High grade inflammation and the lipid paradox: Implications for treatment

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Disclosure

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Translating knowledge of cardiovascular risk into clinical practice

Cardiovascular Disease Assessment in Rheumatoid Arthritis: A guide to translating knowledge of cardiovascular risk into clinical practice

AG Semb, S Rollefstad, P van Riel, GD Kitas, EL Matteson, SE Gabriel
1. Inflammation and lipids
2. Impact on CD risk prediction
3. Implications for treatment
1. Inflammation and lipids

2. Impact on CD risk prediction

3. Impact on CD risk prediction
Inflammation and atherosclerosis

- Rudolf Virchow (1821-1902)
  Über parenchymatöse Entzündung
  Virchows Arch. Path. Anat. 1852:4:261

- Ross R
  Atherosclerosis: an inflammatory disease
Inflammation and atherosclerosis

Inflammation and RA disease activity

Traditional CV risk factors
e.g. BMI, lipid, gender, smoking, hypertension, diabetes, etc.

Systemic inflammation

Inflamed rheumatoid joint

Cytokine release

Increased CV risk associated with anti-inflammatory medication
(e.g. NSAIDs and Cox-2 inhibitors)

Quantitative and qualitative lipid changes

Cardiovascular disease

Treat-to-target

Share common Pathophysiology pathways
Why does RA patients have an increased risk of CVD?

Traditional CVD Risk Factors + Untraditional CVD Risk Factors =

gender
age
cholesterol
smoking
hypertensjon
diabetes
waist circumference / obesity
physical activity
alcohol

inflammation
disease activity
disease burden
CRP is an independent predictor of cardiovascular risk


hsCRP=Highly sensitive C-reactive protein
CRP groups
Group 0: 0–3
Group 1: 3–10
Group 2: >10

Carré study
n=353

Increasing CRP results in lower lipids

CRP, C-reactive protein


Inflammation alter lipids in RA patients
Low lipids – high CVD risk

Results from the Apolipoprotein MORtality RIsk Study - AMORIS

Despite low levels of lipoproteins, patients with RA had a high rate of MI/IS

Non-RA: n=480 406
RA: n=1779
Follow up: 8 years

Liao K et al Arthritis & Rheumatol 2015; 67:2004-10

The complex relationship between LDL-c, HDL-c and risk of MACE was non-linear in RA patients and not different from non-RA subjects.

Lipid levels and risk of MACE in RA vs. Non-RA

**RA**

n=16 085

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>OR MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.29</td>
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</tr>
<tr>
<td>2.6</td>
<td>1.29</td>
</tr>
<tr>
<td>3.9</td>
<td>2.6</td>
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<tr>
<td>5.2</td>
<td>4.0</td>
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</tbody>
</table>

**Non-RA**

n=48 499

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</table>

P values indicate the significance of the association in tests for linearity in the RA and non-RA cohorts.
Lipid paradox in rheumatoid arthritis – the lower lipids the higher CVD risk and this was related to CRP/ESR.

Risk of CVD was increased for lower TCh measures.
A marginal increased risk of CVD for LDL ≤ 2 mmol/l.

HRs for CVD in RA (solid lines). Shaded area represent 95% CIs.

CVD, cardiovascular disease; LDL, low-density lipoprotein; TCh, total cholesterol.

Carotid Plaque Characteristics and Disease Activity in Rheumatoid Arthritis
Anne G. Semb, Silvia Rollefstad, Sella A. Provan, Tore K. Kvien, Einar Stranden, Inge C. Olsen, and Jonny Hisdal

Editorial

Patients with Rheumatoid Arthritis Have More Vulnerable Arterial Plaques, But Lowering Disease Activity May Stabilize This Threat

VOKKO P. VAN HALM, MSc, MD, PhD
Cardiologist, Department of Cardiology

Remission is the mission!
Anti-inflammatory treatment

During the last decades, treatment opportunities in RA have evolved, especially by the introduction of biologic disease modifying anti-rheumatic drugs (bDMARDs)

which are potent anti-inflammatory agents
Biologic agents may be considered already after 6 months treatment with a synthetic DMARD
The inverse relationship between changes in inflammatory and lipid parameters

Increase in inflammation is associated with decrease in lipids

↓ inflammation by various RA treatments - inversely affect lipid levels

Dampening of inflammation and tight disease control with RA treatment

Pre-RA RA

CRP Lipid levels

Modified after Choy E et al Rheum 2014
Effect of TNF-i on lipids

Meta-analysis of 15 studies including 736 RA patients

Approx. 10% increase in total cholesterol

van Sijl AM et al, Semin Arthritis Rheum 2011;41(3):393-400
During the last decades, treatment opportunities in RA have evolved, especially by the introduction of biologic disease modifying anti-rheumatic drugs (bDMARDs).

However, controversies exist regarding the impact of bDMARDs on the risk of CVD in patients with RA.
The Association between reduction in inflammation and LDL, HDL and RCT

Liao KP et al J Am Heart Assoc. 2015;4e001588

Pat’s experiencing a ↓CRP, had an ↑in LDL with a concomitant improvement in HDL efflux capacity

The effect of this on CVD outcome is not known

n=90
2 CRP with 1 year apart
s-DMARDs +/- b-MARDs
Biologic DMARDs

A systematic literature review suggested that treatment with TNF-i is associated with a decreased risk of CVD\(^1\)

- register studies/cohort observations

- a recurrent problem with these studies are the lack of information on whether the anti-rheumatic medication consisted of
  - TNF-i monotherapy or
  - combination TNF-i+MTX

\(^1\)Westlake SL et al, Rheumatology (Oxford) 2011; 50(3):518-31
Ongoing trials targeting inflammation in atherosclerosis - non-RA study populations

**CIRT trial**¹ - *Cardiovascular Inflammation Reduction Trial*

- Stable CHD (**post MI**), on statin ACE/ARB, BB, ASA, persistent elevation in hsCRP >2mg/L
- Intervention: Low dose MTX 15-20 mg/week + folate vs. placebo
- Will enroll approx. 7000 patients

**CANTOS trial**² - *Canakinumab Anti-inflammatory Thrombosis Outcomes Study*

- Similar inclusion criteria as in CIRT
- Intervention: Different doses of canakinumab (IL-1 i) (50 mg, 150 mg, 300 mg) vs. placebo
- 17 200 randomized patients

²Ridker PM *et al*, Am Heart J 2011;162(4):597-605
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**Systematic Coronary Risk Evaluation**

SCORE –
Calculate the 10 year risk of fatal MI

Risk ≥ 5% LLT

Age
Gender
Blood pressure
Lipids
Smoking status

2/3 of RA are female

Conroy RM et al EHJ 2003; 24:987-1003
Usefulness of Risk Scores to Estimate the Risk of Cardiovascular Disease in Patients With Rheumatoid Arthritis

Cynthia S. Crowson, MS\textsuperscript{a,b,*}, Eric L. Matteson, MD, MPH\textsuperscript{a,b}, Veronique L. Roger, MD, MPH\textsuperscript{a,c}, Terry M. Therneau, PhD\textsuperscript{a}, and Sherine E. Gabriel, MD, MSc\textsuperscript{a,b}

Am J Cardiol 2012;110:420–424

CVD risk prediction of CVD events in RA patients from US is generally inaccurate by the Framingham and Reynolds CVD risk calculators.

Comparable effects have been using 4 risk calculators in European RA patients by E Arts \textit{et al}.

Ann Rheum Dis. 2015 Apr;74(4):668-74
Unmet need of an RA specific CVD risk calculator

Steering committee: prof G Kitas, prof P v Riel, prof em S Gabriel, AG Semb
Administrative and Data handling Center: AG Semb, Oslo, Norway
ATACC-RA consortium

17 centers from 12 countries

www.atacc-RA.com

> 5000 RA patients
> 35 000 patient years
> 500 CVD events
Conclusion

- Major heterogeneity exists in CVD event rates across different countries among patients with RA

- Possible explanations include population differences, referral bias, RA treatment effects, statin and antihypertensive use

- Development of an RA specific CVD risk calculator must address these differences
Expanded CV risk prediction score for RA (ESR-RA) a CORRONA registry study

• Does not contain traditional risk factors
  • Lipids & Blood pressure
  • Age, gender, diabetes, hyperlipidemia (y/n), hypertension (y/n), tobacco use (y/n)

• Baseline RA disease specific measures sign in the regression analyses and included in the model was:
  – CDAI > 10 vs ≤ 10
  – MHAQ > 5 or ≤ 5
  – Daily prednisone use
  – Disease duration > 10 yrs vs. less

Expanded CV risk prediction score for RA (ESR-RA) a CORRONA registry study

Used 2013 ACC/AHA risk categories
< 7.5% and ≥ 7.5% 10 year risk of a CVD event

When using the expanded calculator:
• 10.8% were reclassified from ≥7.5% to < 7.5%
• 8.5% were reclassified from < 7.5% to ≥ 7.5%

Thus addition of disease specific factors in this risk calculator resulted in fewer patients being considered for statins

External validation is needed

1. Inflammation and lipids
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3. Implications for treatment
Does inflammation have an implications for Lipid Lowering Treatment?
Results from the Preventive Cardio-Rheuma Clinic

435 patients with IJD

No treatment
SCORE<5%
n=153 (35.2%)

Categorized to treatment
n=282 (64.8%)

1° prevention
no CVD - SCORE >5%
n=66 (23.4%)

2° prevention
CVD/CP – SCORE >10%
n=216 (76.6%)

Lipid lowering treatment was either simvastatin, atorvastatin, rosvastatin or pravastatin

Referral from the rheumatology outpatient clinic
1.3-2009 – 3.3-2012

Percentage change in lipids
First to final consultation in patients with inflammatory joint disease were highly significant

Primary prevention

Secondary prevention

TC, total cholesterol; TG, triglycerides

Proportion of patients reaching ≥ 2 lipid targets

- RA: 88.7%
- AS: 90.8%
- PsA: 92.6%

Number of consultations needed to obtain target:
- RA: 2.54 ± 0.97
- AS: 2.86 ± 1.28
- PsA: 2.54 ± 0.83

Current therapies provide suboptimal results in the general population.


**LDL-C goal attainment**

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>55</td>
</tr>
<tr>
<td>Germany</td>
<td>24</td>
</tr>
<tr>
<td>Italy</td>
<td>14</td>
</tr>
<tr>
<td>Spain</td>
<td>26</td>
</tr>
<tr>
<td>Switzerland</td>
<td>34</td>
</tr>
<tr>
<td>Overall</td>
<td>40.5</td>
</tr>
</tbody>
</table>

**Good results was related to setting**
- spec practice
- highly motivated

Bearing in mind long FU in gen pop – we have weeks to a few months
If LDL goal attainment will be as good over time in the IJD pop is not known
Background inflammation and lipid lowering effect

- 197 patients referred to the Preventive Cardio-Rheuma clinic obtained LDL-C goals

- We evaluated if baseline lipid levels and systemic inflammation in these patients were associated with the statin dose sufficient to achieve LDL-C targets

| LDL-C targets | 1° Prevention: ≤ 2.5 mmol/L | 2° Prevention: ≤ 1.8 mmol/L |

Systemic inflammation or lipid levels at baseline were not associated with the statin dose needed to achieve recommended LDL-c targets.

**Intensive LLT:**
- rosvustatin ≥ 20 mg
- atorvastatin 80 mg
- simvastatin 80 mg

**Conventional LLT:**
- all lower doses

Systemic inflammation or lipid levels at baseline were not associated with the statin dose needed to achieve recommended LDL-c targets.

Intensive LLT:
- rosvastatin $\geq 20$ mg
- atorvastatin 80 mg
- simvastatin 80 mg

Conventional LLT:
all lower doses

A-rheumatic medication did not have an impact on the relation between baseline lipids and inflammation with statin dose needed to obtain LDL goals

Most interestingly..

The baseline inflammatory status and lipid levels in patients who did and did not obtain LDL-c goal were comparable

- CRP/ESR: p-value 0.32 and 0.64 and
- LDL-c/Total chol: p-value 0.20 and 0.83

This illuminates that inflammation did not influence achievement of lipid goals in patients with IJD.

Are statins safe?
Adverse effects

- Tolerable, minor side effects mostly GIT
- No increase in CPK, liver enzymes ≥2 × ULN
- No serious adverse events were observed

GIT, gastrointestinal; ULN, upper limits of normal

Safety

- Any adverse event: 294 (19.7%) atorva vs 292 (19.5%) placebo
- No difference in SAE intensity
- No SUSARs
- No difference in hospitalisation frequency or duration
- No significant, persistent AST, ALT, CPK elevations
- No myopathy
Conclusion

- Patients with IJD referred to the Preventive Cardio-Rheuma clinic had a high probability for the need of CV prevention
  - Supporting the importance and relevance of establishing Preventive Cardio-Rheuma Clinics

- Treatment to lipid targets was successful in ~90% on less than 3 consultations
  - Illustrating that LL medication as statins are effective and safe in patient with IJD

- Inflammation does not affect statin dose needed to obtain recommended LDL levels
The effect of LLT on future CVD events in patients with IJD is not well elucidated because there are scarce data on prospective CVD hard end point studies lipid lowering......
TRIAL OF ATORVASTATIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH RHEUMATOID ARTHRITIS

TRACE RA


(ISRCTN: 41829447)
Trial Design

Main Characteristics

- Prospective
- Multicentre
- Randomised
- Double-blind
- Atorvastatin 40mg vs placebo daily

Primary endpoint
Major Vascular Events
### Primary endpoint

<table>
<thead>
<tr>
<th>Type</th>
<th>Atorvastatin 40mg (n=1492)</th>
<th>Placebo (n=1494)</th>
<th>Atorvastatin to placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (of group)</td>
<td>n</td>
</tr>
<tr>
<td>Coronary events [i.e. non-fatal myocardial infarction, coronary death or coronary revascularisation]</td>
<td>23</td>
<td>1.5</td>
<td>38</td>
</tr>
<tr>
<td>Presumed ischaemic stroke or transient ischaemic attack</td>
<td>6</td>
<td>0.4</td>
<td>13</td>
</tr>
<tr>
<td>Any non-coronary arterial revascularisation</td>
<td>4</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Any other cardiovascular death excluding both confirmed cerebral haemorrhage [ICD I64-99 in the 10th International Classification of Diseases] and non-coronary cardiac death [ICD I00-I15 and I26-I52]</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of events</td>
<td>33</td>
<td>2.2</td>
<td>52</td>
</tr>
<tr>
<td>Patients with any of the above</td>
<td>24</td>
<td>1.6</td>
<td>36</td>
</tr>
</tbody>
</table>
Primary endpoint

Kaplan-Meier PL estimates

Adjusted analyses
- Stratified by centre
- Baseline differences
  - SMOKING
  - NSAIDs/COXIBs
  - ETHNICITY
  - EQ5D VAS
- Compliance + Non-study statin

Estimated HR Atorva/Placebo
0.54 (0.30-0.98) \( p=0.045 \)
Conclusions

In patients with RA, Atorvastatin 40mg daily compared to placebo resulted in:

– Significantly greater reduction of LDL

– A 34% (unadjusted) risk reduction for a major CVD event
  • In line with the CTT collaboration meta-analysis in other populations

– No increase in adverse events
Post hoc analyses in 2 large statin trials with CVD outcome - IDEAL and TNT trials

Patients with and without inflammatory joint disease had comparable LL effect and risk reduction of CV mortality and morbidity (CVMM) after treatment with statins

PsA, psoriatic arthritis

Because few statin RCT with hard CVD endpts excists, longitudinal studies with LLT & surrogate endpoints are of interest

RORA AS study

Rosuvastatin-Induced Carotid Plaque Reggression in Patients With Inflammatory Joint Diseases

The Rosuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and Other Inflammatory Joint Diseases Study


**Primary endpoint:**
Change in carotid plaque height (measured by B-Mode ultrasound) after 18 months treatment with rosuvastatin

Clinicaltrials.gov ID: NCT01389388
Results from the RORA-AS study

CP height at baseline: 1.80 mm (IQR 1.60, 2.10)

Change in CP height: -0.19±0.35 mm (p<0.0001)

**Change in lipids**

- Baseline tot.chol: 6.43±1.09 mmol/L
- Change in tot.chol: -2.41±0.97 mmol/L (p<0.001)
- Baseline LDL: 4.0±0.9 mmol/L
- Change in LDL: -2.3±0.8 mmol/L (p<0.001)

**Mean level of LDL-c (AUC)**

1.7±0.4 mmol/L

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The change in carotid plaque height

Not related to

1. LDL level during the study
2. Degree of change in LDL from baseline
3. Whether LDL goal attainment was achieved or not
Age had a significant impact on plaque height reduction ($p=0.01$).

In that the youngest had the largest CP height regression.

Mixed models analyses
However, in patients using bDMARDs we did not observe a significant reduction in CP height.

<table>
<thead>
<tr>
<th>CP height</th>
<th>Baseline</th>
<th>18 months</th>
<th>Change mean±SD (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.92±0.52</td>
<td>1.72±0.48</td>
<td>-0.19±0.35 (-0.27, -0.12) p&lt;0.0001</td>
</tr>
<tr>
<td>bDMARDs</td>
<td>1.89±0.58</td>
<td>1.80±0.54</td>
<td>-0.09±0.37 (-0.22, 0.04) p=0.15</td>
</tr>
<tr>
<td>Non-users bDMARDs</td>
<td>1.93±0.48</td>
<td>1.67±0.43</td>
<td>-0.26±0.32 (-0.36, -0.17) p&lt;0.0001</td>
</tr>
<tr>
<td>-Difference</td>
<td>-</td>
<td>-</td>
<td>-0.21±0.08 (-0.37, -0.06) p=0.01</td>
</tr>
</tbody>
</table>
Intensive lipid lowering with rosuvastatin induced regression of CP height and reduced LDL-c significantly in patients with IJD.

Without any intervention, atherosclerotic lesions will with a high probability progress. We did not observe a progression of the carotid plaques over the 18 month study period in patients using bDMARDs and rosuvastatin treatment.

Prospective randomized statin studies are warranted to reveal if height reduction of asymptomatic CP will have impact on future CV events.

Overall Conclusions

- RA patients have lower lipids, altered lipoprotein composition and function due to inflammation.
- Inflammation does not affect statin dose needed to obtain recommended LDL levels.
- LLT with statins is effective and can induce atherosclerotic regression.
- Primary and secondary prevention effects from RCT’s are sparse and further studies are warranted.
  - TRACE-RA
  - Post hoc analyses from IDEAL/TNT
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Thank you for Your Attention