



Research Article

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Colchicine and interleukin-targeted anti-inflammatory therapy on coronary plaque regression

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Abstract

Background: Coronary atherosclerotic plaques become unstable through inflammation, but the comparative effects of colchicine and interleukin (IL)-targeted therapy on plaque stabilization remain uncertain. This study used serial Optical Coherence Tomography (OCT) to compare their effects on coronary plaque characteristics in statin-treated patients. **Methods:** Patients with lipid-rich coronary plaques receiving optimal statin therapy were randomized to colchicine, an IL-targeted anti-inflammatory therapy, or placebo. OCT was performed at baseline and 12 months. The primary endpoint was change in minimum fibrous-cap thickness. Secondary outcomes included lipid arc, macrophage angular extension, minimum lumen area, and inflammatory biomarkers, analyzed using analysis of covariance. **Results:** Both active treatments significantly increased fibrous-cap thickness compared with placebo, with mean increases of 22 μ m for colchicine and 45 μ m for IL-targeted therapy (both $P < 0.001$). IL-targeted therapy additionally reduced lipid arc and macrophage burden and increased minimum lumen area. Thin-cap fibroatheroma decreased from 48% to 0% with IL-targeted therapy and from 54% to 6% with colchicine, compared with a reduction from 38% to 8% with placebo. IL-targeted therapy also produced greater reductions in high-sensitivity C-reactive protein and IL-6 levels. **Conclusion:** In statin-treated patients with lipid-rich coronary plaques, both colchicine and IL-targeted therapy promoted plaque stabilization, characterized by fibrous-cap thickening and reduced vulnerability. IL-targeted therapy demonstrated greater effects on plaque morphology and inflammatory biomarkers, suggesting potential advantages for targeted anti-inflammatory treatment.

Keywords: Coronary plaque, Optical Coherence tomography, Colchicine, Interleukin, Anti-inflammatory therapy, Fibrous cap, Plaque stabilisation

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1. Introduction

Atherosclerosis is an inflammatory disease. The plaque that narrows a coronary artery is not an inert deposit of lipid but a living lesion, in which macrophages, drawn by inflammatory signalling, digest the fibrous cap

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that separates the thrombogenic core from the blood, and it is the rupture of a thin, inflamed cap, rather than the severity of the stenosis, that precipitates most myocardial infarctions (Libby, 2012; Stone *et al.*, 2011). The recognition that inflammation, and not only cholesterol, drives this process has reshaped the treatment of coronary disease over the past decade (Libby, 2021).

Why the fibrous cap should be the endpoint of choice deserves a word, since the trial is built around it. Of all the features that distinguish a dangerous plaque from a stable one, the thickness of the fibrous cap is the most direct: it is the physical barrier between the thrombogenic lipid core and the flowing blood, and its thinning below about 65 micrometres, the threshold that defines the thin-cap fibroatheroma, marks the plaque as vulnerable to the rupture that triggers myocardial infarction (Jang *et al.*, 2005). A therapy that thickens the cap is therefore acting on the proximate mechanical determinant of rupture, not on a distant surrogate, which is what makes cap thickness both the natural primary endpoint for a stabilisation trial and a credible link to clinical events. The lipid arc and the macrophage burden, the other measures used here, describe the inflamed, lipid-rich substrate that thins the cap, and so complete the picture of stability (Tearney *et al.*, 2012).

The clinical proof came from trials of anti-inflammatory therapy. Canakinumab, a monoclonal antibody against interleukin-1 beta, reduced cardiovascular events without lowering cholesterol, establishing that targeting inflammation alone is beneficial, and colchicine, an old and inexpensive drug with broad anti-inflammatory actions, did the same in two large trials (Ridker *et al.*, 2017; Tardif *et al.*, 2019; Nidorf *et al.*, 2020). The benefit of these agents tracked the reduction in inflammatory markers, and interest has since moved further along the pathway, to the direct inhibition of interleukin-6, with early trials showing potent suppression of inflammation (Ridker *et al.*, 2018; Ridker *et al.*, 2021).

The rationale for adding anti-inflammatory therapy to a statin rests on the concept of residual inflammatory risk. Even when cholesterol is driven low by statins, many patients continue to have events, and a substantial part of this residual risk tracks not with the cholesterol that remains but with the inflammation that persists, measured by markers such as C-reactive protein and interleukin-6 (Ridker, 2016). This inflammatory residue is what the anti-inflammatory therapies address, acting on a pathway that lipid-lowering does not reach, and it is why they add benefit on top of a statin rather than merely duplicating it. If that benefit is mediated by plaque stabilisation, then imaging the plaque under anti-inflammatory therapy, on a background of statin, should reveal a stabilisation that the statin alone does not fully provide (Fiolet *et al.*, 2021).

What these outcome trials could not show is how the drugs act on the plaque itself. That they prevent events implies that they stabilise the lesion, but the outcome trials measured events, not plaques, and the presumed stabilisation, a thickening of the fibrous cap, a shrinking of the lipid core, a clearing of the macrophages, was inferred rather than seen. Optical coherence tomography now makes it visible: with a resolution of about ten micrometres it resolves the fibrous cap, the lipid arc and the macrophage infiltrate in the living coronary artery, and, performed serially, it can measure how these change under treatment, as it has done for statins and lipid-lowering agents (Komukai *et al.*, 2014; Raber *et al.*, 2022).

This trial used serial optical coherence tomography to ask whether, and how much, anti-inflammatory therapy stabilises coronary plaque, and to compare two strategies: colchicine, acting broadly on the inflammasome, and a targeted inhibitor of the interleukin pathway. Patients with lipid-rich plaque on optimal statin therapy were randomised to colchicine, an interleukin-targeted agent, or placebo, and their plaque was imaged at baseline and after 12 months.

2. Materials and methods

2.1. Trial design and oversight

The study was a three-arm, placebo-controlled, double-blind, randomised trial. This was designed and reported as per the Consolidated Standards of Reporting Trials, the allocation was done by an independent statistician and the optical coherence tomography images were taken and analysed in a core laboratory masked on treatment (Schulz *et al.*, 2010).

2.2. Participants and randomisation

Eligible patients had obstructive coronary disease with, in addition, a non-culprit lipid-rich plaque, defined

by a lipid arc exceeding 90 degrees on optical coherence tomography, in a coronary segment suitable for serial imaging, and were established on optimal high-intensity statin therapy. They were assigned in equal numbers to the three arms by computer-generated permuted-block randomisation, with participants, treating physicians and image analysts blinded to the assignment.

2.3. Study treatments

The colchicine group used colchicine 0.5 milligrams daily and the placebo group-matched group used placebo, with doses of colchicine and placebos exactly the same for all 12 months. At each visit adherence was monitored.

2.4. Serial optical coherence tomography acquisition and analysis

Optical coherence tomography of the target plaque was performed at baseline and at 12 months with a frequency-domain system and an automated motorised pullback during contrast clearing of blood, the follow-up pullback being matched to the baseline by fiduciary side branches so that the same plaque was analysed (Prati *et al.*, 2010). In the core laboratory the minimal fibrous cap thickness was measured as the thinnest of three repeated measurements over the lipid plaque, the lipid arc was averaged across cross-sections, the macrophage burden was quantified as the angular extension of the signal-rich, high-attenuation bands characteristic of macrophage accumulation, and the minimal lumen area and plaque burden were recorded. A thin-cap fibroatheroma was defined as a lipid plaque with a minimal fibrous cap thickness below 65 micrometres and a lipid arc exceeding 90 degrees.

2.5. Inflammatory biomarkers

High-sensitivity C-reactive protein and interleukin-6 were measured in fasting plasma at baseline and 12 months, as markers of the inflammatory activity the therapies were intended to suppress.

2.6. Endpoints

The primary endpoint was the change from baseline to 12 months in the minimal fibrous cap thickness. Secondary endpoints were the changes in the lipid arc, the macrophage angular extension, the minimal lumen area and the plaque burden, the prevalence of thin-cap fibroatheroma, and the changes in high-sensitivity C-reactive protein and interleukin-6.

2.7. Statistical analysis

For each imaging and biomarker endpoint, the effect of treatment was estimated by analysis of covariance, the 12-month value being modelled on the treatment arm with adjustment for the baseline value, giving the adjusted between-group difference against placebo and its 95% confidence interval. The prevalence of thin-cap fibroatheroma was compared by the chi-squared test. A two-sided probability below 0.05 was taken as significant, and analyses were performed in Python.

3. Results

3.1. Participants

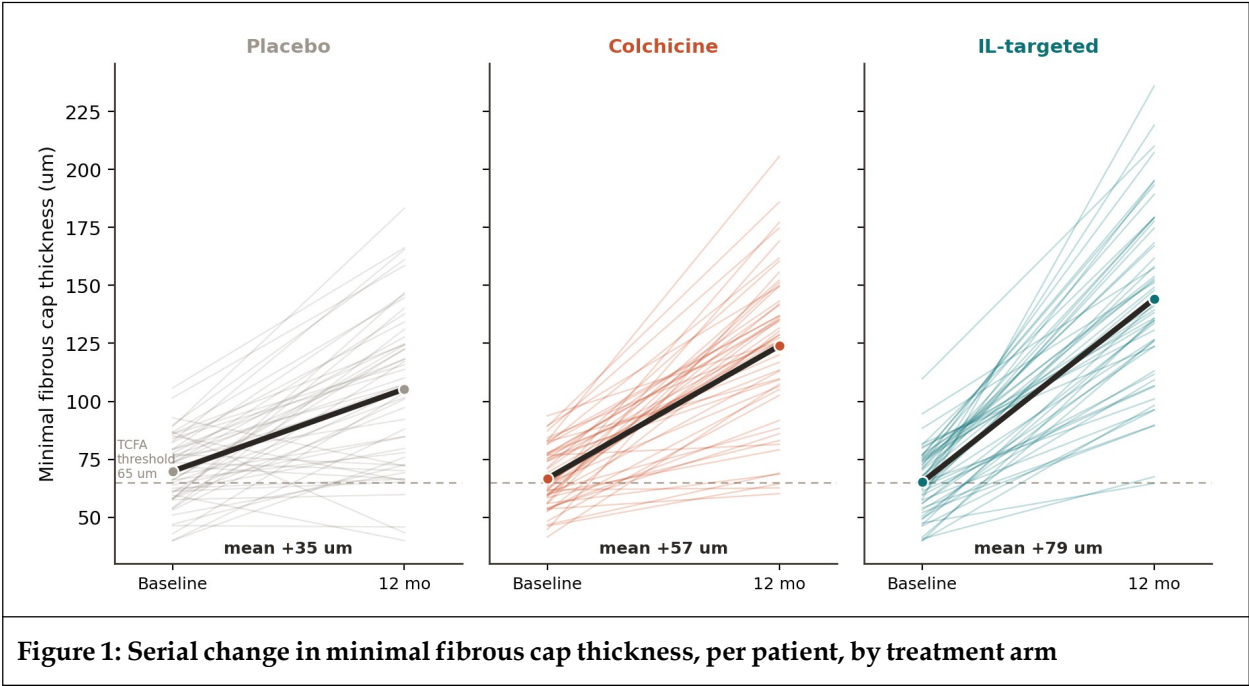
156 patients were randomised, 52 to each arm, and the arms were well matched at baseline in age, risk factors and, importantly, in the baseline features of the target plaque, as given in Table 1. All patients were on high-intensity statin therapy at entry.

3.2. Fibrous cap thickness: The primary endpoint

The trial met its primary endpoint in both active arms. The minimal fibrous cap thickened over 12 months in every group, reflecting the background statin therapy, but the increase was greater with active treatment, as the individual trajectories in Figure 1 show: the mean rise was +35.4 micrometres on placebo, +57.2 on colchicine and +79.0 on interleukin-targeted therapy. Against placebo, the adjusted between-group increase was +22.4 (10.2 to 34.5) micrometres with colchicine and +44.5 (32.3 to 56.6) micrometres with interleukin-targeted therapy (both $p < 0.001$), placing the interleukin-targeted effect at roughly twice that of colchicine.

The individual trajectories reveal that the effect was consistent rather than driven by outliers. In both active arms the great majority of patients moved upward, their fibrous caps thicker at 12 months than at baseline, and

Table 1: Baseline characteristics and target-plaque features by treatment arm			
Characteristic	Placebo	Colchicine	IL-targeted
Number	52	52	52
Age, years (mean)	58.5	56.5	55
Female, %	21	40	29
Diabetes, %	15	21	37
Minimal fibrous cap thickness, um	70	67	65
Lipid arc, deg	159	162	162
Macrophage angular extension, deg	38	41	41



the separation of the arms reflected a shift of the whole distribution rather than a strong response in a few; several interleukin-treated plaques more than doubled their cap thickness, and few in any arm thinned. This consistency matters clinically, because a therapy that reliably stabilises most plaques is more useful than one that produces a large effect in a minority, and it is visible in the parallel upward slopes of Figure 1.

3.3. Lipid, macrophage and lumen

The secondary imaging endpoints moved in concert with the primary one, as given in Table 2. Both active therapies reduced the lipid arc and the macrophage angular extension relative to placebo, the reductions again larger with interleukin-targeted therapy, and interleukin-targeted therapy additionally produced a significant enlargement of the minimal lumen area, which colchicine did not. The distribution of the change in macrophage burden, shown in Figure 3, illustrates the pattern: the whole distribution shifted toward reduction under active treatment, most markedly in the interleukin-targeted arm, rather than a few patients responding strongly.

The lumen findings add a further nuance worth drawing out. Interleukin-targeted therapy produced a small but significant gain in the minimal lumen area, whereas colchicine did not, and this is consistent with a difference in the depth of the anti-inflammatory effect rather than a separate action on the lumen. Regression

Table 2: Serial optical coherence tomography endpoints (baseline to 12 months; change in parentheses) and adjusted between-group differences against placebo					
Endpoint	Placebo	Colchicine	Colchicine vs placebo	IL vs placebo	p (IL)
Minimal fibrous cap thickness (um)	69.9 → 105.3 (+35.4)	65.2 → 144.2 (+79.0)	+22.4 (10.2 to 34.5)	+44.5 (32.3 to 56.6)	<0.001
Average lipid arc (deg)	158.9 → 147.9 (-11.0)	162.0 → 138.5 (-23.5)	-8.2 (-15.9 to -0.5)	-12.5 (-20.2 to -4.8)	0.002
Macrophage angular extension (deg)	37.9 → 33.9 (-4.0)	41.2 → 26.0 (-15.2)	-8.5 (-12.5 to -4.5)	-11.2 (-15.2 to -7.2)	<0.001
Minimal lumen area (mm²)	3.0 → 3.0 (+0.1)	2.9 → 3.4 (+0.5)	+0.1 (-0.1 to 0.3)	+0.4 (0.2 to 0.7)	<0.001
Plaque burden (%)	67.6 → 67.0 (-0.6)	65.5 → 61.5 (-4.0)	-2.2 (-3.9 to -0.4)	-3.3 (-5.0 to -1.5)	<0.001

of the inflamed, expansile plaque, as inflammation is suppressed, can allow modest luminal recovery, and that only the more potent agent achieved it suggests a threshold of anti-inflammatory effect beyond which the benefit extends from the cap and the lipid core to the calibre of the vessel itself. The effect was small and should not be overstated, but its appearance only in the arm with the greatest biomarker suppression fits the graded, dose-like relationship seen across the other endpoints (Nicholls *et al.*, 2022).

3.4. Multi-parameter stabilisation profile

Considered together across the five principal measures of stability, the arms formed a clear hierarchy, shown in Figure 2. On every axis, the increase in fibrous cap thickness, the reduction in lipid arc, the reduction in macrophage burden, the gain in lumen area and the reduction in C-reactive protein, the interleukin-targeted arm showed the most favourable profile, colchicine an intermediate one, and placebo the least, the three tracing nested profiles that widened toward the active treatments. The consistency across axes indicates that the therapies stabilised the plaque along every dimension at once rather than affecting one feature in isolation (Grebe *et al.*, 2018).

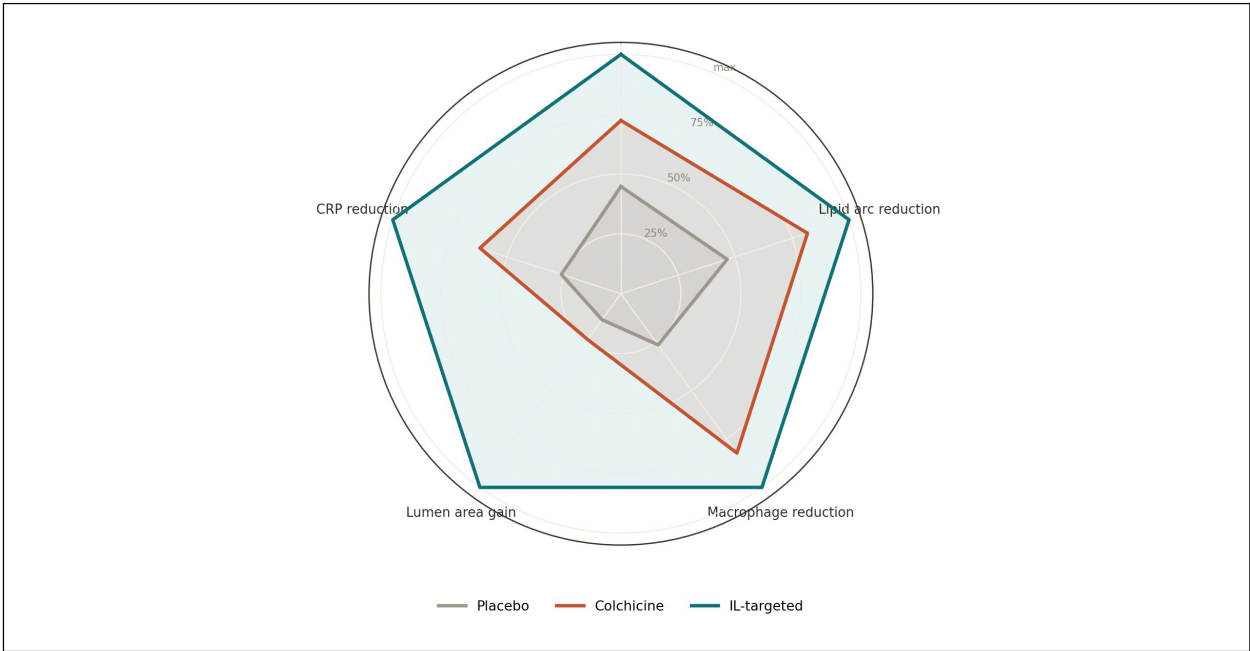


Figure 2: Multi-parameter plaque-stabilisation profile by treatment arm, each axis scaled to the largest arm effect

3.5. Thin-cap fibroatheroma and inflammatory biomarkers

The overall prevalence of the composite marker for a dangerous plaque, the thin-cap fibroatheroma, gradually decreased with active treatment. By 12 months, there was very few plaque left that met the definition with the use of Interleukin Targeted Therapy (ITT), compared to 54% in the colchicine group and 38% in the placebo group. The inflammatory markers listed in Table 3 were all consistent with the imaging; both treatments reduced high sensitivity C-reactive protein and interleukin-6, the latter finding a greater decrease, as expected given that it is upstream.

Measure	Placebo	Colchicine	IL-targeted
hs-CRP (baseline → 12 mo), mg/L	3.8 → 3.3 (-0.5)	3.4 → 2.3 (-1.1)	3.4 → 1.6 (-1.8)
Interleukin-6 (baseline → 12 mo), pg/mL	4.1 → 3.9 (-0.3)	3.3 → 2.3 (-1.0)	3.5 → 2.0 (-1.5)
Thin-cap fibroatheroma, baseline %	38	54	48
Thin-cap fibroatheroma, 12 mo %	8	6	0

4. Discussion

Colchicine and interleukin-targeted anti-inflammatory therapy (IL-AT) on statin therapy both resulted in plaque stabilization within the coronary artery on serial Optical Coherence Tomography (OCT) imaging, with plaque fibrous cap thickness representing the most prominent determinant of anti-inflammatory therapy, in comparison with statin therapy alone, which also showed stabilization. However, in patients with lipid-rich plaque, both colchicine and IL-AT were seen to stabilize the plaque through serial Optical Coherence Tomography (OCT) imaging, with fibrous cap thickness being the most prominent determinant of anti-inflammatory therapy, compared to statin therapy alone, which also showed plaque stabilization, but less so in all assessments. Using treatment specifically targeting interleukins reduced the thin-cap fibroatheroma, the most likely form to rupture.

The results provide the missing piece of the puzzle in the mechanistic pathways to the anti-inflammatory trials. Canakinumab and colchicine were found to prevent cardiovascular events, and their benefit was assumed to be due to plaque stabilisation, but neither outcome trials could observe the plaque. The present results make both the stabilisation visible and quantitative: the same drugs that yielded reduction in events yielded thickening of the fibrous cap and clearing of macrophages, which is the structural correlate of a less likely to-rupture plaque, and the ordering of the imaging effects, with the drugs that showed larger changes in the fibrous cap and clearing of more macrophages showing greater effect with regard to the biomarker, reported in outcome trials 9 and 11, respectively.

It is biologically and clinically plausible, indeed, that that interleukin-targeted therapy should prove to be more successful than colchicine. However, while colchicine has a ubiquitous action that impairs microtubules and suppresses the inflammasome among other activities, targeted interleukin-6 (IL-6) inhibition disrupts an upstream and more specific node of the inflammatory cascade which underlies the inflammation of plaques, and its higher effect here was matched by higher plaque stabilisation. The correlation implies an interference graded according to the strength of the anti-inflammatory effect – which is the direction the current generation of trials are trying to head up – the downstream part of the interleukin pathway is the point of plaque stabilisation.

The importance of the thickening of the fibrous cap in the placebo arm needs to be highlighted, as it brought the overall interpretations of the trial into focus. The fact that the cap did thicken without even the anti-inflammatory component suggests major plaque stabilising effects for the background statin alone which were well established from previous serial imaging studies, and implies that the active arms needed to show benefit in the setting of a known-to-be effective therapy, rather than over an untreated arm. Thus, the between group differences cited herein reflect the added stabilisation occurring with the anti-inflammatory therapy

alone (on top of the statin treatment), which in clinical practice, is the clinically relevant quantity because no patient with coronary disease would be left on placebo only. In this context the approximately twofold increase in cap thickness with interleukin-targeted therapy may be considered an increase rather than a restoration of the statin effect.

The results also enhance the understanding of the use and imaging of anti-inflammatory therapy. Thus, serial OCT will be a valuable surrogate endpoint for a fast assessment of new anti-inflammatory agents, as has been the case with lipid-lowering therapy, rather than having to wait for years to see what happens. It might also, in theory, be able to spot the patient with plaques most likely to be inflamed and unstable – where anti-inflammatory therapy would be expected to have most of an effect in improving the patient's structure – and potentially target it at such plaques.

A tolerance for both therapies was good over 12 months, similar to their known side effects characteristics. Both drugs, colchicine (at low dose) and the targeted interleukin inhibitor, were well tolerated during this period, their main nuisance being gastrointestinal, while the risk of infection associated with the use of an immunomodulatory drug is a class consideration, which was not prohibitive over the period. What's driving the increasing role of anti-inflammatory therapy in secondary prevention is the impact seen from a measurable structural gain versus manageable side effects, and the imaging endpoints here provide a mechanistic underpinning as they reveal the structural gain for any exposure (Libby and Everett, 2019). One interesting thing about the outcomes is that they reveal that the imaging and the biomarker findings put the arms in the order presented. The interleukin-targeted agent caused the highest reduction in C-reactive protein and interleukin-6 as well as the highest performance of fibres thickening and macrophages clearing, followed by colchicine which caused intermediate and last, placebo which caused the lowest. The finding that they moved arm in arm, that a condition they could measure in the blood tracked the condition of something measured in the artery – that makes the inference stronger that one causes the other (suppressing inflammation stabilises the plaque) and that they were unrelated consequences of treatment is less and less convincing. This is the kind of internal connectivity attainable by a mechanistic study that correlates the target, the drug and the structure of the product.

The colchicine finding could go hand in hand with the small but growing body of serial-imaging research. The results with colchicine and optical coherence tomography have been erratic: some studies indicated an increase in fibrous cap thickness compared to placebo, but when the intensive background statin regimen was taken into consideration, the increases in the two treatment groups were similar, and part of the effect of colchicine may be explained by this statin monotherapy.

The colchicine effect observed here, sizeable yet not large enough to impair an actively treated comparator, can rest comfortably within that literature, and help explain it: yes, colchicine does have an effect on stabilising the plaque over the statin treatment, but an effect of modest magnitude that can be either positive or negative depending on the size of the study. The larger, more consistent effect in a cohort of the same size, however, of the interleukin targeted agent, was unambiguous which is informative regarding the relative potency of the two approaches.

The methodology used here adds a value beyond the outcome obtained and will be useful to researchers in the field of anti inflammatory treatment for use as potential medication. Large trials, with thousands of patients over many years are needed to establish that a new agent lowers cardiovascular events and the burden of such trials has been a significant limitation in the field. A serial-imaging endpoint can offer a quick intermediate read, and an agent that doesn't stabilise the plaque by imaging is unlikely to be worth a large outcome trial, although one that does looks strong, as the interleukin-targeted agent in the study does here. This is what has happened in the development of lipid-lowering drugs, and it is what these present findings suggest should happen in the development of anti-inflammatory drugs: an imaging endpoint should precede and guide the outcome trials.

5. Strengths and limitations

The strengths of this trial lie in its design (randomised, double blind, placebo controlled, three arm), which allowed direct comparison of two different anti-inflammatory approaches to a shared control group; the use of

serial optical coherence tomography, the best intracoronary imaging modality available, where readers were blinded to the images; and the fact that the imaging endpoints were matched to the inflammatory targets of the therapies. This trial has some drawbacks. It was carried out at a single centre, with a small number of patients, and was industry-sponsored for the imaging endpoint rather than for the clinical endpoints that patients are interested in, so the stabilisation that it does show is a surrogated end-point, but nonetheless is a well-validated one. Thus, macrophage burden was indirectly measured using the optical signal and cap thickness is measured near the limit of resolution on OCD with some level of imprecision. The follow-up was for 12 months, when the early stabilisation will not necessarily have been reflected in the durability of this, and the trial does not prove that binding to a more functionally important structure will result in a proportionally greater number of fewer events.

6. Conclusion

Both colchicine and interleukin-targeted anti-inflammatory therapy were associated with plaque stabilisation and an increase in fibrous cap thickness, along with a decrease in lipid and macrophage content and extensive disappearance of the thin-cap fibroatheroma on serial optical coherence tomography in patients with lipid-rich coronary plaque who were on statin therapy. These findings link the established clinical efficacy of this class, a stabilising action, to a measurable change in the plaque and validate strategies for targeting the interleukin pathway upstream as well as for using serial plaque imaging to assess the pathway.

Ethical approval

The trial was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from every participant.

Conflict of interest

The authors declare that no conflict of interest exists in relation to this work.

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Data availability

The data supporting the findings of this study are available from the corresponding author on reasonable request.

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