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JACC REVIEW TOPIC OF THE WEEK

Cardiovascular Risk in Patients With Psoriasis

JACC Review Topic of the Week

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease that affects 2% to 3% of the U.S. population. The immune response in psoriasis includes enhanced activation of T cells and myeloid cells, platelet activation, and up-regulation of interferons, tumor necrosis factor-α, and interleukins (ILs) IL-23, IL-17, and IL-6, which are linked to vascular inflammation and atherosclerosis development. Patients with psoriasis are up to 50% more likely to develop cardiovascular disease (CV) disease, and this CV risk increases with skin severity. Major society guidelines now advocate incorporating a psoriasis diagnosis into CV risk prediction and prevention strategies. Although registry data suggest treatment targeting psoriasis skin disease reduces vascular inflammation and coronary plaque burden, and may reduce CV risk, randomized placebo-controlled trials are inconclusive to date. Further studies are required to define traditional CV risk factor goals, the optimal role of lipid-lowering and antiplatelet therapy, and targeted psoriasis therapies on CV risk.
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CASE VIGNETTE

A 50-year-old man comes to your office to establish care. He has a history of plaque psoriasis since 35 years of age, previously involving the elbows, anterior shins, and lower abdomen (covering >10% of his body), which has cleared with an interleukin (IL) 17A inhibitor. He does not smoke and has no family history of early heart disease. On presentation, his resting blood pressure is 138/84 mm Hg, and body mass index is 28 kg/m^2. He has a hemoglobin A1c of 5.4%, total cholesterol of 210 mg/dl, triglycerides of 145 mg/dl, high-density lipoprotein (HDL) cholesterol of 42 mg/dl, calculated low-density lipoprotein (LDL) cholesterol of 139 mg/dl, and a high-sensitivity C-reactive protein (hs-CRP) of 1.5 mg/l. He asks about his future risk of cardiovascular disease (CVD) and what can be done to lower his risk.

THE CLINICAL PROBLEM

Despite advances, CVD remains the leading cause of mortality in the United States (1). Identifying high cardiovascular (CV) risk patients who derive the largest benefit from prevention therapies is a key step toward reducing clinical CV events (2). Standard CV risk calculators, such as the American College of Cardiology (ACC)/American Heart Association (AHA) pooled cohort equations, incorporate traditional CV risk factors, such as age, male sex, race, hypertension,

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HIGHLIGHTS

- Patients with psoriasis are at increased risk of cardiovascular disease.
- Cutaneous and systemic inflammation coupled with a background of traditional cardiovascular risk factors are thought to increase cardiovascular risk in psoriasis.
- Randomized controlled trials are needed to determine if treatment of psoriasis reduces the risk of developing cardiovascular disease.

hyperlipidemia, diabetes, and smoking (2). Recognizing that CV risk scores may underestimate CV risk in certain populations (3), guidelines now incorporate CV risk enhancers including pro-inflammatory conditions, such as psoriasis, when calculating the 10-year risk of a CV event to guide prevention strategies (2). However, uncertainty remains in the assessment and implementation of therapies to reduce CV risk in psoriasis. Therefore, the goal of this review is to discuss the identification and management of CV risk in individuals with psoriasis, areas of uncertainty, and future directions.

Psoriasis, of which psoriasis vulgaris is the most common type, is a chronic, pro-inflammatory condition of the skin presenting primarily as thick, well-demarcated, and erythematous scaly plaques (4). Psoriasis affects 2% to 3% of all Americans (4). There is no sex predilection and is a bimodal age distribution, with incidence peaking between age 30 to 39 and 50 to 69 years (4). Early work starting in the 1970s described a possible connection between psoriasis and vascular disease (5). However, in 2006, a seminal study by Gelfand et al. (6) used a large United Kingdom prospective registry of ~130,000 psoriasis and ~500,000 control subjects with a mean follow-up of 5.4 years to describe an overall 50% elevated risk of myocardial infarction in psoriasis. Since then, many, although not all, studies show a positive association between psoriasis and CVD (7). A meta-analysis encompassing 75 studies with ~500,000 psoriasis patients reported up to a 50% increased odds of CVD in those with psoriasis compared with those without psoriasis (8). Severe psoriasis confers the highest CV risk (compared with control subjects), including up to a 3-fold increased odds of myocardial infarction, 60% higher odds of stroke, and 40% higher odds of CV death (7).

PROPOSED LINK BETWEEN PSORIASIS AND ATHEROSCLEROSIS

The inflammatory milieu within psoriatic lesional skin includes activated T-cell subsets and myeloid cells, which produce tumor necrosis factor (TNF)-α, interferons (IFN), IL-17 isoforms, IL-23, and IL-22 in a cutaneous environment where many innate (and pro-atherosclerotic) cytokines, such as IL-1, IL-6, and IL-8, are coexpressed (4). Collectively, these cytokines display strong synergistic interactions, further amplifying inflammation, and driving keratinocyte proliferation in the skin (**Figure 1**) (4). The blood vessels in psoriasis lesions are dilated and fenestrated, and up-regulated pro-inflammatory cytokines (e.g., TNF-α, IL-17A, IFNγ, IL-23, and IL-6) present in psoriasis lesional skin (**Figure 1**) readily exchange with blood plasma, and circulate systemically (4).

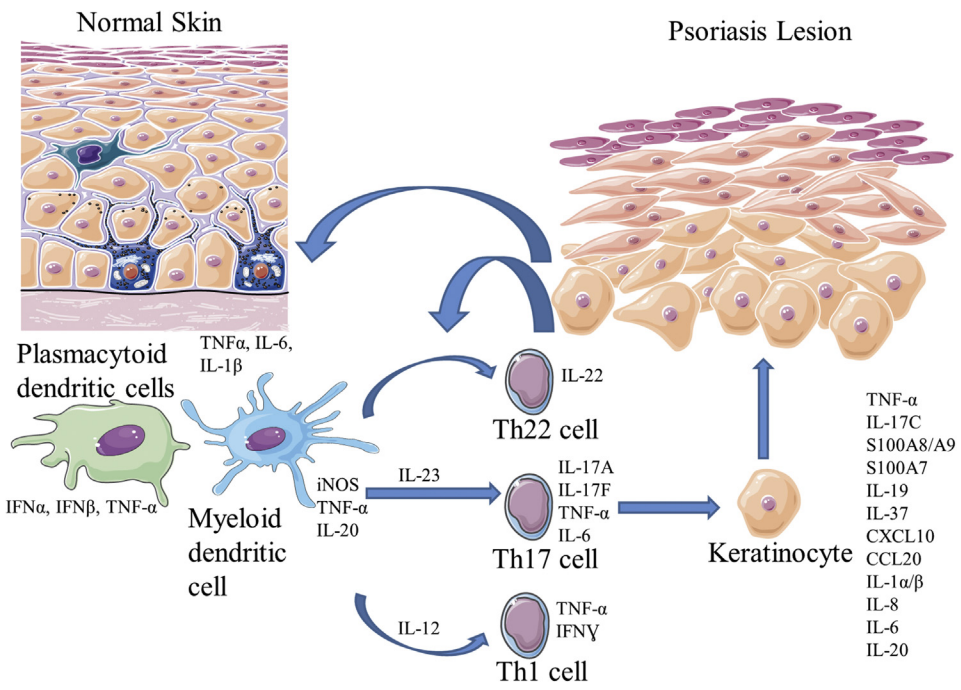
Vascular endothelial activation and dysfunction is a first step in atherosclerosis development (9). A transcriptomic comparison between psoriasis lesional skin and atherosclerotic plaque found a dominant overlap of IFNɣ and TNF-α–driven processes that synergistically inflame the endothelium, including a >5,000-fold increase (relative to control endothelial cells) of transcripts such as *VCAM-1* and *CXCL10* (10). In a murine model of epidermal IL-17A overexpression, endothelial dysfunction, enhanced vascular stiffness, and oxidative stress are present (11). In analysis of directly obtained endothelial cells, patients with psoriasis (compared with control subjects) display a significant 2- to 8-fold up-regulation of pro-inflammatory and chemotactic transcripts, including *VCAM-1, IL-1β, CXCL10*, and *COX-2* (12). These directly obtained endothelial cells exhibit a similar expression profile to endothelial cells stimulated in vitro by combinations of TNF-α, IL-17A, and IFNγ, highlighting the inflammatory pathogenic overlap of psoriasis and atherosclerosis (**Central Illustration**) (12).

Extending beyond direct cytokine-induced endothelial damage, systemic inflammasome signaling (IL-1) with downstream IL-6 production is induced via TNF-α/IL-17A synergism, is the highest differentially expressed systemic pathway in psoriasis, and is causal in atherosclerosis development (12,13). Th1 cells (in psoriasis lesional skin and systemically) are present in atherosclerotic plaques, are chemotactic,

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology
AHA = American Heart Association
CV = cardiovascular
CVD = cardiovascular disease
HDL = high-density lipoprotein
hs-CRP = high-sensitivity C-reactive protein
IFN = interferon
IL = interleukin
LDL = low-density lipoprotein
TNF = tumor necrosis factor

FIGURE 1 Pathogenesis of Psoriasis



External stimuli combined with genetic predisposition generates an inflammatory cascade and activation of dendritic cells. Up-regulated cytokines, including IL-23, lead to T-cell activation and differentiation (Th17 cells). Synergistic action between IL-17 isoforms (A/F) along with TNF-α and IL-1 amplify inflammation and drive keratinocyte proliferation in the skin. IFN = interferon; IL = interleukin; TNF = tumor necrosis factor.

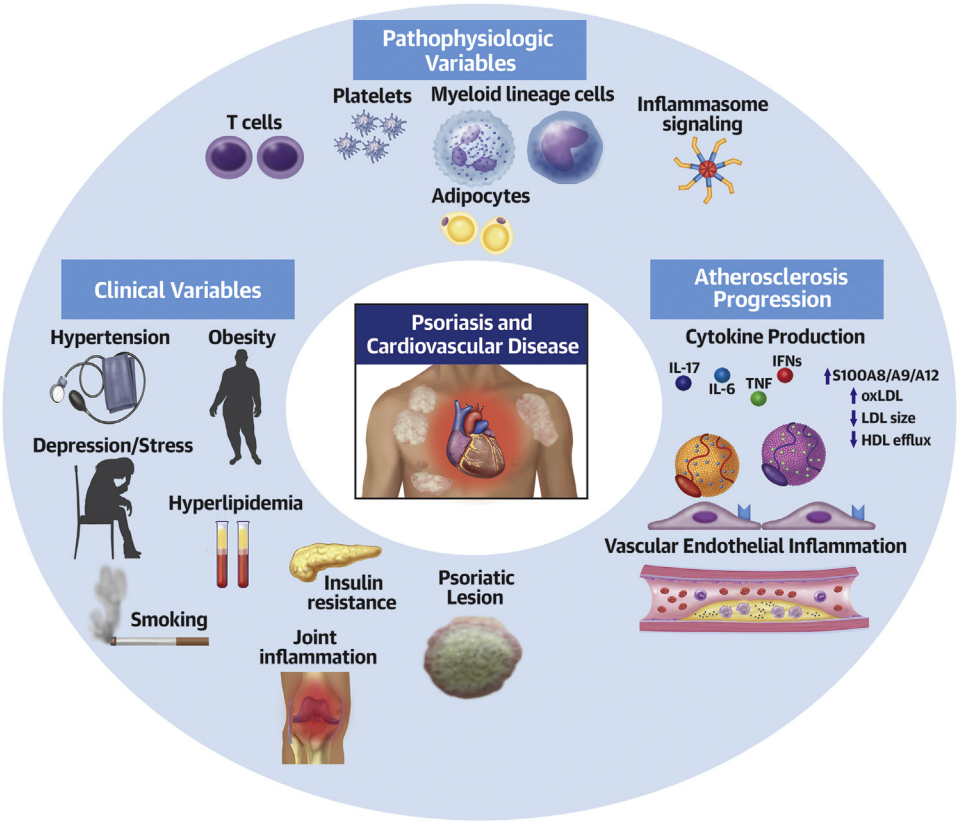
and promote plaque instability (14). Macrophages in a murine model of psoriasis prone to atherosclerosis exhibit increased lipid uptake and foam cell formation (15). Neutrophils, specifically the neutrophil subtype low-density granulocytes, are 30% higher in psoriasis (compared with nonpsoriasis), and correlate with coronary atherosclerosis (16). These low-density granulocytes colocalize with platelets and induce 50% higher in vitro endothelial damage and apoptosis through neutrophil extracellular traps (termed NETosis) when compared with other neutrophil subtypes (normal density granulocytes) (16).

Platelets appear to also be an important factor in the pathogenesis of vascular dysfunction in psoriasis. Markers of platelet activation, including mean platelet volume, platelet-derived P-selectin, platelet-neutrophil, and lymphocyte aggregates, are elevated in psoriasis and correlate with psoriasis severity (17,18). Psoriasis platelet RNA sequencing shows an interferon signature and elevated expression of *COX-1* that correlates with psoriasis skin severity ($r = 0.81$; $p = 0.01$) (19,20). Finally, platelets are preferentially found in psoriasis lesional skin and induce a >20-fold increase in endothelial cell pro-atherosclerotic transcripts compared with platelets from nonpsoriasis patients (19), raising the hypothesis that targeting COX-1 (via aspirin) may be beneficial in psoriasis.

CONTRIBUTION OF TRADITIONAL CV RISK FACTORS TO CVD IN PSORIASIS

In addition to systemic immune activation, cardiometabolic derangements also occur. The traditional modifiable CV risk factors, hypertension, diabetes, hyperlipidemia, obesity, and smoking, along with metabolic syndrome, are highly prevalent (in aggregate >50%), under-recognized, and undertreated in psoriasis (**Figure 2**) (21). Among 3,000 psoriasis participants enrolled in clinical trials (average age ~46 years, 68% men) investigating an IL-12/23 inhibitor to improve psoriasis skin severity, 59% of participants had at least 2 traditional CV risk factors, while 29% had 3 or more (22). Approximately 20% of patients with psoriasis diagnosed with diabetes and hypertension, and nearly 40% with hyperlipidemia, were not treated.

CENTRAL ILLUSTRATION Factors Influencing Cardiovascular Disease in Psoriasis



Garshick, M.S. et al. J Am Coll Cardiol. 2021;77(13):1670–80.

The suspected pathogenesis of cardiovascular disease in psoriasis includes a combination of cutaneous and systemic immune system activation along with the contribution of coexisting cardiometabolic conditions. HDL = high-density lipoprotein; IFN = interferon; IL = interleukin; LDL = low-density lipoprotein; TNF = tumor necrosis factor.

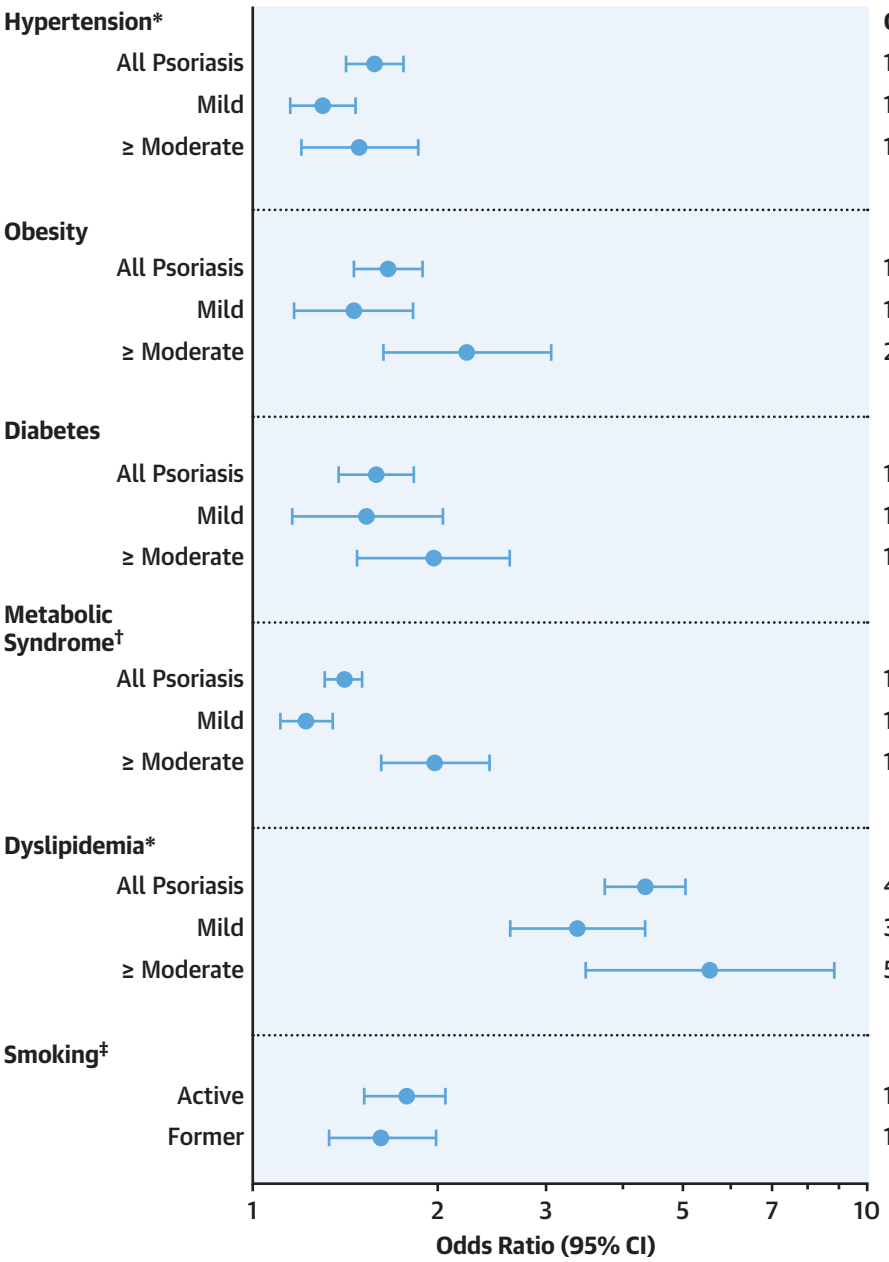
Among psoriasis patients receiving pharmacological therapy to treat CV risk factors, ~60% were not at goal (22). Psoriasis patients are also less physically active (23), almost 40% more likely to carry a diagnosis of depression, and have a reduced quality of life than those without psoriasis (24,25). Smoking is also highly prevalent and exhibits a dose-response relationship with psoriasis severity (26).

Psoriasis patients have up to ~15% lower HDL and almost 80% reduced HDL efflux capacity (27,28). Nuclear magnetic resonance spectroscopy shows a lipid profile similar to diabetic patients, including increased LDL particle concentration and decreased LDL size (29). Compared with control subjects, psoriasis patients have a higher lipoprotein(a) and 15% higher oxidized HDL with the degree of oxidized LDL and oxidized HDL in psoriasis correlating with non-calcified coronary plaque (28). Hypertension severity associates with IL-17A levels and psoriasis skin severity in both human and murine models (30,31). Finally, obesity with metabolically active visceral adipose tissue potentiates insulin resistance and metabolic syndrome in psoriasis, associates with vascular arterial inflammation and atherosclerosis burden, and represents a further link between psoriasis and CVD (**Central Illustration**) (32). Taken together, atherosclerotic development in psoriasis is a combination of psoriasis-induced immune system activation and pan-arterial inflammation, combined with the contribution of coexisting cardiometabolic conditions (**Central Illustration**).

CV RISK SCREENING

Assessment of 10-year CV risk is a core component of primary CVD prevention (2). Traditional 10-year

FIGURE 2 Association Between Psoriasis and Traditional Cardiovascular Risk Factors



From the American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *Some studies find less robust associations among psoriasis, hypertension, and dyslipidemia. †In a meta-analysis encompassing 42,000 psoriasis patients, the odds ratio for metabolic syndrome was as high as 2.26 (95% CI: 1.70 to 3.01). ‡Association between smoking and psoriasis. CI = confidence interval; OR = odds ratio.

risk estimators underestimate CV risk in psoriasis patients, who present with a myocardial infarct, on average, 5 years younger than those without psoriasis (33,34). Patients with psoriasis requiring systemic therapy exhibit an absolute 10-year risk of a coronary event or stroke of 6.2%, beyond what is expected from traditional CV risk estimates (35). Psoriasis chronicity, such as age of diagnosis and duration, tracks with vascular inflammation and up to a 1% absolute increase in CV risk per year of psoriasis (36,37). The

TABLE 1 Considerations to Identify and Treat Cardiovascular Risk in Psoriasis

	Quantifying Cardiovascular Risk	Evidence and Strength of Recommendation
Screening for known variables contributing to CVD	Hypertension, obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, smoking, physical inactivity, depression, stress	AAD/NPF SOR B, LOE: II – III
CV risk score calculation	• 2019 AAD/NPF guidelines—multiply CV risk score by 1.5*	AAD/NPF SOR C, LOE: II - III
	• 2019 ACC/AHA guidelines—use psoriasis as a CV risk enhancer	ACC/AHA Class IIa, LOE: B-NR
	• 2019 ESC guidelines—use of CIID to solely guide lipid-lowering interventions is not recommended.	ESC Class III, LOE: C
Potential ancillary measures	• Psoriasis skin disease severity assessment >10% body surface area involvement Candidates for systemic or phototherapy treatment	In psoriasis, criteria to identify those that deserve more aggressive traditional CV risk factor screening (SOR B, LOE II–III) and/or multiply CV risk by 1.5 (SOR C, LOE: II–III), from AAD/NPF
	• Coronary artery calcium score†	Other ancillary measures Class and LOE: per 2019 ACC/AHA guidelines on the primary prevention of CVD in the general population
	• Lipoprotein (a)	
	• High sensitivity C-reactive protein	
Guideline-directed risk factor reduction	• Lifestyle counseling (e.g., dietary counseling, smoking cessation, exercise)	In psoriasis, lifestyle counseling AAD/NPF SOR B, LOE: II–III
	• Weight management, BMI <25 kg/m^2	In psoriasis, CV risk management, blood pressure, and lipid targets per "national guideline recommendations" AAD/NPF- SOR C, LOE III
	• Blood pressure <130/80 mm Hg	
	• Hemoglobin A1c, ≤7%	Class and LOE per 2019 ACC/AHA guidelines on the primary prevention of CVD in the general population
	• Statin (lipid-lowering) therapy	
	• Low-dose aspirin therapy	
Reducing inflammation	• Biologic therapy (e.g., IL-17A, IL-12/23, TNF-α inhibitors)	Suggested benefit primarily from observational nonrandomized studies Further randomized controlled trials are needed
	• Phototherapy	
	• Oral therapy (e.g., methotrexate, cyclosporine, acitretin, apremilast)	

AAD/NPF guidelines utilize the Strength of Recommendation Taxonomy (SORT). *>10% body surface area of psoriasis involvement or candidates for systemic or phototherapy treatment. †Per the ACC/AHA, in inflammatory conditions, a calcium score of 0 does not necessarily rule out enhanced cardiovascular risk.

AAD/NPF = American Academy of Dermatology/National Psoriasis Foundation; ACC/AHA = American College of Cardiology/American Heart Association; CV = cardiovascular; CVD = cardiovascular disease; CIID = chronic immune-mediated inflammatory diseases; ESC = European Society of Cardiology; IL = interleukin; LOE = Level of Evidence; NPF = National Psoriasis Foundation; NR = nonrandomized; SOR = strength of recommendation; TNF = tumor necrosis factor.

Joint American Academy of Dermatology-National Psoriasis Foundation guidelines, recognizing this, advocate that dermatologists inform psoriasis patients of their elevated CV risk and ensure engagement with their primary care doctor or cardiologist (38). They further suggest that patients with a >10% body surface area of psoriasis or candidates for systemic therapy or phototherapy apply a 1.5 multiplication factor to a 10-year CV risk score (38). In contrast, the ACC/AHA suggests psoriasis as a CV risk-enhancing feature (when assessing CV risk) without specifying a psoriasis severity threshold (**Table 1**) (2).

BIOMARKERS OF CV RISK

Supporting the connection between psoriatic activity and atherosclerosis development, [18F]-fluorodeoxyglucose positron emission tomography evaluation displays a correlation between psoriasis skin severity and pan-arterial vascular inflammation ($\beta = 0.41$; $p < 0.01$) (39). In coronary analyses, psoriasis patients, compared with matched nonpsoriasis patients, have a 2-fold greater odds of coronary artery calcium (any amount >0) and comparable to a diabetic patient without psoriasis (40). Psoriasis patients also have a 15% higher noncalcified coronary plaque burden than matched control subjects with the degree of high-risk noncalcified coronary plaque correlating with psoriasis skin severity (41). Extending beyond the skin, hs-CRP tracks with psoriasis skin severity, vascular inflammation, and coronary atherosclerosis (42–44). However, newer modalities are emerging, such as circulating glycoprotein acetylation (a pro-inflammatory measure of N-glycan side chains attached to acute phase reactants), which is shown to improve the prediction of coronary atherosclerosis in psoriasis beyond traditional CV risk factors and hs-CRP (42,43). In summary, these clinical-translational studies not only suggest that coronary atherosclerosis is prevalent in psoriasis, but also highlight the promise and need for future clinical

trials to prospectively evaluate biomarkers for CV risk stratification (45).

PSORIATIC ARTHRITIS

Up to 25% of patients with psoriasis have psoriatic arthritis, which is also linked to CV comorbidities, including up to a >70% risk of diabetes, 90% higher prevalence of hypertension, and 40% higher prevalence of obesity when compared with nonpsoriasis control subjects (46). Compared with patients with mild psoriasis and a similar traditional CV risk factor profile, psoriatic arthritis associates with a 2-fold higher hs-CRP and 30% higher carotid plaque (47). In a Danish study evaluating 4 million control subjects, ~2,000 patients with severe psoriasis, and ~670 psoriatic arthritis patients, compared with control subjects, those with psoriatic arthritis (relative risk: 1.79; 95% confidence interval: 1.31 to 2.45) and severe psoriasis without joint involvement (relative risk: 1.58; 95% confidence interval: 1.32 to 1.84) displayed a similar risk of myocardial infarction, stroke, or CV death (48). Finally, in psoriatic arthritis, the number of dactylic digits increases CV risk (myocardial infarction, stroke, revascularization, or CV death) by ~20% (46). These data highlight that even with minimal skin activity, joint involvement also predisposes to CV risk in psoriasis.

TREATMENT OF MODIFIABLE CV RISK FACTORS IN PSORIASIS

Optimal lifestyle modification in psoriasis is a cornerstone of strategies to reduce CVD and improve skin severity. In obese or overweight patients with psoriasis, the National Psoriasis Foundation recommends a hypocaloric diet (49). A meta-analysis of 7 randomized controlled trials involving ~900 overweight or obese psoriasis patients found that weight loss via caloric restriction improves psoriasis skin severity, including a 3-fold higher skin clearance rate with diet plus psoriasis treatment as opposed to psoriasis treatment alone (50). There is a weak (strength of recommendation 2B) recommendation from the National Psoriasis Foundation emphasizing a Mediterranean diet, as those psoriasis patients who are more adherent show psoriasis skin improvement, lower fat mass, and lower hs-CRP (49). Finally, smoking cessation should be encouraged as it reduces CVD, and may also improve psoriasis skin severity (26).

Clinical trials evaluating traditional CV risk factor treatment thresholds and goals in the psoriasis population are lacking. However, given the pattern of dyslipidemia, early vascular dysfunction, and higher prevalence of coronary plaque, lipid-lowering should play a key role in CV risk reduction strategies in psoriasis. In a retrospective study of ~9,000 psoriasis patients followed for a median of 4.3 years, statin therapy was associated with a reduction (hazard ratio: 0.31; 95% CI: 0.22 to 0.43) in incident myocardial infarction (51). A post hoc analysis of 2 secondary prevention lipid-lowering (high-intensity vs. low-intensity statin) trials identified ~500 (of ~19,000) patients with psoriasis (52). Psoriasis patients on high-intensity statins displayed a similar reduction in lipids and CV events when compared with nonpsoriasis patients, highlighting the efficacy of statins in this high-risk population. Whether statin therapy in psoriasis confers additional anti-inflammatory benefit beyond lipid-lowering is not yet known. Finally, circulating proprotein convertase subtilisin/kexin type 9 is elevated in psoriasis (compared with nonpsoriasis), preferentially expressed in psoriatic lesional skin, and associated with vascular inflammation, further emphasizing a potential benefit of lipid-lowering in psoriasis (53).

Aspirin in the primary prevention of CVD is controversial even in the nonpsoriatic patient (2). Although older studies suggest aspirin may reduce myocardial infarction and stroke in those with higher circulating inflammatory biomarkers (54), CV outcomes data are lacking in the psoriasis population. In a small randomized controlled trial of 30 patients with psoriasis randomized to *COX-1* inhibition (81 mg of aspirin) or no treatment, vascular endothelial inflammation was reduced over 70% in the aspirin group. The degree of endothelial inflammation improvement significantly correlated with degree of platelet inhibition, highlighting the potential utility of aspirin in the psoriatic population (19). Last, although it is reasonable to promote aggressive blood pressure and hemoglobin A1c goals, in line with ACC/AHA recommendations in those at elevated risk of CVD (**Table 1**), clinical studies evaluating this approach in psoriasis are needed (38).

TARGETING INFLAMMATION IN PSORIASIS TO REDUCE CV RISK

In an observational analysis of almost 9,000 psoriasis patients, in those treated with a biologic (e.g., TNF-α inhibitor) when compared with topical therapy, myocardial infarction was reduced by 50% (51). Consistently, surrogates of CV risk, including hs-CRP, IL-6, glycoprotein acetylation, and platelet-lymphocyte aggregates, are all reduced in psoriasis patients undergoing treatment of their skin disease across a variety of psoriasis therapies (18,45,55). In

TABLE 2 Randomized Placebo Controlled Clinical Trials Assessing the Impact of Biologics on Vascular Health in Psoriasis

Clinical Trial	Year	n	Inclusion Criteria	Treatment (n)	Duration	Primary Outcome	Main Findings*	Miscellaneous
Adalimumab								
NCT01722214 TNF-α Antagonist and Vascular Inflammation in Psoriasis Vulgaris	2017	107	≥5% BSA Elevated TBR	Adalimumab (54) Placebo (53)	16 weeks	Change from baseline in TBR of ascending aorta	−0.002 (−0.048 to 0.053) −0.002 (−0.053 to 0.049)	30% hs-CRP reduction in adalimumab group
NCT01553058 Vascular Inflammation in Psoriasis (VIP)	2018	97	≥10% BSA	Adalimumab (33) Placebo (31) UVB (33)	12 weeks	Change from baseline in maximum aortic TBR	−1.84% (−7.17% to 3.47%) −2.49% (−6.29% to 1.31%) −4.09% (−7.78% to −0.39%)	GlycA reduced in adalimumab group HDL-p increased in phototherapy group
Ustekinumab								
NCT02187172 Vascular Inflammation in Psoriasis (VIP-U)	2020	43	≥10% BSA	Ustekinumab (22) Placebo (21)	12 weeks	Change from baseline of TBR in 5 aortic segments	−6.58% (−13.64% to 0.47%) 12.07% (3.26% to 20.88%)	Difference between groups significant at 12 weeks ($p < 0.01$) TBR reductions not maintain at 52 weeks
Secukinumab								
NCT02690701 Vascular Inflammation in Psoriasis (VIP-S)	2020	91	≥10% BSA	Secukinumab (46) Placebo (45)	12 weeks	Change from baseline in maximum aortic TBR	2.6% (−2.5% to 7.6%) 3.3% (−0.8% to 7.5%)	
NCT02559622 Evaluation of Cardiovascular Risk Markers in Psoriasis Patients treated with Secukinumab (CARIMA)	2020	151	≥10 Psoriasis area and severity index score	Secukinumab 300 mg (48) Secukinumab 150 mg (54) Placebo (26)† Placebo (23)†	12 weeks	Change in brachial artery flow-mediated dilatation	4.6% ± 3.5% → 5.1% ± 5.2% 4.6% ± 4.6% → 4.8% ± 3.9% 3.9% ± 3.9% → 3.6% ± 3.7% 3.7% ± 3.6% → 3.6% ± 4.6%	No difference between groups at 12 weeks

In all listed studies, a crossover to active treatment occurred at the end of the randomized portion. *Values indicate mean (95% confidence interval) or ± SD. †Crossover to Secukinumab 300 and 150 mg doses at week 12 through 52.

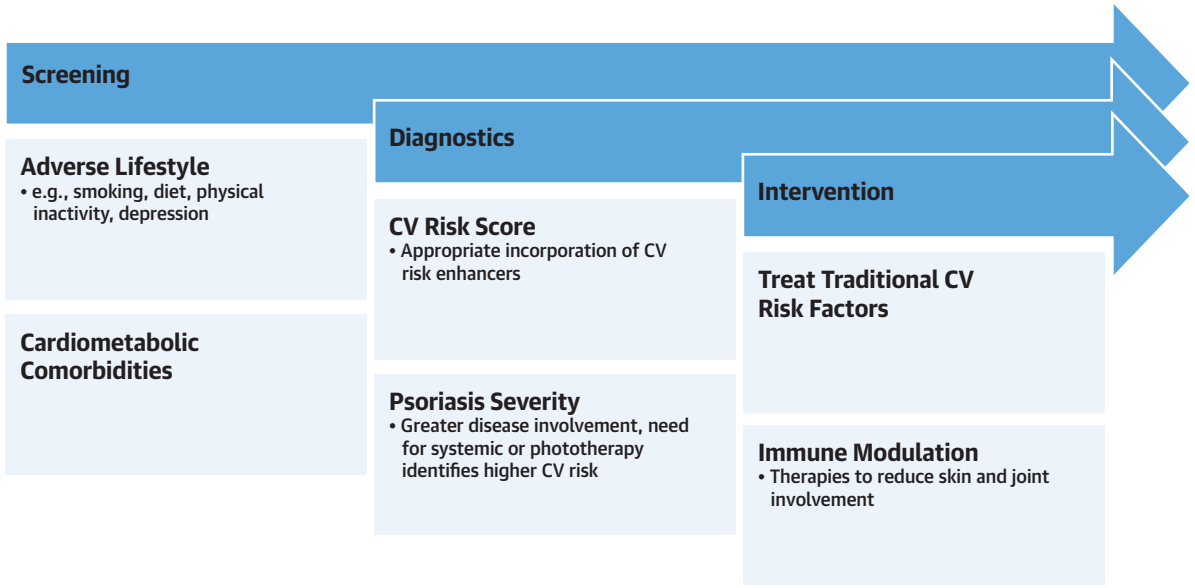
BSA = body surface area (of active psoriasis); CAD = coronary artery disease; HDL-p = high-density lipoprotein particle number; hs-CRP = high-sensitivity C-reactive protein; TBR = target to background ratio (of ^{18}F-fluorodeoxyglucose uptake assessed by positron emission tomography/computed tomography); UVB = ultraviolet B (phototherapy).

prospective studies, improvement in lipid parameters after treatment of psoriasis is also seen, including a small (3%) but statistically significant increase in HDL-C (44) and 75% decrease in oxidized HDL (28). In moderate disease psoriasis patients with low CV risk, at 1-year follow-up, biologic treatment corresponded to a 6% reduction in noncalcified plaques and a 6% reduction in vascular aortic inflammation (45,55). A nonrandomized clinical trial evaluated the impact of an IL-17A inhibitor, cyclosporine, or methotrexate on myocardial and vascular function (56). At 12 months, although psoriasis skin improvement was noted across all groups, the authors observed a 14% improvement in global longitudinal strain and 11% reduction in vascular stiffness (measured by pulse wave velocity) in the IL-17A inhibitor group as opposed to minimal changes with other treatments (56).

Despite these observational data, randomized placebo-controlled trials targeting psoriasis skin disease to reduce vascular inflammation remain inconclusive (**Table 2**). Compared with placebo, 3 months of an IL-17A inhibitor did not improve brachial artery flow-mediated dilatation (57). In randomized placebo controlled clinical trials of TNF-α inhibitor (43), phototherapy (43), and IL-17A inhibitor therapy (58), the majority of treated patients displayed an adequate skin response to treatment and a reduction in circulating pro-inflammatory biomarkers; yet, vascular arterial inflammation, the primary outcome was not reduced after 3 months (**Table 2**). This contrasts to a smaller clinical trial of IL-12/23 inhibition, which found a significant reduction (compared to placebo) in vascular arterial inflammation at 3 months; however, this effect was not sustained at 1 year (**Table 2**) (59).

As opposed to potential benefit, there was early concern of adverse CV effects of biologics in psoriasis (specifically IL-12/23 blockade) (60). However, in a meta-analysis of 38 randomized controlled trials assessing biologics to improve psoriasis skin severity and encompassing almost 18,000 patients, no statistically significant difference in adverse CV events were found across mainstays of psoriasis treatment, including TNF-α, IL-12/23, and IL-17 inhibitors (60). Despite these studies, TNF-α inhibitor use in the heart

FIGURE 3 Approach to Primary Prevention in Psoriasis



A suggested approach to cardiovascular (CV) risk management in psoriasis, including early screening, the appropriate use of diagnostic tests, and therapeutic interventions.

failure population is associated with adverse outcomes and not recommended in patients with psoriasis who have a history of heart failure (38). Oral medications such as cyclosporine exhibit substantial drug-drug interactions and are associated with hypertension, while acitretin can worsen lipid profiles (38). At higher doses than typically used in psoriatic disease, Janus kinase inhibition (high-dose Tofacitinib in rheumatoid arthritis patients with ≥1 CV risk factor), was linked to venous thromboembolism and now carries a black box warning (61). In summary, whether findings from observational studies or ones evaluating surrogates of CV risk translate into reductions in CV events is unknown, and this highlights the need for larger clinical trials with clinically meaningful endpoints to investigate targeting inflammation to reduce CV risk in psoriasis.

RESIDUAL CV RISK IN PSORIASIS

Despite the ability of biologics to reduce visible skin and joint manifestations of psoriasis, once psoriatic pathology occurs, not all is reversible, even in the skin (62). Memory T cells are retained in healed skin lesions, while whole transcriptome data reveal a residual disease signature containing ~25% of affected genes (62). Translating this concept to CV risk, in a clinical study evaluating the impact of various psoriasis therapies on 157 inflammatory or CV risk-associated proteins, many proteins, but not all, were decreased in psoriasis treatment skin responders with variable protein reductions noted across different psoriasis therapies (63). These data highlight the need to define the residual inflammatory burden in psoriasis and the differential impact of psoriasis medications on CV risk reduction.

SUMMARY AND CONCLUSIONS

The clinical approach to identifying and treating CV risk in patients with psoriasis is represented in **Table 1 and Figure 3**. Using the ACC/AHA pooled cohort equation, the patient in the opening clinical vignette has a 10-year risk of CV death, nonfatal stroke, or nonfatal myocardial infarction of 5.1%. Although his psoriasis is minimally active, his use of a biologic, psoriasis duration, and prior severe psoriasis suggests a significant risk of CVD. Consistent with new guidelines, we advocate that prevalent psoriasis is a risk enhancer and should be used in evaluating CV risk. This patient was recommended lifestyle modification and a moderate- to high-intensity statin, given his >5% CV risk and psoriasis.

In conclusion, the bulk of epidemiological and clinical-translational data suggest a strong contribution of psoriasis to CVD. CV risk assessment in

psoriasis requires incorporating traditional CV risk factors (**Table 1, Figure 3**) and other guideline-directed CV risk enhancers as appropriate. A history of moderate-to-severe psoriasis qualifies a patient with psoriasis as having a significant elevation in CV risk. In those who do not meet this criterion, patients with a large burden of psoriatic disease (either extended duration or prolonged history of untreated disease) and psoriatic arthritis also exhibit elevated CV risk, which should be taken into consideration.

Given the heightened CV risk in psoriasis, we advocate for an aggressive approach to both lifestyle and medication therapy, recognizing that clinical trials and observational data on antiplatelet and statin therapy, blood pressure, lipid, and hemoglobin A1c goals are limited in this population and require further study (**Table 1, Figure 3**). Increased patient and provider awareness of the connection between atherosclerosis and psoriasis is also required to facilitate and initiate conversations on CV preventive measures. Despite compelling observational data, adequately powered randomized trials with hard clinical endpoints are necessary to investigate the benefit of CV prevention strategies including targeting inflammation to reduce CV risk in psoriasis.

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REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56–528.

2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary. J Am Coll Cardiol 2019;74:1376–414.

3. Stern R. Discordance of individual risk estimates. J Am Coll Cardiol 2010;56:743. author reply 743–4.

4. Greb JE, Goldminz AM, Elder JT, et al. Psoriasis. Nat Rev Dis Primers 2016;2:16082.

5. McDonald CJ, Calabresi P. Psoriasis and occlusive vascular disease. Br J Dermatol 1978;99:469–75.

6. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296:1735–41.

7. Samarasekera EJ, Neilson JM, Warren RB, Parnham J, Smith CH. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. J Invest Dermatol 2013;133:2340–6.

8. Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. J Am Acad Dermatol 2013;69:1014–24.

9. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation 2004;109:III27–32.

10. Mehta NN, Teague HL, Swindell WR, et al. IFN-gamma and TNF-alpha synergism may provide a link between psoriasis and inflammatory atherogenesis. Sci Rep 2017;7:13831.

11. Karbach S, Croxford AL, Oelze M, et al. Interleukin 17 drives vascular inflammation, endothelial dysfunction, and arterial hypertension in psoriasis-like skin disease. Arterioscler Thromb Vasc Biol 2014;34:2658–68.

12. Garshick MS, Barrett T, Wechter T, et al. Inflammasome signaling and impaired vascular health in psoriasis. Arterioscler Thromb Vasc Biol 2019;39:787–98.

13. Verma D, Fekri SZ, Sigurdardottir G, Eding CB, Sandin C, Enerback C. Enhanced inflammasome activity in patients with psoriasis promotes systemic inflammation. J Invest Dermatol 2021;141:586–95.

14. Armstrong AW, Voyles SV, Armstrong EJ, Fuller EN, Rutledge JC. A tale of two plaques: convergent mechanisms of T-cell-mediated inflammation in psoriasis and atherosclerosis. Exp Dermatol 2011;20:544–9.

15. Baumer Y, Ng Q, Sanda GE, et al. Chronic skin inflammation accelerates macrophage cholesterol crystal formation and atherosclerosis. JCI Insight 2018;3:e97179.

16. Teague HL, Varghese NJ, Tsoi LC, et al. Neutrophil subsets, platelets, and vascular disease in psoriasis. J Am Coll Cardiol Basic Transl Sci 2019;4:1–14.

17. Fan Z, Wang L, Jiang H, Lin Y, Wang Z. Platelet dysfunction and its role in the pathogenesis of psoriasis. Dermatology 2020:1–10.

18. Sanz-Martinez MT, Moga E, Sanchez Martinez MA, et al. High levels of platelet-lymphocyte complexes in patients with psoriasis are associated with a better response to anti-TNF-alpha Therapy. J Invest Dermatol 2020;140:1176–83.

19. Garshick MS, Tawil M, Barrett TJ, et al. Activated platelets induce endothelial cell inflammatory response in psoriasis via COX-1. Arterioscler Thromb Vasc Biol 2020;40:1340–51.

20. Vila L, Cullare C, Sola J, Puig L, de Castellarnau C, de Moragas JM. Cyclooxygenase activity is increased in platelets from psoriatic patients. J Invest Dermatol 1991;97:922–6.

21. Cea-Calvo L, Vanaclocha F, Belinchon I, Rincon O, Julia B, Puig L. Underdiagnosis of cardiovascular risk factors in outpatients with psoriasis followed at hospital dermatology offices: the PSO-RISK Study. Acta Derm Venereol 2016;96:972–3.

22. Kimball AB, Szapary P, Mrowietz U, et al. Underdiagnosis and undertreatment of cardiovascular risk factors in patients with moderate to severe psoriasis. J Am Acad Dermatol 2012;67:76–85.

23. Frankel HC, Han J, Li T, Qureshi AA. The association between physical activity and the risk of incident psoriasis. Arch Dermatol 2012;148:918–24.

24. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. Arch Dermatol 2010;146:891–5.

25. Puig L, Strohal R, Husni ME, et al. Cardiometabolic profile, clinical features, quality of life and treatment outcomes in patients with moderate-to-severe psoriasis and psoriatic arthritis. J Dermatolog Treat 2015;26:7–15.

26. Li W, Han J, Choi HK, Qureshi AA. Smoking and risk of incident psoriasis among women and men in the United States: a combined analysis. Am J Epidemiol 2012;175:402–13.

27. Holzer M, Wolf P, Curcic S, et al. Psoriasis alters HDL composition and cholesterol efflux capacity. J Lipid Res 2012;53:1618–24.

28. Sorokin AV, Kotani K, Elnabawi YA, et al. Association between oxidation-modified lipoproteins and coronary plaque in psoriasis. Circ Res 2018;123:1244–54.

29. Mehta NN, Li R, Krishnamoorthy P, et al. Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. Atherosclerosis 2012;224:218–21.

30. Takeshita J, Wang S, Shin DB, et al. Effect of psoriasis severity on hypertension control: a population-based study in the United Kingdom. JAMA Dermatol 2015;151:161–9.

31. Orejudo M, Rodrigues-Diez RR, Rodrigues-Diez R, et al. Interleukin 17A participates in renal inflammation associated to experimental and human hypertension. Front Pharmacol 2019;10:1015.

32. Wong Y, Nakamizo S, Tan KJ, Kabashima K. An update on the role of adipose tissues in psoriasis. Front Immunol 2019;10:1507.

33. Eder L, Chandran V, Gladman DD. The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. Ann Rheum Dis 2014;73:1990–6.

34. Karbach S, Hobohm L, Wild J, et al. Impact of psoriasis on mortality rate and outcome in myocardial infarction. J Am Heart Assoc 2020;9:e016956.

35. Mehta NN, Yu Y, Pinnelas R, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med 2011;124:775.e1–6.

36. Egeberg A, Skov L, Joshi AA, et al. The relationship between duration of psoriasis, vascular inflammation, and cardiovascular events. J Am Acad Dermatol 2017;77:650–6.e3.

37. Li WQ, Han JL, Manson JE, et al. Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. Br J Dermatol 2012;166:811–8.

38. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol 2019;80:1029–72.

39. Naik HB, Natarajan B, Stansky E, et al. Severity of psoriasis associates with aortic vascular inflammation detected by FDG PET/CT and neutrophil activation in a prospective observational study. Arterioscler Thromb Vasc Biol 2015;35:2667–76.

40. Mansouri B, Kivelevitch D, Natarajan B, et al. Comparison of coronary artery calcium scores between patients with psoriasis and type 2 diabetes. JAMA Dermatol 2016;152:1244–53.

41. Lerman JB, Joshi AA, Chaturvedi A, et al. Coronary plaque characterization in psoriasis reveals high-risk features that improve after treatment in a prospective observational study. Circulation 2017;136:263–76.

42. Joshi AA, Lerman JB, Aberra TM, et al. GlycA is a novel biomarker of inflammation and subclinical cardiovascular disease in psoriasis. Circ Res 2016;119:1242–53.

43. Mehta NN, Shin DB, Joshi AA, et al. Effect of 2 psoriasis treatments on vascular inflammation and novel inflammatory cardiovascular biomarkers: a randomized placebo-controlled trial. Circ Cardiovasc Imaging 2018;11:e007394.

44. Puig L, Strohal R, Fuiman J, et al. Cardiometabolic biomarkers in chronic plaque psoriasis before and after etanercept treatment. J Dermatolog Treat 2014;25:470–81.

45. Elnabawi YA, Dey AK, Goyal A, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. Cardiovasc Res 2019;115:721–8.

46. Eder L, Gladman DD. Atherosclerosis in psoriatic disease: latest evidence and clinical implications. Ther Adv Musculoskelet Dis 2015;7:187–95.

47. Eder L, Jayakar J, Shanmugarajah S, et al. The burden of carotid artery plaques is higher in patients with psoriatic arthritis compared with those with psoriasis alone. Ann Rheum Dis 2013;72:715–20.

48. Ahlehoff O, Gislason GH, Charlot M, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. J Intern Med 2011;270:147–57.

49. Ford AR, Siegel M, Bagel J, et al. Dietary recommendations for adults with psoriasis or psoriatic arthritis from the Medical Board of the National Psoriasis Foundation: a systematic review. JAMA Dermatol 2018;154:934–50.

50. Upala S, Sanguankeo A. Effect of lifestyle weight loss intervention on disease severity in patients with psoriasis: a systematic review and meta-analysis. Int J Obes (Lond) 2015;39:1197–202.

51. Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. Arch Dermatol 2012;148:1244–50.

52. Ports WC, Fayyad R, DeMicco DA, Laskey R, Wolk R. Effectiveness of lipid-lowering statin therapy in patients with and without psoriasis. Clin Drug Investig 2017;37:775–85.

53. Garshick MS, Baumer Y, Dey AK, et al. Characterization of PCSK9 in the blood and skin of psoriasis. J Invest Dermatol 2020;141:308–15.

54. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.

55. Dey AK, Joshi AA, Chaturvedi A, et al. Association between skin and aortic vascular inflammation in patients with psoriasis: a case-cohort study using positron emission tomography/computed tomography. JAMA Cardiol 2017;2:1013–8.

56. Makavos G, Ikonomidis I, Andreadou I, et al. Effects of interleukin 17A inhibition on myocardial deformation and vascular function in psoriasis. Can J Cardiol 2020;36:100–11.

57. von Stebut E, Reich K, Thaci D, et al. Impact of secukinumab on endothelial dysfunction and other cardiovascular disease parameters in psoriasis patients over 52 weeks. J Invest Dermatol 2019;139:1054–62.

58. Gelfand JM, Shin DB, Duffin KC, et al. A randomized placebo-controlled trial of secukinumab on aortic vascular inflammation in moderate-to-severe plaque psoriasis (VIP-S). J Invest Dermatol 2020;140:1784–93.e2.

59. Gelfand JM, Shin DB, Alavi A, et al. A phase IV, randomized, double-blind, placebo-controlled crossover study of the effects of ustekinumab on vascular inflammation in psoriasis (the VIP-U Trial). J Invest Dermatol 2020;140:85–93.e2.

60. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic review and meta-analysis of randomized controlled trials. Br J Dermatol 2017;176:890–901.

61. Voelker R. Higher dose of tofacitinib for rheumatoid arthritis poses risks. JAMA 2019;321:1245.

62. Benezeder T, Wolf P. Resolution of plaque-type psoriasis: what is left behind (and reinitiates the disease). Semin Immunopathol 2019;41:633–44.

63. Kim J, Tomalin L, Lee J, et al. Reduction of inflammatory and cardiovascular proteins in the blood of patients with psoriasis: differential responses between tofacitinib and etanercept after 4 weeks of treatment. J Invest Dermatol 2018;138:273–81.

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