The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction

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Background Following an acute myocardial infarction (MI), patients with persistently elevated biomarkers of inflammation, in particular C-reactive protein (CRP), are at significantly increased risk of further cardiovascular events. Colchicine is a unique anti-inflammatory medication that has shown promise in reducing such events in patients with stable coronary heart disease. The current study tested the ability of low dose colchicine to reduce CRP levels at 30 days after an acute MI, a key marker of future outcome, and its safety and tolerability in this setting.

Methods We conducted a randomized, double-blind, trial of low-dose colchicine (0.5 mg daily) or matching placebo in 237 patients admitted with an acute MI. The primary end-point was the proportion of patients with a residual high sensitivity CRP level ≥2 mg/L after 30 days of treatment, a threshold associated with a worse prognosis.

Results At 30-day follow-up, 44% of patients treated with colchicine had a CRP level ≥2 mg/L compared to 50% of those randomized to placebo (P = .35) and the median CRP in patients randomized to colchicine was 1.6 mg/L (interquartile range [IQR] 0.7–3.5) compared to 2.0 mg/L (IQR 0.9–4.0) in patients randomized to placebo (P = .11). The median absolute reduction in CRP levels was −4.3 mg/L (IQR −1.1 to −14.1) among colchicine treated patients and −3.3 mg/L (IQR −0.9 to −14.4, P = .44) in placebo treated patients. The relative reduction was a fall of 78% compared to a fall of 64% (P = .09). Low dose colchicine was well tolerated and did not reduce compliance with other secondary preventative medications at 30-days.

Conclusion Treatment with low dose colchicine was safe and well tolerated, but was not associated with a significantly increased likelihood of achieving a CRP level <2 mg/L or lower absolute levels of CRP 30 days after an acute MI. (Am Heart J 2019;215:62-9.)

Inflammation is central to the pathogenesis of atherosclerosis and its acute manifestions.[1-3] Likewise, patients with higher levels of the inflammatory biomarker C-reactive protein (CRP) 30 days following an acute myocardial infarction (MI) are at increased risk of recurrent infarction and death due to coronary heart disease (CHD).[4] It has been hypothesized, therefore, that therapies that specifically target inflammatory pathways might reduce recurrent vascular events in this setting. One such approach is to target specific pro-inflammatory cytokines.[5] This strategy was recently tested in the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) which demonstrated that treatment with a therapeutic monoclonal antibody targeting interleukin-1β significantly reduced major adverse cardiovascular events in survivors of an acute MI with persistently elevated CRP levels (≥2 mg/L).[6] Canakinumab is, however, a very costly treatment and was associated with a significant increase in sepsis and fatal infection.[6] There is, therefore, a clear need for cheaper and safe alternatives.

Colchicine, is one of the oldest anti-inflammatory agents available and has been used for decades to treat

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gout, familial Mediterranean fever and pericarditis. Its mechanisms of action are complex and not fully understood but include a reduced responsiveness of neutrophils to inflammatory signals[7,8] and suppressed activation of the NOD-like receptor protein 3 (NLRP3) inflammasome, a similar pathway to that inhibited by canakinumab.

Initial studies of colchicine in patients with CHD have been promising[9-13] but its ability to reduce inflammation in patients following an acute MI has not been adequately tested. Likewise, before embarking on a large and expensive end-point trial, it is essential that the safety and tolerability of colchicine is established in the post infarct setting. This is particularly important as the commonest side effect of colchicine is gastrointestinal upset, which has led to drug withdrawal in 10% to 15% of patients in prior clinical trials,[9,14] and might result in reduced adherence to other important secondary prevention medications. In addition, the combination of colchicine and high-dose statins has been rarely associated with myotoxicity[14] and there is a theoretical interaction between ticagrelor, a weak p-glycoprotein and CYP3A4 inhibitor, and colchicine.

The primary objective of the current study was to test the hypothesis that patients who are commenced on low dose colchicine early after acute MI would have significantly lower levels of CRP at 30 days, suggesting a lower risk of recurrent vascular events. The secondary aims were to test a) the effects of low dose colchicine on interleukin 6 (IL-6), a key regulator of inflammation and hepatic CRP production,[15] and b) the safety and tolerability of colchicine when initiated in patients early after an acute MI.

Methods

Study design and participants

This was an investigator initiated randomized, double-blind placebo controlled clinical trial. Patients were randomized in a 1:1 ratio to receive either colchicine 0.5 mg once daily or matched placebo for 30 days. Adult (>18 years old) patients were eligible for enrolment if they had sustained a type 1 acute MI (by the 3rd universal definition[16]) within the prior 7 days. All patients were recruited at Royal Perth Hospital, Perth, Western Australia.

Exclusion criteria included a) a history of myopathy, leukopenia or thrombocytopenia; b) an estimated glomerular filtration rate <45 mL/min per 1.73m^2; c) severe hepatic dysfunction (alanine aminotransferase >3 upper limit of normal [ULN]); d) therapy with a P-glycoprotein inhibitor (eg, cyclosporin, verapamil or quinidine) or a strong CYP3A4 inhibitor (eg, ritonavir, clarithromycin or ketaconazole); e) pregnancy, lactation or women of childbearing age not using contraception; f) an indication for colchicine therapy or g) any active inflammatory or infective disease process.

The study was registered prospectively with the Australian and New Zealand Clinical Trials Registry (ACTRN12615001194550) and approved by the local human research ethics committee. All participants provided written informed consent. Funding for this research was provided by the National Heart Foundation of Australia (grant number 100616) and the Royal Perth Hospital Medical Research Foundation. Colchicine and placebo were provided free of charge by Aspen Pharmaceuticals.

Trial procedures

Patients were recruited during their index admission following acute MI. Baseline clinical data, medications, biochemistry, full blood count and creatine kinase (CK) levels were recorded and blood tests were be repeated at 30 days. Troponin I levels at presentation and the peak levels during hospitalization were recorded using a high sensitivity assay (Abbott Laboratories, Abbott Park, IL). Left ventricular ejection fraction was assessed using standard methods (wherever possible a biplane Simpsons assessment) and determined by a consultant cardiologist blinded to treatment allocation. Levels of CRP were measured using a high sensitivity assay (Architect c16000 Analyzer, Abbott Laboratories, Abbott Park, IL) at baseline (immediately prior to commencing study treatment) and at 30 days. In addition, EDTA-plasma samples taken at baseline and 30 days were aliquoted and stored at −80 °C. IL-6 levels were subsequently measured by highly sensitive ELISA (R&D Systems, Minneapolis, MN). The sensitivity of this assay is 0.7 pg/mL with inter- and intra-assay coefficients of variation <7% and <5% respectively.

At 30 days patients underwent a standardized questionnaire to document the acceptability of the study procedures and any adverse events. These were graded by the patients as mild, moderate or severe. Patients were also asked to report their compliance with study medication (number of days when this was not taken). In addition, they were asked to return their study medication bottles with any remaining tablets and a pill count was performed.

Outcomes

The primary end-point was the proportion of patients with a residual CRP level ≥2 mg/L at 30 days. Pre-specified secondary end-points included the actual levels of CRP at 30 days and the relative and absolute change in CRP levels from baseline to 30 days. Other important pre-specified outcomes included a) the proportion of recruited patients completing the study; b) adverse events; c) participant-reported compliance with study medications; and d) death and major cardiovascular events (further MI or stroke) at 30 days.

Statistical analyses

Based on prior data[4] we estimated that 30 days after an acute MI approximately 42% of patients receiving a potent statin and aspirin will have a CRP level ≥2 mg/L. On this

basis, a study of 210 patients has 90% power (2 sided α = 0.05) to detect a 50% reduction in the prevalence of CRP levels above this threshold (i.e. to 21% with CRP $\geq$2 mg/L), allowing for 7% data loss. This reduction in levels of CRP is less than previously reported in patients with stable CHD treated with colchicine.[17]

Data are presented as numbers (%), mean (standard deviation) and median (interquartile range), as appropriate. The normality of the distribution of variables was assessed using the Shapiro–Wilk test. Continuous variables with skewed distributions are compared using the Kruskal-Wallis test and categorical variable using the χ^2 test or Fisher's exact test, as appropriate. All analyses were performed according to the intention to treat principle using SPPS v24. All p-values are 2-sided. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

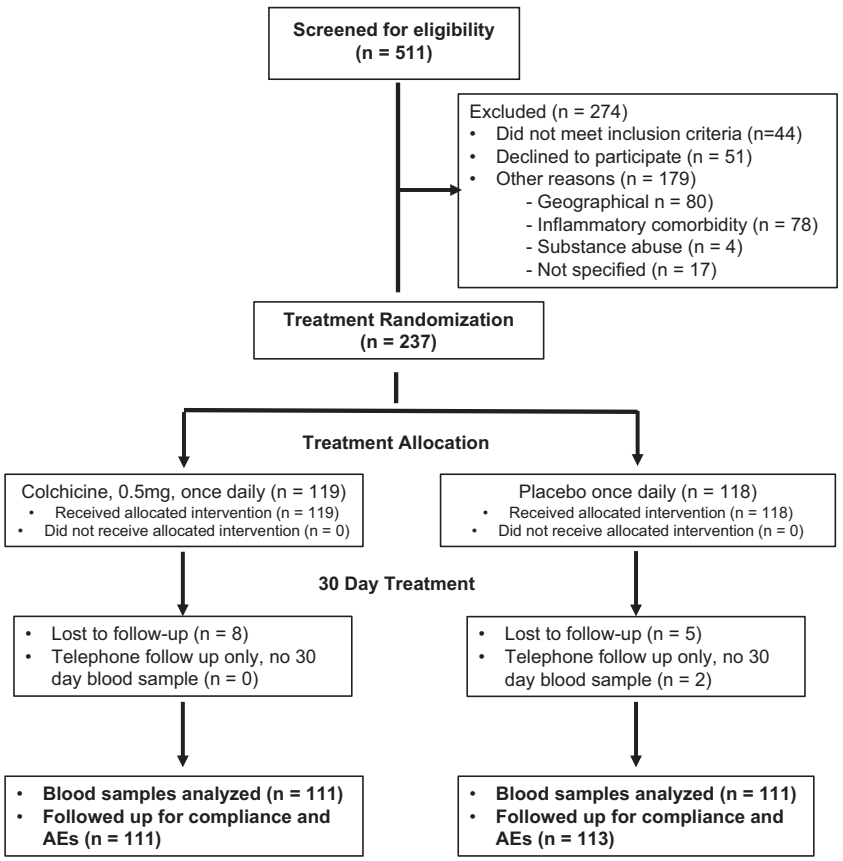
Results

Two hundred thirty seven patients were recruited between February 2016 and July 2017 and 224 patients (95%) completed the study (figure 1). Two patients, both of whom were randomized to placebo, were only able to undergo telephone follow up and did not have a follow up blood sample taken. The baseline demographic and clinical characteristics of both study groups were similar (table 1). The mean age of participants was 61 years and 182 (77%) were men. Baseline blood samples were taken a mean of 1.5 (SD 1.1) days and follow-up samples a mean of 33.3 (SD 5.6) days following the index MI.

Levels of high sensitivity C-reactive protein, interleukin 6 and other blood tests at 30 days

The median level of CRP at baseline was 7.4 mg/L (interquartile range 3.0–16.9) and was similar in both groups (P = .77, table 1 and figure 2a). At 30-day follow up, 44% (49 out of 111 participants) treated with colchicine had a CRP level $\geq$2 mg/L compared to 50% (56 out of 111 participants) of those randomized to placebo (P = .35, table 2) and the median CRP in patients randomized to colchicine was 1.6 mg/L (interquartile range 0.7–3.5) compared to 2.0 mg/L

Figure 1



CONSORT diagram.

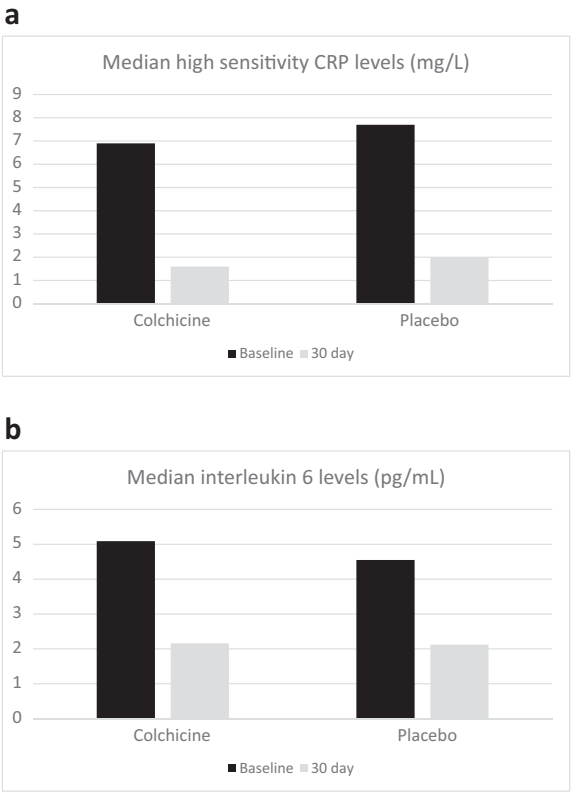
Table 1. Patient characteristics according treatment group

Characteristic	Total (n = 237)	Colchicine (n = 119)	Placebo (n = 118)	*P*
Age in years, mean (standard deviation)	61 (13.0)	61 (13.6)	61 (12.5)	.77
Male	182 (77%)	89 (75%)	93 (79%)	.46
Diabetes	52 (22%)	27 (23%)	25 (21%)	.78
Hypertension	112 (47%)	64 (54%)	48 (41%)	.04
Prior or current smoking	143 (60%)	77 (65%)	67 (57%)	.21
ST-elevation myocardial infarction	134 (56.5%)	63 (53%)	71 (60%)	.26
Previous myocardial infarction	36 (15%)	18 (15%)	18 (15%)	.98
Prior myocardial revascularization	27 (11%)	13 (11%)	14 (12%)	.60
Coronary angiogram during index admission	236 (99.6%)	118 (99%)	118 (100%)	.32
PCI during index admission	213 (90%)	105 (88%)	108 (91.5%)	.40
Left ventricular ejection fraction	52 (42–60)	55 (42–60)	50 (44–60)	.90
Aspirin	237 (99.6%)	118 (99%)	118 (100%)	.32
Second anti-platelet agent	233 (98%)	115 (97%)	117 (99%)	.18
Beta blocker	220 (93%)	111 (93%)	109 (92%)	.79
ACE inhibitor / Angiotensin receptor blocker	223 (94%)	114 (96%)	109 (92%)	.26
Statin	233 (98%)	115 (97%)	118 (100%)	.05
Body mass index,	28 (26–30)	28 (25–30)	28 (26–30)	.98
Admission high sensitivity troponin I (ng/L)	1345 (221–15,525)	885 (521–14,125)	2220 (298–16,425)	.19
Peak high sensitivity troponin I (ng/L)	5920 (611–30,450)	3250 (358–32,450)	9360 (975–28,875)	.18
Baseline hemoglobin, g/L	141 (15)	141 (15)	141 (16)	.94
Baseline white cell count, $x10^9$/L	9.0 (7.4–10.7)	9.0 (7.4–10.7)	9.2 (7.4–10.6)	.88
Baseline neutrophil count, $x10^9$/L	6.0 (4.7–7.7)	5.7 (4.7–7.5)	6.2 (4.7–7.8)	.39
Baseline lymphocyte count, $x10^9$/L	1.9 (1.5–2.4)	1.8 (1.5–2.4)	1.9 (1.5–2.3)	.46
Baseline creatinine, μmol/L	76 (68–87)	75 (68–87)	77 (69–87)	.38
Baseline high sensitivity C-reactive protein, mg/L	7.4 (3.0–16.9)	6.9 (3.1–14.8)	7.7 (3.0–18.9)	.77
Baseline interleukin-6, pg/mL	4.84 (3.10–9.50)	5.09 (3.42–9.99)	4.55 (3.05–8.33)	.15

Categorical data presented as n (%) and continuous data as median (interquartile range), unless otherwise stated.
PCI, percutaneous coronary intervention; ACE, angiotensin converting enzyme.

(interquartile range 0.9–4.0) in patients randomized to placebo ($P = .11$, figure 2a). The median absolute reduction in CRP levels at 30 days among colchicine treated patients was −4.3 mg/L (interquartile range −1.1 to −14.1) and in placebo treated patients it was −3.3 mg/L (interquartile range −0.9 to −14.4, $P = .44$). The relative reduction was a fall of 78% compared to a fall of 64% ($P = .09$).

Figure 2



Median levels of high sensitivity C-reactive protein and interleukin 6 at baseline and 30-days.

Levels of IL-6 at 30 days were similar in both groups both at baseline and follow-up and there were similar absolute and relative decreases in levels between baseline and 30 days (tables 1 and 2 and figure 2b). White cell counts, liver and muscle enzymes and other blood tests were also similar (tables 1 and 2).

Clinical outcomes, tolerability, and safety

There were no recorded deaths during the 30 day follow up period, though the vital status of 2 patients who were lost to trial follow-up was uncertain. Two patients suffered a major cardiac event (myocardial infarction) within 30 days; both of these participants had been randomized to placebo. Overall 38 patients (17% of the 224 who completed the study protocol) experienced any adverse event during 30 day follow up. Of these patients, 18 (of 111 who completed the study, 16%) had received colchicine and 20 (of the 113 who completed the study, 18%) placebo (P = .859). Fifteen patients were readmitted to hospital within 30 days of their index MI (1 due to recurrent non-ST-elevation myocardial infarction, 1 due to stent thrombosis, 7 due to non-cardiac chest pain, 2 due to pericarditic symptoms, 1 due to breathlessness, 1 due to vasovagal syncope, 1 for insertion of an implantable defibrillator and 1 due to hematuria). Of these 3 were in the colchicine treated group (out of 111, 3%) and 12 were in the placebo group (out 113, 11%; P = .029).

Gastrointestinal symptoms occurred in 18 patients (8%), 12 who received colchicine (11% of the 111 patients in this group who completed the study) and 6 who received placebo (5% of the 113 patients in this group who completed the study; P = .147). Nine patients rated these to be moderate or severe (4 who received colchicine and 5 who received placebo).

Adherence with study and other secondary prevention medications was generally good (table 3).

Discussion

The main findings of this study are that treatment with low dose colchicine (0.5 mg daily) is not associated with a significantly increased likelihood of achieving a CRP level <2 mg/L or lower absolute levels of CRP 30 days after an acute MI. Nevertheless, a trend in this direction was observed and, importantly, treatment with colchicine in

Table 2. Blood results at 30-day follow-up

	Colchicine group (n = 111)	Placebo group (n = 111)	*P*
High sensitivity C-reactive protein ≥2 mg/L	49 (44%)	56 (50%)	.35
High sensitivity C-reactive protein, mg/L	1.6 (0.7–3.5)	2.0 (0.9–4.0)	.11
Absolute change in C-reactive protein, mg/L	−4.3 (−1.1 to −14.1)	−3.3 (−0.90 to −14.4)	.44
Relative change in C-reactive protein (%)	−78 (−44 to −92)	−64 (−30 to −88)	.09
White cell count, $x10^9$/L	6.7 (5.8–8.7)	7.2 (6.1–8.8)	.22
Neutrophil count, $x10^9$/L	4.3 (3.4–5.4)	4.3 (3.7–5.8)	.25
Lymphocyte count, $x10^9$/L	1.9 (1.4–2.3)	1.8 (1.5–2.1)	.64
Hemoglobin, g/L	140 (133–151)	142 (132–152)	.36
Creatine kinase, U/L	116 (81–165)	101 (70–138)	.14
Alanine aminotransferase, U/L	33 (25–54)	33 (26–49)	.84
Gamma glutamyl transferase, U/L	30 (20–56)	31 (25–49)	.68
Interleukin-6, pg/mL	2.16 (1.72–2.76)	2.12 (1.66–2.77)	.95
Absolute change in interleukin-6, pg/mL	−2.44 (−0.94 to −7.56)	−2.33 (−0.56 to −5.15)	.21
Relative change in interleukin-6 (%)	−58 (−32 to −79)	−52 (−19 to −66)	.16

Categorical data presented as n (%) and continuous data as median (interquartile range).

this setting was safe and well tolerated. Readmission rates were significantly lower in the colchicine treated patients but the numbers are small, the events were diverse and the majority were for relatively benign reasons and/or events that seem unlikely related to the trial medication. Thus, the observed differences seem likely to be due to chance.

Prior studies

There is great interest in using therapies that specifically target inflammatory mechanisms in order to reduce the risk of atherosclerosis and its acute complications.[18] Potential treatments include monoclonal antibodies that target specific pro-inflammatory cytokines, such as canakinumab directed against IL-1β which has recently

Table 3. Adverse events and adherence to study and concomitant medications at 30-day follow up

	Colchicine group (n = 111)	Placebo group (n = 113)	*P*
Any adverse event	18 (16%)	20 (18%)	.859
Re-admission to hospital	3 (3%)	12 (11%)	.029
Adverse event not requiring hospitalisation[1]	16 (14%)[1]	8 (7%)	.087
Gastrointestinal	12 (11%)	6 (5%)	.147
Other[2]	4 (4%)	2 (2%)	.440
Discontinued study treatment due to adverse event	2 (2%)	4 (4%)	.439
Took ≥25 days of study treatment[3]	102 (92%)	103 (93%)[3]	1.000
Other medications being taken at follow up[3]			
Aspirin	110 (99%)	111 (100%)[3]	1.000
Second anti-platelet agent	106 (95%)	110 (99%)[3]	.212
Statin	107 (96%)	109 (98%)[3]	.683
Beta-blocker	105 (95%)	109 (98%)[3]	.280
ACE inhibitor or angiotensin receptor blocker	104 (94%)	106 (95%)[3]	.768

ACE, angiotensin converting enzyme.
1 One patient had readmission to hospital with chest pain (non-cardiac) and also independently experienced an adverse event not requiring hospitalization (gastrointestinal symptoms); [2] other adverse events consisted of cough (×2), rash, palpitation, breathlessness and bruising; [3] in 2 patients (both in the placebo group) these data were not recorded.

been shown to significantly reduce major adverse cardiovascular events in patients with a previous MI and residual CRP levels ≥2 mg/L, already receiving high quality conventional secondary prevention. Recently, however, the Cardiovascular Inflammation Reduction Trial investigators, reported disappointing results from a trial of 4786 patients with a prior history of myocardial infarction or multi-vessel coronary artery disease plus diabetes or metabolic syndrome randomized to low-dose methotrexate or placebo.[19] This trial was stopped prematurely after a median of 2.3 years follow up, due to crossing the pre-specified futility boundary. Despite well documented anti-inflammatory actions and supportive observational data, low dose methotrexate (15–20 mg weekly) failed to significantly reduce circulating levels of CRP, IL-1β or IL-6 when compared to placebo.[19] Likewise, there was no significant reduction in either the original primary outcome (cardiovascular death, non-fatal MI or non-fatal stroke) or an expanded outcome that also included hospitalization for unstable angina that required urgent revascularisation.[19]

Colchicine is a cheap, once daily, oral treatment that targets similar inflammatory mechanisms to canakinumab, seems safe and well tolerated by patients receiving long term therapy and has shown considerable promise in early studies of patients with CHD.

In the Low Dose Colchicine (LoDoCo) study, treatment with 0.5 mg colchicine per day in addition to standard treatment in patients with stable CHD significantly reduced the risk of developing an acute coronary syndrome, an out of hospital cardiac arrest or non-cardioembolic stroke.[9] This study was not, however, placebo controlled, though end-points were adjudicated by clinicians blinded to what treatment the patients had received. A further double-blind randomized controlled trial in a similar population is currently underway.

In patients with an acute coronary syndrome colchicine reduces the local production of IL-1β, IL-18 and IL-6, as measured in coronary sinus blood samples.[10] These reductions in all 3 inflammatory cytokines were marked (with a reduction in IL-6 of 88%) and occurred after only 24 hours of colchicine therapy. In addition, short term (24 hours) treatment with colchicine also reduces inflammasome-dependent inflammation in patients following an acute coronary syndrome, as measured by the in vitro production of IL-1β and caspase-1 protein by monocytes.[11] Thus, there are plausible biological mechanisms supporting the hypothesis that prompt treatment after acute MI would result in an early reduction in pro-inflammatory pathways and potentially a lower risk of clinical events.

Short term (5 days) treatment with colchicine appears to reduce the extent of myocardial necrosis after ST-elevation MI[12] and long term treatment has been associated with reduced features of plaque instability on coronary artery CT angiography, in particular low intensity plaque volume.[13] In this latter study treatment with colchicine 0.5 mg daily was also associated with a significantly lower level of CRP at 1 year, mean value in colchicine treated patients (n = 40) 1.85 mg/L (SD 0.9) versus 2.26 mg/L (SD 1.05) in controls (n = 40), with a 37% reduction observed in colchicine treated patients compared to a 15% reduction in untreated patients. Although this study was not randomized or placebo controlled the assessment of CT scans was undertaken by observers blinded to whether the subject had received colchicine or not. Likewise, the impact of colchicine on CRP levels was broadly similar to the current double-blinded placebo controlled trial.

Another small study has also assessed the impact of colchicine on CRP levels after an acute coronary syndrome or stroke.[20] This randomized 80 patients (73 out of 80, 91% following an acute coronary syndrome) to colchicine 1 mg daily or placebo for 30 days. At follow-up patients allocated to colchicine had a median CRP level of 1 mg/L compared to a median level of 1.5 mg/L in placebo treated patients (P = .22). Likewise, the percentage of patients with a CRP level <2 mg/l was higher in the colchicine treated group (77%) compared to placebo (62%). Though this did not attain statistical significance (P = .18) this study was very underpowered (CRP levels at 30 days were only available in 68 patients, 31 who had received colchicine and 37 who had received placebo). The results are, however, consistent with the findings from the current study and suggest that colchicine might have a modest, but potentially clinically beneficial, effect in this setting and that further work in this area is required.

Strengths and limitations

This study is the largest to date assessing the tolerability of colchicine following acute MI and its effects on markers of inflammation in patients receiving contemporary treatment, including a range of evidence based secondary preventative medications. Nonetheless, it has several limitations. It is a small, single center study which was not powered to demonstrate any impact of colchicine on adverse cardiovascular events. Likewise, it was powered to demonstrate a large reduction in levels of CRP, which was not observed in the current study, though larger reductions in CRP levels have been reported in patients with stable CHD treated with colchicine (albeit at a slightly higher dose of 0.5 mg twice daily).[17] It is possible that a larger study would have shown a significant reduction in such levels assuming a smaller, but still clinically relevant, effect size.

The other main limitation of the current trial is that it only tested the tolerability of low dose colchicine over 30 days. Other studies have, however, suggested that it is well tolerated at a dosage of 0.5 mg daily in patients with stable CHD. Thus, the main until now unresolved issue was its tolerability in patients receiving many other

medications, some of which have theoretical or known interactions with colchicine, often for the first time after an acute MI: a setting where the adverse effects of one medication may have implications for compliance with other treatments that are known to have important benefits. The current study provides reassurance in this respect.

In conclusion, we found no significant reduction in the median level of CRP, the absolute or relative reduction in levels or the percentage of patients who had levels of CRP below 2 mg/L after 30-days. All were, however, lower in colchicine treated patients which is consistent with prior data. We believe, therefore, that the totality of evidence supports the need for a large scale outcome trial in patients with recent MI. Importantly in this regard the current study demonstrates the safety and tolerability of low dose colchicine after acute MI.

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Declarations of interest

The authors have no conflicts of interest related to this work.

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