Psoriatic arthritis and the association with cardiometabolic disease: a narrative review

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Abstract: Psoriatic arthritis (PsA) is associated with a higher burden of cardiometabolic disorders, such as hypertension, dyslipidemia, diabetes, obesity, and cardiovascular disease (CVD), compared with the general population. These comorbidities are associated with the severity of disease, and adversely affect treatment outcomes in PsA. Comorbidities lead to increased physician visits and medications for patients and make the selection and maintenance of therapies challenging for physicians. Moreover, CVD is a leading cause of mortality in PsA. Therefore, optimal management of PsA should include not only treating the skin and joint disease, but also identifying comorbidities early, and managing them to improve long-term outcomes. Further studies are needed to understand the complex mechanisms, interactions, and trajectories of cardiometabolic comorbidities in psoriatic disease.

Keywords: cardiovascular disease, diabetes, epidemiology, hyperlipidemia, hypertension, metabolic syndrome, obesity, psoriasis, psoriatic arthritis

Introduction
Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal and skin disease affecting approximately 20–30% of patients with psoriasis. Besides musculoskeletal and skin manifestations, patients with PsA have a higher prevalence of comorbidities compared with the general population. More than half of patients with PsA have at least one comorbidity, with up to 40% of patients having more than three comorbidities. PsA has a particularly strong association with metabolic diseases and cardiovascular (CV) outcomes. There is a higher prevalence of metabolic diseases, such as hypertension, dyslipidemia, diabetes, and obesity compared with patients with psoriasis without PsA and the general population. PsA is associated with a higher burden of cardiometabolic disorders, such as hypertension, dyslipidemia, diabetes, obesity, and cardiovascular disease (CVD), compared with the general population. These comorbidities are associated with the severity of disease, and adversely affect treatment outcomes in PsA. Comorbidities lead to increased physician visits and medications for patients and make the selection and maintenance of therapies challenging for physicians. Moreover, CVD is a leading cause of mortality in PsA. Therefore, optimal management of PsA should include not only treating the skin and joint disease, but also identifying comorbidities early, and managing them to improve long-term outcomes. Further studies are needed to understand the complex mechanisms, interactions, and trajectories of cardiometabolic comorbidities in psoriatic disease.
associated with a 55% increased risk of developing cardiovascular diseases (CVD), such as ischemic heart disease, cerebrovascular disease, and congestive heart failure.7 Both higher inflammatory burden and increased incidence and prevalence of traditional CV risk factors, such as hypertension, glucose intolerance, dyslipidemia, and obesity in psoriatic disease seem to play a role in CV risk in PsA.8,9 CVD is a major source of morbidity and a leading cause of mortality in PsA.3,5 Therefore, addressing these comorbidities may improve quality of life and functional status and reduce healthcare costs as well as mortality in PsA. In this review, we will explore the complex relationship of PsA with metabolic and CVD.

Metabolic disease in PsA

The epidemiology of metabolic disease in PsA
Metabolic syndrome (MetS) and its components are significantly elevated in PsA compared with the general population.6,10 While the definition of MetS varies in different studies, the most widely used and validated definition is that from the US National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA).11 According to NHLBI/AHA (revised ATP III criteria, 2005), MetS is defined as ⩾3 of the following five conditions: (1) fasting glucose ⩾100 mg/dl or receiving drug therapy for hyperglycemia; (2) blood pressure ⩾130/85 mmHg or receiving drug therapy for hypertension (HTN); (3) triglycerides ⩾150 mg/dl or receiving drug therapy for hypertriglyceridemia; (4) high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men or <50 mg/dl in women or receiving drug therapy for reduced HDL-C; and (5) for whites, waist circumference ⩾40 inches (⩾102 cm) in men or ⩾35 inches (⩾88 cm) in women.12 Interestingly, the reported incidence of MetS and its components are higher in PsA compared with psoriasis, and notably lower in patients with PsA without diabetes at baseline and found elevated risk with hazard ratio (HR) around 1.4–1.5.4,21,22 Moreover, the risk of DM II seems to be higher in women, and those with more active PsA (HR 1.53 with tender joint counts and HR 1.21 with elevated erythrocyte sedimentation rate).22,23 Therefore, a higher risk of DM II in PsA could be partially explained by increased obesity, unhealthy lifestyle, and possibly insulin resistance related to inflammation in PsA.24,25

Similarly, the subsequent risk of DM II was higher in patients with PsA [odds ratio (OR) 2.18, 95% confidence interval (CI) 1.36–3.50] compared with psoriasis only (OR 1.76, 95% CI 1.59–1.96) in a 2013 meta-analysis.24 In fact, the risk in PsA was higher than that for patients with severe psoriasis (OR 2.10, 1.73–2.55).24 In a study from the Consortium of Rheumatology Researchers of North America (CORRONA) registry, the prevalence of DM II was also higher in PsA compared with RA (15% versus 11%; OR 1.56, 95% CI 1.07–2.28).26 The incidence of DM II was also higher in PsA compared with controls (HR 1.45, 95% CI 1.35–1.56) than in RA compared with controls (HR 1.16, 95% CI 1.12–1.21) in a study from the UK THIN database.4

Hypertension. HTN is another modifiable CV risk factor that has been found to have a higher prevalence in patients with psoriasis and PsA compared with the general population. Data from a large Middle-Eastern PsA cohort similarly showed an increased prevalence of hyperlipidemia (OR 1.54; 95% CI 1.43–1.67), HTN (OR 1.51 95% CI, 1.40–1.6), DM II (OR 1.48, 95% CI 1.36–1.61), and obesity (OR 1.71, 95% CI 1.58–1.84).27 Moreover, the prevalence of HTN was higher in PsA compared with psoriasis alone (29% versus 18%, OR 1.7, 95%CI 1.25–2.30) in a single-center study from Spain.28 A cohort study from the University of Toronto also showed a higher prevalence of HTN in PsA compared with patients with psoriasis only (OR 2.17, 95% CI 1.22–3.83) after
adjusting for several demographic factors, psoriasis-related factors, medications, and comorbidities. In a meta-analysis by Duan et al., the odds of HTN was higher than the general population only in severe psoriasis (OR 1.13, 95% CI 1.03–1.25), and not in mild psoriasis (OR 1.09, 95% CI 0.98–1.22). Therefore, an association with increased systemic inflammation is likely; and PsA is thought to be at the severe end of the psoriatic disease spectrum in general. Similarly, both the prevalence (19.9% versus 18.6%) and incidence of HTN (79.8 versus 74.0 per 1000 patient-years) were higher in PsA compared with RA in a study from the MarketScan claims databases. Also the incidence of HTN was higher in PsA compared with controls (HR 1.37, 95% CI 1.30–1.44) than among patients with RA compared with controls (HR 1.16, 95% CI 1.13–1.19).

Dyslipidemia. Dyslipidemias are disorders of lipoprotein metabolism that comprise elevated serum concentration of total cholesterol, low-density lipoprotein (LDL), triglycerides, and low-density lipoprotein. There is a higher prevalence and incidence of dyslipidemia in psoriatic disease compared with the general population. A cross-sectional study showed a lower prevalence of dyslipidemia in psoriasis and PsA compared with the non-inflammatory control population (13.5 versus 28 versus 33% respectively), although other CV risk factors, such as hypertension, diabetes mellitus, and obesity were significantly higher. The study of lipid levels could be challenging, especially in cross-sectional studies, as inflammation could lower serum LDL levels as described in RA. An inverse association of total cholesterol and LDL levels with CVD has been described (known as the lipid paradox), suggesting that interpretation of hypercholesterolemia as a risk factor for CVD may not apply in inflammatory diseases such as RA. However, patients with psoriatic disease have additional features of metabolic disturbance such as low serum levels of HDL-C, high triglyceride, insulin resistance, and obesity. Moreover, in patients with PsA, dyslipidemia was associated with markers of inflammation [high-sensitivity C-reactive protein (CRP), platelet counts], suggesting a potential relationship with a higher level of inflammation. This relationship is important as there is an association of increased levels of total cholesterol and triglyceride levels with subclinical atherosclerosis in PsA.

Studies also show that dyslipidemia is significantly more prevalent in PsA compared with psoriasis; and PsA patients have worse atherogenic lipid profiles than patients with psoriasis. In a single-center study from Spain, dyslipidemia was more common in PsA than in psoriasis (28% versus 13.5%, OR 2.5 95% CI 1.7–3.3). Another study from a tertiary care center in Taiwan found higher odds of hyperlipidemia in patients with PsA compared with psoriasis (OR 15.94, 95% CI 1.64–154.80). The prevalence of hyperlipidemia and hypertriglyceridemia was also higher than that in RA in two separate studies (9.9% versus 11.6%, and 38% versus 28%, OR 1.51 respectively). Two separate studies showed that the incidence of hyperlipidemia was higher in PsA compared with RA, although a direct comparison was not made. A study from the MarketScan claims database showed a higher incidence of hyperlipidemia in PsA compared with controls (IRR 1.10, 95% CI 1.04–1.17), but not in RA compared with controls (IRR 0.86, 95% CI 0.82–0.89). Similarly, Jafri et al. in a study from the UK THIN database showed that comparative incidence of hyperlipidemia in PsA was higher than that in RA (HR 1.36, 95% CI 1.28–1.46 versus 1.09, 95% CI 1.05–1.12).

Obesity. The overall prevalence of obesity [body mass index (BMI) ⩾30 kg/m²] in US adults was 40% in 2015–16. Most studies have reported a higher prevalence of obesity in patients with psoriatic disease compared with the general population. In a population-based incident cohort of PsA from Olmsted County, Minnesota, the mean BMI was 30.5 kg/m², and 44% of patients were obese. While a cohort study from the UK General Practice Research Database showed a higher risk of new-onset obesity during follow-up (HR 1.18, 95% CI 1.14–1.23), we did not find any studies on the incidence of obesity in PsA.

Most studies show a higher prevalence of obesity in PsA compared with psoriasis or other inflammatory diseases. A systematic review of 201,831 psoriasis patients showed a higher prevalence of obesity with psoriasis compared with controls (OR=1.66, 95% CI 1.46–1.89) and the prevalence was higher with the severity of psoriasis (OR of 1.46 for mild psoriasis versus 2.23 for severe psoriasis). The prevalence of obesity was higher in patients with PsA compared with psoriasis only (22.68 versus 16.75%) in a large cohort study from the UK THIN database. A cohort study from Toronto, however, showed similar odds of obesity in psoriasis and PsA. Another cross-sectional study showed that obesity was more prevalent in psoriasis compared with PsA (36.5 versus 30% respectively).
27.6%, OR 1.5, 95% CI 1.1–2.1).\textsuperscript{28} Compared with other common chronic inflammatory diseases, the prevalence in PsA is higher.\textsuperscript{13,26} Compared with RA and axSpA, the prevalence of HTN and obesity were higher in PsA; the prevalence of hyperlipidemia was similar among the groups. Additionally, as expected, the presence of hyperlipidemia and hypertension increased with increasing age. Conversely, the presence of obesity did not significantly differ by age.\textsuperscript{15} The prevalence of obesity at baseline was higher in PsA compared with RA (22.68 \textit{versus} 17.60%) in a cohort study from the UK.\textsuperscript{5} Similarly in a study by Radner et al.,\textsuperscript{13} the prevalence of obesity in PsA was higher compared with RA or psoriasis (6.0% \textit{versus} 4.4% \textit{versus} 3.8%) and the incidence of obesity had a similar trend (32.9 \textit{versus} 24.4 \textit{versus} 26.4 per 1000 patient-years). Another cross-sectional study from the CORRONA registry demonstrated a higher prevalence of obesity in PsA compared with RA (45% \textit{versus} 39%), although the difference was not statistically significant (OR 1.19, 95% CI 0.90–1.57).\textsuperscript{26}

**Metabolic syndrome.** MetS is defined by the presence of central obesity, HTN, insulin resistance, and dyslipidemia.\textsuperscript{11} Approximately 24–58% of patients with PsA have MetS, which is higher than that reported in the general population.\textsuperscript{10,26,34,46,47} In some cohorts using the validated NHLBI/AHA definition of MetS, the prevalence of MetS in PsA is up to 50%.\textsuperscript{46,48} The odds of having MetS in PsA compared with the general population was 2.68 (95% CI 1.60–4.50) in an outpatient clinic-based study from China.\textsuperscript{10} The prevalence of MetS and its components (as discussed above) are also typically higher in PsA compared with psoriasis alone: HTN (37% \textit{versus} 20%), hyperlipidemia (21% \textit{versus} 15%), diabetes (12% \textit{versus} 7%), and obesity (30 \textit{versus} 27%).\textsuperscript{6} Moreover, there is a higher proportion of PsA patients with MetS compared with RA and other spondyloarthritides (SpAs).\textsuperscript{10,26,49} The prevalence of MetS was higher in PsA compared with RA or ankylosing spondylitis (AS) (OR 2.44, 95% CI 1.48–4.01) in an outpatient arthritis clinic study. The odds were higher for all components of MetS including central obesity, impaired fasting glucose, hypertriglyceridemia, and reduced HDL-C level.\textsuperscript{10}

**The complex relationship of metabolic disease and PsA**

**Metabolic disease as a risk factor for PsA.** While we think of the above comorbidities developing during the disease course in PsA, many of these comorbidities precede the diagnosis of PsA by up to 5 years.\textsuperscript{30} Among the cardiometabolic comorbidities, obesity and hyperlipidemia have been described as risk factors for the development of PsA.\textsuperscript{51} Obesity is one of the strongest risk factors for PsA both in psoriasis as well as the general population and precedes its development by several years.\textsuperscript{51} Moreover, there is a dose effect, such that higher BMI is associated with incrementally increased PsA risk.\textsuperscript{52–54} For example, in a population-based study from UK, relative risk (RR) for PsA was 1.09 (0.93–1.28), 1.22 (1.02–1.47), and 1.48 (1.20–1.81) for psoriasis patients with BMI 25–29.9, 30.0–34.9, and 35.0 kg/m\textsuperscript{2}, respectively.\textsuperscript{53} The relationship between obesity and PsA is further strengthened by surgical weight loss studies on the risk of PsA.\textsuperscript{55,56} While there are no randomized controlled trials (RCTs) on bariatric surgery, results from two large population-based cohort studies showed a protective effect of bariatric surgery on the development of psoriatic disease in obese patients (HR 0.52, 95% CI 0.33–0.81).\textsuperscript{55–57} Egeberg et al.\textsuperscript{55} noted that gastric bypass surgery was associated with a decreased risk of developing both psoriasis and PsA. Maglio et al.\textsuperscript{56} showed a similar protective effect of bariatric surgery on psoriasis, but no reduction in the risk of PsA was observed. By contrast, Green et al.\textsuperscript{57} found that patients with psoriasis who lost weight (by any means) were less likely to develop PsA.

**Impact of metabolic disease on disease activity and severity of PsA.** Patients with PsA who are also obese and/or have MetS are generally found to have higher PsA disease activity and poorer outcomes. There may be several reasons for this difference. First, one study found that obese patients tend to have a longer time to diagnosis compared with patients with normal BMI (5.7 \textit{versus} 2.8 years).\textsuperscript{59} This may be due to difficulty with joint exams in these patients. Next, obese patients may have worse patient-reported disease activity due to functional deficits related to obesity, and obesity is also associated with elevated CRP.\textsuperscript{60} Data from 1943 PsA patients from the Danish and Icelandic biologics registries also showed higher baseline disease activity (28-joint DAS, CRP, and visual analog scale-pain) in obese compared with non-obese patients.\textsuperscript{61} Obese PsA patients also have worse patient-reported outcomes in terms of PsA Impact of Disease (PSAID), and Routine Assessment of Patient Index Data (RAPID3) scores.\textsuperscript{62} This difference in
patient-reported disease activity and CRP may also extend to static outcome measures in particular. Costa et al. also noted that MetS was associated with a lower likelihood of achieving minimal disease activity (MDA) in PsA patients on TNF inhibitor (TNFi) (OR 0.56, \( p < 0.001 \)). Higher consumption of non-steroidal anti-inflammatory agents was reported in obese PsA patients compared with those with normal BMI in a study by Eder et al., although no difference in swollen or tender joint count and radiographic damage was observed. MetS is similarly associated with the severity of PsA (OR 4.47, \( p < 0.001 \)), independent of psoriasis severity and other demographic factors. In the study, severe PsA was defined as PsA patients who required TNFi therapy and/or those with radiographic joint damage.

**Impact of metabolic disease on treatment response.** Obesity and MetS are also associated with poor response to therapy in patients with PsA. Eder et al. reported a lower probability of sustained remission in obese patients, irrespective of therapies used. Similarly, in a study by di Minno et al., obesity was an independent risk factor for not achieving MDA (HR = 4.90, 95% CI 3.04–7.87) and for relapse over 24 months. Among different therapies, TNFi in particular are noted to have a poor response in obese patients. A meta-analysis of 22 studies (11,873 patients) by Singh et al. showed that obesity was associated with inferior TNFi response in patients with psoriasis and PsA (OR 1.57, 95% CI 1.30–1.89); and a dose–response relationship was observed (BMI increase of 1 kg/m² associated with 6.5% higher odds of failure). A more recent study from the US-based CORRONA PsA/SpA registry also found obesity was a strong predictor for not achieving remission with TNFi (OR = 0.51, 95% CI 0.32–0.81). Additionally, in an Italian PsA cohort, MetS was associated with a lower likelihood of achieving MDA on first TNFi at 24 months (OR 0.56, 0.43–0.72, adjusting for PsA disease duration). All of the elements of MDA were affected except the pain score was not different between MetS and not MetS. Moreover, data from Danish and Icelandic biologics registries also showed that obesity is a risk factor for anti-TNF withdrawal (HR 1.6, 95% CI 1.3–2.0) due to poor response. A significantly lower number of obese patients achieved a European League Against Rheumatism (EULAR) good or moderate (EGOM) response (55 versus 65%, \( p = 0.02 \)), and drug adherence was lower in obese patients (2.5 versus 5.9 years) compared with non-obese patients after 6 months. It is unclear if weight-based dosing (available for IV infliximab, golimumab, and ustekinumab) is associated with better outcomes.

There are relatively limited data on other biologics in obese patients with PsA. In particular, data from IL17 inhibitors have been disparate. While obese patients with psoriasis were noted to have a poor therapeutic response to secukinumab in a retrospective study from Spain, recent prospective data from 100 PsA patients on secukinumab interestingly showed that overweight/obese patients had a better Disease Activity in Psoriatic Arthritis (DAPSA) score compared with patients with normal BMI. In the latter study, BMI and DAPSA were inversely related (\( p = 0.05 \)), and serum levels of IL-17 were significantly higher in obese patients compared with non-obese, suggesting a relationship between obesity and IL-17. Obesity has been shown to lead to the expansion of IL-17-producing T-cells in adipose and peripheral tissues. Moreover, insulin resistance is associated with increased expression of IL-17R expression in the liver and muscles in metabolic disease.

**The impact of PsA therapies on metabolic disease**

The association of PsA and metabolic diseases is important for selecting therapy for PsA. While some medications, such as corticosteroids, could worsen glycemic homeostasis and non-steroidal anti-inflammatory drugs (NSAIDs) are associated with increased risk of CVD, other medications, such as TNFi or other biologic therapies aimed at decreasing inflammation, could potentially reduce the cardiometabolic risk. There is limited evidence on the risk of CV associated with NSAIDs and corticosteroids in PsA compared with RA or the general population. Based on studies in RA and the general population, EULAR guidelines recommend minimizing the long-term use of these medications. While an observational study showed a 30% increased risk of diabetes mellitus in patients on oral and topical corticosteroids, the use of TNFi was associated with a lower risk of diabetes mellitus (OR = 0.62) compared with the use of other non-biologic systemic therapy (excluding methotrexate). Some studies show an increase in body weight after starting TNFi for psoriatic disease; however, the weight gain was minimal in general. In contrast, another study found beneficial effects of
TNFi on the components of MetS, such as waist circumference, serum triglycerides, HDL, and blood glucose levels. Biologic therapies, such as TNFi, seem to have a neutral effect on glucose homeostasis. Limited data suggest that TNFi and apremilast could improve diabetes mellitus. A retrospective cohort study of psoriasis patients showed that TNFi was associated with a reduced risk of new-onset diabetes mellitus compared with those receiving non-biologic therapies (HR 0.62, 95% CI 0.42–0.91). Another study from the Optum database found that there may be some benefit of TNFi or methotrexate (MTX) in reducing HbA1c among patients with both diabetes and inflammatory arthritis. In the study, HbA1c decreased after initiation of TNFi [median −0.35, interquartile range (IQR) 1.10–0.30] and MTX (median 0.40, IQR 1.20–0.30), and this reduction was about half (~0.4 units) the decrease observed after initiation of metformin.

In examining pharmacotherapies and their association with cardiometabolic outcomes from observational studies, it is important to consider confounding by indication. In many cases, patients receiving MTX, for example, have a lower prevalence of diabetes, obesity, dyslipidemia, and baseline CV events, suggesting a healthy user effect. Data from RCTs of TNFi in psoriatic disease have not shown any difference in risk of CV events; however, the duration of follow-up is usually short.

**Cardiac diseases in PsA**

**The epidemiology of cardiac diseases in PsA**

Atherosclerotic coronary diseases in psoriatic arthritis. PsA is associated with an increased risk of developing CVD. A meta-analysis of 11 studies found a 43% increased risk of CVD in patients with PsA compared with the general population. Morbidity risks for myocardial infarction and cerebrovascular diseases were increased by 68% and 22%, respectively. This elevated risk is partially independent of traditional CV risk factors, such as diabetes, dyslipidemia, and smoking, supporting the notion that PsA is an independent risk factor for CV events. In a study from the UK THIN database, the risk of incident CV events was in PsA (HR 1.24, 95% CI 1.03–1.49) and psoriasis (HR 1.08, 95% CI 1.02–1.15) with no disease-modifying anti-rheumatic drugs (DMARDs) was similar to RA (HR 1.39, 95% CI 1.28–1.50) after adjustment for age, sex, calendar year, and traditional CV risk factors. Chronic inflammation plays a role in atherosclerosis which is the underlying mechanism of CVD. Data from epidemiologic studies show an independent association between the severity of inflammation related to PsA and CV risk. Markers of PsA disease activity, including polyarthritis, dactylitis, extensive skin psoriasis, and elevated inflammatory markers, have been associated with clinical CV events. Furthermore, patients with PsA tend to exhibit high-risk features for plaque rupture, and the extent of atherosclerotic plaques have been associated with measures of disease activity and inflammatory markers. These findings suggest that appropriate management of CVD in PsA should address both traditional CV risk factors as well as aiming for better control of inflammation.

**Other cardiac disorders in psoriatic arthritis.** Emerging data suggest that additional cardiac structures beyond the coronary arteries, including the myocardium and the cardiac conduction system, are also affected in PsA patients. A population-based study from Sweden has shown that patients with PsA have a higher risk of developing second and third-degree AV blocks and atrial fibrillation compared with the general population (HRs of 1.46 for both disorders). In addition, a higher prevalence of conduction abnormalities was found by electrocardiographic studies in asymptomatic patients with psoriasis and PsA. These abnormalities were associated with elevated levels of inflammatory markers and severe psoriasis. While the presence of HLA-B27 antigen predisposes to fibrosis in the conduction system, this genetic marker is present in only a minority of patients with PsA (~20% in most cohorts), thus it only partially accounts for this increased risk. Another potential mechanism includes the development of left atrial (LA) myopathy, which is characterized by increased chamber stiffness and blood stasis ultimately predisposing to tachyarrhythmias and cardioembolic stroke. This condition is strongly associated with obesity, metabolic abnormalities, and pro-inflammatory state, which are frequently affecting patients with PsA. Indeed, abnormalities in electrical activation of the LA and echocardiographic abnormalities in atrial geometry and filling characteristics, suggestive of LA myopathy, were reported in psoriatic patients. Additionally, abnormal myocardial function, which presents clinically as heart failure, is also
increased in patients with PsA. The risk of developing heart failure is higher by ~30% in patients with PsA compared with the general population.7 Heart failure risk has been associated with a high cumulative burden of musculoskeletal inflammation over time as well as with prior ischemic cardiovascular disease and traditional CV risk factors, while being in a MDA state was protective.97 While accelerated atherosclerosis and subsequent premature ischemic heart disease explain some of these heart failure events, recent studies suggest that inflammation is an important underlying mechanism of heart failure with preserved ejection function (HFP EF).98 Echocardiographic studies in psoriasis and PsA show predominantly impairment in diastolic function which has been associated with obesity and general inflammatory states that characterize PsA, in contrast to heart failure with reduced systolic function (HFrEF) that is more typical of ischemic etiology.99,100 Overall, in addition to the increased risk of developing ischemic heart diseases, emerging data suggest that the risk of tachyarrhythmias, heart blocks, and heart failure is also elevated in PsA. These disorders are also frequently independent of pre-existing ischemic heart diseases and may result from metabolic and pro-inflammatory factors.97

**The impact of PsA therapies on CV risk**

The effects of medications that are used for the treatment of psoriasis and PsA on CV risk are complex. While some medications may have a beneficial effect on CV risk by suppressing inflammation, others, such as NSAIDs and corticosteroids, have been associated with elevated cardiac risk in the general population and among rheumatic patients.71,72,101 The concept of suppression of inflammation as a means to reduce CV risk has been tested in non-rheumatic patients with conflicting results. Two recent RCTs in high-risk patients showed a reduction in CV risk with IL-1 inhibition (canakinumab) and colchicine compared with placebo.102,103 However, another trial with MTX showed negative results.26 In patients with rheumatic diseases, such as PsA, suppression of inflammation is the primary treatment goal, thus it is not ethical to conduct similar trials to simply evaluate the effect of anti-rheumatic treatments against placebo. Therefore, the data about the effect of anti-rheumatic drugs on CV risk are limited to observational studies or short-term randomized placebo-controlled trials that evaluated intermediate outcomes by imaging or laboratory biomarkers.

There is increasing evidence that treatment with TNFi is associated with a reduced risk of developing CVD in patients with psoriasis and PsA, with a reduction of approximately 30% in CV events among patients using TNFi compared with those on non-biologic DMARDs or phototherapy.71,104 This protective effect may be mediated by the reduction of vascular inflammation which may ultimately lead to inhibition of atherosclerotic plaque progression among PsA patients treated with TNF inhibitors.105 Only limited information is available about the effect of other biologic DMARDs targeting IL-23 and IL-17 pathways on CV risk in psoriatic patients. Despite initial concerns regarding increased CV risk resulting in early termination of clinical trials with the IL-12/23 inhibitor briakinumab,106 recent data support the CV safety of this class of biologics. In a randomized placebo-controlled trial, the IL-12/23 inhibitor ustekinumab was more effective than placebo in reducing aortic vascular inflammation in patients with severe psoriasis.107 Another trial showed that IL-12/23 inhibition resulted in a greater improvement of coronary, arterial, and myocardial function than TNF-α inhibition or cyclosporine treatment in psoriasis patients.108 These improvements in surrogate outcomes of CVD may be translated to a lower risk of developing CV events. Data from a large meta-analysis of 38 randomized clinical trials of biologics in patients with psoriasis showed an overall similar risk of developing CV events between TNFi and ustekinumab.109 In line with these findings, observational data from patient registries and drug claim databases suggest that the risk of developing CV events is similar in patients using TNFi and ustekinumab.110,111 There is limited information about the CV risk of newer classes of medications. Secukinumab, an IL-17 inhibitor, improved coronary flow reserve, and left ventricular strain compared with MTX and cyclosporin, indicating an overall beneficial effect on CV function.112 Short-term safety data from clinical trials of IL-17 and IL-23 inhibitors in psoriasis and PsA patients do not show any evidence of increased CV risk, but long-term real-world data are still lacking.113,114 Lastly, there have been recent concerns about veno-thromboembolic risk associated with Janus Kinase (JAK) inhibitors in patients with RA;115 short-term safety data from clinical trials in patients with PsA do not suggest an increased risk of either major CV events or thromboembolic events with this class.116 However, long-term real-world observational data are needed to accurately quantify CV
risk in PsA. Overall, these data support the safety and potential cardio-protective effect of TNF and IL-12/23 inhibitors in psoriatic patients. Information about newer classes of biologics awaits further research.

Management of CVD and CV risk factors

Importance of managing cardiometabolic disease in PsA. Metabolic comorbidities in PsA have important implications for both patients and providers. While these comorbidities may lead to increased physician visits and medications for patients, rheumatologists, dermatologists, and primary care providers involved in their care face challenges in the selection and maintenance of therapies. Therefore, optimal management of psoriatic disease should include not only treating the skin and joint disease, but also identifying comorbidities early, and managing them to improve long-term outcomes. Among patients with PsA, hypertension, diabetes, and high triglycerides are associated with the development of major adverse CV events. In one study, the HRs for these conditions were 1.85 (1.18–2.90), 3.00 (1.79–5.02), and 1.76 (1.10–2.81), respectively (adjusted for sex and PsA disease duration). This alone may be reason enough to address these risk factors for CVD. Unfortunately, there are major gaps in the diagnosis and management of CV risk in patients with psoriatic disease.

Screening for cardiometabolic disease in PsA. CV risk stratification and the management of CV risk factors should be an integral part of patient care. Accepted CV scoring systems, such as the Framingham risk score, help to estimate the future CV risk of an individual patient and thus guide treatment decisions regarding the need for preventative treatment. However, this current standard of practice underestimates CV risk in psoriatic patients. Ernste et al. showed that the observed risk of developing CV events is higher than the estimated risk by the Framingham score. Other studies have shown significant discrepancies between the estimated CV risk by traditional risk score compared with the extent of atherosclerosis by vascular imaging, which is an accurate surrogate for clinical CV risk. These findings can be explained by a residual CV risk that is not explained by traditional risk factors which are included in the risk scores. Potential underlying causes for this residual risk may include the extent of inflammation as reflected by the skin and joint activity, the effect of medications used for PsA, as well as complex interactions between traditional and non-traditional risk factors. A few suggested approaches to address this gap included the use of a multiplier applied to any calculated risk score to accommodate the risk or using vascular imaging, such as carotid ultrasound or coronary calcification, particularly in those with intermediate risk. The EULAR had proposed an increased risk (1.5×) in patients with RA; however, such tools have shown suboptimal performance in estimating CV risk. Currently, there is no disease-specific CV risk score for patients with PsA.

Underdiagnosed and undertreated CV risk factors in patients with PsA are common. Analysis of psoriasis patients enrolled in clinical trials found that 19%, 22%, and 39% of patients with diabetes mellitus, hypertension, and dyslipidemia, respectively, were untreated for these conditions. A study of patients with psoriasis and PsA enrolled in a large, international registry found that 59.2% of patients with hypertension and 65.6% of patients with dyslipidemia were untreated. Under-treatment was associated with younger age, having psoriasis, and male gender. These gaps in the care may be explained by lack of awareness among specialists and family physicians, time constraints and focus on management of the skin and joint disease, limited knowledge about CV prevention strategies among specialists, and the lack of specific recommendations for PsA. Increased awareness regarding the association of PsA with cardiometabolic diseases in both patients and physicians is crucial. Educational strategies similar to those employed for diagnosis of PsA could be helpful. Gaps in knowledge, implementation, and best ways to deliver information to patients and physicians are, however, unclear, and would require further studies. Similarly, qualitative research on how to best empower patients to coordinate their own care may be helpful.

Intervening on CV risk factors. After CV risk assessment, potential interventions include healthy lifestyle changes, and pharmacologic management of specific risk factors and inflammatory burden. EULAR guidelines recommend the adoption of a healthy diet, regular exercise, and smoking cessation in patients with inflammatory arthritis to reduce CV risk. Similarly, weight loss is very important for achieving lower disease activity. Limited data suggest that weight loss can improve pre-existing psoriasis and PsA in obese patients.
Di Minno et al.\(^{130}\) in a prospective study showed that a weight loss of \(\geq 5\%\) was associated with a higher rate of MDA in overweight/obese PsA patients starting TNFi regardless of the type of diet. A dose–response relationship was noted with a higher rate of MDA in patients achieving greater weight loss (OR 6.67 for \(>10\%\) weight loss and OR 3.75 for 5–10\% weight loss compared with those with \(<5\%\) weight loss). Physical activity could have added benefit; however, physical activity alone tends to have lower effectiveness for weight loss compared with dietary intervention.\(^{131}\) Furthermore, patient adherence to these interventions could be suboptimal.\(^{132,133}\) Effective pharmacologic therapy options for obesity in PsA are limited, and studies have shown conflicting and at most minimal benefit on disease activity with GLP-1 agonists.\(^{134,135}\)

Pharmacological treatment and targets for hypertension and hyperlipidemia for PsA are similar to those recommended for the general population.\(^{136–138}\) The one exception is that psoriasis is now considered a “risk-enhancing” factor that may further push the likelihood of initiating a statin.\(^{138}\) There is limited evidence as to the additional benefit of therapies such as statins beyond what is recommended for the general population.\(^{139}\) Given the association of psoriatic disease, systemic inflammation, metabolic disease, and CV events, it is plausible that the control of inflammation may have systemic effects beyond the skin and joints for prevention and improvement of cardiometabolic disease. As a part of CVD management, EULAR also recommends early, tight control of disease activity and reduction in disease flares.\(^{73}\) Further studies are needed to examine the effect of therapies on cardiometabolic diseases in PsA.

### Conclusion
PsA is associated with a higher prevalence and incidence of metabolic disorders, such as hypertension, dyslipidemia, diabetes mellitus, obesity, and MetS, compared with the general population. Furthermore, the risk seems to be higher than that in psoriasis, and other inflammatory arthritides, such as RA and other SpA. Obesity and hyperlipidemia often predate psoriatic disease and have been described as risk factors for the development of PsA. Screening and management of these comorbidities are of utmost importance as they increase the risk of CVD. However, there are several challenges and unanswered questions regarding the management of cardiometabolic diseases in PsA. Patients with PsA often have multiple comorbidities simultaneously, and addressing all of these could be challenging in the usual busy clinical setting. Additionally, patient adherence to multiple interventions could be suboptimal. Development of targeted interventions specifically for patients with psoriatic disease may improve outcomes. Understanding the complex mechanism, interactions, and trajectories of cardiometabolic comorbidities in psoriatic disease will help devise strategies to better address these comorbidities in the real-world scenario.

### Conflict of interest statement
Dr. Ogdie has served as a consultant for AbbVie, Amgen, BMS, Celgene, Corrona, Janssen, Lilly, Novartis, and Pfizer (less than 10,000 each) and has received grants from Novartis and Pfizer to Penn and from Amgen to Forward (grants more than 10,000). Dr Eder has received grants from AbbVie, Pfizer, Novartis, Janssen, Eli Lilly and Amgen (grants more than 10,000).

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