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

This chapter is based on the corresponding chapter in the previous versions of the guideline. [1-3]. A search was conducted, details of which can be found below**.**

**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 [4].
- 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 [5,6].
- 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 TNFi, 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.
- The search in MEDLINE via Ovid did not identify systematic reviews on the efficacy and safety of using deucravacitinib in patients with psoriasis and heart disease.

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| We **suggest against** cyclosporine or acitretin as preferred treatments in patients with psoriasis and ischemic heart disease. | ↓ | STRONG CONSENSUS[1]   EXPERT CONSENSUS |
| 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** TNFi, 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 [7]. 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 is an independent cardiovascular risk factor [8]. 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 subjects [9]. Stern and Huibregtse [10] 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. [11] 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). [11] Geata et al. showed an approximately 25% increased relative risk of cardiovascular disease in patients with psoriasis, independently of smoking, obesity and hyperlipidemia [12]. 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 disease [13]. 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 plaques [14].

It has been proposed that there may be overlapping immune pathways in both psoriasis and ischaemic heart diseases that may underlie this association [15,16] 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 [17,18]. In contrast, systemic retinoids (i. e., acitretin) commonly increase serum triglycerides and cholesterol by shifting high-density lipoproteins to low-density lipoproteins [18,19]. Similarly, ciclosporin can increase serum lipids, plasma glucose and blood pressure in a dose-dependent fashion [20,21].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 arthritis [22-25]. 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 retinoids [26]. Methotrexate therapy decreases carotid intima-media thickness (a marker of arteriosclerosis) in patients with moderate–to- severe psoriasis [27]. Preclinical and pilot studies suggest possible cardioprotective effects of apremilast and fumarates but there is no clinical evidence that either affect cardiovascular risk[28,29].

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 biomarkers [30-34]. Randomized controlled trials show that ustekinumab reduces aortic vascular inflammation and that TNFi and phototherapy reduce CRP and IL-6.[35] Therapy with TNFi improves biomarkers of atherosclerosis by reducing intima media thickness and arterial stiffness in patients with RA, spondyloarthropathies, PsA and psoriasis [36-38]. Secukinumab may have a beneficial effect on cardiovascular risk in patients with psoriasis by improving endothelial function measured by flow-mediated dilation [39].

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 phototherapy[40]. A 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 therapy [41]. A meta-analysis of 22 randomized, placebo-controlled, double-blind studies of IL-12/23 antibodies and TNFi 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 TNFi treatments. However, the authors acknowledged that the study may have been underpowered to identify a significant difference. [42] However, other studies have shown different outcomes. In particular, Wu et al. [43] 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. [43] 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. [44] This is consistent with Wu et al. who found that psoriasis patients receiving TNFi had a lower major cardiovascular event risk compared to those receiving methotrexate and cumulative exposure to TNFi was associated with an 11% cardiovascular event risk reduction [45]. 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 MACEs [46-49]. 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 methotrexate [50]. 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 ustekinumab [51]

A systematic review and meta-analysis of cohort studies or RCTs [52] found that the use of bDMARDs might be associated with reduced risks of CV events in patients with systemic inflammatory conditions. In sensitivity analysis for patients with psoriasis, compared with non-bDMARD users (controls), the risks of myocardial infarction (bDMARD vs. control: 6324 vs. 2675, OR = 0.90, 95% CI, 0.45 to 1.80, $I^2$= 0%), heart failure (bDMARD vs. control: 869 vs. 511, OR = 0.78, 95% CI, 0.14 to 4.33, $I^2$= 0%,), cardiovascular (CV) death (bDMARD vs. control: 2177 vs. 1052, OR = 0.71, 95% CI, 0.18 to 2.85, $I^2$= 0%),

all-cause mortality (bDMARD vs. control: 36677 vs. 1719, OR = 0.80, 95% CI, 0.26 to 2.45, $I^2$= 0%) were not significantly reduced in bDMARD users. When data were pooled across all systemic inflammatory conditions, CV events might be less frequent in TNFi users and in bDMARD users with follow-up over one year compared to controls.[52]

Different studies on psoriatic arthritis, which showed conflicting results, were identified through a hand search. A large cohort study from the UK using a medical record data-base found a higher incidence of MACE in patients with psoriatic arthritis without DMARD prescription (HR 1.24; 95%CI 1.03 to 1.49), while patients with psoriatic arthritis with DMARD prescription did not show a significantly higher incidence (HR 1.17; 95%CI 0.95 to 1.46) when compared with matched control patients (without the diagnosis of psoriasis, PsA or rheumatoid arthritis and without DMARD prescription) [53]. Conversely, Eder et al. [54] investigated the incidence of cardiovascular events in a large psoriatic arthritis clinic and found no difference in MACE between TNFi versus MTX versus untreated patients with PsA, and further no increased incidence in patients treated with glucocorticoids or NSAIDs. Another cohort study from a UK register found a significantly higher incidence rate of MACE in patients receiving glucocorticoids (IRR 4.95; 95%CI 2.04 to 12.01) as compared with patients receiving DMARDs (including MTX and bDMARDs: IRR 1.31, 95%CI 0.99 to 1.73) and patients with psoriatic arthritis without drug prescription (reference group) [55].

**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. [5]
- 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 guidance [56].

- 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 TNFi, 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.

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| We **suggest against** using cyclosporine in patients with psoriasis and advanced congestive heart failure. | ↓ | STRONG CONSENSUS[1]<br>100 % Agreement<br>EXPERT CONSENSUS |
| We **suggest** that methotrexate, acitretin and apremilast are considered as treatment in patients with psoriasis and advanced congestive heart failure*. | ↑ | |
| 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 TNFi 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 models [57]. Moreover, cardiac specific TNF-α levels are regulated by pressure and volume load in animals and in humans [58]. 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 [59,60] 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. [59,60] Infliximab was evaluated in a phase II randomized, double-blind, placebo-controlled pilot study. [61] 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 TNFi 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. [62] 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 placebo [49]. In conclusion, only moderate-to-severe CHF is a concern for initiating TNFi therapy in patients with psoriasis.

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# Review of the evidence on psoriasis and heart diseases

## Methods

### Inclusion criteria

| | |
|---|---|
| Patients | Inclusion: adult patients with a clinical diagnosis of psoriasis and heart diseases or cardiovascular risk factors |
| Intervention | Conventional systemic treatment (acitretin, apremilast, ciclosporin, fumarates, methotrexate) and biologicals (TNFi: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new)) |
| Comparator | Comparisons with another included drug and/or placebo |
| Outcomes | ▪ risk for developing cardiovascular events<br>▪ influence on cardiovascular risk factors (weight, hypertension, dyslipidaemia) |
| Study Design | Inclusion:<br>Primary: Systematic reviews<br>Secondary: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies, case series, case reports, retrospective studies<br>Exclusion:<br>non-systematic reviews, letter, comments, animal, in-vitro or in-silico studies |

### Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid from 1946 was searched for the period October 2019 to 18 January 2023. One methodologist conducted a topic specific but non-systematic screening. The authors of the chapter then screened included full texts based on the above listed eligibility criteria.

### Search strategy

**Filter for detecting systematic reviews:** Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455. https://pubmed.ncbi.nlm.nih.gov/17082841/ (Strategies minimizing difference between sensitivity and specificity)

**Ressource:** Ovid MEDLINE(R) ALL <1946 to January 17, 2023>

| ID | Search term | Result |
|---|---|---|
| 1 | exp Methotrexate/ | 40879 |
| 2 | methotrexate$.mp. | 59566 |
| 3 | amethopterin.mp. | 401 |
| 4 | mtx.ti,ab. | 14592 |

| ID | Search term | Result |
|---|---|---|
| 5 | exp Fumarates/ | 5316 |
| 6 | (fumar$ and esters).mp. | 468 |
| 7 | dimethylfumarate.mp. | 205 |
| 8 | fae.ti,ab. | 1021 |
| 9 | dmf.ti,ab. | 9700 |
| 10 | fumarate$1.mp. | 20781 |
| 11 | Etretinate/ | 1352 |
| 12 | Acitretin/ | 1286 |
| 13 | ((oral or orally or systemic) and retinoid$).ti,ab. | 2931 |
| 14 | Isotretinoin/ | 3942 |
| 15 | isotretinoin.ti,ab. | 3695 |
| 16 | etretin$.mp. | 1745 |
| 17 | acitretin.mp. | 2023 |
| 18 | Retinoids/ | 6308 |
| 19 | Ustekinumab.mp. | 2952 |
| 20 | secukinumab.mp. | 1851 |
| 21 | apremilast.mp. | 1027 |
| 22 | guselkumab.mp. | 524 |
| 23 | exp antibodies, monoclonal/ | 271864 |
| 24 | monoclonal antibod$.mp. | 204408 |
| 25 | exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/ | 30052 |
| 26 | exp Interleukin-12 Subunit p40/ or p40 subunit.mp. | 1901 |
| 27 | exp Tumor Necrosis Factors/ or exp Tumor Necrosis Factor-alpha/ or exp Receptors, Tumor Necrosis Factor, Type II/ or exp Receptors, Tumor Necrosis Factor/ or exp Receptors, Tumor Necrosis Factor, Type I/ or exp TNF-Related Apoptosis-Inducing Ligand/ | 196082 |
| 28 | (anti tumour necrosis factor or anti tumor necrosis factor).mp. | 6177 |
| 29 | (tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp. | 189039 |
| 30 | anti tnf.mp. | 12449 |
| 31 | (tnf antibod$ or tnf alpha antibod$).mp. | 2387 |
| 32 | (tumour necrosis factor antibod$ or tumor necrosis factor antibod$).mp. | 161 |
| 33 | (antitumor necrosis factor or antitumour necrosis factor).mp. | 918 |
| 34 | exp Immunoglobulin Fab Fragments/ | 29391 |
| 35 | (infliximab$ or monoclonal antibody cA2).mp. | 17256 |
| 36 | etanercept$.mp. | 9583 |
| 37 | adalimumab$.mp. | 10560 |
| 38 | Cyclosporine/ | 30456 |
| 39 | (Ciclosporin or cyclosporine or cyclosporin).mp. | 59498 |
| 40 | brodalumab.mp. | 498 |
| 41 | ixekizumab.mp. | 934 |
| 42 | certolizumab.mp. | 1554 |
| 43 | Certolizumab Pegol/ | 726 |
| 44 | tildrakizumab.mp. | 243 |
| 45 | bimekizumab.mp. | 105 |
| 46 | risankizumab.mp. | 336 |
| **47** | **or/1-46** | **777987** |
| 48 | deucravacitinib.mp. | 45 |
| 49 | TYK2 Kinase/ | 609 |
| 50 | (TYK2 or tyrosine kinase 2).ti,ab. | 2131 |
| **51** | **or/48-50** | **2252** |
| 52 | psoria$.ti,ab. | 57249 |
| 53 | exp Psoriasis/ | 46876 |

| ID | Search term | Result |
|---|---|---|
| 54 | palmoplantar$ pustulosis.ti,ab. | 664 |
| 55 | pustulosis palmaris et plantaris.ti,ab. | 173 |
| 56 | (pustulosis and palms and soles).ti,ab. | 107 |
| **57** | **or/52-56** | **63986** |
| 58 | exp Cardiovascular Diseases/ | 2676632 |
| 59 | exp Coronary Artery Bypass/ | 56307 |
| 60 | cardiometabolic risk factors/ | 941 |
| 61 | exp Obesity/ | 253622 |
| 62 | Metabolic Syndrome/ | 37466 |
| 63 | exp Dyslipidemias/ | 86142 |
| 64 | (hypercholesterol* or hypercholesterin* or hypertriglycerid* or dyslipid* or obesity or obese or hyperlipoprotein* or Dyslipoprotein*).ti,ab. | 432416 |
| 65 | (hypertens* or ((high or elevated) and blood pressure)).ti,ab. | 549372 |
| 66 | (myocard* or coronar* or ischemi* or ischaemi* or cardial* or cardiac* or cardio* or heart* or infarct* or STEMI or NSTEMI).ti,ab. | 2452291 |
| 67 | (Arteriosclero* or Atherosclero*).ti,ab. | 183237 |
| 68 | (metabolic adj6 (syndrom* or risk*)).ti,ab. | 78073 |
| **69** | **or/58-68** | **4320576** |
| 70 | 47 and 57 and 69 | 1583 |
| 71 | ("201910*" or "201911*" or "201912*" or "2020*" or "2021*" or "2022*" or "2023*").dt. | 5035956 |
| 72 | 70 and 71 | 417 |
| 73 | 51 and 57 and 69 | 8 |
| 74 | 72 or 73 | 421 |
| 75 | meta analysis.mp,pt. or review.pt. or search:.tw. | 3569837 |
| **76** | **74 and 75** | **126** |
| **77** | **74 not 76** | **295** |

## Results