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Colchicine for symptomatic coronary artery disease after percutaneous coronary intervention

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ABSTRACT

Background Percutaneous coronary intervention (PCI), the preferred coronary reperfusion strategy, induces endothelial trauma which may mount an inflammatory response. This has been shown to increase the likelihood of further major adverse cardiovascular events (MACE). Colchicine, a cheap and widely used anti-inflammatory has shown promise in improving cardiovascular outcomes. We aimed to perform a systematic review and meta-analysis to study the effects of colchicine in patients with symptomatic coronary artery disease (CAD) who have undergone PCI.

Method We systematically reviewed and meta-analysed 7 randomised controlled trials including a total of 6660 patients (colchicine group: 3347, control group: 3313; mean age=60.9±10). Six studies included participants who had a ≤13.5-day history of acute coronary syndrome (ACS). One study included patients with both ACS and chronic coronary syndrome. The follow-up of studies ranged from 3 days to 22.6 months.

Results The use of colchicine in patients who underwent PCI significantly reduced MACE outcomes (risk ratio 0.73 (95% CI 0.61 to 0.87); p=0.0003) with minimal heterogeneity across the analysis (I^2=6%; P for Cochran Q=0.38). These results were driven mainly by the reduction in repeat vessel revascularisation, stroke and stent thrombosis. The number needed to treat to prevent one occurrence of MACE was 41.

Conclusion Colchicine significantly reduced the risk of MACE in patients with CAD who underwent PCI, mostly in the reduction of repeat vessel revascularisation, stroke and stent thrombosis. The efficacy of colchicine should be further studied by distinguishing its use alongside different stent types and dosing regimens.

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Key questions

What is already known about this subject?

► Verma *et al*, Xia *et al* and Samuel *et al* have shown a reduction in composite major cardiovascular adverse outcomes in patients with coronary artery disease (CAD) when low-dose colchicine is used alongside guideline-therapy consisting of pharmaceutical±interventional therapy. Furthermore, Khandkar *et al*, Masson *et al* and Katsanos *et al* showed a reduction specifically of stroke incidence in patients with CAD when treated with low-dose colchicine. However, new results from major primary trials investigating the benefits of colchicine in CAD have emerged recently.

What does this study add?

► Our study adds to the literature by quantifying the benefits of the anti-inflammatory effects of colchicine following percutaneous coronary intervention (PCI). Our study is novel in two ways: (1) we study the effects of colchicine only in patients who underwent both PCI and medical therapy and (2) we provide an updated systematic review and meta-analysis including a recently published major trial - the Colchicine in Patients with Acute Coronary Syndrome (COPS) trial.

How might this impact on clinical practice?

► Colchicine is a cheap and relatively low risk medication which may be beneficial (27% risk reduction, number needed to treat=41) for patients undergoing PCI in reducing major cardiovascular events and disease morbidity. However, more studies need to be conducted to investigate the effects of colchicine in a periprocedural versus secondary prevention setting.

INTRODUCTION

Current coronary artery disease (CAD) treatment is multifaceted, involving a combination of lifestyle modifications, drugs such as antihypertensive regimens, antithrombotic therapy, lipid-lowering therapy and if necessary, medical procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery.[1] Despite these treatments, residual risk of cardiovascular events during the first 365 days after a primary myocardial infarction (MI) remains at 22%,[2] suggesting that the current treatment regime can be further optimised.

The role of inflammation in all stages of pathogenesis of CAD has been long established.[3] Higher levels of inflammatory markers are associated with the occurrence of coronary thrombosis and acute coronary

syndromes (ACS).[4] Endothelial damage during PCI with stent implantation induces a further inflammatory response.[5] The periprocedural inflammatory status of patients undergoing PCI has been shown to independently affect the prognosis of subsequent cardiovascular events.[6 7] Post-PCI, MI occurred in 7.5% of patients with persistent residual inflammatory risk, compared with 4.3% of patients with low residual inflammatory risk.[8] Furthermore, studies have also shown an increased risk of restenosis, target vessel revascularisation (TVR) and death in patients with raised inflammatory markers.[8 9] Thus, it has been hypothesised that reducing inflammation after an acute MI should improve patient outcomes.

Targeting inflammation is an emerging avenue for novel therapeutic agents in an ACS setting. The beneficial role of anti-inflammatories in CAD was emphasised following the publication of the Canakinumab Anti-inflammatory Thrombosis Outcome Study, which demonstrated a reduction of secondary cardiovascular events in patients with a raised high-sensitivity C reactive protein by inhibition of the NLRP3 inflammasome-dependent pathway via interleukin-1β[3] pathway, without affecting lipid levels.[10] Colchicine, a low-cost anti-inflammatory traditionally used in gout, has garnered new research interest as a potential candidate in cardiovascular disease prevention. Recent randomised controlled trials (RCTs) have demonstrated beneficial effects of colchicine for secondary cardiovascular disease prevention in patients with CAD.[11–20] The early administration of colchicine as an adjunct to PCI for secondary prevention of cardiovascular events, however, is still uncertain. Our meta-analysis aimed to pool evidence by including RCTs to assess the efficacy of colchicine when used as an adjunct to PCI for the prevention of major adverse cardiovascular events (MACE).

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis were conducted as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and using the PICO tool (p=patients with symptomatic CAD who underwent PCI; I=colchicine in addition to conventional guideline therapy; C=placebo in addition to conventional guideline therapy; O=major adverse cardiovascular events). A structured search was performed on EMBASE, MEDLINE and Cochrane Library for articles published from inception up to February 2021. Medical subject heading (MESH) terms and keywords were used to search for articles related to colchicine, acute coronary syndrome, acute coronary disease and percutaneous coronary intervention. Further details on the database and search terms used are shown in online supplementary material. After removal of duplicate articles, two reviewers (KLA and AKo) independently screened the articles using a two-step approach. First, abstracts and titles were screened for eligibility. The reviewers then screened the full-text articles. References of articles pertinent to the research question were screened for suitability (backward snowballing). The screening process is outlined in the PRISMA Flow Diagram (online supplementary material figure 1).

Inclusion and exclusion criteria

Our inclusion criteria were as follows; (1) studies which compare the efficacy of colchicine compared with placebo or no colchicine, in patients who underwent PCI, with reporting of MACE, (2) patients treated as per local guidelines for CAD, (3) study must be an RCT and (4) studies must be in English language.

Data collection and risk of bias assessments

Authors KLA and HLL extracted data systematically from the RCTs and used a standardised Microsoft Excel spreadsheet to record study design, population, size in colchicine arm (treatment) versus control arm (placebo or no treatment), age, sex, hypertension, diabetes mellitus, smoking history, PCI, antiplatelet therapy, statin therapy, time of colchicine initiation, colchicine dose, median follow-up, primary outcome and secondary outcome (table 1).

Each included full-text study was appraised using the Cochrane Risk Assessment Tool by authors KLA and AKu. The Cochrane Risk Assessment Tool Analysis and Overview analysis of Cochrane Risk Assessment can be found in online supplementary figures 2 and 3.

Outcomes

Primary outcome measures were the MACE including in-stent restenosis (ISR), repeat vessel revascularisation, stent thrombosis, stroke, resuscitated cardiac arrest and all cause death. Contrary to the outcomes registered on International Prospective Register of Systematic Reviews, we did not include MI as part of MACE because this outcome was not reported in the included studies.

Secondary outcome measures include ISR, repeat vessel revascularisation, stent thrombosis, stroke and all-cause death.

Statistical analysis

The Mantel-Haenszel random effects model[21] was used to calculate the pooled relative risk (RR) and their corresponding 95% CIs of stroke incidence and safety outcomes of the RCTs included in this study. Heterogeneity was assessed using the I^2 and Cochran Q statistics. Number needed to treat (NNT) was calculated using the formula NNT=1/[(1−RR) × outcome incidence in control groups].[22] Funnel plots were assessed for publication bias by visual assessment. Using the 'metafor' package for R, the trim-and-fill method was applied to adjust for potential bias.[23] All statistical analyses were conducted using the Cochrane Collaboration's Review Manager (RevMan V.5.3) Software Package (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014).

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Table 1 Characteristics of studies included in the systematic review.

Study	O'Keefe (1992)[11]	Deftereos (2013)[12]	CISR (2019)[13]	COLCOT (2019)[14]	LoDoCo-MI (2019)[15]	Colchicine-CI (2020)[16]	COPS (2020)[17]
Design	Double blinded RCT	Double blinded RCT	Unblinded RCT	Double blinded RCT	Double blinded RCT	Double blinded RCT	Double blinded RCT
Population	Patients who had undergone successful coronary angioplasty. Premenopausal women excluded.	Patients undergoing PCI with a BMS who are of 40–80 years of age, with DM and a contraindication to DES.	Patients above the age of 40 who underwent PCI with BMS or DES for treatment of stable IHD or ACS. Women of childbearing potential excluded. A: BMS +Colchicine B: BMS only C: DES	Patients who had an MI within 30 days before enrolment and had completed any planned percutaneous revascularisation procedures. Excluded if had stroke within previous 3 months, type two index MI, recent or planned CABG.	Patients who sustained a type one acute MI within the prior 7 days. Pregnant, lactating or women of childbearing age not on contraception excluded.	Patients aged above 18 years with suspected ischaemic heart disease or ACS referred for clinically indicated coronary angiography and PCI.	Patients presented with ACS and had evidence of CAD on coronary angiography, managed with either PCI or medical therapy. Excluded if needing surgical revascularisation.
No (T/C)	197 (130/67)	196 (100/96)	90 (30/30/30)	4745 (2366/2379)	237 (119/118)	400 (206/194)	795 (396/399)
Mean age, yrs ±*SD*	60.0 T: 59 C: 62	63.6±7.0 T: 63.7±6.9 C: 63.5±7.2	60.03±7.3 A: 57.5±6.7 B: 62.6±3 C: 61.8±7	60.5±10.7 T: 60.6±10.7 C: 60.5±10.6	61 ±13.0 T: 61±13.6 C: 61±12.5	66.2±11.4 T: 65.9±9.9 C: 66.6±10.2	59.8±10.3 T: 59.7±10.2 C:60.0±10.4
Males, n (%)	169 (85.8)	128 (65.3)	75 (83.3) A: 228 (93.3) B: 21 (70.0) C: 26 (86.7)	3836 (80.8)	182 (76.8)	374 (93.5)	632 (79.5)
HTN, n (%)	N/A	95 (48.5)	42 (47.8) A: 18 (60.0) B: 11 (36.7) 14 (46.7)	2421 (51.0)	112 (47.3)	367 (91.8)	400 (50.3)
DM, n (%)	24 (8.08)	196 (100)	39 (43.3) A: 15 (50.0) B: 10 (33.3) C: 14 (46.7)	959 (20.2)	52 (21.9)	231 (57.8)	151 (20.0)
Smoking history, n (%)	N/A	74 (37.8)	32 (35.6) A: 9 (30.0) B: 12 (40.0) C: 10 (33.3)	1416 (29.8)	143 (60.3)	282 (70.5)	277 (34.8)
PCI, n (%)	100 (angioplasty)	196 (100)	90 (100) A: 30 (100) B: 30 (100) C: 30 (100)	4408 (92.9)	237 (100)	400 (100)	691 (86.9)
Antiplatelet, n (%)	N/A	N/A	89 (98.9) A: 30 (100) B: 29 (97.0) C: 30 (100)	4686 (98.8)	237 (100)	362 (90.5)	784 (98.6)
Statin, n (%)	N/A	N/A	90 (100) A: 30 (100) B: 28 (93.3) C: 30 (100)	4696 (99.0)	233 (98.3)	362 (90.5)	786 (98.9)
Colchicine dose	0.6 mg BD	0.5 mg BD	0.5 mg BD	0.5 mg OD	0.5 mg OD	One off 1.2 mg, followed by 0.6 mg	0.5 mg BD for first month, followed by 0.5 mg OD for 11 months

Continued

Table 1 Continued

Study	O'Keefe (1992)[11]	Deftereos (2013)[12]	CISR (2019)[13]	COLCOT (2019)[14]	LoDoCo-MI (2019)[15]	Colchicine-CI (2020)[16]	COPS (2020)[17]
Time of colchicine initiation	Before angioplasty or within 24 hours after angioplasty.	From day of index PCI (within 24 hours).	After BMS implantation.	After assignment to group.	Within 7 days post-MI.	1.2 mg given 1 to 2 hours before coronary angiography, followed by 0.6 mg immediately before PCI.	After assignment to group.
Median follow-up	5.5 months	6 months	6 months	22.6 months	30 days	30 days	12 months
Primary outcome	Angiographic ISR measured by electronic callipers.	Angiographic ISR and IVUS-ISR (defined as in-stent minimum lumen area of <4 mm^two at follow-up).	Clinical ISR at 6 months, defined as recurrence of angina pectoris or evidence of MI (>50% restenosis).	Composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalisation for angina leading to coronary revascularisation in a time-to-event analysis.	Proportion of patients with a residual hs-CRP level ≥2 mg/L at 30 days.	PCI-related myocardial injury, according to Troponin I measurements.	Composite of death from any cause, ACS, ischaemia-driven urgent revascularisation and non-cardioembolic ischaemic stroke.
Secondary outcome	Adverse drug effects in placebo or colchicine.	Angiographic and IVUS parameters of lumen loss and in-stent neointimal hyperplasia, including late lumen loss (angiography), lumen area loss, percentage of neointima volume, and normalised neointima volume (IVUS).	Target-vessel revascularisation and stent thrombosis within 6 months.	Secondary end points consisted of the components of the primary efficacy end point; a composite of death from CV causes, resuscitated cardiac arrest, MI or stroke; and total mortality in time-to-event analyses. Coronary revascularisation, hospitalisation for heart failure, atrial fibrillation, and deep vein thrombosis or pulmonary embolus were prespecified as exploratory end points in the protocol.	Actual levels of hs-CRP at 30 days and the relative and absolute change in hs-CRP levels from baseline to 30 days. Others: proportion of recruited patients completing the study, adverse events, participant-reported compliance with study medications, and death and major CV events at 30 days.	Occurrence of 30-day MACE, a composite of the earliest occurrence of death from any cause, nonfatal MI, or target vessel revascularisation, PCI-related MI. Nonfatal MI defined as PCI-related or type 1 MI.	Components of the primary endpoint, as well as hospitalisation for chest pain. Post hoc analysis performed after unblinding of trial using cardiovascular death as an outcome measure.

ACS, acute coronary syndrome; BD, two times per day; BMS, bare metal stent; C, control; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CRP, C reactive protein; CV, cardiovascular; DES, drug-eluting stent; DM, diabetes mellitus; hs-CRP, high-sentivity C reactive protein; HTN, hypertension; ISR, in-stent restenosis; IVUS, intravascular ultrasound; MI, myocardial infarction; N/A, not available; OD, once daily; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; T, treatment; TvC, treatment versus control; UA, unstable angina.

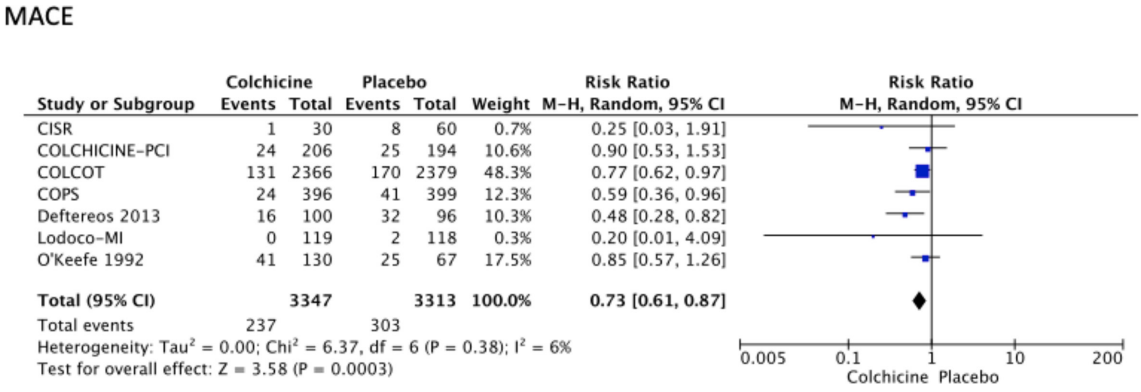

Figure 1 Primary outcome. Forest plot for MACE, showing pooled RRs of RCTs comparing patients who underwent PCI in the colchicine versus control group. RRs are random effects estimates calculated by Mantel-Haenszel (M-H) method. CISR, Colchicine Treatment for Prevention of in Stent Restenosis; COLCHICINE-PCI, Colchicine in Percutaneous Coronary Intervention; COLCOT, Colchicine Cardiovascular Outcomes Trial; COPS, Colchicine for Patients with Acute Coronary Syndrome; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCTs, randomised controlled trials; RRs, risk ratios.

RESULTS

A total of 121 abstracts and titles were screened, of which 105 were excluded as they did not study colchicine use in patients who underwent PCI. Of the 16 full-text articles assessed for eligibility, 7 were included in our systematic review and meta-analysis (figure 1). A list of excluded studies with reasons for exclusion can be found in online supplemental materials.

A total of 6660 participants (mean age: 60.9±10.6, colchicine group=3347, control group=3313) were included in this study. Six studies recruited participants with a history of ACS of ≤13.5 days. O'Keefe *et al*, recruited patients with both ACS and CCS.[11] All participants from four studies,[12 13 15 16] 92.9% from Tardif *et al*[14] and 86.9% from Tong *et al*[17] had PCI for ACS. All participants in O'Keefe *et al* had elective balloon angioplasty. Colchicine was administered to patients after PCI in five studies,[12–15 17] before PCI in one study,[16] and either before or after balloon angioplasty in one study.[11] The median follow-up ranged from 3 days to 22.6 months. The incidence of MACE in the colchicine group and control group were 237 (7.08%) and 303 (9.15%), respectively, and their individual components are summarised in table 2.

Risk of selection and detection bias were unclear in three studies which did not provide information on random sequence generation and outcome blinding (O'Keefe *et al*,[11] Deftereos *et al*[12] and Habib *et al*.[13] A summary of the Cochrane Risk Assessment Tool can be found in online supplemental figures 2 and 3.

Primary outcome

Quantitative analysis of pooled outcomes from seven RCTs showed that colchicine in patients who underwent PCI significantly reduced MACE outcomes (risk ratio 0.73 (95% CI 0.61 to 0.87); p=0.0003) with minimal heterogeneity across the analysis (I^2=6%; P for Cochran Q=0.38) (figure 1).

Secondary outcomes

Three studies[11–13] reported angiographically proven ISR. Meta-analysis showed no statistical significance in colchicine use for reduction of ISR for patients who underwent PCI (risk ratio 0.64 (95% CI 0.36 to 1.15); p=0.14, I^2=58%; P for Cochran Q=0.09) (figure 2).

Meta-analysis of four studies[13 14 16 17] showed a significant reduction in repeat vessel revascularisation when colchicine was used for patients who underwent PCI (risk ratio 0.47 (95% CI 0.31 to 0.72); p=0.0004, I^2=0%; P for Cochran Q=0.58) (figure 2).

Furthermore, there was also a significant reduction in stent thrombosis when colchicine was given to patients who underwent PCI (risk ratio 0.50 (95% CI 0.25 to 0.98); p=0.05, I^2=0%; P for Cochran Q=0.95) (figure 2).

Pooled outcomes of seven RCTs showed a significant risk reduction in stroke when colchicine was used for patients who underwent PCI (risk ratio 0.50 (95% CI 0.31 to 0.81); p=0.005, I^2=0%; P for Cochran Q=0.48) (figure 2).

There was no significant difference in all-cause mortality whether colchicine is used in patients who underwent PCI (risk ratio 1.12 (95% CI 0.49 to 2.58); p=0.79, I^2=23%; P for Cochran Q=0.26) (figure 2).

Publication bias

Visual inspection of the funnel plot (figure 3) reveals asymmetrical scatter with studies of larger effect sizes potentially being suppressed in the positive direction. This indicates significant risk of publication bias for our primary efficacy. The trim-and-fill identified two missing studies on the right side (online supplemental material). This model estimate risk ratio 0.7492 (95% CI 0.5873 to 0.9110); p<0.0001) with minimal heterogeneity across the analysis (I^2=0%; P for Cochran Q=0.9954). The findings remain statistically significant after adjusting for missing studies.

Table 2 Summary of results of studies included in the systematic review

Study	O'Keefe (1992)[11]	Deftereos (2013)[12]	CISR (2019)[13]	Colcot (2019)[14]	LoDoCo-MI (2019)[15]	Colchicine-PCI (2020)[16]	COPS (2020)[17]
N (T/C)	197 (130/67)	196 (100/96)	90 (A: 30/B: 30/C: 30)	4745 (2366/2379)	237 (119/118)	400 (206/194)	795 (396/399)
In-stent restenosis, TvC (%)	41.0v45.0	Angio-ISR: 16.0v33.0 IVUS-ISR: 24.0v43.0	3.3v23.3v0	N/A	N/A	N/A	N/A
Repeat vessel revascularisation, TvC (%)	N/A	4.0v5.2	3.3v26.7v0	1.1v2.1	N/A	N/A	0.8v3.0
Stent thrombosis, TvC (%)	N/A	N/A	0v1.7	N/A	0v0.8	N/A	2.8v5.5
Stroke, TvC (%)	N/A	1v0	N/A	0.2v0.8	N/A	1v0	0.5v1.5
Resuscitated cardiac arrest, TvC (%)	N/A	N/A	N/A	0.2v0.3	N/A	N/A	N/A
All-cause mortality, TvC (%)	0.8v3.0	1.0v1.0	N/A	1.8v1.8	0 (0.00)	0.5v0.5	2.0v3.0

CISR 2019: A-Bare metal stent +colchicine.
CISR, Colchicine Treatment for Prevention of in Stent Restenosis; Colchicine-PCI, Colchicine in Percutaneous Coronary Intervention; COPS, Colchicine for Patients with Acute Coronary Syndrome; ISR, in-stent restenosis; IVUS, intravascular ultrasound; LoDoCo-MI, The Low Dose Colchicine after Myocardial Infarction ; MI, myocardial infarction; N/A, not available; PCI, percutaneous coronary intervention; TvC, treatment vs control.

DISCUSSION

Our meta-analysis provides evidence that administration of colchicine early on, at the time of PCI reduces MACE (27% risk reduction; NTT=41). This risk reduction for the primary end point was mainly driven by lower rates of repeat vessel revascularisation, stroke and stent thrombosis.

The beneficial role of colchicine is likely explained by its wide-ranging effects on the inflammatory process. Colchicine concentrates in leukocytes and has a primary antimitotic effect against microtubule and spindle formation.[24] It also induces downregulation of various inflammatory pathways further impacting neutrophil activation and recruitment, platelet aggregation and the expression of various cytokines and interleukins.[24] From a clinical perspective, several studies demonstrated an increase of intracardiac production of the inflammasome-specific cytokines IL-1β, IL-18 and downstream IL-6 in patients presenting with ACS[25] and that acute colchicine administration was associated with a significant reduction in the transcoronary production of these cytokines.[26 27]

While colchicine showed no significant effect on reducing in-stent stenosis in this study, it should be noted that there was some heterogeneity between the three RCTs studied for this outcome. O'Keefe *et al*[11] included patients who underwent balloon angioplasty with no stent implantation, the pathogenesis of which involves elastic recoil, vessel remodelling and neointimal proliferation.[28] Colchicine possesses antiproliferation and anti-inflammatory properties, which may suggest that it is more suitable for PCI with stent implantation where the pathogenesis involves mainly neointimal proliferation and neoartherosclerosis.[29] Furthermore, all patients in O'Keefe *et al* had a 6-month follow-up angiogram, suggesting that the findings included patients who potentially had asymptomatic in-stent stenosis. Meta-analysis of the other two papers alone (Habib *et al* and Deftereos *et al*) shows a significant reduction of 53% in ISR in the treatment group (risk ratio 0.46 (95% CI 0.28 to 0.78); p=0.003), with no heterogeneity seen across the studies (I^2=0%; P for Cochran Q=0.09). Hence, another plausible explanation and hypothesis could be that colchicine reduces the severity of in-stent stenosis and hence reduces symptomatic stenosis. This is also supported by the fact that the rate of repeat vessel revascularisation is lower than ISR in this meta-analysis.

Limited data are available on the risks and impact of repeat vessel revascularisation. Since the advent of drug-eluting stents (DES), the incidence of repeat vessel revascularisation has improved as compared with the use of bare-metal stents.[30] However, despite optimal medical management and the use of DES, the 5-year cumulative incidence of repeat vessel revascularisation were demonstrated in two trials, to be as high as 20.33[31] and 25.9%.[32] Our study demonstrates that colchicine confers a risk reduction of 53% (risk ratio 0.47 (95% CI 0.31 to 0.72); p=0.0004, I^2=0%; P for Cochran Q=0.58) in repeat vessel

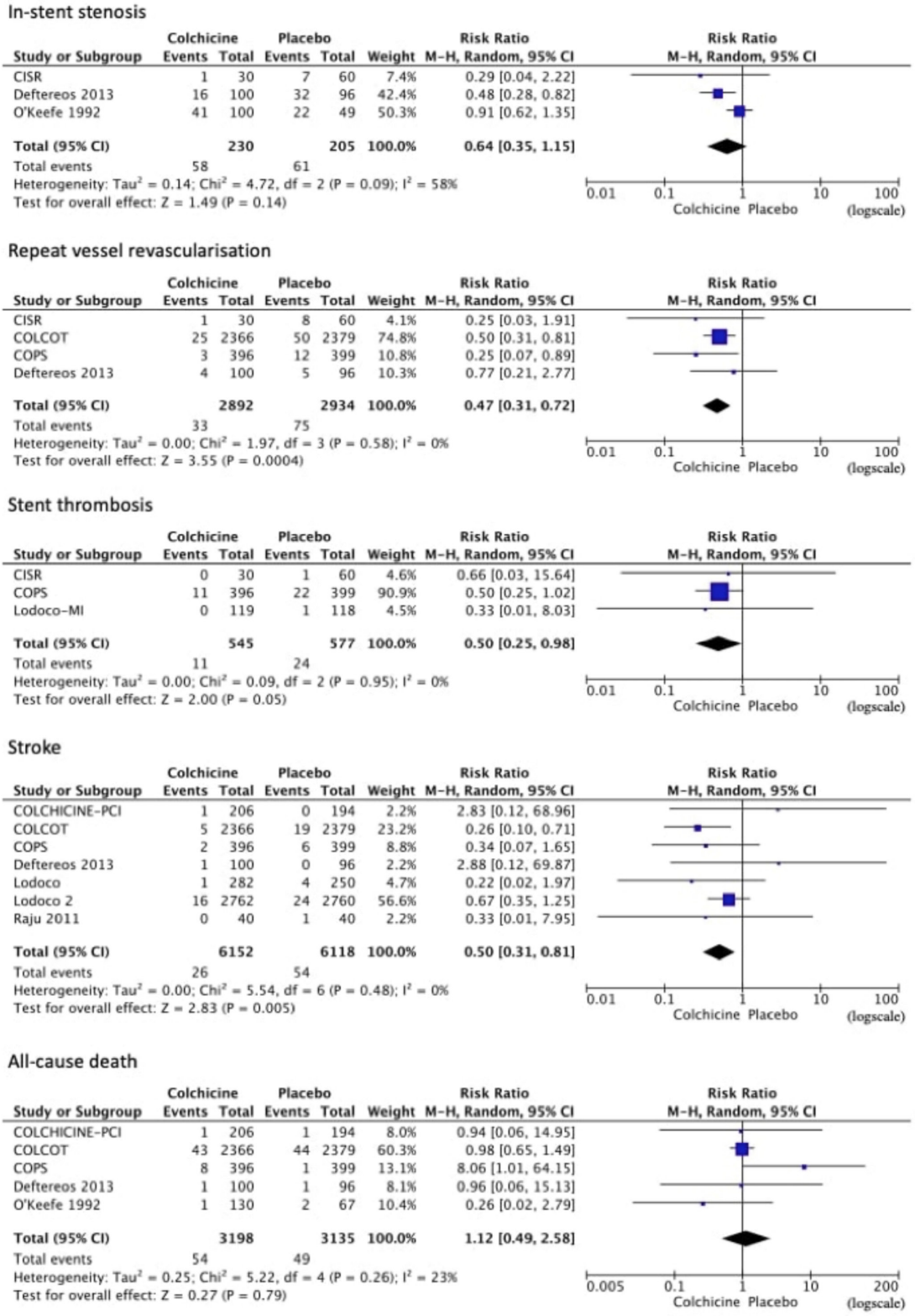

Figure 2 Secondary outcomes. Forest plots showing pooled RRs of RCTs comparing secondary outcomes of in-stent restenosis, repeat vessel revascularisation, stent thrombosis, stroke and all-cause mortality in patients who underwent PCI in the colchicine versus control group. RRs were random effects estimates calculated by Mantel-Haenszel (M-H) method. MI, myocardial infarction; PCI, percutaneous coronary intervention; RCTs, randomised controlled trials; RRs, risk ratios.

revascularisation when used in patients who underwent PCI. Repeat vessel revascularisation may be performed for several reasons: TVR, revascularisation of de novo lesions or more rarely, revascularisation of stent thrombosis. One study[30] showed that more repeat vessel revascularisation was performed for TVR rather than de novo

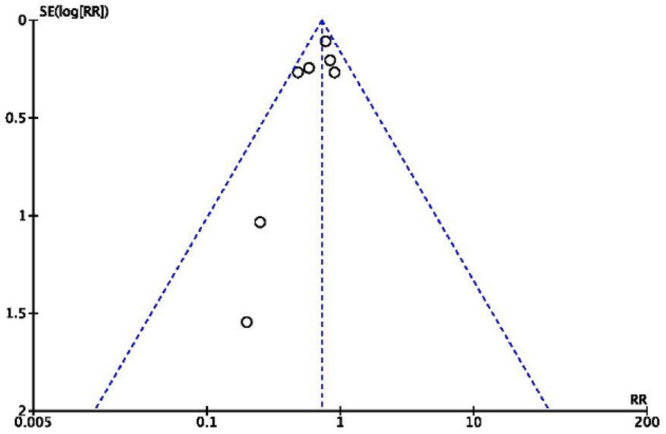

Figure 3 Funnel plot to assess publication bias. RR, risk ratios.

lesions whereas another study showed that both were performed equally. The anti-inflammatory and antiproliferative properties of colchicine likely benefit repeat intervention at both the site of index PCI and de novo lesions caused by ongoing atherosclerotic disease. More data are needed to establish if this beneficial effect is more pronounced in TVR or de novo lesions.

The reduction seen in stroke incidence is in line with previous studies. The risk of ischaemic stroke after a MI has been shown to be 2.7% at 2 years.[31 33] In the acute phase of MI, activated inflammasomes within myocardial fibroblasts mount an intense inflammatory response.[34] For patients undergoing PCI, this is followed by periprocedural inflammation likely secondary to endothelial damage.[5–7] This may contribute to the atherosclerotic plaque destabilisation and thromboembolism, causing cerebrovascular events. Colchicine's anti-inflammatory properties may have a role in the prevention of stroke caused by instability of native atherosclerotic plaques in patients who have undergone PCI.

There was also no significant change in all-cause mortality between patients given colchicine and the control group. In fact, there was a higher rate of total death in the colchicine group observed in the COPS trial.[17] A focused meta-analysis which pooled data from the main trials on the topic showed a significant increase of non-CV death among colchicine-treated patients as compared with controls at an average follow-up of 25.1 months (OR 1.55, 95% CI 1.10 to 2.17; p=0.010). However, this was mostly attributed to the RCTs enrolling CCS patients and no specific cause of death responsible for this excess of deaths has been identified.[24]

Our paper has several limitations. First, O'Keefe *et al* had included patients who underwent balloon angioplasty with no stent implantation, which may be seen as heterogenous compared with other studies. The inflammatory response during balloon angioplasty may be similar to the one seen in stent placement which involves arterial puncture, administration of contrast agent, duration of fluoroscopy and endothelial injury.[35] We hypothesised the cohort of patients undergoing balloon angioplasty will also benefit from the anti-inflammatory properties of colchicine. Second, Tong *et al* reported 86.9% of their study population had undergone PCI, the remaining patients had only been treated with medical management for ACS. We felt the number of patients treated with medical management was inadequate for us to ignore the benefit the study would provide to this review. The absolute number of patients who did not undergo PCI is relatively small and will unlikely affect results.

For colchicine to encounter clinical practice, further studies are required to fully assess its role in the treatment of ischaemic heart disease. There is promising potential in its use in a PCI setting, but further evaluation particularly in distinguishing between different stents (bare-metal vs drug-eluting), categorising patients based on MI type (ST elevation MI (STEMI) vs non-STEMI (NSTEMI)), as well as personalising colchicine use in terms of duration of treatment and dose would be needed. Trials such as the CLEAR SINERGY[36] neutrophil substudy which examines clinical and genetic factors that determine heterogeneity in response to colchicine treatment may be a step in the right direction; suggesting that perhaps colchicine will be used in a selected population in the appropriate clinical setting.

CONCLUSION

Colchicine significantly reduces the risk of MACE in patients with symptomatic CAD who have undergone PCI. The largest benefit was seen in the reduction of ISR, stroke and stent thrombosis. Further clinical trials are required to evaluate the clinical benefits of colchicine use with different types of stents and alternative dosing regimens.

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