Colchicine for acute and chronic coronary syndromes

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ABSTRACT
Colchicine is an ancient drug, traditionally used for the treatment and prevention of gouty attacks; it has become standard of treatment for pericarditis with a potential role in the treatment of coronary artery disease. Atherosclerotic plaque formation, progression, destabilisation and rupture are influenced by active proinflammatory cytokines interleukin (IL)-1β and IL-18 that are generated in the active forms by inflammasomes, which are cytosolic multiprotein oligomers of the innate immune system responsible for the activation of inflammatory responses. Colchicine has a unique anti-inflammatory mechanism: it is not only able to concentrate in leucocytes, especially neutrophils, and block tubulin polymerisation, affecting the microtubules assembly, but also inhibits (NOD)-like receptor protein 3 (NLRP3) inflammasome. On this basis, colchicine interferes with several functions of leucocytes and the assembly and activation of the inflammasome as well, reducing the production of interleukin 1β and interleukin 18. Long-term use of colchicine has been associated with a reduced rate of cardiovascular events both in chronic and acute coronary syndromes, with an overall good safety profile. This review will focus on the influence of colchicine on the pathophysiology of coronary artery disease, reviewing essential pharmacology and discussing the most important and recent clinical studies. On the basis of current literature, colchicine is emerging as a possible new valuable, safe and cheap agent for the treatment of acute and chronic coronary syndromes.

INTRODUCTION
Obstructive coronary artery disease (CAD) is a leading cause of death worldwide, despite improvements of optimal medical therapy (OMT) over years. Current medical therapies are mainly targeted to lowering of serum cholesterol, inhibition of platelet aggregation and control of risk factors. Indeed, growing evidence shows that inflammation plays a key role in the pathogenesis and clinical manifestations of atherosclerosis. The incessant research of newer therapeutic tools, aimed at the improvement of outcomes in patients with CAD, has recently shown a promising role of colchicine, a drug with anti-inflammatory properties. 1-4

Colchicine is a lipophilic tricyclic alkaloid extracted from the Colchicum autumnale plant (figure 1). It is an ancient drug, mentioned as an herbal remedy for osteoarticular pain in the Ebers Papyrus, a manuscript dating back to 1500 BC. Despite well known for centuries and used for decades as anti-inflammatory agent for the treatment of gouty attacks, later Familial Mediterranean Fever, and more recently pericarditis, 5 colchicine is currently revealing emerging applications in a multitude of diseases, especially in the cardiovascular field. 1-4

This review will focus on the influence of colchicine on the pathophysiology of CAD, reviewing essential pharmacology and discussing the most important and recent clinical studies. A literature review was performed using the search terms “colchicine”, AND “coronary artery disease” OR “chronic coronary syndromes” OR “acute coronary syndromes”. We included studies published up to April 2020 in MEDLINE/PubMed, Scopus, BioMed Central, the Cochrane Collaboration Database of Randomised Trials, ClinicalTrials.gov, EMBASE, Google Scholar, and restricted to English language. This research was conducted from inception through April 2020. A team of two independent reviewers (MI, AA) screened titles and abstracts of all studies and potentially eligible studies were appraised as full-text. The most relevant articles quoted in the studies as long as guidelines were also screened. Discrepancies were resolved by consensus or with a third reviewer (AB). One additional reviewer (YA) screened citations and references.

Mechanism of action and pharmacokinetics
Colchicine binds to tubulin affecting mitosis and various additional functions of microtubules: leucocyte movements, exocytosis and phagocytosis. While at lower concentrations colchicine prevents microtubule polymerisation, at higher concentrations it promotes microtubule depolymerisation. 5,7 On this basis, colchicine can affect several functions of inflammatory cells (eg, chemotaxis, adhesion and recruitment to damaged tissues), especially neutrophils where colchicine can be concentrated. 8,9 In endothelial cells, colchicine inhibits the expression of selectins, leading to a decreased adherence of leucocytes to the inflamed endothelium, thus inhibiting neutrophil migration and inflammation. 10

More recently, an additional anti-inflammatory action of colchicine has been described by blocking the activity of the NLRP3 inflammasome at least at four levels: (1) inhibition of the expression of the pyrin MEditerranean FeVer (MEFV) gene, preventing the assembly of the NLRP3 inflammasome, (2) inhibition of the cytoplasmatic colocalisation of inflammasomes (3) direct caspase-1 blockage and (4) inhibition of P2×7-mediated pore formation resulting in decreased K + efflux, and lower levels of reactive oxygen species and interleukin 1 beta (IL-1β). 11,12 As a consequence of inflammasome inhibition, colchicine suppresses the
Colchicine metabolism is mainly hepatic and mediated by the CYP3A4 cytochrome, with subsequent excretion by P-glycoprotein through bile. Colchicine may cross the placenta and be excreted in breast milk.8

Colchicine has a narrow therapeutic index, with effective plasmatic concentrations ranging 0.5–3 ng/mL and toxic effects appearing with concentrations exceeding 3 ng/mL. Gastrointestinal symptoms are the most common side effect and have been shown in 8%–10% patients treated with colchicine.12–13 Transaminase elevation has been reported in about 4% of cases and additional adverse effects (<0.1%) include leukopenia and alopecia.14–16

Colchicine is after colchis, an ancient kingdom located on the mysterious periphery of the heroic world. Its name 'colchicine' is after Colchis, an ancient kingdom located on the coast of the Black sea, where these plants were widespread. According to the Greek mythology, Colchis was a fabulously wealthy land situated on the mysterious periphery of the heroic world.

Colchicum autumnale plant and the molecular structure of colchicine derived from Colchicum autumnale. It is the only species of its family native to Great Britain and Ireland, and it is also widespread in mainland Europe from Portugal to Ukraine. Autumn crocus is frequently grown as a house or garden plant. However, in Europe, it grows in meadows, and livestock poisonings have been reported. The bulb-like corms of the plant contain colchicine, an alkaloid, that inhibits polymerisation of microtubules, with a narrow therapeutic index used as early as 1500 BC to treat joint swelling and later gouty attacks. The name 'colchicine' is after Colchis, an ancient kingdom located on the coast of the Black sea, where these plants were widespread. According to the Greek mythology, Colchis was a fabulously wealthy land situated on the mysterious periphery of the heroic world.

Figure 1

Anti-inflammatory therapies for coronary syndromes

The growing interest toward the inflammatory hypothesis of CAD led to the assessment of the newer agents, such as anti-IL-1β targeted drugs, which already proved to be safe and effective in the setting of other cardiovascular diseases, such as pericardial diseases.26 27 The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial involved >10,000 patients with myocardial infarction and elevated level of high-sensitivity C-reactive protein (hs-CRP), treated with canakinumab, a monoclonal antibody targeting IL-1β. Canakinumab reduced hs-CRP, as well as IL-6, independent of low-density lipoprotein cholesterol (LDLc) level.28 Canakinumab reduces both IL-1β and IL-18. Canakinumab reduces IL-6 and IL-18 production via reactive oxygen species.

IL-1β activates IL-6 signalling pathway, leading to the acute-phase response (further increasing neutrophil activation and recruitment, releasing proteins among which C reactive protein (CRP) and serum amyloid A) and the expression of procoagulant factors (fibrinogen and plasminogen activator inhibitor).21 22 An in vivo randomised study on patients with ACS proved that transcoronary gradients (coronary sinus-artrial) of IL-1β, IL-6 and IL-18 were significantly higher compared with controls.23 The same study showed that periprocedural administration of colchicine significantly reduced transcoronary gradients of all cytokines.21 A similar study showed that the transcoronary levels of chemokine ligand 2 and C-C motif chemokine ligand 1 are increased in the context of ACS and a single dose of colchicine is able to reduce both.24 Moreover, a recent in vitro study showed that colchicine reduces platelet aggregation through the modulation of tubulin polymerisation and inhibition of cytoskeleton proteins, such as myosin phosphatase-targeting subunit 1, LIM domain kinase 1 and coflin.25

Neutrophil infiltration and activity is increasingly recognised in inflammatory arthritis.20 The exposure of neutrophils and monocytes to cholesterol crystals triggers the activation of the NLRP3 inflammasome, leading to the secretion of active proinflammatory cytokines IL-1β and IL-18. Both of them have been associated with plaque formation, progression, destabilisation and rupture. The release of IL-1β triggers the activation of the NLRP3 inflammasome, leading to the secretion of active proinflammatory cytokines IL-1β and IL-18. Both of them have been associated with plaque formation, progression, destabilisation and rupture. The release of IL-1β activates IL-6 signalling pathway, leading to the acute-phase response (further increasing neutrophil activation and recruitment, releasing proteins among which C reactive protein (CRP) and serum amyloid A) and the expression of procoagulant factors (fibrinogen and plasminogen activator inhibitor).21 22 An in vivo randomised study on patients with ACS proved that transcoronary gradients (coronary sinus-artrial) of IL-1β, IL-6 and IL-18 were significantly higher compared with controls.23 The same study showed that periprocedural administration of colchicine significantly reduced transcoronary gradients of all cytokines.21 A similar study showed that the transcoronary levels of chemokine ligand 2 and C-C motif chemokine ligand 1 are increased in the context of ACS and a single dose of colchicine is able to reduce both.24 Moreover, a recent in vitro study showed that colchicine reduces platelet aggregation through the modulation of tubulin polymerisation and inhibition of cytoskeleton proteins, such as myosin phosphatase-targeting subunit 1, LIM domain kinase 1 and coflin.25

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and led to 15% lower risk of cardiovascular events, without reducing all-cause mortality. An alternative approach with methotrexate was attempted in a more recent study by the same authors. The Cardiovascular Inflammation Reduction (CIRT) trial was conducted on patients with myocardial infarction, but failed to prove any efficacy in the reduction of cardiovascular events nor in the reduction of IL-1β or hs-CRP/IL-6 and was associated with higher incidence of non-basal-cell skin cancer and elevation in liver enzymes. In the setting of CAD, the use of traditional anti-inflammatory agents such as non-steroidal anti-inflammatory drugs was associated with an increased risk of myocardial infarction, while corticosteroids were found to be ineffective or associated with an increased risk of cardiac rupture.

Also colchicine gained recent attention and was investigated in several clinical studies, because of its interesting anti-inflammatory properties, inexpensiveness, paucity of side effects and robust clinical experience of good tolerance in patients on long-term treatment.

Effects of colchicine on the pathophysiology of coronary syndromes

A remodelling effect on atherosclerotic plaques has been demonstrated in a recent observational study on 80 patients. Compared with controls, patients receiving colchicine for secondary prevention on top of OMT showed a significant reduction in hs-CRP and low-attenuation plaque volume (LAPV), a marker of plaque instability on coronary CT angiography. LDLc reduction was comparable in both groups, supporting the hypothesis of LDLc-independent, anti-inflammatory-driven improvements in plaque morphology due to colchicine. An animal model study on hyperlipidaemic rats demonstrated the synergistic effect of colchicine on top of atorvastatin, in the enhancement of nitric oxide (NO) production and reduction of lipoprotein-associated phospholipase A2. The same study showed that colchicine-induced CRP decrease and NO enhancement were independent of the lipid-lowering effect.

Nidorf et al showed that colchicine reduced hs-CRP independent of aspirin and high-dose atorvastatin, in a cohort of 64 patients with stable CAD and elevated baseline hs-CRP. Indeed, the effects of colchicine on endothelial function might extend beyond the suppression of hs-CRP. In a study on 28 patients, those receiving colchicine for 7 days had a significantly decreased hs-CRP although there was no correlation with flow-mediated vasodilation (FMD). However, FMD was significantly improved by colchicine in the subgroup of patients with higher leucocyte count. This endothelial improvement might be induced by colchicine through different anti-inflammatory pathways, such as inhibition of neutrophil activation and degradation.

Furthermore, colchicine may have a potential role in the prevention of adverse remodelling after a myocardial infarction. In fact, in the recent study by Akodad et al, a significant reduction of infarct size and area of fibrosis along with improvement of haemodynamic parameters was observed in a myocardial ischaemia/reperfusion mice model. Similar findings were shown in a mice model of myocardial infarction. Nevertheless, neutral studies have also been reported: indeed, in a canine model of ischaemia and reperfusion, no effect of colchicine on infarct size was shown.

Clinical role of colchicine for the prevention of cardiovascular events

The LoDoCo (Low-Dose Colchicine) trial was a large randomised study on 532 patients with stable coronary disease (table 1). This was the first study to show the efficacy of colchicine (0.5 mg daily) on top of OMT, with a dramatic reduction of cardiovascular events (ACS, out-of-hospital cardiac arrest, non-cardioembolic ischaemic stroke): 5.3% vs 16% (HR 0.33, 95% CI 0.18 to 0.59). Such results were mainly driven by the decreased incidence of ACS, mainly unstable angina. It should be noted that 11% patients reported early gastrointestinal intolerance leading to immediate discontinuation. This study will be followed by the LoDoCo 2 trial, an international, multicentre, double-blind trial started in 2014, which is currently ongoing (ANZCTR registration number: ACTRN12614000093684).

In patients without a previously established diagnosis of CAD, a cross-sectional study of 1288 patients with gout showed that the prevalence of myocardial infarction was lower in patients on colchicine treatment (1.2% vs 2.6%, p=0.03). A similar retrospective study showed not only a decreased risk for myocardial infarction, stroke and transient ischaemic attack (HR 0.51, 95%CI 0.30 to 0.88) but also a reduction of all-cause mortality (HR 0.27, 95%CI 0.17 to 0.43).

Table 1. Clinical studies assessing the use of colchicine in patients with chronic coronary syndromes

<table>
<thead>
<tr>
<th>Study, *</th>
<th>Study design</th>
<th>Colchicine dose and duration</th>
<th>Clinical setting</th>
<th>Patient number</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kajikawa et al47</td>
<td>Randomised trial</td>
<td>Colchicine 0.5 mg daily for 7 days</td>
<td>Stable CAD</td>
<td>28</td>
<td>Colchicine improved FMD only in the subgroup of patients with higher leucocyte count &gt;7500/mm³</td>
</tr>
<tr>
<td>Nidorf et al (LoDoCo trial)48</td>
<td>Randomised trial</td>
<td>Colchicine 0.5 mg daily for a median of 36 months plus statins and standard secondary prevention drugs</td>
<td>Stable CAD</td>
<td>532</td>
<td>Colchicine reduced cardiovascular events (ACS, out-of-hospital cardiac arrest, non-cardioembolic ischaemic stroke): 5.3% vs 16% (HR 0.33, 95% CI 0.18 to 0.59)</td>
</tr>
<tr>
<td>Deftereos et al49</td>
<td>Randomised trial</td>
<td>Colchicine 0.5 mg twice daily for 6 months</td>
<td>Diabetic, stable CAD patients undergoing PCI with a bare-metal stent</td>
<td>196</td>
<td>Colchicine reduced in-stent restenosis rate (16% vs 33%, p=0.007)</td>
</tr>
<tr>
<td>Nidorf and Thompson50</td>
<td>Prospective study</td>
<td>Colchicine 0.5 mg twice daily for 1 month plus aspirin and high-dose atorvastatin</td>
<td>Stable CAD patients with elevated hs-CRP</td>
<td>64</td>
<td>Reduction of hs-CRP (from 4.58±2.05 mg/L to 1.78±1.38 mg/L, p&lt;0.001)</td>
</tr>
</tbody>
</table>

*From most recent studies.

ACS, acute coronary syndrome; CAD, coronary artery disease; CRP, C reactive protein; FMD, flow-mediated vasodilation; hs-CRP, high-sensitivity C reactive protein; LoDoCo, Low-Dose Colchicine; PCI, percutaneous coronary intervention.

Colchicine in ACS
The use of colchicine in the setting of ACS produced diverging results (table 2). In a randomised trial on patients with ACS or stroke, colchicine failed to reduce hs-CRP at 30 days (median 1.0 mg/L vs 1.5 mg/L, p=0.22).43 In a similar prospective study in patients with ST-elevation myocardial infarction (STEMI), colchicine on top of OMT did not influence CRP peak values during the index hospitalisation (29.03 mg/L vs 21.86 mg/L, p=0.36), even after adjustment for the culprit artery (27 mg/L vs 25 mg/L, p=0.79).44 These results are apparently in contrast with previous findings in the setting of stable CAD. This inconsistency in the setting of ACS might be explained with a minor anti-inflammatory effect of colchicine following plaque rupture, compared with its effect on plaque progression and destabilisation.

However, in a randomised trial on 151 patients, short-term colchicine was shown to reduce infarct size assessed by MRI (18.3 mL/1.73 m² vs 23.2 mL/1.73 m², p=0.019).37 The recently published COLCOT trial enrolled 4745 patients with recent myocardial infarction, randomised to receive low-dose colchicine (0.5 mg daily) or placebo for a median of 20 months. This trial demonstrated that colchicine was associated with a reduced rate of ischaemic cardiovascular events (composite of cardiovascular death, cardiac arrest, myocardial infarction, stroke or urgent hospitalisations for angina): 5.5% vs 7.1% (HR 0.77, 95% CI 0.61 to 0.96). This difference was mainly driven by the rates of stroke or urgent hospitalisations for angina. Despite similar rates of adverse events, mainly gastrointestinal (16% vs 15.8%, p=0.89), severe pneumonia occurred more frequently during colchicine treatment (0.9% vs 0.4%, p=0.03). A subgroup analysis of this study showed a non-significant difference in hs-CRP levels between colchicine and placebo.48 This finding further supports the hypothesis of different inflammatory (local and systemic) pathways during ACS.

Colchicine in percutaneous coronary interventions (PCIs)
Some studies in the pre-licensing era showed the inefficacy of colchicine in the prevention of restenosis following PCIs.48-50 On the contrary, a subsequent study on patients with diabetes undergoing PCI with a bare-metal stent showed that colchicine reduced in-stent restenosis rate (16% vs 33%, p=0.007).51 In a more recent prospective, single-centre trial, patients referred for PCI were randomised to preprocedural administration of oral colchicine 1.8 mg or placebo. Acute preprocedural administration of colchicine attenuated the increase in hs-CRP and inflammation but did not reduce the risk of death, non-fatal myocardial infarction and target vessel revascularisation at 30 days, and the outcome of PCI-related myocardial infarction.52

Meta-analyses on colchicine and ongoing studies
A Cochrane systematic review assessing 39 randomised trials with 4992 participants concluded that colchicine had no effect on all-cause mortality (RR 0.94, 95% CI 0.82 to 1.09), although the study considered both patients with and without cardiovascular diseases.53 However, in the meta-analysis by Verver et al, focusing on the 3431 patients with cardiac diseases, colchicine was found to be associated with a reduced incidence of composite cardiovascular outcomes (RR 0.44, 95% CI 0.28 to 0.69), with a trend toward reduced all-cause mortality (RR 0.50, 95% CI 0.23 to 1.08).54

The Colchicine and Spironolactone in Patients With STEMI/SYNERGY Stent trial is currently ongoing (ClinicalTrials.gov NCT03497429).
of additional risk factors. Lowering of LDLc, inhibition of platelet aggregation and control of cardiovascular diseases. A narrow therapeutic index and even life-threatening heart failure. Colchicine may have substantial cardiovascular benefits but has no evidence supporting colchicine doses above 1 mg/day. Lighted that treatment with a lower dose of colchicine (0.5 mg/day) has beneficial effects on all-cause mortality, while there is no evidence supporting colchicine doses above 1 mg/day. Colchicine may have substantial cardiovascular benefits but has a narrow therapeutic index and even life-threatening toxicity can occur, especially in the elderly and in case of drug interactions or decreased renal/hepatic function. On this basis, there is a need for additional large-scale trials to further evaluate efficacy, dosing and safety of this inexpensive, promising treatment in cardiovascular diseases.

It is highly probable that, with additional evidence which is expected in the near future, the inhibition of inflammation will become the fourth cornerstone of CAD treatment together with lowering of LDLc, inhibition of platelet aggregation and control of additional risk factors.

Table 3 Ongoing studies on colchicine for cardiovascular indications

<table>
<thead>
<tr>
<th>Trial</th>
<th>Registration</th>
<th>Setting</th>
<th>Study type</th>
<th>Target sample</th>
<th>Drugs</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoDoCo2</td>
<td>ACTRN1261400093684</td>
<td>Stable CAD</td>
<td>RCT, phase 3</td>
<td>5500</td>
<td>Colchicine 0.5 mg/day</td>
<td>Composite of cardiovascular death, MI, ischaemic stroke and ischaemia-driven coronary revascularisation</td>
</tr>
<tr>
<td>COACS</td>
<td>ClinicalTrials.gov identifier: NCT01906749</td>
<td>ACS</td>
<td>RCT, phase 3</td>
<td>500</td>
<td>Colchicine 0.5 mg/day</td>
<td>Overall mortality, new acute coronary syndrome and ischaemic stroke</td>
</tr>
<tr>
<td>CLEAR-SYNERGY</td>
<td>ClinicalTrials.gov identifier: NCT03048825</td>
<td>STEMI with PCI</td>
<td>Randomised, blinded, double-dummy, 2x2 factorial design trial of colchicine versus placebo and spironolactone versus placebo</td>
<td>4000</td>
<td>Colchicine 0.5 mg/day; spironolactone 25 mg/day</td>
<td>MAE at 1 year; composite of cardiovascular death, recurrent MI, or stroke; composite of cardiovascular death or new or worsening heart failure</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>ClinicalTrials.gov identifier: NCT02898610</td>
<td>Transient ischaemic attack; stroke</td>
<td>Open label, phase 3</td>
<td>2623</td>
<td>Colchicine (0.5 mg/day)</td>
<td>Recurrence of non-fatal ischaemic stroke; non-fatal major cardiac event; vascular death</td>
</tr>
</tbody>
</table>

The LoDoCo2 trial: Low-Dose Colchicine for secondary prevention of cardiovascular disease. ACS, acute coronary syndrome; CAD, coronary artery disease; CLEAR-SYNERGY, Colchicine and Spironolactone in Patients With STEMI/SYNERGY Stent Registry; COACS, Colchicine for Acute Coronary Syndromes; CONVINCE, Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; STEMI, ST-elevation myocardial infarction.

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