# Colchicine for secondary prevention of ischaemic stroke and atherosclerotic events: a meta-analysis of randomised trials

## Supplemental Material

**Supplemental Table 1. Search strategy**

*MEDLINE via PubMed (16/05/2024: 509 results)*

1. ("Myocardial Ischemia"[Mesh] OR “myocardial ischemia”[tiab] OR “ischemic heart disease”[tiab] OR “coronary artery disease”[tiab] OR CAD[tiab] OR “coronary disease”[tiab] OR “myocardial infarction”[tiab] OR “angina pectoris”[tiab] OR “acute coronary syndrome”[tiab] OR MACE[tiab] OR “major adverse cardiovascular events”[tiab] OR “cardiovascular events”[tiab] OR “cardiac events”[tiab] OR “cardiac death”[tiab] OR “cardiac mortality”[tiab] OR “cardiovascular death”[tiab] OR “cardiovascular mortality”[tiab] OR “coronary heart disease”[tiab] OR "Arteriosclerosis"[Mesh] OR “Arteriosclerosis”[tiab] OR "Atherosclerosis"[tiab] OR “Cardiovascular Disease”[tiab] OR CVD[tiab] OR ASCVD[tiab] OR “Peripheral Arterial Disease”[tiab] OR PAD[tiab] OR “Intermittent Claudication”[tiab] OR “Fontaine”[tiab] OR “Brain Ischemia”[Mesh] OR “Brain Ischemia”[tiab] OR “Brain infarction”[tiab] OR “Cerebral infarction”[tiab] OR “Brain Stem infarction”[tiab] OR “Transient ischemic attack”[tiab] OR TIA[tiab] OR “Stroke”[Mesh] OR “Stroke”[tiab] OR “Cerebrovascular accident”[tiab] OR CVA[tiab] OR “Carotid Stenosis”[Mesh] OR “Carotid Stenosis”[tiab] OR “Carotid Artery Thrombosis”[MesH] OR “Carotid Artery Thrombosis”[tiab])
2. ("Colchicine"[Mesh] OR colchicine[tiab] OR colchicin[tiab] OR colcemid[tiab] OR demecolcine[tiab] OR colchamine[tiab] OR lumicolchicine OR gamma-lumicolchicine[tiab] OR beta-lumicolchicine[tiab] OR “aqua colchin”[tiab] OR colchicum[tiab] OR colchily[tiab] OR colchimedio[tiab] OR colchiquim[tiab] OR colchisol[tiab] OR colchysat[tiab] OR colcine[tiab] OR colcrys[tiab] OR colgout[tiab] OR goutichine[tiab] OR goutnil[tiab] OR kolkicin[tiab] OR “nsc 757”[tiab] OR tolchicine[tiab] OR colchimax[tiab])
3. ((“randomized controlled trial”[pt] OR “controlled clinical trial”[pt] OR randomized[tiab] OR placebo[tiab] OR “drug therapy”[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh]))
4. #1 AND #2 AND #3

*EMBASE (16/05/2024: 259 results)*

1. (‘ischemic heart disease’/exp OR ‘coronary artery disease’/exp OR ‘ischemic heart disease’:ab,ti,kw OR ‘coronary artery disease’:ab,ti,kw OR CAD:ab,ti,kw OR ‘coronary heart disease’:ab,ti,kw OR ‘myocardial ischemia’:ab,ti,kw OR ‘coronary disease’:ab,ti,kw OR ‘myocardial infarction’:ab,ti,kw OR ‘angina pectoris’:ab,ti,kw OR ‘acute coronary syndrome’:ab,ti,kw OR ‘major adverse cardiovascular events’:ab,ti,kw OR MACE:ab,ti,kw OR ‘cardiovascular events’:ab,ti,kw OR ‘cardiac events’:ab,ti,kw OR ‘cardiovascular death’:ab,ti,kw OR ‘cardiovascular mortality’:ab,ti,kw OR ‘cardiac death’:ab,ti,kw OR ‘cardiac mortality’:ab,ti,kw OR ‘Atherosclerosis’/exp OR ‘Arteriosclerosis’:ab,ti,kw OR ‘Atherosclerosis’:ab,ti,kw OR ‘Cardiovascular Disease’:ab,ti,kw OR CVD:ab,ti,kw OR ASCVD:ab,ti,kw OR ‘Peripheral Arterial Disease’:ab,ti,kw OR PAD:ab,ti,kw OR ‘Intermittent Claudication’:ab,ti,kw OR ‘Fontaine’:ab,ti,kw OR ‘brain ischemia’/exp OR ‘Brain Ischemia’:ab,ti,kw OR ‘Brain infarction’:ab,ti,kw OR ‘Cerebral infarction’:ab,ti,kw OR ‘Brain Stem infarction’:ab,ti,kw OR ‘Transient ischemic attack’:ab,ti,kw OR TIA:ab,ti,kw OR ‘cerebrovascular accident’/exp OR ‘Stroke’:ab,ti,kw OR ‘Cerebrovascular accident’:ab,ti,kw OR CVA:ab,ti,kw OR ‘Carotid atherosclerosis’:ab,ti,kw OR ‘Carotid Stenosis’:ab,ti,kw OR ‘Carotid Artery Thrombosis’:ab,ti,kw)

2. (‘colchicine’/exp OR colchicin*:ab,ti,kw OR colcemid*:ab,ti,kw OR demecolcine:ab,ti,kw OR colchamine:ab,ti,kw OR lumicolchicine*:ab,ti,kw OR gamma-lumicolchicine*:ab,ti,kw OR beta-lumicolchicine*:ab,ti,kw OR ‘aqua colchin’:ab,ti,kw OR colchicum:ab,ti,kw OR colchily:ab,ti,kw OR colchimedio:ab,ti,kw OR colchiquim:ab,ti,kw OR colchisol:ab,ti,kw OR colchysat:ab,ti,kw OR colcine:ab,ti,kw OR colcrys:ab,ti,kw OR colgout:ab,ti,kw OR goutichine:ab,ti,kw OR goutnil:ab,ti,kw OR kolkicin:ab,ti,kw OR ‘nsc 757’:ab,ti,kw OR tolchicine:ab,ti,kw OR colchimax:ab,ti,kw)
3. ((‘randomized controlled trial’/de OR ‘controlled clinical trial’/de OR random*:ti,ab,tt OR ‘randomization’/de OR ‘intermethod comparison’/de OR placebo:ti,ab,tt OR (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt) OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR (open NEXT/1 label):ti,ab,tt OR ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt OR ‘double blind procedure’/de OR (parallel NEXT/1 group*):ti,ab,tt OR (crossover:ti,ab,tt OR ‘cross over’:ti,ab,tt) OR ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt OR (assigned:ti,ab,tt OR allocated:ti,ab,tt) OR (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt OR (volunteer:ti,ab,tt OR volunteers:ti,ab,tt) OR ‘human experiment’/de OR Trial:ti,tt) NOT ((((random* NEXT/1 sampl* NEAR/8 (‘cross section*’ OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT (‘comparative study’/de OR ‘controlled study’/de OR ‘randomised controlled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt OR ‘randomly assigned’:ti,ab,tt)) OR (‘cross-sectional study’/de NOT (‘randomized controlled trial’/de OR ‘controlled clinical study’/de OR ‘controlled study’/de OR ‘randomised controlled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt OR ‘control group’:ti,ab,tt OR ‘control groups’:ti,ab,tt)) OR (‘case control*’:ti,ab,tt AND random*:ti,ab,tt NOT (‘randomised controlled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt)) OR (‘systematic review’:ti,tt NOT (trial:ti,tt OR study:ti,tt)) OR (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt) OR ‘random field*’:ti,ab,tt OR (‘random cluster’ NEAR/4 sampl*):ti,ab,tt OR (review:ab AND review:it NOT trial:ti,tt) OR (‘we searched’:ab AND (review:ti,tt OR review:it)) OR ‘update review’:ab OR (databases NEAR/5 searched):ab OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND ‘animal experiment’/de) OR (‘animal experiment’/de NOT (‘human experiment’/de OR ‘human’/de)))) NOT [medline]/lim
4. #1 AND #2 AND #3

*CENTRAL (16/05/2024: 396 results)*

1. MeSH descriptor: [Myocardial Ischemia] explode all trees
2. MeSH descriptor: [Arteriosclerosis] explode all trees
3. MeSH descriptor: [Brain ischemia] explode all trees
4. MeSH descriptor: [Stroke] explode all trees
5. MeSH descriptor: [Carotid Stenosis] explode all trees
6. MeSH descriptor: [Carotid Artery Thrombosis] explode all trees
7. “ischemic heart disease” OR “coronary artery disease” OR CAD OR “coronary heart disease” OR “myocardial ischemia” OR “coronary disease” OR “myocardial infarction” OR “angina pectoris” OR “acute coronary syndrome” OR “major adverse cardiovascular events” OR MACE OR “cardiovascular

events" OR "cardiac events" OR "cardiovascular death" OR "cardiovascular mortality" OR "cardiac death" OR "cardiac mortality" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Cardiovascular Disease" OR CVD OR ASCVD OR "Peripheral Arterial Disease" OR PAD OR "Intermittent Claudication" OR "Fontaine" OR "Brain Ischemia" OR "Brain infarction" OR "Cerebral infarction" OR "Brain Stem infarction" OR "Transient ischemic attack" OR TIA OR "Stroke" OR "Cerebrovascular accident" OR CVA OR "Carotid Stenosis" OR "Carotid Artery Thrombosis"

8. MeSH descriptor: [Colchicine] explode all trees
9. colcemid* OR demecolcine OR colchamine OR lumicolchicine* OR gamma-lumicolchicine* OR beta-lumicolchicine OR colchicin* OR colchichine OR "aqua colchin" OR colchicum OR colchily OR colchimedio OR colchiquim OR colchisol OR colchysat OR colcine OR colcrys OR colgout OR goutichine OR goutnil OR kolkicin OR "nsc 757" OR tolchicine OR colchimax
10. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9)

*Clinicaltrials.gov (16/05/2024: 122 results)*

1. AREA[ConditionSearch] ("ischemic heart disease" OR "coronary artery disease" OR CAD OR "coronary heart disease" OR "myocardial ischemia" OR "coronary disease" OR "myocardial infarction" OR "angina pectoris" OR "acute coronary syndrome" OR MACE OR "major adverse cardiovascular events" OR "cardiovascular events" OR "cardiac events" OR "cardiovascular death" OR "cardiovascular mortality" OR "cardiac death" OR "cardiac mortality" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Cardiovascular Disease" OR CVD OR ASCVD OR "Peripheral Arterial Disease" OR PAD OR "Intermittent Claudication" OR "Fontaine" OR "Brain Ischemia" OR "Brain infarction" OR "Cerebral infarction" OR "Brain Stem infarction" OR "Transient ischemic attack" OR TIA OR "Stroke" OR "Cerebrovascular accident" OR CVA OR "Carotid Stenosis" OR "Carotid Artery Thrombosis")
2. INTERVENTION (colchicine OR colchicin OR colcemid OR demecolcine OR colchamine OR lumicolchicine OR gamma-lumicolchicine OR beta-lumicolchicine OR "aqua colchin" OR colchicum OR colchily OR colchimedio OR colchiquim OR colchisol OR colchysat OR colcine OR colcrys OR colgout OR goutichine OR goutnil OR kolkicin OR "nsc 757" OR tolchicine OR colchimax)

**Supplemental Table 2. Definition of outcome stroke in the included trials**

| | |
|---|---|
| CONVINCE | 1. A new focal neurological deficit, presumed due to cerebrovascular disease, persisting beyond 24hours, without intracerebral haemorrhage or other mimic condition (eg. abcess, tumour, subdural haematoma) on brain CT or MRI.<br>2. If brain imaging is not performed, a focal neurological deficit which is acute in onset, persists beyond 24 hours, and is consistent with stroke in the opinion of the Outcomes Adjudication Committee.<br>3. If acute new focal symptoms/signs last less than 24 hours but brain CT or MRI demonstrates acute ischaemic change, (i.e. consistent with the 'tissue definition' of TIA).<br>4. Retinal infarction, confirmed by an ophthalmologist.<br>5. Spinal cord infarction, with mimic conditions excluded by spinal MR. |
| LoDoCo2 | Non-Cardio-Embolic Stroke: as evidenced by CT or MRI and coded as such by the treating neurologist occurring in the absence of atrial fibrillation, cerebral hemorrhage, lacunar infarction or small vessel disease. |
| COPS | Computed tomography (CT) or magnetic resonance imaging (MRI)-proven ischaemic stroke judged by the treating neurologist as not being due to atrial fibrillation or intracranial haemorrhage. |
| COLCOT* | An acute episode of focal or global neurological dysfunction causes by brain, spinal cord or retinal avascular injury as a result of hemorrhage or infarction. For the diagnosis of stroke the following 4 criteria should be fulfilled:<br>1. Rapid onset of a focal/global neurological deficit<br>2. Duration of ≥ 24 hours (or < 24 hours due the therapeutic intervention)<br>3. No other readily identifiable non-stroke cause for the clinical presentation and<br>4. Confirmation of the diagnosis by at least one of the following: a) neurology or neurosurgery specialist b) brain imaging (CT, MRI, angiography) c) lumbar puncture d) pathology |
| Deftereos | Not specified. |
| LoDoCo | Noncardioembolic ischemic stroke was defined as computed tomography—or magnetic resonance imaging—proven ischemic stroke judged by the treating neurologist as not being due to atrial fibrillation or intracranial hemorrhage. |

***** Personal communication.

**Supplemental Table 3. Risk of bias assessment**

| Trial acronym or first author | Outcomes | Randomization process | Deviation from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall |
|---|---|---|---|---|---|---|---|
| CONVINCE | Ischemic stroke | + | + | + | + | + | + |
| | MACE | + | + | + | + | + | + |
| LoDoCo2 | Ischemic stroke | + | + | + | + | + | + |
| | MACE | + | + | + | + | + | + |
| COPS | Ischemic stroke | + | + | + | + | + | + |
| | MACE | + | + | + | + | + | + |
| COLCOT | Ischemic stroke | + | + | + | + | + | + |
| | MACE | + | + | + | + | + | + |
| Deftereos | Ischemic stroke | + | + | + | + | ? | ? |
| | MACE | + | + | + | + | ? | ? |
| LoDoCo | Ischemic stroke | + | + | + | + | + | + |
| | MACE | + | + | + | + | + | + |

+ indicates low risk of bias; - indicates high risk of bias; ? indicates unclear risk of bias.
Abbreviation: MACE=Major adverse cardiovascular event

**Supplemental Table 4. Use of run-in period and trial medication discontinuation in the included trials**

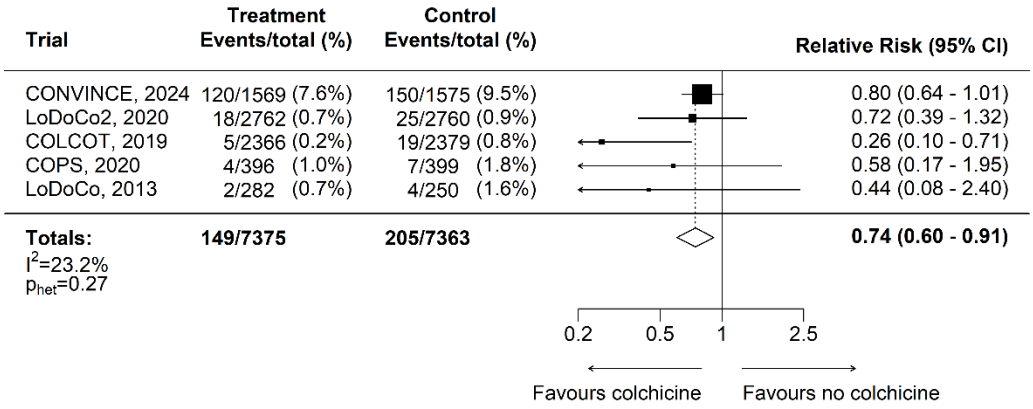
| Trial acronym or first author | Run-in period | Trial medication discontinuation | |
|---|---|---|---|
| | | Colchicine group (%) | Placebo group (%) |
| CONVINCE | No | 20.5 | Not applicable |
| LoDoCo2 | Yes | 10.5 | 10.5 |
| COPS | No | 15.4 | 8.3 |
| COLCOT | No | 18.4 | 18.7 |
| LoDoCo | Yes | 22.0 | Not applicable |
| Deftereos | No | 17.0 | 9.4 |

**Supplemental Table 5. Sensitivity analyses using random-effect models**

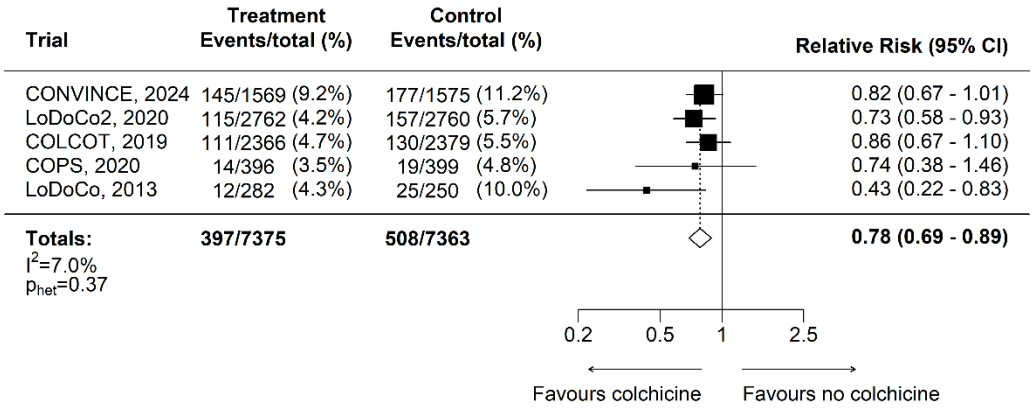
| Outcome | Pooled RR (95% CI) | $P_{het}$ | $I^2$ |
|---|---|---|---|
| **Primary efficacy outcomes** | | | |
| Ischaemic stroke | 0.63 (0.43-0.92) | 0.24 | 27.5% |
| MACE: stroke, myocardial infarction, coronary revascularisation, cardiovascular death | 0.71 (0.61-0.83) | 0.16 | 39.5% |
| **Secondary efficacy outcomes** | | | |
| Stroke, myocardial infarction, and cardiovascular death | 0.78 (0.68-0.89) | 0.37 | 7.0% |
| All stroke | 0.67 (0.48-0.94) | 0.27 | 23.2% |
| Myocardial infarction | 0.80 (0.68-0.96) | 0.43 | 0.0% |
| Coronary revascularization | 0.77 (0.67-0.89) | 0.43 | 0.0% |
| **Main safety outcomes** | | | |
| Hospitalisation for pneumonia | 1.19 (0.69-2.06) | 0.04 | 64.3% |
| Hospitalisation for gastro-intestinal events | 1.15 (0.91-1.44) | 0.50 | 0.0% |
| Hospitalisation for cancer | 0.97 (0.82-1.15) | 0.79 | 0.0% |
| **Mortality** | | | |
| All-cause mortality | 1.08 (0.84-1.39) | 0.28 | 20.7% |
| Cardiovascular mortality | 0.89 (0.65-1.23) | 0.58 | 0.0% |
| Non-cardiovascular mortality | 1.26 (0.97-1.64) | 0.45 | 0.0% |

Abbreviation: MACE=Major adverse cardiovascular event

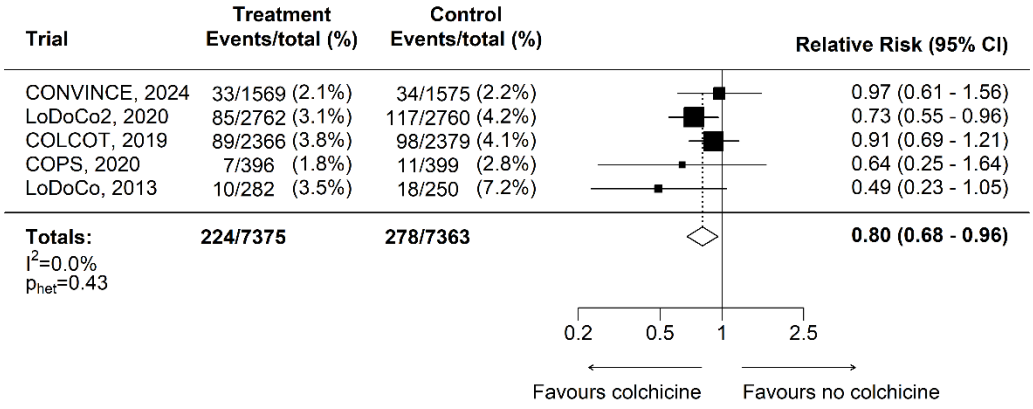
**Supplemental Figure 1. Pooled estimate of colchicine treatment for prevention of all stroke**



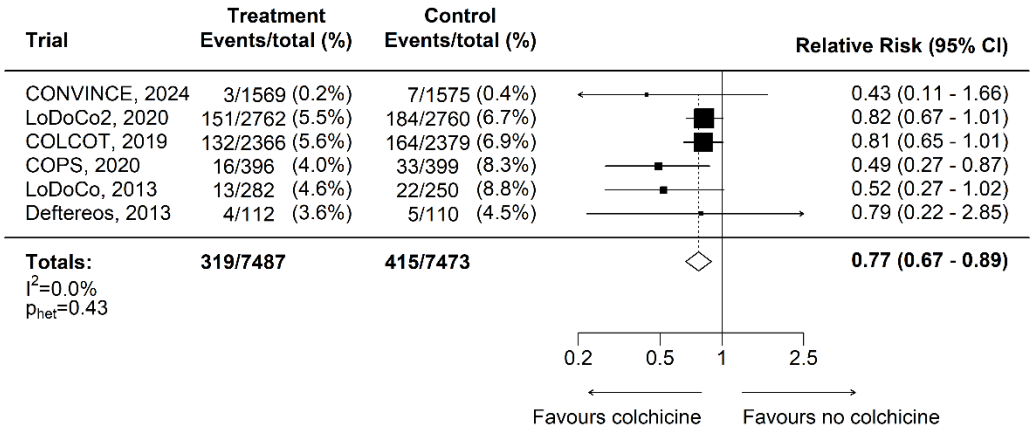
**Supplemental Figure 2. Pooled estimate of colchicine for prevention of stroke, myocardial infarction, or cardiovascular death**



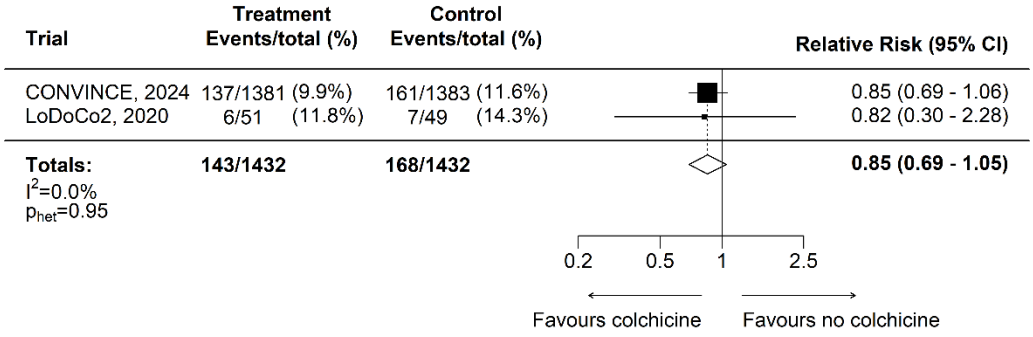
**Supplemental Figure 3. Pooled estimate of colchicine on myocardial infarction**



**Supplemental Figure 4. Pooled estimate of colchicine on coronary revascularisation**

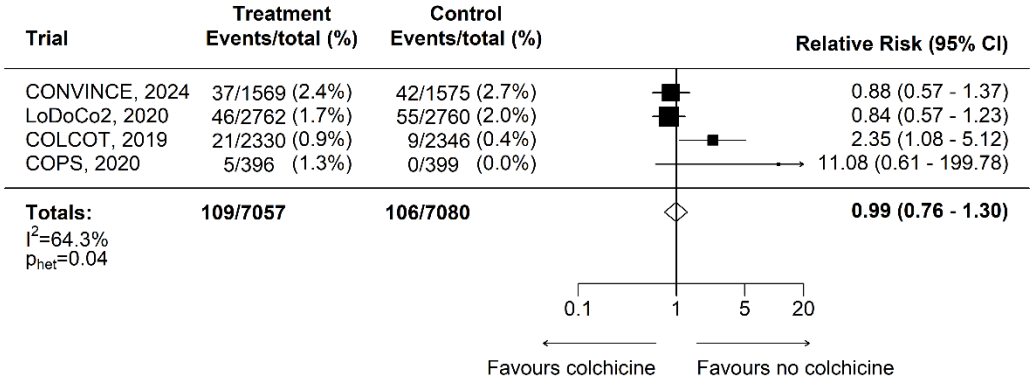


**Supplemental Figure 5. Pooled estimate of colchicine in patients with prior stroke**

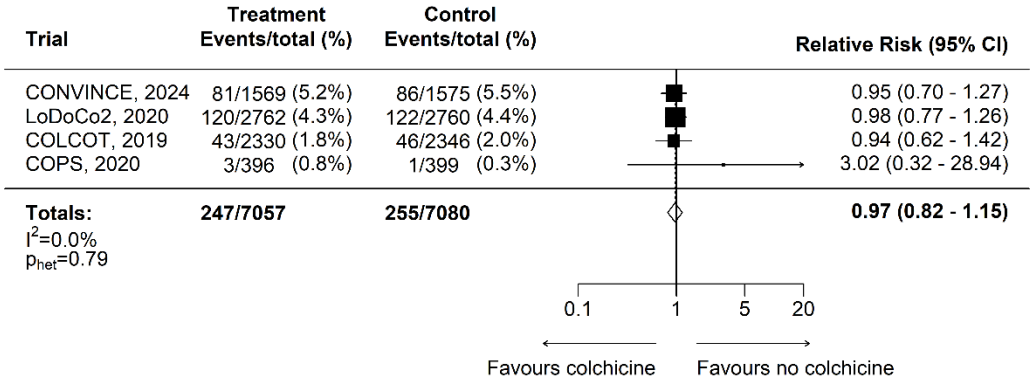


## Supplemental Figure 6: Main safety outcomes

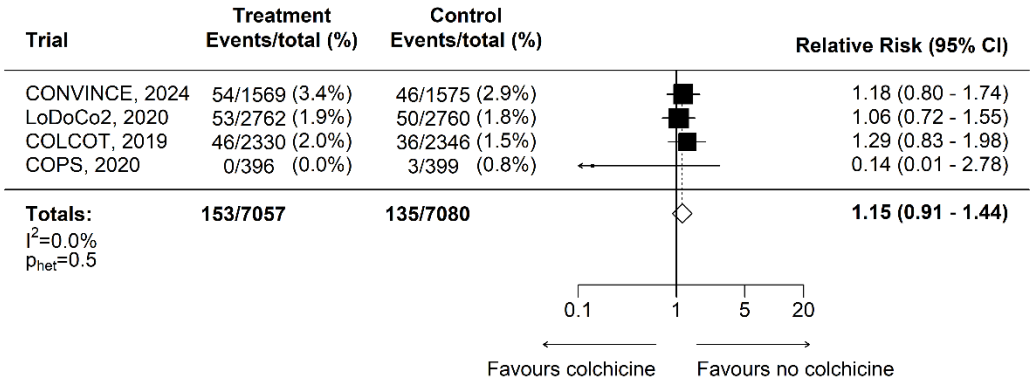
### 6a: Hospitalisation for pneumonia




### 6b: Hospitalisation for newly diagnosed cancer



## 6c: Hospitalisation for gastro-intestinal events



## Reference

1 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71