DR. ARISTEIDIS H KATSANOS (Orcid ID : 0000-0002-6359-0023)

DR. SOTIRIOS GIANNOPOULOS (Orcid ID : 0000-0001-7443-5179)

DR. GEORGIOS TSIVGOULIS (Orcid ID : 0000-0002-0640-3797)

Article type : Original Article

# Colchicine for Stroke Prevention in Patients with Coronary Artery Disease: A Systematic Review and Meta-analysis

Aristeidis H. Katsanos, MD[1,2] Lina Palaiodimou, MD[2] Christopher Price, MD[3] Sotirios Giannopoulos, MD[4] Robin Lemmens, MD[5-7] Maria Kosmidou, MD[8] Marios K. Georgakis, MD[9] Christian Weimar, MD[10] Peter J. Kelly, MD[11] Georgios Tsivgoulis, MD[2,12]

[1]*Division of Neurology, McMaster University / Population Health Research Institute, Hamilton, ON, Canada*

[2]*Second Department of Neurology, "Attikon University Hospital", School of Medicine, National and Kapodistrian University of Athens, Athens, Greece*

[3]*Population Health Sciences Institute, Newcastle University, United Kingdom*

[4]*Department of Neurology, University of Ioannina School of Medicine, Ioannina, Greece*

[5]*Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), KU Leuven - University of Leuven, B-3000 Leuven, Belgium*

[6]*Center for Brain & Disease Research, Laboratory of Neurobiology, VIB, B-3000*

*Leuven, Belgium*

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ENE.14198

[7]*Department of Neurology, University Hospitals Leuven, B-3000 Leuven, Belgium*

[8]*First Department of Internal Medicine, University of Ioannina School of Medicine, Ioannina, Greece*

[9]*Institute for Stroke and Dementia Research, University Hospital, Ludwig-Maximilians-University (LMU), Munich, Germany*

[10]*Department of Neurology, University of Duisburg-Essen, Essen, Germany*

[11]*Health Research Board Stroke Clinical Trials Network Ireland and Mater University Hospital/University College Dublin, Ireland*

[12]*Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA*

**Corresponding author:**

Dr. Georgios Tsivgoulis

Second Department of Neurology, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Iras 39, Gerakas Attikis, Athens, Greece 15344

Email: tsivgoulisgiorg@yahoo.gr

Tel: +30 6937178635

Fax: +30 2105832471

**Abstract**

**Background and aim:** Although clinical trials suggest that colchicine may reduce risk of vascular events in patients with a history of coronary artery disease, its effect on the prevention of cerebrovascular events still remains unclear.

**Methods:** We performed a systematic review and meta-analysis of all available to date randomized-controlled clinical trials (RCTs) reporting on incident strokes during the follow-up of patients with history of cardiovascular disease randomized to colchicine treatment or control (placebo or usual care).

**Results:** We identified 4 RCTs, including a total of 5553 patients (mean age 61 years, 81% males), with a follow-up ranging from 1 to 36 months. Colchicine treatment was associated with a significantly lower risk of incident stroke during follow-up compared to control (Risk Ratio=0.31,95% confidence interval: 0.13-0.71), without heterogeneity across included studies ($I^2$=0%). Based on the pooled incident stroke rate of control groups (0.9%) in the included RCTs, we estimate that administration of low dose colchicine to 161 patients with coronary artery disease would prevent one stroke during a follow-up of 23 months.

**Conclusion:** Colchicine treatment decreases stroke risk in patients with history of coronary artery disease. The effect of colchicine in secondary stroke prevention is currently being evaluated in an ongoing RCT.

## Introduction

Colchicine is an established treatment for gout, Behcet's Disease and Familial Mediterranean Fever [1]. Recent literature suggests that colchicine has cardiovascular benefits in patients with stable coronary disease, with decrease in the risk of myocardial infarction and other cardiac outcomes by reducing inflammation [2]. However, the effect of colchicine on the prevention of cerebrovascular events remains unclear [3].

The aim of the present systematic review and meta-analysis was to assess the effect of colchicine treatment on the risk of stroke in patients with coronary disease by using data from available randomized-controlled trials (RCTs) published to date.

**Methods**

The present systematic review and meta-analysis adheres to the American Heart Association Journals' implementation of the Transparency and Openness Promotion guidelines, while is reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement.

We searched for published RCTs reporting incident strokes during follow-up of patients with history of cardiovascular disease randomized to colchicine treatment or control. Literature search in MEDLINE, SCOPUS and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed using the following terms in combination: “colchicine”, "stroke", "cerebrovascular event", “transient ischemic attack”, and "cerebral ischemia". No language or other search restriction was applied. Last literature search was performed on November 22, 2019. Reference lists of all articles that met the inclusion criteria and of relevant review articles were examined to identify studies that may have been missed by the initial database search.

After retrieving the full texts of highlighted studies from our literature search we excluded non-randomized studies, reports not providing incident stroke rates during follow-up and studies performed in patients undergoing surgical procedures. Literature search, data abstraction and bias identification using the Cochrane risk assessment was independently performed by two authors (AHK, LP). All emerging conflicts were resolved after consultation with the senior author (GT).

Using aggregate data we performed random-effects meta-analyses on the risk of incident stroke during follow-up, according to the definition of each study, between patients randomized to colchicine treatment or placebo. Heterogeneity was assessed with the $I^2$ and Cochran Q statistics. Number needed to treat (NNT) was calculated using the formula NNT=1/[(1-RR) x incident stroke rate in the control groups] [4].

All statistical analyses were conducted using the Cochrane Collaboration’s Review Manager (RevMan 5.3) Software Package (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

*Data availability statement*

All data used for analyses are available within the manuscript and the original publications of included studies.

## Results

Literature search in Medline and Scopus databases retrieved 90 and 178 results respectively (Supplementary Figure I). Of all potentially eligible studies 2 full texts were excluded because one recruited patients undergoing cardiac surgery, and the other did not provide incident stroke rates during follow-up (Supplementary Table I). We included 4 RCTs including a total of 5553 patients (mean age 61 years, 81% males) with history of recent myocardial infarction, stable coronary artery disease or patients with history of diabetes receiving percutaneous coronary intervention (Table 1) [5-8]. Risk of selection and performance bias was marked as unclear in one RCT that did not report on the method of randomization and allocation concealment (Supplemental Figure II and Supplemental Figure III) [6]. Detection and attrition bias was considered unclear in two RCTs reporting no blinding of participants and personnel, while also disclosing more than 5% losses to follow-up [6, 8]. Reporting bias was considered unclear in one RCT with no study protocol publicly available [6], while the risk of performance bias was considered high in another RCT that reported blinding only of the outcome assessors and not of participants and personnel (PROBE design) [7].

In the overall analysis, colchicine treatment was associated with a lower risk of incident stroke during follow-up compared to control groups (placebo or usual care) (Risk Ratio=0.31, 95% confidence interval: 0.13-0.71; p=0.006; Figure 1), without heterogeneity across the included studies ($I^2$=0%, p for Cochran Q=0.56). Based on the 69% risk reduction and pooled incident stroke rate of control groups (0.9%) in the included RCTs, daily administration of low dose colchicine to 161 patients with stable coronary artery disease would prevent one stroke over an average follow up interval of 23 months.

## Discussion

Our meta-analysis provides evidence that colchicine treatment is associated with decreased stroke risk in patients with history of coronary artery disease. Based on the pooled risk reduction, treatment of 161 patients with daily low dose colchicine prevents one incident stroke event within 36 months. **These findings are relevant to neurologists and all other physicians involved in stroke prevention, as low dose colchicine emerges as a novel therapeutic approach for further amelioration of ischemic stroke risk in patients with history of symptomatic coronary atherosclerosis.**

The beneficial role of colchicine is likely to be mediated through attenuation of microtubule-mediated inflammatory processes such as inflammatory cell motility and activation of the nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 (NLRP3) inflammasome. Experimental data show that inflammatory cells are involved in all stages of atherosclerosis development and observational data using circulating blood markers such as high-sensitivity C-reactive protein suggest that the risk of future vascular events is associated with atherosclerotic inflammation [9, 10]. Colchicine thus emerged as a novel and promising therapeutic approach for the prevention and treatment of atherothrombosis-related inflammation [11, 12].

Compared to previous meta-analyses [13, 14], our report is the first to suggest decreased stroke risk in patients with history of coronary artery disease on colchicine treatment, while incorporates data from the largest to date RCT using colchicine amongst patients with a history of recent myocardial infarction [5]. Some limitations also need to be acknowledged. First, it should be highlighted that the effect estimate provided by the current meta-analysis is mostly driven by the most recent large scale trial [5]. Second, it should be noted that no safety endpoints are provided in our meta-analysis. However, in the largest trial no significant difference in patients not completing the 23 month follow-up were reported between patients randomized to colchine (4.1%) or placebo (4.3%) [5], suggesting that long-term colchicine treatment is safe and acceptable for most patients. Third, even though all included studies recruited patients with coronary artery disease some variation was present between the studies on the severity of the disease (stable disease, recent myocardial infarction, symptomatic coronary artery disease) and the follow-up duration (ranging from 1 month to 36 months). One of the trials included only patients with concomitant history of diabetes mellitus and administered colchicine 0.5 mg twice daily [6], while in another trial colchicine 1mg was administered as a single dose [8]. Despite these differences, no evidence of statistical heterogeneity was detected between study estimates. Except for one of the studies reporting that all strokes during follow-up were non-cardioembolic [7], all other included studies provided no further information on the classification of outcome strokes and none provided information on outcome stroke severity. Finally, only two of the studies reported that 3-4% of included patients had a history of previous stroke or transient ischemic attack [5, 8]. Because of the under-representation of patients with history of cerebral ischemia in included trials, the effect of colchicine on secondary stroke prevention and in patients without history of coronary artery disease remains unclear. However the stroke rates are expected to be higher in a secondary stroke prevention potentially resulting in a lower NNT.

Indeed primary evidence is now required to determine whether colchicine can prevent recurrent vascular events following recent stroke or TIA. **Low dose colchicine in addition to optimal antithrombotic, antihypertensive and statin treatment could prove to be beneficial in patients with ischemic stroke due to large artery atherosclerosis.** The effect estimate of our meta-analysis is in accordance to the one used for the estimation of the sample size in Colchicine for prevention of Vascular Inflammation in Non-CardioEmbolic stroke (CONVINCE), which is an ongoing RCT testing the hypothesis that daily low-dose colchicine (0.5mg/day) combined with usual care will have benefit in the prevention of recurrent stroke and major vascular events compared with usual care alone [15]. The present meta-analysis lends support to the rationale of CONVINCE and highlights the potential of anti-inflammatory agents as a novel therapeutic target in stroke prevention.

**Funding**

None

**Acknowledgements**

None

**Disclosures**

None

**References**

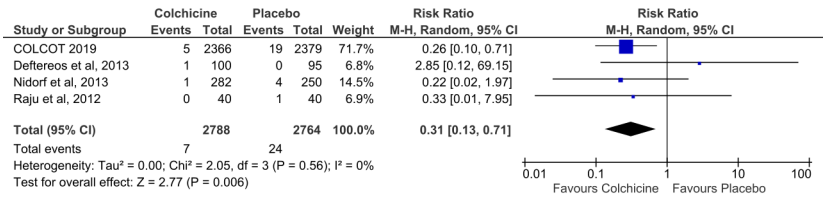

1. Stack J, Ryan J, McCarthy G. Colchicine: New insights to an old drug. *Am J Therapeutics* 2015;**22**: e151-157.
2. Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, et al. Cardiovascular effects and safety of long-term colchicine treatment: Cochrane review and meta-analysis. *Heart.* 2016;**102**:590-6.
3. Kelly PJ, Murphy S, Coveney S, Purroy F, Lemmens R, Tsivgoulis G, Price C. Anti-inflammatory approaches to ischaemic stroke prevention. *J Neurol Neurosurg Psychiatry.* 2018;**89**:211-218.
4. Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: an appraisal. *BMC Med.* 2017;**15**:112.
5. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med.* 2019 Nov 16. doi: 10.1056/NEJMoa1912388 [Epub ahead of print]
6. Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. *J Am Coll Cardiol.* 2013;**61**:1679-85.
7. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol.* 2013;**61**:404-410.
8. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. 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. *J Thromb Thrombolysis.* 2012;**33**:88-94.
9. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011; **473**:317-25.
10. Ridker P. How Common Is Residual Inflammatory Risk? *Circ Res.* 2017;**120**:617-619.
11. Yamashita T, Sasaki N, Kasahara K, Hirata K. Anti-inflammatory and immune-modulatory therapies for preventing atherosclerotic cardiovascular disease. *J Cardiol.* 2015; **66**:1-8.

12. Deftereos S, Giannopoulos G, Panagopoulou V, et al. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. *JACC Heart Fail.* 2014;**2**:131-7.
13. Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, Glinz D, Nordmann AJ, Briel M. Colchicine for prevention of cardiovascular events. *Cochrane Database Syst Rev.* 2016:CD011047.
14. Khandkar C, Vaidya K, Patel S. Colchicine for Stroke Prevention: A Systematic Review and Meta-analysis. *Clin Ther.* 2019;**41**:582-590.e3.
15. Colchicine for prevention of Vascular Inflammation in Non-CardioEmbolic stroke (CONVINCE) – a randomised clinical trial of low-dose colchicine for secondary prevention after stroke. https://clinicaltrials.gov/ct2/show/NCT02898610. Last assessed November 23, 2019.

**Table.** Characteristics of included studies

| **Study name** | **Population** | **Number of patients** | **Dose** | **Follow-up** | **Age (years)** | **Males** | **Smoking history** | **HTN** | **DM** | **History of ACS** | **History of stroke/TIA** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| COLCOT, 2019 [5] | MI within 1 month | 4745 | 0.5 mg OD | 22.6 months (median) | 60.6±10.7 | 81% | 30% | 51% | 20% | 16% | 3% |
| Deftereos et al, 2013 [6] | Diabetics undergoing PCI | 196 | 0.5 mg BID | 6 months | 63.6±7.0 | 65% | 38% | 49% | 100% | 31% | N/A |
| Nidorf et al, 2013 [7] | stable CAD | 532 | 0.5 mg OD | 36 months (median) | 66 ± 9.2 | 89% | 5% | N/A | 30% | 23% | N/A |
| Raju et al, 2012 [8] | ACS or AIS | 80 | 1 mg OD | 1 month | 57.2 ± 10.0 | 89% | 79% | 43% | 16% | 18% | 4% |

**MI: myocardial infarction,** PCI: percutaneous coronary intervention, **CAD: coronary artery disease, ACS: acute coronary syndrome, AIS: acute ischemic stroke,** OD: once daily, BID: twice daily, HTN: hypertension, DM: diabetes mellitus, TIA: transient ischemic attack,




ene_14198_f1.tiff

**Figure.** Forest plot on the association of colchicine treatment with the risk of stroke during follow-up in patients with history of coronary artery disease.