Review

Colchicine in coronary artery disease: limitations and challenges

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ABSTRACT

Colchicine has emerged as a promising anti-inflammatory option for secondary prevention in coronary artery disease, but its role in routine practice remains uncertain. Evidence from randomised trials suggests a more consistent benefit in chronic coronary syndromes and selected post-myocardial infarction populations. In contrast, results in acute coronary syndromes and PCI-related settings have been less convincing. This review summarises the main limitations and unresolved challenges of colchicine use in coronary artery disease, including heterogeneity across trials, lack of biomarker-guided patient selection, uncertainty regarding timing and duration of therapy, and concerns about tolerability, safety, and drug interactions. Current data suggest that colchicine may be useful in selected patients rather than as a universal treatment strategy. Further studies are needed to define its optimal clinical use better and to support a more personalised anti-inflammatory approach.

Introduction

Inflammation has a central role in atherosclerosis and contributes to future atherothrombotic risk to an extent similar to hyperlipidaemia, underscoring that plaque development and progression are sustained not only by lipid deposition but also by chronic immune-inflammatory activation (1-3).

In patients receiving lipid-lowering drugs, persistent low-grade systemic inflammation, reflected by elevated high-sensitivity C-reactive protein (hsCRP), is one of the strongest predictors of recurrent cardiovascular events, cardiovascular death, and all-cause mortality, a phenomenon referred to as residual inflammatory risk (4). Accordingly, multiple clinical trials have investigated whether anti-inflammatory therapies can reduce cardiovascular events in patients with established coronary artery disease, ranging from early studies with methotrexate and canakinumab to more recent evidence supporting the use of colchicine.

Colchicine is a botanical alkaloid compound, derived from Colchicum Autumnale, used for centuries as an anti-inflammatory in the treatment of gout and other inflammatory disorders (5).

However, its use in routine cardiovascular practice has remained limited, partly due to an incomplete appreciation of residual inflammatory risk in patients with established atherosclerotic disease, but also due to ongoing uncertainties in the literature regarding colchicine's true therapeutic impact on cardiovascular event prevention. Additional limitations include concerns about its tolerability in patients with ischaemic heart disease, lack of consensus on the optimal timing of initiation, and a partially elucidated mechanism of action in this clinical context.

As a result, contemporary guidelines do not currently endorse colchicine in a central role in the routine management of coronary artery disease.

This manuscript aims to review the key limitations and unresolved challenges surrounding the current use of colchicine in atherosclerotic cardiovascular disease.

Colchicine mechanism of action

Colchicine exerts pleiotropic anti-inflammatory and antithrombotic effects by impairing multiple cellular pathways, including mitosis, intracellular trafficking, and phagocytosis. Its core mechanism involves disrupting microtubule dynamics by inhibiting tubulin polymerisation, leading to cytoskeletal disorganisation.

In atherosclerosis, this attenuates plaque-related inflammation by modulating leukocyte activity. In neutrophils, colchicine reduces deformability, transendothelial migration, and oxidative stress (6-7), while in monocytes it decreases proliferation, differentiation, monocyte-platelet aggregation, and platelet activation markers.

Colchicine inhibits NLRP3 inflammasome signalling, a pathway relevant to atherosclerosis in which cholesterol crystals, MSU crystals, and extracellular ATP promote the maturation and release of pro-inflammatory cytokines (8-9). Experimental and clinical data suggest that colchicine suppresses inflammasome activation and reduces IL-1β production, supporting its role in modulating vascular inflammation (10-11).

In addition, colchicine may limit ox-LDL-driven endothelial inflammation and thrombosis by interfering with LOX-1/NF-κB signalling and tissue factor surface expression (12).

Colchicine in coronary artery disease

The CANTOS trial further strengthened the inflammatory hypothesis behind atherosclerosis, the first study to show that targeted anti-inflammatory therapy can reduce cardiovascular events independently of lipid-lowering therapy (13).

Building on this concept, Nidorf *et al*. subsequently reported that, in patients with stable coronary artery disease and persistently elevated hs-CRP despite statin and antiplatelet therapy, colchicine 0.5 mg twice daily significantly lowered hs-CRP levels after 30 days (14).

The LoDoCo pilot trial followed this early signal and was the first study to evaluate clinical outcomes with colchicine in coronary disease. In this randomised, open-label trial involving 532 patients with stable CAD, although enrolled irrespective of baseline hs-CRP levels, colchicine 0.5 mg once daily was associated with a substantial reduction in the composite cardiovascular endpoint of acute coronary syndrome, out-of-hospital cardiac arrest, and non-cardioembolic ischaemic stroke compared with control (5.3% *vs*. 16%; HR 0.33, 95% CI 0.18–0.59), an endpoint that was mainly driven by a lower incidence of unstable angina and ACS events (15).

More evidence was subsequently provided by the LoDoCo2 trial, a randomised, double-masked, placebocontrolled study that enrolled 5522 patients with stable CAD following a run-in phase to assess tolerability. Patients were assigned to colchicine 0.5 mg daily or placebo, over a median follow-up of 29 months. Colchicine significantly reduced the primary composite endpoint of cardiovascular death, spontaneous myocardial infarction, ischaemic stroke, or ischaemia-driven coronary revascularisation (HR 0.69, 95% CI 0.57–0.83; $p<0.001$), with benefits emerging early and remaining consistent over time (16).

Based on these findings, low-dose colchicine has been incorporated into recent guidelines as an adjunctive option for secondary prevention in chronic coronary syndromes, receiving a Class IIa recommendation in the 2024 ESC guidelines and a Class IIb recommendation in the 2023 AHA/ACC guidelines (17-18).

Early investigations of colchicine in acute coronary syndrome were largely exploratory and focused on surrogate markers of inflammation and myocardial damage, with overall heterogeneous results.

In a small randomised pilot trial that included patients presenting with ACS or stroke, colchicine failed to produce a significant reduction in hs-CRP at 30 days compared with standard care (median 1.0 mg/L *vs*. 1.5 mg/L; $p=0.22$) (19). Consistently, in a cohort of patients with ST-segment elevation myocardial infarction, Akodad *et al*. found no meaningful effect of colchicine on peak in-hospital hs-CRP levels (20).

On the other hand, more encouraging findings emerged from a study by Vaidya *et al*. in patients with recent ACS, in which colchicine therapy was associated with reductions in both hs-CRP levels and low-attenuation plaque volume on coronary computed tomography angiography (21).

The first adequately powered trial to evaluate the clinical impact of colchicine after ACS was the COLCOT trial. In this study, patients within 30 days of myocardial infarction were randomised to receive colchicine 0.5 mg daily or placebo and were followed for approximately 4 years. Colchicine significantly reduced the incidence of the primary composite endpoint of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalisation for angina (5.5% *vs*. 7.1%; HR 0.77, 95% CI 0.61–0.96). This benefit appeared to be driven mainly by reductions in stroke and urgent coronary revascularisation (22).

In prespecified sub-analyses, colchicine was associated with a 35% relative risk reduction in patients with type 2 diabetes and with greater benefit when initiated within the first 3 days after MI. However, much of the overall clinical advantage became evident during longer-term follow-up after discharge (23).

Subsequent ACS-focused trials provided less consistent evidence.

In the COPS trial, 795 patients presenting with ACS were randomised to colchicine or placebo; although fewer primary endpoint events occurred in the colchicine group over 12 months (24 *vs*. 38 events; $p=0.09$), the trial also showed a signal of increased all-cause mortality, largely driven by non-cardiovascular deaths (24).

However, unlike the LoDoCo and COLCOT trials, the COPS trial showed a signal of increased all-cause mortality with colchicine (8 *vs*. 1; $p=0.017$), largely driven by non-cardiovascular deaths (5 *vs*. 0; $p=0.024$). Rates of other adverse events, including gastrointestinal intolerance, were similar between groups (23.0% *vs*. 24.3%).

Further evidence on colchicine use in ACS settings came from the CLEAR SYNERGY the largest colchicine trial in acute myocardial infarction patients undergoing PCI, wich randomised 7062 patients across 14 countries and found no significant reduction in the primary efficacy outcome, a time-to-event composite of cardiovascular death, recurrent myocardial infarction, stroke, or unplanned ischaemia-driven coronary revascularisation, after a median follow-up of 3 years (9.1% with colchicine *vs*. 9.3% with placebo; HR 0.99, 95% CI 0.85–1.16) (25).

Although colchicine significantly lowered C-reactive protein levels at 3

months in a subgroup of patients, this anti-inflammatory effect did not translate into improved clinical outcomes. Despite its neutral results, the trial had important limitations, including its conduct during the COVID-19 pandemic, dose modification during the study, and reliance on self-reported adherence.

The positive results of the COLCOT trial contributed to subsequent guideline updates. Both the 2023 ESC and 2025 ACC/AHA guidelines for the management of acute coronary syndromes state that low-dose colchicine may be considered for secondary prevention after myocardial infarction in selected patients without contraindications (Class IIb) (26-27).

Limitations and challenges

Efficacy

Depending on one's perspective, colchicine may be regarded either as an underused anti-inflammatory option in cardiovascular prevention or as a drug with limited clinical benefit and not consistently reproducible across all settings.

Overall, evidence from randomised trials supports a potential role for low-dose colchicine in secondary prevention of coronary artery disease (Table I). However, the magnitude of benefit appears to depend on the clinical context, timing of initiation, and patient profile.

Across major randomised trials, the most convincing results have been observed in patients with stable CAD and in selected post-myocardial infarction populations, particularly in the LoDoCo2 and COLCOT trials, where colchicine reduced major cardiovascular events, including myocardial infarction, ischaemic stroke, and ischaemia-driven revascularisation (16, 22).

These findings are also supported by imaging studies, including the CCTA-based EKSTROM study and the OCT-based COLOCT trial, which suggested a favourable effect of colchicine on plaque characteristics and residual inflammatory burden (29-30).

By contrast, results have been less consistent in acute and procedural settings: In COLCHICINE-PCI, acute oral pre-procedural colchicine administration attenuated the post-procedural rise in IL-6 and hs-CRP in 400 patients undergoing PCI, but did not significantly affect enzymatic markers of infarct size (28). While CLEAR SYNERGY, the largest trial conducted in acute myocardial infarction patients undergoing PCI, failed to demonstrate a significant reduction in ischaemic events or cardiovascular mortality (25).

These discrepant findings may partly reflect important differences in trial design and study populations.

The LoDoCo2 trial, for example, included a 30-day run-in phase before randomisation, allowing exclusion of patients who were intolerant to colchicine and thereby selecting a more stable and treatment-tolerant population; notably, approximately 10% of the initially enrolled patients were excluded for this reason, a factor that may have amplified the apparent treatment effect and contributed to the favourable results observed for individual endpoints such as myocardial infarction and unplanned revascularisation (16).

Furthermore, the CLEAR SYNERGY trial enrolled a broader international population across the Americas, Europe, and Australia, whereas LoDoCo2 was limited to Australia and the Netherlands, suggesting that differences in background risk, case mix, and trial setting may also have influenced the efficacy estimates (25).

The currently available trials share several limitations. None of the major trials demonstrating significant clinical benefit selected patients based on inflammatory or biological risk markers, even though colchicine is intended to target residual inflammatory risk. In addition, key baseline variables such as cholesterol levels and blood pressure were not consistently reported, and finally, the study populations were predominantly male.

Taken together, these observations indicate that the benefit of colchicine is unlikely to be universal.

Rather, its efficacy seems more robust in chronic coronary disease and selected post-MI patients than in higher-risk acute settings, which helps explain why contemporary guidelines endorse colchicine more confidently in chronic coronary syndromes, while remaining more cautious in ACS.

Safety

Adverse effects of colchicine are dose-dependent and entail gastrointestinal symptoms, mainly diarrhoea, nausea, vomiting and abdominal pain. Lower gastrointestinal symptoms are the main reason for treatment discontinuation (31). Blood dyscrasias due to bone marrow suppression have been documented in patients receiving therapeutic doses of colchicine. Musculoskeletal symptoms, including muscle pain, weakness and myopathies, have been associated with the use of colchicine, especially during concomitant treatment with statins (32).

These safety concerns are clinically relevant given the pharmacokinetic profile of colchicine, which is metabolised through CYP3A4 and transported by P-glycoprotein, with elimination occurring mainly through biliary (60–80%) and, to a lesser extent, urinary excretion (20–40%) P-glycoprotein, an ATP-dependent efflux transporter expressed in hepatocytes, renal tubular cells and enterocytes, modulates colchicine disposition by promoting its transport into the intestinal lumen (33). Hepatic or renal insufficiency may decrease clearance of colchicine and result in drug accumulation (34); therefore, closer monitoring is warranted in these patients. Colchicine has a narrow therapeutic index and its accumulation can lead to potentially fatal toxicity. No antidote exists and dialysis is ineffective in reversing colchicine toxicity. Periodic laboratory monitoring with complete blood count, liver function tests and serum creatinine should be considered every 6 months in patients receiving colchicine therapy and more frequently in high-risk patients (33).

Dose adjustment is necessary for patients receiving therapy with P-glycoprotein or CYP3A4 inhibitors, since these agents can increase colchicine concentration either by increasing systemic reabsorption or by inhibiting its hepatic metabolism. In the presence of renal or hepatic impairment, the concomitant use of P-glycoprotein or CYP3A4 inhibitors with colchicine is contraindicated (34). Known CYP3A4 inhibitors include macrolide antibiotics such as clarithromycin and erythromycin, grapefruit juice, fluconazole and verapamil, whereas common P-glyco-

Table I. Main randomised trials on the use of colchicine in coronary artery disease.

Trial	Population	Treatment and follow-up	Primary endpoint	Results
Chronic coronary syndromes				
LoDoCo	532 patients.	Colchicine 0.5 mg daily; median follow-up 36 months.	Composite incidence of acute coronary syndrome, out-of-hospital cardiac arrest, or non-cardioembolic ischaemic stroke.	Significant reduction in the primary outcome. (HR 0.33; 95% CI 0.18–0.59; $p<0.001$)
LoDoCo2	5522 patients	Colchicine 0.5 mg daily; median follow-up 28.6 months.	Composite of cardiovascular death, spontaneous myocardial infarction, ischaemic stroke, or ischaemia-driven coronary revascularisation.	Significant reduction in the primary outcome. (HR 0.69; 95% CI 0.57–0.83; $p<0.001$)
Acute coronary syndromes				
COLCOT	4745 patients	Colchicine 0.5 mg daily; median follow-up 22.6 months.	Composite of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalisation for angina leading to coronary revascularisation.	Significant reduction in the primary outcome. (HR 0.77; 95% CI 0.61–0.96; $p=0.02$)
COPS	795 patients	Colchicine 0.5 mg twice daily (first month) then 0.5 mg daily for 11 months; median follow-up 371 days.	Composite of all-cause mortality, acute coronary syndrome, ischaemia-driven urgent revascularisation, and non-cardioembolic ischaemic stroke.	No significant reduction in the primary outcome. (HR 0.65; 95% CI 0.38–1.09; $p=0.10$)
CLEAR SYNERGY	7062 patients	Colchicine 0.5 mg and spironolactone 25 mg daily; median follow-up 36 months.	Composite of cardiovascular death, recurrent myocardial infarction, stroke, or unplanned ischaemia-driven coronary revascularisation.	No significant reduction in the primary outcome. (HR 0.99, 95% CI 0.85–1.16; $p=0.93$)
PCI-based				
COLCHICINE-PCI	400 patients	Colchicine 1.8 mg pre-PCI; 365 days follow-up.	PCI-related myocardial injury and change in plasma IL-6 concentration between baseline and 1hour post-PCI.	No significant reduction in the primary outcome. (57.3% *vs*. 64.2%; $p=0.19$)
Imaging-based				
EKSTROM	72 patients	Colchicine 0.5 mg daily.	The rate of change in low attenuation plaque volume measured by CCTA over 1 year.	No significant reduction in the primary outcome. (0.1 [IQR –0.2-0.2] *vs*. 0.0 [IQR –0.2-0.3]; $p=0.342$).
COLOCT	128 patients	Colchicine 0.5 mg daily; 365 days follow-up.	The change in the minimal fibrous cap thickness from baseline to the 12-month follow-up detected by OCT.	Significant increase in the primary outcome. (Difference 34.2 μm, 95% CI 9.7–58.6; $p=0.006$)

CCTA: coronary computed tomography angiography; CI: confidence interval; HR: hazard ratio; IL6: interleukin-6; IQR: interquartile range; OCT: optical coherence tomography; PCI: percutaneous coronary intervention.

protein inhibitors include cyclosporine, amiodarone and carvedilol (34-35).

The available trials raise several unresolved safety concerns. In the COLCOT trial, the rate of treatment discontinuation due to early colchicine intolerance was not reported, making tolerability more difficult to assess, and a higher incidence of non-fatal respiratory infections was observed (22).

In COPS, a signal toward harm emerged, with a higher incidence of non-cardiovascular death among patients assigned to colchicine. Similarly, in LoDoCo2, 10% of enrolled patients were excluded before randomisation because they were intolerant to colchicine during the run-in phase, a design feature that may have selected a more treatment-tolerant population and therefore may have underestimated potential adverse effects in routine practice. Moreover, as also reported in COPS, the LoDoCo2 trial showed a low but disproportionate number of noncardiovascular deaths in the colchicine group (0.7 *vs*. 0.5 events per 100 person-years; HR 1.51; 95% CI 0.99– 2.31) (16, 24).

Although subsequent meta-analyses did not confirm an increased risk of all-cause mortality or non-cardiovascular death with colchicine, these findings still warrant caution, particularly because the individual trials were not primarily designed or powered to evaluate safety endpoints (36-37.

Overall, although low-dose colchicine appears reasonably safe in many patients, current evidence is insufficient to fully dismiss concerns about tolerability and non-cardiovascular adverse events, and further long-term safety data are needed.

Patient selection and timing

Selecting the right candidates for colchicine therapy is a major challenge in cardiovascular prevention (Fig. 1). Pa-

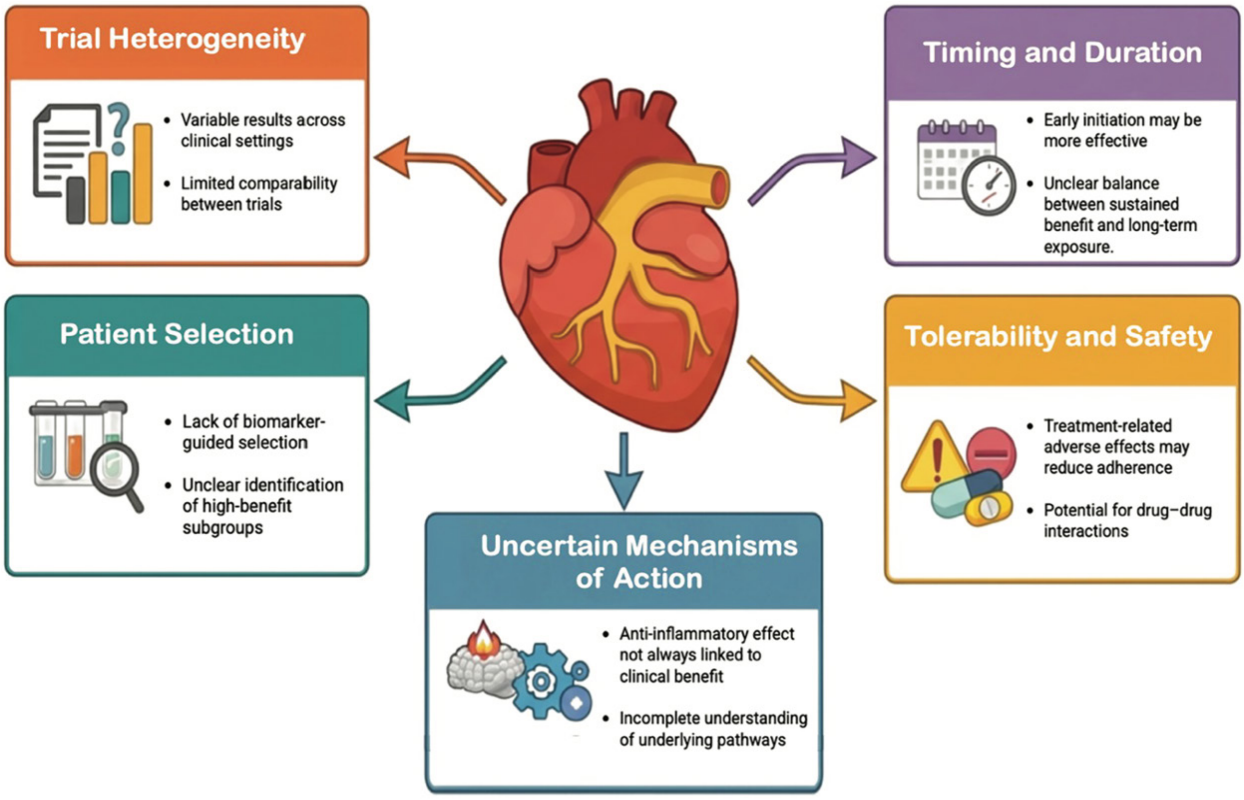

Fig. 1. Key limitations and challenges of the use of colchicine in coronary artery disease.

tients with a more pronounced residual inflammatory profile, particularly those with elevated hs-CRP levels, may represent a subgroup more likely to benefit from colchicine therapy.

This hypothesis is biologically plausible, given that the drug is intended to modulate inflammation-driven cardiovascular risk. However, this strategy has not yet been validated prospectively. In both ACS and CCS, hsCRP has been proposed as a potential tool to identify candidates with greater inflammatory activation, but the current evidence remains limited, since the major randomised trials were not designed to enrol patients on the basis of elevated inflammatory markers. Indeed, neither the LoDoCo studies nor the other major trials limited inclusion to patients with hs-CRP >2 mg/L or other predefined inflammatory thresholds (15, 18). Although a subgroup analysis from the COLCOT trial reported higher baseline CRP values after myocardial infarction (40), the lack of clear differences in CRP changes over time argues against a benefit confined exclusively to patients with overtly elevated biomarkers. Therefore, while a biomarker-guided approach remains attractive, its role in refining colchicine prescription in CAD still requires dedicated investigation.

In contrast, patients with previous gastrointestinal intolerance, hepatic or renal dysfunction, or clinically relevant drug interactions, particularly during therapy with CYP3A4 inhibitors or P-glycoprotein substrates, may be less suitable for colchicine treatment.

The clinical effect of colchicine may depend on patient selection, the timing of initiation and the total duration of treatment.

In ACS, evidence from the COLCOT trial suggests that initiating colchicine within 30 days after myocardial infarction can reduce cardiovascular events, supporting the concept that anti-inflammatory treatment may be more effective when started early in the course of post-infarction inflammation, before irreversible damage and self-sustaining inflammatory pathways are fully established.

In contrast, in CCS, the inflammatory milieu is generally more chronic and less abrupt, providing a rationale for longer-term colchicine administration aimed at suppressing persistent low-grade vascular inflammation and lowering the likelihood of future ischaemic events. However, the most appropriate duration of therapy remains uncertain. A short course may not be sufficient to ensure lasting anti-inflammatory benefit, whereas prolonged or indefinite treatment raises concerns related to long-term safety, adherence, and potential drug interactions (39-40).

In light of the favourable outcomes reported with longer follow-up, colchicine treatment for at least 12 months after ACS and extended therapy in CCS may be reasonable, particularly in patients with elevated inflammatory markers such as hs-CRP, recurrent cardiovascular events despite guideline-directed medical therapy, or other high-risk features, including multivessel CAD and polyvascular atherosclerotic disease, such as coexisting peripheral artery disease or carotid stenosis. Temporary suspension or permanent discontinuation should be considered in patients who develop infectious complications or have severe renal or hepatic dysfunction.

Colchicine is inexpensive and orally administered, which makes it widely accessible, but its role is likely to be optimised when incorporated into a broader management strategy that considers the inflammatory burden, comorbidities, and the risk of adverse effects, underscoring the emerging need for a more personalised antiinflammatory approach in CAD.

Future perspectives

Future studies will be critical to clarify whether colchicine should be used broadly across CAD or reserved for selected patient phenotypes. The role of colchicine in CAD should be supported by future trials designed to better define its indication, timing of initiation, treatment duration and biologic targeting.

The ongoing COL BE PCI trial will evaluate colchicine after PCI in both CCS and ACS, using broad eligibility criteria, no run-in phase, baseline hsCRP assessment, and greater female representation, thereby improving generalisability. The COLCARDIO-ACS trial directly evaluates whether residual inflammatory risk can be used to guide treatment allocation in a post-ACS population with persistent inflammatory activation. The COLCOTT2D further extends this perspective by examining whether low-dose colchicine has a role in high-risk primary prevention among patients with type 2 diabetes without established cardiovascular disease. These ongoing trials may clarify the optimal timing and duration of colchicine therapy in a broad clinical setting and determine whether hs-CRP-guided strategies can improve outcomes (41-43).

Ongoing advances in inflammation-targeted imaging may improve patient stratification and guide patient-tailored anti-inflammatory therapy on the basis of biological, rather than purely clinical, characteristics. Such precision-based strategies could enhance outcomes while limiting overtreatment.

Conclusions

Colchicine represents one of the most extensively studied anti-inflammatory agents in CAD, reinforcing the concept that residual inflammatory risk is clinically relevant and potentially modifiable. Yet, its benefit has not been consistent across all cardiovascular settings. While evidence appears more robust in chronic coronary syndromes and selected post-myocardial infarction populations, results in acute and PCI-related settings remain less conclusive.

These findings do not weaken the inflammatory hypothesis, but rather highlight the emerging need for a more refined application of it. The key question is no longer whether colchicine can work, but in whom, when, and for how long it should be used. In this regard, better patient selection, clearer timing of initiation, and improved risk stratification are essential to precisely define the role of colchicine in contemporary CAD management.

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