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Colchicine and residual inflammation: an old drug with a new trick

Kayla Chiew MBBS BSc MRCP

Cardiology ACF ST3

Barts Health NHS Trust

Take Home Messages

- The United States Food and Drug Administration recently approved colchicine for the secondary prevention of cardiovascular events in June 2023.
- This is the first inflammation-targeted therapy licensed in atherosclerotic cardiovascular disease.
- Clinical application of anti-inflammatory medications has been limited by risk of serious infections. Low dose 0.5mg colchicine daily appears to strike the balance of systemic inflammation suppression without increasing infection risk.
- The application of low dose colchicine in a wide range of atherosclerotic diseases is currently an active field of research.

Introduction

Colchicine, a drug most familiar to cardiologists for treating acute pericarditis, is steadily gaining recognition for its potential role in treating ischaemic heart disease. The recent United States Food and Drug Administration (US FDA) approval of low dose colchicine for the secondary prevention of cardiovascular events in those with established atherosclerotic disease marks a new era in preventative cardiology as the first licensed therapy to target inflammation(1). Whilst the concept of inflammation driving atherosclerosis is not novel, treatments directed at suppressing inflammation have yielded inconsistent results, with translation to clinical practice further hindered by signals of harm from serious infections. Herein we discuss the evidence behind colchicine and the upcoming landscape of inflammation-targeted therapies in cardiovascular disease.

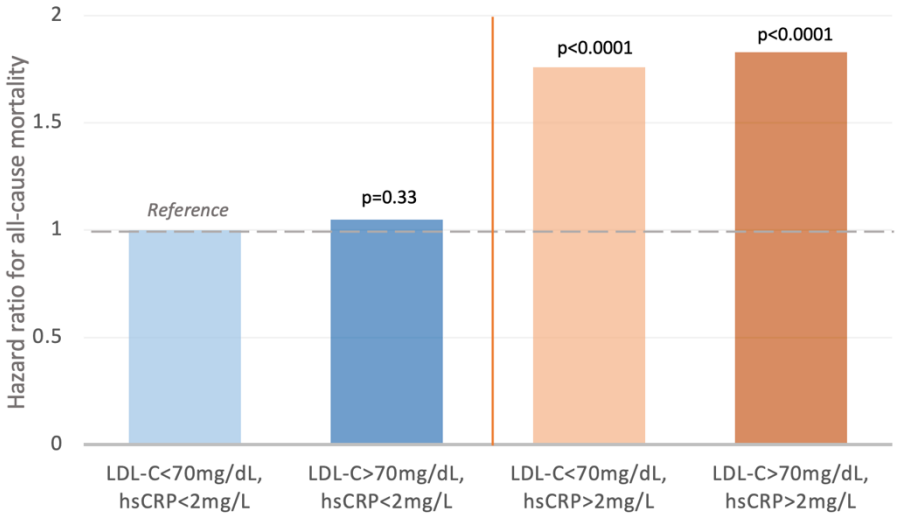
The inflammatory hypothesis of atherosclerosis

Aggressive lipid lowering remains central to cardiovascular risk reduction. Despite the armamentarium of lipid lowering treatments currently available, the occurrence of adverse events in those with adequate lipid control prompts the consideration of alternative models for

evaluating risk(2). Residual inflammatory risk, reflected by elevated high sensitivity C-reactive protein (hsCRP), appears to be a powerful determinant of future adverse events. A recent analysis of 3 randomised controlled trials (PROMINENT, REDUCE-IT and STRENGTH) involving over 30,000 participants on statin therapy found that those with the highest quartile of hsCRP had an almost 2.5-fold increased risk of all-cause mortality compared to the lowest quartile. In contrast, the relationship for residual cholesterol risk appears to be much less substantial (**Figure 1**)(3).

It was the publication of CANTOS in 2017 that bolstered the inflammatory hypothesis of atherosclerosis(4). This trial randomised patients with previous myocardial infarction (MI) and confirmed residual inflammation, defined as hsCRP>2mg/L, to receive the interleukin-1B inhibitor canakinumab or placebo. The intervention resulted in a 12% reduction in the primary composite outcome of non-fatal MI, non-fatal stroke and cardiovascular (CV) death. Notably, this was achieved without any reductions in low density lipoprotein cholesterol (LDL-C). There was however a significantly higher rate of fatal infections and sepsis in those who received canakinumab. Reducing systemic inflammation at the expense of an increased risk of infections has therefore remained the Achilles heel for inflammation-targeted therapies.

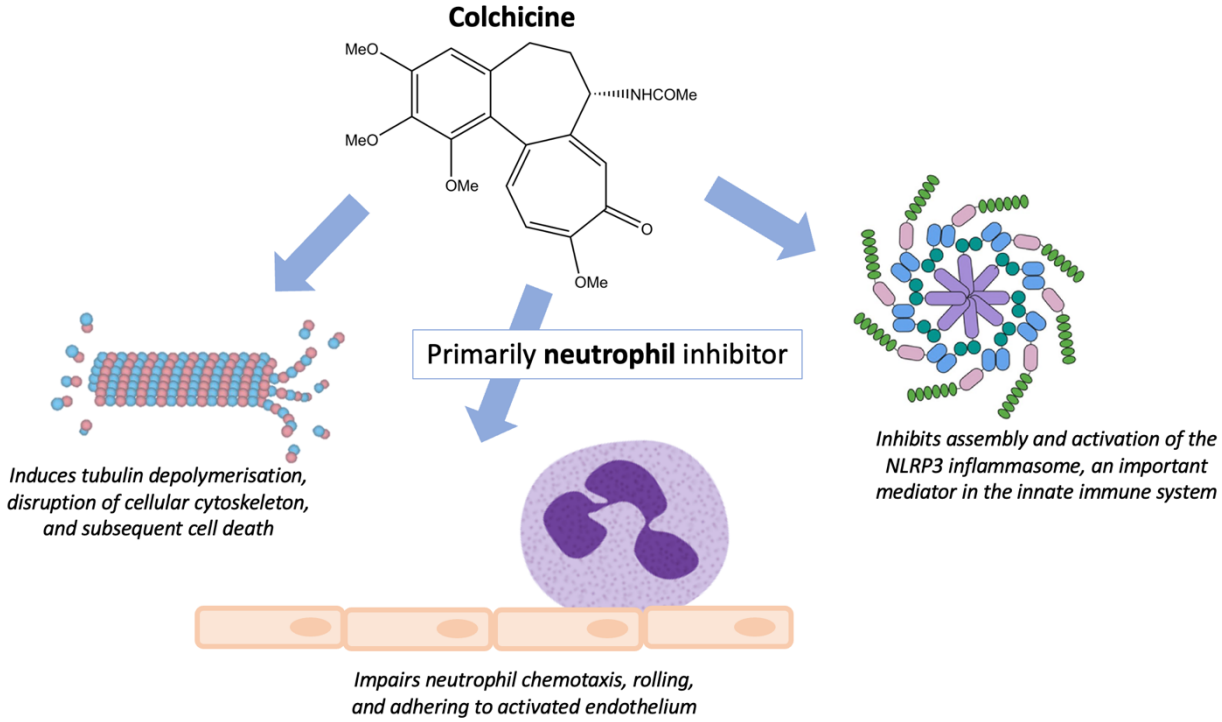
Figure 1. Comparative hazard ratio for all-cause mortality in those with residual cholesterol risk (LDL-C >70mg/dL) and residual inflammatory risk (hsCRP >2mg/L). *Adapted from Ridker et al*(2).



Colchicine

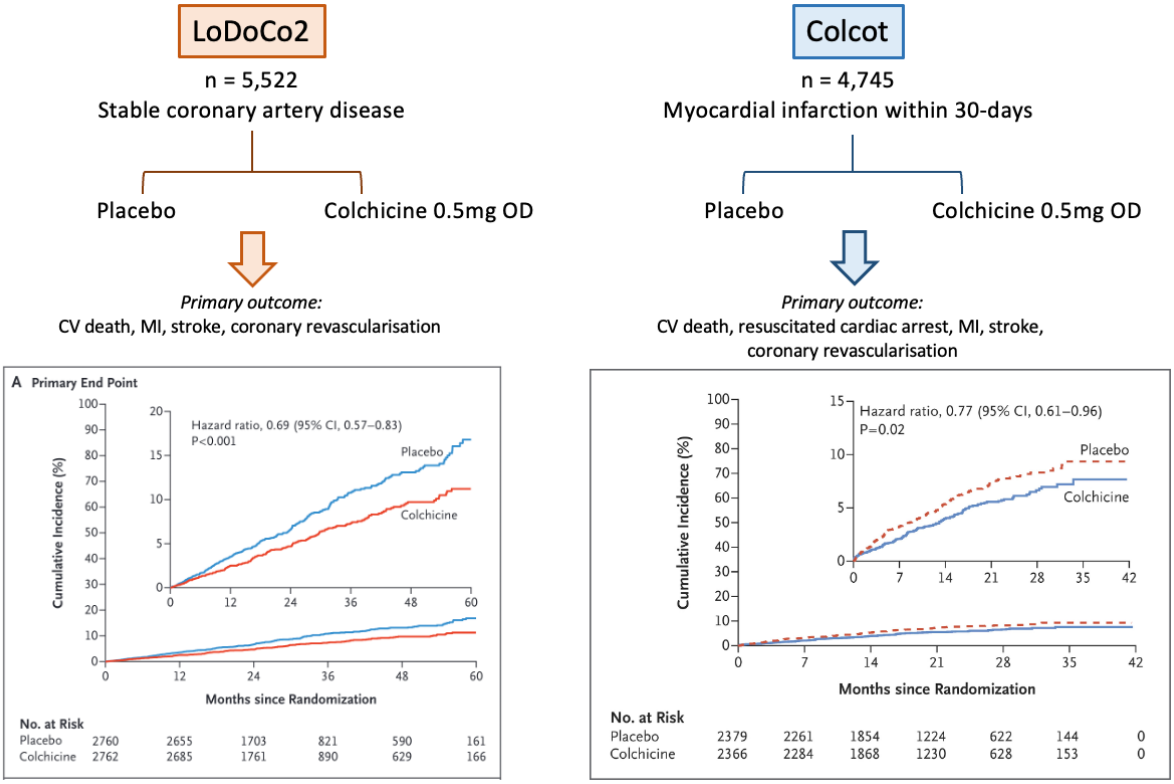
The use of colchicine dates back millennia as a herbal remedy derived from the *Colchicum Autumnale* plant to treat joint pain. **Figure 2** summarises its main mechanisms of action. The benefit of colchicine in ischaemic heart disease was first identified in retrospective analyses of populations with gout and Familial Mediterranean Fever, where very large reductions of almost 50% in cardiovascular events were observed(5). Commonly used in high doses of 0.5mg up to four times a day for short durations to treat these rheumatological conditions, the major cardiovascular trials of colchicine instead employed a low maintenance dose of 0.5mg once a day which has allowed it to have a more favourable side-effect profile. The current European and American guidelines(6,7) both awarding colchicine a class IIb recommendation for the secondary prevention of cardiovascular events were largely informed by 2 randomised controlled trials: LoDoCo2 and COLCOT.

Figure 2. The main mechanisms of action of colchicine. *Original figure created using Creative Commons licensed images.*



LoDoCo2 randomised around 5,500 patients with stable coronary artery disease, the majority of whom were already on a statin, to low dose colchicine versus placebo(8). After a median follow-up of 28 months, colchicine resulted in an impressive 31% relative reduction in the primary composite endpoint of CV death, MI, stroke and coronary revascularisation [HR 0.69, 95% CI 0.57-0.83, p<0.001] (**Figure 3**). This was largely driven by a reduction in revascularisation rates, without a difference in CV death. The higher all-cause mortality with colchicine at 2.6% versus 2.2% [HR 1.51, 95% CI 0.99-2.31], although non statistically significant, hints at a possible increase in non-cardiovascular death. Importantly there were no differences in rates of hospitalisation for infection.

Figure 3. Comparison of LoDoCo2 to Colcot and their primary outcome results. *Adapted from Nidorf et al and Tardif et al*(8,9).



Separate to chronic coronary syndrome, COLCOT randomised almost 5,000 patients with a recent MI within the last 30 days and without left ventricular impairment, to colchicine or placebo(9). The results mirrored those of LoDoCo2: after a median follow-up of 22 months, colchicine resulted in a 33% relative risk reduction in the primary composite endpoint of CV death, resuscitated cardiac arrest, MI, stroke, and urgent coronary revascularisation [HR 0.77, 95% CI 0.61-0.96, p=0.02] (**Figure 3**). Once again, this was largely driven by a reduction in revascularisation rates with non-significant differences in CV and all-cause mortality, or serious infections.

Of note, neither trial utilised hsCRP as a selection criterion, nor evaluated its ability to predict treatment benefit. It remains uncertain whether screening with hsCRP to identify those with elevated inflammatory risk should be the individualised approach we employ in clinical practice. A number of upcoming outcomes-based randomised controlled trials of colchicine within the spectrum of atherosclerotic cardiovascular disease are summarised in **Table 1.**

Conclusion

The approval of colchicine has been a step forward in acknowledging an important modifiable factor driving atherosclerosis, that is low grade systemic inflammation. Residual inflammatory risk may become an increasingly fundamental component in the overall assessment of cardiovascular risk, and should be seen as complementary to aggressive lipid-lowering. Unanswered questions remain about the role of hsCRP and other biomarkers of inflammation in the selection of patients most likely to benefit, as well as the wider application of colchicine beyond secondary prevention.

Disclosures

No relevant disclosures.

Table 1. Upcoming phase 3 clinical trials of colchicine in atherosclerotic disease.

Trial name or NCT number	Country	Estimated enrolment	Population	Intervention	Comparator	Primary outcome
Primary prevention						
COLCOT-T2D	Canada	10,000	Type 2 diabetics with an additional cardiovascular risk factor	Colchicine and/or aspirin	Placebo	CV death, resuscitated cardiac arrest, non-fatal MI, non-fatal stroke, urgent coronary revascularisation
NCT05175274	China	6,792	3 cardiovascular risk factors	Colchicine	Placebo	Incidence of CAD
Acute coronary syndrome						
COLCARDIO-ACS	Australia	3,000	ACS within 6 weeks and hsCRP>2mg/L	Colchicine	Placebo	MI, urgent coronary revascularisation, CV death, non-fatal stroke
NCT06020300	Malaysia	64	STEMI	Colchicine	Pyridoxine	MI, unstable angina requiring hospital admission, cardiac death, unplanned coronary revascularisation, stroke
Percutaneous coronary intervention						
CLEAR SYNERGY	Canada	7,063	STEMI and NSTEMI treated with PCI and SYNERGY stent	Colchicine and/or spironolactone	Placebo	Death, target vessel MI, stroke, ischaemia driven target vessel revascularisation
ORCA	Argentina	450	PCI (elective and ACS)	Colchicine + bare-metal stent	Latest generation drug-eluting stent	Death, MI, target vessel revascularisation
NCT05745818	Egypt	300	Elective PCI	Colchicine	Usual care	Major adverse cardiac events - unspecified
Stroke						
CHANCE-3	China	8,238	Ischaemic stroke or TIA and hsCRP>2mg/L	Colchicine	Placebo	Incidence of stroke
CONVINCE	Europe, Canada	3,154	Ischaemic stroke or TIA	Colchicine	Usual care	Non-fatal ischaemic stroke, non-fatal hospitalisation for unstable angina/MI/cardiac arrest, fatal ischaemic stroke/MI/cardiac arrest
RIISC-THETIS	France	2,800	Ischaemic stroke or TIA, and atherosclerosis of carotid/cerebral/aortic artery	Colchicine + ticagrelor or aspirin	Placebo + ticagrelor or aspirin	Non-fatal ischaemic stroke, non-fatal MI, coronary revascularisation or vascular death

Other						
COLT-HF	Canada	2,500	Heart failure due to ischaemic heart disease	Colchicine +/- thiamine	Placebo	Time to first occurrence of CV death, HF event, MI, stroke, or arterial revascularisation
POPCORN	USA	700	Prior coronary revascularisation, and undergoing intermediate-high risk surgery	Colchicine	Placebo	Non-fatal MI, non-fatal stroke, all-cause mortality, myocardial injury

ACS = acute coronary syndrome, CAD = coronary artery disease, CV = cardiovascular, HF = heart failure, hsCRP = high sensitivity C-reactive protein, MI = myocardial infarction, NCT = National Clinical Trial, NSTEMI = non-ST elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST elevation myocardial infarction, TIA = transient ischaemic attack

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