The Role of Lipid Management in CV Risk Assessment of the Patient with a Rheumatic Disorder: RA, SLE, GCA, CTD, PM, DM

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February 25, 2017
Disclosures

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Objectives

- Explain CV risk for the rheumatologic patient
- Explain when lipids should be assessed
- Explain to patient issues to consider when setting lipid targets and planning therapy
Abbreviations

- RA    Rheumatoid Arthritis
- SLE   Systemic lupus erythematosus
- GCA   Giant Cell Arteritis
- SS    Sjögren’s Syndrome
- CTD   Inflammatory Connective Tissue Disorder
- PM    Polymyositis
- DM    Dermatomyositis
Charlie: 74 y/o white male with RA

- Presents for pre-operative evaluation for toe surgery
  - Toes are crossing over, building large callouses
  - Has neuropathy so numb below knees

- **Current Symptoms:**
  - Less activity tolerance, fatigue, SOB, atypical chest discomfort

- **Medications:**
  - Adalimumab injection weekly, Methotrexate 6mg weekly, Prednisone 4mg qd x years
  - Atorvastatin 40mg PO daily
  - Clopidogrel, Lisinopril-HCT, Lansoprazole, Folic acid, MVI, Nortriptyline
  - PRN: Advair, Alprazolam, Naproxen
Charlie: 74 y/o white male with RA

PMH:
- RA x 40-50 yr, multiple joint surgeries until Humira initiated
  - Rheumatoid nodules in left lung resected lower lobe
- CAD: abnormal nuclear study with fixed inferior defect & reversible ischemia. Inferior Q waves on EKG - no cath; echo showed no wall motion abnormalities
  - Aortic sclerosis, without stenosis
  - Carotid atherosclerosis bilaterally
- Asthma/chronic bronchitis
- Anemia
- T2DM with HTN, dyslipidemia & neuropathy
- TIA/scar in back of right eye due to plaquenil years ago
Charlie: 74 y/o white male with RA

**SH**  Married - wife is supportive and has had him try different diets in the past. Remote hx of smoking. tries to exercise

**FH**  + T1D; son #2 with possible RA. Mom had CHF; Dad had CVA

**Recent Labs**
- TC 201 TG 160 HDL direct 50 LDL calc 119
- Hgb 13.3, Hct 40.6, Plt 209
- Glu 109, BUN 13, Creat 1.1, eGFR 70
- Uric acid 5.5, Total protein 6.3, Albumin 4.0, alk phos 66, AST 33, ALT 46
- TSH 2.16
- Albumin-to-Cr ratio: < 20
- A1c 7.2% (up from 6.8%)
Charlie: 74 y/o white male with RA

Questions to Consider:

- What is Charlie’s CV risk?
- What is Charlie’s target for lipids?
- Should Charlie’s lipid management regimen be changed?
- Will Charlie benefit from dietary intervention?
- Can Charlie take herbs or supplements?
- Can Charlie go for surgery next month?
## CV Risk in Rheumatic Diseases

<table>
<thead>
<tr>
<th>Premature atherosclerosis</th>
<th>Coronary arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Takayasu arteritis</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Kawasaki disease</td>
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<tr>
<td>Psoriatic arthritis</td>
<td>Giant cell arteritis</td>
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<tr>
<td>Gout</td>
<td>Polyarteritis nodosa</td>
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<td>ANCA-associated vasculitis</td>
<td>Granulomatous polyangiitis</td>
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<tr>
<td>Takayasu arteritis</td>
<td>Churg–Strauss syndrome</td>
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<td>Giant cell arteritis</td>
<td>Rheumatoid arthritis</td>
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</table>

CV Risk in RA

- Heart disease is a leading cause of death in patients with RA
- Although RA is typically considered a disease of the joints, the systemic inflammation in RA has effects throughout the body, particularly in the vasculature
- CVD risk is 1.5- to 2-fold higher in RA compared to individuals from the general population with the same age and gender
- This elevated CVD risk in RA is attributed to chronic inflammation leading to accelerated atherosclerosis
- Standard risk factors such as metabolic syndrome, hypertension and diabetes are still predictors of CV risk

Estimating CV risk in RA

no risk calculator has been validated for inflammatory diseases in the US

- Framingham Risk Score: observed CV risk was 2X higher than the calculated in women and 65% higher in men
- Reynolds Risk Score underestimated CV risk in RA
- United Kingdom based QRISK2 incorporates RA as a variable
  - one study showed it overestimated CV risk in RA
- European League Against Rheumatism recommendations in 2009 relied heavily on expert opinion.
  - not adopted in the United States
  - Rec multiplying FRS x 1.5 if patients meets 2/3 criteria:
    - RA disease duration >10 years
    - + for RF or anti-CCP
    - presence of extra-articular manifestations such as bone erosions
- Studies in the US population have found that multiplying the FRS x 1.5 does not improve estimation of CV risk
Frequency of Lipid Assessments

- Baseline
- Annually
  - do not check until you know disease is not flaring
- Consider quarterly if clinical evidence of ASCVD & unstable CTD

Medication Specific Issues
- Steroids may worsen lipids
- tofacitinib and tocilizumab have a specific frequency of lipid measurements recommended
- Methotrexate: blood levels may be increased by atorvastatin
- Rituximab: statin use may also be associated with a reduced clinical response
- Metabolism via Cytochrome P450s: adalimumab carries warning that may alter CYP450 enzyme levels

Chart 12  Recommendations for patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians should be aware that patients with RA are at increased risk for ASCVD. The association of RA and systemic lupus erythematosus with ASCVD risk raises concern that other inflammatory conditions may also be associated with increased ASCVD risk. However, only RA has been studied sufficiently to accurately quantify the degree to which it increases ASCVD risk.</td>
<td>A</td>
<td>High</td>
</tr>
<tr>
<td>The association between RA and ASCVD risk is independent of the risk associated with major established ASCVD risk factors. For primary prevention of ASCVD, RA may be counted as an additional ASCVD risk factor for risk stratification.</td>
<td>A</td>
<td>High</td>
</tr>
<tr>
<td>Risk stratification is based on the NLA Recommendations for the Patient-Centered Management of Dyslipidemia – Part 1(^1) with initial risk stratification based on the number of major ASCVD risk factors (with the caveat that the presence of RA may be counted as an additional risk factor), the use of risk prediction tools, such as the ATP III Framingham Risk Score or the ACC/AHA Pooled Cohort Equations if two risk factors are present, and the use of other clinical indicators to help inform clinical judgment, if needed.</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinicians should be vigilant in ensuring that RA patients are routinely assessed for cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes, family history of early-onset ASCVD, and smoking. Calculation of lifetime ASCVD risk can be considered for patients age 20-59 years.</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>Statins are generally the first-line treatment for dyslipidemia in RA. At this time, atherogenic cholesterol treatment goals for patients with RA and other inflammatory diseases are the same as described in the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1.(^1)</td>
<td>A</td>
<td>Moderate</td>
</tr>
<tr>
<td>If an RA patient has had lipid levels checked during an RA flare, it is recommended that the lipids be re-checked when their disease is controlled.</td>
<td>B</td>
<td>Moderate</td>
</tr>
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CV Risk in SLE

- Despite a reduction in mortality since the 1970s, CHD remains prevalent in SLE, increasing in frequency with duration of disease
- Overall, clinical CHD affects 5–8% in the first decade of disease and up to 28% after four decades of disease
- SLE patients are more likely to die following their first MI than patients with diabetes
- SLE patients are more likely to require prolonged hospitalization following an MI
CV Risk in SLE

Mean age at the time of the first coronary event is 48-50 years

- Pittsburgh data: women with SLE age 35- to 44-years were >50X more likely to have an MI than women of similar age in the Framingham offspring cohort.
- Women with SLE are 5-6 X more likely to have an MI than their population peers.
- Two thirds of all first cardiac events after the diagnosis of SLE were in women < 55 y/o.
- Mean SLE disease duration at the time of the first coronary event averages 7 to 10 years.

SLE: 5 year prospective study of 78 patients without overt ASCVD

Risk Factors:
- Age
- Cholesterol
- HTN
- Prednisone dose

Table 3: Univariate analysis of risk factors for atherosclerosis in 78 patients with SLE: continuous variables (mean (SD))* in patients with (yes) and without (no) carotid lesions. Only significant results are reported.

Table 5: Multiple logistic regression analysis (best model) of factors associated with carotid lesions in the 78 patients with SLE.
Treatment of Lipids in SLE

- There is emerging evidence from observational studies supporting optimal LDL-C levels as low as 2.0mmol/l (77 mg/dL) in SLE, a target recommended for patients with diabetes.

- Novel risk factors that may have a place in assessment of CHD risk in SLE include hsCRP.
  - Toronto data shows that hsCRP level >1.6mg/L is significantly associated with CHD, independently of disease activity & traditional Framingham risk factors.

- There is no direct evidence to support reduction in CHD risk in SLE with use of statins.
  - Lupus Atherosclerosis Prevention Study (LAPS; n=200): SLE patients with SLE without clinical CVD were treated x 2 years with atorvastatin 40mg daily or placebo with no significant difference between the groups in progression of CAC, cIMT or carotid plaque.

What is the Role of Inflammation in the CV Risk?

- RA and SLE each predispose to premature atherosclerosis but the pathophysiology of the inflammation differs
  - RA: TNFα, interleukin (IL)-1, and IL-6 play a central role in RA pathogenesis
  - SLE: type I interferons (IFNs) predominate in pathogenesis
- Both RA & SLE have endothelial dysfunction, aortic stiffness, and atherosclerotic plaque instability, exacerbated by increased traditional risk factors
What is the Role of Inflammation in the CV Risk?
Giant Cell Arteritis (GCA)

- GCA has not been formally associated with accelerated ASCVD
  - Most patients will have some underlying CAD related to age at Dx:
    - GCA is most common in the 6th decade of life
    - An observational cohort study has identified a short-term increased risk of CVD when compared with the age-matched general population
      - The predominant risk was within the first 2 months of diagnosis
      - 2X risk of MI sustained up to 2 years
    - A case–control study also showed increased early mortality
  - The increased short-term mortality is thought to be due to active arteritis, ischemic complications and adverse effects of glucocorticoid therapy
Gout

- Gout affects up to 2% of individuals.

- **Framingham Study**: gout was associated with a 60% excess in CHD in men, but not in women

- **NHANES**: 60% increase in risk for CV mortality with a history of gout
  - There was a stepwise increase in CV mortality with uric acid concentrations

- **Health Professionals Follow-up Study**: 60% increase in risk of fatal CHD in men with history of gout and prior CVD

- The relationship of gout with risk of CV events in women is unclear

- **Mechanism**: presumed to be inflammation: uric acid crystals activate the NLRP3 inflammasome, a supramolecular complex within cells that generates the active form of the prominent pro-inflammatory cytokine IL-1β

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Sjögren's syndrome

- Primary Sjögren’s syndrome shares many clinical, inflammatory and immunological features with RA and SLE
- Unlike RA and SLE, SS frequently presents a benign and indolent course, often without the need for immunosuppressive therapy
- Retrospectively case-control study of 1284 women & 59 men, mean age 57
  - cerebrovascular events: 2.5% vs. 1.4%, P = 0.005
  - MI: 1.0% vs. 0.4%, P = 0.002
  - Increase in CV event risk with CNS involvement & use of immunosuppressives
  - leucopenia associated with an increased risk of angina

Polymyositis/Dermatomyositis

- Lipid changes in untreated patients:
  - ↑ TGs
  - ↓ HDL
  - ↑ hsCRP

- Few studies addressing CV event rate
  - Swedish study reported incidence of CHD in the 12 months after 1st hospitalization for PM/DM
    - 3.81 (95% CI 2.62-5.35)
Polymyositis/Dermatomyositis

- Lipid lowering medications
  - Document baseline CK
  - Initiate treatment after flare has subsided
  - Treatment may have to be held during disease flares, depending upon symptomatology
Connective Tissue Disorders (CTD) & ASCVD

Retrospective study of de-identified data evaluating the prevalence of inflammatory CTD and ASCVD at the University of Chicago

Scientific Reports. 2016 Feb 4;6:20303
Connective Tissue Disorders (CTD) & ASCVD

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Prevalence of ASCVD (%) vs Age

Scientific Reports.
2016 Feb 4;6:20303
Charlie: 74 y/o white male with RA

- Presents for pre-operative evaluation for toe surgery
- Current Symptoms: ↓activity tolerance, fatigue, SOB, atypical chest discomfort
- PMH: + CAD, + carotid disease
- Medications:
  - Adalimumab injection weekly
  - Methotrexate 6mg weekly
  - Prednisone 4mg qd x years
  - Atorvastatin 40mg PO daily
- **LDL target is at least below 70 mg/dL**
Summary
CV Risk in the Patient with a Rheumatic Disorder

- Most observational studies has found that CV risk is increased in Rheumatic Disorders
- Interventional data is not available to demonstrate a specific benefit of lipid lowering in these special populations
  - Increased prevalence of traditional CV risk factors are generally seen so lipid lowering therapy is indicated
  - Consider treating the presence of these disorders as an additional CV risk factor in primary prevention
Questions?
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