Colchicine in Acute Coronary Syndrome: When to Commence?

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Expert Analysis

Quick Takes

- The insights emanating from recent large clinical trials studying the role of colchicine as anti-inflammatory treatment in patients with coronary disease come with new questions for regular clinical practice, such as when to commence treatment.
- Current data suggest initiating treatment early after myocardial infarction (MI) or in patients without cardio-renal failure treated in the outpatient clinic.
- The effect of colchicine persists throughout prolonged treatment, irrespective of timing of a prior acute coronary syndrome (ACS).

Patients with coronary disease have a life-long increased risk of developing new major adverse cardiovascular events. Depending on co-morbidities and atherosclerotic burden, patients have a 5-year risk of up to 20% for MI, ischemic stroke, or death.[1,2] A proportion of this risk is attributable to the inflammatory drivers in atherosclerosis, often referred to as the *residual inflammatory risk*.

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CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) confirmed that modulating the inflammatory response by selective cytokine inhibition using the molecular antibody canakinumab can translate to clinical benefit.[4] Shortly after CANTOS, two major clinical trials reported on the efficacy of the broad-acting anti-inflammatory drug colchicine in both acute and chronic coronary disease. COLCOT (Colchicine Cardiovascular Outcomes Trial) recruited patients within 30 days of MI. A total of 4,745 patients was randomized to colchicine 0.5 mg or placebo once daily. The trial showed a 23% relative risk reduction for the occurrence of the primary endpoint (the composite of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization).[5] The LoDoCo2 (Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease 2) trial recruited patients with chronic coronary disease. The trial randomized 5,522 patients to 0.5 mg colchicine or placebo once daily and demonstrated a 31% relative risk reduction for its primary endpoint (the composite of cardiovascular death, MI, ischemic stroke, or ischemia-driven revascularization) compared to placebo.[6]

When pooled, the results of the low-dose colchicine studies show a relative risk reduction of 25% (relative risk 0.75; 95% confidence interval [CI], 0.61-0.91) for major adverse cardiovascular events, with consistent effects on the individual components and in various clinical subgroups.[7]

Colchicine, originally extracted from the autumn crocus (*Colchicum autumnale*), is a widely available drug that is commonly used to treat gout, familial Mediterranean fever, and pericarditis. The mechanisms of action of the drug are broad and relate strongly to the inhibition of microtubule self-assembly. Microtubules are structural components that form the cytoskeleton, contribute to the shape and movement of cells, and facilitate trafficking of components within the cell. Relevant effects in the pathogenesis of atherosclerosis are the ability of colchicine to diminish neutrophil recruitment and adhesion and to inhibit nucleotide-binding oligomerisation domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 inflammasome activity.[8,9] Concentration of colchicine in leucocytes reaches its maximum within 48 hours of a single dose, and chemokine inhibitory effects occur within 6-24 hours after administration in patients with ACS.[10,11] Colchicine inhibits neutrophil degranulation proteins and is associated with a 30-40% reduction in high-sensitivity C-Reactive protein levels and a 16% reduction in interleukin-6 levels in patients with chronic coronary disease.[12,13]

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Colchicine has a clear dose-response effect for side effects.[8] High-dose colchicine (0.5 mg bi-daily or more) is used in gout, pericarditis, and in familial Mediterranean fever. It is also investigated in clinical studies of coronary interventions, post-thoracotomy syndromes, and ablation in atrial fibrillation. The incidence of any adverse side effect is at least twofold higher in studies using high-dose colchicine than the incidence that was observed in the low-dose colchicine studies in coronary disease.[14] However, these adverse effects are often benign and most often concern gastrointestinal upset. Whether the 20% difference in dosage commonly used in the United States (0.6 mg once daily) versus the dosage used in studies so far (0.5 mg once daily) will translate to a clinically relevant increase in adverse events in patients with coronary disease is not known but seems unlikely.

Data on colchicine 0.6 mg and adverse events in coronary disease are scarce. Indirectly inferring a dose effect from current or future studies using 0.6 mg once daily will be challenging because variation in patient populations and run-in schemes also contribute to differences in incidence of side effects. Data on bioavailability of the two dose regimes are also limited. Determining a difference in side effects between 0.5 mg and 0.6 mg once daily would necessitate extrapolating bioavailability data, designing head-to-head comparisons of the two regimes, or using phase IV observational studies comparing the two dosages. The latter two methods need large study sizes to detect the probably subtle difference, if present.

In translating the findings of benefit in coronary disease to regular clinical care of patients post-MI, one of the most relevant questions is when to commence therapy. Recent ancillary analyses have provided more guidance in this regard.[15,16]

All patients in COLCOT had a prior MI. In 40% of patients, study medication was initiated within the first week after MI. Patients who received treatment early were generally younger, more often smokers, and more often taking beta-blockers. Time to treatment as effect modifier for the primary and secondary endpoint was investigated using a stratified post hoc Cox regression analysis. Effect size was most marked in patients who had treatment initiated within 3 days after MI (hazard ratio [HR] 0.52; 95% CI, 0.32-0.84).[15] The subgroup of patients in which therapy was initiated 8 days or more after MI was twice as large. The effect estimate in this subgroup was directionally consistent, albeit smaller and not st

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whether the differences in observed effect size between strata were statistically significant.

The authors made a notable effort to quantify the relation of treatment effect size and time to treatment initiation by analyzing the latter as continuous factor (Figure 1). This analysis confirmed an early benefit of the treatment initiation but also came with imprecision to detect any signal in patients who started treatment more than 8 days after MI. Interestingly, relative risk reduction was greater in patients who commenced treatment more than 21 days after their index infarction. An important caveat in the interpretation of this finding is that not all unequally distributed characteristics were used in adjustment of these estimators. Second, whether this parabolic relation of treatment initiation and effect size—with greater effect size seen in both very early (<3 days) and very late (>21 days) treatment initiation—reflects separate biologic mechanisms of the drug or is a play of chance cannot be distinguished from these data. Early benefits could be based on the potential of colchicine to lower ischemia-reperfusion injury. A 5-day regimen of colchicine 0.5 mg twice daily in patients with ST-segment elevation MI led to smaller infarct sizes measured with magnetic resonance imaging and troponin-T and creatine kinase-MB levels compared to placebo.[17]

Figure 1: Associations Between Time to Treatment Initiation and the Risk of Occurrence of the Primary Composite Endpoint

The HR for the primary end point of composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization for colchicine 0.5 mg once daily or placebo expressed as function of time-to-treatment initiation. The adjusted HR and 95% CI come from a quadratic multivariable Cox regression model. *Adapted with permission from Bouabdallaoui N, Tardif JC, Waters DD, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT).* Eur Heart J *2020;41:4092-9.*[15]

These data suggest that early initiation of low-dose colchicine is justified in patients with MI. However, less than 25% of the COLCOT cohort had follow-up for more than 28 months. When evaluating treatment effect late after a coronary event, data from the LoDoCo2 trial becomes complementary. In contrast to COLCOT, patients from the LoDoCo2 trial were recruited from outpatient clinics, irrespective of a prior coronary event. A fifth of patients in the LoDoCo2 trial had over 4 years of follow-up. In 50% of patients with a history of prior ACS, the most recent event occurred more than 4 years prior to randomization (median time

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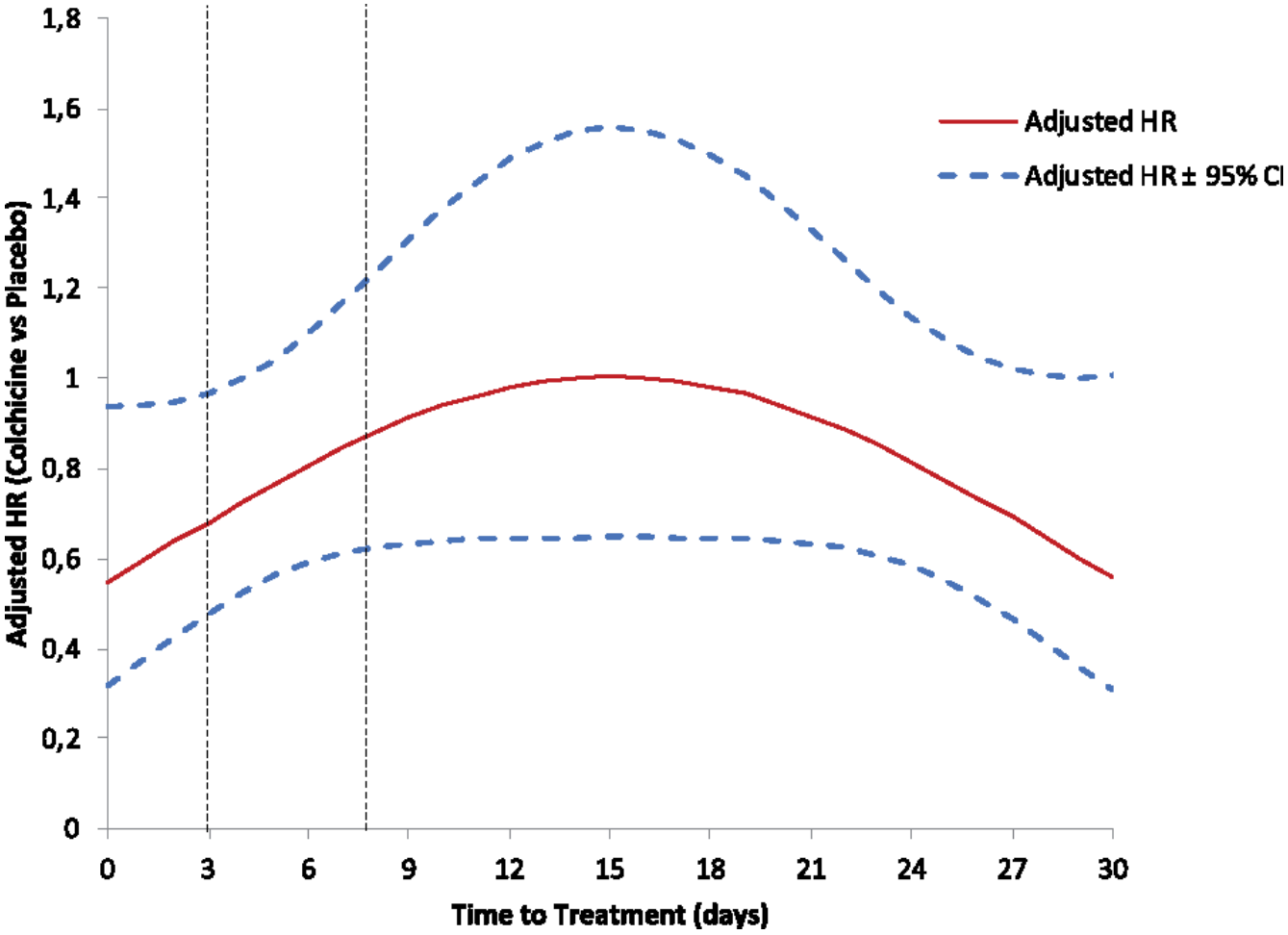

since last ACS = 4 years; interquartile range = 2-10 years). Benefit of treatment in the LoDoCo2 trial was consistently seen in all subgroups of prior ACS (Figure 2):

- For patients with an ACS 6-24 months prior to randomization (HR 0.75; 95% CI, 0.51-1.10)
- For patients with an ACS 2-7 years prior to randomization (HR 0.55; 95% CI, 0.37-0.82)
- For patients with an ACS >7 years prior to randomization (HR 0.70; 95% CI, 0.51-0.96)

Figure 2: Cumulative Incidence of the Primary Composite Endpoint Stratified per Time Since Last ACS

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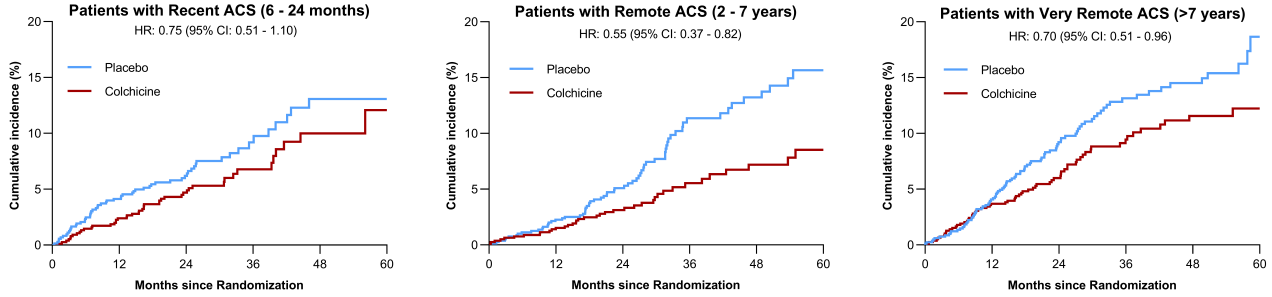
Figure. LoDoCo2 - Cumulative incidence of the primary end point divided by prior ACS status



The primary composite endpoint was cardiovascular death, MI, or ischemic stroke or ischemia-driven coronary revascularization. The HR with 95% CI were estimated from Cox proportional hazard models. *Adapted with permission from Opstal TSJ, Fiolet ATL, van Broekhoven A, et al. Colchicine in Patients With Chronic Coronary Disease in Relation to Prior Acute Coronary Syndrome.* J Am Coll Cardiol *2021;78:859-66.*[16]

Although the relative risk reduction varied from 45% to 25% for these strata, differences were not statistically significant (p for interaction of treatment effect and prior ACS status = 0.590).[16] Trial data on colchicine were collected in a wide range of patients, with and without prior ACS. These data and tabular meta-analyses show consistent effects of treatment, regardless of prior events.[5-7]

Whether a high atherothrombotic risk is associated with greater treatment benefit of colchicine has not yet been confirmed. Although it seems likely that there are atherothrombotic and inflammatory phenotypes that would benefit more from treatment with colchicine, exploratory subgroup analyses from the trials did not yet reveal any clinical effect modifiers. These data come with the caveat that such subgroup analyses are almost always underpowered.

Post hoc sub-analyses from CANTOS did, however, show greatest benefit in those with greatest anti-inflammatory effect.[18] These data are in accordance with the observation that clinical benefit of statins is proportional to their anti-inflammatory effects.[19] Whether such associations also exist for colchicine is not yet known. A large clinical outcomes trial (COLCARDIO-ACS [Colchicine Cardiovascular Outcomes in Acute Coronary Syndrome]) will investigate the effect of the drug in patients with elevated high-sensitivity C-reactive protein. These data will help identify responder populations. As for now, the available evidence suggests that colchicine should be used in the complete range of c

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When generalizing the findings from the colchicine trials, it should be noted that patients with heart failure and renal impairment were excluded from participation, and only a very low number of octogenarians was included in the studies. However, comorbidities were typical of patients with chronic coronary disease, as was concomitant drug use, with almost all patients using intensive lipid-lowering therapy, beta-blockers, and antiplatelet or anticoagulant agents.

The insights emanating from recent large clinical outcome trials on the role of colchicine as anti-inflammatory treatment in patients with coronary disease come with new questions for regular clinical practice. Treatment with colchicine is now incorporated as a recommendation in the 2021 European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice.[20] When considering timing of treatment, the aforementioned subgroup analyses and clinical considerations contribute. Commencing treatment early after MI appears valid, as is starting therapy for patients without cardio-renal failure treated in the outpatient clinic. Current data suggest a consistent effect throughout prolonged treatment, irrespective of timing of a prior ACS.

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Clinical Topics: Acute Coronary Syndromes, Arrhythmias and Clinical EP, Cardiovascular Care Team, Noninvasive Imaging, Pericardial Disease, Prevention, ACS and Cardiac Biomarkers, Implantable Devices, SCD/Ventricular Arrhythmias, Atrial Fibrillation/Supraventricular Arrhythmias, Magnetic Resonance Imaging

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