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# Chronic Inflammation, Cardiometabolic Diseases and Effects of Treatment: Psoriasis as a Human Model

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## Abstract

Chronic inflammation in humans is associated with accelerated development of cardiometabolic diseases such as myocardial infarction, stroke, and diabetes. Strong evidence from animal models and human interventional trials including CANTOS (The Canakinumab Anti-inflammatory Thrombosis Outcome Study) suggests that targeting residual systemic inflammation in humans may impart a benefit in reducing cardiometabolic diseases. Diseases associated with heightened immune-activation and systemic inflammation including psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and human immunodeficiency virus infection are associated with upwards of two to seven-fold risk of future adverse cardiac events even when adjusted for traditional risk factors. Over the past decade, psoriasis has been utilized as a human model to study inflammatory-induced cardiometabolic dysfunction and to better understand residual risk due to inflammation. The high prevalence and early onset of cardiovascular disease in psoriasis enhances the likelihood of discovering novel pathways in vascular disease progression when followed over time. Furthermore, the United States Food and Drug Administration approved treatments for psoriasis include cytokine inhibitors (anti-tumor necrosis factor, anti-interleukin 17, anti-interleukin 12/23) which while treating the skin disease provide a unique opportunity to characterize how treating the inflammatory pathways may impact atherosclerosis. Herein, we provide a review of chronic

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Declarations

Competing interests

1. NNM is a full-time US government employee and has served as a consultant for Amgen, Eli Lilly, and Leo Pharma receiving grants/other payments; as a principal investigator and/or investigator for AbbVie, Celgene, Janssen Pharmaceuticals, Inc, and Novartis receiving grants and/or research funding and as a principal investigator for the National Institute of Health receiving grants and/or research funding.

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inflammation, cardiometabolic disease associations, and treatment effects with a focus on psoriasis as a human model of study.

### Keywords

Psoriasis; inflammation; cardiometabolic disease; immune activation; lipoprotein dysfunction; adipose dysfunction

## Introduction

Despite major advances in our understanding of cardiovascular disease (CVD) and its pathogenesis, 31% of all deaths worldwide are still due to coronary artery disease, stroke, and other vasculopathies (1). Although much of this cardiovascular (CV) risk is due to traditional CVD risk factors including hyperlipidemia, smoking, diabetes, and hypertension, inflammation has been identified as a key driver in the development, progression, and complications of atherosclerosis (2).

Indeed, patients with chronic inflammatory diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and human immunodeficiency virus (HIV) infection have both higher levels of systemic inflammatory markers and a greater incidence of CVD compared to the general population (3). However, RA, SLE and HIV disease pathophysiology and associated treatment modalities including steroid use and retroviral inhibitors hamper using these diseases as clinical models for studying the effects of inflammation, treatment of inflammation, and effects on cardiometabolic disease (CMD). Patients affected by these conditions require ongoing therapy, without which irreversible joint damage or systemic effects would occur (4). Moreover, rarely do these diseases utilize cytokine therapies as in the case of psoriasis, thereby limiting targeted understanding of treatment effects on systemic inflammation in humans.

Inflammation due to innate and adaptive immune cell activation contributes to the development of atherosclerosis in psoriasis (5, 6) and patients with psoriatic arthritis (7). In fact, this past year, psoriasis was noted to be a risk-enhancing condition for developing cardiovascular disease by the American College of Cardiology/American Heart Association prevention guidelines (3). Furthermore, the American Academy of Dermatology/National Psoriasis Foundation guidelines noted these recommendations of psoriasis being a high-risk disease state associated with enhanced cardiovascular disease risk beyond traditional CVD risk factors (8).

While the exact mechanistic links between chronic inflammation and cardiometabolic disease are an active area of investigation, accepted pathways in chronic inflammatory diseases include immune activation and systemic inflammation, lipoprotein dysfunction, and adipose dysfunction including insulin resistance that predispose these patients to cardiometabolic disease. This review aims to describe the links between systemic inflammation and cardiometabolic disease and summarize important evidence of potential mechanisms driving CVD in inflammatory diseases. We highlight the use of psoriasis as a unique human model to study the role of immune activation, lipoprotein dysfunction, and

adipose dysfunction in the development of cardiometabolic diseases. Additionally, this review covers effects of treatment of psoriasis on cardiovascular diseases. The long-term goal of these studies in psoriasis is to inform how pathways in inflammation modulate following treatment and utilizing anti-cytokine therapies that may translate into future treatments for atherosclerosis.

## Inflammation and Cardiometabolic Disease

Systemic inflammation when defined as elevated high-sensitivity C-reactive protein (hs-CRP) has been shown to be associated with incident cardiovascular events (2). CRP levels were found to be better predictors of CV events than low-density lipoprotein (LDL) cholesterol levels in apparently healthy women followed for ten years (2). Moreover, CANTOS (The Canakinumab Anti-inflammatory Thrombosis Outcome Study) carried out in post-myocardial infarction patients with high inflammatory risk by hs-CRP>2 mg/L demonstrated that treatment with canakinumab, an anti-interleukin (IL)-1β antibody, decreased IL6, hs-CRP levels, and the rate of prospective CV events (9). This landmark trial elucidated the potential role of treating residual inflammation to prevent adverse CV events.

While details of the precise mechanism linking systemic inflammation and atherosclerosis are under active investigation, many preclinical and clinical studies have explored heightened immune activity in the development of cardiometabolic disease. Pre-clinical models utilizing apolipoprotein E-deficient murine demonstrated that neutrophil extracellular traps accelerated atherosclerosis. Furthermore, suppression of pro-inflammatory neutrophil extracellular trap formation by a peptidyl-arginine deiminase inhibitor reduced atherosclerotic lesion size and number (10). Human translational studies in young, healthy humans demonstrated that both high (3 ng/kg) and low-doses (0.6 ng/kg) of IV endotoxin led to a transient systemic inflammatory state with increases in tumor necrosis factor (TNF)-α, IL-6 and hs-CRP. Furthermore, insulin resistance and dysfunctional HDL (high density lipoprotein) ensued concurrently with the development of adipose tissue inflammation (11–14) highlighting that innate immune stimuli drive the development of cardiometabolic disease even in the short term. In addition, the role of intracellular activation of the NLRP3 inflammasome, a macromolecular complex activating caspase-1 and promoting the release of inflammatory components such as cytokines, is increasingly being recognized as an early event initiating atherosclerosis. Of note, the NLRP3 inflammasome is upregulated in states of high systemic inflammation such as psoriasis in turn leading to early atherogenesis (15). Furthermore, immune cell subsets of myeloid origin (neutrophils, monocytes and platelets) are elevated and activated in inflammatory disease states and associate with high aortic vascular inflammation (16). Specifically, two subsets of myeloid cells, low-density neutrophils and classical monocytes, were found to be elevated in psoriasis and associated with skin disease severity, destruction of endothelial cells in culture, and coronary artery disease by CCTA (coronary computed tomography angiography) *in vivo* (17, 18). Additionally, a composite inflammatory biomarker GlycA (a subset of glycan N-acetylglucosamine residues on glycosylated acute-phase reactant proteins), was associated with myeloid cells and systemic inflammation by hs-CRP (19), and a prospective observational study demonstrated a positive association between GlycA, aortic vascular inflammation by positron emission tomography computed tomography (PET/CT), and

coronary artery disease by CCTA (20). Finally, vascular inflammation itself drives atherosclerotic plaque development, and a recent study demonstrated that 18F-FDG ($^{18}$F-labeled fluoro-2-deoxyglucose) uptake was high where an atherosclerotic plaque was not yet formed. However, 18F-FDG uptake was not high where an atherosclerotic plaque had already developed, suggesting that high vascular inflammation preceded the development of atherosclerotic plaque (21).

Traditional cardiovascular risk factors are more prevalent in patients with chronic inflammatory diseases including increasing hypertension, metabolic syndrome, and dyslipidemia. For example, patients with psoriasis have lipid profiles with increased apolipoprotein B-containing lipoproteins (LDL and VLDL) (22) and a reduction in apolipoprotein A1-containing lipoproteins (HDL). Furthermore, a triglyceride-rich environment is driven in part by systemic inflammation and an insulin-resistant state termed metabolic dysfunction. Most importantly, HDL function is impaired (~10% less removal of cholesterol by HDL efflux assay). This leads to augmented retention and accelerated oxidation of cholesterol (23), a major driver of early atherosclerosis. Additionally, the receptors of these oxidized lipids were recently demonstrated to be associated with systemic inflammation and *in vivo* coronary burden by CCTA (*Dey et al., JAMA Dermatol., in press*). Thus, heightened systemic inflammation leads to underlying cardiometabolic disease (24, 25) and adverse CV outcomes (26) driven by immune-activation and its sequelae.

## Psoriasis: A Chronic Inflammatory Skin Disease Associated with Cardiometabolic Disease

Psoriasis is a chronic inflammatory skin disease that affects 125 million people worldwide, and 7 million people in the United States, with more than 3 million people undiagnosed (27). Psoriasis affects the skin most commonly with erythematous, thickened plaques on extensor surfaces. Psoriasis is associated with development of psoriatic arthritis in upwards of 35% of patients (28), which imparts more risk for co-morbid disease (4). Psoriasis is multifactorial in etiology, partly genetically driven and associated with heightened innate and adaptive immune activation (28). T helper (Th)1 and Th17 cells drive pro-inflammatory cytokines including TNFα, interferon-γ, IL17A, and IL23 (28, 29). As such, psoriasis has underlying systemic effects (28, 30) more pronounced as skin disease worsens driving the development of cardiometabolic dysfunction (26, 31), especially when the psoriatic diseases are untreated.

Psoriasis is associated with a greater risk of co-morbid CV risk factors (32, 33) as well as elevated CV events including myocardial infarction (26, 34), stroke (35), and cardiovascular death (36, 37). Patients with psoriasis have increased vascular inflammation by 18F-FDG PET/CT (16, 38), lipid-rich non-calcified coronary burden (39), coronary artery calcium by coronary computed tomography (40), and carotid/femoral atherosclerotic plaques by ultrasound (41). Immune activation (32, 33), lipoprotein dysfunction (22, 42), and adipose dysfunction (26, 31) are three of the main factors driving accelerated cardiovascular diseases in psoriasis (Figure 1).

## Immune Activation and Pro-Inflammatory Cytokines in Psoriasis

There are multiple immune cells that are active in psoriatic skin plaque (Figure 1, Panel IIA). Early on, acute inflammatory neutrophils begin the cascade resulting in T cells, macrophages, and response-to-injury mediators secreting cytokines and chemokines (28, 43). Heightened myeloid and lymphoid immune cell activity drives pro-inflammatory cytokines, such as IL1β, IL6, and TNFα. Systemic inflammatory effects in psoriasis and early atherosclerosis are amplified by a broader class of cytokines, including IL17A, IL1β, IL6 and TNFα (Figure 1, Panel IIB) (15, 44). In turn, these cells secrete additional cytokines such as IL12/23, leading to the differentiation of helper T cells (Th1 and Th17) (44). Subsequently, T cells secrete intermediates (e.g., IL17F, IL17A, and IL22) which in turn activate keratinocytes and stimulate more pro-inflammatory cytokines, antimicrobial peptides, chemokines, and S100 proteins (29, 44). The vessel wall is then infiltrated by pro-inflammatory cellular components, cholesterol crystals (45), and various lipoproteins contributing to atherosclerotic cardiovascular disease.

## Lipoprotein Dysfunction

Systemic inflammation impacts lipoprotein composition and function (23). Patients with psoriasis have a high prevalence of dyslipidemia by traditional lipid panels independent of obesity (46). While it is evident that patients with psoriasis are at a greater risk of developing dyslipidemia, the relationship is most likely bi-directional (47). Dyslipidemia affects the distribution of lipid subsets and also impairs their functional components, augmenting the risk of atherosclerotic cardiovascular diseases (22). Increased apolipoprotein B:A1 ratios in psoriasis suggest a paucity of anti-atherogenic (apolipoprotein A1) and an increase in atherogenic species (apolipoprotein B) (22). Furthermore, oxidation modified lipoproteins (OMLs) are elevated in psoriasis. Because of reduced clearance (22) and increased reactive oxygen species, both oxidized LDL and oxidized HDL have been shown to be elevated in psoriasis and associated with non-calcified coronary burden (Figure 1, Panel III) (23). The implications of HDL impairment are tightly linked to a higher burden of inflammation (12), which ultimately drives cholesterol in tissues, thus accelerating atherosclerosis. Reduced HDL function in psoriasis relates directly to the burden of non-calcified coronary burden (48) and to psoriasis severity (45).

## Adipose Dysfunction

Metabolic syndrome is increased in moderate-to-severe psoriasis independent of cardiometabolic disease risk factors (49). Obesity is highly prevalent in psoriasis and may be an indication of underlying inflammation and metabolic dysfunction (50) since psoriasis exhibits a dose response relationship between psoriasis severity and obesity. However traditional measures of obesity, such as body mass index (BMI) and waist-to-hip ratio, do not fully capture the increased cardiovascular risk associated with obesity. Patients with psoriasis have demonstrated increased adipose tissue by computed compartmental measures of subcutaneous adipose tissue and visceral adipose distribution (Figure 1, Panel IV) (51). Additionally, psoriasis is associated with a higher prevalence of diabetes as well as diabetes-related complications when compared to controls (52, 53). Furthermore, elevated visceral

adipose volume in psoriasis positively associates with higher sub-clinical aortic vascular inflammation by FDG PET/CT (54) as well as non-calcified coronary burden (55). Finally, modulation of weight in those with BMI >40 kg/m$^2$ undergoing weight loss by standard methods or gastric bypass procedure was associated with improvement in their psoriasis (56); however relationships between psoriasis and associated adiposity are still under study (57).

## Treatment of Psoriasis

Pro-inflammatory cytokines and other immune pathways provide potential common links between the pathogenesis of psoriasis and atherosclerosis. Therefore, pro-inflammatory cytokines and immune pathways serve as potential targets in the treatment of psoriasis, as well as psoriasis-associated atherosclerosis. Although psoriasis lacks a definitive therapy, newer therapies targeting cytokines of interest are emerging (58). Mild psoriasis [body surface area (BSA) < 3%)] is usually treated with local therapies including ultraviolet phototherapy and topical treatments, which act on the surface of the skin. Systemic therapies targeting more specific immune pathways are reserved for moderate (3–10% BSA)-to-severe (>10% BSA) psoriasis (58). These include systemic agents (such as cyclosporine, methotrexate, and apremilast), and biologics (including anti-TNFα, anti-IL12/23s, anti-IL17s, and anti-IL23s) (58) (Figure 2).

Treatment with cyclosporine has not been associated with reduction in CV events (59). In fact, intermediate to long-term use of cyclosporine has been associated with a number of adverse side effects, including renal dysfunction, hypertension, and hyperlipidemia (60). When compared to cyclosporine, methotrexate was associated with reduction in CRP and CV events in observational studies of psoriasis and rheumatoid arthritis (61, 62). These results were not observed in a recent randomized controlled trial CIRT (Cardiovascular Inflammation Reduction Trial) comparing the effects of methotrexate with placebo on prospective CV events in patients with established coronary artery disease. This trial was neutral compared to CANTOS. However, the baseline populations included in these trials were different in that CANTOS recruited based on hs-CRP and CIRT on the basis of metabolic syndrome. Median hs-CRP at baseline in CANTOS was 4.20 mg/L and in CIRT was 1.60 mg/L suggesting that the CIRT population was not as inflamed on the IL-6/hs-CRP axis as in CANTOS (63).

Anti-TNFα therapy has shown both positive and negative effects on cardiometabolic risk in psoriasis. A large observational study associated anti-TNFα therapy with a 50% reduction in myocardial infarction risk compared to risk with treatment with topical agents (64). Furthermore, patients receiving anti-TNFα therapy have shown a reduction in hs-CRP at 24-week follow-up (65). However, incidence of new-onset diabetes has been observed along with documented worsening of BMI and lipid profiles (66). Treating psoriasis with anti-TNFα therapy in an observational study reduced vascular inflammation by positron emission tomography by ~6–8%, similar to the effect of a low-dose statin on vascular inflammation (Figure 2, Panel I). Anti-TNFα therapy reduced intima media thickness by carotid Doppler ultrasound and the development of coronary artery disease by coronary artery calcium score in observational studies (38, 46, 67). Similarly, echocardiographic data

demonstrated improvement of myocardial function in a small sample of psoriatic subjects treated with anti-TNFα therapy (68). Treatment with anti-TNFα therapy has been associated with stabilization of coronary burden over time and reduction in fibrofatty coronary burden by CCTA (69). Additionally, there was a decrease in peri-coronary inflammation, as assessed by perivascular fat attenuation index, associated with anti-TNFα therapy (70).

Randomized controlled trials (RCTs) of anti-TNFα therapy in patients with severe psoriasis have differed from observational evidence. In a large RCT, adalimumab, a TNFα inhibitor, did not reduce aortic vascular inflammation compared to placebo (71), and there was an increase in carotid vascular inflammation by 18F-FDG PET/CT after 52 weeks of treatment with adalimumab. Another study demonstrated anti-TNFα therapy might not have beneficial effects on aortic vascular inflammation when compared to placebo (72). The placebo group had improved vascular inflammation at 12 weeks, which may be because aortic vascular inflammation is subject to modulation by subtle lifestyle changes. Second, when compared to an observational study that demonstrated beneficial effects with anti-TNFα therapy (38), the study populations in the RCTs were younger with a paucity of CV risk factors (71, 72). Third, anti-TNFα therapy did not have a beneficial effect on vascular inflammation when compared to placebo in psoriasis, but there was a reduction in inflammatory CV disease markers such as GlycA and TNFα, suggesting perhaps longer duration and other vascular beds may be impacted (72). Moreover, vascular inflammation usually precedes the development of atherosclerotic plaque but is usually not high in areas of co-existing atherosclerotic plaque. Therefore, it is possible that vascular inflammation by PET does not capture similar effects observed in the coronary arteries, and ongoing studies over time are needed to better understand vascular inflammation by PET in the context of presence or absence of atherosclerotic plaque (21). Future studies evaluating major adverse cardiovascular events are needed to discern the effects of anti-TNFα therapy on vascular disease.

More recent biologics such as an IL12/23 inhibitor, ustekinumab, have been shown to have effects on coronary and myocardial function in psoriasis patients (73). Following treatment with IL-12/23, vascular inflammation was reduced at 12 weeks. These findings however did not persist at 52 weeks compared to placebo (70) but provide early evidence that selectively blocking the IL-23 pathway may be beneficial.

Additionally, anti-IL17 therapy carries great interest in psoriasis given the immense success it has on reducing psoriasis disease severity (74). Recent pre-clinical, murine studies in psoriasis have shown anti-IL17 therapy has positive effects on peripheral oxidative stress levels, pro-inflammatory cytokines, and vascular inflammation (75). However, in humans, anti-IL17 therapy was not associated with improvement in endothelial function at 1-year (76). Additionally, a randomized controlled trial of secukinumab, an anti-IL17 therapeutic agent, demonstrated no reduction in aortic vascular inflammation (data not published) when compared to placebo. By contrast, when coronary artery disease was evaluated, observational studies found that therapy with anti-IL12/23 and anti-IL17 was associated with a reduction of coronary artery disease indices (Figure 2, Panels II and III) when compared to non-biologic therapy over one year (69, 70). Whether inflammation is an independent risk factor in cardiovascular disease was answered in a recent, large, non-psoriasis RCT, the

CANTOS trial. In this study, 10,061 patients with a history of MI and with a high inflammatory burden as measured by hs-CRP>2mg/L were treated with the IL1β inhibitor, canakinumab, for 48 months (9). There was a dose-dependent reduction in hs-CRP and a reduction in second myocardial event rate with canakinumab compared to placebo, suggesting modulation of residual inflammation leading to a reduction in cardiovascular diseases (9). Randomized control trials of biologic therapies are needed in psoriasis especially since observational studies have shown that treating inflammation is associated with improvement in coronary burden in psoriasis independent of traditional risk factors (69).

## Conclusion

Chronic inflammatory diseases such as psoriasis are associated with increased and accelerated cardiometabolic events, potentially through elevated systemic inflammation, lipoprotein dysfunction, and metabolic dysregulation. Moreover, treatment of psoriasis, especially when severe, has been associated with favorable effects on cardiometabolic dysfunction. Continued follow-up and evaluation of treatment effects on this disease state will inform pathways important both in psoriasis and in the understanding of inflammatory induced cardiometabolic disease.

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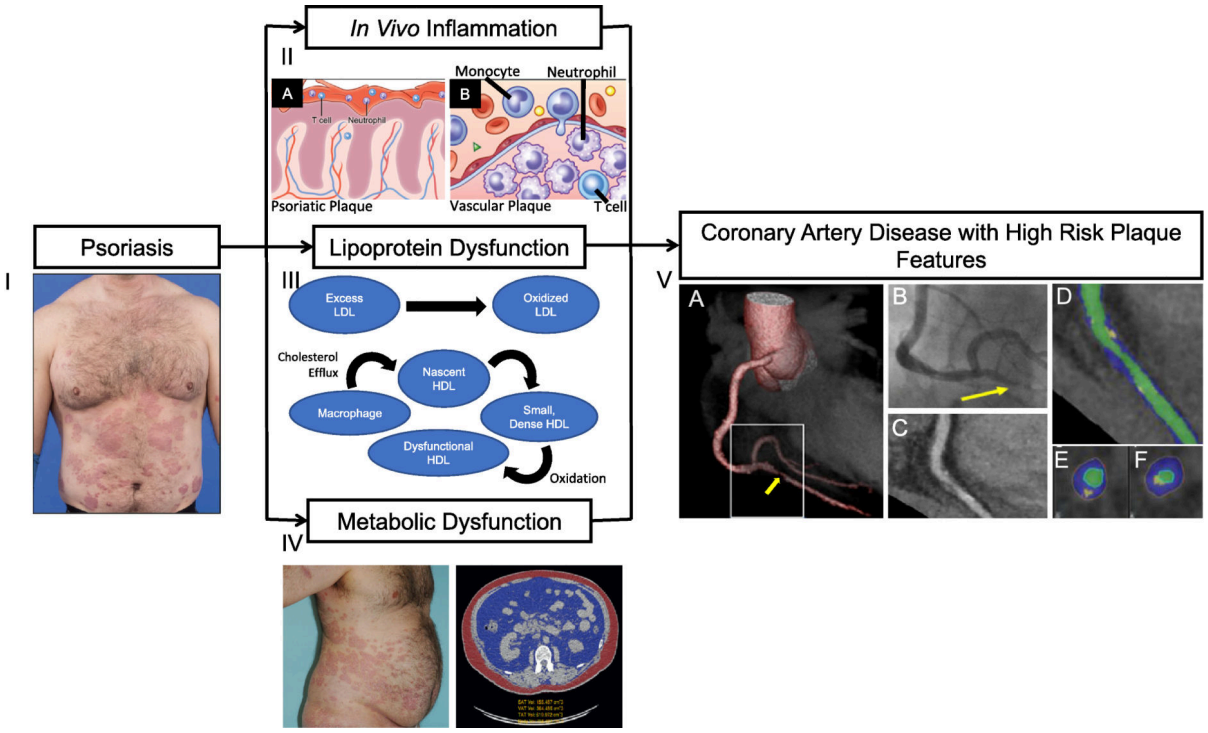


**Figure 1:**

Psoriasis is a chronic inflammatory skin disease associated with cardiometabolic disease. **(I)** Psoriasis patients may develop thick, extensive cutaneous plaques. **(II)** Psoriasis exhibits infiltration of T cells and neutrophils in (A) the cutaneous plaque as well as high systemic inflammation where the (B) vessel wall is infiltrated through a complex interplay of pro-inflammatory cellular components including T cells, monocytes, and neutrophils, leading to atherosclerotic cardiovascular disease. **(III)** Psoriasis associates with abnormal lipid profile and impaired HDL function, which in combination with residual inflammatory stress accelerates the formation of oxidation-modified lipoproteins, such as oxidized LDL and oxidized HDL. **(IV)** Transverse computed tomography (CT) images of an obese patient with psoriasis at the level of the abdominal aorta depicting high visceral adiposity (blue) in comparison with subcutaneous adiposity (red). Psoriasis and concomitant cardiometabolic disease are associated with high body mass index and waist-to-hip ratio. **(V)** CT 3D reconstruction model of a heart (A) depicting critical stenosis (B) due to a high-risk plaque, which was subsequently found to be a culprit for an ST-elevation myocardial infarction during follow-up. (C) Planar reconstruction of vessel demonstrating high-risk plaque. (D) Color-coded, curved multiplanar reconstruction (green, vessel lumen; blue, non-calcified plaque component; yellow, calcified plaque component). (E) and (F) Cross-sectional images. The plaque is only partially calcified, showing spotty calcification and some positive remodeling.

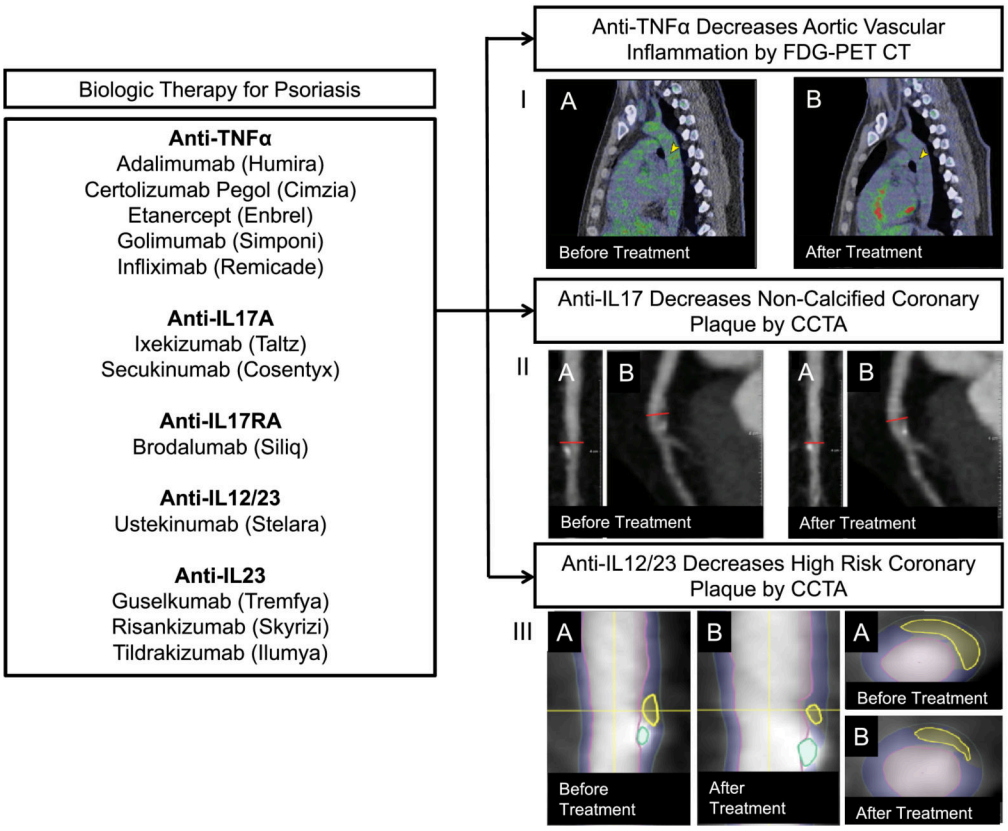


**Figure 2:**

Anti-inflammatory biologic therapy for psoriasis reduces subclinical vascular disease. **(I)** The images show a sagittal section at the level of the mid-aorta at baseline (A) and 1 year of biologic psoriasis treatment (B). Green represents 18-fluorodeoxyglucose tracer uptake in the aorta, which is higher at baseline compared with 1 year later (yellow arrowheads). **(II)** Left anterior descending artery plaque identified before (left) and after (right) biologic therapy for psoriasis (Medis QAngio, Netherlands). (A) Longitudinal planar and (B) curved planar reformat showing reduction of coronary plaque after biologic treatment for psoriasis. **(III, left)** Longitudinal planar view with color overlap displaying reduction in high-risk coronary plaque characteristics (vascuCAP, Elucid Bioimaging, USA). Yellow horizontal line indicates the cross-sectional view in image; (A) is before and (B) is after biologic treatment. **(III, right)** Representative cross-sectional view with color-overlap displaying plaque characteristics (A) before and (B) after biologic therapy for psoriasis.