



Heart disease: How should psoriasis patients with ischaemic heart disease and/or congestive heart failure be managed?

This chapter is based on the previous chapter ^{1,2}. A systematic search was conducted, details of which can be found in the Methods & Evidence Report.

Results/Recommendations


a) Ischaemic heart disease/atherosclerosis

Summary/key points

- Patients with psoriasis have an approximately two- to threefold increased relative risk for developing cardiovascular events such as myocardial infarction or stroke compared to individuals without psoriasis. The cardiovascular risk seems to correlate with disease severity. The link between psoriasis and cardiovascular disease is likely to be driven by an increased prevalence of classical cardiovascular risk factors among patients with psoriasis such as the components of the metabolic syndrome. There is also evidence for an independent risk conferred by the systemic inflammatory nature of the disease.
- A careful history should be obtained from all patients to determine whether they have established cardiovascular disease. Appropriate investigations and treatment should be initiated in accordance with current European Society of Cardiology guidance ³.
- Patients without a history of cardiovascular disease, should have their cardiovascular risk factors assessed and be given lifestyle advice including avoiding smoking, maintaining a healthy diet, increasing physical activity and maintaining a healthy blood pressure with other treatments in accordance with current European Society of Cardiology guidance ^{4,5}.
- With the exception of methotrexate, there are no studies formally evaluating the effect of any anti-psoriatic therapy as a treatment for coronary heart disease. In general, it seems that the reduction of psoriatic inflammation is beneficial in psoriatic patients with cardiovascular comorbidity (indirect effect), but direct effects of treatments for psoriasis on atherosclerotic inflammation may also play a role.
- Multiple studies with different therapies have produced evidence on parameters of cardiovascular risk and/or assessed cardiovascular events during the treatment of patients with psoriasis.
- From these studies it appears that methotrexate, the anti-TNFs, in particular adalimumab, and ustekinumab improve parameters of cardiovascular risk in patients with psoriasis.



- While in some experimental models IL-17 has been associated with stabilizing properties of unstable atherosclerotic disease, treatment with IL-17 inhibitors has not been associated with an increased rate of cardiovascular events. Moreover, inhibition of IL-17, especially with secukinumab, has shown to improve surrogate markers of endothelial dysfunction.
- The data available on inhibitors of IL-23p19 indicate that they are safe in patients with cardiovascular comorbidity, but information on their potential effects on cardiovascular factors risk is limited.
- Treatment with apremilast is associated with weight loss in some patients. Experimental studies indicate potentially beneficial effects of apremilast in models of atherosclerosis. Neither clinical trial data nor observational studies indicate that apremilast is associated with an increased risk of cardiovascular events in psoriasis patients with ischemic heart disease or cardiovascular risk factors.
- There is no evidence that fumarates are associated with increased cardiovascular events in patients with ischemic heart disease.
- Ciclosporine may induce or worsen arterial hypertension, a condition often found in patients with ischemic heart disease, and worsen dyslipidaemia. The metabolism of ciclosporine may interfere with drugs used in patients with ischemic heart disease such as beta-blockers or calcium antagonists.
- Acitretin has very limited anti-inflammatory potential and may induce or worsen hyperlipidaemia.

We suggest against ciclosporine or acitretin as preferred treatments in patients with psoriasis and ischemic heart disease.	↓	<p>STRONG CONSENSUS¹</p>  <p>EXPERT CONSENSUS</p>
We suggest methotrexate as preferred first-line therapy in patients with psoriasis and ischemic heart disease* if other patient characteristics do not preclude its use.	↑	
We suggest anti-TNFs, ustekinumab, and IL-17 inhibitors as preferred targeted therapies in patients with psoriasis and ischemic heart disease*.	↑	

¹ due to personal-financial conflict of interest 3 abstentions

* in case of concomitant congestive heart failure, also note the recommendations from the respective section

Moderate-to-severe psoriasis is associated with several well-established cardiovascular risk factors including obesity, hypertension, diabetes, dyslipidaemia, and metabolic syndrome ⁶. Psoriasis severity has been linked to a higher prevalence of these risk factors. However, there is conflicting evidence as



to whether psoriasis is associated with increased cardiovascular events and whether psoriasis itself represents an independent cardiovascular risk factor⁷. Indeed, a large cohort study in Rotterdam found no difference in the risk of ischemic heart disease hospitalizations in patients with psoriasis compared with matched control subjects⁸. Stern and Huibregtse⁹ found that patients with very severe psoriasis have increased all-cause mortality, but that severe psoriasis is not an independent risk factor for ischaemic heart disease. The aforementioned studies are in contrast to a large and growing body of literature that suggests patients with more severe psoriasis carry a clinically relevant increased risk of mortality due to ischaemic heart disease. Samarasekera et al.¹⁰ critically evaluated 14 cohort studies and meta-analysed the magnitude of cardiovascular risk for the primary outcomes of cardiovascular mortality, stroke, and myocardial infarction (MI). Increased risk was identified only in individuals with severe psoriasis (defined as requiring systemic therapy or hospital admission): the risk ratio relative to the general population was 1.37 (95 % CI, 1.17-1.60) for cardiovascular mortality, 3.04 (95 % CI 0.65-14.35) for MI, and 1.59 (95 % CI, 1.34-1.89) for stroke. The relative risks of cardiovascular disease were highest in the younger, severe psoriasis population (e. g., 3.10 [95 % CI, 1.98-4.86] for MI at 30 years), and absolute risks were greatest in older individuals with severe psoriasis (e. g., 23.2 excess MIs per 10,000 person-years at 60 years).¹⁰ Geata et al. showed an approximately 25% increased relative risk of cardiovascular disease in patients with psoriasis, independently of smoking, obesity and hyperlipidemia¹¹. The pooled relative risks for cardiovascular mortality in psoriasis compared with general population were 1.15 (95% CI 1.09-1.21) in all patients with psoriasis, 1.05 (95% CI 0.92-1.20) in those with mild psoriasis, and 1.38 (95% CI 1.09-1.74) in severe disease¹². A recent systematic review and meta-analysis indicates that subclinical coronary artery disease diagnosed with cardiac computed tomography angiography is more prevalent in patients with psoriasis, with an increased burden of disease and number of high-risk coronary plaques¹³.

It has been proposed that there may be overlapping immune pathways in both psoriasis and ischaemic heart diseases that may underlie this association^{14,15}. It is also a matter of great interest whether systemic anti-psoriatic treatments affect cardiovascular risk by reducing the overall inflammatory burden. It is not known whether systemic treatments could modify cardiovascular outcomes including the rate of MI. However, studies investigating the effects of systemic treatments on cardiovascular risk factors including metabolic parameters (e. g., serum lipids), blood pressure or biomarkers of inflammation and atherosclerosis (e. g., C-reactive protein, endothelial dysfunction) have been completed. Multiple studies have failed to show any significant changes in metabolic parameters in patients receiving both PUVA and narrowband UVB therapy^{16,17}. In contrast, systemic retinoids (i. e.,



acitretin) commonly increase serum triglycerides and cholesterol by shifting high-density lipoproteins to low-density lipoproteins^{17,18}. Similarly, ciclosporin can increase serum lipids, plasma glucose and blood pressure in a dose-dependent fashion^{19,20}. Therapy with MTX is associated with a reduced risk of cardiovascular morbidity and mortality in patients with RA as well as in patients with psoriasis and psoriatic arthritis²¹⁻²⁴. In a longitudinal cohort study of 6902 patients with psoriasis, Ahlehoff et al. found that treatment with methotrexate was associated with a reduced risk of cardiovascular events compared to patients treated with other antipsoriatic therapies such as ciclosporin and retinoids²⁵. Methotrexate therapy decreases carotid intima-media thickness (a marker of arteriosclerosis) in patients with moderate-to-severe psoriasis²⁶. Preclinical and pilot studies suggest possible cardioprotective effects of apremilast and fumarates but there is no clinical evidence that either affect cardiovascular risk^{27,28}.

The effect of biological therapies on the risk of ischaemic heart disease is unclear. Treatment with TNFi and ustekinumab have been shown to reduce aortic vascular inflammation and decrease systemic inflammatory biomarkers²⁹⁻³³. Moreover, therapy with TNFi improves biomarkers of atherosclerosis by reducing either intima media thickness and arterial stiffness in patients with RA, spondyloarthropathies, PsA and psoriasis³⁴⁻³⁶. Secukinumab may have a beneficial effect on cardiovascular risk in patients with psoriasis by improving endothelial function measured by flow-mediated dilation³⁷.

There is conflicting evidence on the effects of biologic therapy on the incidence of cardiovascular incidents in patients with psoriasis. A large cohort study of 25,554 patients with psoriasis followed for eight years using administrative and pharmacy claims data from a large U.S. insurer (i. e., United Health Group) did not show a reduced risk of MI in those receiving systemic therapy compared to those exposed to phototherapy³⁸. A recent comparison of patients with first time hospital-diagnosed psoriasis between 1995 and 2002 (early era cohort) and those diagnosed between 2006 and 2013 (late era cohort), did not show any change in MI risk despite increased cardiovascular disease prevention and the availability of biologic therapy³⁹. A meta-analysis of 22 randomized, placebo-controlled, double-blind studies of IL-12/23 antibodies and anti-TNF- α agents comprising 10,183 adult patients evaluated the possible association between biologic therapies and major adverse cardiovascular events (MACE). Compared with placebo, there was no significant difference in the rate of MACE observed in patients receiving anti-IL-12/IL-23 antibodies or anti-TNF- α treatments. However, the authors acknowledged that the study may have been underpowered to identify a significant difference.⁴⁰ However, other studies have shown different outcomes. In particular, Wu et al.⁴¹



assessed whether patients with psoriasis treated with TNFi inhibitors had a decreased risk of MI compared with those treated with other systemic therapies, phototherapy or topical. This was a retrospective cohort study of 8,845 patients, 1,673 received a TNFi for at least two months, 2,097 received conventional systemic treatments or phototherapy, and 5,075 received only topical treatment. After adjusting for MI risk factors, the TNFi cohort had a significantly lower risk of MI compared with the topical cohort (adjusted hazard ratio, 0.50; 95 % CI, 0.32-0.79). The difference in incidence of MI between TNFi and conventional systemic treatments or phototherapy was not significant.⁴¹ In a Danish nationwide real-world study of 2400 patients with severe psoriasis enrolled in a registry, treatment with biological agents (n=693) or MTX (n=799) was associated with lower cardiovascular disease event rates than treatment with other anti-psoriatic therapies.⁴² This is consistent with Wu et al. who found that psoriasis patients receiving TNFis had a lower major cardiovascular event risk compared to those receiving methotrexate and cumulative exposure to TNFis was associated with an 11% cardiovascular event risk reduction⁴³. Concern was expressed over initial analyses linking IL-12/23 inhibitors with MACE in the first week of therapy. However, additional meta-analysis of clinical trials and data from registries in psoriasis and psoriatic arthritis suggest that licensed biologic therapies, including TNFi (adalimumab, etanercept and infliximab), anti-IL-17A agents (secukinumab and ixekizumab) or ustekinumab are not associated with MACEs⁴⁴⁻⁴⁷. In a large prospective cohort study using the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) there was no significant differences in the risk of major cardiovascular events between etanercept, adalimumab, ustekinumab and methotrexate⁴⁸. Similarly, in 60028 patients with psoriasis or psoriatic arthritis from multiple US databases, no significant difference was found in the risk of MACEs after initiation of therapy with TNFi or ustekinumab⁴⁹.

b) Heart failure


Summary/key points

- Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.⁴
- Common causes include coronary artery disease (previous myocardial infarction), arterial hypertension, atrial fibrillation, valvular heart disease and cardiomyopathies. The condition may, therefore, co-exist with ischemic heart disease.



- Patients with suspected or confirmed heart failure should be referred to a cardiologist for investigation and treatment in accordance with current European Society of Cardiology guidance⁵⁰.
- The NYHA functional classification is commonly used to describe the severity of symptoms and exercise intolerance in patients with heart failure. (<https://manual.jointcommission.org/releases/TJC2018A/DataElem0439.html>)
 - Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
 - Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
 - Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m). Comfortable only at rest.
 - Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
- There is evidence that anti-TNFs, especially adalimumab and infliximab, worsen advanced heart failure and both drugs are contraindicated in patients with congestive heart failure NYHAIII/IV and must be used with caution in patients with milder forms of congestive heart failure (NYHA I/II). Etanercept must be used with caution in patients with congestive heart failure.
- The use of other targeted therapies in patients with psoriasis and congestive heart failure seems to be neutral depending on the underlying cause (caution infection).
- The use of methotrexate, acitretin and apremilast in patients with psoriasis and heart failure seems to be neutral depending on the underlying cause.
- Ciclosporin may increase the blood pressure and reduce kidney function in patients with psoriasis and heart failure and interfere with many drugs used in the treatment of this condition.
- Fumarates may reduce kidney function in patients with psoriasis and heart failure.



We suggest against using cyclosporine in patients with psoriasis and advanced congestive heart failure.	↓	
We suggest that methotrexate, acitretin and apremilast are considered as treatment in patients with psoriasis and advanced congestive heart failure*.	↑	STRONG CONSENSUS ¹  EXPERT CONSENSUS
We suggest that ustekinumab, inhibitors of IL-17 and of IL-23 are considered as treatment in patients with psoriasis and advanced congestive heart failure*.	↑	
We recommend against using anti-TNFs in patients with psoriasis and advanced congestive heart failure	↓↓↓	
We recommend discussing the choice of a systemic therapy in psoriasis patients with advanced congestive heart failure with a cardiologist.	↑↑↑	

¹ due to personal-financial conflict of interest 3 abstentions

* in case of concomitant ischaemic heart failure, also note the recommendations from the respective section

TNF- α in heart failure (HF) stems from the observations that TNF- α exerts negative inotropic effects and is capable of promoting fibrosis, hypertrophy and cardiomyopathy in animal models⁵¹. Moreover, cardiac specific TNF- α levels are regulated by pressure and volume load in animals and in humans⁵². Therefore, a small series of clinical trials was conducted with TNFi to investigate their potential beneficial effects in patients with HF. Both RENAISSANCE and RECOVER^{53,54} were large, multicenter, randomized, double blind, placebo-controlled trials of etanercept in HF. Both studies failed to show improved mortality or decreased hospitalizations due to CHF. The key finding of the RENAISSANCE trial was a trend towards higher mortality in etanercept-treated subjects, a concern heightened by the apparent dose-response relationship. The combined analysis of these studies showed a trend towards increased mortality and/or HF hospitalizations in the combined twice-weekly/thrice-weekly etanercept group compared with placebo.^{53,54} Infliximab was evaluated in a phase II randomized, double-blind, placebo-controlled pilot study.⁵⁵ This pilot study did not show any beneficial effect of infliximab over placebo in terms of efficacy. Higher-dose infliximab (10 mg/kg) was associated with an increase in both all-cause mortality and the number of hospitalizations due to HF at weeks 28 and 54. In summary, the results of randomized, placebo-controlled trials with both etanercept and infliximab suggest a deleterious effect of higher doses of TNF blockers in patients with NYHA class III or IV HF. In particular, there was a trend toward higher mortality and a greater number of hospitalizations for HF. However, a recent Cochrane systematic review including 163 randomized controls trials with 50,010 participants and 46 extension studies with 11,954 participants, found that the rate of new diagnosis of



HF were not statistically significantly different between those patients treated with biologics and those with control treatments.⁵⁶ The cardiovascular safety data extracted from 74 articles and, corresponding to 77 randomised controlled trials of TNFi, anti-IL 12/23, anti-IL 23 and anti-IL 17 agents for the treatment of psoriatic arthritis or psoriasis showed no significant difference in CHF incidence in patients receiving biological agents in comparison to placebo⁴⁷. In conclusion, only moderate-to-severe CHF is a concern for initiating TNFi therapy in patients with psoriasis.

References

1. Nast A, Gisondi P, Ormerod AD *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology* : JEADV 2015; **29**: 2277-94.
2. Nast A, Spuls PI, van der Kraaij G *et al.* European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology*: JEADV 2017; **31**: 1951-63.
3. Knuuti J, Wijns W, Saraste A *et al.* 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European heart journal* 2020; **41**: 407-77.
4. Piepoli MF, Hoes AW, Agewall S *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal* 2016; **37**: 2315-81.
5. Mach F, Baigent C, Catapano AL *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *European heart journal* 2020; **41**: 111-88.
6. Boehncke W-H, Gladman DD, Chandran V. Cardiovascular comorbidities in psoriasis and psoriatic arthritis: pathogenesis, consequences for patient management, and future research agenda: a report from the GRAPPA 2009 annual meeting. *J Rheumatol* 2011; **38**: 567-71.
7. Kimball AB, Szapary P, Mrowietz U *et al.* Underdiagnosis and undertreatment of cardiovascular risk factors in patients with moderate to severe psoriasis. *J Am Acad Dermatol* 2012; **67**: 76-85.
8. Wakkee M, Herings RM, Nijsten T. Psoriasis may not be an independent risk factor for acute ischemic heart disease hospitalizations: results of a large population-based Dutch cohort. *The Journal of investigative dermatology* 2010; **130**: 962-7.
9. Stern RS, Huibregtse A. Very severe psoriasis is associated with increased noncardiovascular mortality but not with increased cardiovascular risk. *The Journal of investigative dermatology* 2011; **131**: 1159-66.
10. Samarasekera EJ, Neilson JM, Warren RB, Parnham J, Smith CH. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. *The Journal of investigative dermatology* 2013; **133**: 2340-6.
11. Gaeta M, Castelvechio S, Ricci C, Pigatto P, Pellissero G, Cappato R. Role of psoriasis as independent predictor of cardiovascular disease: a meta-regression analysis. *International journal of cardiology* 2013; **168**: 2282-8.
12. Dhana A, Yen H, Yen H, Cho E. All-cause and cause-specific mortality in psoriasis: A systematic review and meta-analysis. *J Am Acad Dermatol* 2019; **80**: 1332-43.



13. Kaiser H, Abdulla J, Henningsen KMA, Skov L, Hansen PR. Coronary Artery Disease Assessed by Computed Tomography in Patients with Psoriasis: A Systematic Review and Meta-Analysis. *Dermatology* 2019; **235**: 478-87.
14. Davidovici BB, Sattar N, Prinz JC *et al.* Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. *The Journal of investigative dermatology* 2010; **130**: 1785-96.
15. Ghazizadeh R, Shimizu H, Tosa M, Ghazizadeh M. Pathogenic mechanisms shared between psoriasis and cardiovascular disease. *Int J Med Sci* 2010; **7**: 284-9.
16. Chappel SG, Roenigk HH, Miller AJ, Beeaff DE, Tyrpin L. The effect of photochemotherapy on the cardiovascular system. *J Am Acad Dermatol* 1981; **4**: 561-6.
17. Hugh J, Van Voorhees AS, Nijhawan RI *et al.* From the Medical Board of the National Psoriasis Foundation: The risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. *J Am Acad Dermatol* 2014; **70**: 168-77.
18. Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. *J Am Acad Dermatol* 1999; **41**: 7.
19. Robert N, Wong GW, Wright JM. Effect of cyclosporine on blood pressure. *The Cochrane database of systematic reviews* 2010: CD007893.
20. Gisondi P, Cazzaniga S, Chimenti S *et al.* Metabolic abnormalities associated with initiation of systemic treatment for psoriasis: evidence from the Italian Psocare Registry. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2013; **27**: 30-41.
21. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; **359**: 1173-7.
22. Prodanovich S, Prodanowich S, Ma F *et al.* Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 2005; **52**: 262-7.
23. Westlake SL, Colebatch AN, Baird J *et al.* The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology* 2010; **49**: 295-307.
24. Roubille C, Richer V, Starnino T *et al.* The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Annals of the rheumatic diseases* 2015; **74**: 480-9.
25. Ahlehoff O, Skov L, Gislasen G *et al.* Cardiovascular outcomes and systemic anti-inflammatory drugs in patients with severe psoriasis: 5-year follow-up of a Danish nationwide cohort. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2015; **29**: 1128-34.
26. Martinez-Lopez A, Blasco-Morente G, Perez-Lopez I, Tercedor-Sanchez J, Arias-Santiago S. Studying the effect of systemic and biological drugs on intima-media thickness in patients suffering from moderate and severe psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2018; **32**: 1492-8.
27. Schmieder A, Poppe M, Hametner C *et al.* Impact of fumaric acid esters on cardiovascular risk factors and depression in psoriasis: a prospective pilot study. *Archives of dermatological research* 2015; **307**: 413-24.
28. Imam F, Al-Harbi NO, Al-Harbi MM *et al.* Apremilast prevent doxorubicin-induced apoptosis and inflammation in heart through inhibition of oxidative stress mediated activation of NF-kappaB signaling pathways. *Pharmacological reports : PR* 2018; **70**: 993-1000.
29. Peters MJL, Watt P, Cherry L *et al.* Lack of effect of TNFalpha blockade therapy on circulating adiponectin levels in patients with autoimmune disease: results from two independent prospective studies. *Annals of the rheumatic diseases* 2010; **69**: 1687-90.
30. Strober B, Teller C, Yamauchi P *et al.* Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. *The British journal of dermatology* 2008; **159**: 322-30.



31. Gisondi P, Lora V, Bonauguri C, Russo A, Lippi G, Girolomoni G. Serum chemerin is increased in patients with chronic plaque psoriasis and normalizes following treatment with infliximab. *The British journal of dermatology* 2013; **168**: 749-55.
32. Eder L, Joshi AA, Dey AK *et al.* Association of Tumor Necrosis Factor Inhibitor Treatment With Reduced Indices of Subclinical Atherosclerosis in Patients With Psoriatic Disease. *Arthritis & rheumatology (Hoboken, N.J.)* 2018; **70**: 408-16.
33. Gelfand JM, Shin DB, Alavi A *et al.* A Phase IV, Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Effects of Ustekinumab on Vascular Inflammation in Psoriasis (the VIP-U Trial). *The Journal of investigative dermatology* 2020; **140**: 85-93.e2.
34. Bilborough W, Keen H, Taylor A, O'Driscoll GJ, Arnolda L, Green DJ. Anti-tumour necrosis factor-alpha therapy over conventional therapy improves endothelial function in adults with rheumatoid arthritis. *Rheumatol Int* 2006; **26**: 1125-31.
35. Tam LS, Li EK, Shang Q *et al.* Tumour necrosis factor alpha blockade is associated with sustained regression of carotid intima-media thickness for patients with active psoriatic arthritis: a 2-year pilot study. *Annals of the rheumatic diseases* 2011; **70**: 705-6.
36. Pina T, Corrales A, Lopez-Mejias 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. *The Journal of dermatology* 2016; **43**: 1267-72.
37. von Stebut E, Reich K, Thaci D *et al.* Impact of Secukinumab on Endothelial Dysfunction and Other Cardiovascular Disease Parameters in Psoriasis Patients over 52 Weeks. *The Journal of investigative dermatology* 2019; **139**: 1054-62.
38. Abuabara K, Lee H, Kimball AB. The effect of systemic psoriasis therapies on the incidence of myocardial infarction: a cohort study. *The British journal of dermatology* 2011; **165**: 1066-73.
39. Leisner MZ, Lindorff Riis J, Gniadecki R, Iversen L, Olsen M. Psoriasis and risk of myocardial infarction before and during an era with biological therapy: a population-based follow-up study. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2018; **32**: 2185-90.
40. Ryan C, Leonardi CL, Krueger JG *et al.* Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. *JAMA* 2011; **306**: 864-71.
41. Wu JJ, Poon K-YT, Channual JC, Shen AY-J. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Archives of dermatology* 2012; **148**: 1244-50.
42. Ahlehoff O, Skov L, Gislason G *et al.* Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study. *J Intern Med* 2013; **273**: 197-204.
43. Wu JJ, Guerin A, Sundaram M, Dea K, Cloutier M, Mulani P. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-alpha inhibitors versus methotrexate. *J Am Acad Dermatol* 2017; **76**: 81-90.
44. Reich K, Langley RG, Lebwohl M *et al.* Cardiovascular safety of ustekinumab in patients with moderate to severe psoriasis: results of integrated analyses of data from phase II and III clinical studies. *The British journal of dermatology* 2011; **164**: 862-72.
45. Papp KA, Griffiths CE, Gordon K *et al.* Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *The British journal of dermatology* 2013; **168**: 844-54.
46. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic review and meta-analysis of randomized controlled trials. *The British journal of dermatology* 2017; **176**: 890-901.



47. Champs B, Degboe Y, Barnetche T, Cantagrel A, Ruysen-Witrand A, Constantin A. Short-term risk of major adverse cardiovascular events or congestive heart failure in patients with psoriatic arthritis or psoriasis initiating a biological therapy: a meta-analysis of randomised controlled trials. *RMD open* 2019; **5**: e000763.
48. Rungapiromnan W, Mason KJ, Lunt M *et al.* Risk of major cardiovascular events in patients with psoriasis receiving biologic therapies: a prospective cohort study. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2019.
49. Lee MP, Desai RJ, Jin Y, Brill G, Ogdie A, Kim SC. Association of Ustekinumab vs TNF Inhibitor Therapy With Risk of Atrial Fibrillation and Cardiovascular Events in Patients With Psoriasis or Psoriatic Arthritis. *JAMA dermatology* 2019; **155**: 700-7.
50. Ponikowski P, Voors AA, Anker SD *et al.* 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Revista espanola de cardiologia (English ed.)* 2016; **69**: 1167.
51. Yokoyama T, Vaca L, Rossen RD, Durante W, Hazarika P, Mann DL. Cellular basis for the negative inotropic effects of tumor necrosis factor-alpha in the adult mammalian heart. *The Journal of clinical investigation* 1993; **92**: 2303-12.
52. Torre-Amione G, Bozkurt B, Deswal A, Mann DL. An overview of tumor necrosis factor alpha and the failing human heart. *Current opinion in cardiology* 1999; **14**: 206-10.
53. Deswal A, Bozkurt B, Seta Y *et al.* Safety and efficacy of a soluble P75 tumor necrosis factor receptor (Enbrel, etanercept) in patients with advanced heart failure. *Circulation* 1999; **99**: 3224-6.
54. Coletta AP, Clark AL, Banarjee P, Cleland JG. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. *European journal of heart failure* 2002; **4**: 559-61.
55. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT, Anti TNFTACHFI. 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**: 3133-40.
56. Singh JA, Wells GA, Christensen R *et al.* Adverse effects of biologics: a network meta-analysis and Cochrane overview. *The Cochrane database of systematic reviews* 2011: CD008794.