Canadian Journal of Cardiology 37 (2021) 1837–1845

Review

Colchicine for Prevention of Atherothrombotic Events in Patients With Coronary Artery Disease: Review and Practical Approach for Clinicians

Guillaume Marquis-Gravel, MD, MSc,[a] Shaun G. Goodman, MD, MSc,[b,c,d] Todd J. Anderson, MD,[e] Alan D. Bell, MD,[f] David Bewick, MD,[g] Jafna Cox, BA, MD,[h] Jean C. Grégoire, MD,[a] Anil Gupta, MD,[i] Thao Huynh, MD, MSc, PhD,[j] Heather Kertland, PharmD,[b] Simon Kouz, MD,[k] Philippe L. L'Allier, MD,[a] Mina Madan, MD,[l] G. B. John Mancini, MD,[m] Ruth McPherson, MD, PhD,[n] Derek Y.F. So, MD, MSc,[n] Robert C. Welsh, MD,[o] Graham Wong, MD, MPH,[p] and Jean-Claude Tardif, MD[a]

[a] Montréal Heart Institute, Université de Montréal, Montréal, Québec, Canada; [b] St. Michael's Hospital, University of Toronto, Ontario, Canada; [c] Canadian Heart Research Centre, Toronto, Ontario, Canada; [d] Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada; [e] Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; [f] University of Toronto, Toronto, Ontario, Canada; [g] New Brunswick Heart Center, Saint John, New Brunswick, Canada; [h] Dalhousie University, Capital Health, and Division of Cardiology, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; [i] Trillium Health Centre, Mississauga, Ontario, Canada; [j] Division of Cardiology, McGill University Health Center, Montréal, Québec, Canada; [k] Centre Intégré de Santé et de Services Sociaux de Lanaudière—Centre Hospitalier de Lanaudière, Joliette, Québec, Canada; [l] Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [m] University of British Columbia, Department of Medicine, Division of Cardiology, Vancouver, British Columbia, Canada; [n] University of Ottawa Heart Institute, Ottawa, Ontario, Canada; [o] Mazankowski Alberta Heart Institute and University of Alberta, Edmonton, Alberta, Canada; [p] Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada

ABSTRACT

A better understanding of the central role of inflammation in the development of coronary artery disease (CAD) has been the impetus for the evaluation of therapeutic strategies targeting the interleukin-1ß/interleukin-6 cytokine signaling pathway, involved in both chronic atherogenesis and in triggering of atherosclerotic plaque rupture. As an inexpensive pharmacologic agent with relatively few adverse effects that tend to be mild and tolerable, the role of colchicine in secondary prevention of atherothrombotic events has been the focus of multiple recent large-scale randomized controlled trials involving patients with stable CAD (Low-Dose Colchicine [LoDoCo] and LoDoCo2 trials), a recent myocardial infarction (Colchicine Cardiovascular Outcome Trial [COLCOT], Colchicine in Patients With Acute Coronary Syndrome [COPS], and Colchicine and Spironolactone in Patients With Myocardial Infarction/Synergy Stent Registry [CLEAR SYNERGY] trials),

RÉSUMÉ

Une meilleure compréhension du rôle central de l'inflammation dans le développement de la coronaropathie (CP) a été à l'origine de l'évaluation de stratégies thérapeutiques ciblant la voie de signalisation des cytokines interleukine-1ß/interleukine-6, impliquée à la fois dans l'athérogénèse chronique et dans le déclenchement de la rupture de la plaque d'athérome. En tant qu'agent pharmacologique peu coûteux, dont les effets indésirables sont relativement peu nombreux et généralement légers et tolérables, le rôle de la colchicine dans la prévention secondaire des événements athérothrombotiques a fait l'objet de plusieurs essais contrôlés randomisés à grande échelle menés récemment auprès de patients atteints de CP stable (essais LoDoCo [Low-Dose Colchicine] et LoDoCo2), après un infarctus du myocarde récent (essais COLCOT [Colchicine Cardiovascular Outcome Trial], COPS [Colchicine in Patients With Acute Coronary Syndrome] et

Cardiovascular disease is the leading cause of mortality and disability worldwide, with greater than 17 million yearly deaths globally, the majority of which being attributed to coronary artery disease (CAD).[1] CAD is most often caused by atherosclerosis, which is a complex process involving multiple inflammatory signalling pathways leading to atherogenesis, eventually manifesting as flow-limiting coronary stenoses responsible for stable angina or as plaque disruption causing acute coronary syndromes (ACS).[2-4] Despite existing guideline-based secondary prevention strategies,[5-7] residual risk of subsequent vascular events remains high, emphasizing

Received for publication June 29, 2021. Accepted August 16, 2021.

Corresponding author: Dr Guillaume Marquis-Gravel, 5000 Belanger East Street, Montréal, Québec H1T1C8, Canada. Tel.: +1-514-376-3330.
E-mail: guillaume.marquis.gravel@umontreal.ca

See page 1843 for disclosure information.

https://doi.org/10.1016/j.cjca.2021.08.009
0828-282X/© 2021 Canadian Cardiovascular Society. Published by Elsevier Inc. All rights reserved.

IPR2023-01064
Murray & Poole v. MHI
M&P Ex. 1079

and undergoing percutaneous coronary interventions (**Colchicine** in **P**ercutaneous **C**oronary **I**ntervention [COLCHICINE-PCI] trial). Based on this evidence, low-dose colchicine (0.5 mg once daily) should be considered in patients with recent myocardial infarctions—within 30 days and, ideally, within 3 days—or with stable CAD to improve cardiovascular outcomes. Colchicine should not be used in patients with severe renal or hepatic disease because of the risk of severe toxicity. No serious adverse effect was associated with the combined use of colchicine and high-intensity statin therapy in large trials. The impact of colchicine in high-risk populations of patients with peripheral arterial disease and in those with diabetes for the primary prevention of CAD remains to be established.

CLEAR SYNERGY [Colchicine and Spironolactone in Patients With Myocardial Infarction/Synergy Stent Registry]) et pour des patients subissant une intervention coronarienne percutanée (ICP) (essai COLCHICINE-PCI). Sur la base de ces données, la colchicine à faible dose (0,5 mg une fois par jour) doit être envisagée chez les patients ayant subi un infarctus du myocarde récent - dans les 30 jours et, idéalement, dans les trois jours - ou présentant une CP stable afin d'améliorer le pronostic cardiovasculaire. La colchicine ne doit pas être utilisée chez les patients présentant une affection rénale ou hépatique sévère, en raison d'un risque de toxicité grave. Aucun effet indésirable grave n'a été associé à l'utilisation combinée de la colchicine et d'un traitement par statine de haute intensité dans les essais à grande échelle. L'impact de la colchicine dans les populations à haut risque des patients atteints de maladie artérielle périphérique et chez les diabétiques pour la prévention primaire de la CP reste à établir.

the need to identify additional therapeutic targets in order to further improve patient outcomes.

Colchicine is a drug that has been used for years for the treatment of inflammatory disorders such as gout, pericarditis, and familial Mediterranean fever.[8-10] It is a derivative from the plant *Colchicum automnale*, used as an old Egyptian remedy for joint inflammation, and was isolated by 2 French scientists, Pelletier and Caventou, in the 18th century. As an inexpensive and relatively safe pharmacologic agent, its potential beneficial impact in patients with CAD has been the focus of multiple recent large-scale randomized controlled trials.[11-19] As a result, colchicine extended-release 0.5 mg tablets (MYINFLA™) have been approved by Health Canada in August 2021 for the reduction of atherothrombotic events in adult patients with existing coronary artery disease, in addition to standard therapies, including LDL-C lowering and antithrombotic drug treatment. In this review, the evidence will be summarized to lay the foundation for a practical approach for the use of colchicine in secondary prevention of CAD.

Reduction of Inflammation With Colchicine in CAD

Circulating levels of acute-phase inflammatory biomarkers strongly correlate with prognosis following an ACS, suggesting that inhibition of the acute systemic response may improve cardiovascular outcomes in this population.[20] Accordingly, the central role of inflammation in CAD has been the focus of randomized controlled trials evaluating the impact of therapeutic strategies specifically targeting the interleukin (IL)-1ß/IL-6 cytokine signalling pathway, involved in both chronic atherogenesis and triggering of plaque rupture.[11,15,21-23] Direct inhibition of IL-1ß by the monoclonal antibody canakinumab has been shown to improve cardiovascular outcomes in patients with a previous myocardial infarction (MI) and elevated baseline C-reactive protein (CRP) in the **C**anakinumab **An**ti-inflammatory **T**hrombosis **O**utcome **S**tudy (CANTOS) randomized trial, setting a proof of concept that targeted inhibition of the IL-1ß/IL-6 inflammatory signalling pathway, not confounded by other effects such as lipid lowering, is cardioprotective in this population.[23] However, canakinumab was also associated with a higher risk of sepsis, is extremely expensive, and will not be marketed for treatment of CAD.

Colchicine exerts its mechanism of action through inhibition of leucocyte tubulin polymerization and the NLRP3 inflammasome, which are involved in the activation of the IL-1ß/IL-6 signalling pathway. Its specific actions and effects include, among others, alteration of neutrophil deformability and motility, antimitotic properties in leucocytes, inhibition of cholesterol crystal-induced coronary atherogenesis, and reduction of the expression of cellular adhesion molecules.[24-27] Colchicine also reduces the production of IL-6 (indirectly though inhibition of IL-1ß) and CRP inflammatory biomarkers,[16,19,28]) and stabilizes coronary plaque among patients with a recent ACS.[29] In patients undergoing percutaneous coronary intervention (PCI), colchicine attenuates the increase of circulating IL-6 and high-sensitivity CRP levels at 22 to 24 hours,[16] and attenuates neutrophil extracellular trap formation.[30] In patients with stable CAD, colchicine at a dose of 0.5 mg once daily for 30 days is associated with a significant reduction of inflammatory biomarkers of the NLRP3 inflammasome pathway (IL-6 and IL-18), of circulating high-sensitivity CRP and of proteins involved in neutrophil degranulation.[31]

Clinical Impact of Colchicine in Secondary Prevention of Cardiovascular Events

The role of colchicine for the improvement of cardiovascular outcomes in patients with established atherosclerotic CAD has been studied in randomized controlled trials focusing on the specific populations of patients with stable CAD,[14,15] a recent ACS (mostly MI),[11,12,17] and those undergoing PCI.[13,16]

Stable CAD

The impact of colchicine on CV event reduction was first studied in the **Lo**w-**Do**se **Co**lchicine (LoDoCo) randomized trial, in which 532 patients with angiographically proven stable CAD were randomized to receive colchicine 0.5 mg daily (n = 282) or no colchicine (n = 250).[14] Among the participants randomized to colchicine, 32 stopped the study drug early owing to adverse effects, and the protocol allowed to replace them with additional participants. All participants, whether or not they stopped the study drug because of adverse effects, were included in the intention-to-treat analysis. The

IPR2023-01064
Murray & Poole v. MHI
M&P Ex. 1079

majority of study participants were treated with at least 1 antiplatelet agent and high-dose statin as part of their secondary prevention treatment, and 55% to 60% were also treated with an angiotensin-converting enzyme inhibitor. The primary efficacy endpoint—a composite of ACS, fatal and nonfatal out-of-hospital cardiac arrest, and noncardioembolic ischemic stroke—occurred in 5.3% of the participants in the colchicine group and in 16.0% of participants in the control group (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.18-0.59), after a median follow-up of 36 months. This was largely driven by an excess of non-stent-—related ACS in the control group compared with colchicine. Despite the large magnitude of the absolute and relative-risk reductions, the results of the LoDoCo trial have nevertheless been viewed as hypothesis generating, given the small sample size, lack of a placebo-control or participant blinding, and limited verification of adherence in participants randomized to colchicine.

The results of the subsequent placebo-controlled, double blind, randomized **Lo**w-**Do**se **Co**lchicine 2 (LoDoCo2) trial were consistent with the findings of the original LoDoCo trial.[15] In this study, 6528 patients with evidence of coronary disease on invasive coronary angiography, computed tomography angiography, or a coronary-artery calcium score of at least 400 Agatston units, and considered stable for at least 6 months, were included. Key exclusion criteria were the presence of at least moderate renal impairment, severe heart failure, and at least moderate valvular disease requiring intervention. All participants entered a 1-month run-in period in which all were treated with open-label colchicine 0.5 mg once daily to ascertain tolerance. Following the run-in period, 5522 patients (84.6%) were randomized to either colchicine 0.5 mg daily or placebo; 1006 patients (15.4%) were not randomized, mainly because of perceived adverse effects. The primary endpoint, a composite of cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization, occurred in 6.8% of participants in the colchicine group and in 9.6% of the participants in the placebo group (HR, 0.69; 95% CI, 0.57-0.83; $P < 0.001$) after a median follow-up of 28.6 months. Individual endpoints of MI and ischemia-driven coronary revascularization were significantly lower with colchicine but not ischemic strokes. Death from any cause occurred in 2.6% and in 2.2% of participants randomized to colchicine and placebo, respectively (HR, 1.12; 95% CI, 0.86-1.71). Results were consistent across multiple prespecified subgroups, including in male and female participants.

The consistency of the results of the LoDoCo and LoDoCo2 trials in patients with stable CAD, in addition to the established safety profile of colchicine, position this drug as an important potential addition in secondary prevention of cardiovascular events in patients with CAD. In LoDoCo2, the number-needed-to-treat (NNT) over a mean follow-up duration of 28.6 months was 35, which is consistent with the benefits of aspirin, statin, and antihypertensive therapy in secondary prevention.[32] Notably, this benefit was obtained despite the fact that almost all patients received these other guideline-recommended therapies during the trial.

ACS and PCI

In addition to inhibiting the chronic inflammatory processes involved in atherogenesis, early initiation of colchicine following ACS or PCI may provide incremental value by inhibiting the acute-phase systemic inflammatory reaction. An ACS is characterized by plaque rupture, ulceration, erosion, or disruption caused by calcified nodules. PCI induces mechanical trauma to the coronary vasculature, leading to local IL-6 expression and increased neutrophil adhesion.[33] Colchicine, by inhibiting the acute inflammation in ACS or PCI, may mitigate coronary microcirculation obstruction, endothelial dysfunction, subsequent myocardial damage, and major adverse cardiovascular events (MACE) as well as subsequent in-stent restenosis, by altering formation of neoatherosclerosis.[12,34,35]

There have been several modest-sized trials assessing the impact of colchicine in patients undergoing PCI. In a study by Deftereos et al., 196 patients with diabetes treated with PCI with a bare-metal stent were randomized to receive colchicine 0.5 mg twice daily (beginning within 24 hours of PCI) or placebo for 6 months.[13] At 6 months, rates of angiographic in-stent restenosis were 16% in the colchicine group and 33% in the control group (odds ratio [OR], 0.38; 95% CI, 0.18-0.79; $P = 0.007$), and intravascular ultrasound demonstrated a reduction of 70% in neointima volume with colchicine compared with placebo ($P < 0.01$). Although limited by its sample size, this randomized trial suggests a potential reduction of restenosis in patients with diabetes treated with bare-metal stents, but these results cannot be generalized to the contemporary clinical practice, characterized by a very low rate of bare-metal stent implantation.

The **Colchicine** in **P**ercutaneous **C**oronary **I**ntervention (COLCHICINE-PCI) placebo-controlled randomized trial aimed to evaluate whether short-term, acute use of colchicine, administered before PCI, was associated with a reduction in PCI-related myocardial injury.[16] In this trial, 400 participants with an indication for PCI were randomized to oral colchicine 1.2 mg administered 1 to 2 hours before coronary angiography, followed by colchicine 0.6 mg 1 hour later (or immediately preprocedure), or to matching placebo. There was a numerical—yet not statistically significant—reduction in myocardial injury related to PCI (57.3% with colchicine vs 64.2% with placebo [$P = 0.19$]), a finding that was consistent using different definitions of myocardial injury and in those with stable CAD and ACS. Because no reduction of periprocedural myocardial injury was derived from acute, short-term use of colchicine during the peri-PCI period, the role of colchicine in patients undergoing PCI with a drug-eluting stent for non-ACS indication has not yet been established.

In the ACS setting, Deftereos et al. randomized 151 patients treated with primary PCI for ST-elevated MI (STEMI) to either colchicine (1.5 mg initially, followed by 0.5 mg 1 hour later, then 0.5 mg twice daily) or to placebo for 5 days.[12] In this pilot study, the primary endpoint of infarct size, defined as the area under the curve of creatine kinase-myocardial band fraction (CK-MB) concentration over 72 hours, was lower with colchicine compared with placebo (3144 [1754-6940] ng•h/mL, vs 6184 [4456-6980] ng•h/mL; $P < 0.001$). This finding was supported by smaller infarct size defined by late gadolinium enhancement on cardiac magnetic resonance imaging (MRI) ($P = 0.019$). Although this study was not powered to detect a significant difference in clinical endpoints, it represented an important proof-of-concept study and provided a strong rationale to

IPR2023-01064
Murray & Poole v. MHI
M&P Ex. 1079

conduct trials that could test the hypothesis that colchicine reduces the risk of cardiovascular events following ACS.

The larger double blind, randomized, placebo-controlled **Col**chicine **C**ardiovascular **O**utcomes **T**rial (COLCOT) evaluated the impact of colchicine 0.5 mg once daily in patients with a recent MI ($\leq$ 30 days) for whom any planned PCI had been performed, compared with placebo.[11] Exclusion criteria were severe heart failure, left ventricular ejection fraction $<$ 35%, stroke within the previous 3 months, type 2 index MI, coronary-bypass surgery either within the previous 3 years or planned, a history of noncutaneous cancer within the previous 3 years, inflammatory bowel disease or chronic diarrhea, neuromuscular disease, nontransient creatine kinase level greater than 3 times the upper limit of the normal range (unless caused by infarction), clinically significant nontransient hematologic abnormalities, severe renal disease with a serum creatinine level that was greater than 2 times the upper limit of the normal range, severe hepatic disease, drug or alcohol abuse, systemic glucocorticoid use, or clinically significant sensitivity to colchicine.

The study included 4745 participants from 167 centres in 12 countries. In this trial, the vast majority of participants were treated with dual antiplatelet therapy and statins (98% and 99%, respectively), and 93% of patients in both groups were treated with PCI for their index MI. After a median follow-up of 22.6 months, the primary efficacy endpoint, a composite of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization occurred in 5.5% of participants randomized to colchicine and in 7.1% of participants randomized to placebo (HR, 0.77; 95% CI, 0.61-0.96). The effect of colchicine on all components contributed to the benefit on the primary endpoint, although the efficacy was more pronounced on strokes (HR, 0.26; 95% CI, 0.10-0.70) and urgent hospitalizations for angina leading to revascularization (HR, 0.50; 95% CI, 0.31-0.81). Colchicine was also associated with a reduction in the total number of both first and recurrent primary endpoint events during follow-up (0.29 vs 0.42 events per 100 patient-months; rate ratio, 0.66; 95% CI, 0.51-0.86). The results were consistent in the intention-to-treat population (primary analysis) and the per-protocol analysis, as well as in the subgroup of 4408 participants who underwent PCI for their index MI.[36]

A secondary analysis of the COLCOT trial showed that the timing of colchicine initiation after the index MI affected the magnitude of treatment effect, with a significant reduction in the composite primary endpoint observed among the 1193 participants randomized to colchicine compared with placebo within 3 days of their MIs (HR, 0.52; 95% CI, 0.32-0.84; $P = 0.007$).[37] This subgroup analysis lends support to the hypothesis that early initiation of colchicine following ACS may offer incremental value with inhibition of the acute-phase inflammation response. The possibility of an impact of reduced immune response was monitored closely. An increase in the rate of pneumonia was noted with colchicine compared with placebo (0.9% vs 0.4%; $P = 0.03$) in addition to a numerically higher number of infections (2.2% vs 1.6%; $P = 0.15$). Finally, colchicine was shown to generate a reduction of 69% in lifetime costs to the Canadian health care system (a reduction from $8239 [Canadian dollars] to $2590 [Canadian dollars]) with an increase in quality-adjusted life years (QALY) from 8.82 to 11.68.[38] It was 100% cost effective at a willingness to pay of $0/QALY gained. Colchicine costs less than $40 per month in Canada.

More recently, the **Co**lchicine in **P**atients With Acute Coronary **S**yndromes (COPS) randomized trial evaluated the effect of colchicine (0.5 mg twice daily for the first month, then 0.5 mg daily for 11 months) compared with placebo in 795 patients with ACS and $\geq$ 30% luminal stenosis in any epicardial vessel of $\geq$ 2.5 mm luminal diameter, treated either with PCI or medical treatment alone. Key exclusion criteria were the requirement for surgical revascularization, preexisting long-term use of colchicine or immunosuppressant therapy, severe hepatic and renal insufficiency, and known active malignancy. Among participants, 94% had MI as the qualifying event, and 88% underwent PCI.[17] The primary endpoint—a composite of death from any cause, ACS, ischemia-driven urgent revascularization, or noncardioembolic ischemic stroke—occurred in 6.1% and 9.5% of participants in the colchicine and placebo groups at 1 year, respectively ($P = 0.09$). The smaller than anticipated sample size (original enrolment target n = 1009), and the relatively short duration of follow-up (1 year) may explain the numerically lower but nonstatistically significant difference, observed for the primary endpoint in the COPS trial. In a post hoc analysis evaluating a composite endpoint similar to the COLCOT trial primary endpoint (composite of CV death, stroke, ACS, or urgent revascularization), the event risk among patients receiving colchicine was one-half that seen in the placebo group (5.0% with colchicine vs 9.5% with placebo; HR, 0.51; 95% CI, 0.29-0.89; $P = 0.019$). At 1 year, 3 patients required urgent revascularization in the colchicine group, compared with 12 in the placebo group (HR, 0.26; 95% CI, 0.07-0.92; $P = 0.037$).

The ongoing **Col**chicine and Spironolacton**e** in Patients With Myoc**ar**dial Infarction/**Synergy** Stent Registry (CLEAR SYNERGY trial, NCT03048825) aims to randomize 7000 participants with MI treated with PCI to colchicine 0.5 mg twice daily vs placebo. The primary endpoint will be the first occurrence of cardiovascular death, recurrent MI, or stroke at an average of 2 years. Its results may contribute to shedding light on the effect of colchicine on specific cardiovascular endpoints and identify subgroups that derive the most benefits from colchicine.

Three recent meta-analyses of randomized controlled trials confirmed that colchicine decreases the risk of major cardiovascular events, MI, stroke, and coronary revascularization but not of cardiocascular death, in secondary prevention of CAD. Reassuringly, these benefits were observed without an increase in gastrointestinal safety concerns.[39,40,41] The totality of the evidence regarding the role of colchicine in secondary prevention of CAD is consistent across types of patients (stable CAD, post-MI), making the causal association robust in addition to its biological plausibility. Additional data from other studies in the setting of primary prevention in diabetes (COLCOT-T2D), and noncardioembolic transient ischemic attack and stroke (**Co**lchicine for Prevention of **V**ascular

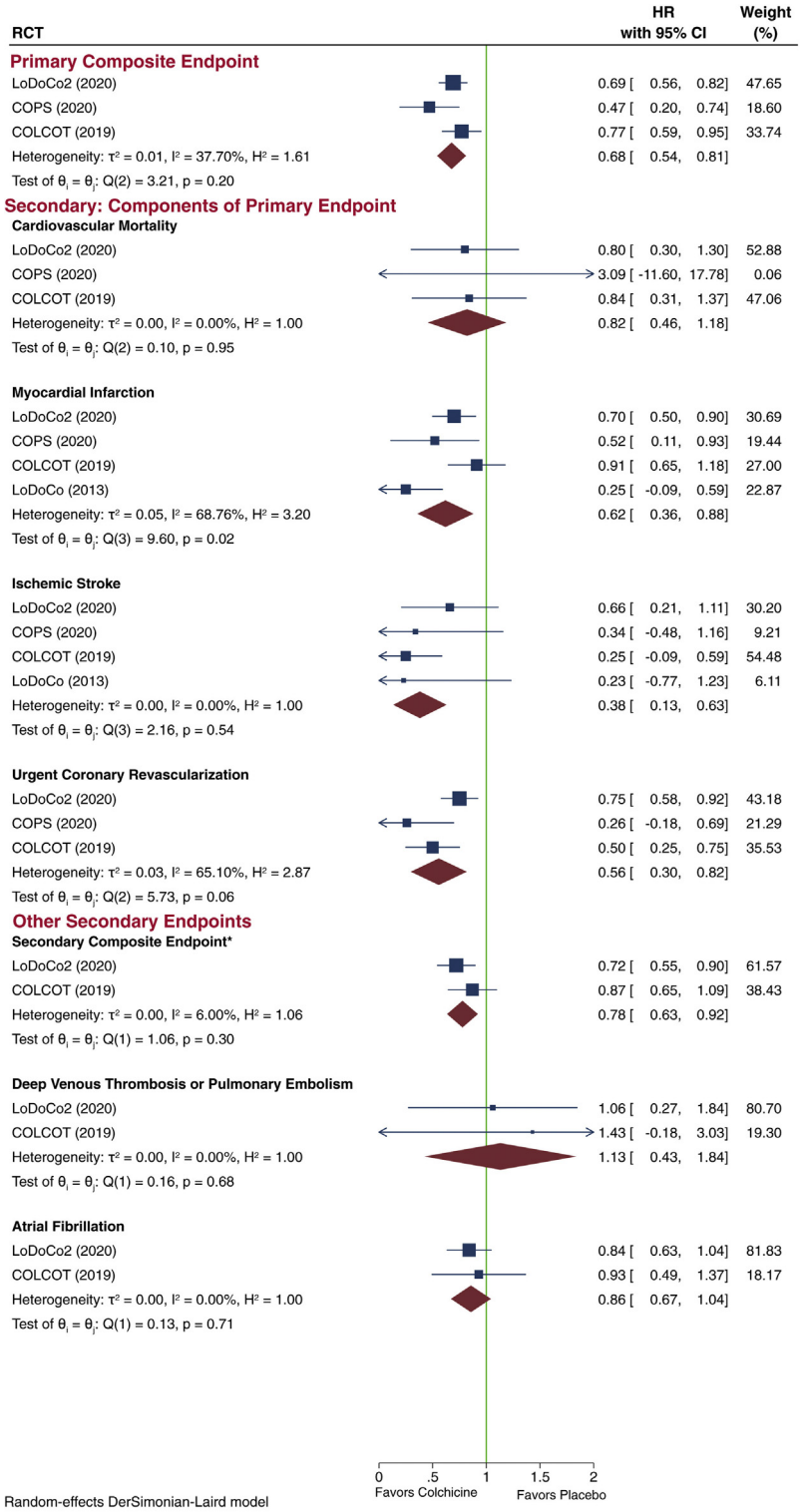


Figure 1. Efficacy of colchicine in secondary prevention of coronary artery disease. CI, confidence interval; COLCOT, **Col**chicine **C**ardiovascular **O**utcome **T**rial; COPS, **Co**lchicine in **P**atients With Acute Coronary **S**yndrome; LoDoCo, **Lo**w-**Do**se **Co**lchicine; HR, hazard ratio; RCT, randomized controlled trials. Reproduced from Samuel et al.[39] with permission from Elsevier.

Inflammation in **N**on-**C**ardio**e**mbolic Stroke [CONVINCE] trial of ~ 2600 patients [NCT02898610]) will shed further light on the role of colchicine in the prevention of cardiovascular disease. Given the impact of colchicine on reduction of stroke observed in the COLCOT trial, results of the latter ongoing trial will be eagerly awaited. In the meantime, low-dose colchicine is safe, well tolerated, inexpensive (generating cost savings in ACS), and reduces the risk of future nonfatal cardiovascular events, thus warranting consideration for its use in addition to established secondary prevention treatments.

Safety and tolerability of colchicine

Colchicine has demonstrated a reassuring safety profile in the major cardiovascular outcomes trials. There was no significant difference in all-cause mortality and in cardiovascular death between patients randomly assigned to receive colchicine or placebo in the 10,799 participants of the COLCOT, LoDoCo, and LoDoCo 2 trials.[11,14,15] In the COPS trial, the number of deaths from any cause was higher with colchicine (n = 8) compared with placebo (n = 1); the numbers of noncardiovascular deaths in the 2 arms were 5 and 0, respectively. However, the validity of this observation has been questioned, given the small sample size of COPS and the fact that there were more than twice the number of patients with incomplete follow-up than that of deaths, which may reflect the play of chance and should be cautiously interpreted.[42] Moreover, the mortality trend seen in COPS is inconsistent with safety results from clinical studies investigating colchicine use in patients with gout, familial Mediterranean fever, and pericarditis, which have not suggested an imbalance in all-cause mortality or noncardiovascular deaths.[43,44] Importantly, median follow-up duration was twice as long in these much larger studies than in COPS. A pooled analysis of the COLCOT, LoDoCo2, and COPS trials did not suggest that colchicine was associated with a higher risk of cardiovascular mortality (HR, 0.82; 95% CI, 0.46-1.18) (Fig. 1).[39] At present, there are not sufficient available data to comment on the potential impact of colchicine on heart failure or on serious arrhythmias.

It is important to highlight that patients with severe kidney disease have been excluded from the COLCOT, LoDoCo2, and COPS trials. Therefore, colchicine should not be used in this population because of the risk of serious and potentially fatal toxicity. Colchicine should also be avoided in patients with severe hepatic disease. Colchicine has been administered to patients with various cardiac diseases including CAD (as was the case in COLCOT and LoDoCo2, which have included more than 10,000 patients followed for more than 2 years), atrial fibrillation,[45,46] and heart failure.[37] In the absence of severe renal disease, colchicine is often used in patients with heart failure who develop gout triggered by the use of a loop diuretic.

Colchicine causes relatively few adverse effects, which tend to be mild and tolerable. The most frequent are gastrointestinal symptoms such as flatulence, nausea, abdominal pain, and diarrhea. However, at the low dose of 0.5 mg once daily used in the COLCOT and the LoDoCo2 trials, the incidence of total gastrointestinal adverse events was not significantly higher with colchicine than with placebo.[11,15] In COLCOT, nausea (1.8% and 1.0%, respectively; $P = 0.02$) and flatulence (0.6% and 0.2%, respectively; $P = 0.02$), were more frequent with colchicine than placebo. Blood dyscrasias, such as agranulocytosis and aplastic anemia, have been reported rarely with colchicine. Therefore, a complete blood count should be considered annually, although such abnormalities were reported in < 1% of participants and not more frequently with colchicine than with placebo in the COLCOT and LoDoCo2 trials.[11,15,17] In COLCOT, a small increase in the risk of pneumonias was observed (21 with colchicine [0.9%] vs 9 with placebo [0.4%]; $P = 0.03$), but no such trend was observed in LoDoCo2, in which hospitalization for pneumonia was observed in 1.7% and 2.0% of participants, respectively (HR, 0.84; 95% CI, 0.56-1.24). A recent meta-analysis has not shown a significant increase in the risk of

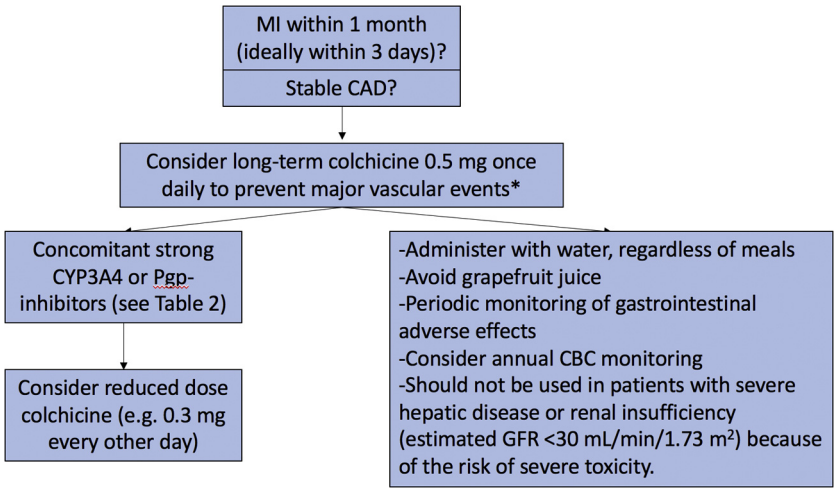


Figure 2. Practical approach to colchicine use in secondary prevention of CAD. *The median duration of follow-up in **Col**chicine **C**ardiovascular **O**utcome **T**rial (COLCOT) and **Lo**w-**Do**se **Co**lchicine (LoDoCo2) trials were of 22.6 and 28.6 months, respectively. The optimal duration of colchicine therapy has not been studied beyond these timelines. CAD, coronary artery disease; CBC, complete blood count; GFR, glomerular filtration rate; MI, myocardial infarction; Pgp, P-glycoprotein.

IPR2023-01064
Murray & Poole v. MHI
M&P Ex. 1079

Table 1. Evidence-based considerations for the use of colchicine in the prevention of atherothrombotic events in patients with coronary artery disease

Colchicine 0.5 mg daily should be considered in patients with chronic coronary disease, to reduce the risk of major cardiovascular events.[14,15]
Colchicine 0.5 mg daily should be considered within 1 month following an acute MI to reduce the risk of major cardiovascular events, preferably within 3 days of the MI.[11]
Colchicine 0.5 mg twice daily can be considered to reduce the risk of restenosis in patients with diabetes undergoing PCI with a bare-metal stent.[13]

MI, myocardial infarction; PCI, percutaneous coronary intervention.

pneumonias with colchicine compared with placebo in patients with CAD.[39] Therefore, in the light of both the good safety and tolerability of colchicine, the risk-to-benefit profile favours the use of colchicine in most eligible patients in secondary prevention of CAD.

Practical Approach to the Use of Colchicine in the Prevention of Atherothrombotic Events in Patients with CAD

A practical approach for the use of colchicine in secondary prevention of CAD is presented in Figure 2, and evidence-based considerations are presented in Table 1. Colchicine can be administered at any time of the day, without regard to meals, but should be administered with a beverage. It is metabolized by CYP3A4 and is a substrate for P-glycoprotein. To prevent colchicine accumulation and toxicity, it should not be used with strong P-glycoprotein inhibitors such as clarithromycin (the use of azithromycin is acceptable) (Table 2). Concomitant use of strong and moderate CYP3A4 inhibitors should also be avoided—including grapefruit juice—especially in patients with hepatic or renal impairment. Strong CYP3A4 inhibitors include—but are not limited to—ritonavir, itraconazole, ketoconazole, and clarithromycin. The dosage of colchicine should be reduced in patients receiving moderate to high doses of diltiazem or verapamil. Concomitant use of colchicine with high-intensity statin therapy has been well tolerated in COLCOT. Colchicine should not be used in patients with an estimated glomerular filtration rate (eGFR) less than 30 mL/min per 1.73 m^2. A recent meta-analysis found that use of colchicine throughout pregnancy was not associated with an increased incidence of miscarriage or major fetal malformations.[47] Indeed, the incidence of miscarriage was significantly lower in women who took colchicine compared with those who did not.[47]

Conclusions

Although the anti-inflammatory agent colchicine has been known for centuries, data have recently positioned the novel use of this inexpensive and safe drug as part of the pharmacologic armamentarium for the prevention of nonfatal atherothrombotic events in patients with CAD. Along with other guideline-recommended secondary prevention strategies and lifestyle modifications, colchicine at a dose of 0.5 mg once daily should be considered in patients with recent MIs or with established stable CAD to improve nonfatal cardiovascular outcomes. It is now approved by Health Canada for this purpose, and is recommended by the European Society of Cardiology (class IIb, level A).[48] Initial studies in patients undergoing PCI are encouraging, including the subgroup analysis of patients who underwent PCI in the COLCOT and LoDoCo2 trials, and additional studies are underway. The optimal dose of colchicine in the peri-PCI period for elective implantation of drug-eluting stents remains to be established and needs to be tested. The impact of colchicine in high-risk populations of patients with peripheral arterial disease, and in those with diabetes for the primary prevention of CAD, remains to be established. Future guidelines on the management of stable CAD and of ACS should incorporate recommendations regarding the role of colchicine in these settings.

Funding Sources

The authors report no funding for this article.

Disclosures

G.M.G. has served as advisory board/speaker for Novartis, JAMP Pharma, Amgen, Alliance BMS-Pfizer, PHRI, Servier, and Canadian Heart Research Center; he has received research funding from Bayer, CIHR, FRQS, DCRI, MHI Foundation, and Université de Montréal. S.G.G. has received research grant support (eg, steering committee or data and safety

Table 2. Pharmacologic interactions with colchicine

Contraindicated agents	Mitigation strategies
Strong CYP 3A4 inhibitors • Macrolides: clarithromycin, telithromycin • Antivirals: atazanavir, darunavir/ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, tipranavir/ritonavir • Antifungals: itraconazole, ketoconazole • Antidepressants: nefazodone Moderate CYP 3A4 inhibitors • Macrolides: erythromycin • Antivirals: amprenavir/ritonavir, fosamprenavir/ritonavir • Antifungals: fluconazole • Calcium channel blockers: diltiazem, verapamil • Antiemetic agents: aprepitant P-glycoprotein inhibitors Cyclosporine Ranolazine Grapefruit juice	• Consider changing agent and/or • Periodic screening for colchicine toxicity and/or • Dose modification: 0.3 mg every other day and/or • Interrupting colchicine temporarily

monitoring committee) and speaker and consulting honoraria (eg, advisory boards) from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Daiichi-Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, GlaxoSmithKline, HLS Therapeutics, JAMP Pharma, Janssen/Johnson & Johnson, Merck, Novartis, Novo Nordisk A/C, Pendopharm, Pfizer, Regeneron, Sanofi, Servier, and Valeo Pharma; he has received salary support and honoraria from the Heart and Stroke Foundation of Ontario/University of Toronto (Polo) Chair, Canadian Heart Research Centre and MD Primer, Canadian VIGOUR Centre, Cleveland Clinic Coordinating Centre for Clinical Research, Duke Clinical Research Institute, New York University Clinical Coordinating Centre, and PERFUSE Research Institute. A.B. has received financial or in kind funding from the following: Amgen, Bristol Myers Squibb, Janssen, AstraZeneca, Novartis, Pfizer, Bayer, Lilly, Boehringer Ingelheim, HLS Therapeutics, Spectrum Therapeutics, Eisai, Sanofi, Bausch Health. Other disclosures: Thrombosis Canada — Vice President, Hypertension Canada — Board of Directors, Canadian Cardiovascular Society — Guideline Author. P.L.L. has served in an advisory board for Pharmascience. T.J.A. has served as local PI for clinical studies for DalCor and Novartis. A.G. has served on the advisory board and as speaker for BMS/Pfizer, Novartis, Astra Zeneca, Servier, and BI. J.C.G. has served as consultant and speaker for Amgen, AstraZeneca, Bayer, BI, BMS/Pfizer Alliance, Novartis, PharmaScience, Sanofi, and Servier. J.C.T. has received research grants from Amarin, AstraZeneca, Ceapro, DalCor Pharmaceuticals, Esperion, Ionis, Novartis, Pfizer, RegenXBio, and Sanofi; honoraria from AstraZeneca, DalCor Pharmaceuticals, HLS Pharmaceuticals, and Pendopharm; and he has minor equity interest in DalCor Pharmaceuticals; he has authorship of patents on pharmacogenomics-guided CETP inhibition, use of colchicine after myocardial infarction, and use of colchicine for coronavirus infection (Dr Tardif has waived his rights in the colchicine patents and does not stand to gain financially). The other authors have no conflicts of interest to disclose.

References

1. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-88.
2. Lawler PR, Bhatt DL, Godoy LC, et al. Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J 2021;42:113-31.
3. Roubille F, Kritikou EA, Tardif JC. Emerging anti-inflammatory therapies for atherosclerosis. Curr Pharm Des 2013;19:5840-9.
4. Libby P, Loscalzo J, Ridker PM, et al. Inflammation, immunity, and infection in atherothrombosis: JACC Review Topic of the Week. J Am Coll Cardiol 2018;72:2071-81.
5. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015;36:1163-70.
6. Marquis-Gravel G, Dalgaard F, Jones Aaron D, et al. Post-discharge bleeding and mortality following acute coronary syndromes with or without PCI. J Am Coll Cardiol 2020;76:162-71.
7. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35.
8. Imazio M, Brucato A, Cemin R, et al. A randomized trial of colchicine for acute pericarditis. N Engl J Med 2013;369:1522-8.
9. Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis 2016;75:644.
10. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res 2020;72:744-60.
11. 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.
12. Deftereos S, Giannopoulos G, Angelidis C, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction. Circulation 2015;132:1395-403.
13. Deftereos S, Giannopoulos G, Raisakis K, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. J Am Coll Cardiol 2013;61:1679-85.
14. 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.
15. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. N Engl J Med 2020;383:1838-47.
16. Shah B, Pillinger M, Zhong H, et al. Effects of acute colchicine administration prior to percutaneous coronary intervention. Circ Cardiovasc Interv 2020;13:e008717.
17. Tong David C, Quinn S, Nasis A, et al. Colchicine in patients with acute coronary syndrome. Circulation 2020;142:1890-900.
18. Hennessy T, Soh L, Bowman M, et al. The low dose colchicine after myocardial infarction (LoDoCo-MI) study: a pilot randomized placebo controlled trial of colchicine following acute myocardial infarction. Am Heart J 2019;215:62-9.
19. Martínez GJ, Robertson S, Barraclough J, et al. Colchicine acutely suppresses local cardiac production of inflammatory cytokines in patients with an acute coronary syndrome. J Am Heart Assoc 2015;4:e002128.
20. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-95.
21. Morton AC, Rothman AMK, Greenwood JP, et al. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. Eur Heart J 2015;36:377-84.
22. Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2018;380(8):752-62.
23. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31.
24. Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest 1995;96:994-1002.
25. Martínez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis 2018;269:262-71.

IPR2023-01064
Murray & Poole v. MHI
M&P Ex. 1079

26. Paschke S, Weidner AF, Paust T, Marti O, Beil M, Ben-Chetrit E. Technical advance: inhibition of neutrophil chemotaxis by colchicine is modulated through viscoelastic properties of subcellular compartments. J Leukocyte Biol 2013;94:1091-6.

27. Rajamäki K, Lappalainen J, Oörni K, et al. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. PLoS One 2010;5:e11765.

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;99:805-7.

29. Vaidya K, Arnott C, Martínez GJ, et al. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: a CT coronary angiography study. JACC Cardiovasc Imaging 2018;11(2 Pt 2):305-16.

30. Vaidya K, Tucker B, Kurup R, et al. Colchicine inhibits neutrophil extracellular trap formation in patients with acute coronary syndrome after percutaneous coronary intervention. J Am Heart Assoc 2021;10:e018993.

31. Opstal Tjerk SJ, Hoogeveen Renate M, Fiolet Aernoud TL, et al. Colchicine attenuates inflammation beyond the inflammasome in chronic coronary artery disease. Circulation 2020;142:1996-8.

32. Bittl JA, Maron DJ. Using absolute event rates to see what works in cardiovascular medicine. J Am Coll Cardiol 2017;70:1376-8.

33. Aggarwal A, Schneider DJ, Terrien EF, Gilbert KE, Dauerman HL. Increase in interleukin-6 in the first hour after coronary stenting: an early marker of the inflammatory response. J Thromb Thrombolysis 2003;15:25-31.

34. Munk PS, Breland UM, Aukrust P, Skadberg O, Ueland T, Larsen AI. Inflammatory response to percutaneous coronary intervention in stable coronary artery disease. J Thromb Thrombolysis 2011;31:92-8.

35. Inoue T, Sakai Y, Morooka S, Hayashi T, Takayanagi K, Takabatake Y. Expression of polymorphonuclear leukocyte adhesion molecules and its clinical significance in patients treated with percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1996;28:1127-33.

36. L'Allier PL, Tardif JC, Kouz S, et al. Low-dose colchicine in patients treated with percutaneous coronary interventions for myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J 2020:41.

37. Bouabdallaoui N, Tardif JC, Waters DD, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J 2020;41:4092-9.

38. Samuel M, Tardif JC, Khairy P, et al. Cost-effectiveness of low-dose colchicine after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J Qual Care Clin Outcomes 2021;7:486-95.

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

40. Xia M, Yang X, Qian C. Meta-analysis evaluating the utility of colchicine in secondary prevention of coronary artery disease. Am J Cardiol 2021;140:33-8.

41. 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.

42. Roubille F, Tardif JC. Colchicine for secondary cardiovascular prevention in coronary disease. Circulation 2020;142:1901-4.

43. Stewart S, Yang KCK, Atkins K, Dalbeth N, Robinson PC. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther 2020;22:28.

44. Hemkens LG, Ewald H, Gloy VL, et al. Cardiovascular effects and safety of long-term colchicine treatment: Cochrane review and meta-analysis. Heart 2016;102:590-6.

45. Deftereos S, Giannopoulos G, Kossyvakis C, et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. J Am Coll Cardiol 2012;60:1790-6.

46. Deftereos S, Giannopoulos G, Panagopoulou V, et al. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. J Am Coll Cardiol HF 2014;2:131-7.

47. Indraratna PL, Virk S, Gurram D, Day RO. Use of colchicine in pregnancy: a systematic review and meta-analysis. Rheumatology 2018;57:382-7.

48. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J 2021;42:3227-337.

IPR2023-01064
Murray & Poole v. MHI
M&P Ex. 1079