Cardiovascular Risk and Rheumatoid Arthritis

KEITH A. REICH DO, FACOI, FACR, RHMSUS, RMSK
EXECUTIVE MEDICAL DIRECTOR FRANCISCAN PHYSICIAN NETWORK
RHEUMATOLOGY FELLOWSHIP DIRECTOR ST. JAMES HEALTH
Discuss the relative risks of RA with cardiovascular disease
Consider some potential pathologic mechanisms
How to monitor CV progression in patients with RA
Does treatment help?
31-year-old female with years of rheumatoid arthritis presents for evaluation. She has 2 hours of morning stiffness, tenderness in multiple joints and dyspnea when climbing stairs.

- She does not smoke or drink
- Medications: Methotrexate and prednisone
- Family history positive for mom with RA. No cancer or early cardiovascular disease
On examination she has active synovitis, clear lungs and her cardiovascular examination is normal.
Further studies reveal normal pulmonary function testing as well as an echocardiogram. However, she fails a stress test and ultimately undergoes cardiac stenting.
Question

- Was this bad luck?
- Strong family history?
- Related to her RA?
Risk Factors
Atherogenesis
Lipid Paradox
What to Measure
Treatments
Goodson et al looked at population cohort at Rochester, MN.

- RA between 1990 and 1994, a total of 1,236
- Survival in this RA lower than that expected in the population ($P < 0.001$) CVD most common cause
- Having $>1$ extra articular manifestation was the strongest risk factor for early mortality
What About Risk Factors?

- Having >1 extra articular manifestation was the strongest risk factor for mortality after adjusting for age, sex, BMI, smoking, and rheumatoid factor positivity.
- Females at greater risk than males.
- The increased mortality is apparent within the first 8–10 years from symptom onset.

How Great is the Risk?
Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies

RA itself is an independent CV risk factor that carries as much weight as diabetes

Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies
What We Know

- RA patients have increased, early mortality
- Mostly secondary to CVD
- Long standing disease?
- Extra-articular manifestations
- Positive CCP or RF
- Risk similar to diabetes

What We Don’t Know

- Why do these patients die early?
- Does treatment effect mortality?
- Is the timing of treatment important?
- What is the mechanism of action of this accelerated atherosclerosis
The full mechanisms resulting in CV risk excess are still to be clarified. Although standard CV risk factors may account for the majority of CV risks, they do not fully explain the CV risk excess observed in rheumatic diseases.

Chronic inflammation that both promotes atherogenesis and exacerbates established CV risk factors may partly explain this increased risk. Moreover, the treatments of rheumatic disease may potentially impact CV risk.
Whatever variables that increases CV mortality in RA are present very early during the natural history of the disease.

New onset RF positive inflammatory arthritis shows evidence of abnormal endothelial function — good predictor of future development of atherosclerosis.
Mechanism

- Full mechanisms resulting in CV risk excess are still to be clarified

- Standard CV risk factors do not fully explain the CV risk

- Inflammation that both promotes atherogenesis and exacerbates established CV risk factors may explain this increased CVD mortality

- Treatments themselves may promote CVD mortality
Does it matter?

Does better control reduce CV risk?
Corrona cohort of 24,989 subject for a median of 2.7 years

CDI as a marker of inflammation

Age, gender, diabetes, hypertension, hyperlipidemia, body mass index, family history of myocardial infarction (MI), aspirin and NSAID use, presence of CV disease, and baseline immunomodulator usage.
Incidence rate per 1,000 person-years for cardiovascular events among CORRONA patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th>Event</th>
<th>Events</th>
<th>Person-years</th>
<th>Incidence rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite cardiovascular events</td>
<td>534</td>
<td>68,576</td>
<td>7.8 (6.7 – 8.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>217</td>
<td>68,873</td>
<td>3.2 (2.5 – 3.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>233</td>
<td>68,856</td>
<td>3.4 (2.7 – 4.1)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>96</td>
<td>69,273</td>
<td>1.4 (0.9 – 1.9)</td>
</tr>
</tbody>
</table>

Notes: Primary study cohort includes subjects with rheumatoid arthritis in CORRONA.
Significant trend towards a reduced risk of CV events with improved disease activity: a 21% reduction in CV risk for each 10 point lowering of the CDAI and a 53% reduction from high disease activity to remission
Risk Factors

- Smoking and having a first degree relative with RA increases your chance of developing RA.
- No reports of mortality
Risk Factors

- The excessive CVD risk persists after adjusting for standard CV risk factors

- Inflammation that promotes atherogenesis and exacerbates CVD risk factors may account for this part of increased risk

Choy et al. 2014; Zhang et al. 2014
In contrast to the general population, low BMI is associated with a significantly increased risk of CVD death and overweight/obesity with reduction in CVD risk.

Likely secondary to cachexia associated metabolic disorder.

Baker et al. 2015; Kremers et al. 2004; Wolfe and Michaud, 2012
Although an association between insulin resistance and RA was reported in several studies [Dessein and Joffe, 2006; Giles et al. 2015], the homeostatic model assessment (HOMA) used to quantify insulin resistance was not correlated with subclinical atherosclerosis measurements among RA patients [Giles et al. 2015].
Several studies demonstrated subclinical atherosclerosis with:

- Altered vascular function
- Endothelial dysfunction
- Increased arterial stiffness
- Increased carotid intima/media thickness

These vascular changes were shown to correlate with the coronary circulation and able to predict CV events.

Bodnar et al. 2011; González-Juanatey et al. 2007; Kimhi et al. 2007; Mathieu et al. 2008; Sandoo et al. 2011
High C-reactive protein (CRP) levels in RA patients without diabetes mellitus or metabolic syndrome were shown to increase two-fold the risk of coronary artery disease

Zhang et al. 2014
Accelerated atherosclerosis

- However, the link between inflammation and disease activity was not demonstrated.

- Conflicting results regarding the effects of conventional and biological disease modifying anti-rheumatic drugs (DMARDs) on both vascular function and morphology.

Bodnar et al. 2011; González- Juanatey et al. 2007; Kimhi et al. 2007; Mathieu et al. 2008; Sandoo et al. 2011
Accelerated atherosclerosis-Inflammation

Alters the nitric oxide (NO) response that controls vasodilatation and interactions with leukocytes and platelets

endothelial dysfunction
atherosclerosis and plaque modification
Its all Immunology

Plaque rupture - interactions between plaque components and proinflammatory mediators- adhesion molecules, cytokines, and chemokines regulated in part by nitrous oxide

Lerman and Zeiher, 2005
Atherogenesis

- Probably combination of inflammation, risk factors and vascular dysfunction lead to the increase in early and aggressive CVD
CV Risk-avoid deleterious treatment

- Avoid NSAIDs and Cyclooxgenase inhibitors
  - Increase risk with diclofenac and rofecoxib
  - naproxen "safest"

- Corticosteroids- could contribute to atherogenesis- linked to increased insulin resistance, and hypertension. But, by reducing inflammation could decrease CV risk.

- Methotrexate has been associated with lower CV risk. A recent meta-analysis found that methotrexate use was associated with 21% fewer CV events

Lipid Paradox
A comprehensive review of the literature was published by the Emerging Risk Factors Collaboration (ERFC) which gathered data relating to risk of CVD from 68 long-term prospective studies involving over 350,000 patients.
Trends in hazard ratios for CHD

Serum levels of HDL-C and non-HDL cholesterol seem to correlate with CHD risk in a log-linear pattern, although the direction of the association differs.

Robertson et al 2009
Active RA leads to a fall in both LDL-C and HDL-C levels is generally accepted. This is the ‘lipid paradox’ phenomenon—the reduction in levels of serum lipids in a disease associated with increased CVD risk.

Also seen in other autoimmune inflammatory diseases as well as sepsis.

Chung et al 2010, peters, et al 2010
The heightened inflammatory state alters the properties of HDL cholesterol, hence, the HDL paradoxically assumes pro-inflammatory properties, thereby accelerating endothelial dysfunction and plaque formation.

In active RA, however, reductions in total cholesterol levels as well as levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) are seen.
Lipid profiles of 577 patients with RA - from 5 years before until 5 years after diagnosis of RA.

Despite having lower rates of statin use, displayed a greater reduction in total cholesterol (10%) and LDL-C (17%) during the 5 years preceding diagnosis.
Figure 1

Myasoedov a, E. et al 2010
From: *Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment*


**Figure Legend:**

Representation of the inverse relationship between changes in inflammatory and lipid parameters.
The mechanisms by which the inflammatory process can lead to these lipid changes are not fully understood, but may include suppression of the reticuloendothelial system and reduced low-density lipoprotein (LDL) particle synthesis.

Additionally, CRP mediates the uptake of LDL and oxidized LDL by macrophages, induces LDL deposition and increases LDL uptake by hepatocytes.
Lipid Paradox

So, a lower cholesterol- should be good- right?
The inflammatory burden induces changes in the lipoprotein composition, thereby altering protective functions of HDL cholesterol (HDLc).

These include anti-oxidative properties and cholesterol efflux capacities.

Pro-inflammatory oxidized low-density lipoprotein (LDL) cholesterol (LDLc) that in turn activates endothelial cells to produce inflammatory cytokines like TNFa, and IL1, while recruiting monocytes into the arterial wall.
Administration TNF or IL-6 decreases serum levels of total cholesterol, HDL-C and LDL-C in humans.

In vitro, IL-6 and TNF upregulate LDL-receptor expression on hepatocytes, and can promote LDL-receptor-independent uptake of oxidize LDL.
Logically, in evolutionary terms, immune defense system forces changes to ensure appropriate energy homeostasis is maintained at times of high demand. I.E Active RA.

Thus, cytokines have direct effects on lipid metabolism, in the same way that an acute inflammatory response alters carbohydrate metabolism and insulin resistance, and can engender a hypercoagulable state.
This lipoprotein is highly heterogeneous with sub-fractions which can be identified by their density, size, charge and protein composition.

In healthy individuals – absence of inflammation, HDL is anti-inflammatory, i.e., with cardio-protective properties.
HDL-Qualitative Aspects

- Anti-inflammatory
- Inhibits thrombosis
- Enhances reverse cholesterol transport
- Promotes antioxidants
  - Nitric acid
  - Inhibition of LDL Oxidation
  - Endothelial inflammation
- Decreases production of inflammatory cytokines and adhesion molecules within the vascular wall
- HDL can also attenuate inflammation (See by infusion of HDL)
Reverse cholesterol transport by which non-esterified cholesterol from peripheral tissues is transferred to HDL and transported to the liver to be excreted in bile.

Ability to prevent oxidation of LDL and to facilitate reverse cholesterol transport are the major mechanisms accounting for the anti-atherogenic properties of HDL.
HDL Metabolism: Role of CETP

A1 = apolipoprotein A1
ABCA1 = ATP-binding cassette transporter A1
CE = cholesterol ester
CETP = cholesterol ester transfer protein
FC = free cholesterol
LCAT = lecithin cholesterol acyltransferase
LDL = low-density lipoprotein
LDLR = LDL receptor
SR-BI = scavenger receptor class-B, type I
TG = triglyceride
VLDL = very low density lipoprotein

Slide Source
Lipids Online Slide Library
www.lipidsonline.org
Lower activity and mass of CETP in RA patients on glucocorticoid therapy compared with controls.

Could imply a functional impairment of HDL given that this enzyme plays a pivotal role in reverse cholesterol transport.

The CEFCR was greater in patients with active RA compared with healthy volunteers; however, no differences in CE production rate, CETP, or HDL-apoA-I and LDL-apoB FCGR were observed (Table 1). Following tofacitinib treatment in patients with RA, the CE FCGR decreased \( (p < 0.0014 \text{ versus baseline}) \) and cholesterol levels increased (Table 1). A significant inverse correlation was noted between the change in CE catabolism and the change in HDL-C. Greater decreases in CE catabolism with tofacitinib treatment were associated with greater increases in HDL-C. These data suggest that lower cholesterol levels in patients with active RA may be driven in part by increases in CE catabolism, which are reversed by tofacitinib [57]. Results of this study are discussed in detail elsewhere in seminars article 2016.
Quantitative measurements of HDL were not predictive of subclinical or clinical atherosclerosis in any studies on patients with rheumatic diseases.

The importance of HDL to atherosclerosis in RA becomes apparent when qualitative rather than quantitative properties of HDL are measured.
In patients with chronic diseases, which are characterized by oxidative stress and systemic inflammation, HDL may have pro-inflammatory properties and lose their cardio-protective function.
The ability of HDL particles to protect LDL particles from oxidation might be impaired in RA.

Feingold 2010

<table>
<thead>
<tr>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Amyloid A (SAA)</td>
<td>Apo A-I</td>
</tr>
<tr>
<td>Apo J (clusterin)</td>
<td>Apo A-II</td>
</tr>
<tr>
<td>Secretory phospholipase A2 (SPLA2)</td>
<td>Apo C I, II, and III</td>
</tr>
<tr>
<td>Apo E</td>
<td>Apo M</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>LCAT</td>
</tr>
<tr>
<td>Apo A-VI and V</td>
<td>CETP</td>
</tr>
<tr>
<td>PAF-acetylhydrolase</td>
<td>Paraoxonase 1 (PON 1)</td>
</tr>
<tr>
<td>PLTP (human)</td>
<td>PLTP (rat)</td>
</tr>
<tr>
<td>Lipopolysaccharide binding protein (LBP)</td>
<td>Transferrin</td>
</tr>
<tr>
<td>Bactericidal/permeability increasing protein (BPI)</td>
<td>Hepatic lipase</td>
</tr>
</tbody>
</table>
Good Cholesterol

It's not easy having an evil twin.
Composition Changes in HDL

Carmen García-Gómez et al 2014
These changes in the pro-arthrogenic lipid profile can be altered with effective RA treatment even without treating with traditional lipid lowering medications.
Size matters

- Small dense LDL particles more readily infiltrate the endothelium and thus become more susceptible to oxidative changes.

- In RA, higher levels of small dense LDL particles and lower levels of small HDL particles
LDL

- Smallest, most dense associated with increase CVD risk
- LDL transports cholesterol from liver to tissues for precursor to form vitamins, hormones and to supply energy.
- Endothelial wall alters with increased space permits entry of LDL especially those small and dense and modified by oxidation
Lipoprotein(a), or Lp(a), which comprises a large glycoprotein linked to an LDL-like particle and is often measured in patients with otherwise unexplained CVD, has been shown to be elevated in the serum of patients with RA in comparison with control individuals.
<table>
<thead>
<tr>
<th><strong>Lipoprotein A</strong></th>
<th>Increased</th>
<th>Inc LDH small, dense</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelet Activating Factor Acetylhydrolase</strong></td>
<td>Increased</td>
<td>Prothrombotic, Interferes with Reverse Cholesterol Transport</td>
</tr>
<tr>
<td><strong>Phospholipas A 2-IIA</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests.”
What to measure?
SCORE- Systematic Coronary Risk Evaluation

- Underestimates risk in RA- (even with HS-CRP)
QRISK2-2016

UK National Health Service and is based on routinely collected data from many thousands of GPs across the country who have freely contributed data for medical research.
QRISK2

- Used in the United Kingdom, includes RA as an independent risk factor and seems to improve risk estimation.
- Some evidence that it may overestimate the risk.

Arts et al. 2015
Hippisley-Cox et al. 2008
1. RA is associated with greater risk for CVD
2. The control of the disease activity is imperative for lowering the CVR
3. Cardiovascular risk assessment according to national guidelines, annually or whenever the antirheumatic treatment changes, is necessary for all patients with RA
4. Risk score models should be adapted for RA patients after the multiplication by a factor of 1.5 if two of the three following criteria are fulfilled:
   - Disease duration >10 years
   - RF or ACPA positivity
   - Extra-articular manifestations
5. When the SCORE model is applied the TC/HDL ratio should be used
6. Pharmacological treatments should follow the national guidelines
7. Statins, ACE inhibitors/A-II blockers are the first treatment options
8. The effect of NSAIDs and coxibs on the CVR is not well established. Caution is required when prescribing them, especially for patients with documented CVD or at high CVR
9. The lowest dose possible of corticosteroids is advised
10. Smoking cessation is recommended
CV risk score in RA seems to be underestimated even after multiplication factor

327 patients by Corrales et al. (2015)

- 96 individuals were classified as low risk according to SCORE
- 201 at moderate risk

After the multiplication for RA only 5 patients (2%) were reclassified as high or very high risk.
EULAR introduced revised recommendations which have not been published yet.

- The integration of carotid ultrasonography in the screening
- The multiplication of the risk score by 1.5 irrespective of risk the 3 risk factors

Nurmohamed, 2015
Why Traditional Calculators Fail

- Developed for men (higher CV in normal population)
- Women represent major population in RA
- 1/4 of women with RA that are classified as very low risk (SCORE) exhibit carotid plaques which places them in the high risk category.

Corrales et al 2015
2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines increased the proportion of patients with RA who were eligible for lipid-lowering therapy although the CV risk estimation remained inaccurate

Kawai et al. 2015; Tournadre et al. 2015
At present, the most useful predictor of CVD seems to be the total cholesterol to HDL-C ratio; this value either does not change or only modestly ‘improves’ with successful anti-inflammatory therapy owing to concomitant rises in both total cholesterol and HDL-C levels in
Carotid Ultrasound
Common Carotid Ultrasound

- Superficial in location
- Relatively stationary
- Runs parallel to the surface of the neck
Objective: To examine the evidence to determine the usefulness of ultrasound in the diagnosis of subclinical atherosclerosis in rheumatic diseases assessed by carotid intima-media thickness (IMT).
Ultrasound image showing measurement of near and far wall CIMT in the distal 1 cm of the CCA.
Stroke Prevention and CIMT Carotid Wall Thickness Ultrasound Exam by SmartHealth Screening
Carotid IMT

- January 2005 to May 2015
- Results: A total of 56 studies were identified for analysis, with almost all (95.7%) reporting an increased IMT in relation to the control group.
- Conclusions: Patients with rheumatic diseases have an increased cardiovascular risk assessed using IMT.

Corrales et al 2014
Treatment - non biologic
Treatment

- Dutch – Combination Therapy in Early RA; COBRA
  - 134 newly diagnosed RA
  - Sulfasalazine or mtx/prednisolone/sulfasalazine

- Results: both groups increased cholesterol with greater increases in TC and HDL-C then group 1. Had better clinical improvement in RA.
TNF -Inhibitors

- Meta-analysis-15 studies, 700 patients 13 studies 338 patients
- Increases in TC and HDL-c
- LDL did not change

- Van Sij et al 2011, Dainen et al 2012
Interest in this drug on lipids has been driven largely by the significant changes in lipids observed during the clinical trial of this drug which acts against the IL-6.
Phase 3 trial of TCZ (OPTION) involving 623 patients with moderate-to-severe active RA despite MTX

Increases 430% above base line in TC/HDL-C ratio occurred in 17% of those receiving 8mg/kg of TCZ

Similar effect has been seen in other studies.
What to do

- Control what we can control:
- Do not stop prescribing statins if prescribed - increase in death
"He said he won't give me a new heart unless I change my lifestyle."
Lifestyle modification

- Exercise- wont cure- appear to have a substantial improvement of the symptoms representing the primary barriers for physical activity and exercise, such as pain and fatigue
Traditional Risk Factors

- Still very important
- Control weight, diabetes, hypertension
- Quit smoking
Impact of Traditional Cardiovascular Risk Factors

- Baghadi et. al Meta-Analysis 2015
- Hypertension, type 2 diabetes (T2D), smoking, hypercholesterolemia, obesity, and physical inactivity] as exposures and MI, CV morbidity (MI, angina, heart failure, stroke, and PAD combined
- Only hypertension, type 2DM, hypercholesterolemia nad obesity increase CV risk in patients with RA
Most importantly

- Refer to someone who has expertise on high risk patients
- Attempt to risk stratify- carotid ultrasound, lipid subsets
- More intense measurements of inflammation i.e. musculoskeletal ultrasound for subclinical synovitis, Vectra

- Treat disease aggressively- should be termed **Rheumatoid Disease** rather than **Rheumatoid Arthritis**