Cardiovascular disease in patients with systemic autoimmune diseases

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URMC
• Conflict of interest disclosure:

• Amgen shareholder
Accelerated CVD with rheumatic diseases

- Defining the problem
  - Heart disease in RA and SLE

- Strategies to reduce the risk
  - Patient education
  - Disease control
  - Risk factor modification
### Annual incidence

\( \times/100,000 \)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>2600</td>
</tr>
<tr>
<td>Gout</td>
<td>1480</td>
</tr>
<tr>
<td>PMR</td>
<td>739</td>
</tr>
<tr>
<td>Rheumatoid</td>
<td>100</td>
</tr>
<tr>
<td>Juvenile IA</td>
<td>54</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>12</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>7.3</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>6.6</td>
</tr>
<tr>
<td>SLE</td>
<td>5.5</td>
</tr>
<tr>
<td>Sjogren’s</td>
<td>3.9</td>
</tr>
</tbody>
</table>

- **Gout**
- **Osteoarthrosis**
- **Polymyalgia**
- **Rheumatoid**
- **Juvenile IA**
- **Temporal Arteritis**

Cardiovascular manifestations of rheumatic (systemic autoimmune) diseases

Myocardial
- CHF
- LVH
diastolic dysfunction
myocardial fibrosis
amyloidosis

Valvular
- Libman-Sacks vegetation
valvular regurgitation
valvular nodule

Pericardial
- pericardial effusion
pericarditis

Rheumatoid arthritis
Systemic lupus
erythematosus
Spondyloarthropathies
Vasculitides

Electrical
- sudden cardiac death
ventricular arrhythmia
SVT
AV block

Vascular
- atherosclerosis
arterial stiffness
vasculitis
thrombosis

Prasad, Nature 2015
Common mechanisms underlying RA and atherosclerosis

Cardiovascular manifestations in patients with RA

Maradit-Kremers, et al. Arth and Rheum, 2005
Survival following PCI (stenting) in Taiwan from 2000 to 2010

Overall survival

- Controls
- RA
- SLE

n = 171,762 controls
525 RA
211 SLE

HR
RA 1.55 p<0.0001
SLE 2.20 p<0.0001

Lai, Ann Rh Dis, 2015
Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease?

Hazard ratios
DM  2.0 (1.1-3.7)
RA  2.2 (1.3-3.6)

Peters, Arthritis Care & Research, 2009
### From: 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Framingham</th>
<th>SCORE</th>
<th>PROCAM</th>
<th>Reynolds (W)</th>
<th>Reynolds (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age sex</td>
<td>Age sex</td>
<td>Age</td>
<td>Age Hgb A1c, smoking SBP</td>
<td>Age sbp T chol HDL smoking hsCRP fam hx MI &lt;60</td>
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<tr>
<td></td>
<td>T chol</td>
<td>LDL</td>
<td>LDL</td>
<td>smoking SBP</td>
<td>T chol HDL smoking hsCRP</td>
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<tr>
<td></td>
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<td>BP med</td>
<td>smoking</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>family history</td>
<td>family history</td>
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<tr>
<td></td>
<td></td>
<td>diabetes, TG</td>
<td>Parental hx</td>
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<td></td>
<td></td>
<td></td>
<td>MI &lt;60</td>
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<td></td>
</tr>
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</tbody>
</table>
EULAR evidence based recommendations for CV risk management

- RA, PsA, ank spondy carry higher risk for CV disease
- Adequate control of disease activity is necessary to lower the cv risk
- Annual CV risk assessment according to local guidelines
- Risk score models should be modified by 1.5 if 2 of 3 present:
  - disease duration greater than 10 years
  - Positive RF or CCP antibody
  - Presence of extraarticular manifestations

Peters et al Ann Rheum Dis, 2010
EULAR evidence based recommendations continued

- Statins, ACE-i and or AT II blockers are preferred
- NSAIDS and COX-2s should be used with extreme caution
- Use lowest dose possible of corticosteroids
- Recommend smoking cessation

Peters et al Ann Rheum Dis, 2010
Mortality HR for methotrexate use compared with no methotrexate use in RA cohort

<table>
<thead>
<tr>
<th>Cause</th>
<th>HR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>0.4</td>
<td>(0.2-0.8)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td><strong>0.3</strong></td>
<td>(0.2- 0.7)</td>
</tr>
<tr>
<td>Non-cardiovascular mortality</td>
<td>0.6</td>
<td>(0.2-1.2)</td>
</tr>
</tbody>
</table>

Choi et al, Lancet 2002

adjusted for:
age, sex, rheumatoid factor, duration of disease, smoking, education, HAQ score, patient global assessment, joint counts, ESR, prednisone use, # of other RA meds
Meta-analysis of current treatment on CV events in patients with RA

<table>
<thead>
<tr>
<th>Tumor necrosis factor inhibitors</th>
<th>RR</th>
<th>p</th>
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<tbody>
<tr>
<td>All CVE</td>
<td>0.70</td>
<td>0.005</td>
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<tr>
<td>MI</td>
<td>0.59</td>
<td>0.04</td>
</tr>
<tr>
<td>CHF</td>
<td>0.75</td>
<td>0.19</td>
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<tr>
<td>Stroke</td>
<td>0.57</td>
<td>0.02</td>
</tr>
<tr>
<td>MACE</td>
<td>0.30</td>
<td>0.003</td>
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<table>
<thead>
<tr>
<th>methotrexate</th>
<th>RR</th>
<th>p</th>
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<tbody>
<tr>
<td>All CVE</td>
<td>0.72</td>
<td>0.007</td>
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<tr>
<td>MI</td>
<td>0.81</td>
<td>0.01</td>
</tr>
<tr>
<td>CHF</td>
<td>0.8</td>
<td>insig</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.78</td>
<td>insig</td>
</tr>
<tr>
<td>MACE</td>
<td>0.38</td>
<td>0.35</td>
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</table>

Roubille, Ann Rheum Dis, 2015
Meta-analysis of anti-inflammatory agents on CV events in RA and PsA

<table>
<thead>
<tr>
<th>corticosteroids</th>
<th>RR</th>
<th>p</th>
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<tr>
<td>All CVE</td>
<td>1.47</td>
<td>0.04</td>
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<tr>
<td>MI</td>
<td>1.41</td>
<td>0.21</td>
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<tr>
<td>CHF</td>
<td>1.42</td>
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<tr>
<td>Stroke</td>
<td>1.57</td>
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<tr>
<td>MACE</td>
<td>1.62</td>
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</table>

<table>
<thead>
<tr>
<th>All NSAID</th>
<th>RR</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>All CVE</td>
<td>1.18</td>
<td>0.04</td>
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<tr>
<td>MI</td>
<td>1.13</td>
<td>0.28</td>
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<td>CHF</td>
<td>0.86</td>
<td>0.11</td>
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<tr>
<td>stroke</td>
<td>2.15</td>
<td>0.01</td>
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<tr>
<td>MACE</td>
<td>1.56</td>
<td>0.18</td>
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<table>
<thead>
<tr>
<th>COX-2</th>
<th>RR</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>All CVE</td>
<td>1.36</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Roubille, Ann Rheum Dis, 2015
Psoriatic arthritis treatment with MTX or TNF-i

significant decrease in risk of all CV events

RR 0.75  95% CI(0.63 to 0.91)

Roubille et al Ann Rheum Dis, 2015
Systemic Lupus Erythematosus

1. Genes
   - C1q, C2, C4
   - HLA-D2, D3, D8
   - MBL
   - FcR 2A, 3A, 2B
   - IL-10
   - MCP-1
   - PTPN22

2. Abnormal Immune Response
   - Ag
   - DC
   - T cell
   - B cell
   - C3
   - C3a

3. Autoantibodies Immune Complexes
   - Rash
   - Nephritis
   - Arthritis
   - Leukopenia
   - CNS dz
   - Carditis
   - Clotting
   - Etc.

4. Inflammation
   - Chr. inflam.
   - Chr. oxid.

5. Damage
   - Renal Failure
   - Atherosclerosis
   - Pulm fibrosis
   - Stroke
   - Damage from Rx
   - Etc.
SLE manifestations in the heart

- Pericarditis
- Myocarditis
- Endocarditis
## Mortality in SLE
the first 5 years from diagnosis

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active SLE</td>
<td>13</td>
<td>29%</td>
</tr>
<tr>
<td>Multisystem sle</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Renal</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>3</td>
<td>7</td>
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<tr>
<td>hematologic</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>neurologic</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CVA</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>PE</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>MI</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>GI bleed</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Infections</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>malignancies</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

Cervera, Medicine (Baltimore), 1999
Pericardial disease in SLE

- Pericarditis w or w/o effusion present in 20 to 50% of studies
- Pericardial effusions
  - Usually seen with disease flares
  - Usually small
  - May be asymptomatic
- Not usually associated with ecg changes
- Complications (tamponade, constriction) not seen (absent renal failure)
Cardiovascular Disease
a leading cause of morbidity and mortality in patients with SLE

- Nurses health study
  - 2.26 (1.45-3.52) RR risk of a cardiovascular event in SLE

Manzi Am J Epidem 1997

Hak et al., Arthr and Rheumatism, 2009
SLE cardiovascular

- Like inflammatory arthritis pathogenesis for increased risk not well understood
- Traditional cardiac risk factors are common in patients with SLE
- The disease itself and duration of disease
- Glucocorticoid use
- Use of immunosuppression

Wajed, Rheumatology, 2004
Treatment and prevention

• Lifestyle modification:
  – Target BMI $<$25$\text{kg/m}^2$
  – Avoid smoking
  – Regular exercise
  – Diet

• Treatment:
  – Statins
  – Anti-hypertensives
  – Reduce corticosteroid dose
  – (hydroxychloroquine)
Take home

• Systemic autoimmune/rheumatic diseases should be considered as risk factors for CVD

• 1.5 X traditional CAD scoring system for risk assessment

• ‘Treating to Target’ reduces this risk in RA, likely psoriatic arthritis and possibly SLE