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Colchicine for Secondary Prevention of Cardiovascular Disease

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Abstract Preliminary evidence demonstrating that adding 0.5 mg of colchicine per day to statin and antiplatelet therapy reduced the risk of acute coronary events in patients with stable coronary artery disease has raised the hope that it may prove effective for the long-term secondary prevention of cardiovascular disease. The ability of colchicine to suppress blood levels of inflammatory mediators and prevent cholesterol-crystal-induced neutrophil-mediated inflammation implicated in the progression and instability of atherosclerosis adds plausibility to this clinical observation. Early intestinal intolerance in some patients is well recognized, but clinical experience gained over more than half a century with the continuous use of colchicine for the prevention of neutrophil-mediated inflammation in patients with familial Mediterranean fever and gout indicates that low-dose long-term therapy is safe. Nonetheless, before colchicine can be recommended for the secondary prevention of cardiovascular disease, further studies are required to confirm its safety and efficacy in a broad range of patients with coronary disease, and to determine whether doses of colchicine less than 0.5 mg/day might be effective and even better tolerated. Trials exploring the role of colchicine in the treatment of patients with acute coronary syndromes would also be of special interest but may require the use of doses higher than those used for long-term secondary prevention.

Keywords Colchicine · Secondary prevention of cardiovascular disease

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Introduction

The annual risk of a major cardiovascular event in patients with stable coronary disease taking statins and antiplatelet therapy is almost 5 %, and this risk more than doubles during the first year following an unstable coronary event [1, 2]. This persistently high risk of clinical events despite routine use of aspirin, statins, β-adrenergic blockers, and angiotensin-converting enzyme inhibitors highlights the need for more effective strategies to prevent the progression and instability of coronary atherosclerosis.

Complex immune-inflammatory pathways are implicated in the development, growth, and instability of atherosclerotic plaque [3, 4••, 5, 6]. Attempts to improve clinical outcomes in patients with cardiovascular disease by suppressing inflammation using corticosteroids [7], conventional nonsteroidal anti-inflammatory drugs [8], and inhibitors selective for cyclooxygenase 2 [9, 10] have proved disappointing. Each of these agents has been demonstrated to be poorly tolerated over the long term and associated with an increased risk of cardiovascular events [11]. In contrast, statins and aspirin are effective for the prevention of cardiovascular disease and both exert indirect anti-inflammatory effects [12, 13]. Statins also prevent the formation of large cholesterol crystals [14], which can cause direct plaque trauma and vascular injury [15, 16•].

Recent evidence suggests that cholesterol crystals within atherosclerotic plaque may also trigger the NLRP3-dependent inflammatory cascade that results in the release of interleukin-1β (IL-1β). [17••, 18••]. IL-1β has the ability to attract

circulating neutrophils to the atherosclerotic bed and to activate them, causing the release of proteolytic enzymes that promote vascular injury and plaque instability, predisposing to acute coronary syndromes, stroke, and cardiovascular death.

Recognition that cholesterol crystals can trigger the same NLRP3-dependent inflammatory cascade that causes acute flares in familial Mediterranean fever (FMF) and gout raises the possibility that therapies used to prevent acute inflammatory flares in these patients may also be of value for the secondary prevention of cardiovascular disease [19•, 20].

In this regard it is notable that colchicine, in contrast to all other anti-inflammatory agents, has remained the treatment of choice for more than half a century for the prevention of neutrophil-mediated inflammation in patients with FMF and gout [21–23]. Over the last few decades there has been increasing evidence that the long-term use of colchicine is safe, and in more recent times there has been increasing evidence to indicate that it may also provide benefits in patients with coronary atherosclerosis.

The purpose of this review is to critically examine the evidence supporting the effectiveness of colchicine for the secondary prevention of cardiovascular disease, explore the possible mechanisms whereby it may exert a favourable effect on atherosclerosis, and consider the potential advantages and limitations of its use in patients with cardiovascular disease.

Clinical Use of Colchicine

Aside from aspirin, colchicine is the oldest anti-inflammatory drug still in routine clinical use. It was originally extracted from plants of the genus *Colchicum* (autumn crocus, *Colchicum autumnale*, also known as "meadow saffron"), and its use has been described for treatment of rheumatism for centuries. The active ingredient of colchicine was isolated in 1820 and then purified and named in 1833, and its molecular structure was described in 1945 [24]. Since then it has remained the first-line therapy for the secondary prevention of FMF and has proven efficacy for the secondary prevention of gout. In recent years, colchicine has also been demonstrated to be of value in the treatment and prevention of pericarditis [25, 26].

The rapid clinical effect of colchicine relates to its rapid absorption and high oral bioavailability, with peak concentrations occurring in the plasma within 1 h of ingestion [27]. The preferential accumulation of colchicine in leukocytes likely explains its therapeutic effects at low dose [28].

Clinical Evidence Supporting the Use of Colchicine for Secondary Prevention of Cardiovascular Disease

The first clinical evidence to suggest that colchicine may affect the development of atherosclerosis emerged from a case–control study in patients with FMF [29]. In this disease a defect in the Mediterranean fever gene (*MEFV*), which is responsible for the regulation of the NLPR3 inflammasome and the production of IL-1β, predisposes patients to premature vascular disease [30]. In this study, patients with FMF who had been taking colchicine lifelong had a reduced prevalence of cardiovascular disease compared with an age- and sex-matched control population not taking colchicine.

Further indirect evidence supporting the efficacy of colchicine for prevention of cardiovascular disease came from a study in patients hospitalized with acute gout which demonstrated that patients who continued to take colchicine for long-term secondary prevention of gout had a reduced risk of subsequent myocardial infarction compared with patients who did not take colchicine [31].

Although these two studies link continuous use of colchicine with a potential benefit in atherosclerosis, they are limited by their retrospective and observational design.

In patients with stable coronary disease, low-dose colchicine therapy has been demonstrated to lower levels of high-sensitivity C-reactive protein (hs-CRP) when added to statin and antiplatelet therapy [32]. This effect of colchicine is clinically relevant because hs-CRP is a predictor of cardiovascular events in at-risk patients, independently of serum levels of cholesterol and other cardiovascular risk factors [33]. These results raise the possibility that colchicine is able to inhibit a specific inflammatory process involved in atherosclerosis that is not otherwise targeted by usual therapy; however, prospective data demonstrating a clinical effect of colchicine therapy in patients with coronary disease are required to support the thesis that the effect of therapy on hs-CRP is of any clinical relevance.

Clinical evidence supporting an independent beneficial effect of colchicine for secondary prevention of cardiovascular disease has come from the Low Dose Colchicine (LoDoCo) trial [34•]. This was a prospective randomized, observer-blinded (assessment of) end point (PROBE) study involving 532 patients with stable coronary artery disease taking statins and antiplatelet therapy who were followed for a median of 3 years. Compared with untreated patients, those who were randomized to receive 0.5 mg colchicine per day had a significantly reduced risk of cardiovascular events, including unstable angina associated with angiographic proof of disease progression and myocardial infarction unrelated to stent disease (Fig. 1). The benefits of colchicine were consistent in younger and older patients, as well as in those with and without a history of diabetes, unstable coronary disease, and previous revascularization.

During the LoDoCo study, 11 % of patients randomized to receive colchicine experienced early gastrointestinal (GI) intolerance. In the more than 1,000 patient life years of subsequent follow-up, however, no serious adverse events occurred that could be directly attributed to colchicine. As discussed

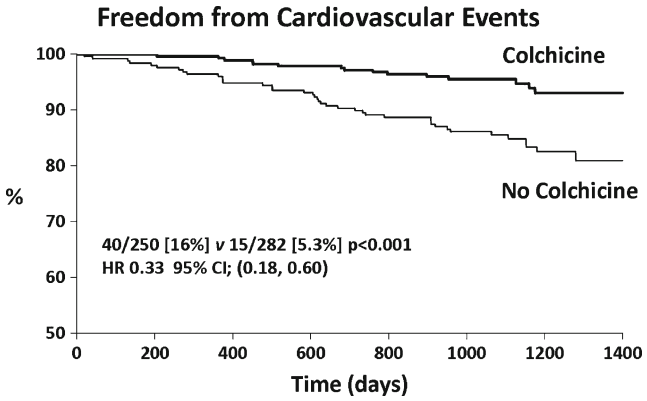

Fig. 1 Freedom from Cardiovascular Events including acute myocardial infarction, unstable angina, out of hospital cardiac death and non-cardioembolic ischemic stroke in patients with proven coronary disease randomised to either colchicine 0.5 mg/day or no colchicine in addition to usual medical therapy. [Number needed to treat to prevent 1 event = 11] [Ref. 34•]

later, these safety data are consistent with long-term experience using colchicine in patients with FMF and gout.

The LoDoCo trial raises the hope that colchicine may be of value in the secondary prevention of cardiovascular disease. Important issues remain to be addressed however, including the possible mechanism by which colchicine might provide a benefit in atherosclerosis and the optimal dose and long-term safety of therapy for secondary prevention of cardiovascular disease in a diverse population taking high-dose statin therapy.

Potential Mechanism of the Beneficial Effect of Colchicine in Atherosclerosis

Colchicine has effects on gene expression and protein assembly in multiple cell lines and produces clinical effects in both early and late stages of atherosclerosis disease progression.

Colchicine has been demonstrated to prevent the development of atherosclerosis in animal models [35–38]. The mechanism for its effect on atherosclerosis is unknown, but it is likely that it acts in the same way in which it exerts its effects on the acute and chronic manifestations of FMF and gout.

In FMF and gout, the clinical effectiveness of colchicine for the secondary prevention and treatment of acute inflammatory flares is believed to relate to its effects on macrophage and neutrophil function. Its ability to suppress the expression of the *MEFV* gene within macrophages [39–41] and its ability to bind tubulin together impair the production and assembly of the NLRP3 inflammasome and the production of IL-1β, thereby reducing the ingress of neutrophils into the inflammatory bed. By targeting tubulin in neutrophils, colchicine also impairs their mobility, adhesion, and activation, further reducing their response to inflammatory signals.

These effects of colchicine likely explain its ability to prevent the neutrophil-mediated inflammatory response to cholesterol crystals that was observed in earlier in vivo studies [42].

The potential of cholesterol crystals to play a causative role in atherosclerosis is supported by experiments in animals demonstrating that when cholesterol crystals are injected into the arterial wall, they can induce atherosclerotic lesions [43]. Cholesterol crystals have also been identified in nascent plaque [44], their presence is recognized as a predictor of plaque instability in more advanced disease [45], and large cholesterol crystals have been demonstrated to cause direct plaque trauma [10, 11, 46]. Furthermore, there is strong evidence that cholesterol crystals within atherosclerotic plaque may trigger resident macrophages to activate the NLRP3 inflammasome to produce and release IL-1β, which is then responsible for recruiting neutrophils to, and activating them within, the plaque bed [7, 8].

Demonstration that the crystal-induced inflammatory cascade first described in gout [47, 48] is also active in atheromatous plaque may also explain the presence of neutrophils in all stages of atherosclerosis [4••]. This inflammatory mechanism is distinct from other inflammatory processes so far described in the disease, and offers a strong rationale to target this pathway in an attempt to improve the clinical outcome in patients with vascular disease [17••, 18••].

It is conceivable that inhibiting crystal-induced inflammation may be particularly advantageous in patients with advanced atherosclerosis who are at greatest risk of cardiovascular events. Although several mechanisms of plaque instability have been proposed [49], activated neutrophils are found in culprit plaques in most patients presenting with acute coronary syndromes [50••], suggesting that therapies that prevent neutrophil-mediated inflammation may hold promise as a means to prevent acute clinical events that are the hallmark of cardiovascular disease.

Colchicine has also been demonstrated to have other effects that may slow the development and progression of atherosclerosis, including an ability to directly inhibit the formation of cholesterol crystals in vitro (George S. Abela, Michigan State University, personal communication, April 10, 2013) and to suppress the activity of mast cells [51], T cells [52], monocytes [53], smooth muscle cells derived from vascular plaques [54], and osetocytes [55].

In addition, long-term use of colchicine has been demonstrated to reverse renal amyloid in patients with FMF [56], prevent gouty arthropathy [57], and reduce blood levels of biomarkers normally associated with vascular injury [58], suggesting that long-term therapy has other disease-modifying effects yet to be understood which may be important in slowing the progression of atherosclerosis.

The Safety of Continuous Use of Colchicine for Secondary Prevention

Therapies used for secondary prevention of a chronic, slowly progressive disease must be safe and well tolerated when taken continuously over decades. In addition, to have a significant impact in a large population, these therapies should ideally be readily available, relatively inexpensive, and easy to administer.

Although there are some concerns that early GI intolerance to and late side effects from colchicine may limit its widespread use, its ready availability, low cost, and apparent benefit in cardiovascular disease all indicate the need to continue to explore its role for secondary prevention of cardiovascular disease [6]. Fortunately, significant insight into the effective dose, relative long-term safety, and general tolerance to colchicine has already been gained from the more than a half a century of clinical experience with its use for the secondary prevention of acute inflammatory flares in gout and FMF.

In both gout and FMF, clinical experience clearly demonstrates that the effectiveness of colchicine is dose-dependent. In patients with gout, colchicine dosages of 0.5 mg/day are commonly prescribed to prevent acute flares, and in patients with renal disease dosages of 0.3 mg/day appear safe and effective [59]. In contrast, in patients with FMF, dosages up to 2 mg/day are routinely prescribed continuously over decades for secondary prevention of acute inflammatory flares [60].

The safety of long-term colchicine therapy in both conditions is well documented. At a dosage of 0.5 mg/day, colchicine may induce GI intolerance in up to 10 % of people during the first month of treatment, although in some patients this settles spontaneously. In contrast, late GI intolerance is uncommon. Low-dose colchicine has been demonstrated to be safe and well tolerated during long-term use in children [61] and elderly patients [62] and during pregnancy [63].

Continuous use of colchicine at dosages up to 2 mg/day has been associated with rare case reports of reversible peripheral neuritis and myopathy [64], alopecia [65], inhibition of spermatogenesis but not fertility [66], vitamin B_{12} deficiency [67], and bone marrow suppression [68]. Rhabdomyolysis has only rarely been reported when colchicine is used alone; there have been isolated case reports of rhabdomyolysis when colchicine has been used in combination with high-dose statins in patients with renal impairment [69, 70].

It is well recognized that colchicine should be used cautiously in patients with advanced renal and liver disease, and with the concomitant use of certain drugs, including cyclosporine, clarithromycin, erythromycin, and ketaconazole. [71] Overdoses of 40-60 mg (80-120 tablets) of colchicine are lethal [72]. Therefore, should colchicine be more widely prescribed in patients with coronary disease, education of physicians and patients and appropriate labeling and packaging will be required

The US Food and Drug Administration (FDA) has produced an audit of all reported fatalities possibly related to colchicine use for the period between 1969 and 2009 [73]. During the last 20 years of this audit period, statin use was known to be widespread.

Over the 40-year period of the audit and millions of patient years of exposure to colchicine, 169 deaths were attributed to the use of orally administered colchicine. In 52 patients, death was due to a deliberate overdose, and in 60 patients death occurred after they had been treated concomitantly with clarithromycin, which is known to dramatically increase serum levels of colchicine. In the remaining 57 patients, no reliable information was available regarding the prescribed dose or duration of colchicine therapy or the presence or absence of renal or hepatic dysfunction. Since almost 4 % of the US population (8.3 million people) have gout [74], and more than three million prescriptions for colchicine are filled each year in the USA [75], in addition to its online availability, these FDA data are generally reassuring as they indicate that serious toxicity related to colchicine use is rare, and that with careful supervision, low-dose therapy should be safe even when administered in association with statins.

Potential Limitations and Unresolved Issues Related to the Use of Colchicine for Secondary Prevention of Cardiovascular Disease

Early GI Intolerance

Although the LoDoCo trial suggests that 0.5 mg colchicine per day is effective for prevention of cardiovascular disease in patients with stable coronary disease, its overall impact in the wider population may be limited by early GI intolerance in up to 10 % of patients. This may be able to be addressed by the development of different formulations of the drug.

Nonresponders

Clinical experience in FMF and gout demonstrates that therapy is ineffective in some patients. Among patients with FMF, colchicine fails to prevent acute inflammatory flares in 5-10 % of patients even at high doses [76]. The failure of low-dose therapy to prevent acute flares of gout in a broad range of patients has not been well documented; however, it is known that the risk of recurrence is reduced when regular use of colchicine is combined with urate-lowering therapy.

Effect of Therapy on Stent-Related Disease

There is uncertainty as to whether colchicine can prevent stent-related disease (including stent thrombosis), which

involves mechanisms distinct from those seen in native atherosclerosis.

In a randomized controlled trial involving 197 patients undergoing simple balloon angioplasty, 0.6 mg colchicine twice daily did not prevent re-stenosis at 6 months of follow-up [77]. In contrast, in a study of similar size (n= 196) and design, 0.5 mg colchicine twice daily significantly reduced the risk of in-stent stenosis following insertion of a bare metal stent in diabetic patients, due to a significant reduction in neointimal hyperplasia [78]. The different effect of therapy observed in these studies may reflect elimination by the stent of early elastic recoil as a cause of early re-stenosis following balloon angioplasty. In the LoDoCo study, the number of patients who had an acute stent-related event was low and appeared to be unaffected by use of colchicine. Possible explanations for these apparently divergent results include different mechanisms of stent-related disease compared with native atherosclerosis or simply the play of chance.

Effect of Low-Dose Therapy in Unstable Coronary Syndromes

Clinical experience indicates that the dose of colchicine required to prevent acute inflammatory flares in FMF and gout is insufficient to treat active inflammation. In patients with acute gout, a dosage of 1 mg/day is generally prescribed for several weeks [79], and even higher doses are required to settle acute inflammatory flares in FMF. The observation that 1 mg colchicine per day was unable to lower hs-CRP levels in patients hospitalized with acute coronary syndromes [80] suggests that the dose of colchicine used for secondary prevention of cardiovascular disease may be insufficient to dampen active inflammation in acutely disrupted plaque. This observation has important implications for studies designed to determine the ability of anti-inflammatory therapy to reduce the risk of recurrent ischemic events in patients with unstable coronary disease.

Future Directions

Optimal Therapeutic Dose of Colchicine for Secondary Prevention in Stable Coronary Disease

In addition to the need to confirm the observations made in the LoDoCo trial in a large randomized double-blind study [6], there is a need to explore the effectiveness and safety of alternative colchicine dosing strategies of for the secondary prevention of cardiovascular disease. Specifically, it is possible that dosages exceeding 0.5 mg/day may offer more benefit, albeit with the risk of intolerance. In contrast, the observations that cholesterol crystals induce a less intense immune response than monosodium urate crystals [81] and that colchicine is avidly taken up by leukocytes [28] suggest that lower-dose therapy may prove beneficial and may be associated with a reduction in the incidence of GI intolerance and may lessen any concern related to the potential for untoward drug interactions [82].

Alternatives to Colchicine Therapy

Ongoing research has led to alternatives to colchicine for prevention of crystal-induced neutrophil-mediated inflammation. Specifically, the formation of human monoclonal antibodies directed against inflammatory mediators has led to the development of canakinumab, an antibody directed against IL-1β, the last step in the macrophage response of the crystal-induced inflammatory cascade. Canakinumab has proved effective in the secondary prevention of gout [83] and acute inflammatory flares in patients with FMF who appear unresponsive to colchicine [84]. On the basis of current evidence, however, the FDA is yet to approve its use for the prevention of gout owing to uncertainty regarding its efficacy and short- and long-term safety [85]. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) will address the issues of safety and efficacy of long-term use of canakinumab in patients with stable coronary disease [86].

The Effect of Anti-inflammatory Therapy in Patients Hospitalized with Unstable Coronary Disease

Since activated neutrophils are known to be associated with unstable atherosclerotic plaques, it would be of interest to examine the effects of both colchicine and canakinumab in patients with acute coronary syndromes in the hope that more rapid resolution of the underlying inflammatory process within the unstable plaque bed will lead to improved clinical outcomes. A feasible algorithm would be to administer canakinumab subcutaneously to patients with unstable coronary disease on hospital admission as it is the more potent and longer-acting agent and would avoid the problems of early GI intolerance related to colchicine. Introducing orally administered colchicine 3 months after admission would then offer benefits of continuing effective therapy without concerns related to the long-term safety, the need for parental administration, and the likely higher costs of canakinumab.

Summary

The observation that cholesterol crystals within atherosclerotic plaque can activate the same inflammatory cascade responsible for acute inflammatory flares in patients with FMF and gout suggests that inhibiting this process with colchicine, which is effective for the secondary prevention of acute

inflammatory flares in these conditions, may also prove effective for the secondary prevention of cardiovascular disease.

This thesis is advanced by the demonstration that the addition of 0.5 mg colchicine per day to statin and antiplatelet therapy reduced the risk of cardiovascular events in patients with stable coronary disease. The clinical experience with the continuous use of colchicine for secondary prevention of acute inflammatory flares in patients with FMF and gout is reassuring as it demonstrates the general safety of long-term use of this therapy.

Together these observations strongly support the need for further studies to confirm the safety and efficacy of colchicine in a broad range of patients with cardiovascular disease, and to determine whether even lower doses of therapy may be effective and better tolerated in patients who are intolerant to currently available low-dose preparations of the drug.

Although exploring the potential role of colchicine in the treatment of patients with unstable coronary disease appears attractive, it is possible that higher doses of therapy or alternative anti-inflammatory approaches may be required to stabilize acutely disrupted atherosclerotic plaque.

Compliance with Ethics Guidelines

Conflict of Interest Stefan M. Nidorf and Peter L. Thompson declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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