

## eJournal Learning Club Submission Feb/March 2020 – Dr Fergal Howley

Title: Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction (COLCOT Study) Journal Article Review

Authors: Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., Petr Ostadal, M.D., Ph.D., Wolfgang Koenig, M.D., Denis Angoulvant, M.D., Jean C. Grégoire, M.D., Marc-André Lavoie, M.D., Marie-Pierre Dubé, Ph.D., David Rhoads, Ph.D., Mylène Provencher, Ph.D., Lucie Blondeau, M.Sc., Andreas Orfanos, M.B., B.Ch., Philippe L. L'Allier, M.D., Marie-Claude Guertin, Ph.D., and François Roubille, M.D., Ph.D.

Journal title: The New England Journal of Medicine

Date, issue, pages of publication: 26<sup>th</sup> December 2019, Vol 381: 2497-2505

Digital object identifier: 10.1056/NEJMoa1912388 Please review the article/trial/study under the following headings where possible

### Introduction:

This randomized, double-blind, placebo-controlled trial studied the effect of colchicine on cardiovascular outcomes in patients who had recently had a myocardial infarction (MI).

### Methods:

4,745 patients from 167 centers across 12 countries underwent randomization to receive either Colchicine 0.5mg daily or placebo. COLCOT used as its primary end point a composite of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke or urgent hospitalization for angina leading to coronary revascularization.

### Eligibility:

Patients who had had an MI within 30 days of enrolment who; -Completed any planned percutaneous revascularization procedures, and; -Were being treated according to national guidelines, including intensive statin therapy

### Results:

COLCOT demonstrated a significant reduction in the composite end point between colchicine vs placebo group (5.5% vs 7.1%; CI 0.61-0.96; p=0.02), largely due to reduced incidence of stroke and urgent hospitalization for angina leading to coronary revascularization. There was no change in mortality.

### Conclusion:

Following a recent MI, 0.5mg colchicine daily resulted in a significantly lower risk of ischaemic cardiovascular events than placebo.

### Analysis/Limitations:

COLCOT is the latest study in the search for an anti-inflammatory treatment to prevent atherosclerotic events among patients with coronary artery disease (CAD). Prior studies of methotrexate showed no significant effect (1), and the monoclonal antibody Canakinumab was not approved despite lowering the risk of cardiovascular events (2). The LoDoCo trial showed that patients with stable CAD who received colchicine had fewer cardiovascular events, but had a sample size of just 532 patients (3). COLCOT's

strengths lie in its double-blinding, randomization, and that patients were treated as per national guidelines (receiving aspirin, a second antiplatelet, and a statin). The median 22.6-month follow-up means that long-term benefits are not evaluated. Furthermore, findings are limited to patients who have recently had an MI. That only 19.2% of participants were female introduces gender bias. Another weakness is the use of a composite primary end point; with a larger sample size, more robust non-composite conclusions may have been reached.

#### Applicability/Future Direction:

I do not envisage significant changes to our daily practice or guidelines based on the COLCOT study alone. Despite achieving statistical significance in its primary composite end point, it fails to demonstrate a significant reduction in mortality or recurrent MI. COLCOT does, however, provide a basis for further research into the effect of colchicine and other anti-inflammatory medications, not only in cardiovascular disease, but also in cerebrovascular disease. Supporting this, a recent meta-analysis of colchicine for stroke prevention concluded that while colchicine has potentially protective effects, current data are inconclusive, requiring further research (4). A continuation study of the same cohort from the COLCOT trial could provide evidence of the long-term effect of colchicine on cardiovascular disease. In an Irish healthcare setting, where stroke and cardiovascular disease constitute major causes of morbidity and mortality, further research in this area could be invaluable in providing a simple and affordable means of reducing the burden of atherosclerotic disease.

#### References:

1. Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;380:752-62.
2. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119-31.
3. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;61: 404-10.
4. Khandkar C, Vaidya K, Patel S. Colchicine for Stroke Prevention: A Systematic Review and Meta-analysis. *Clin Ther.* 2019;41 (3):582-59