Targets for Cardiovascular Disease Prevention in RA

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Disclosures

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  - NIH/NIAMS, American College of Rheumatology Research and Education Foundation, Arthritis Foundation, Pfizer
- Consultant: Genentech
Windows of Opportunity for Prevention: CVD

- Subclinical Disease Onset or Risk Factors
- 1st Sentinel Event
- Recurrence of Disease
- Subclinical Phase
- Primary Prevention
- Secondary Prevention
- Tertiary Prevention
Cardiovascular Disease in RA

• Mortality from CVD events increased 50% relative to non-RA control populations\(^1\)
  - Across 24 cohort studies
  - 111,758 patients
  - 22,927 CV events

• Relative Risk in RA for Women = Men for CVD events leading to death

• Increase in ischemic heart disease events precedes RA diagnosis, but also increased with disease duration\(^2\)

• Atherosclerosis in RA (quantitative)
  - RA patients demonstrate more subclinical atherosclerosis in multiple vascular beds compared with controls\(^3,4\)

• Atherosclerosis in RA (qualitative)
  - Atherosclerotic plaques in RA patients demonstrate more inflammatory features and are more rupture prone\(^5\)

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\(^5\)Aubry et al. *J Rheumatol* 2007;34;937-942
RA Severity is a Determinant of Subclinical Coronary Atherosclerosis

Hypothetical Contribution of Traditional and Disease-Related Factors to CVD Risk in RA

From Symmons DP and Gabriel SE. Nat Rev Rheumatol 2011;7(7):399-408.
RA and CVD: Traditional Risk Factors May Have More Impact in Setting of Inflammation

Level at Which CRP was Associated with Higher Risk of Incident or Progressive Plaque was Modified by Baseline CVD Risk

Low CVD Risk

IRR = 0.86 \quad (p = 0.17)

Higher CVD Risk

IRR = 2.16 \quad (p < 0.05)

Adjusted for baseline age, hormone replacement, and average swollen joint count

Giles et al. *Arthritis Rheum* 2011;
CVD Prevention in RA:
Identifying the At-Risk RA Patient
Possible Approach #1

- Treat every RA patient aggressively to complete remission of disease activity
  - May not address background CVD risk factors
  - Possible carryover effects from prior high-grade inflammation
  - Possible non-inflammatory RA-associated CVD risk factors
    - i.e. genetic risk factors
  - Observational evidence only
    - Focus on pharmacologic agent, not treatment effect, in general
    - No trials
      - Confounding by indication
      - Other biases
Methotrexate and CVD Events in RA (and Other Inflammatory Arthritis)

CVD Reduction with TNF inhibitors in RA Dependent on Response

Table 3. Incidence rates of verified first MI in nonresponders and responders to anti-TNFα treatment*

<table>
<thead>
<tr>
<th></th>
<th>Nonresponders (n = 1,638)</th>
<th>Responders (n = 5,877)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>1,815</td>
<td>9,886</td>
</tr>
<tr>
<td>No. of reported MIs</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>Rate of MIs per 1,000 person-years (95% CI)</td>
<td>9.4 (5.5–15.0)</td>
<td>3.5 (2.5–4.9)</td>
</tr>
<tr>
<td>Incidence rate ratio</td>
<td>Referent</td>
<td>0.38 (0.21–0.67)</td>
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<tr>
<td>Incidence rate ratio, adjusted for age and sex</td>
<td>Referent</td>
<td>0.38 (0.22–0.68)</td>
</tr>
<tr>
<td>Incidence rate ratio, multivariate analysis†</td>
<td>Referent</td>
<td>0.36 (0.19–0.69)</td>
</tr>
<tr>
<td>Incidence rate ratio by sex, multivariate analysis‡</td>
<td>Referent</td>
<td>0.31 (0.12–0.81)</td>
</tr>
<tr>
<td>Male patients</td>
<td>Referent</td>
<td>0.46 (0.20–1.06)</td>
</tr>
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<td>Female patients</td>
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* 95% CI = 95% confidence interval (see Table 1 for other definitions).
† Adjusted for age, sex, disease severity, body mass index, social deprivation, smoking history, comorbidity, and baseline drug use.

Possible Approach #2

- Aggressive management of traditional CVD risk factors in every RA patient
  - Model is CVD risk factor management in diabetes
  - Targets and treatment goals not established
    - Statins and other lipid modulators
    - Aspirin
    - Anti-hypertensives
    - Fish-oil
    - Others

- Evaluation needed
  - Assumption: excess CVD risk in RA is driven through these pathways
    - Inflammation x Traditional CVD risk factors interactions compelling
Extrapolation from the JUPITER trial in RA?

Ridker et al. Lancet. 2009 Apr 4;373(9670):1175-82
Targets for Control of Traditional CVD Risk Factors not Currently Met in RA Patients

Possible Approach #3

- Identify and treat novel CVD risk factors that may directly drive excess CVD risk in RA
  - Over-represented in RA and/or risk factors for incident/severe disease
    - Periodontal Disease
    - Obesity/Adipose Inflammation
    - Insulin Resistance
      - PPAR agonists, etc...
    - Shared genetic risk factors
      - i.e. MHC, others
    - Vitamin D
### Table 1  The 10 recommendations for cardiovascular (CV) risk management in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)

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<th>Recommendations</th>
<th>Level of evidence</th>
<th>Strength of recommendation</th>
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<td>1. RA should be regarded as a condition associated with higher risk for CV disease. This may also apply to AS and PsA, although the evidence base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden.</td>
<td>2b–3</td>
<td>B</td>
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<td>2. Adequate control of disease activity is necessary to lower the CV risk.</td>
<td>2b–3</td>
<td>B</td>
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<td>3. CV risk assessment using national guidelines is recommended for all patients with RA and should be considered annually for all patients with AS and PsA. Risk assessments should be repeated when antirheumatic treatment has been changed.</td>
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<td>4. Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria:</td>
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<td>5. TC/HDL cholesterol ratio should be used when the SCORE model is used.</td>
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ACE, angiotensin-converting enzyme; anti-CCP, anti-cyclic citrullinated peptide; AT-II, angiotensin II; coxibs, cyclo-oxygenase-2 inhibitors; HDL, high-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol.

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Utility of CVD Risk Models in RA


- Framingham underestimated CVD event rate in RA patients
  - Subgroups of importance
- 1.5 multiplier did not improve prediction
- Adding 10 years to age improved prediction for men, not women
Incremental Added Value of Coronary Calcium Scoring in “Low Risk” Women (non-RA study)

- n=2,684 women from the Multi-Ethnic Study of Atherosclerosis
  - “Low Risk” based on Framingham (Risk Score<10%)
  - Age<80, no diabetes

- Higher coronary calcium scores associated with incident CVD events greater than that predicted by Framingham

From Lakoski et al. *Arch Intern Med* 2007;167(22):2437-2442
Incremental Added Value of Coronary Calcium Scoring in “Low Risk” Women (non-RA)

Only 4% of “low risk” women had a CAC > 300; 10% had a score > 100

Arterial Age: A Method for Refining CVD Risk Stratification Using Coronary Calcium Score

Back to MESA CAC

Input your Agatston calcium score, and (optionally) age, gender, total cholesterol, HDL cholesterol, systolic blood pressure, smoking status, use of anti-hypertensive medication, and click "Calculate".

Agatston Calcium Score: 

OPTIONAL (To obtain estimated Framingham 10 year CHD risk)

Age (over 45): 

Gender:  ○ Female  ○ Male

Total cholesterol (mg/dl): 

HDL cholesterol (mg/dl): 

Systolic BP (mmHg): 

Current smoker:  ○ No  ○ Yes

Use of meds for hypertension:  ○ No  ○ Yes

Calculate

http://www.mesa-nhlbi.org/Calcium/ArterialAge.aspx
RA: Does Arterial Age Change Framingham Risk Estimates in RA Patients?

- RA patients vs. non-RA controls
  - age, gender, race matched without diabetes
  - RA: n=185 from ESCAPE RA
  - Control: n=251 from Baltimore MESA Cohort
- All had Coronary Calcium Score
- Age modified for Framingham Risk Equation
  - Arterial Age substituted for Biological Age
CVD risk prevention has the potential to have a large impact on mortality reduction.

Strategies include targeting inflammatory pathways and traditional CVD risk factors:
- Other mechanisms may need to be targeted
- Very little evaluation of efficacy/effectiveness available

Current CVD risk stratification sub-optimal:
- Standard risk stratification tools underestimate risk
- Modifications to tools based on multiplication factors/RA characteristics with little improvement
- Augmented screening tools may be beneficial