Spotlight

Autoimmune diseases and cardiovascular risk

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There are more than 80 different autoimmune diseases which collectively affect 4–8% of the world's population. In a recent study published in *Lancet*, Conrad *et al.* found that 19 autoimmune diseases are associated with a composite of cardiovascular disease (CVD). Inflammation promotes atherosclerotic CVD with psoriasis and rheumatoid arthritis recognized as CVD risk enhancers. New strategies are needed to identify and mitigate the impact of chronic inflammation on CVD-related morbidity and mortality.

Chronic inflammation, assessed by circulating biomarkers including high-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6), is a risk factor for major adverse cardiovascular (CV) events (MACE) and mortality [1]. Mechanistic studies linking type 1 T helper cell (Th1)-mediated inflammation to atherosclerosis have motivated a series of epidemiological and translational studies of chronic inflammatory diseases over the past two decades to determine their impact on the risk of atherosclerotic CVD. These inflammatory diseases are highly variable in terms of their immune pathophysiology (i.e., predominantly Th1-, Th2-, or Th17-mediated) and target organ (i.e., joints, bowels, lungs, skin, etc.), and have yielded positive as well as null associations with CVD. There is a strong consensus that, of >80 autoimmune diseases, both psoriasis and rheumatoid arthritis are CV risk enhancers as defined by American Heart Association (AHA)/American College of Cardiology (ACC) guidelines [1].

In this context, a recent study in *Lancet* from Conrad *et al.* [2] sought to extend our knowledge of inflammation and CVD by examining 446 449 patients with at least one of 19 autoimmune conditions of varying pathophysiology and target organ [Addison's disease, ankylosing spondylitis, celiac disease, type 1 diabetes, Graves' disease, Hashimoto's thyroiditis, inflammatory bowel disease (IBD), multiple sclerosis, myasthenia gravis, pernicious anemia, polymyalgia rheumatica, primary biliary cirrhosis, psoriasis, rheumatoid arthritis (RA), Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, vasculitis, and vitiligo]. The patients were identified through electronic medical records systems in the UK and followed longitudinally for ~6 years. The CV outcomes studied were diverse in their pathophysiology and included a composite of aortic aneurysm, atrial fibrillation, atrial flutter, supraventricular arrhythmia, conduction system disease, heart failure, ischemic heart disease, non-infectious myocarditis or pericarditis, peripheral arterial disease, infective endocarditis, stroke or transient ischemic attack, valve disorder, and venous thromboembolism or pulmonary embolism.

Compared to a cohort of 2 102 830 people without these autoimmune diseases matched for demographic characteristics, Conrad *et al.* found a higher risk of CVD with a hazard ratio (HR) of 1.56 (1.52–1.59) in autoimmune patients, and an HR 1.40 (1.37–1.44) when adjusted for blood pressure, smoking, body mass index, cholesterol, and type 2 diabetes. Importantly, and as previously described, the relative risks were highest in younger individuals with autoimmune conditions, indicating a pattern of accelerated CVD [3]. However, patients and clinicians must recognize that the absolute risk of CV events attributable to an immune disease increases dramatically with age, and thus the clinical significance of these relationships only becomes more pressing in older individuals (Figure 1).

Conrad *et al.* found an increased risk of CVD for all 19 autoimmune diseases studied. The results confirmed well-accepted associations of psoriasis and rheumatoid arthritis with CVD, and newly identified Hashimoto's thyroiditis, myasthenia gravis, pernicious anemia, Graves' disease, and vitiligo as also conferring CV risk. However, for several of the autoimmune diseases evaluated (primary biliary cirrhosis [4], celiac disease [5], and IBD [6]), the results contrast to earlier studies using the same or similar databases, which observed no or minimally increased CV risk when hard atherosclerotic CV endpoints [myocardial infarction (MI) or stroke] were evaluated. Furthermore, the estimate found by Conrad *et al.* was attenuated when the analysis was limited to hard CV endpoints, suggesting that the findings may be due in part to observation bias and may be further attenuated when one considers the presence of incompletely measured confounders.

There is a crucial need to develop treatments that target inflammation and reduce CVD risk. It is estimated that 30% of patients with coronary disease have residual inflammatory risk (i.e., hsCRP ≥2 mg/l) despite optimal management of their traditional CV risk factors [7]. Trials of anti-inflammatory therapy for atherosclerosis have left more questions than answers about how to mitigate inflammation as a risk factor for CVD [8]. Canakinumab (a biologic targeting IL-1β) lowered CV risk in patients with a history of MI but also increased mortality from infection. In contrast to observational studies of patients with RA or psoriasis, methotrexate failed to lower CV risk in patients with previous MI or multivessel coronary disease who had type 2 diabetes or metabolic syndrome. Finally, trials of colchicine in patients with coronary disease have yielded generally favorable results, although some suggested a risk of serious infection.

Randomized placebo-controlled trials of more targeted and well-tolerated immune-modulating treatments in psoriasis patients
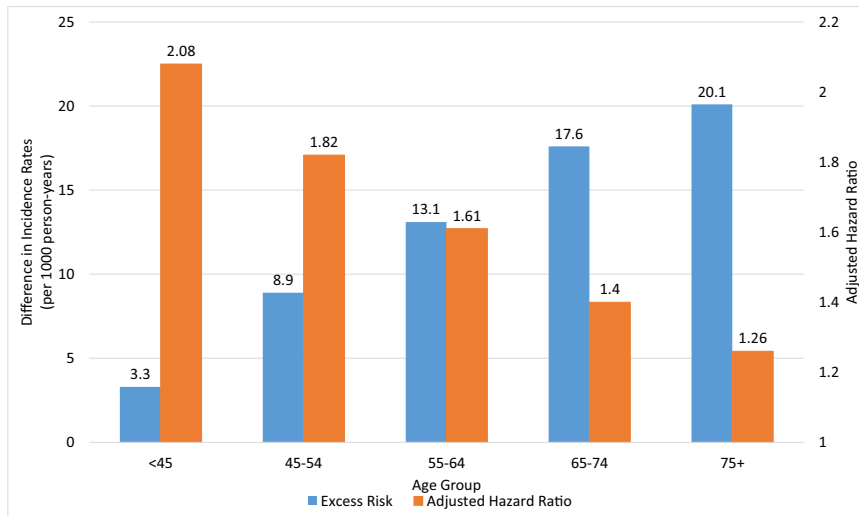
Figure 1. Excess risk and hazard ratio of cardiovascular (CV) outcomes in the autoimmune cohort compared to the matched control cohort by age group, as reported by Conrad et al. [2]. Hazard ratios reported are adjusted for CV risk factors.

have identified potential CV benefits of adalimumab [a tumor necrosis factor (TNF) inhibitor that lowered IL-6, hsCRP, and glycoprotein acetylation (GlycA)], ustekinumab (an IL-12 and IL-23 inhibitor that reduced aortic vascular inflammation), and UV-B phototherapy [lowered IL-6 and hsCRP, and increased high-density lipoprotein particles (HDL-P)], whereas neutral effects on CV pathways were observed for secukinumab (an IL-17 inhibitor) [9]. A recent study of apremilast, a pill that blocks phosphodiesterase 4 (PDE4), demonstrated a reduction in visceral adiposity, IL-1β levels, and metabolomics related to cardiometabolic disease, accompanied by an increase in apolipoprotein A-1 but a reduction in cholesterol efflux [10]. Immune-targeted treatments can have paradoxical effects, and therefore rigorous and event-driven trials in patients at high risk of MACE will be necessary before they can be routinely recommended for primary or secondary prevention of CVD. For example, JAK inhibitors potently reduce hsCRP but can increase the risk of both venous and atherothrombotic events [11].

While the race is on to prove that immune targeted treatments can safely and effectively reduce CV risk, it is incumbent upon clinicians to optimize identification and management of well-established CV risk factors in patients with inflammatory disease. There is a large evidence-to-practice gap in the identification and management of CV risk factors in patients with inflammatory diseases. For example, in psoriasis, statins are severely underutilized; as skin severity assessed by their general practitioner increases, so too does the likelihood that their hypertension will be inadequately controlled [12].

In future work it will be important to confirm the association of a variety of individual autoimmune diseases specifically with atherosclerotic CVD, including estimates of how autoimmune disease severity impacts on these risks, as has been done for psoriasis and rheumatoid arthritis. New strategies to optimally identify and treat traditional CV risk factors are needed, including the earlier use of statins [13] in patients with systemic inflammatory disease, and it will be essential to determine which immune-targeted therapies lower the risk of MACE without increasing the risk of serious infections.

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References

1. Grundy, S.M. *et al.* (2019) 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* 73, e285–e350
2. Conrad, N. *et al.* (2022) Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK. *Lancet* 400, 733–743
3. Gelfand, J.M. *et al.* (2006) Risk of myocardial infarction in patients with psoriasis. *JAMA* 296, 1735–1741
4. Solaymani-Dodaran, M. *et al.* (2008) Risk of cardiovascular and cerebrovascular events in primary biliary cirrhosis: a population-based cohort study. *Am. J. Gastroenterol.* 103, 2784–2788
5. West, J. *et al.* (2004) Risk of vascular disease in adults with diagnosed coeliac disease: a population-based study. *Aliment. Pharmacol. Ther.* 20, 73–79
6. Dregan, A. *et al.* (2014) Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. *Circulation* 130, 837–844
7. Ridker, P.M. (2017) How common is residual inflammatory risk? *Circ. Res.* 120, 617–619
8. Samuel, M. and Tardif, J.C. (2021) Lessons learned from large cardiovascular outcome trials targeting inflammation in cardiovascular disease (CANTOS, CIRT, COLCOT and LoDoCo2). *Futur. Cardiol.* 17, 411–414
9. González-Cantero, A. *et al.* (2021) Impact of biological agents on imaging and biomarkers of cardiovascular

disease in patients with psoriasis: a systematic review and meta-analysis of randomized placebo-controlled trials. *J. Invest. Dermatol.* 141, 2402–2411

10. Gelfand, J.M. *et al.* (2022) Association of apremilast with vascular inflammation and cardiometabolic function in patients with psoriasis: the VIP-A Phase 4, open-label, nonrandomized clinical trial. *JAMA Dermatol.* Published online September 21, 2022. https://doi.org/10.1001/jamadermatol.2022.3862

11. Ytterberg, S.R. *et al.* (2022) Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N. Engl. J. Med.* 386, 316–326

12. Takeshita, J. *et al.* (2015) Effect of psoriasis severity on hypertension control: a population-based study in the United Kingdom. *JAMA Dermatol.* 151, 161–169

13. Garshick, M.S. *et al.* (2022) A randomized open-label clinical trial of lipid-lowering therapy in psoriasis to reduce vascular endothelial inflammation. *J. Invest. Dermatol.* 142, 1749–1752