



Colchicine in Cardiovascular Disease: In-Depth Review

Spyridon G. Deftereos, MD, PhD; Frans J. Beerkens, MD; Binita Shah¹, MD, MS; George Giannopoulos, MD, PhD; Dimitrios A. Vrachatis², MD, MS, PhD; Sotiria G. Giotaki, MD; Gerasimos Siasos³, MD, MS, PhD; Johnny Nicolas⁴, MD; Clare Arnott, MBBS, PhD; Sanjay Patel, MBBS, PhD; Mark Parsons⁵, MD, PhD; Jean-Claude Tardif⁶, MD; Jason C. Kovacic⁷, MD, PhD; George D. Dangas⁸, MD, PhD

ABSTRACT: Inflammation plays a prominent role in the development of atherosclerosis and other cardiovascular diseases, and anti-inflammatory agents may improve cardiovascular outcomes. For years, colchicine has been used as a safe and well-tolerated agent in diseases such as gout and familial Mediterranean fever. The widely available therapeutic has several anti-inflammatory effects, however, that have proven effective in a broad spectrum of cardiovascular diseases as well. It is considered standard-of-care therapy for pericarditis, and several clinical trials have evaluated its role in postoperative and postablation atrial fibrillation, postpericardiotomy syndrome, coronary artery disease, percutaneous coronary interventions, and cerebrovascular disease. We aim to summarize colchicine's pharmacodynamics and the mechanism behind its anti-inflammatory effect, outline thus far accumulated evidence on treatment with colchicine in cardiovascular disease, and present ongoing randomized clinical trials. We also emphasize real-world clinical implications that should be considered on the basis of the merits and limitations of completed trials. Altogether, colchicine's simplicity, low cost, and effectiveness may provide an important addition to other standard cardiovascular therapies. Ongoing studies will address complementary questions pertaining to the use of low-dose colchicine for the treatment of cardiovascular disease.

Key Words: atrial fibrillation ■ cerebrovascular disorders ■ colchicine ■ coronary artery disease ■ inflammation ■ percutaneous coronary intervention ■ pericarditis ■ postpericardiotomy syndrome

Colchicine has carried many names and been used for centuries.^{1,2} The botanical alkaloid compound is derived from the flower *Colchicum autumnale*, a medicinal plant described as early as 1550 BC in the Egyptian *Ebers Papyrus* used to treat pain and swelling. The plant and therapeutic lend their names to the ancient Colchis (home to mythological sorceresses Medea and Circe), roughly corresponding to the current republic of Georgia. Through the years, colchicine has been frequently described both for its medicinal use in gout (as early as 129–200 CE) as well as its poisonous effects at high doses. Having survived years of scrutiny, colchicine use is rapidly expanding as it is currently considered for a variety of inflammatory conditions. It carries Food and Drug Administration–approved indications for prevention and treatment of gout flares, as well as treat-

ment of familial Mediterranean fever (FMF). It is also used off label for other inflammatory conditions including pericarditis, calcium pyrophosphate disease, and Adamantiades-Behcet's syndrome.^{3–6} Over the years, many studies have shown that inflammation may significantly contribute to a wider variety of pathologies than traditionally thought, including cardiovascular diseases such as atherosclerosis and atrial fibrillation (AF). Therefore, anti-inflammatory strategies are now being carefully examined for potential broader application across a range of cardiovascular diseases. Given wide availability, low cost, and a rather favorable side-effect (tolerability) profile, colchicine has emerged as a potentially useful oral cardiovascular treatment targeting the inflammatory axis. We will review the role inflammation plays in cardiovascular disease, including various anti-inflammatory

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: George Dangas, MD, PhD, The Zena & Michael A. Wiener Cardiovascular Institute, Mount Sinai Hospital, One Gustave L. Levy Place, Box 1030, New York, NY 10029. Email george.dangas@mounsinai.org

Supplemental Material, the podcast, and transcript are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.121.056171>.

For Sources of Funding and Disclosures, see page 75.

© 2021 American Heart Association, Inc.

Circulation is available at www.ahajournals.org/journal/circ

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
AF	atrial fibrillation
CAD	coronary artery disease
CRP	C-reactive protein
ESC	European Society of Cardiology
FMF	familial Mediterranean fever
HR	hazard ratio
IL	interleukin
MI	myocardial infarction
NLRP3	NLR family pyrin domain containing 3
PCI	percutaneous coronary intervention
POAF	postoperative atrial fibrillation
PPS	postpericardiotomy syndrome
RCT	randomized clinical trial
RFA PVI	radiofrequency ablation pulmonary vein isolation

strategies, and then examine past and current evidence about colchicine in cardiovascular disease.

MECHANISM OF ACTION

Colchicine is an oral therapeutic agent that binds tubulin and inhibits tubulin polymerization, with subsequent disruption of the cellular cytoskeleton, mitosis, and intracellular transport activities. Colchicine preferentially accumulates in neutrophils because of the lack of the P-glycoprotein membrane efflux pump and thereby largely affects neutrophil activity (Figure 1).⁷ Specifically, colchicine has been shown to inhibit the directed migration of neutrophils to an inflamed focus (chemotaxis)⁸ and decrease adhesion of neutrophils to inflamed endothelium by diminished quantitative surface expression of L-selectin adhesion molecules.⁹ Colchicine further inhibits the adhesion of leukocytes to inflamed endothelium by decreased qualitative expression of E-selectin adhesion molecules on endothelial cells,⁹ downregulation of tumor necrosis factor receptors on macrophages and endothelial cells,¹⁰ and reduced monocyte/macrophage secretion of tumor necrosis factor α .¹¹ Last, colchicine has been shown to suppress protein tyrosine phosphorylation in neutrophils with subsequent inhibition of both intracellular mobilization and extracellular release of granular enzymes, such as matrix metalloproteinases, neutrophil elastase, and α -defensins.^{12,13}

Although the exact mechanism of action remains incompletely elucidated, data show that colchicine also suppresses the assembly and activation of the NLRP3 (NLR family pyrin domain containing 3) inflammasome, with a resultant decrease in inflammasome-mediated production of interleukin (IL)- 1β and IL-18.^{14,15} Both

IL- 1β and IL-18 are also activated extracellularly by neutrophil enzymes (eg, proteinase 3), the release of which is also inhibited by colchicine.^{16–18} Together, these lead to an overall decrease in IL-6 production and CRP (C-reactive protein) concentration. Last, colchicine may suppress the proliferation of myofibroblasts, smooth muscle cell proliferation, and fibrosis.¹⁹

DOSING, SAFETY, AND TOLERABILITY

Colchicine acts in a dose-dependent manner, and most side effects reverse with lower doses or cessation of treatment.²⁰ Although it is approved for higher doses in acute gout (4.8 mg during 6-hour load in patients without advanced kidney disease), colchicine generates similar peak plasma concentrations and is associated with improved tolerability with a lower dose regimen (1.0–1.2 mg followed by 0.5–0.6 mg 1 hour later).²¹ Maintenance dosage is 0.5 to 0.6 mg once or twice daily for acute disease and 0.3 to 0.6 mg daily for chronic prevention. Dosage adjustments are recommended for acutely ill patients with impaired renal function or body weight <70 kg. Furthermore, dosage formulations vary on the basis of geographic location, because low-dose formulation tablets are available in 0.6-mg tablets in the United States versus 0.5-mg tablets in Australia. This disparity is evident in the differing dosages used in randomized clinical trials (RCTs) discussed below. Given the absence of data comparing efficacy and toxicity characteristics between the 2 formulations, preparation strength differences are most likely a result of commercial manufacturing purposes. Proposed dosing of colchicine per indication can be found in Table 1.

Gastrointestinal intolerance including diarrhea, nausea, vomiting, and abdominal pain is the most common adverse effect, occurring in approximately 10% to 20% of patients, followed by myalgias; however, lower daily doses at 0.5 mg daily or longer term treatment durations >12 weeks may attenuate significant gastrointestinal intolerance.²² At high dosage during prolonged periods of time, colchicine may lead to myelosuppression, neuromuscular toxicity, liver damage, and dermatologic issues.²³ A comprehensive safety analysis of colchicine in 35 double-blind randomized trials including 8659 participants with various inflammatory conditions confirmed known gastrointestinal adverse events (relative risk [RR], 1.74 [95% CI, 1.32–2.30]) yet did not demonstrate an increase in mortality or rate of adverse events related to the liver, neuropathy, muscle, infection, or hematologic disturbances.²⁴ Such findings, however, do not incorporate less controlled, real-world environments in which patients often carry several comorbidities and take medications that may alter clearance of the therapeutic.

Colchicine is metabolized by the CYP3A4 enzyme and cleared by the P-glycoprotein efflux pump in the bile and kidneys.²⁰ Colchicine may therefore accumulate to

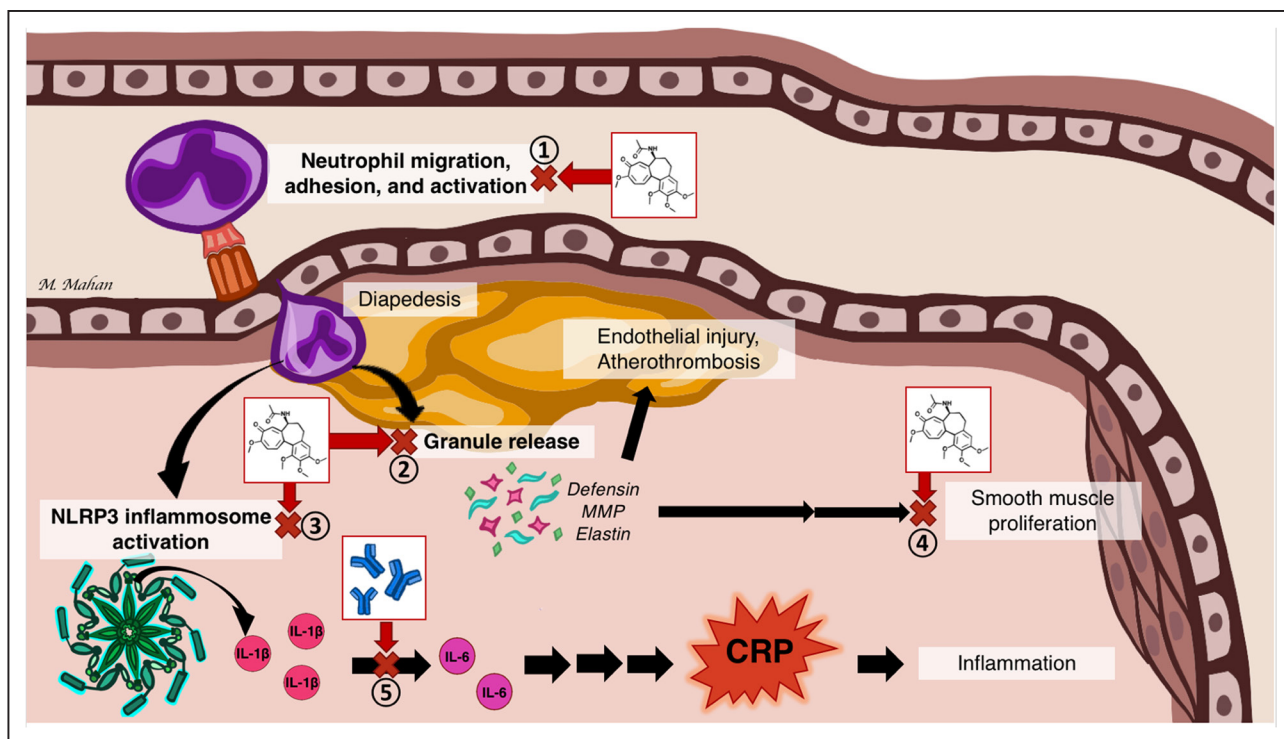


Figure 1. Inflammation in cardiovascular disease and anti-inflammatory targets of colchicine and canakinumab. Colchicine has broad anti-inflammatory effects, here illustrated in atherosclerosis. Colchicine inhibits (1) neutrophil migration, adhesion, activation, (2) neutrophil release of defensins, matrix metalloproteinases (MMP), and elastin, (3) NLRP3 (NLR family pyrin domain containing 3) activation of the inflammatory pathway with release of IL-1β, in turn activating interleukin (IL)-6, and eventually stimulation of CRP (C-reactive protein), and (4) smooth muscle proliferation and vascular stenosis. (5) Canakinumab is a monoclonal antibody that specifically targets the upstream inflammatory mediator IL-1β.

toxic levels in patients with chronic kidney disease if the dose remains unadjusted, especially if chronically used with acute kidney insults or chronically worsening kidney function over time. Significant dosage reductions or even avoidance is recommended for patients on hemodialysis.²⁵ Furthermore, strong inhibitors of the CYP3A4 and P-glycoprotein efflux pathways such as clarithromycin,

certain immunosuppressives, and azole antifungal agents also increase serum or cellular concentrations of colchicine and should be avoided (Figure 2).^{20,26} A few cardiac medications including certain calcium channel blockers (verapamil) and antiarrhythmics (amiodarone) may also alter clearance; lower colchicine dose is then advised (typically once-daily dosage). Statins are generally well tolerated with colchicine despite their own risk of musculoskeletal effects, although rhabdomyolysis has been reported with combination therapy.²⁷ Fatalities related to colchicine are rare, and remain limited to suicide attempts or in patients with advanced organ dysfunction in conjunction with strong P-glycoprotein inhibitors such as clarithromycin.²⁸ A contraindication exists for patients using a potent CYP3A4 or P-glycoprotein inhibitor with either renal or hepatic impairment.

Table 1. Dosing and Duration for Colchicine Stratified by Indication

Clinical Indication	Dose*	Duration
Pericardial disease		
Acute and recurrent pericarditis	≥70 kg: 0.5 mg twice daily†	3 mo
Dressler's syndrome	<70 kg: 0.5 mg once daily†	
Postpericardiotomy syndrome		1 mo after cardiac surgery
Atrial fibrillation		
Postoperative atrial fibrillation	0.5 mg once or twice daily	1–3 mo
Postablation atrial fibrillation		
Coronary artery disease		
Stable coronary artery disease	0.5 mg daily	Possibly indefinite
Acute coronary syndrome		

*In the United States, 0.6-mg tablets are available, whereas 0.5-mg tablets are used in other countries.

†First day loading dose of 1–2 mg optional but not required.

COLCHICINE IN PERICARDIAL DISEASE

Acute and Recurrent Pericarditis

Pericarditis arises from inflammation of the pericardium. Given the rich innervation of the pericardium, pericarditis may be associated with disabling or recurrent chest pain. CRP concentrations are often elevated in cases of acute pericarditis and indicate a higher chance of recurrence.²⁹ Several clinical trials have been conducted for both

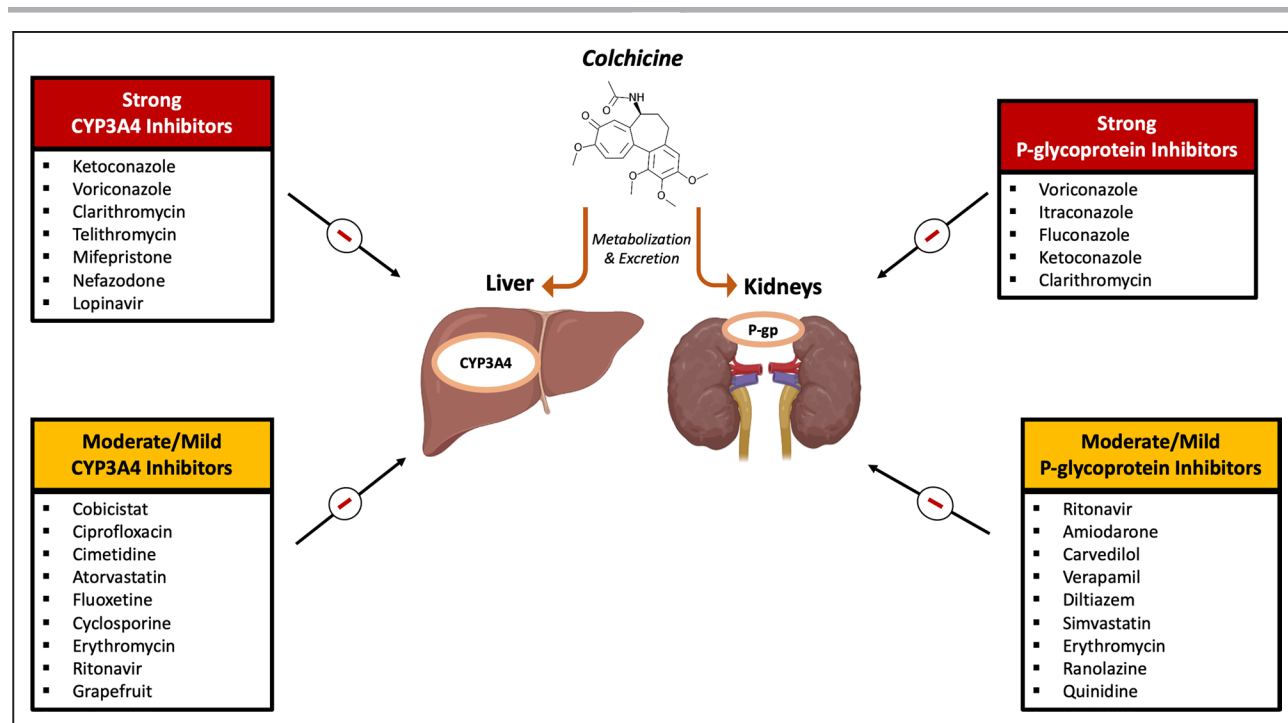


Figure 2. Various CYP-3A4 and P-glycoprotein (P-gp) inhibitors that affect colchicine metabolism.

CYP-3A4 and P-glycoprotein inhibitors may alter the liver's and kidney's ability to clear colchicine. Concomitant administration of strong inhibitors with colchicine should generally be avoided, whereas moderate/mild inhibitors may cautiously be used with colchicine through dose reductions and shared decision making. Figure designed with BioRender.

acute^{30–32} and recurrent pericarditis^{33–35} (Table 2) using a colchicine loading dose ranging from 1 to 2 mg followed by 0.5 to 1 mg daily for subsequent maintenance therapy of variable duration (longer for chronic/recurrent disease). Although all studies were modest in size without more than a few hundred participants, findings have been mostly favorable, apart from a contradicting small study.³² Most studies, however, focused on isolated pericarditis; hence, data about pericarditis with concurrent myocardial injury are scarce. Colchicine is currently recommended by the European Society of Cardiology (ESC) guidelines (class I recommendation, level of evidence A) as a first-line treatment for both acute and recurrent pericarditis and may be administered with conventional anti-inflammatory regimens (aspirin or nonsteroidal anti-inflammatory drugs).⁶ The American College of Cardiology/American Heart Association guidelines thus far only recommend colchicine for pericarditis after myocardial infarction (MI; class IIb recommendation, level of evidence C).⁵ Colchicine treatment is not guided by inflammatory markers or by symptoms but is typically given for 1 to 3 months in acute pericarditis and at least 6 months in recurrent pericarditis.

Dressler's Syndrome

Late post-MI pericarditis (or Dressler's) syndrome is typically diagnosed 2 to 8 weeks after acute MI and is believed to be immune-mediated. In the contemporary era of primary revascularization, it occurs infrequently (0.1%–0.5%).³⁹ Expectedly for a rather rare condition,

data from RCTs are lacking. Extrapolating from studies in pericarditis, both ESC (class IIa recommendation, level of evidence B) and American College of Cardiology/American Heart Association guidelines (class IIb recommendation, level of evidence C) include colchicine in the recommended therapeutic regimen for Dressler's syndrome (in combination with aspirin), dosed in a similar manner as for pericarditis.^{5,6}

Postpericardiotomy Syndrome (PPS)

PPS is an immune-mediated pericardial inflammatory syndrome encountered after surgery involving the pericardium, similar to Dressler's syndrome. PPS should be differentiated from isolated pericardial or pleural effusion seen after cardiac surgery, and specific diagnostic criteria exist.⁴⁰ Colchicine should be considered for PPS treatment according to ESC guidelines (class IIa recommendation, level of evidence B) using the pericarditis treatment regimens.⁶ The role of colchicine in the prevention of PPS has been evaluated in 3 double-blinded placebo-controlled RCTs (Table 2), involving 859 patients in total using colchicine 0.5 to 1.5 mg daily for 1 month postoperatively. One small study (n=163) observed a numerically, but not significantly, lower rate of PPS with colchicine versus placebo (11% versus 17%).³⁶ Two somewhat larger trials including 336 and 360 patients showed a significant effect of colchicine on PPS prevention (9% versus 21% and 19% versus 29%, respectively).^{37,38} Hence, ESC guidelines indicate that colchicine

Table 2. Summary of Key Studies Investigating Colchicine as Adjunct in Inflammatory Pericardial Disease

Study	Design	Population	Intervention	Control	Primary outcome	Colchicine effect	Notable adverse events*
Acute pericarditis							
Colchicine in addition to conventional therapy for acute pericarditis: results of the Colchicine for acute Pericarditis (COPE) Imazio et al, 2005 ³⁰	Prospective, randomized, open-label	Acute pericarditis (n=120)	Colchicine 1.0–2.0 mg for the first day and then 0.5–1.0 mg/d for 3 mo	Conventional treatment	Recurrence rate at 18 mo	10.7% vs 32.3%; $P=0.004$	Gastrointestinal intolerance (8.3%)
A randomized trial of colchicine for acute pericarditis (ICAP) Imazio et al, 2013 ³¹	Prospective, randomized, double-blind, placebo-controlled	Acute pericarditis (n=240)	Colchicine 0.5 mg BID for 3 mo for patients weighing >70 kg; 0.5 mg QD for patients weighing ≤70 kg	Placebo	Incessant or recurrent pericarditis at 18 mo	16.7% vs 37.5%; $P<0.001$; RRR, 0.56 (95% CI, 0.30–0.72)	None
Colchicine administered in the first episode of acute idiopathic pericarditis: a randomized multicenter open-label study Sambola et al, 2019 ³²	Prospective, randomized, open-label	Acute pericarditis (n=110)	Colchicine 1 mg BID for 3 mo for patients weighing >70 kg; 0.5 mg BID for patients weighing ≤70 kg	Conventional treatment	Recurrence rate at 24 mo	10.9% vs 13.5%; $P=0.34$; HR, 1.53 (95% CI, 0.7–3.4)	Gastrointestinal intolerance (13.5%)
Recurrent pericarditis							
Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (Colchicine for Recurrent pericarditis) trial Imazio et al, 2005 ³³	Prospective, randomized, open-label	Recurrent pericarditis (n=83)	Colchicine 1.0–2.0 mg the first day and then 0.5–1.0 mg QD for 6 mo	Conventional treatment	Recurrence rate at 20 mo	24.0% vs 50.6%; $P=0.02$;	Gastrointestinal intolerance (7%)
Colchicine for recurrent pericarditis (CORP): a randomized trial Imazio et al, 2011 ³⁴	Prospective, randomized, double-blind, placebo-controlled	Recurrent pericarditis (n=120)	Colchicine 1.0–2.0 mg on the first day followed by a maintenance dose of 0.5–1.0 mg QD for 6 mo	Conventional treatment	Recurrence rate at 18 mo	24% vs 55%; $P<0.001$; ARR, 0.31 (95% CI, 0.13–0.46); RRR, 0.56 (95% CI, 0.27–0.73)	Gastrointestinal intolerance (7%)
Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicenter, double-blind, placebo-controlled, randomized trial Imazio et al, 2014 ³⁵	Prospective, randomized, double-blind, placebo-controlled	Recurrent pericarditis (n=240)	Colchicine 0.5 mg BID for 6 mo for patients weighing >70 kg or 0.5 mg QD for patients weighing ≤70 kg	Conventional treatment	Recurrence rate at 18 mo	21.6% vs 42.5%; $P=0.0009$; RR, 0.49 (95% CI, 0.24–0.65)	Gastrointestinal intolerance (7.5%) Hepatotoxicity (2.5%)
Postpericardiotomy syndrome							
Colchicine for the prevention of postpericardiotomy syndrome Finkelstein et al, 2002 ³⁶	Prospective, randomized, double-blind, placebo-controlled	Cardiac surgery (n=163)	POD 3: colchicine 1.5 mg QD for 1 mo	Placebo	PPS at 3 mo	10.6% vs 21.9%; $P<0.135$	Not reported
Colchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicenter, randomized, double-blind, placebo-controlled trial Imazio et al, 2010 ³⁷	Prospective, randomized, double-blind, placebo-controlled	Cardiac surgery (n=336)	POD 3: colchicine 1 mg BID for 1 d, followed by 0.5 mg BID until 1 mo (dose reduced for ≤70 kg)	Placebo	PPS at 12 mo	8.9% vs 21.1%; $P=0.002$; RRR, 0.579 (95% CI, 0.273–0.756)	Gastrointestinal intolerance (8.9%)
Colchicine for prevention of post-pericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial Imazio et al, 2014 ³⁸	Prospective, randomized, double-blind, placebo-controlled	Cardiac surgery (n=360)	Colchicine 0.5 mg BID (0.5 mg daily if <70 kg), 48–72 h preoperatively until 1 mo postoperatively	Placebo	PPS at 3 mo	19.4% vs 29.4%; absolute difference, 10.0% (95% CI, 1.1%–8.7%)	Gastrointestinal intolerance (14.4%)

ARR indicates absolute risk reduction; HR, hazard ratio; POD, postoperative day; PPS, postpericardiotomy syndrome; RR, relative risk; and RRR, relative risk reduction.

*Notable adverse events include events significantly increased compared with the control group. If no comparison was made, events were included that were deemed of interest.

should be considered for PPS prevention (class IIa recommendation, level of evidence A) for 1 month after cardiac surgery.⁶ Of note, a recent randomized trial (n=197) focused specifically on patients with a noninflammatory,

moderate- to large-sized pericardial effusion after cardiac surgery demonstrated that delayed administration of colchicine 7 to 30 days after surgery did not reduce effusion size or prevent cardiac tamponade, indicating that

early administration of the therapeutic may be of particular importance.⁴¹

COLCHICINE IN AF

Although inflammatory cytokine signaling is known to be elevated in AF, 1 study suggests it is the activation of the NLRP3 inflammasome that plays a key role in the secretion of the inflammatory cytokines associated with the occurrence of AF.⁴² Increases in inflammatory cytokines not only promote ectopic firing of the atria but also stimulate myocyte remodeling and fibrosis, which leads to more permanent states of arrhythmia.⁴³

Postoperative AF

Postoperative AF (POAF) occurs in around 0.8% of patients undergoing noncardiac surgery and 16% after cardiac surgery, and is associated with significant morbidity, including risk of embolic stroke, increased length of stay, and higher health care costs.⁴⁴ Higher postoperative levels of inflammatory markers such as IL-6 and CRP are associated with POAF, and colchicine may suppress POAF through a variety of pathways, including the NLRP3 inflammasome cascade, which can promote AF.⁴³

A meta-analysis of the 3 largest double-blind RCTs investigating the role of colchicine in the prevention of POAF in 912 patients found that perioperative colchicine reduced the incidence of AF by 35% (RR, 0.65 [95% CI, 0.46–0.91]) during a follow-up period of 1 to 6 months (Table 3).^{40,45,46,51} Two subsequent studies did not show a reduced incidence of POAF after surgery with colchicine treatment. These 2 studies, however, had a smaller, open-label design (n=140 and n=152, respectively) with only a short-term follow-up period (up to hospital discharge).^{47,48} Furthermore, studies investigating colchicine in POAF used varying dosing regimens and durations (Table 3), thereby complicating between-trial comparisons. American College of Cardiology/American Heart Association guidelines suggest that colchicine can be considered for postoperative AF prevention (class IIb recommendation, level of evidence B), whereas ESC guidelines do not include colchicine treatment postoperatively.^{52,53} The ongoing COP-AF study (Colchicine for the Prevention of Perioperative Atrial Fibrillation in Patients Undergoing Thoracic Surgery; NCT03310125) investigates the efficacy of short-term postoperative colchicine administration for the prevention of POAF. The target enrollment is 2800 patients with a primary outcome of POAF at 14 days.

Postablation AF

AF recurrence after catheter-based radiofrequency ablation pulmonary vein isolation (RFA PVI) procedures has been associated, at least in part, with an ongoing

inflammatory process.⁴³ The effect of colchicine in preventing AF recurrence after RFA PVI for paroxysmal AF has been evaluated only in 1 small double-blinded placebo-controlled trial at 3 months (n=161) and in an extension study at 12 months of follow-up (n=223; Table 3).^{49,50} A 3-month regimen of colchicine 0.5 mg twice daily was associated with decreased postprocedural AF recurrence at both 3 months and 12 months. These findings were accompanied by a reduction in IL-6 and CRP levels and an improvement in self-perceived quality of life indices in the midterm. Evidence thus far is scarce, and there are currently no recommendations from scientific society guidelines that address AF after RFA PVI, although a consensus document from American and European scientific societies recommends the use of colchicine for pericardial symptoms after ablation.⁵⁴ The ongoing IMPROVE-PVI pilot (Impact of Short-Course Colchicine Versus Placebo After Pulmonary Vein Isolation; NCT04160117) is planning to investigate AF recurrence with 10 days of 0.6 mg colchicine per day after catheter ablation for long-term recurrence of AF up to 24 months after RFA PVI.

COLCHICINE IN CORONARY ARTERY DISEASE

Although the normal coronary endothelium is relatively resistant to adhesion by circulating leukocytes, inflamed endothelium in the setting of atherosclerosis attracts the migration, adhesion, and activation of leukocytes, of which neutrophils make up a large component.⁵⁵ Subsequent release of neutrophil granular enzymes include matrix metalloproteinases, which play a role in the increased vulnerability of atherosclerotic plaque⁵⁶; neutrophil elastase, which cleaves tissue factor pathway inhibitor and restores factor Xa activity, contributing to the generation of thrombin⁵⁷; and α -defensins, which are associated with altered fibrin formation, larger lipid- and macrophage-rich plaques, and larger thrombus size.^{58,59} Activated neutrophils in addition release neutrophil extracellular traps, externalized nucleosomes with neutrophil enzymes adherent to chromatin that accumulate in rupture-prone plaque and further attract leukocytes and platelets.⁶⁰ Platelets, in turn, adhere to exposed collagen in ruptured or eroded atherosclerotic plaque and aggregate with other circulating leukocytes.⁶¹ Colchicine not only reduces the migration, adhesion, and activation of neutrophils but also may have a potential downstream impact on the inflammatory/thrombotic interface by a reduction in the release of neutrophil granular enzymes related to thrombosis (eg, neutrophil elastase and α -defensin) and inhibition of neutrophil-platelet aggregates.⁶² Furthermore, IL-1 β and IL-18 additionally play a role in the development and instability of atherosclerotic plaque and subsequent IL-6/CRP production.^{16,17} Colchicine not only reduces the NLRP3 inflammasome-mediated production of IL-1 β and IL-18

Table 3. Summary of Key Studies Investigating Colchicine as Adjunct in Postprocedural Atrial Fibrillation

Study	Design	Population	Intervention	Control	Primary outcome	Colchicine effect	Notable adverse events*
Postoperative atrial fibrillation							
Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy Imazio et al, 2011 ⁴⁵	Prospective, randomized, double-blind, placebo-controlled	Any cardiac surgery (n=336)	Colchicine 1 mg BID on day 3 postoperatively, followed by 0.5 mg BID for 1 mo (dose reduced for ≤ 70 kg)	Placebo	Postoperative AF at 1 mo	12.0% vs 22.0%; $P=0.021$; RRR, 0.45 (95% CI, 0.34–0.94)	Gastrointestinal intolerance (9.5%)
Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial Imazio et al, 2014 ⁴⁰	Prospective, randomized, double-blind, placebo-controlled	Any cardiac surgery (n=360)	Colchicine 0.5 mg BID (0.5 mg daily if <math>< 70</math> kg) 48–72 h before surgery, then 1 mo postoperatively	Placebo	PPS (secondary outcome, postoperative AF) at 3 mo	33.9% vs 41.7%; absolute difference, 7.8% (95% CI, –2.2% to 17.6%)	Gastrointestinal intolerance (14.4%)
Low dose colchicine in prevention of atrial fibrillation after coronary artery bypass graft: a double blind clinical trial Sarzaeem et al, 2014 ⁴⁶	Prospective, randomized, blinded, placebo-controlled	Coronary artery bypass surgery (n=216)	Colchicine 1 mg BID 2 doses before surgery, then 0.5 mg BID for 5 d	Placebo	Postoperative AF at 6 mo	14.8% vs 30.6%; $P=0.006$	Not reported
Colchicine to reduce atrial fibrillation in the postoperative period of myocardial revascularization Zarpelon et al, 2016 ⁴⁷	Prospective, randomized, open-label	Elective coronary artery bypass surgery (n=140)	Colchicine 1 mg BID preoperatively, then 0.5 mg BID until hospital discharge	No colchicine therapy	Postoperative AF at hospital discharge	7.04% vs 13.04%; $P=0.271$; RRR, 0.46 (95% CI, –0.53 to 0.81)	Not reported
Effect of colchicine on the incidence of atrial fibrillation in open heart surgery patients: END-AF Trial Tabbalat et al, 2020 ⁴⁸	Prospective, randomized, open-label, placebo-controlled	Elective cardiac surgery (n=152)	Colchicine 1 mg once 12–24 h preoperatively, followed by 0.5 mg QD until hospital discharge	Placebo 12–24 h preoperatively, followed by placebo until hospital discharge	Postoperative AF at hospital discharge	16% vs 18.3%; $P=0.88$; OR, 0.85 (95% CI, 0.37–1.99)	Gastrointestinal intolerance (2.4%)
Postpulmonary vein isolation atrial fibrillation							
Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study Deftereos et al, 2012 ⁴⁹	Prospective, randomized, double-blind, placebo-controlled	Pulmonary vein isolation (n=161)	Colchicine 0.5 mg BID from day 1 after procedure for 3 mo	Placebo	Postprocedure AF at 3 mo	16% vs 33.5%; $P=0.01$; OR, 0.38 (95% CI, 0.18–0.80)	Gastrointestinal intolerance (8.6%)
Colchicine for prevention of atrial fibrillation recurrence after pulmonary vein isolation: Mid-term efficacy and effect on quality of life Deftereos et al, 2014 ⁵⁰	Prospective, randomized, double-blind, placebo-controlled	Pulmonary vein isolation (n=223)	Colchicine 0.5 mg BID from day 1 after procedure for 3 mo	Placebo	Postprocedure AF at 15 mo	31.1% vs 49.5%; $P=0.01$; RRR, 0.37; OR, 0.46 (95% CI, 0.26–0.81)	Gastrointestinal intolerance (9.7%)

AF indicates atrial fibrillation; OR, odds ratio; PPS, postpericardiotomy syndrome; and RRR, relative risk reduction.

*Notable adverse events include events significantly increased compared with the control group. If no comparison was made, events were included that were deemed of interest.

but also reduces the concentration of neutrophil enzymes (eg, proteinase 3) that activate these cytokines extracellularly.¹⁸ In patients with established coronary artery disease (CAD), colchicine has been shown to incrementally reduce CRP concentrations on a background of aspirin and statin therapy,⁶³ as well as reduce low-attenuation plaque volume on coronary computed tomography angiography over time after acute coronary syndrome (ACS).⁶⁴ In patients with gout, colchicine has resulted in improved arterial endothelial function with treatment-associated reductions in CRP concentrations.^{20,65}

Direct support of an independent effect of inflammation on atherosclerosis (ie, the inflammatory hypothesis) came from the large randomized CANTOS study (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study).⁶⁶ Canakinumab, a parenteral anti-IL-1 β monoclonal antibody approved for juvenile idiopathic arthritis and Still's disease, led to a reduction in major adverse cardiovascular events, whereas low-density lipoprotein cholesterol concentrations remained unaffected in patients with previous MI and elevated high-sensitivity CRP. Patients who received canakinumab and achieved

on-treatment reductions in IL-6 and high-sensitivity CRP had improved outcomes compared with placebo and with those who did not achieve on-treatment reductions in inflammatory markers.⁶⁷ However, canakinumab is costly, appeared associated with an increased incidence of fatal infections, and yet was also associated with a large reduction in lung cancer mortality; hence, an oncological indication was further pursued by the manufacturer instead. Conversely, another large randomized trial demonstrated no reduction in major adverse events with low-dose methotrexate, an antimetabolite that blocks the alternate adenosine-mediated inflammatory pathway; however, concentrations of IL-1 β , IL-6, and CRP also did not change with treatment.⁶⁸ Taken together, the data support the IL-1 β /IL-6/CRP pathway as an important focus of therapeutic investigations in targeting cardiovascular inflammation.

Stable CAD

Colchicine's effect in CAD was initially examined retrospectively in the gout and FMF populations. An early case-control series of patients with FMF suggested that taking long-term prophylactic colchicine decreased the incidence of CAD compared with their untreated counterparts.⁶⁹ Colchicine use was also associated with a lower rate of CAD when compared with nonusers in a retrospective study of patients with gout; this risk was lower in patients without concomitant kidney disease.⁷⁰ A retrospective analysis of 1288 patients with gout first hinted that prophylactic long-term colchicine use was associated with a lower rate of MI.⁷¹ However, no adjustment for potential confounders was performed, and the optimal timing of colchicine treatment remained unclear. A subsequent retrospective study of 1002 patients with gout also indicated that colchicine was associated with a 49% lower risk of the composite of MI, stroke, or transient ischemic attack and a 73% relative risk reduction in all-cause mortality compared with untreated patients.⁷² Acknowledging the important limitations that retrospective studies carry, these studies provided a foundation for RCTs investigating colchicine in CAD (Table 4).

The LoDoCo study (Low-Dose Colchicine) was an open-label pilot trial (n=532) studying low-dose colchicine in patients with angiographically proven CAD who were clinically stable for at least 6 months on optimal medical therapy.⁷³ At a median 3-year follow-up, the colchicine group had a significantly lower composite rate of ACS, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke (5.3% versus 16%; $P<0.001$). Because of the small size and lack of placebo control in this study, larger studies were warranted to confirm such positive findings in this pilot study. Subsequently, the larger LoDoCo2 trial was designed as a multicenter, double-blind placebo-controlled randomized trial with clinically stable, optimally treated patients from Australia and the

Netherlands with documented CAD.⁷⁴ The investigators implemented a 30-day open-label run-in period of colchicine treatment for 6582 patients initially enrolled, during which $\approx 10\%$ withdrew because of perceived side effects (mostly gastrointestinal). A total of 5522 patients eventually underwent randomization. Although focused on stable patients with CAD, most patients (85%) randomized had a history of ACS, and almost all were treated with statins (94%) and other optimal guideline-directed therapy. At a median follow-up of 29 months, colchicine reduced the risk of the primary composite cardiovascular end point of cardiovascular death, MI, ischemic stroke, or ischemia-driven coronary revascularization by 31% compared with placebo (6.8% versus 9.6%; $P<0.001$) driven mostly by the occurrence of spontaneous MI and ischemia-driven revascularization. There were no significant mortality differences between groups, although there was a nonsignificant increase in noncardiovascular death noted in the colchicine arm compared with placebo (53 versus 35 events, respectively; hazard ratio [HR], 1.51 [CI 95%, 0.99–2.31]). No potential pathogeneses of such noncardiovascular deaths, including causes as infection or cancer, were able to explain illustrated differences. Furthermore, there were no observed differences in hospitalizations caused by infection, pneumonia, or gastrointestinal reasons between the colchicine and placebo groups. There was a higher rate of myalgia with the colchicine group compared with placebo (21.2% versus 18.5%; HR, 1.15 [95% CI, 1.01–1.31]; data on myalgias were collected only in the Netherlands cohort). Within prespecified subgroup analyses, the effects of colchicine on the primary end point were generally consistent, with important exceptions including females or patients with moderate chronic kidney disease stage 3A (although such subgroups had lower power, representing 15.3% and 5.5% of the total population, respectively). There was also a region-dependent variation of treatment effect, larger in Australia (HR, 0.51 [95% CI, 0.39–0.67]) compared with the Netherlands (HR, 0.92 [95% CI, 0.72–1.20]). Because geographical baseline characteristics were similar, this finding may have been rooted in chance but should call for further investigation. Last, a subgroup analysis of LoDoCo2 confirmed the benefit of colchicine treatment in stable patients with CAD regardless of the history and timing of a previous ACS within the patient population.⁷⁵ Altogether, the LoDoCo2 trial served as a strong validation for the benefit colchicine may carry in stable atherosclerotic coronary disease.

ACUTE CORONARY SYNDROME

Colchicine also has been investigated immediately after ACS. Preliminary in vivo data illustrated how pharmacological inhibition of the NLRP3 inflammasome with colchicine could attenuate MI reperfusion injury and limit infarct size in mouse models.⁷⁹ A pilot study (n=151; n=60

Table 4. Summary of Key Studies Investigating Colchicine as Adjunct in Atherosclerosis Including Acute Coronary Syndrome and Stable Coronary Artery Disease

Study	Design	Population	Intervention	Control	Primary outcome	Colchicine effect	Notable adverse events*
Stable coronary artery disease							
Low-dose colchicine for secondary prevention of cardiovascular disease (LoDoCo trial) Nidorf et al, 2013 ⁷³	Prospective, randomized, observer-blinded, open-label	Stable CAD (n=532)	Colchicine 0.5 mg QD until study completion	Conventional treatment	Composite of ACS, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke at median follow-up of 3 y	5.3% vs 16%; $P<0.001$; HR, 0.33 (95% CI, 0.18–0.59)	Gastrointestinal intolerance (2.5%) Myalgia (0.9%) Myositis (1 case)
Colchicine in patients with chronic coronary disease (LoDoCo2 trial) Nidorf et al, 2020 ⁷⁴	Prospective, randomized, double-blind, placebo-controlled	Stable CAD (n=5522)	Colchicine 0.5 mg QD until study completion	Placebo	Composite of CV death, spontaneous (nonprocedural) MI, ischemic stroke, or ischemia-driven coronary revascularization at median follow-up of 28.6 mo	6.8% vs 9.6%; $P<0.001$; HR, 0.69 (95% CI, 0.57–0.83)	Noncardiovascular death (1.9%; HR, 1.51 [95% CI, 0.99–2.31]) Myalgia [‡] (21.2%; cumulative incidence ratio, 1.15 [95% CI, 1.01–1.31]) Gastrointestinal intolerance (15.4% during run-in period)
Acute coronary syndrome							
Colchicine in patients with acute coronary syndrome: the Australian COPS randomized clinical trial Tong et al, 2020 ⁷⁵	Prospective, randomized, double-blind, placebo-controlled	Patients hospitalized with ACS (n=795)	Colchicine 0.5 mg BID for the first month, then 0.5 mg QD for 11 mo	Placebo	Composite of all-cause mortality, ACS, ischemia-driven (unplanned) urgent revascularization, and noncardioembolic ischemic stroke at 12 mo†	6.1% vs 9.5%; $P=0.09$; HR, 0.65 (95% CI, 0.38–1.09)	Total death (8 vs 1; $P=0.017$) Noncardiovascular death (5 vs 0; $P=0.024$)
Effect of Colchicine on Myocardial Injury in Acute Myocardial Infarction Mewton et al, 2021 ⁷⁶	Phase 2, prospective, randomized, double-blind, placebo-controlled	ACS (n=194)	Colchicine 2 mg bolus followed by colchicine 0.5 mg BID for 5 d	Placebo	Infarct size by CMR at 5 d	mean of 26 g (IQR 16–44) vs 28.4 g (IQR 14–40); $P=0.87$	LV thrombus (22.2% vs 7.4%; $P=0.01$) Gastrointestinal intolerance (34.4% vs 10.1%; $P=0.0001$)
After myocardial infarction							
Efficacy and safety of low-dose colchicine after myocardial infarction (COLCOT trial), Tardif et al, 2019 ⁷⁷	Prospective, randomized, double-blind, placebo-controlled	Acute MI within 30 days (n=4745)	Colchicine 0.5 mg QD until study completion	Placebo	Composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization at median follow-up of 22.6 mo	5.5% vs 7.1%; $P=0.02$; HR, 0.77 (95% CI, 0.61–0.96)	Pneumonia (0.9% vs 0.4%; $P=0.03$)

ACS indicates acute coronary syndrome; CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CV, cardiovascular; HR, hazard ratio; IQR, interquartile range; LV, left ventricular; and MI, myocardial infarction.

*Notable adverse events include events significantly increased compared with the control group. If no comparison was made, events were included that were deemed of interest.

†Longer follow-up results still awaited.

‡Only reported among the cohort from The Netherlands.

in the magnetic resonance imaging substudy) illustrated how colchicine may also reduce the levels of cardiac biomarkers and late gadolinium enhancement–defined infarct size when administered within 12 hours of symptom onset in patients with ST-segment–elevation MI.⁸⁰ However, the following double-blind LoDoCo-MI pilot study (Low-Dose Colchicine After Myocardial Infarction) did not observe a significant difference in high-sensitivity CRP levels among 237 patients admitted with an acute MI after 30 days of treatment with daily low-dose colchicine (0.5 mg daily) compared with placebo.⁸¹

Larger randomized studies were necessary to adequately investigate colchicine's effect after ACS. In the COPS study (Colchicine in Patients With Acute Coro-

nary Syndromes) (n=795), colchicine was started during index hospitalization of ACS, with a higher dose of colchicine (0.5 mg twice daily) compared with LoDoCo2 during the first month.⁷⁵ The composite primary end point of all-cause mortality, ACS, ischemia-driven (unplanned) urgent revascularization, and noncardioembolic ischemic stroke did not differ significantly between colchicine and control arms after 12 months of low-dose colchicine after ACS ($P=0.09$). However, in a post hoc analysis using a primary outcome similar to the LoDoCo and LoDoCo2 trials (a composite of cardiovascular death, ACS, stroke, and urgent revascularization; excluding noncardiovascular death), there was a significant benefit found within the colchicine group ($P=0.019$). COPS did

illustrate a statistically significant increase in noncardiovascular deaths in the colchicine arm, with 5 and 0 in the colchicine and control arms, respectively ($P=0.024$). The cause of death was related to sepsis in 4 out of the 5 events, although of note, most of these patients (3 out of 5) had discontinued colchicine within the first 30 days of the trial and were not taking colchicine at the time of death. Longer-term follow-up of the COPS trial is currently being collected, and results should further clarify the effect of colchicine in CAD and whether this statistical difference in noncardiovascular death is upheld.

The COVERT-MI multicenter study (Colchicine for Left Ventricular Infarct Size Reduction in Acute Myocardial Infarction) ($n=192$) investigated colchicine's effect targeting the initial inflammatory response that occurs with reperfusion injury in ACS.⁷⁶ Patients admitted for percutaneous coronary intervention (PCI) after a first episode of ST-segment–elevation MI were randomized to 5 days of high-dose colchicine (2 mg loading dose followed by 0.5 mg twice daily) or placebo. In contrast with the earlier pilot study,⁸⁰ no differences were demonstrated between groups in the primary outcome of gadolinium-enhanced infarct size on cardiac magnetic resonance imaging ($P=0.87$), in biomarkers of inflammation (including CRP), or in myocardial injury (at 6, 24, and 48 hours of follow-up). There were furthermore no differences in longer term secondary outcomes of infarct size and left ventricle remodeling (defined as change in left ventricle end-diastolic volume) at 3 months of follow-up. The study demonstrated a higher number of patients with left ventricle thrombus in the colchicine group (18) than in the placebo group (6) at 5 days, a difference that was no longer observed at 3 months. There was no significant difference in the number of embolic events. There have not been any prothrombotic reports of colchicine previously, and given the small sample size, the increased incidence of left ventricle thrombus may again be by chance.

Although the LoDoCo trials illustrated a significant benefit of low-dose colchicine in patients with stable CAD, the therapeutic has yet to illustrate benefit during index hospitalization for ACS. This may be a result of differences in ACS pathophysiology, proposed to feature a series of phenotypes, not all of them inflammation-dependent.⁸² Variations in trial design including the dosing and timing of colchicine administration may also account for disparities. Ongoing studies should further explore such differences.

After MI

The large double-blind, placebo-controlled COLCOT trial (Colchicine Cardiovascular Outcomes Trial) tested low-dose colchicine in 4745 patients randomized within 30 days after MI.⁷⁷ Treatment was started with a median of 14 days after stabilization from initial MI. The majority

of patients were on established optimal treatment including a statin (98% to 99%). Median follow-up was 23 months. Colchicine significantly reduced the primary composite end point of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization by 23% (HR, 0.77 [95% CI, 0.61–0.96]; $P=0.02$). The benefit of colchicine was most pronounced in the components of urgent hospitalizations for angina requiring revascularization (HR, 0.50 [95% CI, 0.31–0.81]) and stroke (HR, 0.26 [95% CI, 0.10–0.70]). Colchicine was also associated with a 34% reduction in the total number of both first and recurrent primary end point events during follow-up (rate ratio, 0.66 [95% CI, 0.51–0.86]). The therapeutic was well tolerated with minimal adverse events, although there was a small increase in hospitalization for nonfatal pneumonia in the treatment group versus control (0.9% versus 0.4%; $P=0.03$). COLCOT has been the only trial powered enough to investigate improved outcomes from colchicine within a month of an MI.

Pooled Efficacy, Guidelines, and Adverse Effects

Pooled data from these large RCTs further emphasize the value that colchicine carries in CAD. A 2020 meta-analysis pooling data from the above COLCOT, COPS, LoDoCo, and LoDoCo2 trials included a total of 11 594 patients and showed that, compared with placebo, colchicine was associated with significant reductions of 32% in the incidence of the composite of cardiovascular mortality, MI, ischemic stroke, and urgent coronary revascularization, 38% for MI, 62% for stroke, and 44% for urgent coronary revascularization.⁸³ There were no significant differences in mortality end points or other adverse events such as hospitalization for gastrointestinal events, infection, or pneumonia, although there was a numeric nonsignificant increase in noncardiovascular death in colchicine-treated patients (RR, 1.38 [95% CI, 0.99–1.93]). Another meta-analysis from 2021 illustrated similar results with addition of a randomized trial investigating colchicine after bare metal stent implantation in patients with diabetes (discussed in Colchicine in Percutaneous Coronary Interventions below).^{84,85} It is important to note that neither meta-analysis established significant drug-drug interactions with colchicine and aspirin, statins, or other guideline-directed cardiovascular therapeutics. On the basis of notable RCTs such as COLCOT and LoDoCo2, 2021 ESC guidelines on the prevention of cardiovascular disease have recommended that colchicine be considered for the secondary prevention of cardiovascular disease, in particular for those with uncontrolled risk factors and recurrent cardiac events despite optimal medical therapy (class IIb recommendation, level of evidence A).⁸⁶ Health Canada has since also approved low-dose colchicine for the re-

duction of atherothrombotic events in patients with existing coronary disease.⁸⁷

Nonetheless, signals of a noncardiovascular mortality effect suggest caution in colchicine treatment for atherosclerosis.^{74,75} Such concerns are new and have not been illustrated during treatment for approved indications such as gout and FMF, and thus far, no clear biological root cause for the noncardiovascular deaths observed has been determined. Although the increased incidence of sepsis illustrated in the noncardiovascular deaths of COPS may raise concern considering the potential immunosuppressive effect of colchicine, the majority of treated patients had discontinued the medication long before their fatal event. Higher doses of colchicine in the initial month also could have affected outcomes, and if so, it would be pertinent to further investigate this concern. In addition, noncardiovascular deaths in LoDoCo2 were unable to be attributed to a specific cause such as infection or cancer. Given the low number of events and wide CIs, observed differences in noncardiovascular mortality may be attributed to limited power and play of chance. Nonetheless, continued pharmacovigilance is advisable. Upcoming randomized trials should increase power with longer follow-up and improve quality of evidence with on-treatment analyses to further understand the nuances of such mortality signals.

COLCHICINE IN PERCUTANEOUS CORONARY INTERVENTION

PCI involves an induced endovascular injury and an increased local inflammatory response.⁸⁸ Initial studies focused on the prevention of restenosis because colchicine may target inflammatory factors and halt local smooth muscle cell proliferation (Table 5). However, 2 early studies using daily colchicine after balloon angioplasty, in 130 and 50 patients, respectively, failed to show any impact on restenosis.^{89,90} Postangioplasty restenosis is largely driven by arterial elastic recoil and remodeling, whereas in-stent restenosis is mainly driven by neointimal hyperplasia and local inflammation. Such in-stent restenosis processes may be more effectively targeted by colchicine. A subsequent randomized trial examined the effect of 6 months of treatment with colchicine on neointima formation and restenosis in 196 patients with diabetes after bare-metal stent implantation.⁸⁵ The intravascular ultrasound-defined restenosis rate and in-stent lumen area loss were significantly lower in the colchicine arm. Given these early positive results, the ongoing ORCA trial (Oral Colchicine in Argentina to Prevent Restenosis; NCT04382443) is comparing bare-metal stent plus colchicine versus drug-eluting stent alone with a planned enrollment of 450 patients. If comparable, adjunctive colchicine with bare-metal stent implantation may offer a safe alternative for those with a contraindication to drug-eluting stents.

It is interesting that elevations in inflammatory markers may be detectable as early as 1 hour after PCI, and periprocedural inflammation has been associated with short- and long-term major adverse cardiovascular events even in the contemporary era.^{93,94} Given that a loading dose of high-intensity statin reduces PCI-related MI, colchicine's effect was also examined recently as a "prophylactic" regimen initiated in conjunction with PCI.⁹⁵ The double-blind Colchicine-PCI randomized trial included 400 patients with either ACS or stable CAD treated with either colchicine (1.2 mg before and 0.6 mg after PCI) versus placebo 1 to 2 hours preprocedure.⁹¹ There were no significant differences in the primary outcome of type 4 MI/injury (57.3% versus 64.2%; $P=0.19$) or any other clinical outcomes at 30-day follow-up. However, the rise in inflammatory markers (IL-6 and high-sensitivity CRP) was significantly dampened in the colchicine compared with placebo group at approximately 24 hours after PCI. The subsequent double-blind COPE-PCI trial (Colchicine to Prevent Periprocedural Myocardial Injury in PCI) demonstrated a significant reduction in periprocedural MI when administering a loading dose of colchicine earlier (1 mg followed by 0.5 mg 1 hour later, 6–24 hours pre-PCI) in 75 patients with non-ST-segment-elevation MI and stable angina undergoing PCI.⁹² The biomarker analyses of Colchicine-PCI and COPE-PCI are forthcoming. Considering the limited sample sizes thus far in PCI trials and their mixed results, these results should only be considered as hypothesis-generating.

COLCHICINE IN CEREBROVASCULAR DISEASE

Atherosclerotic cerebrovascular disease accounts for half of all ischemic strokes, whether caused by large artery disease (eg, carotid, proximal middle cerebral artery) or small vessel disease (deep perforating arteries). Despite current optimal medical therapy that includes antihypertensive agents, antithrombotic agents, and lipid-lowering therapy, the annualized risk of recurrent stroke or transient ischemic attack after initial event is up to 5%.⁹⁶ In those with known large artery atherosclerosis, the risk is doubled. Therefore, new therapeutic approaches to prevent atherosclerotic stroke are warranted, particularly targeting the inflammatory component, which has been relatively neglected thus far despite data showing the link between plaque inflammation and higher risk of stroke recurrence.⁹⁷

Initial data suggest colchicine reduces risk of stroke in high-risk populations. After recent ACS, COLCOT showed a markedly lower risk of stroke in the colchicine group compared with the placebo group (HR, 0.26 [95% CI, 0.10–0.70]).⁷⁷ Multiple meta-analyses have thus far reported impressive stroke reductions associated with colchicine use compared with placebo, which has led to many ongoing prospective investigations.^{83,84}

Table 5. Summary of Key Studies Investigating Colchicine as Adjunct in Percutaneous Coronary Interventions

Study	Design	Population	Intervention	Control	Primary outcome	Colchicine effect	Notable adverse events*
Percutaneous coronary intervention							
Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty O'Keefe et al, 1992 ⁸⁹	Prospective, randomized, double-blind, placebo-controlled	PTCA (n=130)	Colchicine 0.6 mg BID until study completion	Placebo	Restenosis at 6 mo	46% vs 45%; <i>P</i> value nonsignificant	Gastrointestinal intolerance (28%)
Combination of lovastatin, enalapril, and colchicine does not prevent restenosis after percutaneous transluminal coronary angioplasty Freed et al, 1995 ⁹⁰	Prospective, open-label	PTCA (n=50)	Colchicine 0.6 mg BID + lovastatin 20 mg QD + enalapril 2.5–10 mg BID (titrated to SBP >100 mm Hg) + aspirin 81 mg QD until study completion	N/A	Late loss in lumen diameter at 16 wk	0.5 mm±0.8 mm†	Gastrointestinal intolerance (18%)
Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients Deffereos et al, 2013 ⁸⁵	Prospective, randomized, double-blind, placebo-controlled	BMS PCI in patients with diabetes (n=196)	Colchicine 0.5 mg BID until study completion	Placebo	Angio- and IVUS-ISR at 6 mo	Angio-ISR: 16% vs 33%; <i>P</i> =0.007; OR, 0.38 (95% CI, 0.18–0.79); IVUS-ISR: 24% vs 43%; <i>P</i> =0.006; OR, 0.42 (95% CI, 0.22–0.81)	Gastrointestinal intolerance (16% vs 7%; <i>P</i> =0.058)
Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI randomized trial Shah et al, 2020 ⁹¹	Prospective, randomized, double-blind, placebo-controlled	ACS or stable CAD PCI (n=400)	Colchicine 1.2 mg once before PCI, and 0.6 mg once after PCI	Placebo at matching time points	PCI-related myocardial injury at 6–8 h and 22–24 h after PCI	57.3% vs 64.2%; <i>P</i> =0.19	Gastrointestinal intolerance (9.3% vs 3.2%; <i>P</i> =0.001)
Colchicine to prevent periprocedural myocardial injury in percutaneous coronary intervention: the COPE-PCI pilot trial Cole et al, 2021 ⁹²	Prospective, randomized, double-blind, placebo-controlled	NSTEMI or stable angina (n=75)	Colchicine 1 mg followed by 0.5 mg 1 h later, 6–24 h before procedure	Placebo at matching time points	Periprocedural MI; Secondary outcomes include major and minor periprocedural myocardial injury at 24 h after PCI	No periprocedural MI occurred in either group Minor: 58% vs 85%; <i>P</i> =0.01 No periprocedural MI occurred in either group Major: 31% vs 54%; <i>P</i> =0.04	None

ACS indicates acute coronary syndrome; BMS, bare metal stent; CAD, coronary artery disease; ISR, in-stent restenosis; IVUS, intravascular ultrasound; NSTEMI, non-ST-segment-elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; and PTCA, percutaneous coronary angioplasty.

*Notable adverse events include events significantly increased compared with the control group. If no comparison was made, events were included that were deemed of interest.

†Indicating no prevention of restenosis.

There are currently 2 larger randomized trials examining the effects of colchicine in stroke survivors. The ongoing open-label CONVINC trial (Colchicine for Prevention of Vascular Inflammation in Noncardioembolic Stroke; NCT02898610) will assess its effects in patients who have recently suffered a noncardioembolic transient ischemic attack or ischemic stroke, with a planned recruitment of 2623. The second study is the planned Australian-based multicenter CASPER trial (Colchicine After Stroke to Prevent Event Recurrence), which will test the effects of adding colchicine to optimal medical therapy to reduce major adverse cardiovascular events in stroke survivors with a persistently elevated high-sensitivity CRP of >2 mg/L. Thus far, evidence of colchicine in stroke is only preliminary; however, if confirmed by larger randomized trials such as the CONVINC and CONVINC trials, stroke may be only 1 of many clinical manifestations of inflammatory cerebrovascular

atherosclerotic processes that may be targeted with anti-inflammatory therapies such as colchicine.

Ongoing and Future Trials of Colchicine in Atherosclerosis

No studies have specifically examined the effects of colchicine on chronic peripheral artery disease, another partly inflammatory process. Given promising results with colchicine in CAD, further investigation is anticipated in patients with peripheral artery disease and peripheral percutaneous arterial interventions. In addition, there are other large studies ongoing that will further add to our understanding of colchicine in atherosclerosis. The ongoing, placebo-controlled, randomized CLEAR SYNERGY trial (Colchicine and Spironolactone in Patients With MI/SYNERGY Stent Registry; NCT03048825) has a 2 × 2 factorial design and plans to enroll 7000 participants with large MI under-

going primary PCI. It will include investigation of low-dose colchicine initiated within 3 days of PCI on the composite primary end point of cardiovascular death, MI, or stroke compared with placebo up to 5 years of follow-up. The COLCARDIO-ACS study (Colchicine Effects on Cardiovascular Outcomes in Acute Coronary Syndrome Study; ACTRN12616000400460) plans to recruit 3000 survivors of ACS with a persistently elevated high-sensitivity CRP (>2 mg/L 4–6 weeks after event) in a prospective, randomized, placebo-controlled trial.

CLINICAL IMPLICATIONS

Already standard of care for pericarditis, colchicine's possible role is expanding to other areas of cardiovascular inflammation in a stepwise fashion. Examining the expanding body of evidence of colchicine in cardiovascular disease, we can summarize the following: (1) although not Food and Drug Administration–approved per se, the use of colchicine for pericarditis has strong evidence and is currently recommended by the practice guidelines; (2) colchicine can effectively decrease AF and PPS after cardiac surgery; however, additional RCTs are warranted to determine colchicine's effect after RFA PVI; (3) recent large, well designed RCTs and meta-analyses have illustrated substantial benefit of colchicine in CAD; (4) larger RCTs should further examine the use and timing of colchicine in relation to PCI after mixed preliminary evidence; and (5) retrospective analyses indicate a possible indication for colchicine in atherosclerotic cerebrovascular disease, and ongoing prospective studies are eagerly awaited.

Colchicine's dosing, timing, and duration of administration should continue to be clarified for each condition treated (Table 1). Although higher doses are used in gout and FMF, randomized cardiovascular trials used low-dose daily colchicine with success in secondary prevention.^{74,77} Given its dose-dependent side effect profile, higher doses should only be used short-term in acute cardiovascular conditions (ie, acute pericarditis, acute POAF, etc), whereas a lower dose regimen appears preferable for longer-term treatment exceeding ≈1 week. Particularly for indications such as chronic CAD or after MI, colchicine can be taken in conjunction with other optimal secondary prevention medical therapy for years given periodic evaluations of tolerability and shared physician-patient decision making. This may especially serve those with uncontrolled cardiovascular risk factors and recurrent cardiovascular events, as indicated by the 2021 ESC guidelines.⁸⁶ In addition, given the suggested benefits of long-term colchicine administration in CAD, longer-term colchicine administration may be further examined for many other parallel cardiovascular indications, such as after PCI or coronary artery bypass graft surgery. Accumulating evidence in the various cardiovas-

cular indications will likely further help elucidate optimal timing and use.

Yet target populations that may benefit from colchicine need to be further delineated. Neither LoDoCo, LoDoCo2, nor COLCOT selected patients based on elevated inflammatory risk, currently defined as high-sensitivity CRP >2 mg/L.^{73,74,77} Indeed, after excluding patients with highly elevated high-sensitivity CRP concentration (>10 mg/L), a substudy of LoDoCo2 (n=174) demonstrated a median baseline high-sensitivity CRP concentration of 1.52 mg/L, which was significantly reduced 34% with colchicine treatment.⁹⁸ Although a subgroup of COLCOT (n=207) demonstrated an elevated median baseline high-sensitivity CRP concentration of 4.28 mg/L early after MI, reductions in this inflammatory marker did not differ over time by treatment group.⁷⁷ Colchicine, therefore, may improve clinical outcomes irrespective of CRP concentrations and could be considered for all patients with CAD. However, a biomarker-specific strategy may provide a targeted patient subset that may enable precision medicine and amplify the benefit/risk ratio. The 2020 proteomic study of 174 colchicine-treated patients nested within the 30-day run-in phase of LoDoCo2 demonstrated not only a significant reduction in high-sensitivity CRP with colchicine treatment but also reductions in various proteins associated with NLRP3 inflammasome (ie, IL-1 β , IL-6, and IL-18) and others related to neutrophil function as well.⁹⁸ Many of these protein reductions, however, did not necessarily correlate with change in high-sensitivity CRP, and we should therefore continue to scrutinize our current definition of high inflammatory risk. The ongoing biomarker substudy of CLEAR SYNERGY (NCT03874338) plans to examine detailed neutrophil profiles and determine clinical, biomarker, and genetic predictors of heterogeneity to colchicine treatment response in survivors of a large MI. Certain pharmacogenomic determinants of colchicine safety have already been identified in COLCOT.⁹⁹ Further studies investigating the role of inflammatory markers and clinical outcomes in parallel may clarify if the overall population benefits are rather uniform or mostly driven by a major response among patients with an exaggerated inflammatory profile.

One must recognize that colchicine is not tolerated by everyone. Early gastrointestinal intolerance has been common in many cardiovascular trials and should be monitored in patients when starting colchicine therapy. Furthermore, the majority of RCTs to date excluded patients with severe renal dysfunction, and findings cannot be extrapolated to this population. Preliminary data from LoDoCo2 among patients with chronic kidney disease stage 3A or worse may even indicate that colchicine loses its beneficial cardiovascular effect with worsening renal disease. Given that patients with chronic kidney disease represent a

substantial proportion of the CAD population, it will be imperative to investigate whether renal dosing of colchicine in such patients could safely lead to similar positive clinical outcomes. Until then, colchicine treatment in patients with severe renal dysfunction should remain relatively contraindicated given its partial renal clearance.

All in all, although anti-inflammatory therapy with canakinumab would have likely been too costly to implement on a large scale, colchicine has been a widely available oral agent for centuries and is reasonably inexpensive in most areas of the world. A cost effectiveness study of COLCOT reported cost savings with the addition of colchicine to standard therapy after MI.¹⁰⁰ However, colchi-

Table 6. Ongoing Major Registered Randomized Clinical Trials With Colchicine in Cardiovascular Disease

Study	Design	Target population	Intervention	Primary outcome	Planned follow-up	Country
Atrial fibrillation						
Colchicine for the Prevention of Perioperative Atrial Fibrillation in Patients Undergoing Thoracic Surgery (COP-AF) NCT03310125	Phase 3, prospective, randomized, double-blind	Major thoracic surgery patients (n=2800)	Colchicine 0.5 mg BID for 10 d	POAF	14 d	Canada
Colchicine in Cardiac Surgery (COCS) NCT04224545	Phase 4, prospective, randomized, double-blind	Patients with CABG or AVR (n=1000)	Colchicine 1 mg QD a day before surgery, and 2, 3, 4, and 5 d after surgery	POAF	7 d	Russia
Impact of Short-Course Colchicine Versus Placebo After Pulmonary Vein Isolation (IMPROVE-PVI Pilot) NCT04160117	Phase 3, prospective, randomized, double-blind	RFA PVI (n=200)	Colchicine 0.6 mg BID for 10 d	AF recurrence	2 y	Canada
Coronary artery disease						
Colchicine and Spironolactone in Patients With MI/SYNERGY Stent Registry (CLEAR SYNERGY) NCT03048825	Phase 3, prospective, randomized, blinded, double-dummy 2 × 2 factorial design	STEMI or NSTEMI status after PCI (n=7000)	Drug 1: colchicine 0.5 mg BID Drug 2: spironolactone 25 mg QD Device: SYNERGY Bio-absorbable Polymer Drug-Eluting Stent	MACE	1 y	New York, USA
Colchicine Effects on Cardiovascular Outcomes in Acute Coronary Syndrome Study (COLCARDIO-ACS) ACTRN12616000400460	Prospective, randomized, double-blind, placebo-controlled	ACS + hs-CRP >2 mg/L 4–6 wk after event (n=3000)	Colchicine 0.5 mg QD for 3 y	Cardiac events	3 y	Australia
Effect of Colchicine in Patients With Myocardial Infarction NCT04218786	Phase 2, prospective, randomized, double-blind	ACS (n=800)	Colchicine 0.5 mg QD for 3 mo	MACE	3 mo	Pakistan
PCI						
Oral Colchicine in Argentina to Prevent Restenosis (ORCA) NCT04382443	Phase 4, prospective, randomized, open-label	PCI (n=450)	Arm 1: colchicine 0.5 mg BID for 3 mo + BMS Arm 2: DES	MACE	1 y	Argentina
Cerebrovascular disease						
Colchicine for Prevention of Vascular Inflammation in Noncardio Embolic Stroke (CONVINCE) NCT02898610	Phase 3, prospective, randomized, open-label	Stroke/TIA (n=2623)	Conventional treatment + colchicine 0.5 mg QD for 60 mo	MACE	60 mo	Ireland
Colchicine After Stroke to Prevent Event Recurrence (CASPER) Registration ID to be confirmed	Prospective, randomized, double-blind, placebo-controlled	Stroke/TIA + hs-CRP >2 mg/L at 4–6 wk after event (n = unknown)	Conventional treatment + colchicine 0.5 mg QD for 60 mo	MACE	To be confirmed	Australia

ACS indicates acute coronary syndrome; AF, atrial fibrillation; AVR, aortic valve replacement; BMS, bare metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; hs-CRP, high-sensitivity C-reactive protein; MACE, major adverse cardiac event; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; POAF, postoperative atrial fibrillation; RFA PVI, radiofrequency ablation pulmonary vein isolation; STEMI, ST-segment-elevation myocardial infarction; and TIA, transient ischemic attack.

icine may cost more in certain countries, including areas such as the United States that were not included in the study. The ever-growing evidence of cardiovascular benefit that colchicine carries may forecast relevant updates in upcoming practice guidelines for indications such as CAD or cardiac surgery. If colchicine use does expand over the coming years, caution must be taken to avoid cost increases because of supply limitations or other reasons.

CONCLUSIONS

There is broad evidence about colchicine's benefits in acute and recurrent pericarditis, and emerging indications for its use in postprocedural AF, CAD, and stroke on the basis of its targeting of cardiovascular inflammation. Indeed, colchicine may potentially become an important addition to other standard cardiovascular therapies. Guidelines already recommend colchicine for cardiovascular diseases such as pericarditis, and ESC has recently included CAD as a potential indication as well. However, questions remain about its use in patients with severe chronic kidney disease and its potential effect on noncardiovascular mortality. Large ongoing trials (Table 6) should further clarify how best to use this old therapeutic agent in cardiac disease in the most safe and effective manner. Given colchicine's promise, they are eagerly awaited.

ARTICLE INFORMATION

Affiliations

Medical School, National Kapodistrian University of Athens, Greece (S.G.D., D.A.V., S.G.G., G.S., G.D.D.). Mount Sinai Hospital, Icahn School of Medicine at Mount Sinai, New York (F.J.B., J.N., J.C.K., G.D.D.). VA New York Harbor Healthcare System, New York University School of Medicine, New York (B.S.). Medical School, Aristotelian University, Thessaloniki, Greece (G.G.). The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia (C.A.). Department of Cardiology, Royal Prince Alfred Hospital, Sydney Medical School, University of Sydney, Australia (C.A., S.P.). Department of Neurology, Liverpool Hospital and Ingham Institute for Applied Medical Research at South Western Sydney Clinical School, University of New South Wales, Australia (M.P.). Montreal Heart Institute, Université de Montréal, Canada (J.-C.T.). Victor Chang Cardiac Research Institute, Darlinghurst, Australia (J.C.K.). St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia (J.C.K.).

Acknowledgments

The authors thank Marielle Mahan for her expert assistance with the medical illustrations.

Sources of Funding

C.A. holds a National Health and Medical Research Council/Medical Research Future Fund Priority Investigator Grant and a New South Wales Health Early-Mid Career Research Grant (both of which are not for colchicine studies). S.P. holds the following Australian National Health and Medical Research Council/Medical Research Future Fund colchicine grants: COLCARDIO-ACS GA65779, CASPER GA82107, and IMPACT-ICO GA85492. These studies are supported by Aspen Pharmacare Australia, who are providing drug and placebo. S.P. also holds a New South Wales Cardiovascular Health Fellowship to support colchicine research. M.P. receives funding from the National Health and Medical Research Council Program Grant in Stroke (ID 1113352). J.C.K. received funding from the National Institutes of Health (R01HL130423, R01HL135093, R01HL148167-01A1) and a New South Wales health grant (RG194194).

Disclosures

B. Shah reports funding from the Veterans Affairs Office of Research and Development (iK2CX001074) and the National Heart, Lung, and Blood Institute of the National Institutes of Health (R01HL146206) for studies of colchicine in coronary artery disease; is on the advisory board for Philips Volcano; and serves as a consultant for Terumo Medical. Dr Tardif has received research grants from Amarin, AstraZeneca, Ceapro, DalCor Pharmaceuticals, Esperion, Ionis, Novartis, Pfizer, RegenXBio, and Sanofi; has received honoraria from AstraZeneca, DalCor Pharmaceuticals, HLS Pharmaceuticals, and Pendopharm; has received minor equity interest from DalCor Pharmaceuticals; and is an author of patents on pharmacogenomics-guided cholesteryl ester transfer protein inhibition, use of colchicine after MI, and use of colchicine in coronavirus infection (Dr Tardif has waived his rights in patents on colchicine and does not stand to gain financially). The other authors report no conflicts.

REFERENCES

- Nerlekar N, Beale A, Harper RW. Colchicine – a short history of an ancient drug. *Med J Aust.* 2014;201:687–688. doi: 10.5694/mja14.00846
- Imazio M, Nidorf M. Colchicine and the heart. *Eur Heart J.* 2021;42:2745–2760. doi: 10.1093/eurheartj/ehab221
- Beck C, Morbach H, Richl P, Stenzel M, Girschick HJ. How can calcium pyrophosphate crystals induce inflammation in hypophosphatasia or chronic inflammatory joint diseases? *Rheumatol Int.* 2009;29:229–238. doi: 10.1007/s00296-008-0710-9
- Esatoglu SN, Hatemi G. Update on the treatment of Behçet's syndrome. *Intern Emerg Med.* 2019;14:661–675. doi: 10.1007/s11739-019-02035-1
- O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362–e425. doi: 10.1161/CIR.0b013e3182742cf6
- Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, Brucato A, Guert P, Klingel K, Lionis C, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2015;36:2921–2964. doi: 10.1093/eurheartj/ehv318
- Klimecki WT, Futscher BW, Grogan TM, Dalton WS. P-glycoprotein expression and function in circulating blood cells from normal volunteers. *Blood.* 1994;83:2451–2458. doi: 10.1182/blood.V83.9.2451.2451
- Caner JE. Colchicine inhibition of chemotaxis. *Arthritis Rheum.* 1965;8:757–764. doi: 10.1002/art.1780080438
- 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. doi: 10.1172/JCI118147
- Ding AH, Porteu F, Sanchez E, Nathan CF. Downregulation of tumor necrosis factor receptors on macrophages and endothelial cells by microtubule depolymerizing agents. *J Exp Med.* 1990;171:715–727. doi: 10.1084/jem.171.3.715
- Li Z, Davis GS, Mohr C, Nain M, Gems D. Inhibition of LPS-induced tumor necrosis factor- α production by colchicine and other microtubule disrupting drugs. *Immunobiology.* 1996;195:624–639. doi: 10.1016/s0171-2985(96)80027-1
- Roberge CJ, Gaudry M, de Médicis R, Lussier A, Poubelle PE, Naccache PH. Crystal-induced neutrophil activation. IV. Specific inhibition of tyrosine phosphorylation by colchicine. *J Clin Invest.* 1993;92:1722–1729. doi: 10.1172/JCI116759
- Wright DG, Malawista SE. Mobilization and extracellular release of granular enzymes from human leukocytes during phagocytosis: inhibition by colchicine and cortisol but not by salicylate. *Arthritis Rheum.* 1973;16:749–758. doi: 10.1002/art.1780160608
- Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature.* 2006;440:237–241. doi: 10.1038/nature04516
- Park YH, Wood G, Kastner DL, Chae JJ. P2Y₆ inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. *Nat Immunol.* 2016;17:914–921. doi: 10.1038/ni.3457

16. Kirii H, Niwa T, Yamada Y, Wada H, Saito K, Iwakura Y, Asano M, Moriwaki H, Seishima M. Lack of interleukin-1 β decreases the severity of atherosclerosis in ApoE-deficient mice. *Arterioscler Thromb Vasc Biol*. 2003;23:656–660. doi: 10.1161/01.ATV.0000064374.15232.C3
17. Mallat Z, Corbaz A, Scoazec A, Besnard S, Lesèche G, Chvatchko Y, Tedgui A. Expression of interleukin-18 in human atherosclerotic plaques and relation to plaque instability. *Circulation*. 2001;104:1598–1603. doi: 10.1161/hc3901.096721
18. Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. *Immunity*. 2013;39:1003–1018. doi: 10.1016/j.immuni.2013.11.010
19. Bauriedel G, Heimerl J, Beinert T, Welsch U, Höfling B. Colchicine antagonizes the activity of human smooth muscle cells cultivated from arteriosclerotic lesions after atherectomy. *Coron Artery Dis*. 1994;5:531–539.
20. Slobodnick A, Shah B, Krasnokutsky S, Pillinger MH. Update on colchicine, 2017. *Rheumatology (Oxford)*. 2018;57(suppl_1):i4–i11. doi: 10.1093/rheumatology/kex453
21. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum*. 2010;62:1060–1068. doi: 10.1002/art.27327
22. Andreis A, Imazio M, Avondo S, Casula M, Paneva E, Piroli F, De Ferrari GM. Adverse events of colchicine for cardiovascular diseases: a comprehensive meta-analysis of 14188 patients from 21 randomized controlled trials. *J Cardiovasc Med (Hagerstown)*. 2021;22:637–644. doi: 10.2459/JCM.0000000000001157
23. Nidorf SM, Eikelboom JW, Thompson PL. Colchicine for secondary prevention of cardiovascular disease. *Curr Atheroscler Rep*. 2014;16:391. doi: 10.1007/s11883-013-0391-z
24. Stewart S, Yang KCK, Atkins K, Dalbeth N, Robinson PC. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomized controlled trials. *Arthritis Res Ther*. 2020;22:28. doi: 10.1186/s13075-020-2120-7
25. Medani S, Wall C. Colchicine toxicity in renal patients - are we paying attention? *Clin Nephrol*. 2016;86:100–105. doi: 10.5414/CN108343
26. U. S. Food and Drug Administration. FDA Center for Drug Evaluation and Research, Guidance for Industry; Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. Clinical Drug Interaction Studies. January 2020. <https://www.fda.gov/media/134581/download>. Accessed October 19, 2021.
27. Tufan A, Dede DS, Cavus S, Altintas ND, Iskit AB, Topeli A. Rhabdomyolysis in a patient treated with colchicine and atorvastatin. *Ann Pharmacother*. 2006;40:1466–1469. doi: 10.1345/aph.1H064
28. Hung IF, Wu AK, Cheng VC, Tang BS, To KW, Yeung CK, Woo PC, Lau SK, Cheung BM, Yuen KY. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis*. 2005;41:291–300. doi: 10.1086/431592
29. Imazio M, Brucato A, Maestroni S, Cumetti D, Dominelli A, Natale G, Trincherro R. Prevalence of C-reactive protein elevation and time course of normalization in acute pericarditis: implications for the diagnosis, therapy, and prognosis of pericarditis. *Circulation*. 2011;123:1092–1097. doi: 10.1161/CIRCULATIONAHA.110.986372
30. Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, Moratti M, Gaschino G, Giammaria M, Ghisio A, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COLchicine for acute PERicarditis (COPE) trial. *Circulation*. 2005;112:2012–2016. doi: 10.1161/CIRCULATIONAHA.105.542738
31. Imazio M, Brucato A, Cemin R, Ferrua S, Maggolini S, Beqaraj F, Demarie D, Forno D, Ferro S, Maestroni S, et al; ICAP Investigators. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2013;369:1522–1528. doi: 10.1056/NEJMoa1208536
32. Sambola A, Roca Luque I, Mercé J, Alguersuari J, Francisco-Pascual J, García-Dorado D, Sagristà-Sauleda J. Colchicine administered in the first episode of acute idiopathic pericarditis: a randomized multicenter open-label study. *Rev Esp Cardiol (Engl Ed)*. 2019;72:709–716. doi: 10.1016/j.rec.2018.11.016
33. Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, Ghisio A, Belli R, Trincherro R. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (Colchicine for REcurrent pericarditis) trial. *Arch Intern Med*. 2005;165:1987–1991. doi: 10.1001/archinte.165.17.1987
34. Imazio M, Brucato A, Cemin R, Ferrua S, Belli R, Maestroni S, Trincherro R, Spodick DH, Adler Y; CORP (Colchicine for Recurrent Pericarditis) Investigators. Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med*. 2011;155:409–414. doi: 10.7326/0003-4819-155-7-201110040-00359
35. Imazio M, Belli R, Brucato A, Cemin R, Ferrua S, Beqaraj F, Demarie D, Ferro S, Forno D, Maestroni S, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. *Lancet*. 2014;383:2232–2237. doi: 10.1016/S0140-6736(13)62709-9
36. Finkelstein Y, Shemesh J, Mahlab K, Abramov D, Bar-El Y, Sagie A, Sharoni E, Sahar G, Smolinsky AK, Schechter T, et al. Colchicine for the prevention of postpericardiotomy syndrome. *Herz*. 2002;27:791–794. doi: 10.1007/s00059-002-2376-5
37. Imazio M, Trincherro R, Brucato A, Rovere ME, Gandino A, Cemin R, Ferrua S, Maestroni S, Zingarelli E, Barosi A, et al; COPPS Investigators. Colchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. *Eur Heart J*. 2010;31:2749–2754. doi: 10.1093/eurheartj/ehq319
38. Imazio M, Brucato A, Ferrazzi P, Pullara A, Adler Y, Barosi A, Caforio AL, Cemin R, Chirillo F, Comoglio C, et al; COPPS-2 Investigators. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. *JAMA*. 2014;312:1016–1023. doi: 10.1001/jama.2014.11026
39. Imazio M, Negro A, Belli R, Beqaraj F, Forno D, Giammaria M, Trincherro R, Adler Y, Spodick D. Frequency and prognostic significance of pericarditis following acute myocardial infarction treated by primary percutaneous coronary intervention. *Am J Cardiol*. 2009;103:1525–1529. doi: 10.1016/j.amjcard.2009.01.366
40. Imazio M, Brucato A, Ferrazzi P, Spodick DH, Adler Y. Postpericardiotomy syndrome: a proposal for diagnostic criteria. *J Cardiovasc Med (Hagerstown)*. 2013;14:351–353. doi: 10.2459/JCM.0b013e328353807d
41. Meurin P, Lelay-Kubas S, Pierre B, Pereira H, Pavy B, Iliou MC, Bussièrè JL, Weber H, Beugin JP, Farrokhi T, et al; French Society of Cardiology. Colchicine for postoperative pericardial effusion: a multicentre, double-blind, randomised controlled trial. *Heart*. 2015;101:1711–1716. doi: 10.1136/heartjnl-2015-307827
42. Yao C, Veleva T, Scott L Jr, Cao S, Li L, Chen G, Jeyabal P, Pan X, Alsina KM, Abu-Taha I Dr, et al. Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation. *Circulation*. 2018;138:2227–2242. doi: 10.1161/CIRCULATIONAHA.118.035202
43. Varghese B, Feldman DI, Chew C, Vallis E, Blumenthal RS, Sharma G, Calkins H. Inflammation, atrial fibrillation, and the potential role for colchicine therapy. *Heart Rhythm O2*. 2021;2:298–303. doi: 10.1016/j.hrroo.2021.03.011
44. Gialdini G, Nearing K, Bhavé PD, Bonuccelli U, Iadecola C, Healey JS, Kamel H. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA*. 2014;312:616–622. doi: 10.1001/jama.2014.9143
45. Imazio M, Brucato A, Ferrazzi P, Rovere ME, Gandino A, Cemin R, Ferrua S, Belli R, Maestroni S, Simon C, et al; COPPS Investigators. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. *Circulation*. 2011;124:2290–2295. doi: 10.1161/CIRCULATIONAHA.111.026153
46. Sarzaem M, Shayan N, Bagheri J, Jebelli M, Mandegar M. Low dose colchicine in prevention of atrial fibrillation after coronary artery bypass graft: a double blind clinical trial. *Tehran Univ Med J*. 2014;72:147–154.
47. Zarpelon CS, Netto MC, Jorge JC, Fabris CC, Desengrini D, Jardim Mda S, Silva DG. Colchicine to reduce atrial fibrillation in the postoperative period of myocardial revascularization. *Arq Bras Cardiol*. 2016;107:4–9. doi: 10.5935/abc.20160082
48. Tabbalat RA, Alhaddad I, Hammoudeh A, Khader YS, Khalaf HA, Obaidat M, Barakat J. Effect of Low-dose Colchicine on the Incidence of Atrial Fibrillation in Open Heart Surgery Patients: END-AF Low Dose Trial. *J Int Med Res*. 2020;48:300060520939832. doi: 10.1177/0300060520939832
49. Deftereos S, Giannopoulos G, Kossyvakis C, Efremidis M, Panagopoulou V, Kaoukis A, Raisakis K, Bouras G, Angelidis C, Theodorakis A, et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. *J Am Coll Cardiol*. 2012;60:1790–1796. doi: 10.1016/j.jacc.2012.07.031
50. Deftereos S, Giannopoulos G, Efremidis M, Kossyvakis C, Katsivas A, Panagopoulou V, Papadimitriou C, Karageorgiou S, Doudoumis K, Raisakis K, et al. Colchicine for prevention of atrial fibrillation recurrence after pulmonary vein isolation: mid-term efficacy and effect on quality of life. *Heart Rhythm*. 2014;11:620–628. doi: 10.1016/j.hrthm.2014.02.002
51. Lee JZ, Singh N, Howe CL, Low SW, Huang JJ, Ortega G, Lee KS, Pandit A. Colchicine for prevention of post-operative atrial fibrillation: a meta-analysis. *JACC Clin Electrophysiol*. 2016;2:78–85. doi: 10.1016/j.jacep.2015.09.016

52. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellnor PT, Ezekowitz MD, Field ME, et al; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199–e267. doi: 10.1161/CIR.0000000000000041
53. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, et al; ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210
54. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, et al. 2017 HRS/EHRA/ECAS/APHSR/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Europace*. 2018;20:157–208. doi: 10.1093/europace/eux275
55. Naruko T, Ueda M, Haze K, van der Wal AC, van der Loos CM, Itoh A, Komatsu R, Ikura Y, Ogami M, Shimada Y, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. *Circulation*. 2002;106:2894–2900. doi: 10.1161/01.cir.0000042674.89762.20
56. Shu J, Ren N, Du JB, Zhang M, Cong HL, Huang TG. Increased levels of interleukin-6 and matrix metalloproteinase-9 are of cardiac origin in acute coronary syndrome. *Scand Cardiovasc J*. 2007;41:149–154. doi: 10.1080/14017430601164263
57. Petersen LC, Bjørn SE, Nordfang O. Effect of leukocyte proteinases on tissue factor pathway inhibitor. *Thromb Haemost*. 1992;67:537–541. doi: 10.1182/blood.V79.7.1712.bloodjournal7971712
58. Higazi M, Abdeen S, Abu-Fanne R, Heyman SN, Masarwy A, Bdeir K, Maraga E, Cines DB, Higazi AA. Opposing effects of HNP1 (α -defensin-1) on plasma cholesterol and atherogenesis. *PLoS One*. 2020;15:e0231582. doi: 10.1371/journal.pone.0231582
59. Abu-Fanne R, Stepanova V, Litvinov RI, Abdeen S, Bdeir K, Higazi M, Maraga E, Nagaswami C, Mukhitov AR, Weisel JW, et al. Neutrophil α -defensins promote thrombosis in vivo by altering fibrin formation, structure, and stability. *Blood*. 2019;133:481–493. doi: 10.1182/blood-2018-07-861237
60. Quillard T, Araújo HA, Franck G, Shvartz E, Sukhova G, Libby P, TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion. *Eur Heart J*. 2015;36:1394–1404. doi: 10.1093/eurheartj/ehv044
61. Furman MI, Barnard MR, Krueger LA, Fox ML, Shilale EA, Lessard DM, Marchese P, Frelinger AL III, Goldberg RJ, Michelson AD. Circulating monocyte-platelet aggregates are an early marker of acute myocardial infarction. *J Am Coll Cardiol*. 2001;38:1002–1006. doi: 10.1016/s0735-1097(01)01485-1
62. Shah B, Allen N, Harchandani B, Pillinger M, Katz S, Sedlis SP, Echagarruga C, Samuels SK, Morina P, Singh P, et al. Effect of colchicine on platelet-platelet and platelet-leukocyte interactions: a pilot study in healthy subjects. *Inflammation*. 2016;39:182–189. doi: 10.1007/s10753-015-0237-7
63. 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;99:805–807. doi: 10.1016/j.amjcard.2006.10.039
64. Vaidya K, Arnott C, Martínez GJ, Ng B, McCormack S, Sullivan DR, Celermajer DS, Patel S. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: a CT coronary angiography study. *JACC Cardiovasc Imaging*. 2018;11(2 pt 2):305–316. doi: 10.1016/j.jcmg.2017.08.013
65. Toprover M, Shah B, Oh C, Igel TF, Romero AG, Pike VC, Curovic F, Bang D, Lazaro D, Krasnokutsky S, et al. Initiating guideline-concordant gout treatment improves arterial endothelial function and reduces intercritical inflammation: a prospective observational study. *Arthritis Res Ther*. 2020;22:169. doi: 10.1186/s13075-020-02260-6
66. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914
67. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ; CANTOS Trial Group. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet*. 2018;391:319–328. doi: 10.1016/S0140-6736(17)32814-3
68. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, et al; CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med*. 2019;380:752–762. doi: 10.1056/NEJMoa1809798
69. Langevit P, Livneh A, Neumann L, Buskila D, Shemer J, Amolsky D, Pras M. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. *Isr Med Assoc J*. 2001;3:9–12.
70. Shah B, Toprover M, Crittenden DB, Jeurling S, Pike VC, Krasnokutsky S, Xia Y, Fisher MC, Slobodnick A, Tenner CT, et al. Colchicine use and incident coronary artery disease in male patients with gout. *Can J Cardiol*. 2020;36:1722–1728. doi: 10.1016/j.cjca.2020.05.026
71. Crittenden DB, Lehmann RA, Schneck L, Keenan RT, Shah B, Greenberg JD, Cronstein BN, Sedlis SP, Pillinger MH. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. *J Rheumatol*. 2012;39:1458–1464. doi: 10.3899/jrheum.111533
72. Solomon DH, Liu CC, Kuo IH, Zak A, Kim SC. Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. *Ann Rheum Dis*. 2016;75:1674–1679. doi: 10.1136/annrheumdis-2015-207984
73. 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. doi: 10.1016/j.jacc.2012.10.027
74. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, et al; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020;383:1838–1847. doi: 10.1056/NEJMoa2021372
75. Tong DC, Quinn S, Nasir A, Hiew C, Roberts-Thomson P, Adams H, Sriamereswaran R, Htun NM, Wilson W, Stub D, et al. Colchicine in patients with acute coronary syndrome: the Australian COPS Randomized Clinical Trial. *Circulation*. 2020;142:1890–1900. doi: 10.1161/CIRCULATIONAHA.120.050771
76. Mewton N, Roubille F, Bresson D, Prieur C, Bouleti C, Bochaton T, Ianes F, Dubreuil O, Biere L, Hayek A, et al. Effect of colchicine on myocardial injury in acute myocardial infarction. *Circulation*. 2021;144:859–869. doi: 10.1161/CIRCULATIONAHA.121.056177
77. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381:2497–2505. doi: 10.1056/NEJMoa1912388
78. Opstal TSJ, Fiolet ATL, van Broekhoven A, Mosterd A, Eikelboom JW, Nidorf SM, Thompson PL, Duyvendak M, van Eck JWM, van Beek EA, et al; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease in relation to prior acute coronary syndrome. *J Am Coll Cardiol*. 2021;78:859–866. doi: 10.1016/j.jacc.2021.06.037
79. Mastrocola R, Penna C, Tullio F, Femminò S, Nigro D, Chiazza F, Serpe L, Colotta D, Alloati G, Cocco M, et al. Pharmacological inhibition of NLRP3 inflammasome attenuates myocardial ischemia/reperfusion injury by activation of RISK and mitochondrial pathways. *Oxid Med Cell Longev*. 2016;2016:5271251. doi: 10.1155/2016/5271251
80. Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, Sianos G, Goudevenos J, Alexopoulos D, Pyrgakis V, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. *Circulation*. 2015;132:1395–1403. doi: 10.1161/CIRCULATIONAHA.115.017611
81. Hennessy T, Soh L, Bowman M, Kurup R, Schultz C, Patel S, Hillis GS. 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;215:62–69. doi: 10.1016/j.ahj.2019.06.003
82. Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, Ridker PM. Targeting cardiovascular inflammation: next steps in clinical translation. *Eur Heart J*. 2021;42:113–131. doi: 10.1093/eurheartj/ehaa099
83. Samuel M, Tardif JC, Bouabdallaoui N, Khairy P, Dubé MP, Blondeau L, Guertin MC. Colchicine for secondary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. *Can J Cardiol*. 2021;37:776–785. doi: 10.1016/j.cjca.2020.10.006
84. Fiolet ATL, Opstal TSJ, Mosterd A, Eikelboom JW, Jolly SS, Keech AC, Kelly P, Tong DC, Layland J, Nidorf SM, 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;42:2765–2775. doi: 10.1093/eurheartj/ehab115
85. Deftereos S, Giannopoulos G, Raisakis K, Kossyvakis C, Kaoukis A, Panagopoulou V, Driva M, Hahalis G, Pyrgakis V, Alexopoulos D, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. *J Am Coll Cardiol*. 2013;61:1679–1685. doi: 10.1016/j.jacc.2013.01.055

86. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Böck M, Benetos A, Biffi A, Boavida JM, Capodanno D, et al; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227–3337. doi: 10.1093/eurheartj/ehab484
87. Health Canada Approval of Low-Dose Colchicine for Cardiovascular Disease Based on the COLCOT Study. Institute de Cardiologie de Montreal. August 27, 2021. <https://www.icm-mhi.org/en/pressroom/news/health-canada-approval-low-dose-colchicine-cardiovascular-disease-based-colcot-study>. Accessed October 19, 2021.
88. Almagor M, Keren A, Banai S. Increased C-reactive protein level after coronary stent implantation in patients with stable coronary artery disease. *Am Heart J*. 2003;145:248–253. doi: 10.1067/mhj.2003.16
89. O'Keefe JH Jr, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol*. 1992;19:1597–1600. doi: 10.1016/0735-1097(92)90624-v
90. Freed M, Safian RD, O'Neill WW, Safian M, Jones D, Grines CL. Combination of lovastatin, enalapril, and colchicine does not prevent restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol*. 1995;76:1185–1188. doi: 10.1016/s0002-9149(99)80334-8
91. Shah B, Pillinger M, Zhong H, Cronstein B, Xia Y, Lorin JD, Smilowitz NR, Feit F, Ratnapala N, Keller NM, et al. Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI randomized trial. *Circ Cardiovasc Interv*. 2020;13:e008717. doi: 10.1161/CIRCINTERVENTIONS.119.008717
92. Cole J, Htun N, Lew R, Freilich M, Quinn S, Layland J. Colchicine to prevent periprocedural myocardial injury in percutaneous coronary intervention: the COPE-PCI pilot trial. *Circ Cardiovasc Interv*. 2021;14:e009992. doi: 10.1161/CIRCINTERVENTIONS.120.009992
93. Herrmann J, Lennon RJ, Barsness GW, Sandhu GS, Gulati R, Best PJ, Sorajja P, Bresnahan JF, Mathew V, Bell MR, et al. High sensitivity C-reactive protein and outcomes following percutaneous coronary intervention in contemporary practice. *Circ Cardiovasc Interv*. 2012;5:783–790. doi: 10.1161/CIRCINTERVENTIONS.112.972182
94. Shah B, Baber U, Pocock SJ, Krucoff MW, Ariti C, Gibson CM, Steg PG, Weisz G, Witzentrichler B, Henry TD, et al. White blood cell count and major adverse cardiovascular events after percutaneous coronary intervention in the contemporary era: insights from the PARIS Study (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients Registry). *Circ Cardiovasc Interv*. 2017;10:e004981. doi: 10.1161/CIRCINTERVENTIONS.117.004981
95. Di Sciascio G, Patti G, Pasceri V, Gasparone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) randomized trial. *J Am Coll Cardiol*. 2009;54:558–565. doi: 10.1016/j.jacc.2009.05.028
96. Amarencio P, Lavallée PC, Labreuche J, Albers GW, Bornstein NM, Canhão P, Caplan LR, Donnan GA, Ferro JM, Hennerici MG, et al; TIARegistry.org Investigators. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med*. 2016;374:1533–1542. doi: 10.1056/NEJMoa1412981
97. Tarkin JM, Joshi FR, Rudd JH. PET imaging of inflammation in atherosclerosis. *Nat Rev Cardiol*. 2014;11:443–457. doi: 10.1038/nrcardio.2014.80
98. Opstal Tjerk SJ, Hoogeveen Renate M, Fiolet Aernoud TL, Silvis Max JM, The Salem HK, Bax Willem A, de Kleijn Dominique PV, Mosterd A, Stroes Erik SG, Cornel Jan H. Colchicine attenuates inflammation beyond the inflammasome in chronic coronary artery disease. *Circulation*. 2020;142:1996–1998. doi: 10.1161/CIRCULATIONAHA.120.050560
99. Dubé MP, Legault MA, Lemaçon A, Lemieux Perreault LP, Fouodjio R, Waters DD, Kouz S, Pinto FJ, Maggioni AP, Diaz R, et al. Pharmacogenomics of the efficacy and safety of colchicine in COLCOT. *Circ Genom Precis Med*. 2021;14:e003183. doi: 10.1161/CIRCGEN.120.003183
100. Samuel M, Tardif JC, Khairy P, Roubille F, Waters DD, Grégoire JC, Pinto FJ, Maggioni AP, Diaz R, Berry C, 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;7:486–495. doi: 10.1093/ehjqcc/qcaa045