.64</td>
<td>1.85</td>
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<tr>
<td>Acute coronary syndrome</td>
<td>1.16</td>
<td>0.69</td>
<td>1.95</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
<td>0.60</td>
<td>0.38</td>
<td>1.00</td>
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<tr>
<td>ACE-Inhibitors</td>
<td>1.00</td>
<td>0.53</td>
<td>1.88</td>
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<tr>
<td>AT1-Antagonists</td>
<td>0.75</td>
<td>0.32</td>
<td>1.72</td>
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<tr>
<td>Diuretics</td>
<td>1.19</td>
<td>0.73</td>
<td>1.96</td>
</tr>
</tbody>
</table>
Adjusted risk on major CV events stratified by CRP and RPA

Cumulative incidence of major adverse events (combination of non-fatal MI and death)

Stratum I: RPA + CRP < median
Stratum II: RPA > median + CRP ≤ median
Stratum III: RPA ≤ median + CRP > median
Stratum IV: RPA + CRP > median

Log rank:
- stratum IV vs. I: <0.001,
- vs. II: <0.001,
- vs. III: 0.06
- stratum III vs. I: 0.01, vs. II: ns
- stratum I vs. II: ns

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Adjusted risk on stent thrombosis (ST) stratified by CRP and RPA

Early ST (<30d) = 1.8% (0.5% definite; 1.3% probable)
Late and very late ST = 3.5% (0.7% definite, 1.8% probable, 1.0% possible)

Log rank:
stratum IV vs. I: 0.002, vs. II: <0.001, vs. III: 0.04
stratum III vs. I + II: ns
stratum I vs. II: ns

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Conclusions

Inflammation influences platelet response to dual antiplatelet therapy

- Periprocedural CRP correlates with RPA under dual antiplatelet therapy

- Synergistic effect of CRP and RPA for prediction of myocardial infarction, mortality and stent thrombosis

- Need for further risk stratification and evaluation of multimodal approaches for antiplatelet and anti-inflammatory treatment (PAR-1/TP-receptor antagonists?)
Thank you for your attention!
Association of residual platelet function and CRP with early and late stent thrombosis (ST)

Early ST (<30d) = 1.8% (0.5% definite; 1.3% probable)
Late and very late ST = 3.5% (0.7% definite, 1.8% probable, 1.0% possible)

RPA

ADP induced LTA (%)

CRP

Baseline CRP levels mg/dl

P=0.036
P=0.028
P=0.478
P<0.001
P<0.001
P<0.001