Colchicine and the Heart

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Colchicine, a natural and ancient drug still used today, is traditionally considered the staple therapy for gout and a second-line treatment for pericarditis, as well as a basic part of familial Mediterranean fever and Behcet’s disease management. It is commonly classified as an anti-inflammatory agent, although its mechanism of action does not involve the arachidonic acid pathway affected by non-steroid anti-inflammatory drugs and glucocorticoids. Colchicine inhibits microtubule polymerization by binding to tubulin, thus affecting any process that requires cytoskeletal changes, including cell mitosis and neutrophil motility. Recent studies suggest that colchicine may prove to be useful in a much wider spectrum of cardiovascular diseases than previously suspected, rekindling the interest in this old drug. In this review we briefly present the biochemical characteristics, mechanism of action and side-effects of colchicine, as well as examine what is currently known about the promising role of colchicine in cardiovascular medicine beyond pericardial disease. (J Am Coll Cardiol 2013;62:1817–25) © 2013 by the American College of Cardiology Foundation

Colchicine, the extract from the Colchicum autumnale plant (autumn crocus), used by ancient Greeks more than 2,000 years ago (1), is one of the oldest known drugs still prescribed today. In 1820, the French chemists P. S. Pelletier and J. B. Caventou were the first to extract colchicine as the active alkaloid of colchicum (2). While colchicine in combination with probenecid has been approved by the U.S. Food and Drug Administration (FDA) prior to 1982, until recently colchicine was widely used for the treatment of gout without official FDA evaluation. On July 30, 2009, the FDA approved colchicine for the treatment of familial Mediterranean fever and acute gout and for prophylaxis against gouty arthritis (3). Colchicine is also used today as a second-line treatment for pericarditis (4).

Colchicine is widely used in in vitro experiments requiring cytoskeleton disruption. Since colchicine was “officially” endorsed by the FDA, several human studies have emerged examining the possible potential of this low-cost drug for other clinical indications. In this review we refer to studies claiming a wider role for colchicine in cardiovascular disease, beyond traditional indications in pericarditic syndromes, as well as examine whether our current knowledge about colchicine mechanisms of action can offer insights relevant to clinical findings. It is true that data from really large, randomized trials of colchicine for potential novel indications in cardiovascular disease with hard clinical endpoints are lacking. As a result, a true systematic review or a meta-analysis (with the statistical processing that these terms imply) is implausible at the moment. This does not mean, however, that the existing evidence is negligible. It is clear from Table 1 that a number of well-planned and well-conducted studies have been published. For these reasons, the scope of the present review encompasses 2 main goals: 1) presenting an exhaustive account of clinical studies indicating potential new uses of colchicine in heart disease; and 2) stimulating interest among cardiovascular specialists for this old and, possibly, underutilized medicine.

Pharmacokinetics

Colchicine is a lipid-soluble drug with a \( [\text{pKa}] = 12.8 \) that can penetrate easily into body tissues after uptake in the jejunum and ileum (5). After oral ingestion it has a 44% bioavailability and binds relatively weakly to albumin (32% bound) (6). Its peak plasma concentration occurs in about 1 h, with a long terminal half-life (5). Colchicine enters red blood cells and leucocytes where it remains in much higher concentrations than the plasma (6). Colchicine can be found inside leukocytes for up to several days after administration (7), with this local pooling and long half-life explaining why a once- or twice-daily dosage scheme is
inhibits the formation of microtubules while at higher concentrations, neutrophil L-selectin family-dependent adhesiveness, affecting both endothelial E-selectin and, at higher concentrations, neutrophil L-selectin. Colchicine diminishes endothelial selectin expression (12). It has also been found to increase leukocyte cyclic adenosine monophosphate levels, inhibit interleukin-1 (IL-1) production by activated neutrophils and down-regulate tumor necrosis factor alpha receptors in macrophages and endothelial cells (8).

Recently, colchicine was associated with another anti-inflammatory mechanism in gout. Colchicine appears to block the crystal-induced activation of the NLRP3 inflammasome protein complex, which proteolytically cleaves caspase-1 and leads to secretion of proinflammatory cytokines IL-1β and IL-18 (13). Other studies have shown the close interaction of microtubules and NLRP3 inflammasome activation (14). Inflammasomes have recently been associated with atherosclerotic disease (15) and cardiac ischemia/reperfusion injury (16). However, any direct effects of colchicine on inflammasome activation in the heart or vessels have not been studied.

Depending on concentration, colchicine could have other effects as well. A study by Ben-Chetrit et al. (17) showed that colchicine has the potential to induce changes at the transcriptional level (affecting cell-cycle-regulatory genes) in human umbilical vein endothelial cell line cells. However, the concentration used was almost 100-fold the average plasma concentration in patients under colchicine treatment, therefore it is not clear if these results have any clinical meaning. In another recent in vitro study, colchicine prevented the contractile and mitochondriald dysfunction caused by the macrophage migration inhibitory factor in human atrial cells (18).

Colchicine and Pericarditis

Until relatively recently, colchicine use in treating idiopathic pericarditis was empiric, based on small-scale studies and anecdotal reports (19). In 2004, the European Society of Cardiology guidelines on the diagnosis and management of pericardial diseases endorsed colchicine as an acceptable second-line treatment in acute and recurrent pericarditis (20). In the subsequent COPE (Colchicine in Acute Pericarditis) and CORE (Colchicine for Recurrent Pericarditis) and the more recent and almost synonymous CORP trials, colchicine as an adjunct therapy to NSAIDs was found to be an effective addition to treatment in this clinical setting (21–23). In the COPE trial the addition of colchicine to aspirin therapy in 120 patients with a first episode of acute pericarditis was associated with a faster symptomatic relief (36.7% of patients in the aspirin group vs. 11.7% in the aspirin plus colchicine group after 72 h) as well as with significantly less recurrent pericarditis episodes over the subsequent 18 months (10.7% vs. 32.3% in the aspirin group). The benefits of colchicine addition in prevention and treatment of recurrent pericarditis were also verified in the CORE and CORP trials. Today, when treating pericardial inflammation, colchicine is preferred over corticosteroids for coadministration with NSAIDs (24). For a thorough study of the use of colchicine in pericarditis, excellent reviews have been published (25).
<table>
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<th>First Author (Ref. #)</th>
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<td>Imazio et al. (29)</td>
<td>Secondary analysis of a multicenter, double-blind, randomized trial</td>
<td>Post-cardiothoracic surgery atrial fibrillation</td>
<td>Reduction of post-operative atrial fibrillation incidence (12.0% vs. 22.0%; p = 0.021; relative risk reduction: 45%) with shorter in-hospital stay (9.4 ± 3.7 days vs. 10.3 ± 4.3 days; p = 0.040) and rehabilitation (12.1 ± 6.1 days vs. 13.9 ± 6.5 days; p = 0.009).</td>
<td>336</td>
<td>Loading dose 1.0 mg twice on the first day, followed by 0.5 mg twice daily for 1 month</td>
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<td>Prevention of early atrial fibrillation recurrences after pulmonary vein isolation (16% vs. 33.5% placebo; odds ratio: 0.38; 95% confidence interval: 0.18 to 0.80) in the absence of antiarrhythmic drug treatment.</td>
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<td>64</td>
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<td>Nidorf et al. (57)</td>
<td>PROBE (Prospective, Randomized, Observer-Blinded Endpoint) trial</td>
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<td>Colchicine in addition to statins and other standard secondary prevention therapies was associated with reduced rate of the composite of acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke (hazard ratio: 0.33; 95% confidence interval: 0.18 to 0.80).</td>
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<td>Crittenden et al. (58)</td>
<td>Retrospective, cross-sectional study</td>
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<td>Gout patients who took colchicine had a significantly lower prevalence of myocardial infarction (1.2% in the colchicine vs. 2.6% in the no-colchicine group; p = 0.03) and exhibited trends toward reduced all-cause mortality and lower CRP levels.</td>
<td>1,288</td>
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<td>Raju et al. (59)</td>
<td>Single-center double-blind pilot randomized controlled trial</td>
<td>Acute coronary syndrome or stroke</td>
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<td>80</td>
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<td>O’Keefe et al. (72)</td>
<td>Double-blind, prospective, randomized trial</td>
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<td>Freed et al. (73)</td>
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<td>The combined administration of lovastatin, enalapril, and colchicine does not appear to inhibit restenosis after PTCA.</td>
<td>50</td>
<td>0.6 mg twice daily for at least 4 months</td>
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<tr>
<td>Deftereos et al. (76)</td>
<td>Double-blind, prospective, randomized trial</td>
<td>Percutaneous coronary intervention with bare-metal stent implantation</td>
<td>Colchicine is associated with less neointimal hyperplasia and reduced in-stent restenosis rate when administered to diabetic patients after PCI with BMS (16% vs. 33% in controls (p = 0.007; odds ratio: 0.38; 95% confidence interval: 0.18 to 0.79)</td>
<td>196</td>
<td>0.5 mg twice daily for 6 months</td>
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BMS — bare-metal stent(s); hs-CRP — high-sensitivity C-reactive protein; PCI — percutaneous coronary intervention; PTCA — percutaneous transluminal coronary angioplasty.
Colchicine and Atrial Fibrillation

Post-operative atrial fibrillation. Atrial fibrillation (AF) after cardiac surgery (post-operative atrial fibrillation [POAF]), occurring in 10% to 65% of all cardiac surgery patients (26), is a significant problem, in view of the associated increased morbidity and mortality and lengthening of hospital stays (27). Besides the obvious atrial trauma, other factors have also been implicated in its pathogenesis, including surgery-related pericardial inflammatory processes, autonomic disturbance, and changes in plasma volume regulation (28).

Colchicine came to the forefront in a pivotal substudy of the COPPS (Colchicine for the Prevention of the Post-pericardiotomy Syndrome) trial by Imazio et al. (29), a multicenter, double-blind, randomized trial. The administration of colchicine from post-operative day 3 and for up to 1 month was associated with a 45% reduction in the incidence of POAF, followed not unexpectedly by reduced in-hospital and rehabilitation stay, while halving the mean duration of POAF episodes. There has been some controversy (30) as to whether post-operative day 3 is the optimum time for treatment initiation. The COPPS main study was designed to test colchicine efficacy in preventing post-pericardiotomy syndrome and not POAF. The incidence of POAF is high on the first few post-operative days and this was reflected in the fact that 43% of the POAF episodes documented in the COPPS substudy occurred before the onset of colchicine treatment. It is reasonable to assume that an earlier (maybe even pre-operative) initiation of treatment would be even more effective, but this remains unproven. In any case, more answers are expected from the COPPS-2 trial (a multicenter study planning to include 360 cardiac surgery patients), which will have POAF as a primary endpoint.

- Figure 1: Microtubule Structure
- Figure 2: Colchicine Binding Site
- Figure 3: Colchicine Mechanism of Action
Another plausible hypothesis is that colchicine exerted its prophylactic action, at least in part, thanks to its anti-inflammatory properties. Although the COPPS substudy did not correlate POAF reduction with the fall of inflammatory markers, atrial or possibly pericardial inflammation seems to have a causative relationship with POAF. The peak incidence of POAF has been correlated with the peak concentration rise of C-reactive protein (CRP) in cardiac surgery patients (31) and elevated white blood cell counts (32). However, the strongest evidence in favor of this proposition comes from the fact that glucocorticoids significantly reduced POAF incidence in animal models (33,34) and clinical studies (35).

**Colchicine for AF recurrence after ablation therapy.** The positive results of the COPPS substudy were followed by an investigation by our group into the possible role of colchicine administration in another population at risk for AF, namely patients who have undergone pulmonary vein isolation as part of AF ablation therapy (36). In this prospective randomized double-blind study, the administration of colchicine monotherapy for 3 months was associated with preventing AF recurrences after pulmonary vein isolation within that timeframe (16% colchicine vs. 33.5% for the placebo group). Kaplan-Meier curves of the cumulative hazard of AF recurrence are illustrated in Figure 4. This effect was accompanied by a significant decrease in inflammatory mediators, IL-6 and CRP. This study was prompted by the strong link between inflammation and early post-ablation AF recurrence (37), with persistently elevated CRP for up to 3 months after AF ablation (38), and followed another study, by Koyama et al. (39). In that study, patients undergoing pulmonary vein isolation received hydrocortisone (2 mg/kg) on the day of the procedure and prednisolone (0.5 mg/kg/day) per os for the following 3 days. The prevalence of immediate post-ablation AF (<3 days after ablation) was significantly lower in the corticosteroid (7%) than in the placebo group (31%). The prevalence however of early post-ablation AF (4 to 30 days after ablation), when patients were not receiving corticosteroids, was the same between the 2 groups.

In retrospect, it could be expected that patients undergoing AF ablation therapy would benefit from inflammation suppression, similarly to post–cardiac surgery patients, although early post-ablation AF occurrence does not necessarily have the same causes as POAF. AF ablation is a minimally invasive procedure where there is local inflammation, but no excessive catecholamine production, fluid shift or major surgery trauma. So, the key mechanism is probably inflammation, either alone or together with the remodeling of ablated areas. Inflammation has been shown to be a cause for AF (40,41), leading to adverse atrial remodeling and making the atria substrate vulnerable to AF. However, each episode of AF may become responsible for more adverse structural and electrical remodeling, creating a vicious circle (42,43). In the 5A (Antiarrhythmics After Ablation of Atrial Fibrillation) study, the only predictor of a 6-month free AF period was the absence of early (<6 weeks) post-ablation AF recurrence (44). Therefore, although our group administered colchicine for 3 months post-ablation (36), positive results may persist for a longer period of time. This expectation, however, will have to be validated with follow-up studies (our group has unpublished data indicating that the benefit of colchicine in terms of lower AF recurrence rate extends well beyond 1 year after a single ablation procedure in the absence of antiarrhythmic treatment).

While inflammation seems to be causatively linked to early post-ablation AF, and colchicine administration is a promising prevention strategy, the optimum duration and dose of treatment have not been defined. A shorter colchicine treatment period has not been tested but, if effective, would certainly have advantages over a 90-day treatment, especially since a considerable proportion of patients (12.3%) in our study (36) discontinued colchicine, mainly due to gastrointestinal complaints.

The anti-inflammatory properties of colchicine do not preclude other mechanisms playing a role in the reduction of POAF or post-ablation AF, besides inflammation suppression. In several in vitro or animal studies, colchicine administration has been shown to exert electrophysiological effects related to cytoskeletal disruption. In rat atrial fibroblasts, colchicine completely blocked both hole-cell and single-channel currents of mechano-gated channels, activated by cell mechanical deformations (45). Mechanically induced potentials in rat atrial fibroblasts have also been shown by the same researchers to depend on actin and tubulin polymerization (46). In another study, the modulation of L-type I (Ca) current by muscarinic and beta-adrenergic agonists required an intact microtubule network (47) and was affected in a colchicine environment.
Abnormal Ca(2+) handling plays an important role in the induction and maintenance of AF (48).

**Colchicine in Coronary Artery Disease**

Traditionally, acute coronary syndromes (ACS) were considered the clinical manifestation of an intra-coronary thrombotic event, usually resulting from erosion or rupture of an unstable atherosclerotic plaque that caused platelet aggregation and partial or total vessel occlusion. Over the past years, however, this has proven an incomplete depiction, with more attention being given to the role of inflammation (49,50), both during plaque formation (51) and after plaque rupture (52). One of the realizations of this notion has been the addition of high-dose statin therapy to standard ACS treatment, believed to be beneficial not only thanks to its lipid-lowering effects but also due to its anti-inflammatory properties (53,54). While research for better antiplatelet drugs has been extensive, with new drugs such as ticagrelor and prasugrel being approved for use in ACS, anti-inflammatory treatment research has not progressed, especially as corticosteroids and NSAIDS have proved to be harmful in the setting of ACS (55). Colchicine with its unique anti-inflammatory mechanism and potential for long-term use could theoretically be a candidate to fill this gap, especially after it was found that colchicine treatment was accompanied by a reduction in high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease (CAD) (56).

A large prospective, randomized, observer-blinded endpoint trial by Nidorf et al. (57) (LoDoCo [Low Dose Colchicine] study) examined the efficacy of continuous low-dose colchicine treatment in patients with stable CAD. The administration of 0.5 mg colchicine per day in addition to standard CAD therapy proved effective in reducing the composite of ACS, out-of-hospital cardiac arrest or non-cardioembolic ischemic stroke (5.3% vs. 16%, p < 0.001; number needed to treat: 11). The difference was predominantly driven by a marked decrease in ACS in a median follow-up of 3 years. When excluding patients who did not tolerate or refused to take the drug, results were even more in favor of colchicine (4.5% vs. 16%).

In another recent study by Crittenden et al. (58), patients under treatment with colchicine for gout prophylaxis had a lower risk for myocardial infarction in comparison to gout patients who were not treated with colchicine. Although results were close to borderline in terms of statistical significance in favor of colchicine (myocardial infarction 1.2% in the colchicine vs. 2.6% in the no-colchicine group, p = 0.03), this is to be expected as this retrospective study spanned 1 year only and was not limited to patients with known CAD, who would potentially draw the most benefit.

Only 1 relatively small study examined the effects of colchicine in the setting of ACS (59). In this pilot study, 80 patients were followed-up for 30 days after an ACS or acute ischemic stroke episode. The study examined whether patients on colchicine showed any decrease in high-sensitivity CRP and platelet aggregation compared with patients on placebo. No difference was shown, even though the colchicine dose was moderate (1 mg/day). There were no deaths during follow-up. Potential explanations for these results are that inflammation suppression by colchicine may be less pronounced in the setting of an ACS, inflammation may play a relatively minor role after plaque rupture in contrast to plaque formation and destabilization, or that colchicine was unnecessary for inflammation suppression in patients taking high doses of statins as part of ACS treatment. The authors, however, did not specify how many hours after ACS diagnosis colchicine was administered or what treatment ACS patients were subjected to (percutaneous coronary intervention [PCI] or thrombolysis). Patient numbers were also inadequate to detect evidence of clinical benefit or harm, therefore leaving the role of colchicine in ACS undecided.

The effects of colchicine on stable CAD may not be completely attributable to inflammation suppression. Patients with familial Mediterranean fever who were treated with colchicine showed a reduction in biomarkers related with vascular injury independently of decreased inflammatory activity, as assessed by high-sensitivity CRP (60). In in vitro experiments, colchicine has also been shown to reduce thrombin-induced platelet aggregation in a concentration-dependent manner (61,62). Mean platelet volume (MPV), a marker of platelet activity and predictor of cardiovascular risk (63–65), was reduced in patients taking colchicine (66) and was negatively correlated with the duration of colchicine treatment (67) in patients with familial Mediterranean fever. The same results were seen in pediatric patients (68,69). It is not clear, however, if colchicine effects on MPV are direct or the result of inflammation suppression or even if there is any clinical significance in these findings. The only study that directly assessed platelet aggregation 30 days after an ACS in patients taking colchicine showed no difference from the placebo group (59). These patients though were already under dual antiplatelet therapy, so these results cannot be safely extrapolated in a population with stable CAD under aspirin only, who were shown to benefit from colchicine administration for primary prevention of ACS (57).

**Colchicine and angioplasty.** Coronary artery restenosis after PCI remains a serious problem. Neointimal hyperplasia and local inflammation are key components of the restenosis process (70). Colchicine, with its antimitotic and anti-inflammatory properties (11), is theoretically attractive as an agent that could prevent restenosis. Although a relatively recent study in a dog model had encouraging results (71), experiments in the pre-stent era were disappointing. Two clinical studies evaluating colchicine failed to show benefit. O’Keefe et al. (72) studied patients who underwent plain balloon angioplasty and found restenosis in 45% of patients in the placebo-treated group compared with 41% in the colchicine-treated group (nonsignificant difference), and similar results were reported by Freed et al. (73).
The advent of bare-metal and especially drug-eluting stents marked a new era for angioplasty, with substantially lower rates of restenosis (74,75). However, even in the modern era there are patient populations that are still plagued by high restenosis rates. Our group set out to study the effect of colchicine in diabetic patients who underwent PCI and could not, for various reasons, have a drug-eluting stent implanted, and received a bare-metal stent instead (76). In-stent restenosis rate was shown to be less than one-half in the colchicine group (16% vs. 33%) compared with placebo at 6 months after PCI, with a similar benefit in terms of lumen area loss, as determined by intravascular ultrasound. The authors suggested that the discrepancy with previous studies was due to the difference in mechanisms of vessel restenosis after plain old balloon angioplasty and in-stent restenosis. In balloon-only angioplasty, neointimal hyperplasia is only partly responsible for restenosis, while artery elastic recoil and remodeling play a substantial role in the restenotic process. Colchicine cannot be expected to have any effect on recoil or remodeling. In contrast, in-stent restenosis is almost exclusively due to neointima formation (77–79). Although results were favorable for colchicine in this study, no clinical outcomes were measured. It is therefore too early to suggest a role for colchicine in post-PCI treatment.

**Pre-clinical hints for other potential uses.** Although this review focused on clinical studies, there are several in vitro and animal experiments where colchicine was shown to have important effects on myocardial cells in different settings, not related to inflammation but rather to microtubule disruption. Colchicine attenuates pressure-overload heart failure in dogs (80) and rats (81,82). These results are relevant with the fact that microtubules seem to play a pivotal role in cardiac hypertrophy progression (83,84). On the cellular level, colchicine reduced myocardial cell stiffness in normal rat cardiomyocytes (85) and a hamster model of congestive heart failure (86). Colchicine also increased Ca++ currents in rat cardiac cells (87,88). All these results point toward novel possible areas of clinical studies for colchicine, namely arrhythmias, heart failure, and cardiac hypertrophy.

**Conclusions**

Over the past few years, colchicine has gained momentum in cardiovascular medicine, being tested in a variety of clinical settings. In addition to known “traditional” indications, namely pericarditis, novel potential settings where colchicine could be beneficial, including AF and CAD, are actively researched. Colchicine is a unique drug: No other medication with potent anti-inflammatory action has been shown to be suitable for safe, long-term use (up to 3 years in the LoDoCo study) in patients with cardiovascular disease. However, considering the complex cross-talk between the multifarious inflammatory mediators, one could argue that therapies with targeted immunomodulatory effects would be more attractive (from a pathophysiologic perspective) than agents with broad biological actions. This is something that remains to be investigated. In any case, the results of recent studies with colchicine are encouraging and suggest that it may just be worth the effort exploring the full potential of this ancient drug.

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