The effect of low-dose colchicine in patients with stable coronary artery disease: The LoDoCo2 trial rationale, design, and baseline characteristics

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Background Because patients with stable coronary artery disease are at continued risk of major atherosclerotic events despite effective secondary prevention strategies, there is a need to continue to develop additional safe, effective and well-tolerated therapies for secondary prevention of cardiovascular disease.

Rationale and Design The LoDoCo (Low Dose Colchicine) pilot trial showed that the anti-inflammatory drug colchicine 0.5 mg once daily appears safe and effective for secondary prevention of cardiovascular disease. Colchicine's low cost and long-term safety suggest that if its efficacy can be confirmed in a rigorous trial, repurposing it for secondary prevention of cardiovascular disease would have the potential to impact the global burden of cardiovascular disease.

LoDoCo2 is an investigator-initiated, international, multicentre, double-blind, event driven trial in which 5522 patients with stable coronary artery disease tolerant to colchicine during a 30-day run-in phase have been randomized to colchicine 0.5 mg daily or matching placebo on a background of optimal medical therapy. The study will have 90% power to detect a 30% reduction in the composite primary endpoint: cardiovascular death, myocardial infarction, ischemic stroke and ischemia-driven coronary revascularization. Adverse events potentially related to the use of colchicine will also be collected, including late gastrointestinal intolerance, neuropathy, myopathy, myositis, and neutropenia.

Conclusion The LoDoCo2 Trial will provide information on the efficacy and safety of low-dose colchicine for secondary prevention in patients with stable coronary artery disease. (Am Heart J 2019;218:46-56.)

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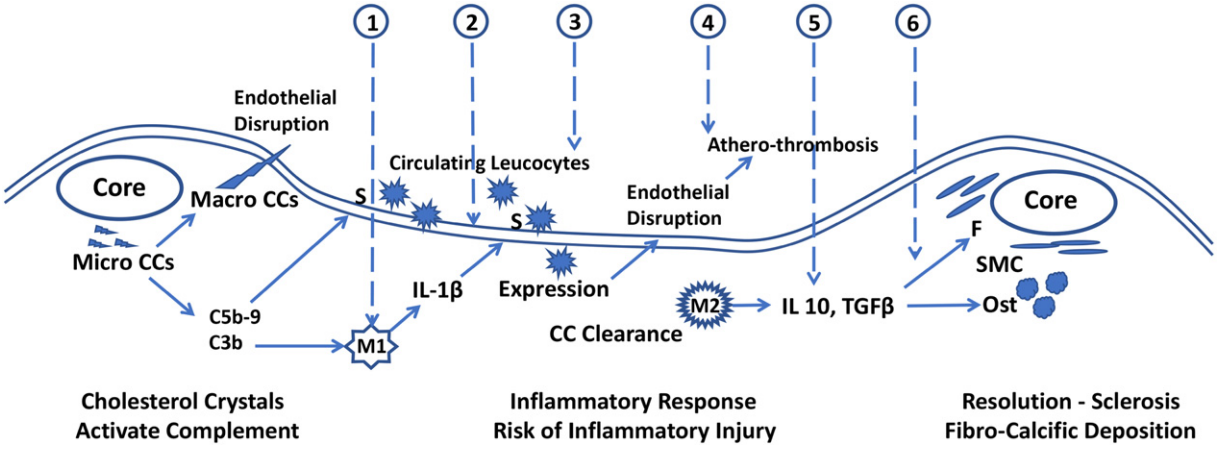
Atherosclerosis remains the major cause of death, disability and rising health care costs in many parts of the world. Reducing the global burden of cardiovascular (CV) disease requires the development and widespread deployment of effective and affordable therapies for secondary prevention of atherosclerosis that are safe and well tolerated when used over decades.

Aggressive secondary prevention can improve CV outcomes in patients with established atherosclerosis. Lifestyle changes and intensive combined modification of multiple risk factors, including lowering low-density lipoprotein-cholesterol (LDLc), blood pressure and glucose, as well as antithrombotic therapy, have been demonstrated to significantly improve the long-term outcomes among patients with coronary artery disease.[1-7] Despite this, a considerable residual CV risk persists.

Atherosclerosis is a complex inflammatory disease. In spite of the recognition of the central role of

Figure 1



Effects of colchicine on inflammatory injury and healing in atherosclerotic plaque. The formation of cholesterol crystals (CC) in atherosclerotic plaques may lead to injury. Microscopic CCs may enlarge to form macroscopic CCs which can cause sudden unheralded disruption of the endothelium, or they may activate complement to trigger an inflammatory response by promoting entry of circulating leucocytes into the vascular bed by either directly activating endothelium to produce selectins (S) or by stimulating pro-inflammatory macrophage (M1) to release interleukin (IL)-1β which also acts to enhance recruitment of inflammatory cells into the vascular bed. If the CCs are not rapidly cleared the inflammatory response can persist, increasing the risk of inflammatory injury that may disrupt the endothelium and lead to atherothrombosis. As CCs are cleared, anti-inflammatory macrophages (M2) begin to dominate the milieu and release of anti-inflammatory cytokines including IL-10 and transforming growth factor (TGF)-β that suppress pro-inflammatory signals and promote the ingrowth of smooth muscle cells (SMC), fibrocytes (F) and cells with osteogenic potential (O) leading to the formation of fibro-calcific plaques. Colchicine inhibits the pro-inflammatory response to CCs by; (1) reducing macrophage expression of IL-1β and the release of various cytokines including tumor necrosis factor (TNF)–α (2) reducing endothelial expression of selectins and (3) inhibiting the actions of circulating leucocytes including suppressing their ability to release lytic enzymes including Matrix Metalloproteinase and super-oxide. In addition, colchicine also (4) impairs platelet-leucocyte interactions that promote atherothrombosis and it can promote resolution and healing by (5) inhibiting over expression of IL-10 and TGF-β and (6) by limiting the growth of smooth muscle cells, fibroblasts and osteophytes that if unchecked leads to vascular thickening, deformity and calcification. (Reproduced with permission).[42]

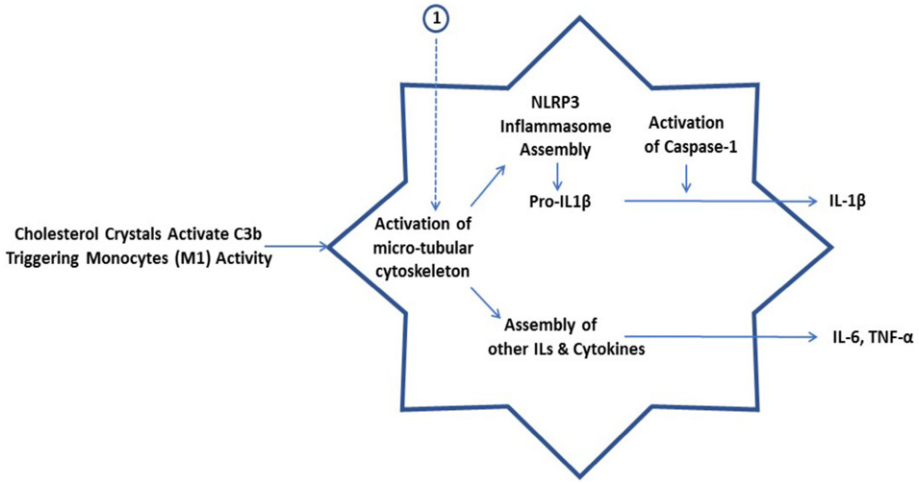
inflammation in unstable coronary syndromes, the lack of complete understanding of the underlying mechanisms leading to plaque instability has hampered efforts for the development of anti-inflammatory treatments to prevent CV events.

Recent evidence suggests an important role of the NOD-like receptor family pyrin containing domain 3 (NLRP3) inflammasome by various triggers. Complement activation also triggers an inflammatory response activating endothelium to produce selectins thereby promoting entry of circulating leucocytes into the vascular bed, which may predispose to plaque instability (Figure 1).[8-11] The proof of concept CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) study supports the hypothesis that dampening the downstream effects of activation of the NLRP3 inflammasome by specifically targeting interleukin-1β (IL-1β) with the monoclonal antibody canakinumab can reduce the risk of major adverse CV events.[12]

In contrast to canakinumab, colchicine is a microtubule inhibitor with broad cellular effects and has additional actions both up and downstream of the NLRP3 inflammasome (Figures 1 and 2). Microtubules are involved in various cellular processes including maintenance of cell shape, intracellular trafficking, cytokine and chemokine secretion, cell migration, and cell division. Colchicine is a classical anti-mitotic drug that blocks mitotic cells in metaphase. Colchicine can therefore dampen the activity of the full palette of cellular players that mediate inflammatory injury in atherosclerotic plaque including neutrophils, macrophages, mast cells and T-cells. In addition, it affects endothelial and platelet function, alter the function of E-selectin on endothelial cells and decrease the adherence of leukocytes to inflamed endothelium. [13] It also can dampen the growth of vascular smooth muscle cells and fibrocytes that become activated in the healing response to vascular injury.[14-19] Importantly colchicine has proven safe and effective when used continuously over decades for the secondary prevention of acute inflammatory flares in patients with Familial Mediterranean Fever (FMF) and gout.[20-22]

There is mounting evidence that colchicine's effects on the cellular processes continually at play in the vascular bed may translate into clinically meaningful

Figure 2



Colchicine effects in monocytes.Detail of the effect of colchicine on macrophage and monocyte activation showing how its effects on tubulin inhibits the assembly of the Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing (NLRP3) inflammasome resulting in *upstream inhibition* of the pivotal pro-inflammatory cytokines. IL, interleukin; TNF-A, tumor necrosis factor-A.

benefits (Figure 3, Table I). Animal studies have demonstrated that colchicine can inhibit the development of atherosclerosis independent of statin therapy and observational studies in man indicate that low-dose colchicine can favorably modify plaque morphology and reduce stent stenosis.[11,23-29] Furthermore, the LoDoCo pilot demonstrated for the first time in a randomized study that colchicine 0.5 mg daily could safely reduce the risk of CV events in patients with stable coronary disease.[30]

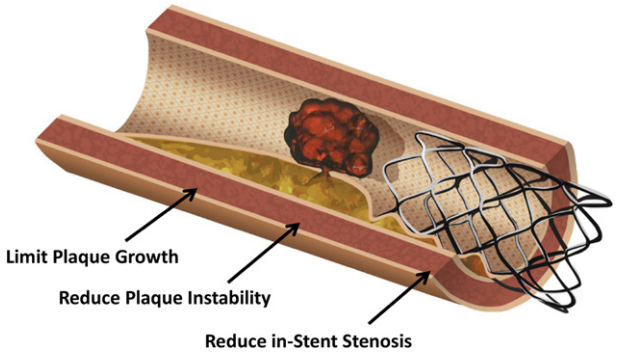
Together, these data justify a rigorous randomized controlled trial to confirm whether low-dose colchicine can be repurposed as a safe and effective treatment for secondary prevention in patients with stable coronary artery disease.

Methods

Study objective

The primary purpose of the LoDoCo2 (the second Low Dose Colchicine) trial is to determine whether colchicine 0.5 mg once daily can safely reduce the composite endpoint: CV death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization in patients with stable coronary artery disease.

Figure 3



Processes continually active within the vascular bed.Multiple cellular processes, continually active within the vascular bed, affect the growth and instability of atherosclerotic plaque as well as stent-related disease that predispose to cardiovascular events including cardiovascular death, myocardial infarction, worsening angina and ischemic stroke.

Table I. Actions of colchicine relevant to atherosclerosis.

Action	Effect	Demonstrated in atherosclerosis	Reference number
Antitubulin	Inhibits tubule action	No	58,59
Inhibits assembly of NRLP3 inflammasome	Delays initiation of innate immune response	Yes	29,59,60
Uptake and concentration in leukocytes	Prolonged anti-inflammatory action	No	61
Limitation of IL-1β uptake in NETs	Inhibits IL-1β action	No	62
Inhibits platelet leucocyte interaction	Indirect effect on platelet function	Yes	19
Inhibits the expression of E Selectin	Reduces leukocyte adhesion to endothelial cells	Yes	13
Inhibits release of IL-1β	Limits release of cytokines IL-6, TNFα and CRP	Yes	29,63,64

Abbreviations: CRP, C-Reactive Protein; IL, interleukin; NET, Neutrophil extracellular trap; NLR3, NOD-like receptor family pyrin containing domain 3; TNF, tumor necrosis factor.

Study conduct

The trial is being conducted in Australia and the Netherlands. The Steering Committee is responsible for the development of the protocol and for the conduct and oversight of the study. The protocol was approved by ethics committees in Australia and the Netherlands and the trial is registered with the Australian Clinical Trial Registry (ACTRN12614000093684).

Both active and matching placebo medication has been supplied by Aspen in Australia, and Tiofarma, Oud-Beijerland in the Netherlands. Neither company had any involvement in the design or conduct of the study and will not have a role in the analysis, interpretation of the data, or the writing of manuscripts.

Study design

LoDoCo2 is an investigator-initiated randomized, placebo-controlled, double blind trial that includes participants with known stable coronary artery disease who have proven tolerant to colchicine 0.5 mg daily during a 30-day open label run in phase (Figure 4).

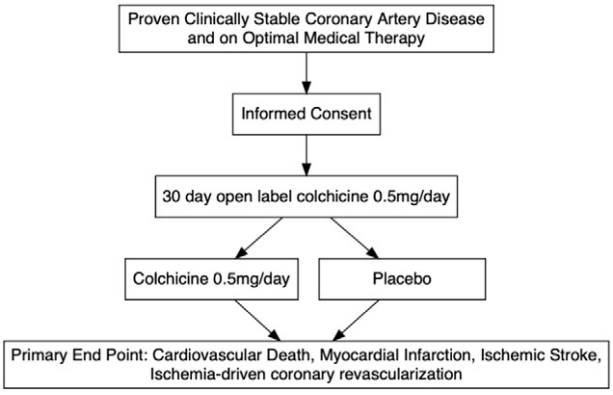
Participating sites. In Australia, participants were recruited from the private practices of members of GenesisCare located across metropolitan Perth and regional centers in Western Australia. In the Netherlands, participants were recruited from 30 hospitals within the network of the Dutch Network for Cardiovascular Research (WCN) that represents most hospitals in the Netherlands.

Study procedures

Inclusion and exclusion criteria. The inclusion and exclusion criteria were similar as those used in the LoDoCo pilot.[30] Accordingly the study includes male and female patients aged between 35–82 years with proven coronary artery disease who have been clinically stable for at least 6 months and do not have advanced heart failure, severe valvular heart disease, advanced renal impairment, known intolerance to colchicine, pre-existing peripheral neuritis, myositis or marked myo-sensitivity to statins and are able to provide informed consent (Table II).

A broad age range of participants was mandated to ensure the hypothesis was tested in a cohort representative of those seen in routine practice. The upper age range was set to ensure octogenarians were included in the trial, but truncated at 82 years of age with regard to the reality that those recruited in their early 80s would be in their mid-80s by the end of the trial. Those with advanced heart failure

Figure 4



Trial flow chart. Schematic representation of trial design.

Table II. Eligibility criteria and exclusions.

Eligibility criteria:
1) Age >35 and ≤82 years.
2) Proven coronary disease; as evidenced by coronary angiography, CT angiography or a Coronary Artery Calcium Score≥ 400 Agatston Units. Individuals with a history of coronary artery bypass surgery are only eligible if they had undergone bypass surgery more than 10 years before or have angiographic evidence of graft failure or have undergone coronary intervention since their bypass surgery.
3) Clinically stable for at least 6 months.

Exclusions:
1) Women who are pregnant, breastfeeding or may be considering pregnancy during the study period.
2) Renal impairment: serum creatinine >150 mmol/l or eGFR <50 mL/min.
3) Heart failure – NYHA Class 3 or 4.
4) Valvular heart disease considered likely to require intervention.
5) Dependent or frail or have a life expectancy <5 years.
6) Peripheral neuritis, myositis or marked myo-sensitivity to statins.
7) Already taking long-term colchicine therapy for any other reason.
8) Known intolerance to colchicine.
9) Currently enrolled in a competing trial.

CT, computed tomography; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

and those with valvular disease likely to require intervention were excluded as we were focused on the effect of therapy of atherosclerosis per se. All participants had objective invasive or non-invasive radiologic evidence of coronary artery disease. Patients with recent successful coronary artery bypass grafting (CABG) without any early post-procedural new coronary re-interventions are generally recognized as being at low risk of CV events and were therefore excluded from the trial.

Run-in phase. Eligible patients who provided informed consent received a 30-day open label trial of colchicine 0.5 mg daily. During this time, patients were instructed to take a tablet of colchicine each day in addition to their usual therapy.

Randomization phase. At the end of the run-in phase, patients who were tolerant to colchicine, had remained clinically stable and willing to continue in the study, were randomized to receive colchicine 0.5 mg once daily or matching placebo. Because short-term exposure to therapy was considered unlikely to affect long-term clinical outcomes, there was no prescribed wash out period between the 30-day open label period and randomization.

Participants and their doctors were advised about the need to avoid co-administration of macrolide antibiotics (azithromycin, clarithromycin, erythromycin) and to temporally cease their trial medication should they be prescribed non-study colchicine for any purpose.

Follow-up. Every 6 months participants are required to present in person to be resupplied with trial medication and provide feedback about the status of their health. Outcomes are recorded including admission to hospital for myocardial infarction, coronary intervention, stroke or atrial fibrillation. Participants are asked to report if they interrupted their trial medication for any reason, and the reason noted. To ensure participants do not inadvertently run out of their trial medication, they are supplied with adequate tablets for 7 months. Compliance is assessed by visual estimate of the remaining supply of trial medication returned.

In addition, all participants are followed according to standard care. All correspondence related to clinical visits, any hospital admissions, investigations and reports are obtained to determine and verify the occurrence of and potential primary, secondary and tertiary outcome events.

Study outcomes

Primary outcome. The primary outcome of the study is the composite of CV death, myocardial infarction, ischemic stroke, and ischemia-driven coronary revascularization.

Secondary outcomes. The secondary outcomes include (1) Myocardial infarction, (2) Ischemia-driven coronary revascularization, (3) Cardiovascular death or myocardial infarction, (4) Cardiovascular death, (5) Death from any cause, and (6) the composite of sudden cardiac death, non-fatal out of hospital cardiac arrest, acute myocardial infarction, unstable angina irrespective of revascularization, or atherosclerotic ischemic stroke (the primary outcome of the first LoDoCo trial).[30]

Tertiary outcomes. Three tertiary outcomes associated with a pro-inflammatory state are also being tracked, including (1) new onset or recurrence of atrial onset fibrillation or atrial flutter,[31,32] (2) new onset of diabetes,[33] and (3) deep vein thrombosis and/or pulmonary embolism[34].

Safety measures of interest

Safety measures include (1) neutropenia, defined as absolute neutrophil count <1500/μL (<1.5 × 109/L), (2) neuropathy, and (3) myotoxicity as evidenced by myositis or myopathy as classified by the European Consensus document.[35]

End-point definitions

Universal definitions have been used for CV death, myocardial infarction, and ischemic stroke.[36]

Cardiovascular death is defined as any death with a clear relationship to underlying CV disease, including death secondary to acute myocardial infarction causing sudden death, or acute heart failure, a complication of a coronary revascularization procedure where the cause of death is clearly related to the procedure, death due to CV hemorrhage and death due to other CV causes. Death due to myocardial infarction refers to a death by any CV mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after a myocardial infarction.

Acute myocardial infarction is defined by the ACC/AHA/ESC 3rd universal definition of (acute) myocardial

infarction.[37] *Ischemia-driven coronary revascularization* requires a history of new or accelerating ischemic symptoms without a rise in serum troponin together with angiographic evidence of a new culprit lesion and/or supporting clinical evidence of ischemia including fractional flow reserve and/or other forms of functional testing, which then leads to coronary revascularization.

Ischemic stroke

Stroke is defined as symptoms of acute focal cerebral, spinal, or retinal dysfunction due to a vascular cause with other non-vascular etiologies excluded. The symptoms must last >24 hours in the absence of brain imaging. The symptoms may last <24 hours in the presence of pathological, imaging or other objective evidence of acute, focal cerebral, spinal, or retinal ischemia or hemorrhage. *Ischemic stroke* requires pathological, imaging, or other objective evidence of acute, focal cerebral, spinal, or retinal ischemic injury in a defined vascular distribution; or clinical evidence of acute, focal cerebral spinal cord, or retinal ischemic injury based on symptoms persisting >24 hours or until death, and other etiologies excluded. Ischemic stroke includes hemorrhagic infarction but not intra-cerebral or subarachnoid hemorrhage. The primary outcome will therefore include atherosclerotic, cardio-embolic and lacunar stroke.

Tertiary outcomes

(1) New onset or first recurrence of symptomatic or asymptomatic atrial fibrillation or atrial flutter. (2) New onset of diabetes: Initiation of medication for the treatment of glucose control or fasting glucose ≥126 mg/dl (≥7 mmol/L) or Hb1Ac ≥6.5% or 2 hour post oral glucose tolerance test value of 11.1 mmol/L (WHO criteria). (3) Venous thromboembolism including new deep-vein thrombosis and/or pulmonary embolism as evidenced by imaging.

Adjudication of outcomes

All potential primary and secondary events are assessed by members of an independent Adjudication Committee comprised of 6 members (3 each in Australia and the Netherlands) with expertise in cardiology and neurology. In addition, all cases of suspected myotoxicity are reviewed by an independent expert adjudicator.

Data and safety monitoring

The Data and Safety Monitoring Board (DSMB) is comprised of 5 independent members with expertise in trial methodology, CV disease and biostatistics. Per protocol the trial will continue until all participants have been followed for at least 12 months and the required number of 331 primary events has been accrued unless the Steering Committee is advised otherwise by the DSMB. The full mandate of the DSMB is described in a separate charter.

Statistical considerations

The sample size determination for the study was event-driven, i.e. based on a requirement for the number of patients reaching the primary efficacy endpoint. Design assumptions included a 10% drop-out rate after the open label run-in phase, a per annum rate for the composite primary endpoint in the control group of 2.6% and a hazard ratio of 0.70. It was estimated that the occurrence of at least 331 composite primary endpoints would provide the trial with 90% power to statistically detect the expected treatment benefit at a two-sided significance level of 0.05. Based on these assumptions the sample size was set at 5447 randomized participants.

In accordance with the intent-to-treat principle outlined in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for human use — the ICH Harmonized Tripartite Guideline Statistical Principles for Clinical Trials E9, the primary analyses for efficacy will be based on time to first event for the primary composite end-point in all randomized patients who took at least 1 tablet of their assigned trial medication using events adjudicated by the Clinical Events Committee.[38] In addition, a per protocol analysis for the primary outcome in patients who remained compliant with the trial medication through the duration of the trial will be conducted. The occurrence of the primary endpoint over time will be depicted with Kaplan–Meier curves. The hazard ratio (HR), its 95% confidence interval (CI) and the corresponding P value will be derived from a Cox proportional hazards model with a factor for treatment group (colchicine versus control). $P < .05$ for the primary endpoint will be considered statistically significant. Secondary endpoints will be analyzed in a similar fashion using HRs and 95% CIs derived from a Cox proportional hazards model. The testing of the primary and secondary endpoints will be assessed in a closed testing procedure to preserve alpha as specified in the statistical analysis plan.

Study status

Recruitment began in Australia in August 2014 and in The Netherlands in November 2016 and was completed on December 3, 2018. By that date 5522 participants were randomized into the trial, 1.4% more than planned due to slight variance in the drop-out rate during the open label run-in phase. Global end of study was defined as the time when 331 primary endpoints would have occurred with the requirement of a minimal follow-up of 1 year. Based upon projections performed in February 2019, it was decided to set the global end-date for the trial at 4 December 2019. According to this timeline, the median follow-up will be approximately 2.5 years.

Table III summarizes baseline demographic and clinical characteristics of all participants in the trial cohort based upon an interim snapshot taken at April 29, 2019 after completion of enrolment but during ongoing trial and

Table III. Baseline characteristic of participants randomized into the LoDoCo2 Trial (based upon non-final data, as of April 29, 2019)

Characteristic	Randomized patients (n = 5522)
Age (years), mean (SD)	65.8 (± 8.6)
Male, n (%)	4676 (84.7)
Country	
Australia, n (%)	1904 (34.5)
Netherlands, n (%)	3618 (65.5)
Medical history	
Current Smoker, n (%)	654 (11.8)
Hypertension, n (%)	2807 (50.8)
Diabetes, n (%)	979 (17.7)
Insulin Dependent, n (%)	279 (5.1)
Renal Function	
Stage1,2, n (%)	5216 (94.5)
Stage 3A, n (%)*	306 (5.5)
Prior ACS, n (%)	4658 (84.4)
Prior PCI, n (%)	4177 (75.6)
Prior CABG, n (%)	710 (12.9)
Atrial Fibrillation, n (%)	637 (11.5)
Gout, n (%)	445 (8.1)
Medication use at baseline	
Antiplatelet therapy, n (%)	5021 (90.9)
Anti-coagulant (vitamin K antagonist or direct oral anticoagulants), n (%)	668 (12.1)
No anti-coagulant or antiplatelet, n (%)	26 (0.5)
Statin, n (%)	5180 (93.8)
Ezetimibe, n (%)	1068 (19.3)
ACE Inhibitor or ARB, n (%)	3950 (71.5)
Beta-Blocker, n (%)	3423 (62.0)
Calcium Channel Blocker, n (%)	1228 (22.2)

Participants were categorized at baseline into estimated glomerular filtration rate (eGFR) stages 1, 2, 3a (≥90, 60–89 or 45–59 ml/min/1.73 m^2, respectively). * known GFR <50 is exclusion & GFR 50–60 or creatinine 120-150 mmol/l is considered as mild renal failure (stage 3a).
Abbreviations: ACS, acute coronary syndrome; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

data cleaning. The mean age of the cohort is 66 years and 85% are male. A high proportion of participants are receiving secondary prevention therapy, with 93.8% taking statins (61.6% with dosages equivalent to atorvastatin 40 mg or 80 mg) and 19.3% using ezetimibe. Almost all (99.5%) participants are treated with anti-platelet therapy or anti-coagulation therapy.

Discussion

There is a need to develop safe effective well-tolerated and affordable therapies for secondary prevention of CV disease, which remains among the major causes of morbidity and mortality throughout the world.[39] Even after lowering LDLc to extremely low levels and optimization of anti-thrombotic therapies, considerable residual risk remains. Encouragingly, the CANTOS trial demonstrated that targeting the IL-1β inflammatory cytokine pathway further improved clinical outcomes in high risk patients with stable coronary disease suggesting that it may be possible to modify the inflammatory processes that drive the atherosclerosis, however the reduction in major adverse CV events was modest and accompanied by a small increase in fatal infections. The CV registration of canakinumab has been halted by Novartis.[40]

It is now appreciated that once cholesterol crystallizes in atherosclerotic plaque, it can initiate an innate immune response by triggering complement and by activating macrophages to produce IL-1β.[41] In addition, larger cholesterol crystals that are not readily ingested can induce a cycle of frustrated phagocytosis that results in an indolent, and at times a more intense acute inflammatory response.[10] Hence, extracellular cholesterol crystals trigger inflammatory processes up and downstream of the IL-1β pathway, suggesting that a much broader approach is required to more fully address the inflammatory processes that may drive the atherosclerotic process.[42]

In contrast to canakinumab, which selectively inhibits IL-1β, colchicine has broad cellular effects that targets multiple aspects of the innate immune response (Figure 1) and long-term colchicine has proven effective in gout and FMF in which these same inflammatory processes are active.[43,44] The LoDoCo pilot that used a prospective randomized observer-blinded endpoint (PROBE) design in 532 patients demonstrated that low-dose colchicine was safe and effective in reducing the risk of CV events in patients with stable coronary disease when used in combination with statins and anti-platelet therapy. The results showed that the colchicine group had a robust reduction in the primary endpoint (HR 0.33, 95% CI 0.18-0.59).[30]

The second LoDoCo trial (LoDoCo2) has been designed to confirm the safety and benefit of colchicine 0.5 mg daily for secondary prevention of CV events. The trial cohort includes a broad range of patients seen in general cardiology practice, and unlike CANTOS, participants were not selected on the basis of a predefined level of hs-CRP or other clinical markers of CV risk.

Development of diabetes mellitus and atrial fibrillation are common inflammatory driven conditions in patients with coronary artery disease. Colchicine has shown to reduce post-operative atrial fibrillation and might improve metabolic status in diabetes.[45,46] Whether colchicine has any effect in modulating the involved inflammatory pathways in such a manner that it might reduce their incidence has thus been added as a part of the exploratory tertiary outcomes.

Aside early intolerance to colchicine that may occur in up to 10% of people, long term use of low-dose (0.5 mg daily) colchicine is well tolerated, safe, and already approved by the United States Food and Drug Administration for the long-term secondary prevention of gout and FMF.[47] Of importance in patients with CV disease,

colchicine 0.5 mg daily does not affect lipid levels, bleeding time or blood pressure, is not pro-arrhythmic, and has never been reported to cause any clinically important drug interaction when prescribed with the full range of medications commonly used in the treatment of CV disease. Of the potential drug interactions between colchicine and drugs eliminated via hepatic cytochrome (CYP) 3A4, just the interaction with the macrolide clarithromycin appears clinically important and only when colchicine is administered at doses >1 mg/day.[48]

In addition, colchicine does not directly affect renal or liver function and can be used safely at low-dose in patients with renal and liver disease.[49,50] In patients with FMF, long-term colchicine can reverse renal amyloid and it is also known to be beneficial in some forms of cirrhosis.

Although colchicine has no direct myotoxic effects, isolated case reports of myotoxicity have been reported with its use at doses >1 mg daily in patients with moderate renal impairment soon after the commencement of each class of statin.[51-53] In the current study, patients with moderate renal impairment were excluded and statin dosing left to the discretion of the treating physician. Significant bone marrow toxicity and death related to colchicine has only occurred in the setting of intentional overdose or co-administration with clarithromycin.[48]

Currently three other phase 3 randomized trials are examining the effects of colchicine in patients following an acute coronary syndrome and one in cerebrovascular disease (Table IV).[54] The Colchicine Cardiovascular Outcomes Trial (COLCOT) includes participants within 1 month of an acute myocardial infarction.[55] The Colchicine and Spironolactone in Patients With STEMI/SYNERGY (CLEAR-Synergy) trial is using a 2x2 factorial design to examine the effect of colchicine and spironolactone in patients presenting within 24 hours of ST-elevation myocardial infarction who have had primary percutaneous coronary intervention.[56] Finally, the Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke (CONVINCE) study focuses on the

Table IV. Ongoing clinical trial investigating the effect of colchicine in cardiovascular disease.

Principal investigator and location	Initiation	Acronym & Name	Study population	Sample size	Intervention	Outcome	Proposed/ mean follow-up	Clinical trial identifier
Acute coronary syndrome								
Imazio et al.[63] Italy	2013	COACS Colchicine for Acute Coronary Syndromes	Acute coronary syndrome	500	Colchicine 0.5 mg/day vs. placebo	Overall mortality, new acute coronary syndrome, and ischemic stroke.	24 months	NCT01906749
Tardif et al.[55] Canada	2015	COLCOT Colchicine Cardiovascular Outcomes Trial	Myocardial infarction	4,500	Colchicine 0.5 mg/day vs. placebo	Cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, angina pectoris requiring hospitalization	3–4 years	NCT02551094
Jolly et al.[56] Canada	2018	CLEAR-SYNERGY OASIS-9 Colchicine and Spironolactone in Patients With STEMI / SYNERGY Stent Registry	ST – elevated myocardial infarction	4000	Colchicine 1 mg/ day and/or spironolactone 25 mg/day and/or placebo and/or SYNERGY stent (2x2 factorial design), 4 study arms	Cardiovascular death, recurrent myocardial infarction, or stroke in the colchicine comparison	2 years	NCT03048825
Cerebrovascular disease								
Kelly et al.[64] Ireland, Belgium, Spain, Greece	2016	CONVINCE Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke	Ischemic stroke or high risk transient ischemic attacks	2,623	Colchicine 0.5 mg/day vs. placebo	Recurrence of non-fatal ischemic stroke, non-fatal major cardiac event and vascular death	5 years	NCT02898610

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effect of low-dose colchicine in patients following a stroke of transient ischemic attack.[57]

In summary, the LoDoCo2 Trial will provide information on the efficacy and safety of low-dose colchicine for secondary prevention in patients with stable coronary artery disease.

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References

1. Ueki K, Sasako T, Okazaki Y, et al. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label. randomised controlled trial Lancet Diabetes Endocrinol 2017;5(12):951-64. https://doi.org/10.1016/S2213-8587(17)30327-3.
2. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-97. https://doi.org/10.1056/NEJMoa1410489.
3. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet.* 2010;376(9753):1670–1681. doi: https://doi.org/10.1016/S0140-6736(10)61350-5
4. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018:1-10. https://doi.org/10.1056/NEJMoa1801174.
5. Berlowitz DR, Foy CG, Kazis LE, et al. Effect of intensive blood-pressure treatment on patient-reported outcomes. N Engl J Med 2017;377(8):733-44. https://doi.org/10.1056/NEJMoa1611179.
6. Bethel MA, Neil HAW, Paul SK, et al. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359(15):1577-89. https://doi.org/10.1056/nejmoa0806470.
7. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377(14):1319-30. https://doi.org/10.1056/NEJMoa1709118.
8. Niyonzima N, Halvorsen B, Sporsheim B, et al. Complement activation by cholesterol crystals triggers a subsequent cytokine response. Mol Immunol 2017;84:43-50. https://doi.org/10.1016/j.molimm.2016.09.019.
9. Duewell P, Kono H, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010;464(7293):1357-61.
10. Mulay SR, Anders H-J. Crystallopathies. N Engl J Med 2016;374(25):2465-76. https://doi.org/10.1056/NEJMra1601611.
11. Vaidya K, Arnott C, Martínez GJ, et al. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: A CT coronary angiography study. JACC Cardiovasc Imaging 2018;11(2):305-16. https://doi.org/10.1016/j.jcmg.2017.08.013.
12. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377(12):1119-31. https://doi.org/10.1056/NEJMoa1707914.
13. Cronstein BN, Molad Y, Reibman J, et al. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest 1995;96(2):994-1002. https://doi.org/10.1172/JCI118147.

14. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368(21):2004-13. https://doi.org/10.1056/NEJMra1216063.
15. Libby P, Tabas I, Fredman G, et al. Inflammation and its resolution as determinants of acute coronary syndromes. Circ Res 2014;114(12): 1867-79. https://doi.org/10.1161/CIRCRESAHA.114.302699.
16. Dalbeth N, Lauterio TJ, Wolfe HR. Mechanism of action of colchicine in the treatment of gout. Clin Ther 2014;36(10):1465-79. https://doi.org/10.1016/j.clinthera.2014.07.017.
17. Leung YY, Yao Hui LL, Kraus VB. Colchicine-update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum 2015;45(3): 341-50. https://doi.org/10.1016/j.semarthrit.2015.06.013.
18. Artlett CM. Inflammasomes in wound healing and fibrosis. J Pathol 2013;229(2):157-67. https://doi.org/10.1002/path.4116.
19. Shah B, Allen N, Harchandani B, et al. Effect of colchicine on platelet-platelet and platelet-leukocyte interactions: a pilot study in healthy subjects. Inflammation 2016;39(1):182-9. https://doi.org/10.1007/s10753-015-0237-7.
20. Zemer D, Revach M, Pras M, et al. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. N Engl J Med 1974;291(18):932-4.
21. Yang LPH. Oral colchicine (Colcrys®). Drugs 2010;70(12):1603-13. https://doi.org/10.2165/11205470-000000000-00000.
22. Terkeltaub RA, Furst DE, Bennett K, et al. 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(4):1060-8. https://doi.org/10.1002/art.27327.
23. Kong J, Deng Y, Dong Q, et al. Colchicine reduces restenosis after balloon angioplasty treatment for in-stent restenosis. Arch Med Res 2015;46(2):101-6. https://doi.org/10.1016/j.arcmed.2015.01.004.
24. Verma S, Eikelboom JW, Nidorf SM, et al. Colchicine in cardiac disease: A systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2015;15(96). https://doi.org/10.1186/s12872-015-0068-3.
25. Hemkens LG, Gloy VL, Olu KK, et al. Colchicine for prevention of cardiovascular events. Cochrane Database Syst Rev 2014;2014(3). https://doi.org/10.1002/14651858.CD011047.
26. Crittenden DB, Lehmann RA, Schneck L, et al. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. J Rheumatol 2012;39(7):1458-64. https://doi.org/10.3899/jrheum.111533 [doi].
27. Solomon DH, Liu CC, Kuo IH, et al. *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*. November: Ann Rheum Dis. 2015 doi:annrheumdis-2015-207984 [pii].
28. Deftereos S, Giannopoulos G, Raisakis K, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. J Am Coll Cardiol 2013;61(16):1679-85. https://doi.org/10.1016/j.jacc.2013.01.055.
29. Martinez GJ, Robertson S, Barraclough J, et al. Colchicine acutely suppresses local cardiac production of inflammatory cytokines in patients with an acute coronary syndrome. J Am Heart Assoc 2015;4(8), e002128. https://doi.org/10.1161/JAHA.115.002128 [doi].
30. Nidorf SM, Eikelboom JW, Budgeon CA, et al. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol 2013;61(4):404-10. https://doi.org/10.1016/j.jacc.2012.10.027.
31. Harada M, Van Wagoner DR NS. Role of inflammation in atrial fibrillation pathophysiology and management. Circ J 2015;79(3): 495–502. doi:https://doi.org/10.1253/circj.CJ-15-0138. Epub 2015 Feb 16
32. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. Circulation 2011;124(21):2290-5. https://doi.org/10.1161/CIRCULATIONAHA.111.026153.
33. Dinarello CA, Donath MYM-PT. Role of IL-1beta in type 2 diabetes. Curr Opin Endocrinol Obes 2010;17(4):314-21. https://doi.org/10.1097/MED.0b013e32833bf6dc.
34. Branchford BRCS. The role of inflammation in venous thromboembolism. Front Pediatr 2018;6(142). https://doi.org/10.3389/fped.2018.00142. eCollection 2018.
35. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015;36(17):1012-22. https://doi.org/10.1093/eurheartj/ehv043.
36. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials. *J Am Coll Cardiol*. 2015;66(4):403–469. doi: 10.1016/j.jacc.2014.12.018
37. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60(16):1581-98. https://doi.org/10.1016/j.jacc.2012.08.001.
38. ICH. *ICH Harmonised Tripartite* Guideline—Statistical Principles For Clinical Trials; 1998.
39. World Health Organisation (WHO). Top 10 causes of death worldwide. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Published 2018. Accessed March 10, 2019.
40. *Withdrawal of the Marketing Authorisation Application for Canakinumab Novartis (Canakinumab)*. London; 2018. https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-withdrawal-marketing-authorisation-application-canakinumab-novartis-canakinumab_en.pdf. Accessed March 30, 2019.
41. Janoudi A, Shamoun FE, Kalavakunta JK, et al. Cholesterol crystal induced arterial inflammation and destabilization of atherosclerotic plaque. Eur Heart J 2016;37(25):1959-67. https://doi.org/10.1093/eurheartj/ehv653.
42. Nidorf SM, Thompson PL. Why colchicine should be considered for secondary prevention of atherosclerosis: an overview. Clin Ther 2019;41(1):41-8. https://doi.org/10.1016/j.clinthera.2018.11.016.
43. Hentgen V, Grateau G, Kone-Paut I, et al. Evidence-based recommendations for the practical management of Familial Mediterranean Fever. In: *Seminars in Arthritis and Rheumatism*. Vol 43. Elsevier; 2013:387–391. doi:https://doi.org/10.1136/annrheumdis-2014-206844
44. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology (Oxford) 2007;46 (8):1372-4. https://doi.org/10.1093/rheumatology/kem056a.
45. Demidowich AP, Levine JA, Onyekaba GI, et al. Effects of colchicine in adults with metabolic syndrome: A pilot randomized controlled trial. *Diabetes, Obes Metab*. 2019;21(7):dom.13702. doi:https://doi.org/10.1111/dom.13702
46. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. JAMA 2014;312(10):1016-23.

47. U.S. Food & Drug Administration. Postmarket Drug Safety Information for Patients and Providers - Colchicine (marketed as Colcrys) Information. June 30.
48. Hung IFN, Wu AKL, Cheng VCC, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. Clin Infect Dis 2005;41(3):291-300. https://doi.org/10.1086/431592.
49. Solak Y, Atalay H, Biyik Z, et al. Colchicine toxicity in end-stage renal disease patients. Am J Ther 2014;21(6):e189-95. https://doi.org/10.1097/MJT.0b013e31825a364a.
50. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken).* 2012;64(10): 1431–1446. doi:https://doi.org/10.1002/acr.21772.
51. Wilbur K, Makowsky M. Colchicine myotoxicity: case reports and literature review. Pharmacother J Hum Pharmacol Drug Ther 2004;24 (12):1784-92.
52. Tufan A, Dede DS, Cavus S, et al. Rhabdomyolysis in a patient treated with colchicine and atorvastatin. Ann Pharmacother 2006;40(7–8): 1466-9. https://doi.org/10.1345/aph.1H064.
53. Baker SK, Goodwin S, Sur M, et al. Cytoskeletal myotoxicity from simvastatin and colchicine. Muscle and Nerve 2004;30(6):799-802. https://doi.org/10.1002/mus.20135.
54. Fiolet ATL, Nidorf SM, Mosterd A, et al. Colchicine in stable coronary artery disease. Clin Ther 2019;41(1):30-40. https://doi.org/10.1016/j.clinthera.2018.09.011.
55. ClinicalTrials.gov. Colchicine Cardiovascular Outcomes Trial (COLCOT). NCT02551094. https://clinicaltrials.gov/ct2/show/NCT02551094. Published 2015. Accessed August 15, 2019.
56. ClinicalTrials.gov. Colchicine and Spironolactone in Patients With STEMI / SYNERGY Stent Registry (CLEAR-SYNERGY). https://clinicaltrials.gov/ct2/show/NCT03048825. Published 2017. Accessed August 15, 2019.
57. ClinicalTrials.gov. Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke (CONVINCE). NCT02898610.
58. Misawa T, Takahama M, Kozaki T, et al. Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome. Nat Immunol 2013;14(5):454-60. https://doi.org/10.1038/ni.2550.
59. Martinon F, Pétrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440(7081):237-41. https://doi.org/10.1038/nature04516.
60. Fordham JN, Kirwan J, Cason J, et al. Prolonged reduction in polymorphonuclear adhesion following oral colchicine. Ann Rheum Dis 1981;40(6):605-8. https://doi.org/10.1136/ard.40.6.605.
61. Apostolidou E, Skendros P, Kambas K, et al. Neutrophil extracellular traps regulate IL-1β-mediated inflammation in familial Mediterranean fever. Ann Rheum Dis 2016;75(1):269-77. https://doi.org/10.1136/annrheumdis-2014-205958.
62. Raju NC, Yi Q, Nidorf M, et al. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: A pilot randomized controlled trial. J Thromb Thrombolysis 2012;33(1):88-94. https://doi.org/10.1007/s11239-011-0637-y.
63. ClinicalTrials.gov. COACS colchicine for acute coronary syndromes; NCT01906749. 2013. https://clinicaltrials.gov/ct2/show/NCT01906749. Accessed August 15, 2019.
64. ClinicalTrials.gov. Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke (CONVINCE). NCT02898610. https://clinicaltrials.gov/ct2/show/NCT02898610. Published 2016. Accessed August 15, 2019.