Long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE): a randomised controlled trial

Peter Kelly, Robin Lemmens, Christian Weimar, Cathal Walsh, Francisco Purroy, Mark Barber, Ronan Collins, Simon Cronin, Anna Czlonkowska, Philippe Desfontaines, Adinda De Pauw, Nicholas Richard Evans, Urs Fischer, Catarina Fonseca, John Forbes, Michael D Hill, Dalius Jatuzis, Janika Kõrv, Peter Kraft, Christina Kruuse, Catherine Lynch, Dominick McCabe, Robert Mikulik, Sean Murphy, Paul Nederkoorn, Martin O'Donnell, Peter Sandercock, Bernadette Schroeder, Gek Shim, Katrina Tobin, David J Williams, Christopher Price

Summary

Background Anti-inflammatory therapy with long-term colchicine prevented vascular recurrence in coronary disease. Unlike coronary disease, which is typically caused by atherosclerosis, ischaemic stroke is caused by diverse mechanisms including atherosclerosis and small vessel disease or is frequently due to an unknown cause. We aimed to investigate the hypothesis that long-term colchicine would reduce recurrent events after ischaemic stroke.

Methods We did a randomised, parallel-group, open-label, blinded endpoint assessed trial comparing long-term colchicine (0·5 mg orally per day) plus guideline-based usual care with usual care only. Hospital-based patients with non-severe, non-cardioembolic ischaemic stroke or high-risk transient ischaemic attack were eligible. The primary endpoint was a composite of first fatal or non-fatal recurrent ischaemic stroke, myocardial infarction, cardiac arrest, or hospitalisation (defined as an admission to an inpatient unit or a visit to an emergency department that resulted in at least a 24 h stay [or a change in calendar date if the hospital admission or discharge times were not available]) for unstable angina. The p value for significance was 0·048 to adjust for two prespecified interim analyses conducted by the data monitoring committee, for which the steering committee and trial investigators remained blinded. The trial was registered at ClinicalTrials.gov (NCT02898610) and is completed.

Findings 3154 patients were randomly assigned between Dec 19, 2016, and Nov 21, 2022, with the last follow-up on Jan 31, 2024. The trial finished before the anticipated number of outcomes was accrued (367 outcomes planned) due to budget constraints attributable to the COVID-19 pandemic. Ten patients withdrew consent for analysis of their data, leaving 3144 patients in the intention-to-treat analysis: 1569 (colchicine and usual care) and 1575 (usual care alone). A primary endpoint occurred in 338 patients, 153 (9·8%) of 1569 patients allocated to colchicine and usual care and 185 (11·7%) of 1575 patients allocated to usual care alone (incidence rates 3·32 *vs* 3·92 per 100 person-years, hazard ratio 0·84; 95% CI 0·68–1·05, p=0·12). Although no between-group difference in C-reactive protein (CRP) was observed at baseline, patients treated with colchicine had lower CRP at 28 days and at 1, 2, and 3 years (p<0·05 for all timepoints). The rates of serious adverse events were similar in both groups.

Interpretation Although no statistically significant benefit was observed on the primary intention-to-treat analysis, the findings provide new evidence supporting the rationale for anti-inflammatory therapy in further randomised trials.

Funding Health Research Board Ireland, Deutsche Forschungsgemeinschaft (German Research Foundation), and Fonds Wetenschappelijk Onderzoek Vlaanderen (Research Foundation Flanders), Belgium.

Lancet 2024; 404: 125–33

Published Online June 7, 2024 https://doi.org/10.1016/S0140-6736(24)00968-1

See Comment page 96

Mater Misericordiae University Hospital, Dublin, Ireland (Prof P Kelly MD, S Murphy MD); **School of Medicine, University College Dublin, Dublin, Ireland** (Prof P Kelly, S Murphy); **Health Research Board Stroke Clinical Trials Network Ireland, Dublin, Ireland** (Prof P Kelly, R Collins MD, Prof J Forbes PhD, C Lynch MSc, Prof D McCabe PhD, S Murphy, Prof M O'Donnell MD, K Tobin MSc, Prof D J Williams MD); **Department of Neurology, University Hospitals Leuven, Leuven, Belgium** (Prof R Lemmens MD); **Department of Neurosciences, Department of Experimental Neurology, and Leuven Research Institute for Neuroscience and Disease (LIND), KU Leuven–University of Leuven, Leuven, Belgium** (Prof R Lemmens); **Institute for Medical Informatics, Biometry, and Epidemiology, University Hospital, University Duisburg–Essen, Essen, Germany** (Prof C Weimar MD); **TCD Biostatistics Unit, Discipline of Public Health and Primary Care, School of Medicine, Trinity College Dublin, Dublin, Ireland** (Prof C Walsh PhD); **Stroke Unit, Department of Neurology, Hospitalt Universitari Arnau de Vilanova de Lleida, Lleida, Spain** (Prof F Purroy MD); **Biomedical Research Institute of Lleida, Universitat de Lleida, Lleida, Spain** (Prof F Purroy); **University Hospital Monklands, Airdrie, UK** (Prof M Barber MD); **Department of Neurology and Department of Geriatric and Stroke Medicine, Tallaght**

Introduction

Stroke is the second leading cause of death worldwide, with an estimated global prevalence of more than 100 million people in 2019.[1] New treatments to reduce the recurrence of vascular events after stroke are needed, ideally with the potential to be widely-implemented in low-income and middle-income countries, as well as high-income countries.[2,3] Inflammation is associated with first-ever and recurrent stroke.[4–8] In the CANTOS trial, canakinumab, a monoclonal antibody that inhibits interleukin-1b (IL-1b), prevented recurrent vascular events in patients with coronary artery disease.[9] Colchicine is a widely available, inexpensive agent that inhibits inflammatory cell mitosis, motility, intracellular inflammasome activation, and expression of pro-inflammatory cytokines.[10] In the LoDoCo2 and COLCOT trials of patients with coronary disease, long-term colchicine therapy prevented recurrent vascular events with an acceptable safety profile.[11,12]

Unlike atherosclerotic coronary disease, stroke is caused by several biological mechanisms and frequently affects older patients with multiple comorbid diseases.

University Hospital—The Adelaide and Meath Hospital, Dublin, Ireland incorporating the National Children's Hospital and Academic Unit of Neurology, School of Medicine, Trinity College Dublin, Dublin, Ireland (R Collins, Prof D McCabe); Cork University Hospital, Cork, Ireland (Prof S Cronin PhD); School of Medicine, University College Cork, Cork, Ireland (Prof S Cronin); Institute of Psychiatry and Neurology, Warsaw, Poland (Prof A Czlonkowska MD); Stroke Unit, Department of Neurology, CHC-Groupe Santé, Liège, Belgium (P Desfontaines MD); AZ Oostende, Ostend, Belgium (A De Pauw MD); Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK (N R Evans PhD); Department of Neurology, University Hospital Bern and University of Bern, Bern, Switzerland (Prof U Fischer MD); Department of Neurosciences and Mental Health (Neurology), Hospital Santa Maria-CHLN, Centro de Estudos Egas Moniz, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal (C Fonseca MD); School of Medicine, University of Limerick, Limerick, Ireland (Prof J Forbes); Department of Clinical Neurosciences & Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary and Foothills Medical Centre, Calgary, AB, Canada (Prof M D Hill MD); Centre of Neurology, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania (Prof D Jatuzis PhD); Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia (Prof J Kõrv MD); Klinikum Main-Spessart, Lohr, Germany (P Kraft MD); Department of Neurology, Herlev and Gentofte Hospital, and Department of Brain and Spinal Cord Injury, Rigshospitalet Hospital, Copenhagen University Hospital, Copenhagen, Denmark (Prof C Kruuse MD); International Clinical Research Center and Department of Neurology, St Anne's University Hospital and

Research in context

Evidence before this study

Members of our consortium (PKe, MO'D, and SM) conducted a Cochrane systematic review of randomised clinical trials of anti-inflammatory agents including colchicine for the secondary prevention of stroke and coronary events. Sources searched (all languages), on May 29, 2019, included the Cochrane Central Register of Controlled Trials (CENTRAL; from database inception), MEDLINE (from 1948), Embase (from 1980), CINAHL (from 1982), and Scopus (from 1995), plus citations of systematic reviews and grey literature, up to May, 2019. Search terms included "brain ischaemia" and "stroke" (and relevant synonyms) and "randomised clinical trials" and "colchicine" (and their synonyms). No publications reporting randomised trials of long-term colchicine therapy for secondary prevention after stroke were identified. We updated this systematic review by searching PubMed (all languages and human studies only) from May 1, 2019, to April 24, 2024, using the search terms "Brain Ischemia" AND "colchicine" AND "randomized controlled trial" (and their synonyms). No additional trials were identified. An as-yet unpublished trial (CHANCE3) presented data reporting no benefit of short-term (90 days) colchicine for the prevention of early recurrent events (mostly in the first week) after non-cardioembolic stroke or transient ischaemic attack. A separate systematic review conducted in 2021 examined the efficacy and safety of colchicine for the prevention of cardiovascular outcomes in randomised trials of patients with coronary artery disease. This review reported a pooled reduction in the risk of myocardial infarction, stroke, and vascular death (relative risk 0·75, 95% CI 0·61–0·92; p=0·005) and stroke (0·54, 0·34–0·86; p=0·009).

Added value of this study

Although the intention-to-treat analysis did not meet the prespecified threshold for statistical significance and the overall result was neutral, the CONVINCE findings support data from the 2021 meta-analysis in trials of coronary patients, suggesting that long-term low-dose colchicine might reduce the risk of future vascular events in patients with non-cardioembolic ischaemic stroke or transient ischaemic attack.

Implications of all the available evidence

The combined evidence provides a strong rationale for conducting further randomised clinical trials of colchicine for secondary prevention after stroke. Future studies might investigate efficacy in patients selected with evidence of atherosclerosis and should investigate mechanisms of colchicine intolerance.

The efficacy and safety of long-term colchicine after stroke is unknown. In CONVINCE, we aimed to investigate the hypothesis that long-term colchicine treatment added to guideline-based usual care would reduce recurrent vascular events compared with usual care only.

Methods

Study design

CONVINCE was an investigator-led, parallel-group prospective, randomised open-label, blinded-endpoint assessed controlled phase 3 trial. The protocol description has been published[13] (appendix p 47). Briefly, the trial was conducted at 144 hospital sites in 13 European countries and Canada. The trial protocol was approved by national regulators in each participating country and by institutional review boards or ethics committees in each participating hospital (the first ethics approval was by the Mater University Hospital Dublin, reference 1/478/75). Oversight was provided by a steering committee and an independent data monitoring committee regularly reviewed accumulating adverse event data to safeguard participant safety.

The academic and clinical investigators designed the trial, collected and managed the data, conducted the statistical analysis, and wrote the manuscript. The trial drug was purchased from wholesale suppliers (Actavis, Ireland; Morningside, UK; Tiofarma, Netherlands). Study drug supply logistics were managed by an independent contract research organisation (Modepharma). Colchicine was centrally (UK and France) purchased, repackaged, and distributed, ensuring that the same medicinal preparation was used by all participating sites. The steering committee members and trial statisticians vouch for the completeness and accuracy of the data and analysis and for the fidelity of the trial to the protocol.

Participants

Patients were included if they were clinically stable, aged at least 40 years, with non-severe ischaemic stroke or high-risk transient ischaemic attack, for whom the qualifying event was most likely caused by large artery atherosclerosis of an ipsilateral carotid, vertebral, or intracranial artery, lacunar disease, or cryptogenic embolism after assessment by the treating clinicians (appendix p 8). Non-severe ischaemic stroke was defined as a modified Rankin Scale score of 3 or less (no or mild-to-moderate disability but able to walk independently). High-risk transient ischaemic attack was defined as transient focal motor or speech symptoms with an ABCD2 score of 4 or greater, large artery lumen stenosis of at least 50% on imaging, or hyperintensity on diffusion-weighted MRI consistent with symptoms. The interval between qualifying event and randomisation was required to be between 72 hours and 28 days.

Patients were ineligible if the qualifying stroke or transient ischaemic attack was likely caused by atrial fibrillation, other cardiac embolism, or other defined causes such as arterial dissection. Patients with pre-existing moderate-to-severe renal, liver, or blood disorders,

peripheral neuropathy, myopathy, inflammatory bowel disease or chronic diarrhoea were excluded. Patients using regular immune-suppressant medications, moderate-to-strong CYP3A4 inhibitors, or P-glycoprotein inhibitors were ineligible (appendix p 8).

Randomisation and masking

Following written informed consent, patients were randomly assigned (1:1) by trained study personnel at each hospital site via a web-based computerised algorithm to receive low-dose colchicine orally (0·5 mg daily) plus guideline-based usual care or to usual care alone. A minimisation algorithm was used to ensure that treatment groups were balanced for important mandatory prognostic variables: age (<70 years or ≥70 years), time since qualifying event (7 days or >7 days), and type of qualifying event (stroke or transient ischaemic attack).

Patients, treating clinicians, and study investigators were aware of the randomised treatment allocation. All site-suspected outcomes were required to have anonymised additional clinical and imaging documentation provided by sites, which was assessed by an independent adjudication committee masked to the treatment allocation. The independent adjudication committee comprised two stroke physicians and two cardiologists. Concordance of both independent adjudicators was required for verification of outcome status. In the event of discordant adjudication, the case was assessed by a third independent blinded adjudicator and outcome status decided by the majority opinion.

Procedures

At baseline, demographic, clinical, laboratory, health-related quality of life (using the EQ-5D questionnaire), and cognition (using the Montreal Cognitive Assessment) were recorded. Follow-up assessments were done at 28 days, 90 days (telephone), and 6-month intervals after randomisation. If an in-person visit could not be conducted, a telephone assessment was permitted. At follow-up, modified Rankin score, suspected endpoints, adverse events, and adherence were assessed. Site teams assessed adherence by recording temporary drug interruptions or complete discontinuation, and by counting the remaining tablets from the last-dispensed packs. Non-adherence was defined as complete drug discontinuation. As a non-mandatory procedure, blood levels of C-reactive protein (CRP) and other laboratory tests were measured at local hospital laboratories at baseline, 28 days, and annually at follow-up visits.

The main protocol modifications throughout the trial period related to upward revision of the sample size, modifications to include more remote trial procedures during the COVID-19 pandemic, and specific changes in response to requests by European regulatory bodies. All protocol modifications are listed in detail in the protocol (appendix p 90), which is publicly available.[13]

Outcomes

The primary efficacy outcome was the centrally adjudicated composite of first recurrent non-fatal ischaemic stroke, myocardial infarction, cardiac arrest, or hospitalisation (ie, an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 h stay or a change in calendar date if the hospital admission or discharge times are not available) for unstable angina or vascular death (appendix p 12). A fatal outcome was defined as death from recurrent stroke or cardiac event within 30 days. Fatal and non-fatal stroke and cardiac events were included in the primary outcome. The prespecified key secondary outcome was the composite of first recurrent non-fatal ischaemic stroke, myocardial infarction, cardiac arrest, or vascular death. Other secondary outcomes were all ischaemic stroke (fatal and non-fatal), non-fatal ischaemic stroke, vascular death, non-fatal myocardial infarction and cardiac arrest, and hospitalisation for unstable angina. The exploratory outcomes, none of which are reported in this Article, were the effects of colchicine therapy on: recurrent disabling ischaemic stroke (modified Rankin score of 3–5); disability (modified Rankin score) of recurrent strokes measured across the entire range of the modified Rankin score; recurrent severe ischaemic stroke (fatal or modified Rankin score of 4–5); direct health-care resource costs; cognitive decline and dementia, measured by the Montreal Cognitive Assessment; health-related quality of life, measured by EuroQoL; the cumulative total number of component events in the primary outcome cluster detected over the duration of the trial; and primary and secondary outcome events stratified by baseline and on-treatment high-sensitivity C-reactive protein.

All reported serious and non-serious adverse events were recorded regardless of treatment allocation. Serious adverse events were reported within 24 h to the sponsor pharmacovigilance office, assessed for causality with the study drug, monitored by the data safety monitoring committee, and reported to national regulators annually. Following the onset of the COVID-19 pandemic, all cases of COVID-19 in participants were required to be reported as serious adverse events.

Statistical analysis

The original sample size was 2623 participants. In response to accumulating evidence suggesting reduced rates of recurrent outcome events, the sample size was subsequently increased in 2018 to 3154 participants with the protocol updated accordingly. The revised sample size was calculated to detect a 26% reduction in event rates of the adjudicated primary outcome by colchicine (relative hazard 0·75 after accounting for 15% non-adherence) after a median follow-up of 36 months, corresponding to 13·5% in the control group and 9·99% in the colchicine-treated group. The sample size calculation assumed non-uniform enrolment and an accrual window from December, 2016 to

Masaryk University Brno, Brno, Czech Republic (Prof R Mikulik MD); **Department of Neurology, Amsterdam University Medical Centers, Amsterdam, Netherlands** (P Nederkoorn PhD); **HRB Clinical Research Facility, University of Galway, Galway, Ireland** (Prof M O'Donnell); **Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK** (Prof P Sandercock DM); **Center for Clinical Trials Essen, University Hospital Essen, Essen, Germany** (B Schroeder Dipl Oecotroph); **University Hospital of North Durham, Durham, UK** (G Shim MBBCh); **RCSI University of Medicine and Health Sciences and Beaumont Hospital, Dublin, Ireland** (S Murphy, Prof D J Williams); **Population Health Sciences Institute, Newcastle University, Newcastle, UK** (Prof C Price MD)

Correspondence to:
Prof Peter Kelly,
Mater Misericordiae University Hospital, Dublin D07 KX5K, Ireland
pjkelly@mater.ie

See **Online** for appendix

June, 2020 (43 months). At this sample size, the trial would require 367 primary outcome endpoints, providing 80% power at a 5% two-sided significance level. Interim analyses were accounted for by adjustment of the prespecified p value to 0·048.

The primary analysis was by intention-to-treat, including all consenting randomly assigned patients with positively adjudicated primary outcomes. The between-group effect size was analysed by Cox proportional hazards modelling, adjusting for mandatory randomisation minimisation variables, with censoring at non-outcome death or last follow-up assessment for patients with incomplete follow-up. The proportional hazards assumption was examined by inspection of log–log plots and examination of Schoenfeld residuals. The p value for significance was adjusted to 0·048 to account for two interim analyses conducted by the data monitoring committee when approximately 50% and 75% of patients had been recruited (May 18, 2021, and April 25, 2022). These analyses were conducted by the data monitoring committee statistician (not the trial statistician) and reviewed in a closed session by the data monitoring committee. The steering committee, study investigators, and trial statistician remained blinded to the results of the interim analyses.

To assess the effect of colchicine non-adherence, a prespecified on-treatment analysis was done, excluding patients who did not begin colchicine treatment, with censoring at the time of death in patients who died from causes other than outcome events, or at last follow-up assessment (for patients with incomplete follow-up), or at last reported compliance (for patients who permanently discontinued colchicine). We did a prespecified per-protocol analysis of colchicine-compliant patients as defined previously, further excluding patients with major protocol deviations relating to eligibility. As the on-treatment and per-protocol analyses were not by intention-to-treat, these results should be interpreted as hypothesis-generating.

For secondary outcomes, a hierarchical strategy was prespecified, with a p value of <0·05 required on each analysis for interpretation of the subsequent analysis as confirmatory. If the threshold for statistical significance was not reached on the primary or a secondary analysis, each subsequent analysis was considered as hypothesis-generating. The order of the analysis hierarchy was: (1) analysis of the primary outcome in the per-protocol and on-treatment populations; (2) key secondary outcome (composite of first non-fatal recurrent ischaemic stroke, non-fatal myocardial infarction,

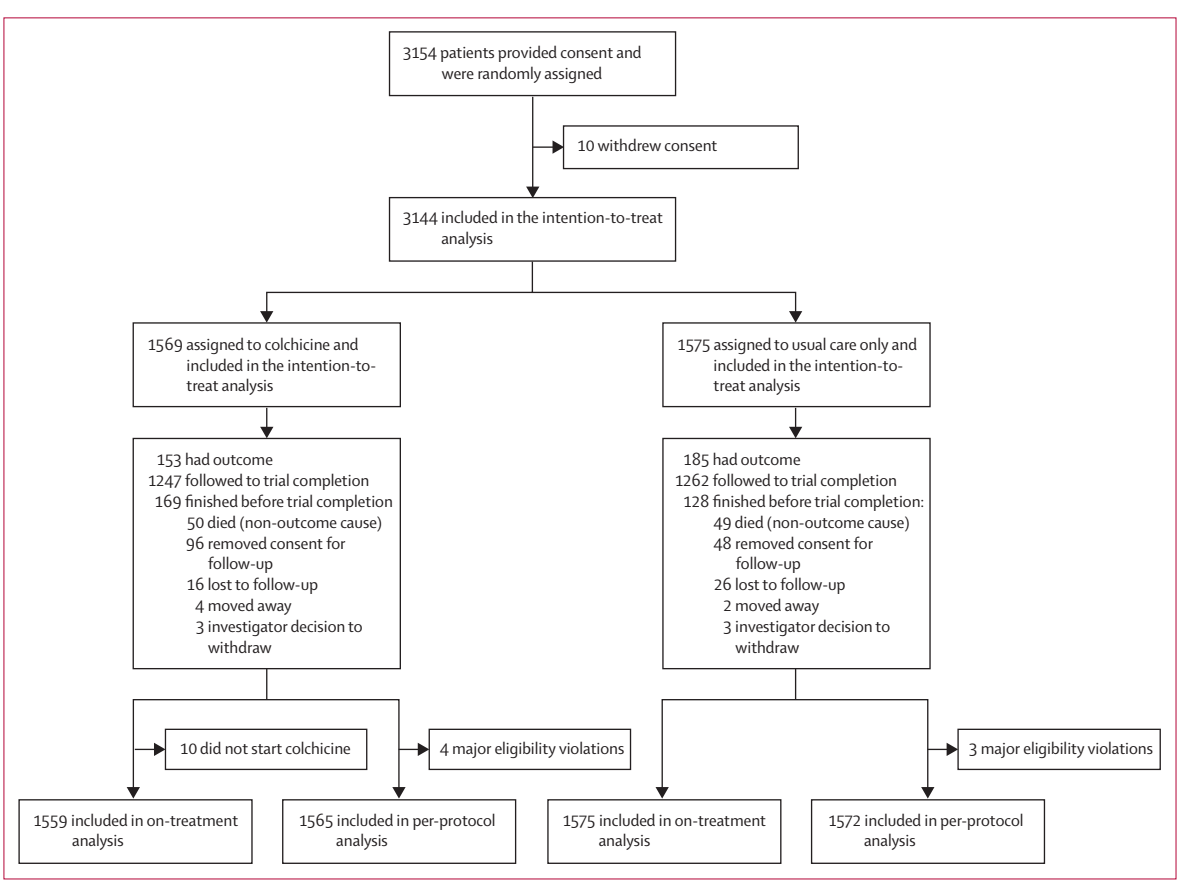

Figure 1: **Trial profile**

non-fatal cardiac arrest, or vascular death); and (3) individual components of the primary composite outcome, defined as fatal and non-fatal recurrent ischaemic stroke combined, non-fatal ischaemic stroke, vascular death, non-fatal myocardial infarction and cardiac arrest, and unstable angina requiring hospitalisation. No statistical adjustment for multiple comparisons was applied. The effect of colchicine on the overall primary outcome stratified by subgroups was analysed. The statistical analysis plan was published on Jan 9, 2024, before the data lock. Analyses were conducted in R (version 4.3.3, 2024-02-29).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The first patient was randomly assigned on Dec 19, 2016. At the onset of the COVID-19 pandemic, recruitment was paused from March 21, 2020, to May 22, 2020, before resuming. The last patient was randomly assigned on Nov 21, 2022. Due to the COVID-19 pandemic, trial recruitment was slower than projected. Consequently, the steering committee extended the trial duration from the originally planned end date of Sept 30, 2022, to Jan 31, 2024, at which time follow-up was ended due to budgetary reasons before the number of outcomes planned in the sample size was reached.

Of 3154 patients randomly assigned, ten patients withdrew consent for inclusion of their data and were excluded from the intention-to-treat analysis (figure 1). The intention-to-treat population included 3144 patients; 1569 randomly assigned to colchicine and 1575 to usual care only. The mean age was 66 years (SD 10), 953 (30·3%) of 3144 patients were female, the mean National Institutes of Health Stroke Scale score was 1·65, 694 (22·1%) were smokers, and 279 (8·9%) had previous coronary disease coronary disease (table 1). At randomisation, 3066 (97·5%) were on antiplatelet therapy and 2950 (93·8%) were on statins.

The last patient follow-up visit was done on Jan 31, 2024. The database was locked on March 6, 2024. At this time, 338 centrally adjudicated primary outcome events had occurred (92·1% of 367 originally planned outcomes). Outcomes were as follows: non-fatal stroke (234 patients), non-fatal myocardial infarction (55 patients), non-fatal hospitalisation for unstable angina (14 patients), non-fatal cardiac arrest (two patients), and vascular death (33 patients: ten fatal strokes, 23 fatal coronary events; table 2). The median follow-up duration was 33·6 months. Incomplete follow-up occurred in 198 patients (6·3%). Reasons for incomplete follow-up were: withdrawal of consent for follow-up (n=144 [4·6%]), lost to follow-up (n=42 [1·3%]), moved away (n=6 [0·2%]), and investigator withdrew patient (n=6 [0·2%]; figure 1).

	Colchicine and usual care (n=1569)	Usual care alone (n=1575)
Age, years	66·4 (10·0)	66·2 (9·9)
Female	488 (31·1%)	465 (29·5%)
Male	1081 (68·9%)	1110 (70·5%)
Race		
White	1494 (95·2%)	1507 (95·7%)
Black	36 (2·3%)	39 (2·5%)
Asian	27 (1·7%)	19 (1·2%)
Other	12 (0·8%)	10 (0·6%)
Onset to randomisation, days	9 (5–17)	9 (5–18)
Qualifying event		
Stroke	1381 (88·0%)	1383 (87·8%)
Transient ischaemic attack	188 (12·0%)	192 (12·2%)
Modified Rankin Scale score	1 (0–2)	1 (0–2)
National Institutes of Health Stroke Scale score	1 (0–3)	1 (0–3)
ABCD2 score (transient ischaemic attack only)	5 (4–6)	4 (3–5)
Lacunar stroke	468 (29·8%)	485 (30·8%)
Carotid stenosis (>50%)	349 (22·2%)	345 (21·9%)
Carotid revascularisation at 28 days	45 (2·9%)	35 (2·2%)
Emergency treatment		
Thrombolysis	256 (16·3%)	217 (13·8%)
Thrombectomy	87 (5·5%)	85 (5·4%)
Previous stroke	157 (10·0%)	174 (11·0%)
Hypertension	1026 (65·4%)	1031 (65·5%)
Diabetes	358 (22·8%)	343 (21·8%)
Smoker	350 (22·3%)	344 (21·8%)
Previous coronary artery disease	126 (8·0%)	153 (9·7%)
Peripheral artery disease	63 (4·0%)	65 (4·1%)
Gout	52 (3·3%)	64 (4·1%)
Baseline C-reactive protein, mg/L	3 (1·1–6)	3 (1–6)
Medications at randomisation		
Any antiplatelet	1524 (97·1%)	1542 (97·9%)
Any statin	1470 (93·7%)	1480 (94·0%)

Data are n (%), mean (SD), or median (IQR).

Table 1: **Baseline characteristics**

321 (20·5%) of 1569 patients randomly assigned to colchicine were classified as non-adherent during the follow-up period, including ten (0·6%) who did not begin treatment. Two (0·1%) of 1572 patients randomly assigned to usual care alone took colchicine for gout treatment during follow-up (one for 3 days and one for 7 days).

When analysed by intention-to-treat, the primary composite endpoint occurred in 153 patients randomly assigned to colchicine (9·8%) compared with 185 on usual care (11·7%; incidence rates 3·32 *vs* 3·92 per 100 person-years; figure 1). The adjusted hazard ratio

	Colchicine and usual care (n=1569)		Usual care alone (n=1575)		Hazard ratio (95% CI)	p value
	n (%)	Events per 100 person-years	n (%)	Events per 100 person-years		
Primary endpoint	153 (9·8%)	3·33	185 (11·7%)	3·92	0·84 (0·68–1·05)	0·12
Secondary endpoints						
Key secondary endpoint*	147 (9·4%)	3·20	177 (11·2%)	3·77	0·85 (0·68–1·05)	..
All ischaemic stroke (fatal and non-fatal)	108 (6·9%)	2·39	136 (8·6%)	2·96	0·80 (0·62–1·03)	..
Non-fatal ischaemic stroke	103 (6·6%)	2·24	131 (8·3%)	2·77	0·80 (0·62–1·03)	..
Non-fatal myocardial infarction	26 (1·7%)	0·57	29 (1·8%)	0·61	0·93 (0·55–1·58)	..
Hospitalisation for unstable angina (non-fatal)	6 (0·4%)	0·13	8 (0·5%)	0·17	0·75 (0·26–2·17)	..
Non-fatal cardiac arrest	2 (0·1%)	0·04	0	0	NC	..
Vascular death	16 (1·0%)	0·37	17 (1·1%)	0·38	0·97 (0·49–1·92)	..
Non-fatal myocardial infarction and cardiac arrest	28 (1·8%)	0·64	29 (1·8%)	0·64	1·00 (0·59–1·67)	..
All cardiac events (fatal and non-fatal)	45 (2·9%)	1·01	49 (3·1%)	1·07	0·95 (0·64–1·43)	..

NC=not calculable. *Defined as the first non-fatal recurrent ischaemic stroke, non-fatal myocardial infarction, non-fatal cardiac arrest, or vascular death.

Table 2: **Primary and secondary endpoints in the intention-to-treat population**

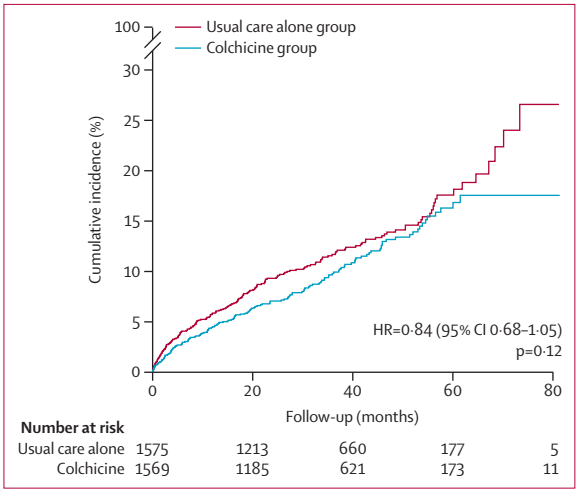

Figure 2: **Cumulative incidence of cardiovascular events in the primary outcome, intention-to-treat population**
Kaplan–Meier curve of the cumulative incidence of first ever stroke, myocardial infarction, cardiac arrest, or hospitalisation for unstable angina (non-fatal and fatal within 30 days).

(HR) was 0·84 (95% CI 0·68–1·05, p=0·12; figure 2, table 2). The key secondary endpoint (non-fatal ischaemic stroke, myocardial infarction, cardiac arrest, or vascular death) occurred in 147 patients (9·4%) treated with colchicine compared with 177 (11·2%) patients treated with usual care (incidence rates 3·20 *vs* 3·77 per 100 person-years, HR 0·85, 95% CI 0·68–1·05; table 2). Ischaemic stroke (fatal and non-fatal) occurred in 108 (6·9%) patients treated with colchicine versus 136 (8·6%) patients treated with usual care (HR 0·80, 95% CI 0·62–1·03).

Blood concentrations of CRP were available in 2715 patients at baseline (86·4%) and 2553 (81·2%), 1965 (62·5%), 1258 (40·0%), 831 (26·4%), and 532 (16·9%) patients at 28-day, 1, 2, 3, and 4-year follow-up visits, respectively (figure 3). At baseline, median CRP was 3 mg/L in both groups (table 1, figure 3). By 28 days, CRP had reduced, with greater reduction in patients treated with colchicine versus patients treated with usual care only (p=0·0007). CRP remained lower in the colchicine group at 1 year (p=0·0005) and at further follow-up measurements at 2 years (p=0·0002) and 3 years (p=0·02; figure 3; appendix p 27).

In the intention-to-treat population, the results were consistent in subgroups defined by age, sex, qualifying event, time to randomisation, hypertension, diabetes, smoking, and carotid stenosis (appendix pp 26–27). In patients with coronary artery disease, the benefit in patients treated with colchicine was greater (HR 0·57, 95% CI 0·35–0·94) than in those without coronary disease (0·95, 0·75–1·21) but this did not meet statistical significance on a test for interaction (p=0·4; appendix p 26).

In a prespecified analysis in the on-treatment population, a primary endpoint occurred in 309 patients, 124 (8·0%) of 1559 in the colchicine group compared with 185 (11·7%) of 1575 in the usual care group (incidence rates 3·2 *vs* 3·92 per 100 person-years; appendix pp 22, 25). The adjusted HR was 0·796 (95% CI 0·63–0·9992; appendix p 25). In the per-protocol population, after exclusion of seven patients with major protocol deviations, the results for the primary endpoint were consistent (HR 0·794, 95% CI 0·63–0·998; appendix pp 23, 25).

Over the follow-up period, 2211 serious adverse events (substantial medical issues or events causing hospital admission, disability, or death) were reported in trial patients (table 3). No excess in serious adverse events was observed in patients treated with colchicine. The risk of death from causes other than outcome events and of serious adverse events related to cancer, infection, and bleeding was similar in both treatment groups. As anticipated, gout was less frequent and diarrhoea or loose

stools and nausea more frequent in patients treated with colchicine than in patients treated with usual care only. Rash, itch, or alopecia were reported more commonly in patients treated with colchicine. No increase in serious myopathy or myalgia, or other prespecified adverse events was observed.

Discussion

As an inexpensive and widely available therapy with an acceptable safety profile, colchicine is a promising candidate with potential for widespread use in low-income and middle-income countries where the global stroke burden is greatest, if efficacy is confirmed in randomised trials. In CONVINCE, patients treated with long-term colchicine on a background of guideline-based therapy had numerically fewer recurrent stroke and coronary events compared with those on guideline-based therapy only, but the difference was not statistically significant for the intention-to-treat analysis. The observed range of the 95% CI on the intention-to-treat analysis (HR 0·68–1·05) included the estimate of treatment effect in the original sample size calculation (HR of 0·746), indicating that this treatment effect was not ruled out in the primary analysis. The findings were consistent for the endpoint of ischaemic stroke and for the key secondary endpoint of stroke, myocardial infarction, and cardiac arrest, indicating that they were not driven by the small number of outcome events caused by hospitalisation for unstable angina (14 patients). Overall, the direction of effect is consistent with the findings of trials and several meta-analyses in coronary patients, which reported reductions in the risk of ischaemic stroke.[11,12,14–16]

Few long-term cardiovascular secondary prevention trials have continued during the COVID-19 pandemic. The pandemic impacted CONVINCE and is likely to have influenced the trial results. During the initial lockdowns in early 2020, trial recruitment was paused for a 2-month period, and the recruitment rate did not recover to pre-pandemic levels due to logistical difficulties at sites. Although the planned sample size was recruited, the complete duration of follow-up could not be achieved in the full cohort before the trial ended for budgetary reasons. This likely contributed to the detection of 8% fewer outcomes than anticipated, which reduced statistical power for the primary analysis. Additionally, the incidence of stroke and myocardial infarction increased internationally during the COVID-19 pandemic.[17–19] In CONVINCE, the rates of stroke and coronary events increased during the later follow-up period in both treatment groups. Although the trial was not designed to measure the impact of COVID-19 on event rates, it is possible that pandemic-related changes in risk in the trial sample contributed to the results.

In an on-treatment sensitivity analysis including only patients compliant with colchicine therapy, the magnitude of effect was marginally increased. Although

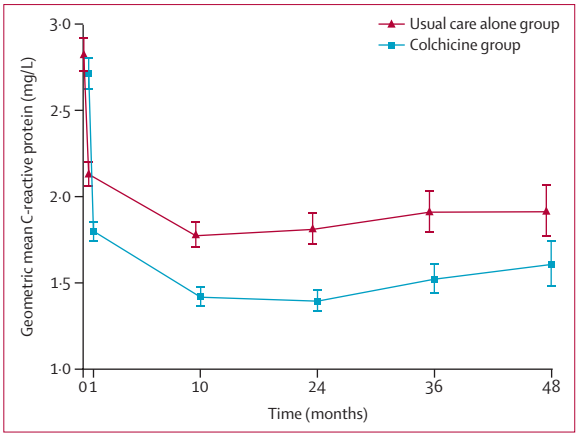

Figure 3: **Geometric mean C-reactive protein overtime**
Vertical lines are standard errors. Patient numbers at each timepoint are: baseline 2715 (p=0·42); 28 days 2553 (p=0·0007); 1 year 1965 (p=0·0005); 2 years 1258 (p=0·0002); 3 years 831 (p=0·02).

	Colchicine and usual care (n=1569)	Usual care alone (n=1575)	Relative risk (95% CI)
Serious adverse events			
All serious adverse events	1096 (69·9%)	1115 (70·8%)	0·99 (0·94–1·03)
Non-cardiovascular deaths	45 (2·9%)	41 (2·6%)	1·10 (0·73–1·67)
Non-outcome deaths	55 (3·5%)	49 (3·1%)	1·13 (0·77–1·65)
Serious adverse events due to cancer	81 (5·2%)	86 (5·5%)	0·95 (0·71–1·27)
Fatal cancer	13 (0·8%)	10 (0·6%)	1·30 (0·57–2·96)
Serious adverse events due to infection	313 (19·9%)	325 (20·6%)	0·97 (0·84–1·12)
Fatal infections	7 (0·4%)	14 (0·9%)	0·5 (0·20–1·25)
Serious adverse events due to haemorrhage			
All	28 (1·8%)	31 (2·0%)	0·91 (0·55–1·51)
Intracranial	12 (0·8%)	14 (0·9%)	0·86 (0·40–1·86)
Gastrointestinal	13 (0·8%)	14 (0·9%)	0·93 (0·44–1·98)
Other	3 (0·2%)	3 (0·2%)	1·0 (0·20–4·97)
Adverse events of special interest			
Serious adverse events due to muscle symptoms (rhabdomyolysis, myopathy, or myalgia)	0	2 (0·1%)	NC
Other adverse events			
Gout	6 (0·4%)	18 (1·1%)	0·34 (0·13–0·85)
Myelosuppression causing neutropenia	0	4 (0·3%)	NC
Loose stools or diarrhoea	190 (12·1%)	32 (2·0)	5·42 (3·75–7·84)
Nausea	54 (3·4%)	22 (1·4%)	2·42 (1·48–3·95)
Raised transaminases or hepatic enzymes	44 (2·8%)	28 (1·8%)	1·56 (0·98–2·50)
Renal impairment	63 (4·0%)	79 (5·0%)	0·81 (0·59–1·12)
Neuropathy	10 (0·6%)	3 (0·2%)	3·33 (0·92–12·08)
Rash, itch, or alopecia	29 (1·8%)	10 (0·6%)	2·88 (1·41–5·88)
Oligospermia or azoospermia	1 (0·1%)	0	NC

Data are n (%) unless otherwise stated. Numbers refer to events, not patients, as some patients had more than one adverse event. NC=not calculated.

Table 3: **Adverse events for the intention-to-treat population**

the on-treatment analysis should be cautiously interpreted as hypothesis-generating, these findings suggest that the results of the intention-to-treat analysis might have been influenced by off-treatment events in patients who were non-adherent to colchicine. On subgroup analysis, patients with known coronary disease had greater benefit in the colchicine group, which might indicate greater therapeutic efficacy in patients with pre-existing atherosclerosis. Unlike coronary disease, which is usually atherogenic in origin, ischaemic stroke is caused by atherosclerosis, small artery lacunar disease, cardiogenic embolism, and cryptogenic causes (with a competing or unknown mechanism). Although patients with evidence of cardiac embolism at baseline were excluded, we included small vessel disease and cryptogenic stroke, as such patients frequently have atherosclerosis in cerebral penetrator or large arteries, and because genetic and epidemiological studies have reported associations with inflammation and recurrent events in these subtypes.[6,20–24]

Compared with other trials of long-term colchicine, which did not collect inflammatory biomarker data in most patients, CRP data were available in a higher proportion of trial participants in CONVINCE. Although no difference was observed at baseline, patients treated with colchicine had greater CRP reductions compared with the usual care only group, beginning at 28 days and persisting to 3 years post-randomisation. These data support a biological effect of colchicine at low daily doses over several years and are consistent with experimental and clinical studies reporting inhibition by colchicine of NLRP3 inflammasome activation and reduced levels of IL-1b, IL-18, and the downstream inflammatory markers IL-6 and CRP.[25–28]

The CHANCE3 trial (currently unpublished) recently reported no benefit for prevention of recurrent events at 90 days in patients with stroke or transient ischaemic attack, selected with CRP ≥2 mg/L, and randomised to low-dose colchicine or placebo within 24 h of symptom onset. No efficacy signal was apparent for the primary endpoint (6·3% in the colchicine group compared with 6·5% in placebo group) or secondary endpoints. By comparison, the median follow-up duration in CONVINCE was almost 3 years, comparable to the coronary trials that showed a benefit of low-dose colchicine. These observations suggest that sustained treatment is likely to be required for optimal secondary prevention of cardiovascular events.

We deliberately included patients with high-risk transient ischaemic attack, did not require a threshold National Institutes of Health Stroke Scale score (appendix p 17), and allowed up to 28 days for inclusion to broaden the generalisability of the results and as pragmatic measures to encourage recruitment. CONVINCE included 294 (9·4%) of 3144 patients aged at least 80 years (appendix p 17) and had a relatively long follow-up period compared with similar trials in coronary disease. No serious safety concerns were observed. The rates of all serious adverse events were similar in treatment groups, and no excess of non-cardiovascular deaths, deaths due to causes other than outcome events, serious infections, cancer, or other prespecified adverse events were observed. As expected, patients treated with colchicine had higher rates of loose stools and nausea, which was typically self-limiting on dose reduction or interruption, than those treated with usual care alone. Overall, the safety profile was consistent with that reported in trials of colchicine in coronary disease. Rates of permanent non-adherence were similar to other long-term colchicine trials that did not include a run-in period, and to trials of statin therapy in patients with stroke.[29] We believe that adverse events were unlikely to have been underestimated in the small excess of patients who withdrew consent in the treatment group, as adverse events were systematically collected in all patients, including those who withdrew consent at the time of last follow-up.

We acknowledge some limitations. Budget constraints meant that incorporation of a placebo control was not possible. However, we do not believe that the open-label design introduced bias in the ascertainment of outcomes as these were clearly defined, supported by objective results of imaging tests and cardiac biomarkers provided by sites, and independently adjudicated by a panel of blinded expert assessors. We included hospitalisation for unstable angina in the composite outcome. However, we believe that this component of the composite is unlikely to have introduced variability to the trial results, as a centrally adjudicated standardised definition, which required objective biomarker and cardiac imaging data, was used; only 14 patients (4% of all outcomes) were classified as such and the findings were consistent in the key secondary outcome, which excluded these events. The COVID-19 pandemic and budget limitations resulted in the stopping of the trial before the originally planned full cohort follow-up was completed, which likely led to underpowering for the intention-to-treat analysis. Most participants were of White European ethnic origin and the results might not be generalisable to other ethnic groups. Although more women were included compared with the LoDoCo2 (15%) and COLCOT (19%) trials, women were under-represented in CONVINCE (953 [30·3%] of 3144), despite regular communications to trial investigators to encourage the recruitment of women in the trial. Further research is needed to understand the factors contributing to the under participation of women in secondary prevention trials of stroke, and to modify the design of such trials to ensure balanced representation of both sexes.

In conclusion, although the primary analysis did not meet the prespecified threshold for statistical significance, CONVINCE provides important new randomised evidence supporting the hypothesis that long-term anti-inflammatory therapy with colchicine could reduce recurrent stroke and other vascular events in patients with stroke, consistent with observational

studies and randomised trials in coronary disease. When considering the design of future randomised trials, our findings suggest that large sample sizes and long follow-up durations will be needed, and consideration should be given to including patients with objective evidence of atherosclerosis, combined with a run-in phase to improve adherence.

Contributors

PKe (chief investigator) contributed to the conceptualisation of the study, data curation, data analysis, funding acquisition, trial design, supervision of the trial, and wrote the original manuscript draft and subsequent edits. CWa (trial statistician and Steering Committee member) contributed to the conceptualisation of the study, data analysis, funding acquisition, designing the method, supervision of the trial, and reviewing and editing subsequent drafts of the manuscript. RL, CWe, DJW, CP, MO'D, FP, UF, CF, JF, MDH, DJ, JK, AC, CK, RM, SM, PN, and PS (Steering Committee members and national lead investigators) contributed to the conceptualisation of the study, funding acquisition, investigation, study design and methodology, trial administration, national supervision, and reviewing and editing subsequent drafts of the manuscript. RC, SC, MB, PD, ADP, NRE, PKr, GS, and DM (hospital site leads and members of Stroke Trials Network Ireland) contributed to funding acquisition, resource provision, supervision of the trial, and reviewing and editing subsequent drafts of the manuscript. CL, BS, and KT (study coordinators) contributed to project administration, supervision of the trial, and reviewing and editing subsequent drafts of the manuscript. PKe and CWa accessed and verified the underlying data reported in the manuscript. All authors had full access to the data and take responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data will be shared upon reasonable request for scientific analysis, in a de-identified form, following completion of all planned analyses, and upon review and approval (by the CONVINCE Steering Committee) of a submitted study plan and signed data sharing agreement by the requesting investigators. Requests should be made to the corresponding author.

Acknowledgments

This study was funded by the Health Research Board Ireland, Deutsche Forschungsgemeinschaft (German Research Foundation 397530000), and Fonds Wetenschappelijk Onderzoek Vlaanderen (Research Foundation Flanders), Belgium. We sincerely thank the patients and families who contributed to the trial.

References

1 Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021; **20:** 795–820.

2 Boulanger M, Béjot Y, Rothwell PM, Touzé E. Long-term risk of myocardial infarction compared to recurrent stroke after transient ischemic attack and ischemic stroke: systematic review and meta-analysis. *J Am Heart Assoc* 2018; **7:** e007267.

3 Feigin VL, Owolabi MO, Feigin VL, et al. Pragmatic solutions to reduce the global burden of stroke: a World Stroke Organization–*Lancet Neurology* Commission. *Lancet Neurol* 2023; **22:** 1160–206.

4 Kelly PJ, Lemmens R, Tsivgoulis G. Inflammation and stroke risk: a new target for prevention. *Stroke* 2021; **52:** 2697–706.

5 Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010; **375:** 132–40.

6 McCabe JJ, Walsh C, Gorey S, et al. C-reactive protein, interleukin-6, and vascular recurrence according to stroke subtype. *Neurology* 2024; **102:** e208016.

7 Georgakis MK, Gill D, Rannikmäe K, et al. Genetically determined levels of circulating cytokines and risk of stroke. *Circulation* 2019; **139:** 256–68.

8 Kelly PJ, Camps-Renom P, Giannotti N, et al. Carotid plaque inflammation imaged by ^{18}f-fluorodeoxyglucose positron emission tomography and risk of early recurrent stroke. *Stroke* 2019; **50:** 1766–73.

9 Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377:** 1119–31.

10 Leung YY, Yao Hui LL, Kraus VB. Colchicine—update on mechanisms of action and therapeutic uses. *Semin Arthritis Rheum* 2015; **45:** 341–50.

11 Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020; **383:** 1838–47.

12 Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; **381:** 2497–505.

13 Kelly P, Weimar C, Lemmens R, et al. Colchicine for prevention of vascular inflammation in Non-CardioEmbolic stroke (CONVINCE)—study protocol for a randomised controlled trial. *Eur Stroke J* 2021; **6:** 222–28.

14 Fiolet ATL, Opstal TSJ, Mosterd A, et al. Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. *Eur Heart J* 2021; **42:** 2765–75.

15 Katsanos AH, Palaiodimou L, Price C, et al. An updated meta-analysis of RCTs of colchicine for stroke prevention in patients with coronary artery disease. *J Clin Med* 2021; **10:** 3110.

16 Samuel M, Tardif JC, Bouabdallaoui N, et al. Colchicine for secondary preventioin of cardiovascular disease: a systematic review and meta-analysis of randomised controlled trials. *Can J Cardiol* 2021; **37:** 776–85.

17 Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly A-M. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet* 2021; **398:** 599–607.

18 Modin D, Claggett B, Sindet-Pedersen C, et al. Acute COVID-19 and the incidence of ischaemic stroke and acute myocardial infarction. *Circulation* 2020; **142:** 2080–82.

19 Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022; **28:** 583–90.

20 Fisher CM. Capsular infarcts: the underlying vascular lesions. *Arch Neurol* 1979; **36:** 65–73.

21 Yoon Y, Lee DH, Kang D-W, Kwon SU, Kim JS. Single subcortical infarction and atherosclerotic plaques in the middle cerebral artery: high-resolution magnetic resonance imaging findings. *Stroke* 2013; **44:** 2462–67.

22 Kamtchum-Tatuene J, Wilman A, Saqqur M, Shuaib A, Jickling GC. Carotid plaque with high-risk features in embolic stroke of undetermined source. Systematic review and meta-analysis. *Stroke* 2020; **51:** 311–14.

23 Boehme AK, McClure LA, Zhang Y, et al. Inflammatory markers and outcomes after lacunar stroke: levels of inflammatory markers in treatment of stroke study. *Stroke* 2016; **47:** 659–67.

24 Elkind MS, Sciacca R, Boden-Albala B, Homma S, Di Tullio MR. Leukocyte count is associated with aortic arch plaque thickness. *Stroke* 2002; **33:** 2587–92.

25 Misawa T, Takahama M, Kozaki T, et al. Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome. *Nat Immunol* 2013; **14:** 454–60.

26 Silvis MJM, Fiolet ATL, Opstal TSJ, et al. Colchicine reduces extracellular vesicle NLRP3 inflammasome protein levels in chronic coronary disease: a LoDoCo2 biomarker substudy. *Atherosclerosis* 2021; **334:** 93–100.

27 Van Broekhoven A, Mohammadnia N, Silvis MJM, et al. End-of-trial inflammatory biomarkers, lipid levels, creatine kinase, and markers of renal and liver function in the LoDoCo2 trial. *Eur Heart J* 2022; **43:** ehac544.1266.

28 Nidorf M, Thompson PL. Effect of colchicine (0·5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. *Am J Cardiol* 2007; **99:** 805–07.

29 Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; **355:** 549–59.