Supplemental Material includes:

Search strategy
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Figures 1 to 22

This supplementary material has been provided by the authors to give readers additional information about their work.
Search strategy

Search strategy on PubMed

("Colchicine"[tiab]) AND ("coronary artery disease" [tiab] OR "CAD" [tiab] OR "chronic ischemic heart disease" [tiab] OR "atherosclerosis" [tiab] OR "angina" [tiab] OR "acute coronary syndrome" [tiab] OR "myocardial infarction" [tiab] OR "percutaneous coronary intervention" [tiab] OR "PCI" [tiab] OR "angioplasty" [tiab] OR "drug eluting stent" [tiab] OR "DES" [tiab] OR "BMS" [tiab])

Search strategy on Embase

('colchicine':ab OR 'colchicine') AND ('coronary artery disease':ab OR 'cad':ab OR 'chronic ischemic heart disease':ab OR 'atherosclerosis':ab OR 'angina':ab OR 'acute coronary syndrome':ab OR 'myocardial infarction':ab OR 'percutaneous coronary intervention':ab OR 'pci':ab OR 'angioplasty':ab OR 'drug eluting stent':ab OR 'des':ab OR 'bms':ab)

Search strategy on Cochrane

("Colchicine") AND ("coronary artery disease" OR "CAD" OR "chronic ischemic heart disease" OR "atherosclerosis" OR "acute coronary syndrome" OR "myocardial infarction" OR "percutaneous coronary intervention" OR "PCI" OR "angioplasty" OR "drug eluting stent" OR "DES" OR "BMS")
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| Name          | Study Enrolment | Inclusion Criteria                                                                                                                                                                                                 | Main Exclusion Criteria                                                                                                                                                                                                 | Secondary Endpoints                                                                                       |
|--------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| O’Keefe et al.| NA             | Successful elective coronary angioplasty; single or multivessel angioplasty; bypass graft angioplasty; angioplasty of previously undilated (new) and restenosed lesions; angioplasty performed for silent ischemia and stable or unstable angina pectoris. | Direct angioplasty for acute myocardial infarction; unsuccessful coronary angioplasty; premenopausal women; baseline leukopenia; active peptic ulcer disease; active diarrhoea; creatinine ≥2.5 mg/dL at baseline; known colchicine intolerance. | NA                                                                                                         |
| COOL         | April 2008 - August 2009 | Adult patients (>18 years); diagnosis of acute coronary syndrome or acute ischemic stroke.                                                                                                                                 | Hypersensitivity to colchicine; moderate renal dysfunction (creatinine clearance <50 mL/min) or hepatic dysfunction (ALT>1.5 x upper limit of normal range); thrombocytopenia or leukopenia; pregnant or lactating women and women at risk of pregnancy; patients taking moderate-strong CYP3A4 inhibitors; patients already taking colchicine; evidence of active infection or inflammatory conditions; patients taking other anti-inflammatory therapies. | Platelet function measured by turbidimetric platelet aggregometry; occurrence of death, myocardial infarction, or stroke at 30 days. |
| LoDoCo       | August 2008 – May 2010 | Angiographically proven coronary disease; age 35 to 85 years; clinically stable for at least 6 months; no major competing comorbidities or contraindication to colchicine therapy; considered to be compliant with therapy and attending routine cardiology follow-up appointments; willing to provide consent and be randomized into the study; history of bypass surgery only if >10 years ago. | Any clinically significant co-morbidity; clinical instability within prior 6 months; CABG<10 years ago unless intervention has been required; unwilling to enrol or uncertainty re compliance; already on long-term colchicine for unrelated condition; known sensitivity to colchicine; pregnancy. | Individual components of the primary outcome and the components of ACS unrelated to stent disease. |
| Study         | Intervention                                                                 | Outcomes                                                                 |
|--------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Defteros et al. | Diabetic; 40 to 80 years of age; undergoing PCI in a coronary artery with a diameter of at least 2.5 mm with a BMS. | Left main artery disease (>30% in angiography); PCI performed as primary treatment for ST-segment elevation myocardial infarction, hepatic impairment (Child-Pugh class B or C); target vessel segment presenting particular technical challenges for intravascular ultrasound (IVUS) (e.g., marked tortuosity, vessel with steep take-off angle); severe or end stage renal failure (estimated glomerular filtration rate ≤20 ml/min/1.73 m² or requiring dialysis); history of intolerance to colchicine, myopathy, and statin hepatotoxicity or myotoxicity; women with child-bearing potential; and inability or unwillingness to adhere to standard treatment or to provide consent. | 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 normalized neointima volume (IVUS). |
| COLIN        | December 2014 – My 2015 STEMI, with occlusion of one of the main coronary arteries (TIMI grade 0 or 1 flow); successfully treated with primary percutaneous coronary intervention (PCI); Adult (18-90y). | Cardiogenic shock; severe chronic kidney failure (clearance < 30 mL/kg/min); colchicine intolerance or contraindication. | Troponin peak, tolerance of colchicine, hospitalization duration, major adverse cardiac events (death, resuscitated cardiac arrest, ventricular arrhythmias, stent thrombosis, myocardial infarction, urgent coronary revascularization, and acute heart failure) at 1-month follow-up, cardiac remodelling on echocardiography (left ventricular end-systolic and end-diastolic volumes) and MRI data. |
| LoDoCo-MI    | February 2016 – July 2017 Adult (>18 years old) patients were eligible for enrolment if they had sustained a type 1 acute MI (defined according to the 3rd universal definition) within the prior 7 days. | A history of myopathy, leukopenia or thrombocytopenia; an estimated glomerular filtration rate <45 mL/min per 1.73m²; severe hepatic dysfunction (alanine amino transferase >3 ULN); therapy with a P-glycoprotein inhibitor (e.g., cyclosporin, verapamil or quinidine) or a strong CYP3A4 inhibitor (e.g., ritonavir, clarithromycin or ketoconazole); pregnancy, lactation or women of childbearing age not using contraception; an indication for colchicine therapy or any active inflammatory or infective disease process. | 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: the proportion of recruited patients completing the study; adverse events; participant-reported compliance with study medications; and death and major cardiovascular events (further MI or stroke) at 30 days. |
| COLCOT | December 2015 – August 2018 |
|--------|---------------------------|
| Myocardial infarction within 30 days before enrolment; completed planned percutaneous revascularization procedures; treated according to national guidelines that included the intensive use of statins. | Severe heart failure (left ventricular ejection fraction of less than 35%); stroke within the previous 3 months, a type 2 index myocardial infarction, coronary-bypass surgery either within the previous 3 years or planned, a history of non-cutaneous cancer within the previous 3 years, inflammatory bowel disease or chronic diarrhoea, neuromuscular disease or a non-transient creatine kinase level that was greater than three times the upper limit of the normal range (unless due to infarction), clinically significant non-transient hematologic abnormalities, severe renal disease with a serum creatinine level that was greater than two times the upper limit of the normal range; severe hepatic disease, drug or alcohol abuse, current or planned long-term systemic glucocorticoid therapy, or a history of clinically significant sensitivity to colchicine. |
| Components of the primary efficacy end point; a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, or stroke; total mortality. |

| COPS | December 2015–September 2018 |
|------|-------------------------------|
| Age between 18 to 85 years old; able to provide written informed consent; acute coronary syndromes (defined as symptoms of acute myocardial ischemia with elevated troponin or ECG changes); presence of coronary artery disease (defined by >30% luminal stenosis in epicardial vessel of >2.5mm luminal diameter on visual angiographic assessment); coronary artery disease which is managed with PCI or medical therapy at the discretion of the treating team. | Coronary artery disease requiring planned surgical revascularization; Pre-existing long-term colchicine use for other medical conditions; pre-existing, or plan for, administration of other immunosuppressant therapy; severe liver impairment (defined by elevated serum ALT and/or AST levels twice the upper limit of normal with either) a) total serum bilirubin level twice the upper limit of normal, or b) coagulopathy (INR>1.5); severe renal insufficiency (defined by eGFR<30mL/min/1.73m²2); pre-existing use of strong CYP3A4 or P-glycoprotein inhibitors (e.g. cyclosporine, antiretroviral drugs, antifungals, erythromycin and clarithromycin) and no other alternative medical therapy can be used; known active malignancy; known allergy or hypersensitivity to colchicine; pregnant and lactating woman or woman with childbearing potential without effective birth control methods. |
| Hospitalization for chest pain. |
| COLCHICINE-PCI | May 2013-August 2019 | Adults aged ≥18 years with suspected ischemic heart disease or acute coronary syndromes referred for clinically indicated coronary angiography with possible PCI. Use of oral steroids or nonsteroidal anti-inflammatory agents other than aspirin within the longer of 72 hours or 3 x the agent’s half-life; high-intensity statin treatment started within 24 hours of procedure; glomerular filtration rate <30 mL/min or on dialysis; use of strong cytochrome P450 3A4/P-glycoprotein inhibitors; chronic colchicine use or history of intolerance to colchicine; active malignancy or infection; history of myelodysplasia; participation in a competing study; inability to provide informed consent; any condition that, in the investigator’s opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject’s ability to adhere with study procedures. Occurrence of 30-day MACE, a composite of the earliest of death from any cause, nonfatal MI, or target vessel revascularization; PCI-related MI as defined by the Society for Cardiovascular Angiography and Interventions. |
| LoDoCo2 | August 2014-December 2018 | Age >35 and <82 years; proven coronary artery disease, as evidenced by coronary angiography, CT coronary angiography or a Coronary Artery Calcium Score (Agatston score >400); individuals with a history of bypass surgery are only eligible if they have undergone coronary artery bypass surgery more than 10 years before or have angiographic evidence of graft failure or have undergone percutaneous intervention since their bypass surgery; clinically stable for at least six months. Women who are pregnant, breast feeding or may be considering pregnancy during the study period; renal impairment as evidenced by a serum creatinine >150 μmol/L or eGFR <50mL/min/1.73m²; severe heart failure – systolic or diastolic New York Heart Association Functional classification 3 or 4; moderate or severe valvular heart disease considered likely to require intervention; dependency or frailty or an estimated life expectancy < 5 years; peripheral neuritis, myositis or marked myo-sensitivity to statins; requirement for long term colchicine therapy for any other reason; current enrolment in another trial. The composite of cardiovascular death, myocardial infarction, or ischemic stroke; the composite of myocardial infarction or ischemia-driven coronary revascularization; the composite of cardiovascular death or myocardial infarction; ischemia-driven coronary revascularization; myocardial infarction; ischemic stroke; death from any cause; cardiovascular death. |

ACS, Acute Coronary Syndrome; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BMS, Bare Metal Stent; CABG, Coronary Artery By-pass Graft; COLCHICINE-PCI: COLCHICINE in Percutaneous Coronary Intervention; COLCOT: COLchicine Cardiovascular Outcomes Trial; COLIN: Interest of COLchicine in the treatment of patients with acute myocardial INfarction and with inflammatory response; COOL: Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial; COPS: COLchicine in Patients with acute coronary Syndrome; CRP, C-Reactive Protein; CT, Computed Tomography; eGFR, estimated Glomerular Filtration Rate; INR, International Normalized Ratio; ISR, In-Stent Restenosis; IVUS, IntraVascular UltraSound; LoDoCo: Low Dose Colchicine for secondary prevention of cardiovascular disease; LoDoCo2: Low Dose Colchicine for secondary prevention of cardiovascular disease.
Colchicine for secondary prevention of Cardiovascular Disease 2; NA Not Available; MACE, Major Adverse Cardiac Events; MI, Myocardial Infarction; PCI, Percutaneous Coronary Intervention; TIMI, Thrombolysis in Myocardial Infarction.
Table 2. Heterogeneity measures in the overall population.

| Event                              | $I^2$ (95% CI)* | $\tau^2$ | $Q$ (Heterogeneity) | $P$ value |
|-----------------------------------|-----------------|----------|----------------------|-----------|
| MACE                              | 37.4 (0.0-72.3) | <0.0001  | 11.18                | 0.131     |
| Myocardial infarction             | 4.5 (0.0-72.1)  | <0.0001  | 6.29                 | 0.392     |
| Stroke                            | 61.4 (11.9-83.1)| 0        | 15.55                | 0.0164    |
| Coronary revascularisation        | 51.2 (0.0-83.9) | 0.0091   | 6.15                 | 0.105     |
| Gastrointestinal adverse events   | 73.4 (45.7-86.9)| 0.2044   | 26.27                | 0.0004    |
| All-cause death                   | 34.1 (0.0-72.1) | 0        | 9.10                 | 0.168     |
| Cardiovascular death              | 24.2 (0.0-69.2) | 0        | 5.28                 | 0.260     |
| Noncardiovascular death           | 57.7 (0.0-84.3) | 0        | 9.46                 | 0.0505    |

CI: confidence interval; MACE: major adverse cardiac events.
*Values of $I^2$ are percentages. 95% confidence intervals are calculated as proposed by Higgins and Thompson.
| Event                                | IRR  | 95% CI        | P value |
|--------------------------------------|------|---------------|---------|
| MACE                                 | 0.69 | 0.60-0.79     | <0.0001 |
| Myocardial infarction                | 0.77 | 0.64-0.93     | 0.005   |
| Stroke                               | 0.48 | 0.30-0.76     | 0.002   |
| Coronary revascularisation           | 0.66 | 0.41-1.05     | 0.078   |
| Gastrointestinal adverse events      | 1.69 | 1.12-2.54     | 0.012   |
| All-cause death                      | 1.09 | 0.85-1.40     | 0.489   |
| Cardiovascular death                 | 0.75 | 0.51-1.12     | 0.158   |
| Noncardiovascular death              | 1.45 | 1.04-2.02     | 0.0282  |

CI: confidence interval; IRR: incidence rate ratio; MACE: major adverse cardiac events, MI: myocardial infarction.
Table 4. Absolute treatment effect measures in the overall population: colchicine vs control.

| Event                     | Absolute risk difference | NNTB/NNTH  | 95% CI NNTB/NNTH       | No of events avoided/caused per 1000 (95% CI) |
|---------------------------|--------------------------|------------|------------------------|---------------------------------------------|
| MACE                      | -0.0353 (-0.046 to -0.024) | NNTB 28.4  | NNTB 22.0 to 41.9      | Avoided 35.3 (23.9 to 45.5)                  |
| Myocardial infarction     | -0.0105 (-0.016 to -0.003) | NNTB 95.4  | NNTB 60.9 to 313.4     | Avoided 10.5 (3.2 to 16.4)                   |
| Stroke                    | -0.0064 (-0.009 to -0.003) | NNTB 155.3 | NNTB 115.4 to 336.4    | Avoided 6.4 (3.0 to 8.7)                     |
| Coronary revascularisation| -0.0196 (-0.034 to -0.003) | NNTB 51.1  | NNTB 29.4 to ∞ to NNTH 347.4 | Avoided 19.6 (34.0 to “0” to caused 2.9)    |
| Gastrointestinal adverse events | 0.0989 (0.017 to 0.221)   | NNTH 10.1  | NNTH 4.5 to 58.2       | Caused 98.9 (17.2 to 220.7)                  |
| All-cause death           | 0.0011 (-0.002 to 0.005)  | NNTH 927.7 | NNTH 562.6 to ∞ to NNTH 208.7 | Caused 1.1 (avoided 1.8 to “0” to caused 4.8) |
| Cardiovascular death      | -0.0019 (-0.004 to 0.001) | NNTB 521.2 | NNTB 265.9 to ∞ to NNTH | Avoided 1.9 (3.8 to “0” to caused 0.9)      |
| Noncardiovascular death   | 0.0025 (0.0002 to 0.006)  | NNTH 396.4 | NNTH 174.9 to 4459.3   | Caused 2.5 (0.22 to 5.7)                     |

CI: confidence interval; MACE: major adverse cardiac events; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm.
Table 5. Treatment effects: colchicine vs control in subgroup analysis according to colchicine dose.

|                          | IRR   | 95% CI       | P for interaction |
|--------------------------|-------|--------------|-------------------|
| **MACE**                 |       |              | 0.20              |
| Low dose                 | 0.60  | (0.43-0.84)  |                   |
| High dose                | 0.91  | (0.53-1.55)  |                   |
| **Myocardial infarction**|       |              | 0.68              |
| Low dose                 | 0.76  | (0.63-0.92)  |                   |
| High dose                | 0.87  | (0.49-1.53)  |                   |
| **Stroke**               |       |              | 0.25              |
| Low dose                 | 0.45  | (0.26-0.78)  |                   |
| High dose                | 1.94  | (0.18-21.4)  |                   |
| **Gastrointestinal adverse events** | <0.0001 |              |                   |
| Low dose                 | 1.03  | (0.91-1.15)  |                   |
| High dose                | 2.91  | (1.91-4.44)  |                   |
| **All-cause death**      |       |              | 0.37              |
| Low dose                 | 1.11  | (0.86-1.42)  |                   |
| High dose                | 0.55  | (0.12-2.48)  |                   |

CI: confidence interval; high dose: ≥1 mg/die; IRR: incidence rate ratio; low dose: <1 mg/die; MACE: major adverse cardiac events.
Table 6. Heterogeneity measures. Subgroup analysis according to colchicine dose.

| Event                      | Low dose | I²   | Tau² |
|----------------------------|----------|------|------|
| **MACE**                   |          |      |      |
| Low dose                   | 54.8     | 0.0456 |
| High dose                  | 0        | 0    |
| **Myocardial infarction**  |          |      |      |
| Low dose                   | 27.4     | 0    |
| High dose                  | 0        | 0    |
| **Stroke**                 |          |      |      |
| Low dose                   | 3.1      | 0.0009 |
| High dose                  | 0        | 0    |
| **Gastrointestinal adverse events** | | | |
| Low dose                   | 0        | 0    |
| High dose                  | 0        | 0    |
| **All-cause death**        |          |      |      |
| Low dose                   | 61.5     | 0    |
| High dose                  | 0        | 0    |

High dose: ≥1 mg/die; low dose: <1 mg/die; MACE: major adverse cardiac events.
Table 7. Treatment effects: colchicine vs control in subgroup analysis according to clinical syndrome.

|                          | IRR   | 95% CI           | P for interaction |
|--------------------------|-------|------------------|-------------------|
| MACE                     |       |                  |                   |
| ACS                      | 0.75  | (0.61-0.91)      | 0.19              |
| CCS                      | 0.53  | (0.34-0.85)      |                   |
| ACS (0.71-1.18)          | 0.91  | (0.71-1.18)      | 0.07              |
| CCS (0.50-0.84)          | 0.65  | (0.50-0.84)      |                   |
| ACS (0.12-0.65)          | 0.28  | (0.12-0.65)      | 0.15              |
| CCS (0.33-1.09)          | 0.59  | (0.33-1.09)      |                   |
| ACS (0.50-4.55)          | 1.51  | (0.50-4.55)      | 0.50              |
| CCS (0.32-2.50)          | 0.89  | (0.32-2.50)      |                   |

ACS: acute coronary syndrome; CCS: chronic coronary syndrome; CI: confidence interval; IRR: incidence rate ratio; MACE: major adverse cardiac events.
Table 8. Heterogeneity measures. Subgroup analysis according to clinical syndrome.

|                      | $\text{i}^2$ (95% CI) | $\tau^2$ |
|----------------------|------------------------|----------|
| **MACE**             |                        |          |
| ACS                  | 30.8                   | 0        |
| CCS                  | 68.2                   | 0.0651   |
| **Myocardial infarction** |                      |          |
| ACS                  | 0                      | 0        |
| CCS                  | 49.3                   | 0        |
| **Stroke**           |                        |          |
| ACS                  | 0                      | 0        |
| CCS                  | 0                      | 0        |
| **All cause death**  |                        |          |
| ACS                  | 47.3                   | 0.2363   |
| CCS                  | 74.9                   | 0.1049   |

ACS: acute coronary syndrome; CCS: chronic coronary syndrome; MACE: major adverse cardiac events.
Table 9. Sensitivity analysis of treatment effects of colchicine vs control by leaving out exactly one study.

|                  | MACE        | MI           | Stroke       | Revascularisation | Gastrointestinal AE | All-cause death |
|------------------|-------------|--------------|--------------|-------------------|----------------------|------------------|
|                  | IRR (95% CI)| IRR (95% CI) | IRR (95% CI) | IRR (95% CI)      | IRR (95% CI)         | IRR (95% CI)     |
| Overall          | 0.69 (0.60 to 0.79) | 0.77 (0.64 to 0.93) | 0.48 (0.30 to 0.76) | 0.66 (0.41 to 1.05) | 1.69 (1.12 to 2.54) | 1.09 (0.66 to 1.79) |
| Omitting O'keefe et al. | 0.69 (0.60 to 0.78) | 0.77 (0.64 to 0.93) | 0.48 (0.30 to 0.76) | 0.66 (0.41 to 1.05) | 1.39 (0.98 to 1.97) | 1.09 (0.66 to 1.79) |
| Omitting COOL    | 0.69 (0.60 to 0.90) | 0.77 (0.64 to 0.93) | 0.49 (0.30 to 0.78) | 0.66 (0.41 to 1.05) | 1.68 (1.07 to 2.63) | 1.09 (0.66 to 1.79) |
| Omitting LoDoCo  | 0.72 (0.63 to 0.82) | 0.80 (0.67 to 0.97) | 0.50 (0.30 to 0.84) | 0.66 (0.41 to 1.05) | 1.69 (1.12 to 2.54) | 1.16 (0.70 to 1.93) |
| Omitting Defteros et al. | 0.69 (0.60 to 0.79) | 0.77 (0.64 to 0.93) | 0.46 (0.25 to 0.84) | 0.65 (0.40 to 1.06) | 1.65 (1.06 to 2.57) | 1.09 (0.66 to 1.79) |
| Omitting COLIN   | 0.69 (0.61 to 0.79) | 0.78 (0.65 to 0.93) | 0.48 (0.30 to 0.76) | 0.66 (0.41 to 1.05) | 1.69 (1.12 to 2.54) | 1.09 (0.66 to 1.79) |
| Omitting LoDoCo-MI | 0.69 (0.61 to 0.79) | 0.78 (0.65 to 0.93) | 0.48 (0.30 to 0.76) | 0.66 (0.41 to 1.05) | 1.68 (1.07 to 2.62) | 1.09 (0.66 to 1.79) |
| Omitting COLCOT  | 0.59 (0.43 to 0.81) | 0.69 (0.55 to 0.87) | 0.59 (0.35 to 1.01) | 0.73 (0.59 to 0.91) | 1.89 (1.22 to 2.94) | 1.15 (0.80 to 1.70) |
| Omitting COLCHICINE-PCI | 0.61 (0.44 to 0.84) | 0.76 (0.63 to 0.92) | 0.46 (0.25 to 0.84) | 0.66 (0.41 to 1.05) | 1.89 (1.22 to 2.94) | 1.09 (0.66 to 1.79) |
| Omitting COPS    | 0.71 (0.62 to 0.81) | 0.78 (0.65 to 0.94) | 0.50 (0.30 to 0.81) | 0.71 (0.58 to 0.86) | 1.86 (1.17 to 2.96) | 1.03 (0.66 to 1.79) |
| Omitting LodDoCo2 | 0.60 (0.42 to 0.85) | 0.81 (0.64 to 1.02) | 0.33 (0.16 to 0.67) | 0.48 (0.32 to 0.73) | 1.86 (1.18 to 2.94) | 0.97 (0.66 to 1.43) |

AE: adverse events; CI: confidence interval; IRR: incidence rate ratio; MACE: Major adverse cardiac events; MI: myocardial infarction.
Figure 1. Flowchart of the study selection process.
**Figure 2:** Risk of bias assessment.

| Study                  | D1 | D2 | D3 | D4 | D5 | Overall |
|------------------------|----|----|----|----|----|---------|
| O'Keefe et al          | +  | -  | X  | +  | -  | X       |
| COOL                   | +  | +  | -  | +  | -  | -       |
| LoDoCo                 | +  | -  | -  | +  | -  | -       |
| Defteros et al.        | +  | +  | -  | +  | -  | -       |
| COLIN                  | +  | -  | -  | +  | -  | -       |
| LoDoCo-MI              | +  | -  | +  | +  | +  | -       |
| COLCOT                 | +  | +  | +  | +  | +  | +       |
| COPS                   | +  | +  | +  | +  | +  | +       |
| COLCHICIN-PCI          | +  | +  | -  | +  | -  | -       |
| LoDoCo2                | +  | +  | +  | +  | +  | +       |

**Domains:**
- D1: Bias arising from the randomization process.
- D2: Bias due to deviations from intended intervention.
- D3: Bias due to missing outcome data.
- D4: Bias in measurement of the outcome.
- D5: Bias in selection of the reported result.

**Judgement**
- **X**: High
- **Yellow**: Some concerns
- **Green**: Low
Figure 3: Contour-enhanced funnel plot for the endpoint of major adverse cardiac events.
Figure 4: Contour-enhanced funnel plot for the endpoint of myocardial infarction.
Figure 5: Contour-enhanced funnel plot for the endpoint of stroke.
Figure 6: Contour-enhanced funnel plot for the endpoint of coronary revascularization.
Figure 7: Contour-enhanced funnel plot for the endpoint of gastrointestinal adverse events.
Figure 8: Contour-enhanced funnel plot for the endpoint of all-cause death.
Figure 9: Contour-enhanced funnel plot for the endpoint of cardiovascular death.
Figure 10: Contour-enhanced funnel plot for the endpoint of noncardiovascular death.
### Figure 11: Incidence rate ratios for the endpoint of coronary revascularisation in the overall population.

#### Coronary revascularization

| Study          | Colchicine Events | Person-years | Control Events | Person-years | Incidence Rate Ratio | IRR   | 95% CI      |
|----------------|-------------------|--------------|----------------|--------------|----------------------|-------|-------------|
| O’keefe et al. | NA                | 59.71        | NA             | 30.77        |                      |       |             |
| COOL           | NA                | 3.39         | NA             | 3.39         |                      |       |             |
| LoDoCo         | NA                | 847.74       | NA             | 751.54       |                      |       |             |
| Defteros et al.| 4                 | 50.10        | 5              | 48.10        | 0.77 [0.21; 2.86]    |       |             |
| COLIN          | NA                | 1.92         | NA             | 1.75         |                      |       |             |
| LoDoCo-MI      | NA                | 9.77         | NA             | 9.69         |                      |       |             |
| COLCOT         | 25                | 4465.12      | 50             | 4489.65      | 0.50 [0.31; 0.81]    |       |             |
| COLCHICINE-PCI | NA                | 16.92        | NA             | 15.93        |                      |       |             |
| COPS           | 3                 | 433.68       | 12             | 436.96       | 0.25 [0.07; 0.89]    |       |             |
| LodDoCo2       | 135               | 6596.28      | 177            | 6591.51      | 0.76 [0.61; 0.95]    |       |             |

**Overall (random effects model)**

Heterogeneity: $R^2 = 51\%$, $r^2 = 0.0091$, $p = 0.10$
**Figure 12:** Incidence rate ratios for the endpoint of cardiovascular death in the overall population.

### Cardiovascular death

| Study          | Colchicine | Control | Incidence Rate Ratio | IRR  | 95% CI    |
|----------------|------------|---------|----------------------|------|-----------|
| Events Person-years | Events Person-years | | | | |
| O’keefe et al. | NA 59.71   | NA 30.77 | 1.00 [0.02; 50.40]   |      |           |
| COOL           | 0 3.39     | 0 3.39  | 0.06 [0.00; 1.03]    |      |           |
| LoDoCo         | 0 847.74   | 7 751.54 | 0.96 [0.06; 15.35]   |      |           |
| Defteros et al.| 1 50.10    | 1 48.10 | 0.91 [0.02; 46.01]   |      |           |
| COLIN          | 0 1.92     | 0 1.75  | 0.99 [0.02; 49.97]   |      |           |
| LoDoCo-MI      | 0 9.77     | 0 9.69  | 0.84 [0.46; 1.52]    |      |           |
| COLCOT         | 20 4465.12 | 24 4489.65 | 0.94 [0.02; 47.46]  |      |           |
| COLCHICINE-PCI | 0 16.92    | 0 15.93 | 3.02 [0.31; 29.06]   |      |           |
| COPS           | 3 433.68   | 1 436.96 | 0.80 [0.44; 1.44]    |      |           |
| LodDoCo2       | 20 6596.28 | 25 6591.51 | \(0.75 [0.51; 1.12]\) |      |           |

**Overall** (random effects model)

Heterogeneity: \(I^2 = 24\%, \tau^2 = 0\, p = 0.26\)
Figure 13: Incidence rate ratios for the endpoint of non-cardiovascular death in the overall population.

| Study            | Colchicine | Control | Incidence Rate Ratio | IRR    | 95% CI      |
|------------------|------------|---------|----------------------|--------|-------------|
|                  | Events     | Person-years | Events | Person-years |                |             |
| O'keefe et al.   | NA         | 59.71   | NA      | 30.77       | 1.00 [0.02; 50.40]|
| COOL             | 0          | 3.39    | 0       | 3.39        | 1.18 [0.26; 5.28]|
| LoDoCo           | 4          | 847.74  | 3       | 751.54      | 0.96 [0.02; 48.38]|
| Defteros et al.  | 0          | 50.10   | 0       | 48.10       | 0.91 [0.02; 46.01]|
| COLIN            | 0          | 1.92    | 0       | 1.75        | 0.99 [0.02; 49.97]|
| LoDoCo-MI        | 0          | 9.77    | 0       | 9.69        | 1.16 [0.64; 2.11]|
| COLCOT           | 23         | 4465.12 | 20      | 4489.65     | 0.94 [0.06; 15.06]|
| COLCHICINE-PCI   | 1          | 16.92   | 1       | 15.93       | 1.08 [0.61; 200.44]|
| COPS             | 5          | 433.68  | 0       | 436.96      | 1.51 [0.99; 2.32]|
| LodDoCo2         | 53         | 6596.28 | 35      | 6591.51     | 1.45 [1.04; 2.02]|

**Overall** (random effects model)

Heterogeneity: $I^2 = 58\%$, $\tau^2 = 0$, $p= 0.05$
Figure 14: Incidence rate ratios for the endpoint of gastrointestinal adverse events stratified by colchicine dose.

### Gastrointestinal adverse events

| Study                | Colchicine ≥ 1 mg/die | Control | Incidence Rate Ratio | IRR  | 95% CI |
|----------------------|------------------------|---------|----------------------|------|--------|
|                      | Events | Person-years | Events | Person-years | | |
| O'keefe et al.       | 36     | 59.71        | 3      | 30.77        | 6.18 | [1.90; 20.08] |
| COOL                 | 14     | 3.39         | 7      | 3.39         | 2.00 | [0.81; 4.96]  |
| Defteros et al.      | 16     | 50.10        | 7      | 48.10        | 2.19 | [0.90; 5.33]  |
| COLIN                | NA     | 1.92         | NA     | 1.75         | 2.94 | [1.49; 5.80]  |
| COLCHICINE-PCI       | 34     | 30.06        | 11     | 28.58        | 2.91 | [1.91; 4.44]  |
| **Subtotal (I² = 0%, p = 0.46)** | | | | | | |
| Colchicine < 1 mg/die|         |              |        |              | 2.91 | [1.91; 4.44]  |
| LoDoCo               | NA     | 847.74       | NA     | 751.54       | 1.98 | [0.74; 5.28]  |
| LoDoCo-MI            | 12     | 9.77         | 6      | 9.69         | 1.98 | [0.74; 5.28]  |
| COLCOT               | 408    | 4397.18      | 414    | 4427.37      | 0.99 | [0.87; 1.14]  |
| COPS                 | 91     | 433.68       | 83     | 436.96       | 1.10 | [0.82; 1.49]  |
| LodDoCo2             | 53     | 6596.28      | 50     | 6591.51      | 1.06 | [0.72; 1.56]  |
| **Subtotal (I² = 0%, p = 0.53)** | | | | | | |
| **Overall** (random effects model) | | | | | 1.69 | [1.12; 2.54] |

Heterogeneity: $I^2 = 73\%$, $\tau^2 = 0.2044$, $p < 0.001$

$p$ for interaction $< 0.0001$
Figure 15: Incidence rate ratios for the endpoint of major adverse cardiac events stratified by colchicine dose.

| Study               | Colchicine          | Control          | Incidence Rate Ratio | IRR     | 95% CI           |
|---------------------|---------------------|------------------|----------------------|---------|------------------|
| Colchicine ≥ 1 mg/die | Events Person-years | Events Person-years |                        |         |                  |
| O’keefee et al.     | NA 59.71            | NA 30.77         | 1.00                 | [0.06; 15.99] |                  |
| COOL                | 1 3.39              | 1 3.39           | 0.91                 | [0.13; 6.48]  |                  |
| Defteros et al.     | NA 50.10            | NA 48.10         | 0.90                 | [0.51; 1.60]  |                  |
| COLIN               | 2 1.92              | 2 1.75           | 0.91                 | [0.53; 1.55]  |                  |
| COLCHICINE-PCI      | 23 16.92            | 24 15.93         | 0.91                 | [0.53; 1.55]  |                  |
| Subtotal (I^2 = 0%, p = 1.00) | |                  |                     |         |                  |
| Colchicine < 1 mg/die | Events Person-years | Events Person-years |                        |         |                  |
| LoDoCo              | 15 847.74           | 40 751.54        | 0.33                 | [0.18; 0.60]  |                  |
| LoDoCo-MI           | 0 9.77              | 2 9.69           | 0.20                 | [0.01; 4.13]  |                  |
| COLCOT              | 131 4465.12         | 170 4489.65      | 0.77                 | [0.62; 0.97]  |                  |
| COPS                | 19 433.68           | 41 436.96        | 0.47                 | [0.27; 0.80]  |                  |
| LodDoCo2            | 187 6596.28         | 264 6591.51      | 0.71                 | [0.59; 0.85]  |                  |
| Subtotal (I^2 = 55%, p = 0.06) | |                  |                     |         |                  |
| Overall (random effects model) | |                  |                     |         |                  |
| Heterogeneity: I^2 = 37%, r^2 < 0.0001, p = 0.13 | |                  |                     |         |                  |

p for interaction = 0.20
Figure 16. Incidence rate ratios for the endpoint of myocardial infarction stratified by colchicine dose.

**Myocardial infarction**

| Study             | Colchicine | Control | Incidence Rate Ratio | IRR     | 95% CI   |
|-------------------|------------|---------|----------------------|---------|----------|
|                   | Events     | Person-years | Events     | Person-years |          |          |
| Colchicine ≥ 1 mg/die |           |         |                      |         |          |
| O’keefe et al.    | NA         | 59.71   | NA                   | 30.77   |          | 1.00 [0.02; 50.40] |
| COOL              | 0          | 3.39    | 0                    | 3.39    |          | 0.30 [0.01; 7.47]  |
| Defteros et al.   | NA         | 50.10   | NA                   | 48.10   |          | 0.90 [0.51; 1.60]  |
| COLIN             | 0          | 1.92    | 1                    | 1.75    |          | 0.87 [0.49; 1.53]  |
| COLCHICINE-PCI    | 23         | 16.92   | 24                   | 15.93   |          |          |
| Subtotal (I² = 0%, p = 1.00) |          |         |                      |         |          |          |
| Colchicine < 1 mg/die |           |         |                      |         |          |
| LoDoCo            | 4          | 847.74  | 14                   | 751.54  |          | 0.25 [0.08; 0.77]  |
| LoDoCo-MI         | 0          | 9.77    | 2                    | 9.69    |          | 0.20 [0.01; 4.13]  |
| COLCOT            | 89         | 4465.12 | 98                   | 4489.65 |          | 0.91 [0.69; 1.22]  |
| COPS              | 7          | 433.68  | 11                   | 436.96  |          | 0.64 [0.25; 1.65]  |
| LodDoCo2          | 85         | 6596.28 | 117                  | 6591.51 |          | 0.73 [0.55; 0.96]  |
| Subtotal (I² = 27%, p = 0.24) |          |         |                      |         |          | 0.76 [0.63; 0.92]  |

**Random effects model**

Heterogeneity: $I^2 = 5\%$, $r^2 < 0.0001$, $p = 0.39$

$p$ for interaction = 0.68

0.01 0.1 1 10 100

Favors colchicine  Favors control

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Figure 17: Incidence rate ratios for the endpoint of stroke stratified by colchicine dose.

| Study                  | Colchicine | Control | Incidence Rate Ratio | IRR    | 95% CI        |
|------------------------|------------|---------|----------------------|--------|---------------|
|                        | Events     | Person-years | Events     | Person-years |                  |                  |
| Colchicine ≥ 1 mg/die  |            |          |                     |        |               |
| O'keefe et al.         | NA         | 59.71    | NA                  | 30.77  | 0.33 [0.01; 8.18] |
| COOL                   | 0          | 3.39     | 1                   | 3.39   | 2.88 [0.12; 70.70] |
| Defteros et al.        | 1          | 50.10    | 0                   | 48.10  | 2.85 [0.12; 70.02] |
| COLIN                  | NA         | 1.92     | NA                  | 1.75   | 1.94 [0.18; 21.40] |
| COLCHICINE-PCI         | 1          | 30.06    | 0                   | 28.58  |               |
| Subtotal (I² = 0%, p = 1.00) |          |          |                     |        |               |
| Colchicine < 1 mg/die  |            |          |                     |        |               |
| LoDoCo                 | 1          | 847.74   | 4                   | 751.54 | 0.22 [0.02; 1.98] |
| LoDoCo-MI              | NA         | 9.77     | NA                  | 9.69   |               |
| COLCOT                 | 5          | 4465.12  | 19                  | 4489.65| 0.26 [0.10; 0.71] |
| COPS                   | 2          | 433.68   | 6                   | 436.96 | 0.34 [0.07; 1.66] |
| LodDoCo2               | 16         | 6596.28  | 24                  | 6591.51| 0.67 [0.35; 1.25] |
| Subtotal (I² = 3%, p = 0.38) |          |          |                     |        | 0.45 [0.26; 0.78] |

Overall (random effects model)

Heterogeneity: I² = 61%, τ² = 0, p = 0.02

p for interaction = 0.25

Favors colchicine  Favors control
Figure 18: Incidence rate ratios for the endpoint of all-cause death stratified by colchicine dose.

### All-cause death

| Study               | Colchicine | Control | Incidence Rate Ratio | IRR       | 95% CI       |
|---------------------|------------|---------|----------------------|-----------|--------------|
|                     | Events     | Person-years | Events     | Person-years |               |             |
| Colchicine ≥ 1 mg/die |           |          |                      |           |              |
| O'keefe et al.      | 1          | 59.71    | 2                    | 30.77     | 0.26 [0.02; 2.84] |
| COOL                | 0          | 3.39     | 0                    | 3.39      | 1.00 [0.02; 50.40] |
| Defteros et al.     | 1          | 50.10    | 1                    | 48.10     | 0.96 [0.06; 15.35] |
| COLIN               | 0          | 1.92     | 0                    | 1.75      | 0.91 [0.02; 46.01] |
| COLCHICINE-PCI      | 1          | 16.92    | 1                    | 15.93     | 0.94 [0.06; 15.06] |
| Subtotal (I² = 0%, p = 0.95) |           |          |                      |           | **0.55 [0.12; 2.48]** |
| Colchicine < 1 mg/die |           |          |                      |           |              |
| LoDoCo              | 4          | 847.74   | 10                   | 751.54    | 0.35 [0.11; 1.13] |
| LoDoCo-MI           | 0          | 9.77     | 0                    | 9.69      | 0.99 [0.02; 49.97] |
| COLCOT              | 43         | 4465.12  | 44                   | 4489.65   | 0.98 [0.65; 1.50] |
| COPS                | 8          | 433.68   | 1                    | 436.96    | **8.06 [1.01; 64.45]** |
| LodDoCo2            | 73         | 6596.28  | 60                   | 6591.51   | 1.22 [0.86; 1.71] |
| Subtotal (I² = 61%, p = 0.10) |           |          |                      |           | **1.11 [0.86; 1.42]** |

**Overall** (random effects model)

- Heterogeneity: $I^2 = 34\%$, $t^2 = 0$, $p = 0.17$
- $p$ for interaction = 0.37

| 0.1 | 0.5 | 1 | 2 | 10 |
|-----|-----|---|---|----|
| favors colchicine |     | favors control |     | 1.09 [0.85; 1.40] |
Figure 19: Incidence rate ratios for the endpoint of major adverse cardiac events stratified by clinical presentation: chronic coronary syndrome (CCS) vs acute coronary syndrome (ACS).

| Study            | MACE   | Events | Person-years | Incidence Rate Ratio | IRR   | 95% CI       |
|------------------|--------|--------|--------------|----------------------|-------|--------------|
|                  | Colchicine |        |              |                      |       |              |
| CCS              | Events | Person-years |          |                      |       |              |
| LoDoCo          | 15     | 847.74 | 40          | 751.54               | 0.33  | [0.18; 0.60] |
| COLCHICINE-PCI CCS | 6         | 8.46 | 13          | 8.13                 | 0.44  | [0.17; 1.17] |
| LoDoCo2         | 187    | 6596.28 | 264        | 6591.51              | 0.71  | [0.59; 0.85] |
| Subtotal (I² = 68%, p = 0.04) |          |        |              |                      | **0.54** | [0.34; 0.85] |
| ACS              | Events | Person-years |          |                      |       |              |
| COLIN           | 2      | 1.92    | 2           | 1.75                 | 0.91  | [0.13; 6.48] |
| LoDoCo-MI      | 0      | 9.77    | 2           | 9.69                 | 0.20  | [0.01; 4.13] |
| COLCOT         | 131    | 4465.12 | 170         | 4489.65              | 0.77  | [0.62; 0.97] |
| COLCHICINE-PCI ACS | 17        | 8.46 | 11          | 7.80                 | 1.43  | [0.67; 3.04] |
| COPS            | 19     | 433.68  | 41          | 436.96               | 0.47  | [0.27; 0.80] |
| Subtotal (I² =31%, p = 0.22) |          |        |              |                      | **0.75** | [0.61; 0.91] |
| **Overall** (random effects model) |        |        |              |                      |       |              |
| Heterogeneity: I² = 51%, τ² = 0.0628, p = 0.05 |        |        |              |                      |       |              |
| p for interaction = 0.19 |        |        |              |                      |       |              |
Figure 20: Incidence rate ratios for the endpoint of myocardial infarction stratified by clinical presentation: chronic coronary syndrome (CCS) vs acute coronary syndrome (ACS).

### Myocardial infarction

| Study                  | Colchicine | Control | Incidence Rate Ratio | IRR   | 95% CI    |
|------------------------|------------|---------|----------------------|-------|-----------|
|                        | Events     | Person-years | Events     | Person-years |               |
| **CCS**                |            |          |                      |       |           |
| LoDoCo                 | 4          | 847.74  | 14                   | 751.54| 0.25 [0.08; 0.77]|
| COLCHICINE-PCI CCS     | 6          | 8.46    | 13                   | 8.13  | 0.44 [0.17; 1.17]|
| LoDoCo2                | 85         | 6596.28 | 117                  | 6591.51| 0.73 [0.55; 0.96]|
| **Subtotal (I² = 49%, p = 0.14)** |          |          |                      |       | **0.65 [0.50; 0.84]** |
| **ACS**                |            |          |                      |       |           |
| COLIN                  | 0          | 1.92    | 1                    | 1.75  | 0.30 [0.01; 7.47]|
| LoDoCo-Mi              | 0          | 9.77    | 2                    | 9.69  | 0.20 [0.01; 4.13]|
| COLCOT                 | 89         | 4465.12 | 98                   | 4489.65| 0.91 [0.69; 1.22]|
| COLCHICINE-PCI ACS     | 17         | 8.46    | 11                   | 7.80  | 1.43 [0.67; 3.04]|
| COPS                   | 7          | 433.68  | 11                   | 436.96| 0.64 [0.25; 1.65]|
| **Subtotal (I² = 0%, p = 0.77)** |          |          |                      |       | **0.91 [0.71; 1.18]** |
| **Overall** (random effects model)** |          |          |                      |       |           |
| Heterogeneity: I² =29%, r² <0.0001, p = 0.20 | | | | | |
| p for interaction = 0.07 | | | | | |
Figure 21: Incidence rate ratios for the endpoint of stroke stratified by clinical presentation: chronic coronary syndrome (CCS) vs acute coronary syndrome (ACS).

| Study                         | Colchicine | Control | Incidence Rate Ratio | IRR      | 95% CI     |
|-------------------------------|------------|---------|----------------------|----------|------------|
|                               | Events     | Person-years | Events     | Person-years |            |            |
| CCS                           |            |          |                      |          |            |
| LoDoCo                        | 1          | 847.74   | 4                    | 751.54   | 0.22 [0.02; 1.98] |
| COLCHICINE-PCI CCS            | NA         | 8.46     | NA                   | 8.13     |            |
| LoDoCo2                       | 16         | 6596.28  | 24                   | 6591.51  | 0.67 [0.35; 1.25] |
| Subtotal ($I^2 = 0\%, p = 0.34$) |            |          |                      |          | **0.60 [0.33; 1.09]** |
| ACS                           |            |          |                      |          |            |
| COLIN                         | NA         | 1.92     | NA                   | 1.75     |            |
| LoDoCo-MI                     | NA         | 9.77     | NA                   | 9.69     |            |
| COLCOT                        | 5          | 4465.12  | 19                   | 4489.65  | 0.26 [0.10; 0.71] |
| COLCHICINE-PCI ACS            | NA         | 8.46     | NA                   | 7.80     |            |
| COPS                          | 2          | 433.68   | 6                    | 436.96   | 0.34 [0.07; 1.66] |
| Subtotal ($I^2 = 0\%, p = 0.80$) |            |          |                      |          | **0.28 [0.12; 0.65]** |
| **Overall** (random effects model) |            |          |                      |          | **0.45 [0.24; 0.83]** |

Heterogeneity: $I^2 = 23\%, r^2 = 0.0074, p = 0.27$

$p$ for interaction = 0.15
**Figure 22:** Incidence rate ratios for the endpoint of all-cause death stratified by clinical presentation: chronic coronary syndrome (CCS) vs acute coronary syndrome (ACS).

### All-cause death

| Study          | Incidence Rate Ratio | IRR    | 95% CI  |
|----------------|----------------------|--------|---------|
| **CCS**        |                      |        |         |
| LoDoCo        | 0.35                 | 0.35   | [0.11; 1.13] |
| COLCHICINE-PCI CCS | 0.96               | 0.96   | [0.02; 48.44] |
| LoDoCo2       | 1.22                 | 1.22   | [0.86; 1.71] |
| Subtotal ($I^2 = 75\%, \ p = 0.14$) | 0.90               | 0.90   | [0.32; 2.50] |
| **ACS**        |                      |        |         |
| COLIN         | 0.91                 | 0.91   | [0.02; 46.01] |
| LoDoCo-MI     | 0.99                 | 0.99   | [0.02; 49.97] |
| COLCOT        | 0.98                 | 0.98   | [0.65; 1.50] |
| COLCHICINE-PCI ACS | 0.92              | 0.92   | [0.06; 14.75] |
| COPS          | 8.06                 | 8.06   | [1.01; 64.45] |
| Subtotal ($I^2 = 47\%, \ p = 0.43$) | 1.51               | 1.51   | [0.50; 4.55] |
| **Overall** (random effects model) | 1.11               | 1.11   | [0.86; 1.42] |

Heterogeneity: $I^2 = 65\%, \ r^2 = 0, \ p = 0.02$

$p$ for interaction = 0.50

Favors colchicine   Favors control