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Colchicine in Patients with Stable Coronary Disease: should we consider basal inflammation - and how?

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Editorial

Coronary artery disease (CAD) continues to be the leading cause of death worldwide, despite advancements in management. Inflammation plays a role in atherosclerosis and cardiovascular diseases (CVD), contributing to both the early formation and the later rupture of vulnerable plaques. Consistently, cytokine-targeted treatment approaches have been proven to be a possible way in the management of atherosclerotic disease. The inhibition of interleukin-1 β by canakinumab reduced cardiovascular events by 15% in the CANTOS study (Canakinumab Anti-inflammatory Thrombosis Outcomes Study)¹. However, the use of canakinumab may lead to significant side effects (mainly increased risk of fatal infections), and its high cost hinders widespread clinical application in secondary prevention. Above all, colchicine, a low-cost anti-inflammatory agent widely used for pericarditis, gout, and familial Mediterranean fever, is well-established to inhibit pathways involving IL-1 β , IL-6, and IL-18.

Large international clinical studies have demonstrated that colchicine is associated with significantly fewer non-fatal cardiovascular events in patients with coronary disease compared to placebo.

In the COLCOT trial² (Colchicine Cardiovascular Outcomes Trial), 4,745 patients were randomly assigned to receive colchicine 0.5 mg once daily or placebo within 30 days after a myocardial infarction (MI). A Low-dose colchicine led to a significantly lower risk of the primary efficacy end point (a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization events) when compared to the placebo (hazard ratio 0.77, 95% CI:0.64–0.96). Moreover, earlier initiation (within 3 days) was associated with incremental clinical benefits³. In the LoDoCo-2 trial⁴, 5,522 patients with chronic coronary artery disease were randomized to placebo or colchicine 0.5 mg once daily. The primary endpoint of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia driven coronary revascularization occurred less frequently in the colchicine arm (hazard ratio 0.69, 95% CI 0.57–0.83). Numerous meta-analyses have confirmed these positive impacts.

During last years, both European and American guidelines on CAD integrated colchicine in the medical armamentarium, but with some limitations in some clinical settings or high-risk patients. The latest ESC 2024 guidelines are more favorable with a class IIa, level A in patients with chronic stable CAD, to recommend low-dose colchicine (0.5 mg daily), to reduce myocardial infarction, stroke and need for revascularization⁵, without any restriction to specific clinical profiles. Whether the use of colchicine should be preferable in specific patients remains debatable.

Here, the manuscript entitled « The Effects of Colchicine on Lipoprotein(a) and Oxidized Phospholipid Associated Cardiovascular Disease Risk" is an interesting exploratory subanalysis of the large LoDoCO2 trial⁶. Indeed, the authors are actively seeking patients who could derive greater benefits from the drug and exploring potential clinical settings that might offer more efficient pathways.¹²

This approach is crucial for tailoring more personalized treatment plans and accurately targeting patients to ensure they receive the most appropriate medications. This concept applies not only to colchicine but also to all cardiovascular drugs, as no CV drug has been administered based on a pharmacogenomic approach -or other really personalized plan- until now. Our current management is based on targets (such as statins and LDL targets) and clinical parameters (like blood pressure), but only a few trials have explored more pharmacological or pathophysiological avenues. The best example remains the DalGene trial, which had mixed results⁷.

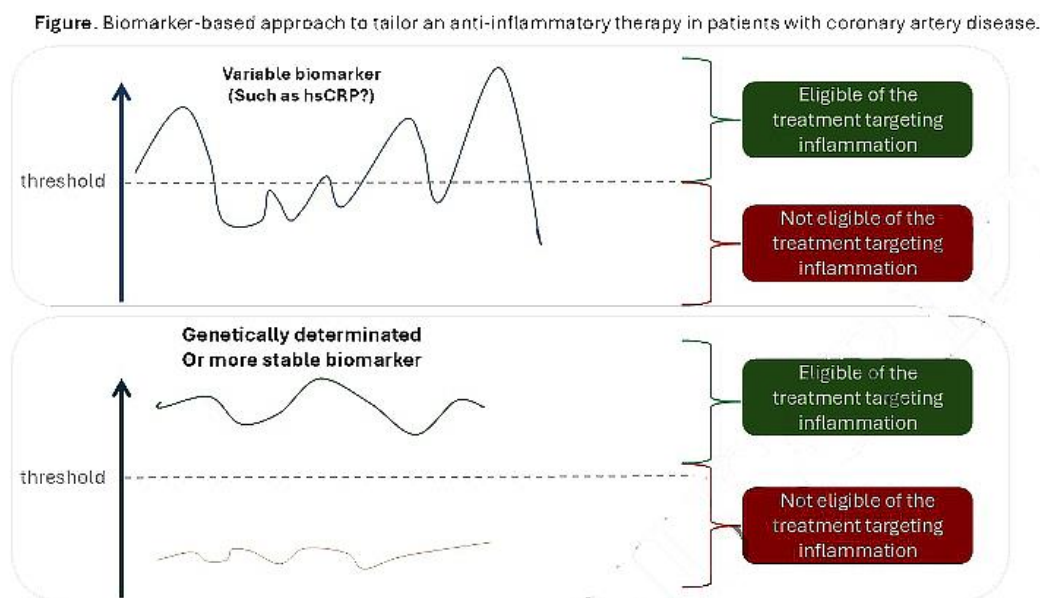
From a practical perspective, if inflammatory processes are involved in CAD, it seems logical to provide anti-inflammatory treatment to all patients, regardless of imperfect biomarkers. However, a more specific approach would require stratifying the 'inflammatory risk' in CAD patients. Stratifying patient risk remains challenging based on traditional parameters, including clinical, biological, and other factors. The LoDoCo2 team, which recently presented results at ESC2024, suggests a consistent impact across different risk levels among various patient groups. Similarly, the Colcot team indicates that all subgroups can benefit from colchicine, with patients with diabetes—a well-known pro-inflammatory condition—potentially drawing even greater benefits⁸.

For this purpose, hs-CRP is increasingly considered a good candidate for risk stratification⁹. This approach is supposed to allow therapeutic decisions based on patients' levels of micro-inflammation to allocate the best treatment. However, this method was not utilized in either the COLCOT or LoDoCo2 trials. One reason might be the variability of hs-CRP (see Figure), which could risk excluding patients who might benefit from the drug. Secondly, basing treatment decisions on a single point of measurement would overlook/underconsider the overall exposure to inflammation (the area under the curve). One limitation of the current work is that hs-CRP is not available to evaluate this hypothesis. Conversely, the authors search for more stable biomarkers and suggest that colchicine may be more effective in subjects with heightened oxidation-driven inflammation. Specifically regarding Lpa, as this biomarker is genetically determined and minimally modified by treatments or aging, such biomarkers are more likely to be helpful in selecting patients who could derive greater benefits (see Figure).

However, the effect is suggested to be indirect, as colchicine appears to have no impact on Lp(a) levels in this study. In brief, this subgroup analysis stratifies patients by Lp(a), oxidized phospholipid of Lp(a) (OxPL-apo(a)), or OxPL-apoB. The effects of colchicine did not significantly differ between high and low levels of Lp(a) or OxPL apo(a). Nevertheless, colchicine had significantly better effects among subjects with elevated OxPL apoB, suggesting that patients with more oxidized lipoprotein-driven inflammation could derive greater benefit from this approach.

In conclusion, colchicine has been well-known for centuries, and clinical experience has demonstrated the safety of its long-term use across a wide range of conditions. The presented results generate hypotheses that are interesting from a mechanistic point of view, as the pleiotropic effects of colchicine still need to be better elucidated. This study suggests one aspect of inflammation, in relation to lipids, which makes clinical sense. Other effects are likely, ranging from impacts on microtubule, molecular trafficking, to modulation of the inflammasome. Recently, innovative pathophysiological impacts have been suggested, such as protection against sympathetic denervation¹⁰. Other unknown pathophysiological impacts are likely, and translational approaches need to be developed, as well as use in clinical practice.

Figure. Biomarker-based approach to tailor an anti-inflammatory therapy in patients with coronary artery disease



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