CRP and Atherosclerosis, the JUPITER-Study and Rosuvastatin

A story of confusion and commercial interest
Background

CRP

- Pentamer protein, synthesized by the liver
- Part of acute-phase reaction
- Binds strongly to bacterial LPS
- Activates complement reaction and macrophage binding

http://www.ebi.ac.uk/pdbe-srv/view/images.entry/1b09600.png
European Bioinformatics Institute
Background
Atherosclerosis

- **Arteriosclerosis** = pathological process that leads to thickening, hardening and loss of elasticity of vessel walls
- **Atherosclerosis** = narrowing arteries from building up a plaque (cholesterol, fatty acids, cell waste products) by chronic inflammation in medium to large vessels
Background

Atherosclerosis

• Risk factors:
  – high cholesterol/dyslipidaemia,
  – Smoking
  – Hypertonus

• Chronic inflammation, CRP?

\[ R = \frac{8 \times l}{\pi \times r^4 \times \eta} \]

Impedence \( R \) in blood vessels

J. Steffel, T. Lüscher: Herz-Kreislauf, Springer 2014

25.4.2016

Vera Vorstandlechner
Background
Statins

• Inhibit synthesis of Cholesterol by binding to HMG-CoA-Reductase

• Lova/Simva/Prava/Atorva/Fluva/Rosuvastatin

• Pleiotropic effects: antioxidative, antithrombotic, vasculoprotective, plaque stabilization

Antiinflammatory?
James T. Willerson

- BA UT of Austin 1961, Varsity swimming scholarship
- MD Baylor University of Medicine 1965
- Postgraduate Training at Harvard Medical School
- Fellow at Massachusetts General Hospital
- Clinical associate in Bethesda, Maryland
James T. Willerson

- Published over 980 articles
- Editor of *Circulation* from 1993 to 2004
- Editorial board for *New England Journal of Medicine*, *American Journal of Medicine* and others
- Member of board American Heart Association (AHA)
- Current President at the Texas Heart Institute

http://www.texasheart.org/AboutUs/History/willerson.cfm
Paul M. Ridker

• Eugene Braunwald
  Professor of Medicine at Harvard medical school
• Graduate of Brown University (1981)
• Harvard Medical School (1986)
• Principle investigator in many multi-national randomized trials
• More than 500 publications

Pasceri V. et al. 2000


- HUVECs incubated + recombinant bacterial CRP →
  - 10-fold increase of ICAM-1
  - „significant expression“ of VCAM-1
Pasceri V. et al. 2000

- HUVECs incubated with highly purified human CRP →
  - “also showed biological activity“
  - “Data not shown“?

- HCAECs incubated with CRP (unclear human or recombinant) →
  - “significant proinflammatory effects“
  - Inducing high levels of ICAM-1, VCAM-1 and E-Selectin
Fig. 1: Induction of adhesion molecule expression by CRP
Pasceri V. et al. 2000

„CRP (...) induces significant expression of adhesion molecules (...) and is not merely a marker of inflammation, but has modulatory functions that may contribute to the development of inflammation/atherosclerosis“
Pasceri V et al. 2001


• Incubation of HUVECS with CRP (recombinant or human?) →
  – Induced significant secretion of MCP-1
  – No increased secretion on RANTES

- Incubation of HUVECS with CRP (recombinant or human?) + Simvastatin →
  - Reduced to 43% of maximal MCP-1 response
„...Our findings support the hypothesis of a direct role of CRP in the pathogenesis of inflammation/atherosclerosis and open the way to new pharmacological strategies for treatment.“

- In vitro CRP lack robust controls
- Authors generated own recombinant CRP
- Incubation of HUVECs with
  - Commercial CRP (cCRP) from *E. coli*
  - Own recombinant CRP (rCRP)
    - Lipopolysaccharide (LPS) and azide-free
• HUVECs cultured with rCRP showed morphology to controls
• HUVECs cultured with azide appeared similar to cCRP →

azide and not CRP inhibits cell proliferation!

Fig. 1: Azide in cCRP is responsible for reduced cell proliferation, change in morphology and increased cell apoptosis
ICAM-1 expression observed only in HUVECs with cCRP

No ICAM-1 expression in rCRP

Dialysis of cCRP removed ICAM-1-inducing activity

– Contamination with LPS induced ICAM-1-expression
• Not a single direct effect of CRP on endothelial cells!

„… all other studies in which cCRP preparations have been used are most likely artifacts to azide of LPS contamination.“

• „….. Intravenous injection of highly purified, structurally intact and fully functional active human CRP (…) did not induce an acute phase response“

• „… injection of the same quantity of recombinant CRP induced acute phase response.“
The CRP-testing patent held by PM Ridker
CRP-testing patent

- Applied for in June 2005 by PM Ridker and Charles Hennekens
- Granted in June 2011
- Introduction of hsCRP-test by Siemens in 2004
- Siemens hsCRP-test approved by the FDA in 2009 after the JUPITER-trial
- hsCRP tests sold by Siemens and AstraZeneca
The CRP-testing patent

http://www.healthcare.siemens.com/point-of-care/poc-cardiac-topics/cardiac-assays/cardiophase-hscrp
The JUPITER study
Ridker et al. 2008


Justification for the Use of Statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin
The JUPITER study

- Randomized, double blind, placebo-controlled study
- 17,802 healthy men and women with low LDL<130mg/dl and CRP > 2,0mg/l
- Rosuvastatin 20mg 1/d vs. Placebo
- Follow-up of 9 years
  - End-points: myocardial infarction, stroke, combined, cardiovascular death, death from any cause
The JUPITER Study

- Early study closure after 1.9 years (393 endpoints) due to significant risk reduction for patients in the Rosuvastatin group

“... in apparently healthy men and women who did not have hyperlipidemia but had elevated levels of hsCRP, the rates of a first major cardiovascular event and death from any cause were significantly reduced among participants who received Rosuvastatin...“
The JUPITER study
Results

Table. A Summary of the JUPITER Trial Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Rosuvastatin Group (n=8901)</th>
<th>Placebo Group (n=8901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>142</td>
<td>251</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>22</td>
<td>62</td>
</tr>
<tr>
<td>Any myocardial infarction</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>Any stroke</td>
<td>33</td>
<td>64</td>
</tr>
<tr>
<td>Arterial revascularization</td>
<td>71</td>
<td>131</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, or confirmed</td>
<td>83</td>
<td>157</td>
</tr>
<tr>
<td>deaths from cardiovascular causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause on known date</td>
<td>190</td>
<td>235</td>
</tr>
</tbody>
</table>

DeLorgeril et al. 2010
Adapted from Ridker et al.
Primary endpoints: occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes
The JUPITER study
Results

C. Revascularization or Hospitalization for Unstable Angina

D. Death from Any Cause

No. at Risk
Rosuvastatin 8901 8640 8426 6550 3905 1966 1359 989 541 158
Placebo 8901 8641 8390 6542 3895 1977 1346 963 535 176

No. at Risk
Rosuvastatin 8901 8847 8787 6999 4312 2268 1602 1192 676 227
Placebo 8901 8852 8775 6987 4319 2295 1614 1196 681 246

P<0.00001
P=0.02
The JUPITER study

Results

• NNT (2y) = 95, NNT (5y) = 31

• Serious adverse events: similar in the rosuvastatin and placebo group

• „Small but significant increase in the rate of physician-reported diabetes with Rosuvastatin“
The JUPITER study

Conflicts of interest

• Study sponsored by AstraZeneca
• AstraZeneca holder of Rosuvastatin (Crestor®)
• 11/14 authors report receiving grants and/or consulting/lecture fees from AstraZeneca
The JUPITER study
Conflicts of interest

- PM Ridker coinventor of patents in the use of hsCRP, licensed to AstraZeneca
- “…The sponsor collected the trial data and monitored the study sites…”
- Increase of sales number of statins from AstraZeneca after reporting the trial results
DeLorgeril et al. 2010


• Results: „The trial was flawed.“
• …“major discrepancy between reduction of nonfatal stroke and myocardial infarction but no effect on mortality“
• Troubling questions concerning the role of commercial sponsors
DeLorgeril et al.

Methological flaws

- Early study closure: closed after only 240 hard end points
- Prespecified rules for study closure not published in study protocol
- All cause mortality curves were converging → not published in subsequent paper
DeLorgeril et al. Methologial flaws

Ridker PM et al., NEJM 359;21 2008

DeLorgeril et al.

Epidemiological problems

• Surprisingly low cardiovascular mortality:
  • case-fatality rate
    – To be expected: 40%
    – JUPITER placebo group: 8,8%
    – JUPITER Rosuvastatin group: 29%

• „JUPITER-patients highly resistant to ischemia and infarction?“

• No mention on numbers of sudden cardiac death
DeLorgeril et al.  
Statistical inconsistencies

![Table. A Summary of the JUPITER Trial Results](image)

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No significant difference in mortality!
Other Rosuvastatin studies

• ASTEROID: high intensity statin therapy (40mg Rosuvastatin) may regress coronary atherosclerosis

• AURORA: reduction of LDL, but no significant effect on primary outcome in patients with hemodialysis

• COMETS: significantly greater effect of Rosuvastatin than Atorvastatin
Other Rosuvastatin studies

• CORONA: no reduction of primary outcome, but less hospitalization
• GISSI-HF: no effect of Rosuvastatin in chronic heart failure

- 20,536 Patients in the UK categorized into CRP-baseline groups
- Simvastatin 40mg daily vs. Placebo
- Reduction of cardiovascular risk by a quarter in the Simvastatin group
- But: CRP baseline does not modify vascular benefits of statin therapy
The ESC/EAS Guidelines for dyslipidaemias


- „Presently, hs-CRP as a secondary target of therapy is not recommended for everybody; based on available data, it may be useful in people close to high risk category to better stratify their total CV risk. “
• „The contribution of hs-CRP to absolute CV risk estimation for individual patients is generally modest.“

• WHO guideline 2007:
  „CVD risk may be higher than indicated in the presence of (...) raised levels of CRP“
Conclusion, Comments

• Trying to find out the „truth“ can be quite confusing
• Commercial interests are a scientific and clinical issue and raise troubling questions
• First-glance good scientific practice might not be reliable after all
• Statistics „too good to be true“ are to be questioned and evaluated critically
Fragen, Kritik, Anregungen?
Herzlichen Dank!
References

References