Cardiovascular risk in psoriasis: Implications for your clinical practice

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Learning Objectives

1. Identify the impact of cardiovascular risk on patients with psoriasis
2. Lower the risk of cardiovascular disease through age appropriate screening and management of risk factors
**Mediating factors**

- **Pathophysiology**
  - Th1/17 inflammation (atherosclerosis, thrombosis, lipid metabolism)
  - Epidermal proliferation (↑uric acid, oxidative stress)
  - Angiogenesis (endothelial dysfunction)

- **Treatment**
  - Increase CV risk (e.g. cyclosporine, acitretin)?
  - Decrease CV risk (e.g. methotrexate, TNF inhibitors)?

- **Psychosocial impact**
  - Depression, alcohol and smoking, lower socioeconomic status

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**Environmental risk factors**

- Smoking
- Obesity

**Genes and loci associated with psoriasis, diabetes and CV diseases**

- PSORS2/3/4
- CDKAL1
- ApoE4
- TNFAIP3

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Figure from Kivelevitch et al Circ 2017;136:277-280

Risk of Cardiometabolic Disease in Psoriasis: Retrospective studies

Clinical significance
- Increased risk of MI, stroke, CV death, diabetes
- 5 years of life lost
- Risk of MACE similar to that conferred by diabetes
- Patients treated for severe psoriasis are 30X more likely to experience MACE (attributable to psoriasis) than to develop a melanoma.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adj. RR Mild</th>
<th>Adj. RR Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI¹</td>
<td>1.05</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke²</td>
<td>1.06</td>
<td>1.4</td>
</tr>
<tr>
<td>CV Death³</td>
<td>Not done</td>
<td>1.6</td>
</tr>
<tr>
<td>MACE⁴</td>
<td>Not done</td>
<td>1.5</td>
</tr>
<tr>
<td>Diabetes⁵</td>
<td>1.11</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Comparison of cardiometabolic outcomes: Psoriasis vs. RA vs PsA

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diabetes (all patients)</th>
<th>CV Death (DMARD)</th>
<th>All cause mortality (DMARD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>1.2</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>RA</td>
<td>0.9</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>PsA</td>
<td>1.33</td>
<td>0.96</td>
<td>0.94</td>
</tr>
</tbody>
</table>


Psoriasis BSA predicts death independent of mortality risk factors (N=8760)

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Naldi L JID 2018;138:20-22
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Noe MH et al J Invest Dermatol 2017
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BSA affected by psoriasis predicts diabetes (N=8124)

- **BSA ≤2%**: HR 1.2
  - 199 extra cases of DM per year per 100,000
- **BSA >10%**: 1.6
  - 625 extra cases of DM per year per 100,000
- For each 10% increase in BSA above 10% there is a 20% increase in risk
- 125,650 new cases of DM each year world wide attributable to psoriasis

Wan MT et al JAAD doi: 10.1016/j.jaad.2017.10.050
Arterial Stiffness in Psoriasis

- Arterial stiffness is an early independent predictor of CV events
- Large (N=171,125) UK Biobank population based study (age 40-70) Psoriasis N 2091
- Detailed assessment of CV risk

18-FDG PET CT demonstrates diffuse vascular inflammation, coronary CT reveals increased non calcified plaque and high risk plaque burden.

Naik HB et al Arterioscler Thromb Vasc Biol. 2015 Dec;35(12):2667-76
Lerman et al Circ 2017;136:263-276
Clinical Care Recommendations: Educate and Screen for CV risk factors

AJC Editor’s Consensus: Psoriasis and Coronary Artery Disease

Vincent E. Friedewald, MD, Jennifer C. Cather, MD, Joel M. Gelfand, MD, MSCE, Kenneth B. Gordon, MD, Gary H. Gibbons, MD, Scott M. Grundy, MD, PhD, Michael T. Jarratt, MD, James G. Krueger, MD, Paul M. Ridker, MD, Neil Stone, MD, and William C. Roberts, MD

National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening

Alexa B. Kimball, MD, MPH, Dafna Gladman, MD, Joel M. Gelfand, MD, MSCE, Kenneth Gordon, MD, Elizabeth J. Horn, PhD, MBL, Neil J. Korman, MD, PhD, Gretchen Korver, MD, PhD, Gerald G. Krueger, MD, Bruce E. Strober, MD, PhD, and Mark G. Lebwohl, MD, for the National Psoriasis Foundation

Boston, Massachusetts; Toronto, Ontario, Canada; Philadelphia, Pennsylvania; Skokie, Illinois; Portland, Oregon; Cleveland, Ohio; Salt Lake City, Utah; and New York, New York

Clinical Implications: Elevated cv Risk in Psoriasis

Standard screening recommendations

• Hypertension
  – Normal is <120/80 mmHg
  – Age 18-39, no risk factors & BP <130/85 mmHg: every 3-5 years
  – Age ≥40 and those at increased risk for high BP (BP 130-139/85-89 mmHg, overweight/obese, African Americans): yearly

• Diabetes (fasting plasma glucose, HbA1c, or OGTT)
  – Adults 40-70 with BMI ≥25kg/m2
  – Repeat every 3 years

• Cardiovascular risk assessment
  – Traditional risk factors every 4–6 years in patients 20–79
  – Estimate 10-year risk in those 40–79

TNF inhibitors are cardioprotective in RA and psoriasis meta-analysis of observational studies


Biologics fail to achieve statistically significant differences in CV events in meta-analysis of psoriasis RCTs

<table>
<thead>
<tr>
<th>Class</th>
<th>Meta estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF α inhibitors (adalimumab, etanercept and infliximab)</td>
<td>OR 0.67, 95% CI 0.10-4.63</td>
</tr>
<tr>
<td>anti-IL-17A agents (secukinumab and ixekizumab)</td>
<td>OR 1.00, 95% CI 0.09-11.09</td>
</tr>
<tr>
<td>ustekinumab</td>
<td>OR 4.48, 95% CI 0.24-84.77</td>
</tr>
</tbody>
</table>

Q: Should psoriasis be aggressively treated to lower the risk of CV disease?
A: We don’t know (for certain)

- Observational data suggest methotrexate and TNF inhibitors lower the risk of CV events
- Data do not yet exist to demonstrate a protective effect of phototherapy, apremilast, ustekinumab, secukinumab, ixekizumab, guselkumab on CV events

Proof of Principle: Biologic Inhibition of IL-1B lowers MACE

- Prior MI, CRP≥2 mg/L
- N= 6717, Median follow up 3.7 years
- Canakinumab q 12 weeks IL1-beta (50, 150, or 300 mg)

Ridker PM et al NEJM 2017; 377: 1119-1131
TRIALS Evaluating Impact of Therapies on CV Risk

- **Vascular Inflammation in Psoriasis Trials (VIP):** assessing effects on vascular inflammation and lipid metabolism in moderate-severe psoriasis of:
  - RCT: adalimumab or phototherapy vs. placebo (NCT01553058)
  - RCT: ustekinumab vs. placebo (NCT02187172)
  - RCT: secukinumab vs. placebo (NCT02690701)
  - Open label: apremilast (NCT03082729)

- **Cardiovascular Inflammation Reduction Trial (CIRT) – NOT psoriasis population**
  - Does methotrexate lower the risk of major vascular events in patients with a history of MI and diabetes or metabolic syndrome? (NCT01594333)
## Imaging Endpoints and hs-CRP: Changes from Baseline

<table>
<thead>
<tr>
<th>PET/CT Endpoints</th>
<th>Week 16</th>
<th>52 Wks after First Dose of Adalimumab (All Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>MeanMax TBR from Ascending Aorta</td>
<td>n=53, -0.002 (-0.053 to 0.049)</td>
<td>n=54, 0.002 (-0.048 to 0.053)</td>
</tr>
<tr>
<td></td>
<td>MeanMax TBR of Carotid Arteries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=46, 0.018 (-0.019 to 0.055)</td>
<td>n=50, 0.031 (-0.005 to 0.066)</td>
</tr>
<tr>
<td></td>
<td>% Change in Carotid Wall Area</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=15, -0.27 (-4.10 to 3.71)</td>
<td>n=20, -1.33 (-4.62 to 2.07)</td>
</tr>
<tr>
<td></td>
<td>% Change in hs-CRP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=53, 1.09 (-16.30 to 22.10)</td>
<td>n=54, -28.67 (-40.83 to -14.01)</td>
</tr>
</tbody>
</table>

MeanMax: mean of maximum values; hs-CRP: high-sensitivity C-reactive protein; TBR: target-to-background ratio

Potential Interpretations

- TNF may not play a major role in aortic vascular inflammation in psoriasis?
- Biologics may not be penetrate the aorta?
- More insights to be gained through:
  - Biomarker and exploratory analyses
  - VIP-Ustekinumab, VIP-Secukinumab, and VIP-Apremilast
<table>
<thead>
<tr>
<th>Scenario</th>
<th>TNF</th>
<th>IL12/23</th>
<th>IL-23</th>
<th>IL-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term data</td>
<td>![Star]</td>
<td>Emerging</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>![Star]</td>
<td>FDA approved</td>
<td>TBD</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>![Star]</td>
<td>FDA approved</td>
<td>TBD</td>
<td>![Stop]</td>
</tr>
<tr>
<td>Associated with decreased MI and stroke</td>
<td>Yes</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
</tr>
<tr>
<td>CHF</td>
<td>![Stop]</td>
<td>No warning</td>
<td>No warning</td>
<td>No warning</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>![Stop]</td>
<td>No benefit or harm phase II</td>
<td>No warning</td>
<td>Promising phase II</td>
</tr>
<tr>
<td>Ease of administration</td>
<td>![Star]</td>
<td>![Star]</td>
<td>![Star]</td>
<td></td>
</tr>
<tr>
<td>Patient is obese</td>
<td>Infliximab preferred</td>
<td>Weight-based dosing</td>
<td>Flexible dosing*</td>
<td></td>
</tr>
<tr>
<td>Rapid onset</td>
<td>![Star]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term persistence</td>
<td>![Star]</td>
<td>TBD</td>
<td>TBD</td>
<td></td>
</tr>
</tbody>
</table>

**Biologic Selection Depends on Many Factors**

* = gold standard

Flexible dosing relevant for secukinumab
Psoriasis and comorbid diseases

Epidemiology

Junko Takeshita, MD, PhD, MSCE, Sungat Grewal, BS, Sinéad M. Langan, MB, BCh, BAO, MRCP, MSc, PhD, Nehal N. Mehta, MD, MSCE, Alexis Ogdie, MD, MSCE, Abby S. Van Voorhees, MD, and Joel M. Gelfand, MD, MSCE

Philadelphia, Pennsylvania; London, United Kingdom; Bethesda, Maryland; and Norfolk, Virginia

Psoriasis and comorbid diseases

Implications for management

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