

# Psoriasis and cardiovascular disease: epidemiology, mechanisms, and clinical implications

Kelly C Pearson<sup>1</sup>  
April W Armstrong<sup>2</sup>

<sup>1</sup>Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL,

<sup>2</sup>Department of Dermatology, University of California, Davis, Sacramento, CA, USA

**Abstract:** Psoriasis is a systemic inflammatory disorder, which has been reported to be associated with adverse cardiovascular (CV) risks. CV comorbidities, such as diabetes, dyslipidemia, hypertension, and obesity appear to be increased in psoriasis patients compared with the general population. Psoriasis may contribute independently to adverse cardiac outcomes after accounting for traditional CV risk factors. In this article, it was aimed to summarize large population studies that examine the relationship between psoriasis and CV risk factors and major adverse cardiac outcomes, and highlight proposed mechanisms for the observed epidemiologic link. Specifically, large population-based studies with over 1000 total subjects from 1975 to September 2008 in the English literature are highlighted. The relevant search terms in the Ovid Medline database were applied. The majority of the studies presented evidence for an increased incidence of CV risk factors and an increased risk for major adverse cardiac outcomes in patients with severe psoriasis. The increased risk in severe psoriasis necessitates regular screening for other comorbidities. Current guidelines for screening CV risk factors among psoriasis patients are discussed. Also reviewed is the scarce literature in therapeutic strategies to reduce CV risk factors and major adverse cardiac outcomes in psoriasis patients. Specifically, an emerging area of research on the effects of biologic agents on CV risk factors and CV adverse outcomes in psoriasis is discussed.

**Keywords:** cardiovascular disease, cardiovascular risk factors, psoriasis, diabetes mellitus, myocardial infarction, major adverse cardiovascular events, MACE, hypertension

## Introduction

Psoriasis is a chronic inflammatory disease that affects approximately 2%–4% of the US population.<sup>1</sup> Comorbidities associated with psoriasis include psoriatic arthritis, depression, and cardiovascular (CV) diseases. A growing body of literature suggests a link between psoriasis and cardiovascular disease (CVD). An increased prevalence of CV risk factors in psoriasis patients has been observed in several cross-sectional studies.<sup>2–6</sup> In particular, patients with severe psoriasis have an increased risk of developing CV risk factors and experiencing major adverse cardiac outcomes such as myocardial infarction (MI), stroke, and CV mortality.<sup>7–14</sup> Psoriasis may represent a risk factor for major adverse cardiac outcomes independent of conventional CV risk factors. The understanding of the mechanistic basis for the observed epidemiologic association between psoriasis and CVD has evolved.<sup>15,16</sup> In this review, we first discuss pivotal studies that investigated the relationship between psoriasis and CV factors and outcomes. While numerous epidemiologic studies have examined the association of psoriasis and CVD, the focus of this article is *not* to exhaustively present all studies,

Correspondence: April W Armstrong  
Dermatology Clinical Research Unit,  
Director, Teledermatology Program  
Department of Dermatology, University  
of California Davis Health System,  
3301 C Street, Suite 1400, Sacramento,  
CA 95816, USA  
Tel +1 916 871 9688  
Fax +1 916 442 1630  
Email aprilarmstrong@post.harvard.edu

but to discuss findings from selected, large, population-based studies from well-characterized populations. Most but not all studies suggest that severe psoriasis appears to be an independent risk factor for CVD risk factors and adverse cardiac outcomes. We then discuss how to evaluate CV risk factors in psoriasis patients using guidelines recommended by the National Psoriasis Foundation (NPF), which include regular evaluations of CV risk factors starting at the age of 20. We explore some of the proposed mechanistic links that associate psoriasis with CVD. Lastly, we discuss therapeutic strategies to reduce CV risk factors and major adverse cardiac outcomes in psoriasis patients. Specifically, more recent studies have focused on the effects of anti-TNF agents on the reduction of CV risk factors and events in psoriasis patients.<sup>17–20</sup> In this article, we aim to highlight relevant literature on epidemiology, mechanisms, and the clinical implications for the association between psoriasis and CVD.

## Epidemiology of psoriasis and cardiovascular risk factors

### Large cohort studies on the association between psoriasis and CV risk factors

The established CV risk factors include diabetes, hypertension, obesity, dyslipidemia, smoking, and a family history of cardiovascular diseases.<sup>21</sup> In this section, research findings from selected cohort studies that use large population databases to examine the relationship between psoriasis and CV risk factors such as diabetes, hypertension, dyslipidemia, and obesity are discussed.<sup>10,22,23</sup> The results are summarized in Table 1.

The risk of diabetes in psoriasis patients has been studied in a number of large population-based analyses.<sup>10,22</sup> In an observational study using the UK-based General Research Practice Database (GRPD), investigators reported the cumulative incidences of risk factors for myocardial infarction (MI) and other vascular diseases after psoriasis diagnosis.<sup>10</sup> The investigators found a moderately increased relative risk (RR) of incident diabetes in psoriasis patients (hazard ratio [HR] 1.33, 95% confidence interval [CI] 1.25–1.42) compared with the general population. Another large, population-based study examined the risk of diabetes in US female nurses.<sup>22</sup> The authors found an elevated RR of diabetes in women with psoriasis (RR 1.63, 95% CI 1.25–2.12) compared with women without psoriasis. Among the women with psoriasis, the incidence of diabetes was 3.3% compared with 1.9% in women without psoriasis. In a different study, the authors of a British Colombian

**Table 1** Risk of cardiovascular (CV) risk factors and major adverse cardiac outcomes in psoriasis from highlighted studies

Study	Risk factor or adverse cardiac outcome	Statistical measure	Risk	95% CI
Kaye et al <sup>10</sup>	Diabetes mellitus	RR	1.33	1.25–1.42
Qureshi et al <sup>22</sup>	Diabetes mellitus	RR	1.63	1.25–2.12
Solomon et al <sup>24</sup>	Diabetes mellitus	HR	1.4	1.3–1.5
Kaye et al <sup>10</sup>	Hypertension	HR	1.09	1.05–1.14
Qureshi et al <sup>22</sup>	Hypertension	RR	1.17	1.06–1.30
Kaye et al <sup>10</sup>	Obesity	HR	1.18	1.14–1.23
Kaye et al <sup>10</sup>	Dyslipidemia	HR	1.17	1.11–1.23
Gelfand et al <sup>14</sup>	MI:	RR		
	30 y/o, mild		1.29	1.14–1.46
	30 y/o, severe		3.10	1.98–4.86
	60 y/o, mild		1.08	1.03–1.13
	60 y/o, severe		1.36	1.13–1.64
Lin et al <sup>8</sup>	MI	HR	2.10	1.27–3.43
Brauchli et al <sup>27</sup>	MI:	OR		
	<60 y/o		1.66	1.03–2.66
	>60 y/o		0.99	0.77–1.26
Gelfand et al <sup>11</sup>	Stroke:	HR		
	Mild psoriasis		1.06	1.0–1.1
	Severe psoriasis		1.43	1.1–1.9
Mehta et al <sup>13</sup>	CV mortality:	HR		
	40 y/o		2.69	1.45–4.99
	60 y/o		1.92	1.41–2.62
Ahlehoff et al <sup>9</sup>	CV mortality:	RR		
	Mild		1.14	1.06–1.22
	Severe		1.57	1.27–1.94
Mallbris et al <sup>25</sup>	CV mortality	SMR	1.52	1.44–1.60
Stern and Huibregtse <sup>28</sup>	CV mortality	SMR	1.02	0.9–1.6

**Abbreviations:** CI, confidence interval; HR, hazard ratio; OR, odds ratio; SMR, standard mortality ratio.

epidemiologic investigation compared the risk of diabetes in patients with rheumatoid arthritis (RA), psoriasis, and/or psoriatic arthritis to nonrheumatic controls.<sup>24</sup> Compared with the controls, patients with moderate-to-severe psoriasis and/or psoriatic arthritis had increased hazard of developing diabetes mellitus (HR 1.4, 95% CI 1.3–1.5).

Various cohort studies have reported the incidence of hypertension in psoriasis patients compared with the general population.<sup>10,22</sup> From two large population databases, the investigators found that the incidence of hypertension was moderately increased in psoriasis patients compared with those without psoriasis.<sup>10,22</sup> Specifically, the authors of the GRPD cohort study found that psoriasis patients are at increased hazard for hypertension (HR 1.09, 95% CI 1.05–1.14).<sup>10</sup> In the cohort analysis of US female nurses, 21.3% of psoriasis patients developed hypertension compared with 19.6% in women without psoriasis.<sup>22</sup> The authors concluded that psoriasis was independently associated with hypertension (RR 1.17, 95% CI 1.06–1.30).

Obesity is a common comorbidity of psoriasis, and the incidence of obesity in psoriasis patients was also evaluated by investigators in the GRPD cohort study.<sup>10</sup> The investigators aimed to determine the risk of obesity and dyslipidemia in patients with psoriasis.<sup>10</sup> A greater incidence of obesity (HR 1.18, 95% CI 1.14–1.23) and dyslipidemia (HR 1.17, 95% CI 1.11–1.23) was found in patients with psoriasis compared with the general population. The investigators concluded that patients with psoriasis are at a moderately higher risk of subsequently developing CV risk factors, including obesity and dyslipidemia, than the general population.

## Large cohort studies on the association between psoriasis and CV outcomes

The risk of developing major adverse cardiac outcomes in psoriasis patients has been the focus of research for many investigators in the past decade. Several large cohort studies examined the risk of MI, coronary artery disease (CAD), stroke, and CV mortality in psoriasis patients.<sup>7–9,11–14,25–27</sup> The GRPD 1987–2002 was well used in several large population-based studies focusing on the association between psoriasis and cardiovascular diseases. In these studies, severe psoriasis was commonly defined as the diagnosis of psoriasis with a history of systemic therapy.<sup>8,11,12,13,27,30</sup> The results are summarized in Table 1.

Researchers investigated the risk of MI in patients with psoriasis compared with the general population.<sup>8,14,27</sup> Using the GRPD, the investigators reported a greater incidence of MI for severe psoriasis patients (5.13 per 1000 person-years, 95% CI 4.22–6.17) compared with the general population (3.58, 95% CI 3.52–3.65).<sup>14</sup> The adjusted RR was greatest in young, more severe psoriasis patients. For example, in 30-year-old patients, the RR of MI was 1.29 (95% CI, 1.14–1.46) in those with mild psoriasis and 3.10 (95% CI, 1.98–4.86) in those with severe psoriasis. For 60-year-old patients with psoriasis, the RR of MI was 1.08 (95% CI, 1.03–1.13) in those with mild psoriasis and 1.36 (95% CI, 1.13–1.64) in those with severe psoriasis. In a different study using a Taiwanese population-based database, the hazard of MI was  $2.1 \times$  (HR 2.10, 95% CI 1.27–3.43) greater in patients with psoriasis than controls matched by age and sex.<sup>8</sup> Among the patients with psoriasis who had MI, 13.6% occurred within 3 months of initial psoriasis diagnosis and 45.5% occurred within the first year.

Not all cohort studies showed a clear association between psoriasis and increased risk of MI.<sup>27</sup> One study using the GRPD from 1994 to 2005 did not report a clear association

of psoriasis with an overall increased risk of MI.<sup>27</sup> While a slightly increased incidence of MI was observed in patients with psoriasis aged <60 years (odds ratio [OR] 1.66, 95% CI 1.03–2.66), an increased incidence of MI was not observed in those aged >60 years (OR 0.99, 95% CI 0.77–1.26). The authors concluded that the risk of an adverse cardiac outcome was not elevated for patients with psoriasis. However, there was an increased RR of MI in patients with severe psoriasis < 60 years.

At least two large cohort studies examined the incidence of stroke in patients with psoriasis.<sup>7,11</sup> In the GRPD cohort, the investigators reported an increased hazard of stroke in mild (HR 1.06, 95% CI 1.0–1.1) and severe (HR 1.43, 95% CI 1.1–1.9) psoriasis patients compared with patients without psoriasis.<sup>11</sup> The excess risk of stroke attributable to psoriasis in patients with mild and severe disease was 1/4115 per year and 1/530 per year, respectively. To estimate the 10-year risk of stroke in patients with psoriasis, the investigators of another study calculated the increased risk of stroke using the Framingham Risk Score algorithm using patients enrolled in Phase II and Phase III trials evaluating adalimumab.<sup>7</sup> Patients with moderate-to-severe psoriasis had an 11.8% ( $P = 0.2$ ) increased RR of stroke compared with the general population. The risk did not differ between patients with moderate or severe psoriasis.

The association between psoriasis and CAD has been evaluated through a variety of methods.<sup>7,30</sup> In a large Dutch cohort from 1997 to 2008, researchers compared the risk of CAD hospitalizations between psoriasis patients and a matched cohort without psoriasis.<sup>30</sup> The risk of CAD was comparable in both populations. No differences were found in the risk of CAD among patients who used only topical steroids, those who received systemic therapies, and those who received inpatient care. The incidence rate of CAD was 611 versus 559 per 100,000 person-years ( $P = 0.066$ ) for psoriasis patients compared with matched controls, respectively. In this study, the authors stated that their results showed only a borderline significantly increased risk of CAD among psoriasis patients and therefore psoriasis did not appear to be a significant risk factor for CAD.<sup>30</sup> To estimate the 10-year risks of CAD, investigators in a previously mentioned study applied the Framingham Risk Score algorithm to patients in the Phase II and Phase III trials evaluating adalimumab.<sup>7</sup> Patients with moderate-to-severe psoriasis (Psoriasis Area and Severity Index [PASI] scores  $\geq 10$ ) had a 28% ( $P < 0.001$ ) higher risk of CAD compared with the general population. This risk did not differ between patients with moderate versus severe psoriasis.

A number of published reports cite an increased risk of CV mortality in patients with severe psoriasis.<sup>9,13,28,31</sup> Another large population-based study using the GRPD reported that there was an increased hazard of CV mortality in patients with severe psoriasis independent of the traditional risk factors (HR 1.57, 95% CI 1.26–1.96).<sup>13</sup> Patients with severe psoriasis experienced one extra CV mortality per 283 patients each year. The relation between age and psoriasis played a role in the RR of CV death. The RR was greater in a 40-year-old with severe psoriasis (RR 2.69, 95% CI 1.45–4.99) compared with a 60-year-old with severe psoriasis (RR 1.92, 95% CI 1.41–2.62).<sup>13</sup> This excess risk at 40 years was associated with 6.05 extra deaths per 10,000 person-years and 41.3 extra deaths per 10,000 person-years in the 60-year age group.<sup>13</sup> The authors stated that severe psoriasis was at least as potent a risk factor for CV mortality as other major risk factors, such as smoking, dyslipidemia, and hypertension. In another study, the investigators, using a Danish population ( $\geq 18$  years) from 1997 to 2006, found an associated risk of major adverse cardiac outcomes, including CV death, in psoriasis patients.<sup>9</sup> The patients were identified as “severe” if they had received hospital-based treatment for their psoriasis. The RR of CV death was elevated in mild (RR 1.14, 95% CI 1.06–1.22) and severe (RR 1.57, 95% CI 1.27–1.94) psoriasis patients. The authors concluded that those who were young with severe disease and/or psoriatic arthritis had the greatest risk. The researchers of a historical cohort from Sweden investigated the differences in risk of CAD based on severity of psoriasis.<sup>28</sup> Psoriasis patients who had been hospitalized at least once had a 50% increased overall risk of CV death (standard mortality ratio [SMR] 1.52, 95% CI 1.44–1.60) compared with the general population. A young age at first admission further increased the risk of CV mortality among patients who were repeatedly admitted. Psoriasis patients who never required hospitalization for treatment did not have an increased risk of CV mortality compared with the general population. The investigators concluded that psoriasis disease severity was a risk factor for CV mortality, and a diagnosis of psoriasis without hospital admission did not increase the risk of CV mortality.<sup>28</sup>

Divergent findings to the reports of increased CV mortality risk in psoriasis patients included a 10-year study where investigators used a defined group of photochemotherapy patients.<sup>28</sup> CV mortality rates in a cohort of patients from a clinical trial of psoralen plus ultraviolet A at a tertiary-care center were compared within the cohort based on severity as well as with the general population.<sup>28</sup> Psoriasis severity was assessed based on the extent of body surface

area affected. Patients with exceptionally severe psoriasis had greater than 42% body surface area affected. The number of deaths due to CVD among all psoriasis patients (SMR 1.02, 95% CI 0.9–1.6) was not increased compared with the general population. Patients in the clinical trial with exceptionally severe psoriasis were found to have increased RR of death due to all causes (HR 1.42, 95% CI 1.18–1.69) compared with less severely affected patients and the general population. However, the excess mortality appeared to be secondary to causes other than CVD. The causes of death in the cohort paralleled those in the general population, except that a large increase in liver-related deaths was observed in psoriasis patients (SMR 4.04, 95% CI 2.76–5.70). The investigators concluded that their data did not support the hypothesis that severe psoriasis is an independent risk factor for CVD.

In another study using the GRPD, the authors compared the risk of major adverse cardiac outcomes between patients with psoriasis and the general population and estimated the attributable risk of severe psoriasis.<sup>12</sup> The authors found that severe psoriasis was a risk factor for major adverse cardiac outcomes (HR 1.53, 95% CI 1.26–1.85), and they concluded that severe psoriasis conferred an additional 6.2% *absolute* risk of 10-year major adverse cardiac outcomes, including MI, stroke, and CV mortality.<sup>12</sup>

## How to evaluate CV risk factors in psoriasis patients

The US Preventive Services Task Force outlines various screening guidelines for preventative services in primary care.<sup>32</sup> The growing evidence linking psoriasis with CV risk factors and adverse cardiac outcomes, initiated the development of additional screening guidelines in psoriasis patients.<sup>33,34</sup> The NPF and *The American Journal of Cardiology (AJC)* have each published their own screening guidelines and recommendations for managing CV risk factors in psoriasis patients.<sup>33,34</sup>

The NPF and *AJC* guidelines emphasize the need to approach psoriasis as a potentially multisystem disorder.<sup>34</sup> Both guidelines follow the general CV risk factor assessment set by the American Heart Association’s (AHA) 2002 update on the prevention of CVD and stroke.<sup>35</sup> It is recommended that CV risk factor screening starts at age 20. The AHA advises physicians to assess smoking status, alcohol intake, diet, and physical activity at each routine visit.

Recommendations of the NPF and *AJC* are for patients not already known to have any CV risk factors.<sup>36</sup> Patients with diabetes, a family history of premature CAD, or other CV risk factors may need to be followed more closely. Recommendations for risk-factor screening by the AHA and

endorsed by the NPF are summarized in Table 2. Hypertension screening is recommended every 2 years in adults, with a blood pressure target of less than 120/80 mmHg. The US Preventive Services Task Force also includes screening every year for those with systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg. Body mass index should be calculated every 2 years with a target of  $<25 \text{ kg/m}^2$ . Waist circumference is to be measured every 2 years, targeted to  $<35$  inches in women and  $<40$  inches in men. Pulse rate should be measured at least every 2 years. Fasting glucose should be evaluated every 5 years unless risk factors are present, with a target of  $<100 \text{ mg/dL}$ . Fasting serum lipoprotein or total cholesterol and high-density lipoprotein (HDL) should be evaluated at least every 5 years, or every 2 years if positive for other risk factors (eg, family history, diabetes, tobacco use). Targets are total cholesterol  $< 200 \text{ mg/dL}$ , HDL  $\geq 50 \text{ mg/dL}$ , optimal low-density lipoprotein of  $<100 \text{ mg/dL}$  (near/above optimal: 100–129 mg/dL; borderline high: 130–159 mg/dL; high: 160–189 mg/dL, very high:  $\geq 190 \text{ mg/dL}$ ).

In addition to lipid profiles, the *AJC* states that plasma high-sensitivity C-reactive protein (hs-CRP) determination is optional because various authorities believe elevated plasma hs-CRP may provide help in determining how aggressive standard risk factors should be modified, including modifying lifestyle changes.<sup>33</sup> Patients with moderate-to-severe psoriasis should undergo CV risk assessment by their primary care physicians (PCPs), and dermatologists should provide recommendations for risk assessment to PCPs.<sup>33</sup>

Despite the guideline recommendations by the NPF and *AJC*, uncertainty exists as to whether screening guidelines

are implemented in clinical practice.<sup>37</sup> Investigators have assessed the screening practices by PCPs and cardiologists.<sup>37</sup> The authors revealed that increased experience in caring for psoriasis patients appeared to be associated with greater adherence to screening guidelines. Less than half of all physicians were aware of the increased risk of major adverse cardiac outcomes in psoriasis patients, and less than half of the physicians screened psoriasis patients for CV risk factors starting at age 20. Compared with PCPs, cardiologists were more likely to be aware of the increased CV diseases in psoriasis patients and were more likely to screen these patients for dyslipidemia than PCPs. Further physician education on the increased CV risk in psoriasis will serve to increase the physicians' role in preventing CVD in these at-risk patients.

## Mechanisms shared between psoriasis and atherosclerosis

### Convergent inflammatory mechanisms of psoriasis and atherosclerosis

The mechanisms underlying psoriasis provide the basis for linking psoriasis and the increased risk of CVD.<sup>15</sup> Helper T cells type 1 (Th1) and type 17 (Th17) and regulatory T cells (Treg) play integral roles in psoriasis and atherosclerosis pathogenesis. Differentiation of T lymphocytes to Th1 cells may be biased in the hematopoietic progenitor cells of those with psoriasis.<sup>38</sup> Th1 cells activate macrophages, neutrophils, and CD8+ cytotoxic T cells. The disease cycle is perpetuated through Th1 cytokines (interferon [IFN]- $\gamma$ , interleukin [IL]-2, and tumor necrosis factor [TNF]- $\alpha$ ), stimulate keratinocytes, as well as the production of more cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) and chemokines.<sup>15,39</sup>

**Table 2** Recommendations for cardiovascular risk factor screening adapted from the AHA Guidelines<sup>38</sup>

Measurement	Recommendations
Blood pressure	Evaluated every 2 years; target $< 120/80 \text{ mmHg}$
Body mass index	Evaluated every 2 years; target $< 25 \text{ kg/m}^2$
Waist circumference	Evaluated every 2 years; target: $< 35$ inches for women $< 40$ inches for men
Heart rate	Evaluated every 2 years
Fasting blood glucose	Evaluated every 5 years or every 2 years if risk factors present; target $< 100 \text{ mg/dL}$
Fasting serum lipoprotein or total and HDL cholesterol	Evaluated every 5 years or every 2 years if risk factors; targets: Total cholesterol: $\leq 200 \text{ mg/dL}$ HDL: $\geq 50 \text{ mg/dL}$ LDL optimal: $< 100 \text{ mg/dL}$ Near/above optimal: 100–129 mg/dL Borderline high: 130–159 mg/dL High: 160–189 mg/dL Very high: $\geq 190 \text{ mg/dL}$

**Abbreviations:** AHA, American Heart Association; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**Note:** From: <http://circ.ahajournals.org/content/106/3/388.full>. The information is used with permission and all requests to reuse this information must go through the AHA.

The recruitment and localization of T cells to the dermis and epidermis are mediated through various adhesion molecules and integrins. Psoriasis involves upregulation of adhesion molecules (ie, E-selectin, intracellular adhesion molecule-1).<sup>40,41</sup> In atherosclerotic plaques, endothelial dysfunction is associated with an increased level of TNF- $\alpha$  and other cytokines.<sup>42</sup> Dendritic cells within the plaques are activated to express IL-12 in higher quantities, initiating transcription of IFN- $\gamma$ .<sup>43</sup> Increased IFN- $\gamma$  transcription factors exist in T cells of patients with acute coronary syndrome.<sup>44</sup> The initiation and perpetuation of these Th1 responses known in psoriasis and atherosclerotic plaques demonstrates a link between these two conditions.<sup>15</sup>

The Th17 cells elaborate cytokines IL-17 and IL-22, which activate keratinocyte proliferation and release of other inflammatory proteins.<sup>39</sup> The complex of proteins released, with DNA of dying keratinocytes, allows the DNA to be presented to other T cells as self-antigens, continuing T-cell activation and proliferation.<sup>45</sup> Synergistic effects of IL-17 with TNF- $\alpha$  increase production of inflammatory and angiogenic factors, such as vascular endothelial growth factor (VEGF).<sup>15,46</sup> IL-17 is undetectable in normal skin but has been found to correlate with lesion area, severity, and reduction with therapy.<sup>47,48</sup>

In patients with acute coronary syndrome, IL-17 levels appear to parallel hs-CRP and IL-6, which predict MI risk.<sup>49,50</sup> Endothelial cell injury leads to cytokine release and Th17 differentiation. Similar to psoriasis, TNF- $\alpha$  and IL-17 synergistically upregulate further cytokine transcription.<sup>51</sup> IL-17 and IFN- $\gamma$  levels are undetectable in healthy volunteers but are elevated in patients with CAD. The utility of measuring IL-17 levels in psoriasis patients to identify those at a higher risk for MI is under investigation.<sup>15</sup>

Treg inhibit T-cell activation and proliferation through IL-10, transforming growth factor- $\beta$  (TGF- $\beta$ ), and cell-cell interaction.<sup>52-54</sup> The inhibitory function of Treg may be reduced in psoriasis patients.<sup>55</sup> Increased levels of TGF- $\beta$  exist in the serum and epidermis of psoriasis patients, correlating with psoriasis disease severity.<sup>56,57</sup> A decrease in TGF- $\beta$  receptors in psoriatic epidermis may indicate a reduced activity of TGF- $\beta$ .<sup>52-54,58</sup> In atherosclerosis, TGF- $\beta$  and IL-10 may inhibit plaque formation.<sup>59,60</sup> Several lines of evidence suggest that psoriasis and CAD have reductions in the inhibitory function of Treg.<sup>15</sup>

## Angiogenic and oxidative processes in psoriasis and atherosclerosis

Angiogenesis is pathologic in inflammatory diseases and atherosclerosis, while the role of oxidative stress is

less understood.<sup>16</sup> Psoriatic lesions consist of dilated, tortuous, and proliferative capillaries in the upper one-third of the dermis.<sup>16</sup> Microvascular changes precede keratinocyte hyperplasia and the appearance of any psoriatic plaques.<sup>16,61</sup> Pathologic angiogenesis is triggered by hypoxia or injury due to epidermal disruption in psoriasis and endothelial dysfunction in atherosclerosis. Angiogenesis inducers, including VEGF, basic fibroblast growth factor, hypoxia inducible factor-1, TNF- $\alpha$ , TGF- $\alpha$ , and IL-17, activate endothelial cells to generate new vessels.<sup>16,47,62-66</sup> VEGF in psoriasis is overexpressed, thereby increasing leukocyte migration.<sup>67</sup> VEGF levels also correlate with disease severity.<sup>67</sup>

Atherosclerosis shares many of the same mechanisms as psoriasis, but neovascularization occurs later in the course of the disease.<sup>16,68</sup> After an inciting event, VEGF and other angiogenic factors are released. Plaque size may be related to VEGF through its role in attracting macrophages in the arterial endothelium.<sup>68</sup> Macrophages stimulated by oxidized phospholipids degrade the plaque fibrous cap and increase the risk of plaque rupture.<sup>69</sup> TNF- $\alpha$  and VEGF increase endothelial production of tissue factor, which, in turn, possibly increases the risk of thrombotic events.<sup>16,70</sup> VEGF levels in atherosclerosis patients correlate and possibly predict adverse cardiac outcomes.<sup>71</sup> The increased VEGF in psoriasis may influence and worsen atherosclerosis as well as psoriasis.<sup>16,72</sup>

Reactive oxygen species (ROS) generated through enzymatic sources and ischemia are common to psoriasis and atherosclerosis.<sup>16</sup> ROS act as second messengers and modulate transcription factors common to both diseases. Several of these ROS-influenced signaling pathways lead to elevated cell adhesion and vascular permeability implicated in psoriasis and atherosclerosis.<sup>16,69,73</sup> All of the shared mechanisms that exist between psoriasis and atherosclerosis may be used as a basis for advancement of rational therapeutic strategies.<sup>16</sup>

## Therapeutic approaches to reducing CV risk factors and adverse outcomes in psoriasis

### Decreasing CV risk factors in psoriasis

As understanding of the increased CV risks in psoriasis evolves, treatment choices for patients with moderate-to-severe psoriasis will need to account for these comorbidities. Novel investigations have focused on how disease-modifying antirheumatic drugs (DMARDs), including biologics, used in psoriasis may affect patients' CV risk factors and adverse cardiac outcomes.

Whether systemic immunomodulatory agents used to treat psoriasis and RA affect incident diabetes risk is an area of active investigation.<sup>17</sup> In a retrospective cohort, researchers examined the relationship between four DMARD regimens and the risk of developing diabetes in patients with psoriasis or RA.<sup>17</sup> The author examined incident diabetes in psoriasis and RA patients based on the following medication categories: (1) TNF inhibitors with or without other DMARDs; (2) methotrexate without TNF inhibitors or hydroxychloroquine; (3) hydroxychloroquine without TNF inhibitors or methotrexate; or (4) reference group consisting of other nonbiologic DMARDs without TNF inhibitors, methotrexate, or hydroxychloroquine. Compared with the reference group of other nonbiologic DMARDs, psoriasis patients on hydroxychloroquine had the lowest hazard of diabetes (HR 0.54, 95% CI 0.36–0.80), followed by patients on TNF inhibitors (HR 0.62, 95% CI 0.42–0.91), and then patients on methotrexate (HR 0.77, 95% CI 0.53–1.13). The authors concluded that the risk of diabetes was lower in psoriasis patients starting a TNF inhibitor or hydroxychloroquine compared with those initiated on other nonbiologic DMARDs. Methotrexate initiation was not associated with any significant diabetes risk reduction, whereas TNF inhibitors and hydroxychloroquine showed reduction within 90 days of exposure.

Several studies reported the effects of immunomodulatory agents on glucose and insulin metabolism in psoriasis or RA patients.<sup>74,75</sup> When insulin metabolism was measured immediately before and after infusion in patients with RA, infliximab appeared to improve insulin sensitivity and decrease insulin resistance.<sup>75</sup> Another study that examined insulin resistance over 14 weeks of infliximab therapy found a gradual improvement in insulin resistance.<sup>76</sup> In a study on the effects of etanercept on insulin in psoriasis patients, the investigators found a reduction in insulin levels and an improvement in insulin sensitivity.<sup>77</sup> The authors concluded that the beneficial effects of infliximab on insulin sensitivity may support the long-term use of TNF inhibitors to reduce the mechanisms implicated in atherogenesis.<sup>75</sup>

While the effects of TNF inhibitors on dyslipidemia and biomarkers for CAD are not well understood in psoriasis, a literature exists on their effects in RA.<sup>78–80</sup> In RA patients, TNF inhibitors transiently increase HDL levels, but it is unknown whether these increases in HDL levels can be sustained over time.<sup>78,79,81</sup> One well-characterized inflammatory biomarker for CAD is hs-CRP, which is predictive of CVD, including MI, stroke, peripheral arterial disease, and sudden cardiac death.<sup>82</sup> In psoriasis, decreased levels of CRP were found in patients treated with 12 weeks of etanercept.<sup>80</sup>

As lipid abnormalities are frequently seen in psoriasis patients, statins are helpful in normalizing lipid levels in psoriasis patients with dyslipidemia.<sup>83</sup> Statins' pleiotropic properties include anti-inflammatory and immunomodulatory activities, which may be beneficial to psoriasis as well as the CV risk profile.<sup>29,84,85</sup> By inhibiting cholesterol synthesis in the mevalonate pathway, statins may decrease intracellular signal transduction.<sup>29,84</sup> Statin treatment increases circulating Treg, which suggests they modulate atherosclerosis by facilitating the conversion of Th cells to Treg.<sup>15,86</sup> A pilot study investigated the efficacy of simvastatin on psoriasis severity in seven patients with PASI scores >12.<sup>87</sup> After 8 weeks of therapy, the investigators found a statistically significant reduction of PASI score, a decrease in the self-reported Dermatology Life Quality Index, and a decrease in severity based on the physician's assessment. In a separate, French, case-controlled study, the authors found that the intake of statins was associated with a decreased risk of psoriasis (OR 0.64, 95% CI 0.43–0.97) compared with matched controls in the French population.<sup>88</sup> In another study, researchers examined the effects of the addition of simvastatin to topical betamethasone to treat psoriasis in 30 patients in Iran.<sup>89</sup> The researchers found that the PASI score decreased significantly in both groups, but the decrease of PASI score was more significant in patients who received simvastatin (Mann–Whitney test; *P* value = 0.001). The authors concluded that oral simvastatin enhances the therapeutic effect of topical steroids against psoriasis.

## Decreasing CV outcomes in psoriasis

The immunological mechanisms shared between psoriasis and atherosclerosis present opportunities for therapeutic targets to reduce adverse cardiac outcomes in psoriasis patients. Few studies have examined the effects of psoriasis treatment on major adverse cardiac outcomes.<sup>18,20,90,91</sup> Researchers investigated the effect of systemic psoriasis therapies on the risk of acute MI in psoriasis patients.<sup>20</sup> Data from the administrative and pharmacy claims of a large US insurer were used to compare MI risk in patients treated with systemic immunomodulators to controls treated with ultraviolet-B (UVB) phototherapy.<sup>20</sup> Among the systemic immunomodulators, traditional oral agents included cyclosporine and methotrexate, and the biologics included alefacept, etanercept, adalimumab, efalizumab, and infliximab. In the overall study population, the investigators did not observe statistical differences in the risk of MI (HR 1.33, 95% CI 0.90–1.96) for those who received systemic therapy compared to UVB phototherapy. Differences in systemic treatments (ie, traditional systemic

and biologics) did not appear to account for differences in MI risk. Compared with young patients on phototherapy, patients aged <50 years on systemic treatment had a nonsignificant reduced MI risk (HR 0.65, 95% CI 0.32–1.34). In a study presented at the 2011 American Academy of Dermatology Meeting, investigators studied over 24,000 patients from the Kaiser Permanente Southern California psoriasis cohort retrospectively and compared the risk of MI in psoriasis patients on various treatments, including TNF inhibitors, oral therapy (cyclosporine, methotrexate, acitretin), and phototherapy (broad-band ultraviolet B, narrow-band ultraviolet B, psoralen plus ultraviolet A).<sup>19</sup> While the full length of this study is not yet published, the authors found that TNF inhibitors were associated with a significant reduction in the risk of MI compared with methotrexate (HR 0.588, 95% CI 0.347–0.996).

Researchers investigated the effects of methotrexate therapy and TNF inhibitors on CVD in patients with psoriasis and RA.<sup>18,90,91</sup> In a cohort study of veterans diagnosed with psoriasis or RA, the authors analyzed the risk of vascular disease in patients treated with methotrexate compared with psoriasis or RA patients without methotrexate.<sup>90</sup> Psoriasis patients treated with methotrexate had a significantly reduced incidence of vascular disease (RR 0.73, 95% CI 0.55–0.98), and a further reduction with the addition of folic acid (RR 0.56, 95% CI 0.39–0.80). The decreased incidence of vascular disease was greatest for the lowest cumulative methotrexate dose (RR 0.50, 95% CI 0.31–0.79). Further evidence from other studies suggested that methotrexate and TNF inhibitors may reduce the risk of adverse cardiac outcomes in RA.<sup>18,91</sup> When TNF inhibitors were compared with nonbiological DMARDs on the effect of adverse cardiac outcomes in RA patients, the patients using TNF inhibitors experienced a reduced hazard of adverse cardiac outcomes including non-fatal MI, transient ischemic attack, stroke, and CV death (HR 0.39, 95% CI 0.19–0.82) compared with the nonbiological DMARDs.<sup>18</sup> In a cohort study on the effect of methotrexate on mortality in rheumatoid patients, patients who had received methotrexate had a reduced hazard of CV mortality (HR 0.3, 95% CI 0.2–0.7) compared with RA patients without methotrexate.<sup>91</sup>

## Conclusion

Most but not all studies confirm that patients with severe psoriasis appear to be at increased risk for the development of CV risk factors and major adverse cardiac outcomes. Differences in study populations, study design, and the analytic methods to control for confounding factors account for some

of the differences in the study findings. While increasing epidemiologic research continues to refine the question and explore differences among different patient populations, basic researchers are beginning to develop basic and translational evidence that helps explain the observed epidemiologic link. The shared immune mechanisms may explain the additional CV risk conferred by psoriasis in selected studies. Whether certain types of systemic psoriasis treatments reduce CV outcomes in psoriasis patients is relatively unknown and necessitates more in-depth examination.

At the current time, we encourage regular screening of psoriasis patients for the established CV risk factors. Young patients with severe psoriasis especially need to be screened regularly for the development of CV risk factors and be actively managed for their psoriasis and CV comorbidities. Physicians will need to work together through a multidisciplinary approach to effectively manage psoriasis patients and their comorbidities. Future translational and clinical research efforts aimed at elucidating the relationship between psoriasis and cardiovascular diseases, and improving health care delivery for psoriasis patients, will be valuable.

## Disclosure

The authors report no conflicts of interest in this work.

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