



Review

# Psoriasis and Atherosclerosis—Skin, Joints, and Cardiovascular Story of Two Plaques in Relation to the Treatment with Biologics

Karina Wierzbowska-Drabik <sup>1</sup>, Aleksandra Lesiak <sup>2</sup>, Małgorzata Skibińska <sup>2,\*</sup>, Michał Niedźwiedz <sup>2</sup>,  
Jarosław D. Kasprzak <sup>1</sup> and Joanna Narbutt <sup>2</sup>

<sup>1</sup> Department of Cardiology, Medical University of Lodz, 91-347 Lodz, Poland; wierzbowska@ptkardio.pl (K.W.-D.); kasprzak@ptkardio.pl (J.D.K.)

<sup>2</sup> Department of Dermatology, Pediatric Dermatology and Oncology, Medical University of Lodz, 91-347 Lodz, Poland; aleksandra.lesiak@umed.lodz.pl (A.L.); michal.niedzwiedz@stud.umed.lodz.pl (M.N.); joanna.narbutt@umed.lodz.pl (J.N.)

\* Correspondence: malgorzata.skibinska@umed.lodz.pl

**Abstract:** It is known that both psoriasis (PSO) limited to the skin and psoriatic arthritis (PSA) increase the risk of cardiovascular complications and atherosclerosis progression by inducing systemic inflammatory response. In recent decades, the introduction of biological medications directed initially against TNF- $\alpha$  and, later, different targets in the inflammatory cascade brought a significant breakthrough in the efficacy of PSO/PSA treatment. In this review, we present and discuss the most recent findings related to the interplay between the genetics and immunology mechanisms involved in PSO and PSA, atherosclerosis and the development of cardiac dysfunction, as well as the current PSO/PSA treatment in view of cardiovascular safety and prognosis.

**Keywords:** psoriasis; psoriatic arthritis; atherosclerosis; heart muscle function; biologic treatment; TNF alfa inhibitors; anti-IL12/23; anti-IL17



**Citation:** Wierzbowska-Drabik, K.; Lesiak, A.; Skibińska, M.; Niedźwiedz, M.; Kasprzak, J.D.; Narbutt, J. Psoriasis and Atherosclerosis—Skin, Joints, and Cardiovascular Story of Two Plaques in Relation to the Treatment with Biologics. *Int. J. Mol. Sci.* **2021**, *22*, 10402. <https://doi.org/10.3390/ijms221910402>

Academic Editor: Naoko Kanda

Received: 30 August 2021

Accepted: 24 September 2021

Published: 27 September 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction and Methods

Both psoriasis (PSO) and psoriatic arthritis (PSA) are connected to chronic systemic inflammation which also plays a key role in the development of atherosclerosis (Ath) and its cardiovascular complications resulting in myocardial infarctions and strokes. The prevalence of left ventricular hypertrophy and progression to symptomatic heart failure with preserved ejection fraction is significantly increased in both PSO and PSA [1,2]. Beyond the impact of inflammation, the increased prevalence of traditional cardiovascular risk factors is observed in both entities. This may lead to an endothelial dysfunction, which is the recognized preliminary stage for the development of atherosclerosis and its cardiovascular complications. In review, we focus on the most recent data on:

- Epidemiology and pathophysiology of cardiovascular risk factors and complications in patients with PSO/PSA;
- Molecular background of links between PSO and Ath development;
- Impact of traditional and new treatments on cardiovascular risk in PSO;
- Possibilities of early diagnosis, prevention strategies and effective cardiovascular treatment as well as novel therapeutic perspectives in PSO/PSA.

The PubMed database was searched for publications in English until August 2021 with the usage of MeSH search terms: psoriasis and psoriatic arthritis, in combination with cardiovascular disease, atherosclerosis and each of the standard and new treatments described in the article. Further publications were searched manually from the reference list in the papers. Only full text articles were considered for the reference list.

## 2. Cardiovascular Risk Factors and Complications in PSO/PSA

PSO affects 2–3% of the adult population and 1.4% of children worldwide with significant geographical differentiation (reaching, e.g., 0.91% in the U.S. and 8.5% in Norway), and it is related, especially in its severe forms, to the higher prevalence of cardiovascular (CV) risk factors and complications and other comorbidities representing a wide spectrum of internal diseases [3–7].

The doubled risk of major adverse cardiovascular events (MACE) was described for the first time in 1973 in PSO patients who were compared to patients with other dermatological disorders [8]. This was further confirmed by meta-analysis including 14 cohort studies identifying increased CVD (cardiovascular disease) risk in patients with severe PSO, defined as requiring systemic therapy or hospitalization [9]. This risk was also related to the severity and duration of the skin disease. Cardiovascular mortality, myocardial infarctions (MI) incidence, and, to a lesser extent, strokes as well as chest pains related to angina, symptoms of peripheral artery disease and atrial fibrillation were all reported in the studies including psoriatic patients [10–13].

The increased CVD risk in patients with milder form of PSO has not been well proven and some inconsistencies exist regarding definitions and classifications of mild, moderate and severe PSO in various studies, e.g., related to area of the affected skin, use of systemic therapy or the possibility of treatment in the outpatient settings. Moreover, patients with psoriasis treated with conventional systemic treatments (e.g., ciclosporin and acitretin) may develop hyperlipidemia, which may result in an increased CVD risk in those patients. As far as the impact of psoriasis severity on CVD risk is concerned, Ahlehoff et al. [12], in Danish population-based study, reported that the odds ratio of predicting cardiovascular mortality in severe psoriasis was very similar to that observed in diabetic patients (1.57 with 95% CI 1.27–1.94 for PSO vs. 1.59 with 95% CI 1.56–1.63 for diabetes). Assessments of psoriasis severity used in the studies and the relationship between traditional risk factors (dyslipidemia, family history, arterial hypertension, age, cigarette smoking, diabetes mellitus, obesity and physical inactivity) and psoriasis may all cause methodological problems hampering the accurate assessment of CV risk in PSO [8].

Beyond the “hard” and “soft” clinical endpoints, the prevalence of various indices of atherosclerosis progression or its consequences were assessed in numerous studies of PSO patients, finding the correlation between PSO and calcification of coronary arteries, higher prevalence of traditional risk factors, increased arterial stiffness and carotid intima-media thickness, as well as a connection between the femoral atherosclerotic plaques thickness and the duration of PSO [14–17]. Other studies found impairments in flow-mediated dilatation of arteries, increased epicardial adipose tissue measured by CT, MRI or transthoracic echocardiography or hypertrophy and deterioration of heart ventricular and atrial function in echocardiography [18–22].

Interestingly, large cohort analysis did not reveal any association with the short to medium-term risk for major CV events for psoriasis overall and severe psoriasis when adjusted for known CVD risk factors [23].

Nevertheless, endothelial dysfunction, being the starting point for Ath development, seems to be strongly related to various autoimmune and inflammatory diseases also in the absence of traditional CV risk factors [24]. The microvascular dysfunction itself can lead to increased number of CV complication and myocardial functional impairment even preceding full development of macroscopic atherosclerotic plaques [25,26]. Therefore, proinflammatory and pro-atherosclerotic phenotypical modulation of endothelium forms a crucial link between traditional and novel risk factors and atherosclerotic or *sensu lato* CV complications.

Moreover, in recent years, the evidence regarding increased cardiovascular mortality, which may also be described as a possible shortening of life expectancy of about 5–6 years in patients with severe PSO, has been continuously accumulating [27–29].

The main examples of comorbidities in psoriatic patients and their postulated pathophysiological links are presented in Table 1.

**Table 1.** Comorbidities in psoriatic patients and their postulated pathophysiological links.

Disease/State Related to Psoriasis	Pathophysiologic Link and Chosen References
Psoriatic arthritis (PSA)	This form of psoriasis (PSO) involving joints is related to higher prevalence of cardiovascular and metabolic risk factors, atherosclerosis progression, as well as cardiovascular complications including myocardial infarction and strokes as compared to psoriasis limited only to the skin [30–33].
Metabolic syndrome	Increased prevalence of traditional risk factors: arterial hypertension (HTN), dyslipidemia (abnormalities found even in pediatric populations as well as data suggesting increased risk of PSO development in long-lasting dyslipidemia), obesity, diabetes mellitus and their clustering in psoriatic patients [34–36], evidence of more difficult control of risk factors in psoriatic population [37], impaired cholesterol efflux capacity from macrophages observed in psoriasis because of higher level of oxidized high-density lipoprotein (oxHDL) [38], higher lipoprotein (a), apolipoprotein B and oxidized low-density lipoprotein (oxLDL) levels [39], as well as increased epicardial fat amount (expressed as thickness or area) [40]. Well-controlled glycaemia in diabetics was related to better control of skin psoriasis [41].
Nonalcoholic fatty liver disease	High triglycerides and abnormal serum fatty acid profile were also described in PSO [42]. In obese psoriatic patients treated with anti-TNF-alpha medications, dose–response relationship and particular tendency to central obesity were described. Beneficial effect of weight loss on improvement of PSO, including the increase in the efficacy of the treatment, was also observed [43–46].
Inflammatory bowel disease (IBD): Crohn’s disease and ulcerative colitis	Increased levels of IL-17 in both IBD (both in serum and bowel mucosa) and PSO [47]. Common pleiotropic susceptibility loci identified in PSO, type II diabetes and Crohn’s disease (genes related to locus 6p21 coding the major histocompatibility complex—MHC, genes related to IL23R and IL12B, the latter encoding p40 subunit essential in pathogenesis of IBD and PSO), shared clinical course and immunologic features [48–50]. Postulated similar abnormalities of gut microbiota and role of gut–skin axis in IBD and PSO/PSA, characterized generally by decreased bacterial diversity of gut microbiota beyond skin dysbiosis typical for PSO [51–53]. Increased risk of Crohn’s disease and ulcerative colitis in PSO as well as in PSA [54].
Cardiovascular disorders	Reciprocal relationship between the increased prevalence of HTN in psoriasis as well as more frequent development of PSO in hypertensives observed, e.g., in a Nurses’ Health Study—the use of beta-blockers for HTN treatment was postulated as a potential mechanism [55]. The amount of adipose tissue which in PSO is increased also around vessel walls is the source of angiotensinogen, converted then to angiotensin II, which further stimulates Th17 cells and enhanced hypertension by vascular dysfunction [56]. Increased cigarette smoking and alcohol use reported in PSO as well as an association between smoking and PSO severity. The increased amount of Th17 cells in blood in psoriatic patients who smoke was observed [57,58]. Evidence for increased number of myocardial infarctions and strokes as well as CV mortality in PSO, PSA, as well as rheumatoid arthritis patients [59–61]. Some studies indicated the increased number of venous thrombosis (VTE) in PSO patients. This trend was confirmed by meta-analysis although without reaching statistical significance [62–66]. Augmented risk of new-onset heart failure showing severity-dependence in psoriatic patients was observed in a Danish nationwide cohort study [67]. Increased prevalence of dilated cardiomyopathy was observed in PSO [68].

Table 1. *Conts.*

Disease/State Related to Psoriasis	Pathophysiologic Link and Chosen References
Lymphoma and other malignancies	<p>PSO seem to be related to an increased risk of cancer, especially keratinocyte cancers and lymphomas, including cutaneous T-cell lymphomas (CTCL) [69–72].</p> <p>PSO treated with psoralen-UV-A (PUVA) therapy shows highly increased risk of squamous cell carcinomas [73].</p> <p>The increased risk of CTCL in PSO may be explained by persistent immune activation leading to the development of a dominant clone [74].</p> <p>Certain known risk factors for cancerogenesis (such as alcohol and smoking) are more prevalent in psoriatic patients and some studies postulated the increased risk of lung, bladder, breast (observed in PSA patients in 3 studies) and colorectal cancer in psoriatic patients [75,76] as well as an increased risk of overall cancers after adjustment for confounders may be connected to this phenomenon [77].</p> <p>The impact of conventional vs biologic treatment as well as potential differences in patients with PSA needs further analysis.</p>
Depression	<p>Chronic inflammation and endothelial dysfunction as well as higher incidence of traditional risk factors in PSO; additionally, sleep and anxiety disorders as well as depression led to further increases in CV complications [78–80].</p> <p>Impaired quality of life, typical for chronic, systemic inflammatory disease, as well as for significant skin and joint involvement [81,82].</p> <p>Observed reciprocal association between decreased probability of performing more intense physical activity when suffering from PSO, as well as reduced risk of PSO incidence in those performing vigorous physical activity [83,84].</p>

### 3. Molecular Background of Links between PSO and Ath Development

Immune-mediated inflammation of the skin is a key feature of PSO that can be modified by different genetic and environmental factors. Whereas the role of Th1 cells response driven by IFN- $\gamma$  and IL-12 in PSO has been established for over three decades, recent developments added the importance of the chronic activation of IL-23 and Th17 axis, in which IL-23 maintains the activity of Th17 cells [85].

In 2011, Boehncke et al. [86] proposed and developed the concept of “psoriatic march” to describe how systemic psoriatic inflammation may lead to insulin resistance as well as endothelial cell dysfunction, causing atherosclerosis preceding cardiovascular complications. Although increased risk of CVD is present in various autoimmune diseases (such as rheumatoid arthritis or inflammatory bowel diseases), Ath and PSO also share a joint profile of inflammatory cells (T lymphocytes, monocytes and macrophages) as well as cytokines. This concept led to further development of the theory of “two plaques for one syndrome” which was supported by the evidence of a shared pattern of T helper cells and Th17 cytokine upregulation with increased expression of adhesion molecules and documented displacement of inflammatory cells between psoriatic skin lesions, peripheral circulation and atherosclerotic plaques driven by cytokines released from PSO lesions [87–90].

Furthermore, pro-inflammatory cytokines known as key factors for PSO lesions development, IFN- $\gamma$  (interferon gamma), TNF- $\alpha$  (tumor necrosis factor alpha) and IL-17, were found in increased amounts in unstable atherosclerotic plaques in patients with acute coronary syndromes, whereas cardiovascular biomarkers such as MCP-1 (monocyte chemoattractant protein) as well as macrophage-derived chemokines were measured in skin and serum in PSO patients [91–93].

Similarly, patients with ischemic heart disease have higher levels of Th17-related cytokines (IL17, IL6 and IL8) circulating in their blood and there are data showing that overexpression of Th17 cytokines in PSO may mediate the development of Ath and cardiovascular comorbidities [94,95]. Moreover, also in patients with psoriatic arthritis (PSA), without significant burden of traditional cardiovascular risk factors or history of CVD, levels of pro-atherogenic inflammation markers such as CRP (C-reactive protein) and soluble ICAM-1 (intracellular adhesion molecule-1) when compared to healthy subjects were related to the duration and severity of PSA. This underlines the need for considering

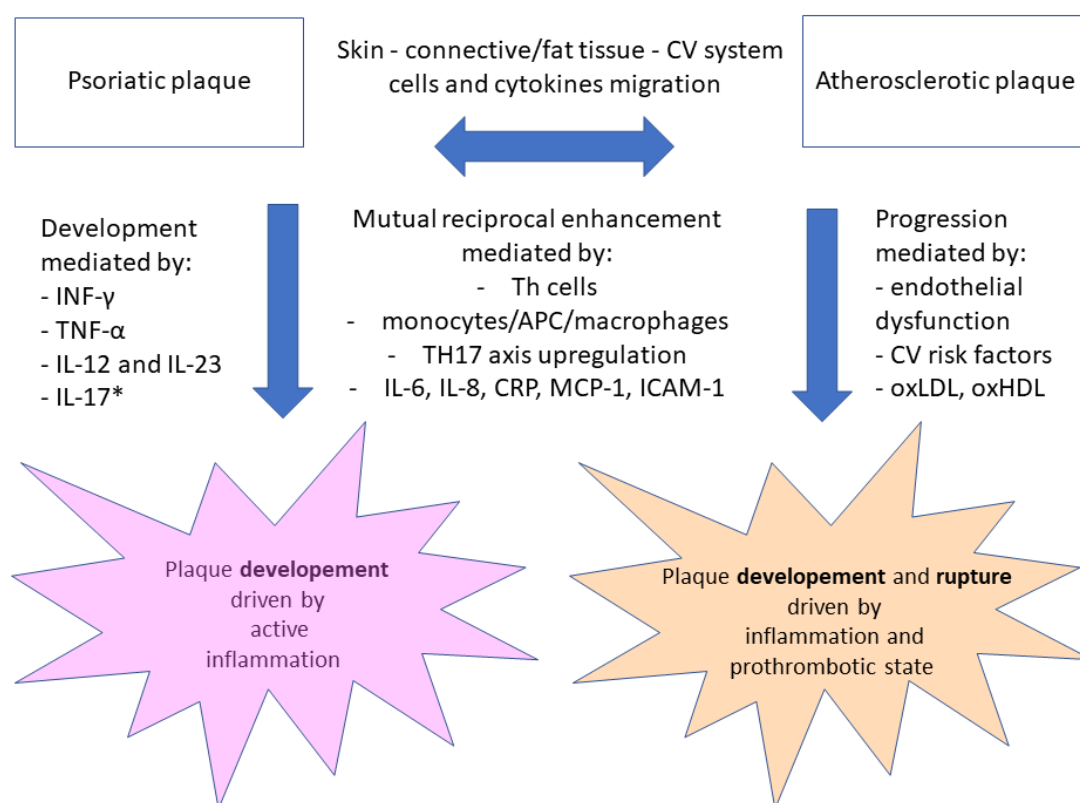
primary prevention measures in such patients [96]. Because of common inflammatory pathways (Th1 and Th17 cytokines, etc.) chronic skin inflammation in PSO may lead to vascular, subcutaneous and systemic inflammation, which may be confirmed by PET/CT scans in particular organs, e.g., aorta or liver, and may further result in Ath development and thrombotic complications [97–99].

Recently, closer attention has been paid to the role of activated inflammasomes in the pathogenesis of psoriasis, which are large protein complexes able to cleave the pro-inflammatory cytokines: pro-interleukin-1 $\beta$  and pro-interleukin-18 into active forms which contribute to PSO development [100–102].

Going beyond common phenotypic expression of systemic inflammation, there is an ongoing search for shared genetic background between PSO/PSA and Ath [103]. Joint genetic factors were postulated for PSO, type II diabetes and Crohn's disease [48]. Other authors showed that polymorphism of apolipoprotein E (*APOE*) gene and common variation of *IL12B*, *IL23R* and *IL23A* genes may play a role in patients with PSO, PSA and DM type 2 [48,104,105].

Although psoriatic or wider “inflammatory skin march” theory assumes the causative role of skin inflammation causing the atherosclerosis and its thrombotic cardiovascular complications, the question of exact time relationship between PSO and Ath or “plaque precedence issue” remains unresolved since strong evidence on a higher risk of PSO development in patients with CV risk factors exist (see Table 1) [106].

Present knowledge regarding two plaques' interaction and the connection between fat tissue, cardiovascular and gastrointestinal system and their circulating mediators is illustrated in Figure 1.



**Figure 1.** Interconnection between PSO and Ath—two plaques' interactions. Notes: IL-12 and IL-2—interleukins sharing common p40 subunit, IL-17\*—interleukin with potential pro- and anti-atherosclerotic activity in PSO plaque stimulates hyperproliferation and differentiation of keratinocytes, maturation of dendritic cells and recruitment of neutrophils and macrophages in psoriatic lesions. Abbreviations: CV—cardiovascular, INF- $\gamma$ —interferon gamma, TNF- $\alpha$ —tumor necrosis factor alfa, IL—interleukin, APC—antigen presenting cell, CRP—C-reactive protein, MCP-1—monocyte chemoattractant protein-1, ICAM-1—intracellular adhesion molecule-1, oxLDL—oxidized low-density lipoprotein, oxHDL—oxidized high-density lipoprotein.

An increasing amount of evidence supporting joint pathomechanisms in psoriasis severity and CV complications raise the question related to the possible beneficial impact of systemic anti-inflammatory treatment, applied with great success in recent decades in PSO/PSA patients, on lowering the prevalence of cardiovascular complications as well as cardiac and general mortality [107].

#### 4. Impact of Traditional and New Treatment on Cardiovascular Risk in PSO

Traditional systemic drugs used in PSO/PSA treatment show varied impact on Ath progression and cardiac complications. Consistently detrimental impact on CVD and risk factor burden was observed for cyclosporine due to the possible development of dyslipidemia, hypertension, and impairment of renal function, which all should be limited by shortening the period of cyclosporine treatment [108]. Data related to acitretin influence on CV risks are conflicting. The increase in the risk of hypertension and dyslipidemia as well as CVD was described in acitretin treatment, but on the other hand, some beneficial effects on atherosclerotic plaques formation were also reported [109]. Beneficial changes in the profile of CV risk biomarkers with lowering CRP serum levels and increasing adiponectin resulting in the improvement of endothelial function were described for therapy with fumaric acid esters in patients with moderate to severe PSO [110]. The reduction of 21% in CVD and 18% in MI incidence was reported in meta-analysis in PSO patients treated with widely used oral or subcutaneous methotrexate [111].

Systemic biological therapies brought significant, short and long-term improvement in the PSO and PSA treatment, confirmed by the reduction in skin lesions severity, functional and QoL improvement as well as the reduction in hospitalization and lowering the number of rheumatological complications. High clinical efficacy of biological therapies blocking the activity of TNF- $\alpha$  and interleukins (12/23, 17) provided the “ex iuvantibus” evidence of the cytokine roles in the skin and joints’ psoriatic involvement. Less certain and with varied data is the impact of various cytokine inhibitors on the incidence of cardiovascular events, with more evidence gathered on the protective role of TNF- $\alpha$  compared to, e.g., IL 17 inhibitors, which have been used for a shorter time [112]. In Table 2, we present biologic medications frequently used nowadays in PSO/PSA treatment with their respective target of action and the connection with CVD.

**Table 2.** Biologic medications used in PSO/PSA treatment with their respective target of action and the connection with CVD.

Group of Medication	Name of Drug	Specific Targets and Actions in Immune System/Role in Pathogenesis and Treatment
TNF- $\alpha$ inhibitors	Infliximab Etanercept Adalimumab Certolizumab-pegol Golimumab	Target elevated levels of TNF- $\alpha$ ; cause CRP, VEGF and resistin as well as chemotactics factors’ reduction: VCAM-1, E-selectin, IL-8, MCP-1 [113]. Additionally, decreases Th17 cell count in blood by stopping CD4+ T cells differentiation into Th1, Th17 and Th22. Improvement of insulin sensitivity [114] and showing antiplatelet activity, especially in patients with increased platelet activation prior to treatment, as evidenced by decreases in P-selectin levels [115] (data for TNF inhibitors and ustekinumab). Reducing level of circulating retinol-binding protein 4: RBP4 (showed to be linked to subclinical atherosclerosis with positive correlation with intima-media thickness) [116]. Adalimumab therapy improved pulse wave velocity (being strong predictor of CV events) after 6 months of therapy [117].
Inhibitors of the p40 subunit to IL-12 and IL-23	Ustekinumab Briakinumab	Human monoclonal antibodies from this group showed improvement of myocardial and vascular function as compared to treatment with cyclosporine or TNF alfa inhibitors [118]. During the initial stage, the temporary increase in pro-atherogenic mediators was observed. Small, randomized trials showed the increase in CV events with briakinumab (but not with ustekinumab), which was then withdrawn from application for psoriasis treatment [119,120].

Table 2. *Conts.*

Group of Medication	Name of Drug	Specific Targets and Actions in Immune System/Role in Pathogenesis and Treatment
IL-17A inhibitors	Secukinumab Ixekizumab	Confirmed high, dose-dependent efficacy in improving PSO during short-term 12–16-week treatment [121,122]. Moreover, secukinumab improved myocardial and vascular function as assessed by global longitudinal strain and pulse wave velocity measurements, respectively, which achieved significance in comparison to MTX and cyclosporine therapy after 12 months of follow-up [123].
IL-17 receptor antagonist	Brodalumab	
Novel inhibitors of IL-23 (blocking p19 unit of IL23)	Guselkumab Risankizumab Tildrakizumab Mirikizumab	Data are still being gathered; risankizumab being a new type of IL-23 inhibitor, seems to present better short-term efficacy [122]. In comparison with IL-17 antagonists, the novel group seems to show a better safety profile [122].

Elevated levels of TNF- $\alpha$  and its soluble receptors present in severe PSO lead to the development of atherosclerosis, the deterioration of cardiac function and the remodeling of smooth muscles. Similarly, the treatment with TNF- $\alpha$  and IL12/23 inhibitors was reported to improve various “soft” endpoints in the cardiovascular system, including the reduction in aortic inflammation in PET assessment, slowing the calcification of coronaries in CT study or enhancing the myocardial left and right ventricular function in echocardiography [124–127].

Nevertheless, there are also data revealing the lack of improvement, as it was shown for mortality or hospitalization (etanercept) in a RENEWAL study in 1500 patients with heart failure, or even detrimental effects on mortality in patients treated with high doses of infliximab [128,129]. To sum the contemporary data, it may be stated that beyond patients with symptomatic heart failure, anti-TNF- $\alpha$  agents exert protective impacts on cardiovascular risk, similar for all three widely used in PSO/PSA medications (etanercept, infliximab and adalimumab), better when compared to patients treated only with topical therapy, phototherapy or methotrexate.

Interleukins 12 and 23 play an important role in the pathogenesis of inflammatory process both in psoriasis and atherosclerosis. Released by macrophages and dendritic cells, they activate Th1 and Th17 lymphocytes to produce other cytokines, including TNF- $\alpha$  and IL17 as well as IFN- $\gamma$ , IL17F and IL22, whose role in PSO and Ath has been recently documented [130,131]. Moreover, both IL12 and 23 share common subunit p40, the lack of which in knocked-out laboratory mice cause resistance in developing autoimmune conditions, including psoriasis. Therefore, anti-IL12/23p40 biologic therapy was introduced with ustekinumab and briakinumab [132]. For both agents mentioned above, safety concerns related to the possible increase in CV events, especially in early phase of treatment, were raised, which then seemed to be effaced in the longer-term follow-up [119,133]. The pathophysiologic background for these clinical observations related to a temporary increase in pro-atherogenic mediators during the initial stage of therapy, which, however, significantly decreased further into the duration of the treatment [134]. Nonetheless, the usage of briakinumab was stopped and the exact impact of the inhibitors of IL12/23p40 needs further detailed analyses.

The studies and discovery of the increased activity of Th17 cells and IL 17 levels in patients with PSO were followed by the successful introduction of several anti-IL-17 agents to the treatment of psoriasis [135,136]. Anti-IL-17 monoclonal antibodies secukinumab, ixekizumab as well as brodalumab, being an anti-IL-17 receptor antibody, showed both good efficacy and safety in patients with moderate to severe PSO. However, since IL-17 has been shown to exhibit both pro- and anti-atherogenic effects depending on inflammatory background, the potential impact of the anti-IL17 drugs on CV complications is uncertain. Overall, in pooled analysis including 10 studies, the incidence of cardiovascular complications in patients with PSO treated with secukinumab was low and they were mostly recorded in patients with present CVD risk factors such as arterial hypertension

and dyslipidemia [137]. Likewise, analysis of seven trials revealed similar or even better long-term CV safety profile of ixekizumab as compared to etanercept, which was also consistent with earlier reports on ixekizumab's safety [138,139]. Reports on the beneficial effects of anti-IL-17 drugs in renal function are also available [140]. As far as brodalumab is concerned, present data are too sparse to draw conclusions about the impact of this drug on cardiovascular outcomes, since only some preliminary suggestions toward both protective and detrimental effects have been so far published [141,142].

Bimekizumab is a humanized monoclonal antibody, a dual inhibitor of interleukin IL-17A and IL-17F, which was recently approved in Europe for the treatment of moderate to severe plaque psoriasis in adults [143]. Clinical phase II trials already showed good efficacy in both psoriasis and psoriatic arthritis [144,145]. No major adverse cardiac events were reported in the published studies [143–145].

To summarize this part of the review, it seems that anti-TNF- $\alpha$  agents have a better confirmed role in diminishing CV complications in the short-term treatment of PSO, whereas the role of newer drugs remains, at this moment, conflicting [146].

## 5. Novel Diagnostic and Therapeutic Perspectives in PSO/PSA

Given the well-confirmed relationship between PSO, Ath and cardiovascular complications, the reduction in detrimental outcomes may be closely related to effective global risk stratifications and preventive treatment reaching beyond the pharmacotherapy limited to the skin and joints [147]. As the traditional scores based on classical risk factors underestimate the CV risk in PSO/PSA (similarly to autoimmune diseases such as lupus or rheumatoid arthritis), the reclassification to the higher risk group is needed for psoriatic patients (especially with PSA), as documented in the Framingham and other popular scores [148,149]. The proposed solution for an improvement in the risk assessment in patients with PSO was to apply 1.5 multiplier to calculated CV risk score in psoriatic patients or to add other tests revealing subclinical atherosclerosis, such as carotid ultrasound with intima-media thickness assessment, pulse wave velocity measurements or coronary calcium score evaluation [150].

Taking into account current European and North American guidelines regarding primary and secondary prevention of cardiovascular complications, the increased burden of CV events in PSO as well as data underlining the potential of statin therapy for reducing psoriasis severity, Masson et al. [6] recommended high-intensity statin treatment for secondary prevention in PSO patients with severe hypercholesterolemia (LDL-C > 190 mg/dL or familial) and high CV risk scores (calculated in patients with psoriasis with adjustment of 1.5 multiplier). Psoriatic patients with diabetes mellitus or subclinical atheromatosis should have a choice between starting moderate or high-intensity statin, whereas moderate-intensity statins were recommended for moderate CV risk scores and moderate to severe chronic kidney disease in those patients [6].

In the treatment of HTN, the long-term use of beta-blockers was associated with PSO development related to blocking beta receptors in the skin as well as increasing phosphorylation in T cells and favoring cellular proliferation and the release of cytokines [54,151]. Additionally, the exacerbation of PSO was also observed in patients taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers [152]. As a potential result of these drug-related side-effects, patients with PSO achieved worse control of hypertension [37].

Contrarily, hypoglycemic agents such as GLP-1 agonists, DPP-4 inhibitors, thiazolidinediones and biguanides seem to reduce incidence of autoinflammatory and autoimmune disorders including PSO and alleviate the disease severity [41,153–155].

Novel systemic biologic drugs in PSO/PSA treatment include agents blocking IL12/23, IL-17 and, recently, IL-23p19 units. Recently published meta-analysis showed that IL-17 inhibitors were the most effective in achieving improvement in PSO severity (e.g., as reported with PASI score) at 12 weeks as compared to IL12/23 and IL-23 inhibitors [122]. On the other hand, ustekinumab (older type IL12/23 inhibitor blocking p40 common unit) had a moderate efficacy and safety assessment. Among the novel drugs, risankizumab is



an IL-23 inhibitor with good efficacy and safety profile, probably better than those of IL-17 blocking agents [156].

Mirikizumab is currently at the stage of clinical trials (examined in OASIS-1/2/3 studies), showing, so far, non-inferiority at week 16 and superiority at week 52 as compared to secukinumab [157]. Preliminary results also seem to report a similar clinical effectiveness between new anti-IL-23 drugs and anti-IL-17 inhibitors [158].

Janus kinase (JAK) inhibitors belong to a relatively new class of small-molecule drugs [159]. So far, they have been registered in various countries for ulcerative colitis, rheumatoid arthritis, atopic dermatitis and psoriatic arthritis treatment [159]. Clinical trials in moderate to severe psoriasis are currently ongoing [160,161]. JAK inhibitors act inside the cells, blocking the pathway mediated by JAK and STAT (signal transducer activator of transcription) proteins, leading to inhibited gene transcription for inflammatory cytokines [159]. Oral route of administration and potentially lower cost are advantages of this group of medications [159]. Tofacitinib in combination with methotrexate is indicated for the treatment of active psoriatic arthritis [162]. In clinical trials for rheumatic arthritis and psoriasis, an increase in both HDL and LDL cholesterol levels as well as triglycerides was described during treatment with tofacitinib [163]. However, in the summary of product characteristics, those side effects were described as uncommon, while HTN was reported in 2.2% of patients [162]. Venous thromboembolism (VTE) in the form of pulmonary embolism and deep vein thrombosis have been described in patients taking tofacitinib; therefore, it should be used with caution in patients with risk factors for VTE in all indications and dosages [162,164]. At least four other JAK inhibitors are currently undergoing clinical trials in psoriasis [159].

In a recently published review by Piros et al. [165], the authors underline the need for holistic care of patients with severe PSO, which goes beyond skin and joints and by self-reinforcing Th1 and Th17 cell-dependent systemic inflammation, accelerating the progression of metabolic and cardiovascular diseases. Although the intrinsic anti-atherotic potential of novel systemic biologic treatment is still improving, their action should be accompanied, and for older agents, counterbalanced, by further safe and effective preventive measures.

## 6. Conclusions

PSO and Ath share common biochemical pathways, including oxidative stress, endothelial dysfunction, monocyte and neutrophil recruitment, T cell activation, increased angiogenesis and prothrombotic state.

To optimize care for PSO/PSA patients, the connection between inflammation and atherosclerosis should be kept in mind and the multidirectional aspect of systemic therapies should be considered. Together with significant progress in the biologic therapy respective screening methods, adjusted global cardiovascular risk assessment and additional tests revealing initial stages of vascular and organ damage should be advocated.

The repeated yearly evaluation and patient education on a healthy lifestyle and non-pharmacologic and pharmacologic risk factor management is recommended. The introduction of early and vigorous prevention measures may help to avoid significant lifespan shortening observed in moderate to severe PSO/PSA, depending on CV complications as well as the impairment of life quality.

**Author Contributions:** Conceptualization, K.W.-D., A.L. and J.N., writing—original draft preparation, K.W.-D. writing—review and editing, M.S. and M.N., visualization K.W.-D., M.S. and M.N., supervision A.L., J.D.K. and J.N. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by statutory activities of Medical University of Lodz, grant no. 503/5-064-04/503-01.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

- Koppikar, S.; Colaco, K.; Harvey, P.; Akhtari, S.; Chandran, V.; Gladman, D.D.; Cook, R.; Eder, L. Incidence of and Risk Factors for Heart Failure in Patients with Psoriatic Disease—A Cohort Study. *Arthritis Care Res.* **2021**. [[CrossRef](#)] [[PubMed](#)]
- Packer, M.; Lam, C.S.P.; Lund, L.H.; Maurer, M.S.; Borlaug, B.A. Characterization of the Inflammatory-Metabolic Phenotype of Heart Failure with a Preserved Ejection Fraction: A Hypothesis to Explain Influence of Sex on the Evolution and Potential Treatment of the Disease. *Eur. J. Heart Fail.* **2020**, *22*, 1551–1567. [[CrossRef](#)] [[PubMed](#)]
- Parisi, R.; Symmons, D.P.M.; Griffiths, C.E.M.; Ashcroft, D.M.; Identification and Management of Psoriasis and Associated Comorbidity (IMPACT) project team. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. *J. Investig. Dermatol.* **2013**, *133*, 377–385. [[CrossRef](#)] [[PubMed](#)]
- Boehncke, W.-H.; Schön, M.P. Psoriasis. *Lancet* **2015**, *386*, 983–994. [[CrossRef](#)]
- Nestle, F.O.; Kaplan, D.H.; Barker, J. Psoriasis. *N. Engl. J. Med.* **2009**, *361*, 496–509. [[CrossRef](#)] [[PubMed](#)]
- Masson, W.; Lobo, M.; Molinero, G. Psoriasis and Cardiovascular Risk: A Comprehensive Review. *Adv. Ther.* **2020**, *37*, 2017–2033. [[CrossRef](#)]
- Michalek, I.M.; Loring, B.; John, S.M. A Systematic Review of Worldwide Epidemiology of Psoriasis. *J. Eur. Acad. Dermatol. Venereol.* **2017**, *31*, 205–212. [[CrossRef](#)] [[PubMed](#)]
- McDonald, C.J.; Calabresi, P. Occlusive Vascular Disease in Psoriatic Patients. *N. Engl. J. Med.* **1973**, *288*, 912.
- Samarasekera, E.J.; Neilson, J.M.; Warren, R.B.; Parnham, J.; Smith, C.H. Incidence of Cardiovascular Disease in Individuals with Psoriasis: A Systematic Review and Meta-Analysis. *J. Investig. Dermatol.* **2013**, *133*, 2340–2346. [[CrossRef](#)] [[PubMed](#)]
- Kaye, J.A.; Li, L.; Jick, S.S. Incidence of Risk Factors for Myocardial Infarction and Other Vascular Diseases in Patients with Psoriasis. *Br. J. Dermatol.* **2008**, *159*, 895–902. [[CrossRef](#)]
- Wakkee, M.; Herings, R.M.C.; Nijsten, T. Psoriasis May Not Be an Independent Risk Factor for Acute Ischemic Heart Disease Hospitalizations: Results of a Large Population-Based Dutch Cohort. *J. Investig. Dermatol.* **2010**, *130*, 962–967. [[CrossRef](#)]
- Ahlehoff, O.; Gislason, G.H.; Charlott, M.; Jørgensen, C.H.; Lindhardsen, J.; Olesen, J.B.; Abildstrøm, S.Z.; Skov, L.; Torp-Pedersen, C.; Hansen, P.R. Psoriasis Is Associated with Clinically Significant Cardiovascular Risk: A Danish Nationwide Cohort Study: Psoriasis and Cardiovascular Risk. *J. Intern. Med.* **2011**, *270*, 147–157. [[CrossRef](#)] [[PubMed](#)]
- Xu, T.; Zhang, Y.-H. Association of Psoriasis with Stroke and Myocardial Infarction: Meta-Analysis of Cohort Studies: Psoriasis, Stroke and Myocardial Infarction. *Br. J. Dermatol.* **2012**, *167*, 1345–1350. [[CrossRef](#)] [[PubMed](#)]
- Ludwig, R.J.; Herzog, C.; Rostock, A.; Ochsendorf, F.R.; Zollner, T.M.; Thaci, D.; Kaufmann, R.; Vogl, T.J.; Boehncke, W.-H. Psoriasis: A Possible Risk Factor for Development of Coronary Artery Calcification. *Br. J. Dermatol.* **2007**, *156*, 271–276. [[CrossRef](#)]
- Gisoni, P.; Fantin, F.; Del Giglio, M.; Valbusa, F.; Marino, F.; Zamboni, M.; Girolomoni, G. Chronic Plaque Psoriasis Is Associated with Increased Arterial Stiffness. *Dermatology* **2009**, *218*, 110–113. [[CrossRef](#)]
- Jókai, H.; Szakonyi, J.; Kontár, O.; Marschalkó, M.; Szalai, K.; Kárpáti, S.; Holló, P. Impact of Effective Tumor Necrosis Factor-Alpha Inhibitor Treatment on Arterial Intima-Media Thickness in Psoriasis: Results of a Pilot Study. *J. Am. Acad. Dermatol.* **2013**, *69*, 523–529. [[CrossRef](#)] [[PubMed](#)]
- González-Cantero, A.; Gonzalez-Cantero, J.; Sanchez-Moya, A.I.; Perez-Hortet, C.; Arias-Santiago, S.; Martin-Rodriguez, J.L.; Schoendorff-Ortega, C.; Gonzalez-Calvin, J.L. Femoral Artery Ultrasound for Improving the Detection of Atherosclerosis in Psoriasis. *J. Am. Acad. Dermatol.* **2019**, *80*, 784–786. [[CrossRef](#)]
- Fang, N.; Jiang, M.; Fan, Y. Association between Psoriasis and Subclinical Atherosclerosis: A Meta-Analysis. *Medicine* **2016**, *95*, e3576. [[CrossRef](#)]
- Villasante Fricke, A.C.; Iacobellis, G. Epicardial Adipose Tissue: Clinical Biomarker of Cardio-Metabolic Risk. *Int. J. Mol. Sci.* **2019**, *20*, 5989. [[CrossRef](#)]
- Milaniuk, S.; Pietrzak, A.; Mosiewicz, B.; Mosiewicz, J.; Reich, K. Influence of Psoriasis on Circulatory System Function Assessed in Echocardiography. *Arch. Derm. Res.* **2015**, *307*, 855–861. [[CrossRef](#)] [[PubMed](#)]
- Atas, H.; Kepez, A.; Bozbay, M.; Gencosmanoglu, D.S.; Cincin, A.; Sunbul, M.; Bozbay, A.Y.; Darvishova, R.; Ergun, T. Assessment of Left Atrial Volume and Function in Patients with Psoriasis by Using Real Time Three-Dimensional Echocardiography. *Wien. Klin. Wochenschr.* **2015**, *127*, 858–863. [[CrossRef](#)] [[PubMed](#)]
- Rana, A.; Mahajan, V.K.; Mehta, K.S.; Chauhan, P.S.; Kumar, M.; Sharma, A.; Sharma, R.; Dhatarwal, N.; Sondhi, M. Cardiomyopathy and Echocardiographic Abnormalities in Indian Patients with Psoriasis: Results of a Pilot Study. *Int. J. Clin. Pract.* **2021**, *75*, e13756. [[CrossRef](#)] [[PubMed](#)]
- Parisi, R.; Rutter, M.K.; Lunt, M.; Young, H.S.; Symmons, D.P.M.; Griffiths, C.E.M.; Ashcroft, D.M.; Identification and Management of Psoriasis Associated Comorbidity (IMPACT) project team. Psoriasis and the Risk of Major Cardiovascular Events: Cohort Study Using the Clinical Practice Research Datalink. *J. Investig. Dermatol.* **2015**, *135*, 2189–2197. [[CrossRef](#)] [[PubMed](#)]
- Zinger, H.; Sherer, Y.; Shoenfeld, Y. Atherosclerosis in Autoimmune Rheumatic Diseases—Mechanisms and Clinical Findings. *Clin. Rev. Allergy Immunol.* **2009**, *37*, 20–28. [[CrossRef](#)] [[PubMed](#)]
- Sitia, S.; Tomasoni, L.; Atzeni, F.; Ambrosio, G.; Cordiano, C.; Catapano, A.; Tramontana, S.; Perticone, F.; Naccarato, P.; Camici, P.; et al. From Endothelial Dysfunction to Atherosclerosis. *Autoimmun. Rev.* **2010**, *9*, 830–834. [[CrossRef](#)] [[PubMed](#)]

26. Lerman, A.; Zeiher, A.M. Endothelial Function: Cardiac Events. *Circulation* **2005**, *111*, 363–368. [[CrossRef](#)]
27. Mehta, N.N.; Azfar, R.S.; Shin, D.B.; Neimann, A.L.; Troxel, A.B.; Gelfand, J.M. Patients with Severe Psoriasis Are at Increased Risk of Cardiovascular Mortality: Cohort Study Using the General Practice Research Database. *Eur. Heart J.* **2010**, *31*, 1000–1006. [[CrossRef](#)]
28. Siegel, D.; Devaraj, S.; Mitra, A.; Raychaudhuri, S.P.; Raychaudhuri, S.K.; Jialal, I. Inflammation, Atherosclerosis, and Psoriasis. *Clin. Rev. Allergy Immunol.* **2013**, *44*, 194–204. [[CrossRef](#)]
29. Abuabara, K.; Azfar, R.S.; Shin, D.B.; Neimann, A.L.; Troxel, A.B.; Gelfand, J.M. Cause-Specific Mortality in Patients with Severe Psoriasis: A Population-Based Cohort Study in the U.K. Cause-Specific Mortality in Patients with Severe Psoriasis. *Br. J. Dermatol.* **2010**, *163*, 586–592. [[CrossRef](#)]
30. Li, L.; Hagberg, K.W.; Peng, M.; Shah, K.; Paris, M.; Jick, S. Rates of Cardiovascular Disease and Major Adverse Cardiovascular Events in Patients with Psoriatic Arthritis Compared to Patients without Psoriatic Arthritis. *J. Clin. Rheumatol.* **2015**, *21*, 405–410. [[CrossRef](#)]
31. Polachek, A.; Touma, Z.; Anderson, M.; Eder, L. Risk of Cardiovascular Morbidity in Patients with Psoriatic Arthritis: A Meta-Analysis of Observational Studies. *Arthritis Care Res.* **2017**, *69*, 67–74. [[CrossRef](#)]
32. Shen, J.; Wong, K.-T.; Cheng, I.T.; Shang, Q.; Li, E.K.; Wong, P.; Kun, E.W.; Law, M.Y.; Yip, R.; Yim, I.; et al. Increased Prevalence of Coronary Plaque in Patients with Psoriatic Arthritis without Prior Diagnosis of Coronary Artery Disease. *Ann. Rheum. Dis.* **2017**, *76*, 1237–1244. [[CrossRef](#)]
33. Chin, Y.-Y.; Yu, H.-S.; Li, W.-C.; Ko, Y.-C.; Chen, G.-S.; Wu, C.-S.; Lu, Y.-W.; Yang, Y.-H.; Lan, C.-C.E. Arthritis as an Important Determinant for Psoriatic Patients to Develop Severe Vascular Events in Taiwan: A Nation-Wide Study: Psoriasis with or without Joint Involvement. *J. Eur. Acad. Dermatol. Venereol.* **2013**, *27*, 1262–1268. [[CrossRef](#)]
34. Langan, S.M.; Seminara, N.M.; Shin, D.B.; Troxel, A.B.; Kimmell, S.E.; Mehta, N.N.; Margolis, D.J.; Gelfand, J.M. Prevalence of Metabolic Syndrome in Patients with Psoriasis: A Population-Based Study in the United Kingdom. *J. Investig. Dermatol.* **2012**, *132*, 556–562. [[CrossRef](#)]
35. Tom, W.L.; Playford, M.P.; Admani, S.; Natarajan, B.; Joshi, A.A.; Eichenfield, L.F.; Mehta, N.N. Characterization of Lipoprotein Composition and Function in Pediatric Psoriasis Reveals a More Atherogenic Profile. *J. Investig. Dermatol.* **2016**, *136*, 67–73. [[CrossRef](#)] [[PubMed](#)]
36. Wu, S.; Li, W.-Q.; Han, J.; Sun, Q.; Qureshi, A.A. Hypercholesterolemia and Risk of Incident Psoriasis and Psoriatic Arthritis in US Women: Hypercholesterolemia and Risk of Incident Psoriasis and PsA. *Arthritis Rheumatol.* **2014**, *66*, 304–310. [[CrossRef](#)] [[PubMed](#)]
37. Takeshita, J.; Wang, S.; Shin, D.B.; Mehta, N.N.; Kimmell, S.E.; Margolis, D.J.; Troxel, A.B.; Gelfand, J.M. Effect of Psoriasis Severity on Hypertension Control: A Population-Based Study in the United Kingdom: A Population-Based Study in the United Kingdom. *JAMA Dermatol.* **2015**, *151*, 161–169. [[CrossRef](#)] [[PubMed](#)]
38. Holzer, M.; Wolf, P.; Curcic, S.; Birner-Gruenberger, R.; Weger, W.; Inzinger, M.; El-Gamal, D.; Wadsack, C.; Heinemann, A.; Marsche, G. Psoriasis Alters HDL Composition and Cholesterol Efflux Capacity. *J. Lipid Res.* **2012**, *53*, 1618–1624. [[CrossRef](#)]
39. Ramezani, M.; Zavattaro, E.; Sadeghi, M. Evaluation of Serum Lipid, Lipoprotein, and Apolipoprotein Levels in Psoriatic Patients: A Systematic Review and Meta-Analysis of Case-Control Studies. *Postepy Dermatol. Alergol.* **2019**, *36*, 692–702. [[CrossRef](#)]
40. Wang, X.; Guo, Z.; Zhu, Z.; Bao, Y.; Yang, B. Epicardial Fat Tissue in Patients with Psoriasis: A Systematic Review and Meta-Analysis. *Lipids Health Dis.* **2016**, *15*, 103. [[CrossRef](#)]
41. Ip, W.; Kirchhof, M.G. Glycemic Control in the Treatment of Psoriasis. *Dermatology* **2017**, *233*, 23–29. [[CrossRef](#)]
42. Myśliwiec, H.; Baran, A.; Harasim-Symbor, E.; Myśliwiec, P.; Milewska, A.J.; Chabowski, A.; Flisiak, I. Serum Fatty Acid Profile in Psoriasis and Its Comorbidity. *Arch. Derm. Res.* **2017**, *309*, 371–380. [[CrossRef](#)]
43. Setty, A.R.; Curhan, G.; Choi, H.K. Obesity, Waist Circumference, Weight Change, and the Risk of Psoriasis in Women: Nurses' Health Study II: Nurses' Health Study II. *Arch. Intern. Med.* **2007**, *167*, 1670–1675. [[CrossRef](#)] [[PubMed](#)]
44. Gutmark-Little, I.; Shah, K.N. Obesity and the Metabolic Syndrome in Pediatric Psoriasis. *Clin. Dermatol.* **2015**, *33*, 305–315. [[CrossRef](#)] [[PubMed](#)]
45. Babino, G.; Giunta, A.; Bianchi, L.; Esposito, M. Morbid Obesity and Psoriasis: Disease Remission after Laparoscopic Sleeve Gastrectomy. *Obes. Res. Clin. Pract.* **2017**, *11*, 370–372. [[CrossRef](#)] [[PubMed](#)]
46. Al-Mutairi, N.; Nour, T. The Effect of Weight Reduction on Treatment Outcomes in Obese Patients with Psoriasis on Biologic Therapy: A Randomized Controlled Prospective Trial. *Expert Opin. Biol. Ther.* **2014**, *14*, 749–756. [[CrossRef](#)] [[PubMed](#)]
47. Fujino, S.; Andoh, A.; Bamba, S.; Ogawa, A.; Hata, K.; Araki, Y.; Bamba, T.; Fujiyama, Y. Increased Expression of Interleukin 17 in Inflammatory Bowel Disease. *Gut* **2003**, *52*, 65–70. [[CrossRef](#)] [[PubMed](#)]
48. Wolf, N.; Quaranta, M.; Prescott, N.J.; Allen, M.; Smith, R.; Burden, A.D.; Worthington, J.; Griffiths, C.E.M.; Mathew, C.G.; Barker, J.N.; et al. Psoriasis Is Associated with Pleiotropic Susceptibility Loci Identified in Type II Diabetes and Crohn Disease. *J. Med. Genet.* **2008**, *45*, 114–116. [[CrossRef](#)]
49. Cargill, M.; Schrodi, S.J.; Chang, M.; Garcia, V.E.; Brandon, R.; Callis, K.P.; Matsunami, N.; Ardlie, K.G.; Civello, D.; Catanese, J.J.; et al. A Large-Scale Genetic Association Study Confirms IL12B and Leads to the Identification of IL23R as Psoriasis-Risk Genes. *Am. J. Hum. Genet.* **2007**, *80*, 273–290. [[CrossRef](#)] [[PubMed](#)]
50. Skroza, N.; Proietti, I.; Pampena, R.; La Viola, G.; Bernardini, N.; Nicolucci, F.; Tolino, E.; Zuber, S.; Soccodato, V.; Potenza, C. Correlations between Psoriasis and Inflammatory Bowel Diseases. *Biomed. Res. Int.* **2013**, *2013*, 983902. [[CrossRef](#)]

51. Belkaid, Y.; Hand, T.W. Role of the Microbiota in Immunity and Inflammation. *Cell* **2014**, *157*, 121–141. [[CrossRef](#)] [[PubMed](#)]
52. Scher, J.U.; Ubeda, C.; Artacho, A.; Attur, M.; Isaac, S.; Reddy, S.M.; Marmon, S.; Neimann, A.; Brusca, S.; Patel, T.; et al. Decreased Bacterial Diversity Characterizes the Altered Gut Microbiota in Patients with Psoriatic Arthritis, Resembling Dysbiosis in Inflammatory Bowel Disease: Gut Microbiota in PsA. *Arthritis Rheumatol.* **2015**, *67*, 128–139. [[CrossRef](#)] [[PubMed](#)]
53. Olejniczak-Staruch, I.; Ciężyńska, M.; Sobolewska-Sztychny, D.; Narbutt, J.; Skibińska, M.; Lesiak, A. Alterations of the Skin and Gut Microbiome in Psoriasis and Psoriatic Arthritis. *Int. J. Mol. Sci.* **2021**, *22*, 3998. [[CrossRef](#)] [[PubMed](#)]
54. Fu, Y.; Lee, C.-H.; Chi, C.-C. Association of Psoriasis with Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *JAMA Dermatol.* **2018**, *154*, 1417–1423. [[CrossRef](#)]
55. Wu, S.; Han, J.; Li, W.-Q.; Qureshi, A.A. Hypertension, Antihypertensive Medication Use, and Risk of Psoriasis. *JAMA Dermatol.* **2014**, *150*, 957–963. [[CrossRef](#)]
56. Egeberg, A.; Gisoni, P.; Carrascosa, J.M.; Warren, R.B.; Mrowietz, U. The Role of the Interleukin-23/Th17 Pathway in Cardiometabolic Comorbidity Associated with Psoriasis. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, 1695–1706. [[CrossRef](#)]
57. Richer, V.; Roubille, C.; Fleming, P.; Starnino, T.; McCourt, C.; McFarlane, A.; Siu, S.; Kraft, J.; Lynde, C.; Pope, J.E.; et al. Psoriasis and Smoking: A Systematic Literature Review and Meta-Analysis with Qualitative Analysis of Effect of Smoking on Psoriasis Severity: A Systematic Literature Review and Meta-Analysis with Qualitative Analysis of Effect of Smoking on Psoriasis Severity. *J. Cutan. Med. Surg.* **2016**, *20*, 221–227. [[CrossRef](#)]
58. Torii, K.; Saito, C.; Furuhashi, T.; Nishioka, A.; Shintani, Y.; Kawashima, K.; Kato, H.; Morita, A. Tobacco Smoke Is Related to Th17 Generation with Clinical Implications for Psoriasis Patients: Letter to the Editor. *Exp. Dermatol.* **2011**, *20*, 371–373. [[CrossRef](#)]
59. Gelfand, J.M.; Neimann, A.L.; Shin, D.B.; Wang, X.; Margolis, D.J.; Troxel, A.B. Risk of Myocardial Infarction in Patients with Psoriasis. *JAMA* **2006**, *296*, 1735–1741. [[CrossRef](#)]
60. Gelfand, J.M.; Dommasch, E.D.; Shin, D.B.; Azfar, R.S.; Kurd, S.K.; Wang, X.; Troxel, A.B. The Risk of Stroke in Patients with Psoriasis. *J. Investig. Dermatol.* **2009**, *129*, 2411–2418. [[CrossRef](#)]
61. Ogdie, A.; Yu, Y.; Haynes, K.; Love, T.J.; Maliha, S.; Jiang, Y.; Troxel, A.B.; Hennessy, S.; Kimmel, S.E.; Margolis, D.J.; et al. Risk of Major Cardiovascular Events in Patients with Psoriatic Arthritis, Psoriasis and Rheumatoid Arthritis: A Population-Based Cohort Study. *Ann. Rheum. Dis.* **2015**, *74*, 326–332. [[CrossRef](#)]
62. Chung, W.-S.; Lin, C.-L. Increased Risks of Venous Thromboembolism in Patients with Psoriasis. A Nationwide Cohort Study: A Nationwide Cohort Study. *Thromb. Haemost.* **2017**, *117*, 1637–1643. [[CrossRef](#)]
63. Lutsey, P.L.; Prizment, A.E.; Folsom, A.R. Psoriasis Is Associated with a Greater Risk of Incident Venous Thromboembolism: The Iowa Women’s Health Study: Letters to the Editor. *J. Thromb. Haemost.* **2012**, *10*, 708–711. [[CrossRef](#)] [[PubMed](#)]
64. Ahlehoff, O.; Gislason, G.H.; Lindhardsen, J.; Charlott, M.G.; Jørgensen, C.H.; Olesen, J.B.; Bretler, D.-M.; Skov, L.; Torp-Pedersen, C.; Hansen, P.R. Psoriasis Carries an Increased Risk of Venous Thromboembolism: A Danish Nationwide Cohort Study. *PLoS ONE* **2011**, *6*, e18125. [[CrossRef](#)] [[PubMed](#)]
65. Elmets, C.A.; Leonardi, C.L.; Davis, D.M.R.; Gelfand, J.M.; Lichten, J.; Mehta, N.N.; Armstrong, A.W.; Connor, C.; Cordoro, K.M.; Elewski, B.E.; 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*, 1073–1113. [[CrossRef](#)] [[PubMed](#)]
66. Hillary, T.; Clijmans, J.; Vermeire, S.; Lambert, J.; Garmyn, M.; Imbrechts, M.; Vanassche, T. Venous Thrombotic Events in Psoriasis Patients: A Systematic Review with Meta-Analysis. *Ann. Med.* **2021**, *53*, 1074–1081. [[CrossRef](#)]
67. Khalid, U.; Ahlehoff, O.; Gislason, G.H.; Kristensen, S.L.; Skov, L.; Torp-Pedersen, C.; Hansen, P.R. Psoriasis and Risk of Heart Failure: A Nationwide Cohort Study: Psoriasis and Risk of Heart Failure: A Nationwide Cohort Study. *Eur. J. Heart Fail.* **2014**, *16*, 743–748. [[CrossRef](#)] [[PubMed](#)]
68. Eliakim-Raz, N.; Shuvy, M.; Lotan, C.; Planer, D. Psoriasis and Dilated Cardiomyopathy: Coincidence or Associated Diseases? *Cardiology* **2008**, *111*, 202–206. [[CrossRef](#)] [[PubMed](#)]
69. Vaengebjerg, S.; Skov, L.; Egeberg, A.; Loft, N.D. Prevalence, Incidence, and Risk of Cancer in Patients with Psoriasis and Psoriatic Arthritis: A Systematic Review and Meta-Analysis: A Systematic Review and Meta-Analysis. *JAMA Dermatol.* **2020**, *156*, 421–429. [[CrossRef](#)]
70. Geller, S.; Xu, H.; Lebwohl, M.; Nardone, B.; Lacouture, M.E.; Khetarpal, M. Malignancy Risk and Recurrence with Psoriasis and Its Treatments: A Concise Update. *Am. J. Clin. Dermatol.* **2018**, *19*, 363–375. [[CrossRef](#)]
71. Egeberg, A.; Thyssen, J.P.; Gislason, G.H.; Skov, L. Skin Cancer in Patients with Psoriasis. *J. Eur. Acad. Dermatol. Venereol.* **2016**, *30*, 1349–1353. [[CrossRef](#)]
72. Kamstrup, M.R.; Skov, L.; Zachariae, C.; Thyssen, J.P.; Egeberg, A. Psoriasis and Risk of Malignant Lymphoma: A Population-Based Cohort Study. *Br. J. Dermatol.* **2018**, *178*, 1435–1436. [[CrossRef](#)]
73. Stern, R.S.; PUVA Follow-Up Study. The Risk of Squamous Cell and Basal Cell Cancer Associated with Psoralen and Ultraviolet A Therapy: A 30-Year Prospective Study. *J. Am. Acad. Dermatol.* **2012**, *66*, 553–562. [[CrossRef](#)] [[PubMed](#)]
74. Nikolaou, V.; Marinos, L.; Moustou, E.; Papadavid, E.; Economidi, A.; Christofidou, E.; Gerochristou, M.; Tasidou, A.; Economaki, E.; Stratigos, A.; et al. Psoriasis in Patients with Mycosis Fungoides: A Clinicopathological Study of 25 Patients. *J. Eur. Acad. Dermatol. Venereol.* **2017**, *31*, 1848–1852. [[CrossRef](#)] [[PubMed](#)]
75. Pouplard, C.; Brenaut, E.; Horreau, C.; Barnette, T.; Misery, L.; Richard, M.-A.; Aractingi, S.; Aubin, F.; Cribier, B.; Joly, P.; et al. Risk of Cancer in Psoriasis: A Systematic Review and Meta-Analysis of Epidemiological Studies. *J. Eur. Acad. Dermatol. Venereol.* **2013**, *27*, 36–46. [[CrossRef](#)] [[PubMed](#)]

76. Gross, R.L.; Schwartzman-Morris, J.S.; Krathen, M.; Reed, G.; Chang, H.; Saunders, K.C.; Fisher, M.C.; Greenberg, J.D.; Putterman, C.; Mease, P.J.; et al. A Comparison of the Malignancy Incidence among Patients with Psoriatic Arthritis and Patients with Rheumatoid Arthritis in a Large US Cohort: Malignancy in Psoriatic Arthritis and Rheumatoid Arthritis. *Arthritis Rheumatol.* **2014**, *66*, 1472–1481. [[CrossRef](#)] [[PubMed](#)]
77. Lee, J.H.; Kim, H.J.; Han, K.D.; Kim, H.-N.; Park, Y.M.; Lee, J.Y.; Park, Y.-G.; Lee, Y.B. Cancer Risk in 892 089 Patients with Psoriasis in Korea: A Nationwide Population-Based Cohort Study. *J. Dermatol.* **2019**, *46*, 95–102. [[CrossRef](#)]
78. Chiu, H.-Y.; Hsieh, C.-F.; Chiang, Y.-T.; Tsai, Y.-W.; Huang, W.-F.; Li, C.-Y.; Wang, T.-S.; Tsai, T.-F. Concomitant Sleep Disorders Significantly Increase the Risk of Cardiovascular Disease in Patients with Psoriasis. *PLoS ONE* **2016**, *11*, e0146462. [[CrossRef](#)]
79. Lan, C.-C.E.; Yu, H.-S.; Li, W.-C.; Ko, Y.-C.; Wu, C.-S.; Lu, Y.-W.; Yang, Y.-H.; Chen, G.-S. Anxiety Contributes to the Development of Cerebrovascular Disease in Taiwanese Patients with Psoriasis: A Population-Based Study. *Eur. J. Dermatol.* **2013**, *23*, 290–292. [[CrossRef](#)]
80. Egeberg, A.; Khalid, U.; Gislason, G.H.; Mallbris, L.; Skov, L.; Hansen, P.R. Impact of Depression on Risk of Myocardial Infarction, Stroke and Cardiovascular Death in Patients with Psoriasis: A Danish Nationwide Study. *Acta Derm. Venereol.* **2016**, *96*, 218–221. [[CrossRef](#)]
81. Augustin, M.; Radtke, M.A. Quality of Life in Psoriasis Patients. *Expert Rev. Pharmacoecon. Outcomes Res.* **2014**, *14*, 559–568. [[CrossRef](#)]
82. Dowlatshahi, E.A.; Wakkee, M.; Arends, L.R.; Nijsten, T. The Prevalence and Odds of Depressive Symptoms and Clinical Depression in Psoriasis Patients: A Systematic Review and Meta-Analysis. *J. Investig. Dermatol.* **2014**, *134*, 1542–1551. [[CrossRef](#)]
83. Amin, M.; Lee, E.B.; Bhutani, T.; Wu, J.J. Do Psoriasis Patients Engage in Vigorous Physical Activity? *Cutis* **2018**, *101*, 198–200. [[PubMed](#)]
84. Frankel, H.C.; Han, J.; Li, T.; Qureshi, A.A. The Association between Physical Activity and the Risk of Incident Psoriasis. *Arch. Dermatol.* **2012**, *148*, 918–924. [[CrossRef](#)] [[PubMed](#)]
85. Raimondo, A.; Balato, A.; Megna, M.; Balato, N. Limitations of Current Monoclonal Antibodies for Plaque-Type Psoriasis and an Outlook for the Future. *Expert Opin. Biol. Ther.* **2018**, *18*, 605–607. [[CrossRef](#)] [[PubMed](#)]
86. Boehncke, W.-H.; Boehncke, S.; Tobin, A.-M.; Kirby, B. The “Psoriatic March”: A Concept of How Severe Psoriasis May Drive Cardiovascular Comorbidity: The ‘Psoriatic March’. *Exp. Dermatol.* **2011**, *20*, 303–307. [[CrossRef](#)] [[PubMed](#)]
87. Armstrong, A.W.; Voyles, S.V.; Armstrong, E.J.; Fuller, E.N.; Rutledge, J.C. A Tale of Two Plaques: Convergent Mechanisms of T-Cell-Mediated Inflammation in Psoriasis and Atherosclerosis: T-Cell Immunology in Psoriasis and Atherosclerosis. *Exp. Dermatol.* **2011**, *20*, 544–549. [[CrossRef](#)] [[PubMed](#)]
88. Flammer, A.J.; Ruschitzka, F. Psoriasis and Atherosclerosis: Two Plaques, One Syndrome? *Eur. Heart J.* **2012**, *33*, 1989–1991. [[CrossRef](#)] [[PubMed](#)]
89. Davidovici, B.B.; Sattar, N.; Prinz, J.C.; Puig, L.; Emery, P.; Barker, J.N.; van de Kerkhof, P.; Stähle, M.; Nestle, F.O.; Girolomoni, G.; et al. Psoriasis and Systemic Inflammatory Diseases: Potential Mechanistic Links between Skin Disease and Co-Morbid Conditions. *J. Investig. Dermatol.* **2010**, *130*, 1785–1796. [[CrossRef](#)]
90. Ryan, C.; Kirby, B. Psoriasis Is a Systemic Disease with Multiple Cardiovascular and Metabolic Comorbidities. *Dermatol. Clin.* **2015**, *33*, 41–55. [[CrossRef](#)]
91. Ghazizadeh, R.; Shimizu, H.; Tosa, M.; Ghazizadeh, M. Pathogenic Mechanisms Shared between Psoriasis and Cardiovascular Disease. *Int. J. Med. Sci.* **2010**, *7*, 284–289. [[CrossRef](#)]
92. Chen, S.; Crother, T.R.; Arditi, M. Emerging Role of IL-17 in Atherosclerosis. *J. Innate Immun.* **2010**, *2*, 325–333. [[CrossRef](#)]
93. Mehta, N.N.; Li, K.; Szapary, P.; Krueger, J.; Brodmerkel, C. Modulation of Cardiometabolic Pathways in Skin and Serum from Patients with Psoriasis. *J. Transl. Med.* **2013**, *11*, 194. [[CrossRef](#)]
94. Hashmi, S.; Zeng, Q.T. Role of Interleukin-17 and Interleukin-17-Induced Cytokines Interleukin-6 and Interleukin-8 in Unstable Coronary Artery Disease. *Coron. Artery Dis.* **2006**, *17*, 699–706. [[CrossRef](#)]
95. Owczarczyk-Saczonek, A.; Placek, W. Interleukin-17 as a factor linking the pathogenesis of psoriasis with metabolic disorders. *Int. J. Dermatol.* **2017**, *56*, 260–268. [[CrossRef](#)] [[PubMed](#)]
96. Kolliker Frers, R.A.; Cosentino, V.; Tau, J.; Kerzberg, E.M.; Urdapilleta, A.; Chioconi, M.; Kogan, N.; Otero-Losada, M.; Capani, F. Immune-Mediated Inflammation Promotes Subclinical Atherosclerosis in Recent-Onset Psoriatic Arthritis Patients without Conventional Cardiovascular Risk Factors. *Front. Immunol.* **2018**, *9*, 139. [[CrossRef](#)] [[PubMed](#)]
97. Hjuler, K.F.; Gormsen, L.C.; Vendelbo, M.H.; Egeberg, A.; Nielsen, J.; Iversen, L. Increased Global Arterial and Subcutaneous Adipose Tissue Inflammation in Patients with Moderate-to-Severe Psoriasis. *Br. J. Dermatol.* **2017**, *176*, 732–740. [[CrossRef](#)]
98. Youn, S.W.; Kang, S.Y.; Kim, S.A.; Park, G.Y.; Lee, W.W. Subclinical Systemic and Vascular Inflammation Detected by (18) F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Patients with Mild Psoriasis. *J. Dermatol.* **2015**, *42*, 559–566. [[CrossRef](#)] [[PubMed](#)]
99. Wang, Y.; Gao, H.; Loyd, C.M.; Fu, W.; Diaconu, D.; Liu, S.; Cooper, K.D.; McCormick, T.S.; Simon, D.I.; Ward, N.L. Chronic Skin-Specific Inflammation Promotes Vascular Inflammation and Thrombosis. *J. Investig. Dermatol.* **2012**, *132*, 2067–2075. [[CrossRef](#)]
100. Hu, J.; Yang, R.; Wen, C.; Li, H.; Zhao, H. Expression of NLRP3 inflammasome in BALB/c mice with imiquimod-induced psoriasis-like inflammation and therapeutic effect of mustard seed (*Sinapis Alba* Linn). *Nan Fang Yi Ke Da Xue Xue Bao* **2013**, *33*, 1394–1398. [[PubMed](#)]

101. Jiang, W.; Zhu, F.-G.; Bhagat, L.; Yu, D.; Tang, J.X.; Kandimalla, E.R.; La Monica, N.; Agrawal, S. A Toll-like Receptor 7, 8, and 9 Antagonist Inhibits Th1 and Th17 Responses and Inflammasome Activation in a Model of IL-23-Induced Psoriasis. *J. Investig. Dermatol.* **2013**, *133*, 1777–1784. [[CrossRef](#)] [[PubMed](#)]
102. Ciałczyńska, M.; Olejniczak-Staruch, I.; Sobolewska-Sztychny, D.; Narbutt, J.; Skibińska, M.; Lesiak, A. The Role of NLRP1, NLRP3, and AIM2 Inflammasomes in Psoriasis: Review. *Int. J. Mol. Sci.* **2021**, *22*, 5898. [[CrossRef](#)] [[PubMed](#)]
103. Lu, Y.; Chen, H.; Nikamo, P.; Qi Low, H.; Helms, C.; Seielstad, M.; Liu, J.; Bowcock, A.M.; Stahle, M.; Liao, W. Association of Cardiovascular and Metabolic Disease Genes with Psoriasis. *J. Investig. Dermatol.* **2013**, *133*, 836–839. [[CrossRef](#)] [[PubMed](#)]
104. Campalani, E.; Allen, M.H.; Fairhurst, D.; Young, H.S.; Mendonca, C.O.; Burden, A.D.; Griffiths, C.E.M.; Crook, M.A.; Barker, J.N.W.N.; Smith, C.H. Apolipoprotein E Gene Polymorphisms Are Associated with Psoriasis but Do Not Determine Disease Response to Acitretin: ApoE Gene Polymorphisms, Psoriasis and Acitretin. *Br. J. Dermatol.* **2006**, *154*, 345–352. [[CrossRef](#)] [[PubMed](#)]
105. Eiris, N.; González-Lara, L.; Santos-Juanes, J.; Queiro, R.; Coto, E.; Coto-Segura, P. Genetic Variation at IL12B, IL23R and IL23A Is Associated with Psoriasis Severity, Psoriatic Arthritis and Type 2 Diabetes Mellitus. *J. Dermatol. Sci.* **2014**, *75*, 167–172. [[CrossRef](#)] [[PubMed](#)]
106. Furue, M.; Kadono, T. “Inflammatory Skin March” in Atopic Dermatitis and Psoriasis. *Inflamm. Res.* **2017**, *66*, 833–842. [[CrossRef](#)] [[PubMed](#)]
107. Libby, P.; Ridker, P.M.; Hansson, G.K.; Leducq Transatlantic Network on Atherothrombosis. Inflammation in Atherosclerosis: From Pathophysiology to Practice. *J. Am. Coll. Cardiol.* **2009**, *54*, 2129–2138. [[CrossRef](#)]
108. Hu, S.; Lan, C.-C.E. Psoriasis and Cardiovascular Comorbidities: Focusing on Severe Vascular Events, Cardiovascular Risk Factors and Implications for Treatment. *Int. J. Mol. Sci.* **2017**, *18*, 2211. [[CrossRef](#)]
109. Mahmoudi, M.J.; Saboor-Yaraghi, A.-A.; Zabetian-Targhi, F.; Siassi, F.; Zarnani, A.H.; Eshraghian, M.R.; Shokri, F.; Rezaei, N.; Kalikias, Y.; Mahmoudi, M. Vitamin A Decreases Cytotoxicity of Oxidized Low-Density Lipoprotein in Patients with Atherosclerosis. *Immunol. Investig.* **2016**, *45*, 52–62. [[CrossRef](#)]
110. Boehncke, S.; Fichtlscherer, S.; Salgo, R.; Garbaraviciene, J.; Beschmann, H.; Diehl, S.; Hardt, K.; Thaçi, D.; Boehncke, W.-H. Systemic Therapy of Plaque-Type Psoriasis Ameliorates Endothelial Cell Function: Results of a Prospective Longitudinal Pilot Trial. *Arch. Derm. Res.* **2011**, *303*, 381–388. [[CrossRef](#)]
111. Micha, R.; Imamura, F.; Wyler von Ballmoos, M.; Solomon, D.H.; Hernán, M.A.; Ridker, P.M.; Mozaffarian, D. Systematic Review and Meta-Analysis of Methotrexate Use and Risk of Cardiovascular Disease. *Am. J. Cardiol.* **2011**, *108*, 1362–1370. [[CrossRef](#)]
112. Caiazzo, G.; Fabbrocini, G.; Di Caprio, R.; Raimondo, A.; Scala, E.; Balato, N.; Balato, A. Psoriasis, Cardiovascular Events, and Biologics: Lights and Shadows. *Front. Immunol.* **2018**, *9*, 1668. [[CrossRef](#)]
113. Rich, S.J.; Bello-Quintero, C.E. Advancements in the Treatment of Psoriasis: Role of Biologic Agents. *J. Manag. Care Pharm.* **2004**, *10*, 318–325. [[CrossRef](#)]
114. Pina, T.; Armesto, S.; Lopez-Mejias, R.; Genre, F.; Ubilla, B.; Gonzalez-Lopez, M.A.; Gonzalez-Vela, M.C.; Corrales, A.; Blanco, R.; Garcia-Unzueta, M.T.; et al. Anti-TNF- $\alpha$  Therapy Improves Insulin Sensitivity in Non-Diabetic Patients with Psoriasis: A 6-Month Prospective Study. *J. Eur. Acad. Dermatol. Venereol.* **2015**, *29*, 1325–1330. [[CrossRef](#)]
115. Kwiek, B.; Narbutt, J.; Sysa-Jędrzejowska, A.; Langner, A.; Lesiak, A. Long-Term Treatment of Chronic Plaque Psoriasis with Biological Drugs Can Control Platelet Activation: Targeting the Bridge between Inflammation and Atherothrombosis. *Postepy Dermatol. Alergol.* **2017**, *34*, 131–137. [[CrossRef](#)]
116. Pina, T.; Genre, F.; Lopez-Mejias, R.; Armesto, S.; Ubilla, B.; Mijares, V.; Dierssen-Sotos, T.; Corrales, A.; Gonzalez-Lopez, M.A.; Gonzalez-Vela, M.C.; et al. Anti-TNF- $\alpha$  Therapy Reduces Retinol-Binding Protein 4 Serum Levels in Non-Diabetic Patients with Psoriasis: A 6-Month Prospective Study. *J. Eur. Acad. Dermatol. Venereol.* **2016**, *30*, 92–95. [[CrossRef](#)]
117. Pina, T.; Corrales, A.; Lopez-Mejias, R.; Armesto, S.; Gonzalez-Lopez, M.A.; Gómez-Acebo, I.; Ubilla, B.; Remuzgo-Martínez, S.; Gonzalez-Vela, M.C.; Blanco, R.; et al. Anti-Tumor Necrosis Factor-Alpha Therapy Improves Endothelial Function and Arterial Stiffness in Patients with Moderate to Severe Psoriasis: A 6-Month Prospective Study. *J. Dermatol.* **2016**, *43*, 1267–1272. [[CrossRef](#)] [[PubMed](#)]
118. Ikonomidis, I.; Papadavid, E.; Makavos, G.; Andreadou, I.; Varoudi, M.; Gravanis, K.; Theodoropoulos, K.; Pavlidis, G.; Triantafyllidi, H.; Moutsatsou, P.; et al. Lowering Interleukin-12 Activity Improves Myocardial and Vascular Function Compared with Tumor Necrosis Factor- $\alpha$  Antagonism or Cyclosporine in Psoriasis. *Circ. Cardiovasc. Imaging* **2017**, *10*, e006283. [[CrossRef](#)] [[PubMed](#)]
119. Gordon, K.B.; Langley, R.G.; Gottlieb, A.B.; Papp, K.A.; Krueger, G.G.; Strober, B.E.; Williams, D.A.; Gu, Y.; Valdes, J.M. A Phase III, Randomized, Controlled Trial of the Fully Human IL-12/23 MAb Briakinumab in Moderate-to-Severe Psoriasis. *J. Investig. Dermatol.* **2012**, *132*, 304–314. [[CrossRef](#)] [[PubMed](#)]
120. Krueger, G.G.; Langley, R.G.; Leonardi, C.; Yeilding, N.; Guzzo, C.; Wang, Y.; Dooley, L.T.; Lebwohl, M.; CNTO 1275 Psoriasis Study Group. A Human Interleukin-12/23 Monoclonal Antibody for the Treatment of Psoriasis. *N. Engl. J. Med.* **2007**, *356*, 580–592. [[CrossRef](#)] [[PubMed](#)]
121. Langley, R.G.; Elewski, B.E.; Lebwohl, M.; Reich, K.; Griffiths, C.E.M.; Papp, K.; Puig, L.; Nakagawa, H.; Spelman, L.; Sigurgeirsson, B.; et al. Secukinumab in Plaque Psoriasis—Results of Two Phase 3 Trials. *N. Engl. J. Med.* **2014**, *371*, 326–338. [[CrossRef](#)]
122. Bai, F.; Li, G.G.; Liu, Q.; Niu, X.; Li, R.; Ma, H. Short-Term Efficacy and Safety of IL-17, IL-12/23, and IL-23 Inhibitors Brodalumab, Secukinumab, Ixekizumab, Ustekinumab, Guselkumab, Tildrakizumab, and Risankizumab for the Treatment of Moderate to Severe Plaque Psoriasis: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. *J. Immunol. Res.* **2019**, *2019*, 2546161. [[CrossRef](#)]

123. Makavos, G.; Ikonomidis, I.; Andreadou, I.; Varoudi, M.; Kapniari, I.; Loukeri, E.; Theodoropoulos, K.; Pavlidis, G.; Triantafyllidi, H.; Thymis, J.; et al. Effects of Interleukin 17A Inhibition on Myocardial Deformation and Vascular Function in Psoriasis. *Can. J. Cardiol.* **2020**, *36*, 100–111. [[CrossRef](#)] [[PubMed](#)]
124. Bissonnette, R.; Tardif, J.-C.; Harel, F.; Pressacco, J.; Bolduc, C.; Guertin, M.-C. Effects of the Tumor Necrosis Factor- $\alpha$  Antagonist Adalimumab on Arterial Inflammation Assessed by Positron Emission Tomography in Patients with Psoriasis: Results of a Randomized Controlled Trial: Results of a Randomized Controlled Trial. *Circ. Cardiovasc. Imaging* **2013**, *6*, 83–90. [[CrossRef](#)]
125. Hjuler, K.F.; Bøttcher, M.; Vestergaard, C.; Bøtker, H.E.; Iversen, L.; Kragballe, K. Association between Changes in Coronary Artery Disease Progression and Treatment with Biologic Agents for Severe Psoriasis. *JAMA Dermatol.* **2016**, *152*, 1114–1121. [[CrossRef](#)] [[PubMed](#)]
126. Ahlehoff, O.; Hansen, P.R.; Gislasen, G.H.; Frydland, M.; Bryld, L.E.; Elming, H.; Jemec, G.B.E. Myocardial Function and Effects of Biologic Therapy in Patients with Severe Psoriasis: A Prospective Echocardiographic Study. *J. Eur. Acad. Dermatol. Venereol.* **2016**, *30*, 819–823. [[CrossRef](#)]
127. Herédi, E.; Végh, J.; Pogácsás, L.; Gáspár, K.; Varga, J.; Kincse, G.; Zeher, M.; Szegedi, A.; Gaál, J. Subclinical Cardiovascular Disease and It's Improvement after Long-Term TNF- $\alpha$  Inhibitor Therapy in Severe Psoriatic Patients. *J. Eur. Acad. Dermatol. Venereol.* **2016**, *30*, 1531–1536. [[CrossRef](#)]
128. Mann, D.L.; McMurray, J.J.V.; Packer, M.; Swedberg, K.; Borer, J.S.; Colucci, W.S.; Djian, J.; Drexler, H.; Feldman, A.; Kober, L.; et al. Targeted Anticytokine Therapy in Patients with Chronic Heart Failure: Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL): Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* **2004**, *109*, 1594–1602. [[CrossRef](#)]
129. Chung, E.S.; Packer, M.; Lo, K.H.; Fasanmade, A.A.; Willerson, J.T.; Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor-Alpha, in Patients with Moderate-to-Severe Heart Failure: Results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) Trial. *Circulation* **2003**, *107*, 3133–3140. [[CrossRef](#)] [[PubMed](#)]
130. Chan, J.R.; Blumenschein, W.; Murphy, E.; Diveu, C.; Wiekowski, M.; Abbondanzo, S.; Lucian, L.; Geissler, R.; Brodie, S.; Kimball, A.B.; et al. IL-23 Stimulates Epidermal Hyperplasia via TNF and IL-20R2-Dependent Mechanisms with Implications for Psoriasis Pathogenesis. *J. Exp. Med.* **2006**, *203*, 2577–2587. [[CrossRef](#)] [[PubMed](#)]
131. Abbas, A.; Gregersen, I.; Holm, S.; Daissormont, I.; Bjerkeli, V.; Krohg-Sørensen, K.; Skagen, K.R.; Dahl, T.B.; Russell, D.; Almås, T.; et al. Interleukin 23 Levels Are Increased in Carotid Atherosclerosis: Possible Role for the Interleukin 23/Interleukin 17 Axis. *Stroke* **2015**, *46*, 793–799. [[CrossRef](#)]
132. Mitra, A.; Fallen, R.S.; Lima, H.C. Cytokine-based therapy in psoriasis. *Clin. Rev. Allergy Immunol.* **2013**, *44*, 173–182. [[CrossRef](#)] [[PubMed](#)]
133. Reich, K.; Langley, R.G.; Lebwohl, M.; Szapary, P.; Guzzo, C.; Yeilding, N.; Li, S.; Hsu, M.-C.; Griffiths, C.E.M. Cardiovascular Safety of Ustekinumab in Patients with Moderate to Severe Psoriasis: Results of Integrated Analyses of Data from Phase II and III Clinical Studies: Cardiovascular Safety of Ustekinumab in Clinical Trials of Psoriasis. *Br. J. Dermatol.* **2011**, *164*, 862–872. [[CrossRef](#)] [[PubMed](#)]
134. Reddy, M.; Torres, G.; McCormick, T.; Marano, C.; Cooper, K.; Yeilding, N.; Wang, Y.; Pendley, C.; Prabhakar, U.; Wong, J.; et al. Positive Treatment Effects of Ustekinumab in Psoriasis: Analysis of Lesional and Systemic Parameters: Ustekinumab Has Minimal Systemic Effects. *J. Dermatol.* **2010**, *37*, 413–425. [[CrossRef](#)] [[PubMed](#)]
135. Kagami, S.; Rizzo, H.L.; Lee, J.J.; Koguchi, Y.; Blauvelt, A. Circulating Th17, Th22, and Th1 Cells Are Increased in Psoriasis. *J. Invest. Dermatol.* **2010**, *130*, 1373–1383. [[CrossRef](#)]
136. Wu, D.; Hou, S.-Y.; Zhao, S.; Hou, L.-X.; Jiao, T.; Xu, N.-N.; Zhang, N. Efficacy and Safety of Interleukin-17 Antagonists in Patients with Plaque Psoriasis: A Meta-Analysis from Phase 3 Randomized Controlled Trials. *J. Eur. Acad. Dermatol. Venereol.* **2017**, *31*, 992–1003. [[CrossRef](#)] [[PubMed](#)]
137. van de Kerkhof, P.C.M.; Griffiths, C.E.M.; Reich, K.; Leonardi, C.L.; Blauvelt, A.; Tsai, T.-F.; Gong, Y.; Huang, J.; Papavassilis, C.; Fox, T. Secukinumab Long-Term Safety Experience: A Pooled Analysis of 10 Phase II and III Clinical Studies in Patients with Moderate to Severe Plaque Psoriasis. *J. Am. Acad. Dermatol.* **2016**, *75*, 83–98.e4. [[CrossRef](#)]
138. Strober, B.; Leonardi, C.; Papp, K.A.; Mrowietz, U.; Ohtsuki, M.; Bissonnette, R.; Ferris, L.K.; Paul, C.; Lebwohl, M.; Braun, D.K.; et al. Short- and Long-Term Safety Outcomes with Ixekizumab from 7 Clinical Trials in Psoriasis: Etanercept Comparisons and Integrated Data. *J. Am. Acad. Dermatol.* **2017**, *76*, 432–440.e7. [[CrossRef](#)]
139. Gordon, K.B.; Blauvelt, A.; Papp, K.A.; Langley, R.G.; Luger, T.; Ohtsuki, M.; Reich, K.; Amato, D.; Ball, S.G.; Braun, D.K.; et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. *N. Engl. J. Med.* **2016**, *375*, 345–356. [[CrossRef](#)]
140. Amoroso, G.F.; Nisticò, S.P.; Iannone, L.; Russo, E.; Rago, G.; Patruno, C.; Bennardo, L. Ixekizumab May Improve Renal Function in Psoriasis. *Healthcare* **2021**, *9*, 543. [[CrossRef](#)]
141. Papp, K.A.; Reich, K.; Paul, C.; Blauvelt, A.; Baran, W.; Bolduc, C.; Toth, D.; Langley, R.G.; Cather, J.; Gottlieb, A.B.; et al. A Prospective Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Brodalumab in Patients with Moderate-to-Severe Plaque Psoriasis. *Br. J. Dermatol.* **2016**, *175*, 273–286. [[CrossRef](#)]
142. Lebwohl, M.; Strober, B.; Menter, A.; Gordon, K.; Weglowska, J.; Puig, L.; Papp, K.; Spelman, L.; Toth, D.; Kerdel, F.; et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. *N. Engl. J. Med.* **2015**, *373*, 1318–1328. [[CrossRef](#)]

143. European Medicines Agency. Summary of Product Characteristics—Bimzelx. Available online: [https://www.ema.europa.eu/en/documents/product-information/bimzelx-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/bimzelx-epar-product-information_en.pdf) (accessed on 19 September 2021).
144. Blauvelt, A.; Papp, K.A.; Merola, J.F.; Gottlieb, A.B.; Cross, N.; Madden, C.; Wang, M.; Cioffi, C.; Griffiths, C.E.M. Bimekizumab for Patients with Moderate to Severe Plaque Psoriasis: 60-Week Results from BE ABLE 2, a Randomized, Double-Blinded, Placebo-Controlled, Phase 2b Extension Study. *J. Am. Acad. Dermatol.* **2020**, *83*, 1367–1374. [CrossRef]
145. Ritchlin, C.T.; Kavanaugh, A.; Merola, J.F.; Schett, G.; Scher, J.U.; Warren, R.B.; Gottlieb, A.B.; Assudani, D.; Bedford-Rice, K.; Coarse, J.; et al. Bimekizumab in patients with active psoriatic arthritis: Results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial. *Lancet* **2020**, *395*, 427–440. [CrossRef]
146. Rungapiromnan, W.; Yiu, Z.Z.N.; Warren, R.B.; Griffiths, C.E.M.; Ashcroft, D.M. 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. [CrossRef] [PubMed]
147. Choudhary, S.; Patel, R.; Pradhan, D.; Deval, R.; Singh, H.; Thomas, G.; Jain, A.K. Psoriasis and Cardiovascular Disorders: Association or Epiphenomenon? Meta-Analysis of Observational Studies. *3 Biotech* **2020**, *10*, 104. [CrossRef] [PubMed]
148. Eder, L.; Chandran, V.; Gladman, D.D. The Framingham Risk Score Underestimates the Extent of Subclinical Atherosclerosis in Patients with Psoriatic Disease. *Ann. Rheum. Dis.* **2014**, *73*, 1990–1996. [CrossRef]
149. Fernández-Torres, R.; Pita-Fernández, S.; Fonseca, E. Psoriasis and Cardiovascular Risk. Assessment by Different Cardiovascular Risk Scores: Psoriasis and Cardiovascular Risk Scores. *J. Eur. Acad. Dermatol. Venereol.* **2013**, *27*, 1566–1570. [CrossRef] [PubMed]
150. Agca, R.; Heslinga, S.C.; Rollefstad, S.; Heslinga, M.; McInnes, I.B.; Peters, M.J.L.; Kvien, T.K.; Dougados, M.; Radner, H.; Atzeni, F.; et al. EULAR Recommendations for Cardiovascular Disease Risk Management in Patients with Rheumatoid Arthritis and Other Forms of Inflammatory Joint Disorders: 2015/2016 Update. *Ann. Rheum. Dis.* **2017**, *76*, 17–28. [CrossRef] [PubMed]
151. O'Brien, M.; Koo, J. The Mechanism of Lithium and Beta-Blocking Agents in Inducing and Exacerbating Psoriasis. *J. Drugs Dermatol.* **2006**, *5*, 426–432.
152. Baccino, D.; Merlo, G.; Cozzani, E.; Rosa, G.M.; Tini, G.; Burlando, M.; Parodi, A. Cutaneous Effects of Antihypertensive Drugs. *G. Ital. Dermatol. Venereol.* **2020**, *155*, 202–211. [CrossRef]
153. Singh, S.; Bhansali, A. Randomized Placebo Control Study of Insulin Sensitizers (Metformin and Pioglitazone) in Psoriasis Patients with Metabolic Syndrome (Topical Treatment Cohort). *BMC Dermatol.* **2016**, *16*, 1–11. [CrossRef]
154. Buyschaert, M.; Baeck, M.; Preumont, V.; Marot, L.; Hendrickx, E.; Van Belle, A.; Dumoutier, L. Improvement of Psoriasis during Glucagon-like Peptide-1 Analogue Therapy in Type 2 Diabetes Is Associated with Decreasing Dermal  $\Gamma\delta$  T-Cell Number: A Prospective Case-Series Study. *Br. J. Dermatol.* **2014**, *171*, 155–161. [CrossRef]
155. Kim, S.C.; Schneeweiss, S.; Glynn, R.J.; Doherty, M.; Goldfine, A.B.; Solomon, D.H. Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes May Reduce the Risk of Autoimmune Diseases: A Population-Based Cohort Study. *Ann. Rheum. Dis.* **2015**, *74*, 1968–1975. [CrossRef]
156. Gordon, K.B.; Strober, B.; Lebwohl, M.; Augustin, M.; Blauvelt, A.; Poulin, Y.; Papp, K.A.; Sofen, H.; Puig, L.; Foley, P.; et al. Efficacy and Safety of Risankizumab in Moderate-to-Severe Plaque Psoriasis (UltIMMa-1 and UltIMMa-2): Results from Two Double-Blind, Randomised, Placebo-Controlled and Ustekinumab-Controlled Phase 3 Trials. *Lancet* **2018**, *392*, 650–661. [CrossRef]
157. Lilly's Mirikizumab Superior to Cosentyx (Secukinumab) in a Phase 3 Study for Patients with Moderate to Severe Plaque Psoriasis. Available online: <https://investor.lilly.com/node/43481/pdf> (accessed on 19 September 2021).
158. Dattola, A.; Silvestri, M.; Tamburi, F.; Amoroso, G.F.; Bennardo, L.; Nisticò, S.P. Emerging Role of Anti-IL23 in the Treatment of Psoriasis: When Humanized Is Very Promising. *Dermatol. Ther.* **2020**, *33*, e14504. [CrossRef]
159. Kvist-Hansen, A.; Hansen, P.R.; Skov, L. Systemic Treatment of Psoriasis with JAK Inhibitors: A Review. *Dermatol. Ther.* **2020**, *10*, 29–42. [CrossRef] [PubMed]
160. Papp, K.; Gordon, K.; Thaçi, D.; Morita, A.; Gooderham, M.; Foley, P.; Girgis, I.G.; Kundu, S.; Banerjee, S. Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis. *N. Engl. J. Med.* **2018**, *379*, 1313–1321. [CrossRef] [PubMed]
161. Papp, K.A.; Menter, M.A.; Abe, M.; Elewski, B.; Feldman, S.R.; Gottlieb, A.B.; Langley, R.; Luger, T.; Thaci, D.; Buonanno, M.; et al. Tofacitinib, an Oral Janus Kinase Inhibitor, for the Treatment of Chronic Plaque Psoriasis: Results from Two Randomized, Placebo-Controlled, Phase III Trials. *Br. J. Dermatol.* **2015**, *173*, 949–961. [CrossRef] [PubMed]
162. European Medicines Agency. Summary of Product Characteristics—Xeljanz. Available online: [https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf) (accessed on 19 September 2021).
163. Wolk, R.; Armstrong, E.J.; Hansen, P.R.; Thiers, B.; Lan, S.; Tallman, A.M.; Kaur, M.; Tatulych, S. Effect of Tofacitinib on Lipid Levels and Lipid-Related Parameters in Patients with Moderate to Severe Psoriasis. *J. Clin. Lipidol.* **2017**, *11*, 1243–1256. [CrossRef]
164. Desai, R.J.; Pawar, A.; Weinblatt, M.E.; Kim, S.C. Comparative Risk of Venous Thromboembolism in Rheumatoid Arthritis Patients Receiving Tofacitinib versus Those Receiving Tumor Necrosis Factor Inhibitors: An Observational Cohort Study. *Arthritis Rheumatol.* **2019**, *71*, 892–900. [CrossRef] [PubMed]
165. Piros, É.A.; Szilveszter, B.; Vattay, B.; Maurovich-Horvat, P.; Szalai, K.; Dósa, E.; Merkely, B.; Holló, P. Novel Anti-Inflammatory Therapies to Reduce Cardiovascular Burden of Psoriasis. *Dermatol. Ther.* **2021**, *34*, e14721. [CrossRef] [PubMed]