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Editorial: Role of colchicine in atherosclerosis

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Editorial on the Research Topic Role of colchicine in atherosclerosis

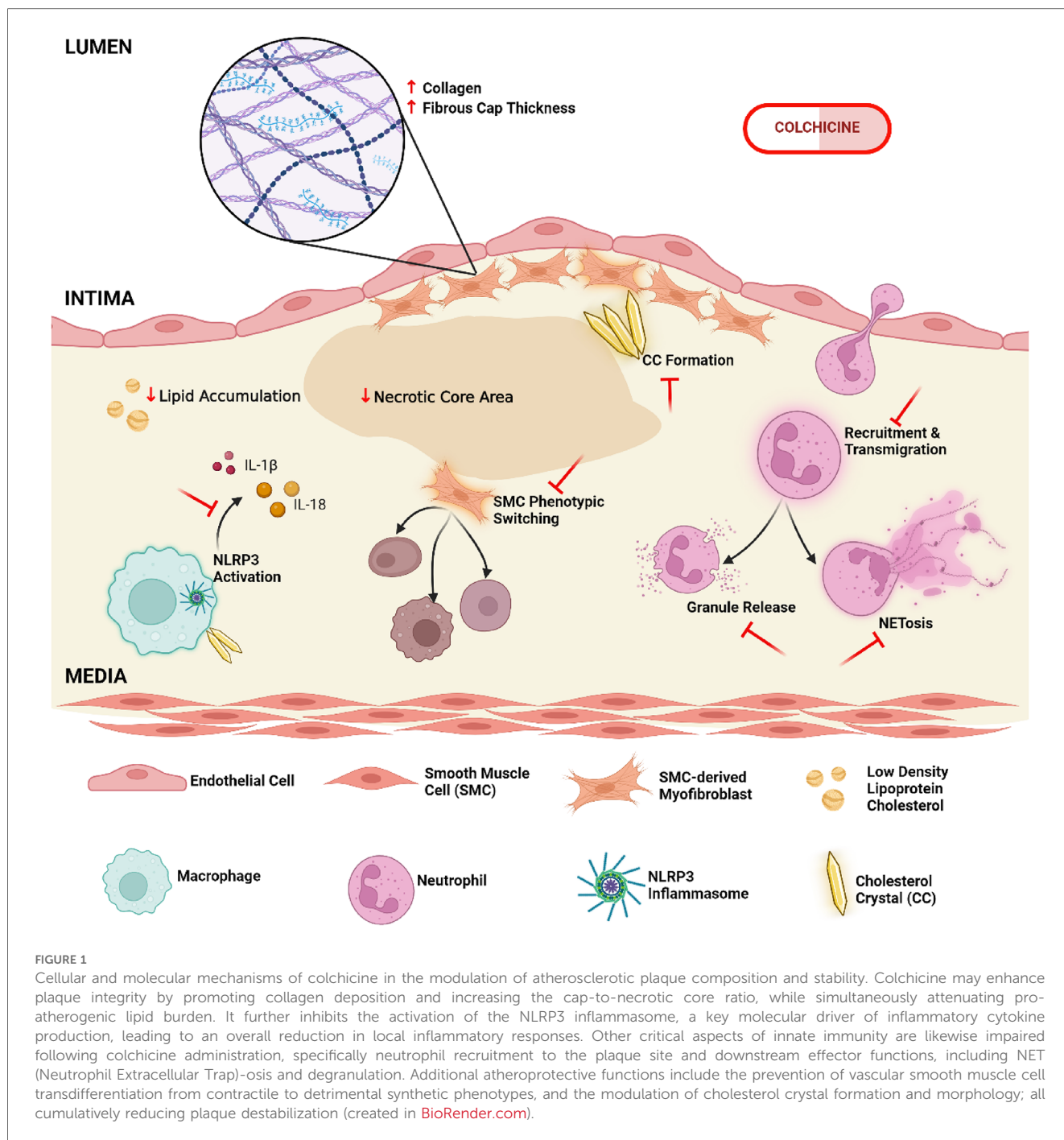
Colchicine, an ancient drug with a well-established safety record, that is now approved for secondary prevention of atherosclerosis based upon its proven efficacy and safety.

Atherosclerosis evolves due to the accumulation of cholesterol and inflammatory cells in the artery wall, resulting in the development of vessel-occluding plaques that can lead to chronic ischemia and risk of life-threatening cardiovascular complications, including stroke and myocardial infarction (MI) due to acute plaque rupture (1). Although commonly viewed as a condition driven predominantly by cholesterol, it has been known for over 160 years to also be driven by an inflammatory response to cholesterol that has recently been demonstrated to occur as it forms into crystals in the arterial wall. Thus, despite use of potent cholesterol-lowering agents, patients face a substantial life-time risk of recurring major adverse cardiovascular events (MACE) (2–4) due to failure to adequately dampen the inflammatory process.

Over the last decade landmark clinical trials, such as CANTOS (5), COLCOT (6) and LoDoCo2 (7), have provided strong evidence that dampening inflammation leads to better clinical outcomes in patients with atherosclerotic cardiovascular disease. Despite the effectiveness of canakinumab demonstrated in CANTOS (5), low-dose colchicine (0.5 mg daily) is currently the only FDA approved anti-inflammatory agent available for clinical use in patients with established coronary disease.

In a recent meta-analysis Zhou et al. of five large, long-term randomised trials that included >14,000 patients, it was found that long-term use of low-dose colchicine decreased both MACE and its individual components of MI, stroke and need for revascularisation in patients with established atherosclerosis. However, while it is known that colchicine has broad anti-inflammatory effects, the exact mechanisms by which it confers cardiovascular protection is still the subject of ongoing research (Figure 1).

In their review article Bulnes et al. published in this special issue on colchicine in cardiovascular disease, Bulnes and co-workers elaborate on the converging evidence from both animal and clinical studies that show the suppressive effect of colchicine upon the NLRP3 inflammasome, a protein complex that, when activated in inflammatory cells, promotes the production of potent inflammatory, pro-atherosclerotic cytokines, namely interleukin (IL)-1 β and IL-18. Cholesterol crystals, which form in the artery wall as the



consequence of cholesterol accumulation in plaque, are one such triggering agent for NLRP3 activation.

In their research paper, [Abideen et al.](#) detail an inverse relationship between the dose of colchicine used and the formation and expansion of cholesterol crystals *in vitro*, potentially elucidating the drug's indirect effects on inhibiting NLRP3 activation. This is important as there is striking evidence that the accumulation of cholesterol crystal in atherosclerotic plaque can lead to acute plaque rupture (8, 9). *In vitro* assays of rat and rabbit biological membranes viewed using scanning electron microscopy (SEM) showed that cholesterol crystals were

able to distort and protrude through the tissue using their sharp geometric edges (8). This was similarly noted in *ex vivo* findings from human arterial tissues and plaques, prepared using vacuum dehydration for SEM, detecting cholesterol crystals disrupting the plaque and penetrating the intimal surface (8, 9).

[Abideen et al.](#) provide a novel mechanism by which colchicine may reduce the risk of acute plaque rupture, by showing that it can also slow the rate of cholesterol crystal formation and alter its morphology. Post-drug treatment, SEM of both *in vitro* samples and *ex vivo* samples of human carotid atherosclerotic plaques showed evidence of morphological changes in cholesterol crystals

relating to the loss of their sharp edges which, as mentioned, can directly perforate the plaque and trigger atherothrombosis. It remains to be seen if these findings can be replicated *in vivo*.

One of the most recognised actions of colchicine on inflammation, is its inhibitory effect on neutrophil function. However, it is also well-documented to affect the properties of macrophages, endothelium and smooth muscle cells, and dampen the interaction between neutrophils and platelets, which may mitigate against plaque growth, improve plaque stability and reduce the risk of thrombotic occlusion (10, 11). These atheroprotective effects have been exhibited in a mouse model of unstable carotid plaques induced by tandem stenosis surgery, where colchicine was shown to decrease lesion size and necrotic core area, along with increasing collagen and the cap-to-necrotic ratio (10). Interestingly, it has also been recently identified to modulate the transition of detrimental smooth muscle cell phenotypes (11).

Tubulin binding, and subsequent disruption of microtubulin formation, prevents the recruitment and invasion of neutrophils into plaques by disrupting their motility and expression of adhesion molecules. Colchicine further suppresses the formation of neutrophil extracellular traps (NETs): web-like structures released upon neutrophil activation that enhance platelet aggregations and potent cytokine release within the plaque microenvironment (10, 12). A 2021 study by Vaidya et al., showed that colchicine was able to restore cytoskeletal dynamics, and prevent NET formation, in neutrophils of acute coronary syndrome patients post-percutaneous coronary intervention (12). Based on this evidence, Bulnes and colleagues suggest that early administration of colchicine may also modulate initial tissue-damaging responses to ischaemic and reperfusion injury in the setting of acute MI, by preventing detrimental recruitment and activation of innate immune cells.

In another paper in this series, Mohammadnia et al. report on a *post hoc* analysis of the effect of colchicine in patients with diabetes from the LoDoCo2 trial. They identified that colchicine resulted in similar reductions in the rate of MACE in people with stable coronary artery disease, irrespective of diabetes status. They also explored whether colchicine might influence the onset of new diabetes and provided weak evidence that it may be protective, which requires further investigation. Indeed, larger prospective trials designed to assess the effect of colchicine specifically in patients with diabetes or on the incidence of new onset diabetes have yet to be seen. Apart from monitoring changes in diabetic treatment and glycaemic control, these studies would need to account for other variables influencing inflammation such as body mass index and diet.

It is recognised that even at low dose, colchicine can cause gastrointestinal symptoms including diarrhea and nausea, however these are typically mild and self-limiting. More importantly, physicians need to be aware that in patients with advanced renal disease or liver failure there is an increased potential for adverse drug interactions, most especially with clarithromycin, cyclosporin and some anti-fungal and anti-viral

agents. Those issues aside, low-dose colchicine is safe, as it does not affect renal or liver function, and there have been no reports of drug-drug interactions with other cardiovascular medications, including all forms of statins even when used at high dose (13).

Thus, based upon updated cardiovascular guidelines throughout the world, low-dose colchicine should be considered in patients with high risk of future cardiovascular events based upon a history of MI, stroke or prior revascularisation, as well as those with high coronary calcium scores (14).

Clearly, we have entered a new and exciting era of cardiovascular management in which anti-inflammatory therapy will contribute to the care of patients with ASCVD. Going forward, ongoing and future studies will help determine if there is also a role for newer anti-inflammatory agents with more pathway-targeted actions than colchicine, as these will be needed to treat patients with renal disease in whom colchicine is contraindicated and those who are intolerant to colchicine therapy.

Author contributions

AM: Conceptualization, Writing – original draft. PP: Writing – review & editing. SN: Writing – original draft.

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Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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