Lipids are optimized, but CAD persists. Is inflammation the real enemy?

Written by The Life Science Feed Editorial Team · Published 23 July 2026 · Edited by Mara Voss

> Coronary artery disease remains a leading cause of morbidity and mortality across Europe, despite advances in lipid management and revascularisation. The persistent residual risk in many patients has long pointed to mechanisms beyond traditional risk factors. Inflammation, once a theoretical contributor, now stands as a central, actionable target.

KEY TAKEAWAYS

- The Pivot: Inflammation is no longer a secondary consideration in CAD; it is a primary therapeutic target, with low-dose colchicine demonstrating clear benefits.
- The Data: Low-dose colchicine reduced major adverse cardiovascular events (MACE) by 31% (HR 0.69; 95% CI, 0.57-0.83; P=.0001) in patients with established CAD.
- The Action: Consider low-dose colchicine for patients with stable atherosclerotic cardiovascular disease, particularly those with persistent inflammatory markers, and screen for social isolation.

For decades, clinicians focused on lipids, blood pressure, and glucose control to manage coronary artery disease (CAD). But a significant proportion of patients, even those achieving guideline-recommended targets, still experience recurrent cardiovascular events. This persistent risk has driven a renewed focus on inflammation, a long-suspected but historically difficult-to-target pathway in atherosclerosis. Recent evidence solidifies inflammation's role, not just as a marker, but as a driver of disease progression.1,2,3

The understanding of inflammation's role in CAD has evolved significantly. Early observations noted elevated C-reactive protein (CRP) in patients with acute coronary syndromes, but the question remained: was it a bystander or an active participant? Now, the evidence points to a direct causal link, with inflammatory processes contributing to plaque initiation, progression, and rupture. This shift in understanding has opened the door for inflammation-targeted pharmacotherapy, moving beyond the traditional lipid-lowering and antiplatelet strategies.3

The return of inflammation-targeted pharmacotherapy

Low-dose colchicine has emerged as a key player in this re-evaluation of inflammation in CAD. Ali and Siraj, writing in Expert Opinion on Pharmacotherapy in 2026, reviewed the evidence for colchicine, highlighting its mechanism of action in inhibiting neutrophil activation and inflammasome pathways.3 This anti-inflammatory effect, distinct from its anti-gout properties, directly addresses the inflammatory component of atherosclerosis. Colchicine, an old drug, has found a new purpose in cardiology.3

Clinical trials have demonstrated the efficacy of low-dose colchicine in reducing cardiovascular events. In patients

with stable atherosclerotic cardiovascular disease, colchicine 0.5 mg once daily reduced the risk of major adverse cardiovascular events (MACE) by 31% (HR 0.69; 95% CI, 0.57-0.83; P=.0001). This included a significant reduction in myocardial infarction and ischaemic stroke. The drug was generally well-tolerated, with gastrointestinal side effects being the most common, though typically mild and transient.3

The mechanism behind colchicine's benefit is its ability to interfere with the inflammatory cascade at multiple points. It inhibits microtubule polymerisation, which in turn impairs neutrophil chemotaxis, adhesion, and activation. Colchicine also suppresses the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, a key component in the innate immune response that drives the production of pro-inflammatory cytokines like IL-1²and IL-18. These cytokines play a critical role in atherosclerotic plaque development and instability.3

The re-emergence of colchicine signals a broader acceptance of inflammation as a direct therapeutic target in CAD. This is not merely about reducing a biomarker; it is about interrupting a fundamental pathological process. The evidence is clear: targeting inflammation directly improves patient outcomes.3

Beyond traditional risk factors: social isolation and novel biomarkers

But inflammation is not a standalone phenomenon. Emerging research points to broader systemic influences, including social factors, that contribute to the inflammatory burden and subsequent cardiovascular risk. Li and Xia, in a 2026 review in Current Atherosclerosis Reports, detailed the link between social isolation, loneliness, and subclinical atherosclerosis.1 These adverse social experiences are not just psychological stressors; they translate into measurable biological changes that drive cardiovascular disease.

The mechanisms linking social isolation to atherosclerosis are complex, involving neuroendocrine, autonomic, and inflammatory pathways. Chronic social isolation can activate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, leading to increased cortisol and catecholamine levels. These hormonal changes, in turn, promote systemic inflammation, endothelial dysfunction, and increased arterial stiffness. Socially isolated individuals often exhibit higher levels of pro-inflammatory cytokines, such as IL-6 and TNF-±which directly contribute to atherosclerotic plaque progression.1

The impact of social isolation extends to vascular health. It correlates with increased arterial stiffness and vascular calcification, both markers of advanced atherosclerosis. Katz, Cvejkus, and Wang, writing in the International Journal of Hypertension in 2026, identified novel protein biomarkers associated with arterial stiffness and vascular calcification.2 While their study primarily focused on identifying these biomarkers, the broader context of their work aligns with the understanding that systemic factors, including social ones, influence these vascular measures. The proteins identified could serve as future targets or diagnostic tools for early detection of vascular damage.2

The implication for clinicians is clear: a patient's social environment is a legitimate part of their cardiovascular risk profile. Screening for loneliness and social isolation, though not yet standard practice, may become as important as assessing other lifestyle factors. The biological pathways are now sufficiently understood to warrant this consideration.1

What the evidence means for practice

The evidence for low-dose colchicine in established CAD is compelling. Its efficacy in reducing MACE, coupled with a manageable safety profile, positions it as a valuable addition to the therapeutic armamentarium. Clinicians should consider its use in patients with stable atherosclerotic cardiovascular disease, particularly those who continue to have

elevated inflammatory markers despite optimal lipid and blood pressure control. The drug offers a direct attack on the inflammatory component of the disease, addressing a residual risk that other therapies often miss.3

But the conversation around inflammation and CAD extends beyond pharmacotherapy. The recognition of social isolation and loneliness as significant cardiovascular risk factors demands a more holistic approach to patient care. These are not merely psychosocial issues; they are biological determinants of health, driving inflammation and vascular damage. Addressing these factors, through social prescribing or community interventions, could complement pharmacological strategies in reducing cardiovascular burden.1

The open-label design of some earlier colchicine trials is an obvious caveat, but the consistent benefit across multiple studies strengthens the overall evidence base. The trial was not powered to detect differences in specific inflammatory biomarker subgroups, and that gap matters for precision medicine. Future research needs to identify which patients benefit most from anti-inflammatory therapy, moving beyond a blanket approach.3

The evidence is clear: targeting inflammation directly improves patient outcomes.Ali S, Expert Opinion Pharmacotherapy 2026The integration of novel protein biomarkers, as identified by Katz and colleagues, could eventually refine risk stratification and guide treatment decisions. These biomarkers might help identify individuals at higher risk of arterial stiffness and vascular calcification, allowing for earlier intervention. For now, the focus remains on established risk factors and proven therapies, but the pipeline for more precise diagnostics is active.2 For a comprehensive guide to modern cardiological practice, the Oxford Handbook of Cardiology remains an essential reference.

The next trial needs to show whether anti-inflammatory therapies can prevent the initial development of atherosclerosis in high-risk but asymptomatic individuals, not just reduce events in those with established disease. That would represent a true shift in primary prevention.

CLINICAL IMPLICATIONS

The message for clinicians is unequivocal: inflammation is a legitimate, actionable target in coronary artery disease. Low-dose colchicine is not a 'nice to have' but a therapy with demonstrated efficacy in reducing major adverse cardiovascular events. GPs and specialists should integrate it into their management algorithms for patients with stable atherosclerotic disease, especially those with residual inflammatory risk. This is not about chasing biomarkers; it is about preventing heart attacks and strokes.

But the implications extend beyond prescribing a pill. The data on social isolation and loneliness as drivers of subclinical atherosclerosis forces a re-evaluation of how we assess cardiovascular risk. We cannot ignore the profound biological impact of a patient's social environment. Asking about social connections, and considering social prescribing, should become as routine as checking blood pressure. This is a public health issue with direct clinical consequences.

The industry, particularly pharmaceutical companies, will undoubtedly explore further anti-inflammatory agents. But the success of colchicine, an inexpensive generic, highlights that innovation does not always mean novel molecules. It means understanding disease mechanisms and applying existing tools effectively. The challenge now is to identify which patients will benefit most from these therapies, moving towards a more personalised approach to inflammation management.

For patients, these developments offer hope beyond traditional risk factor control. It means that even with optimal statin and antihypertensive therapy, there is another avenue to reduce their risk. It also underscores

> the importance of social connection, turning a quality-of-life issue into a direct contributor to cardiovascular health. Clinicians must communicate this holistic view, empowering patients to address both their biological and social determinants of health.

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