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Colchicine in Patients With Acute Coronary Syndrome

The Australian COPS Randomized Clinical Trial

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Colchicine for Secondary Cardiovascular Prevention in Coronary Disease

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Abstract

Background:

Inflammation plays a crucial role in clinical manifestations and complications of acute coronary syndromes (ACS). Colchicine, a commonly used treatment for gout, has recently emerged as a novel therapeutic option in cardiovascular medicine owing to its anti-inflammatory properties. We sought to determine the potential usefulness of colchicine treatment in patients with ACS.

Methods:

This was a multicenter, randomized, double-blind, placebo-controlled trial involving 17 hospitals in Australia that provide acute cardiac care service. Eligible participants were adults (18–85 years) who presented with ACS and had evidence of coronary artery disease on coronary angiography managed with either percutaneous coronary intervention or medical therapy. Patients were assigned to receive either colchicine (0.5 mg twice daily for the first month, then 0.5 mg daily for 11 months) or placebo, in addition to standard secondary prevention pharmacotherapy, and were followed up for a minimum of 12 months. The primary outcome was a composite of all-cause mortality, ACS, ischemia-driven (unplanned) urgent revascularization, and noncardioembolic ischemic stroke in a time to event analysis.

Results:

A total of 795 patients were recruited between December 2015 and September 2018 (mean age, 59.8±10.3 years; 21% female), with 396 assigned to the colchicine group and 399 to the placebo group. Over the 12-month follow-up, there were 24 events in the colchicine group compared with 38 events in the placebo group ($P=0.09$, log-rank). There was a higher rate of total death (8 versus 1; $P=0.017$, log-rank)

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were predominantly gastrointestinal symptoms (colchicine, 23.0% versus placebo, 20.8%).

Conclusions:

The addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months in patients with ACS and was associated with a higher rate of mortality.

Registration:

URL: <https://www.anzctr.org.au>; Unique identifier: ACTRN12615000861550.

Clinical Perspective

What Is New?

- Our study demonstrated that addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months in an acute coronary syndromes population.
- Colchicine may be associated with a higher rate of mortality in patients with acute coronary syndromes.

What Are the Clinical Implications?

- Although our trial was negative, exploratory analysis suggested a potential role for colchicine to improve cardiovascular outcomes.
- Despite evidence for its use in acute coronary syndromes, the results of this study suggest further clinical trials are required before colchicine can be safely administered in patients with acute coronary syndromes.

Introduction

Editorial, see p [1901](#)

Despite optimal medical therapy, patients with acute coronary syndromes (ACS) have a substantial ongoing risk of morbidity and mortality.¹ Inflammation plays a pivotal role in all stages of atherosclerosis, from initiation through progression, and ultimately may contribute to the ongoing complications of ACS.^{2–4} Colchicine has recently emerged as a promising novel therapeutic option for cardiovascular disease owing to its potent anti-inflammatory properties.⁵ The recently published CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) demonstrated that a reduction in cardiovascular events after ACS can be achieved through inhibition of interleukin (IL)–1 β .⁶ Colchicine is thought to exert its

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pathogenesis of coronary artery disease (CAD) and thrombotic events of ACS.⁴

Both COLCOT (Colchicine Cardiovascular Outcomes Trial) and the LoDoCo trial (Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease) demonstrated a significant reduction in adverse cardiovascular events in patients with ACS and stable CAD who received colchicine 0.5 mg/d in addition to standard secondary prevention therapies compared with standard medical therapy alone.^{8,9} These data are in line with previous work demonstrating that short-term colchicine therapy significantly reduces levels of inflammatory cytokines in ACS and limits infarct size in patients with ST-segment–elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention.^{10,11} This study was conducted to determine the potential clinical usefulness of colchicine among a broad ACS population.

Methods

All supporting data are available within the article and in the [Data Supplement](#).

Study Design

This study was a randomized, double-blind, placebo-controlled trial to assess the effect of oral colchicine versus placebo in addition to standard secondary prevention therapies on cardiovascular events in patients presenting with ACS. Patients were treated at 17 hospitals in Australia.

Study Patients

Eligible patients were adults (18–85 years of age) who presented with ACS and had evidence of CAD (defined by $\geq 30\%$ luminal stenosis in any epicardial vessel of ≥ 2.5 mm luminal diameter) on coronary angiography, managed with either percutaneous coronary intervention or medical therapy at the discretion of the treating team. ACS was defined as symptoms of acute myocardial ischemia associated with either elevated troponin or ECG changes, which included STEMI, non-STEMI, and unstable angina. Patients with CAD requiring surgical revascularization, with preexisting long-term colchicine use or immunosuppressant therapy, with severe hepatic and renal insufficiency, or with known active malignancy were excluded. Detailed inclusion and exclusion criteria are outlined in the [Supplemental Material in the Data Supplement](#). Eligible patients were approached by the research team after coronary angiography.

Randomization

Patients were randomly assigned to receive either oral colchicine (intervention group) or placebo (control group). Stratified permuted-block randomization, which was concealed from the investigators, was performed with the use of a computer-generated random-sequence and Web-response system. Patients were stratified according to preexisting history of myocardial infarction (MI), diabetes, and recruitment site. Packing and distribution of study medications was performed by an independent pharmaceutical packaging company that was not involved in the rest of the trial. Care was taken to ensure the blinding was maintained among the investigators, patients, research team conducting the follow-up, and clinical event adjudication committee.

To maintain the overall quality and legitimacy of the trial, unblinding of treatment allocation was only permissible in exceptional circumstances when knowledge of the actual treatment was essential for management of an acutely unwell patient.

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management guidelines. Patients who were randomized to the intervention group received 0.5 mg oral colchicine twice daily for the first month, followed by 0.5 mg daily for 11 months; patients in the control group received placebo tablets. Dose reduction of study medication to once daily was permitted if participants developed severe gastrointestinal symptoms within the first month of treatment. Follow-up was conducted by a research team member, who was blinded to the treatment allocation, by structured telephone interviews at 1, 6, and 12 months (or as close to these times as could be managed), and by reviewing primary and secondary care records. Patients who prematurely discontinued the study drug were also followed up and included in the primary intention-to-treat analysis. Medication adherence was assessed by pill count during scheduled interviews and at the end of treatment period. Very few participants completed follow-up at 365 days. All follow-up was completed by 400 days and a secondary analysis was performed at this time point. Blinding of the research team to outcomes was maintained out to 400 days.

Study Outcomes

The primary outcome was a composite of death from any cause, ACS (STEMI/non-STEMI/unstable angina), ischemia-driven urgent revascularization, and noncardioembolic ischemic stroke. The secondary outcome consisted of the components of the primary end point as well as hospitalization for chest pain. We also performed a post hoc analysis after unblinding of the trial using cardiovascular death as opposed to total death as an outcome measure, in line with the recently published COLCOT trial.⁸ Definitions of the major clinical outcomes are provided in the [Table in the Data Supplement](#). Safety was assessed based on adverse events that occurred during treatment or within 7 days after the last dose of a study drug, and were classified according to the Common Terminology Criteria for Adverse Events.⁸

Statistical Analysis

All analyses were conducted using Stata V16 (StataCorp, College Station, Texas). Summary mean (SD), median (interquartile range), or n (%) statistics are presented for all baseline characteristics by treatment group in [Table 1](#). Although not expected, we assessed continuous attributes for differences at baseline using *t* tests or Mann-Whitney *U* tests as appropriate, and categorical variables using χ^2 tests. The primary outcome was a time to event analysis via the log-rank test. Each patient was followed up for a minimum duration of 12 months. A sensitivity analysis accounted for multiple correlated events within an individual by using Cox regression with group assignment as the independent variable, clustering over individual and reporting robust standard errors. The same sensitivity analysis was rerun with confounders age, sex, diabetes status, hypertension, hypercholesterolemia, previous MI, and smoking status (current smoker, ex-smoker, nonsmoker) added into the model. In addition, a secondary prespecified on-treatment analysis was performed based on patients who were both tolerant to and compliant with therapy beyond the first month of randomization. All Cox regression models were validated by checking the proportional hazards assumption (Stata estat phtest command). A multivariable competing risks analysis using the method of Fine and Gray (with confounders as listed above) of all-cause death versus other events was conducted using Stata stcrreg command, clustering over individual. No adjustment was made for multiple comparisons. Results are reported as hazard ratios (HRs) with 95% CI. A *P* value <0.05 (2-tailed) was deemed to be statistically significant.

Table 1. Baseline Characteristics

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Age, y	59.7±10.2	60.0±10.4
Male sex	322 (81)	310 (78)
Hypertension	201 (51)	199 (50)
Diabetes	75 (19)	76 (19)
Current smoking	128 (32)	149 (37)
Hypercholesterolemia	180 (46)	185 (46)
Family history of IHD*	177 (45)	144 (36)
BMI >30 kg/m ²	116 (29)	102 (26)
History of myocardial infarction	59 (15)	59 (15)
History of PCI	51 (13)	50 (13)
History of CABG	15 (4)	19 (5)
History of stroke	5 (1)	11 (3)
History of peripheral vascular disease	9 (2)	9 (2)
Hemoglobin, g/L	143±20	144±18
White cell count, 10 ⁹ /L	9.5±3.2	10.2±8.4
Platelet count, 10 ⁹ /L	238±62	241±96
Creatinine, μmol/L	83±20	81±19
Total cholesterol, mmol/L	4.9±1.2	5.1±1.4
Fasting glucose, mmol/L	6.8±2.5	6.9±5.2
Peak CK, U/L	1143±85	1151±103

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Discharge medications		
Aspirin	393 (99)	391 (98)
Other antiplatelet agent	384 (97)	388 (97)
Statin	389 (98)	397 (99)
β-blocker	320 (81)	337 (85)
ACEi/ARB	350 (88)	341 (86)
Oral hypoglycemic agents	58 (15)	59 (15)
Insulin	26 (7)	19 (5)
Admission diagnosis		
STEMI	182 (48)	208 (53)
NSTEMI	183 (48)	174 (44)
UA	15(4)	11 (3)
Number of patients who underwent PCI	349 (88)	351 (88)
PCI to culprit vessel		
LAD	151 (38)	128 (32)
LCx	73 (18)	84 (21)
RCA	125 (32)	139 (35)
<p>Values are mean±SD or n (%). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CK, creatine kinase; IHD, ischemic heart disease; NSTEMI, non-ST–segment elevation myocardial infarction; LAD, left anterior descending; LCx, left circumflex; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.</p>		

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Sample Size Justification

On the basis of previously published data, we postulated that the control and treatment groups would have combined annual event rates of 7.2% and 3.5%, respectively.^{1,9,12} On this basis, we estimated that a sample size of 1009 patients would provide 80% power at 5% significance to detect this difference, using a log-rank test. We anticipated a total of 49 events in the study cohort, which corresponded to an HR of approximately 0.47, assuming participant attrition of 10% over the period of the study.

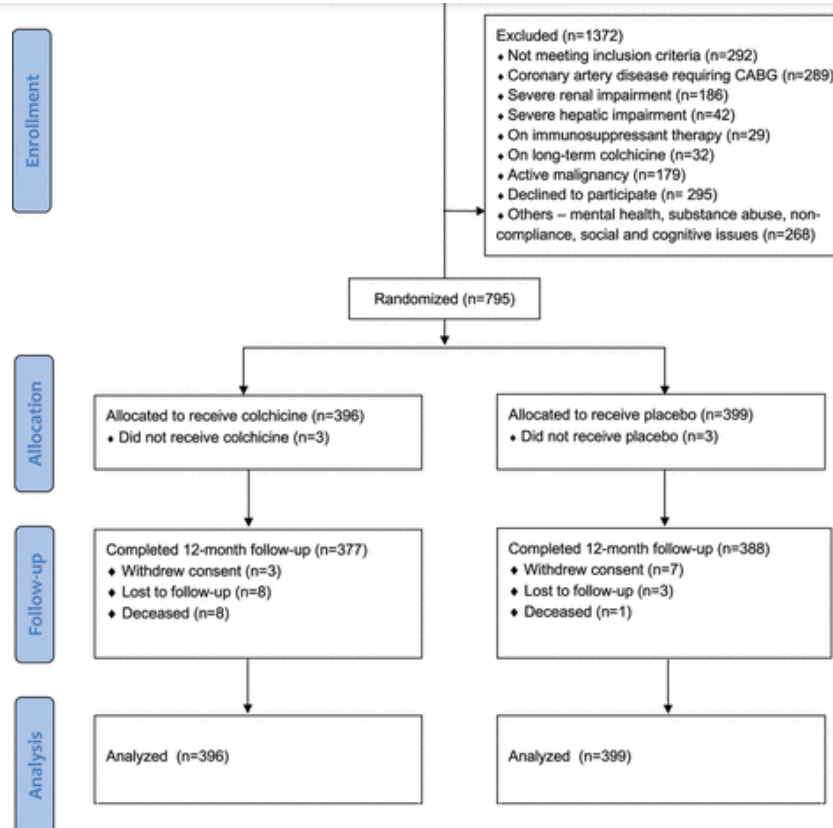
Study Oversight

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by the St Vincent's Hospital Melbourne Human Research Ethics Committee. All the patients provided written informed consent before study entry. An independent ethics committee approved the clinical protocol at each participating center. Safety data were reviewed by an independent academic data monitoring committee every 6 months or at the discretion of the committee. Cardiovascular outcome events were adjudicated by a Clinical Event Committee comprising 2 cardiologists who were independent of the trial and were blinded to the treatment allocations. A list of investigators and committee members is provided in the [Data Supplement](#). Patient enrollment was halted earlier following advice from the trial steering committee because of slower than expected recruitment rate. The steering committee had no knowledge of any trial outcomes before making this decision. The trial was publicly registered (ACTRN12615000861550).

Results

Patients

The trial randomized its first patient in December 2015 and finished recruitment in September 2018. Out of 2167 patients screened (295 declined to participate and 1077 did not meet eligibility criteria), 795 were randomized, with reasons for nonparticipation shown in the consort diagram ([Figure 1](#)). The mean age of the participants was 59.8±10.3 years; 21% of participants were female, 19% had diabetes, 15% had previous MI, and 13% had previous percutaneous coronary intervention ([Table 1](#)). At discharge, 97% of patients were taking dual antiplatelet therapy, 99% statins, 87% renin–angiotensin system inhibitors, and 83% β -blockers.

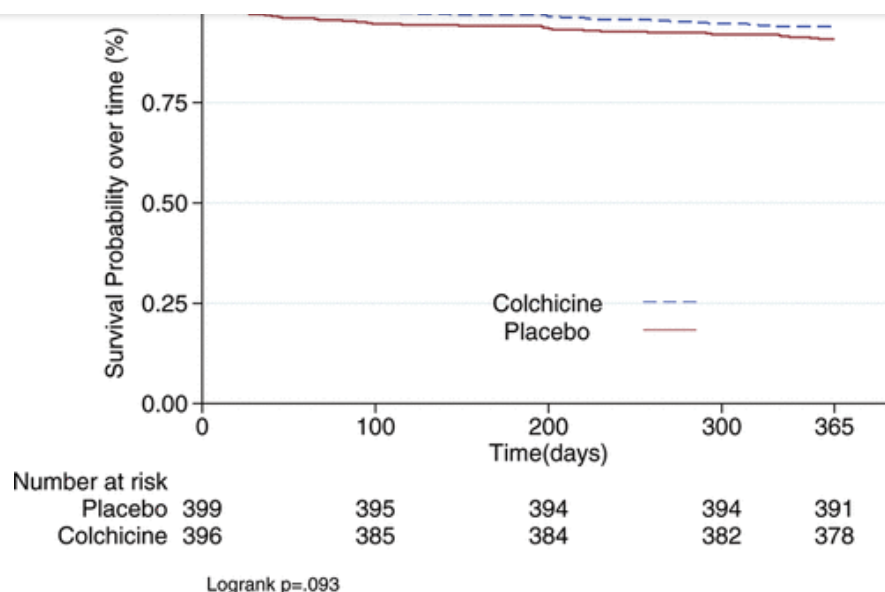
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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the COPS trial (Colchicine in Patients With Acute Coronary Syndromes). CABG indicates coronary artery bypass grafting.

Follow-Up and Clinical End Points

At the end of the study period, 61 (15%) patients in the colchicine group had discontinued the study medication, compared with 33 (8%) patients in the placebo group ($P=0.88$; Fisher exact χ^2). The main reasons for this were gastrointestinal intolerance (9% versus 4%) and personal choice (4% versus 2%). Over the 12-month follow-up period, there was no significant difference in the primary end point in the colchicine group compared with the placebo group (24 [6.1%] versus 38 [9.5%]; $P=0.09$, log-rank test; [Figure 2](#)).

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Figure 2. Kaplan-Meier survival for primary end point in the intention-to-treat population at 365 days. Kaplan-Meier event curves for the primary composite end point of death from all causes, acute coronary syndrome, stroke, and urgent revascularization in the colchicine group and placebo group in a time-to-event analysis.

Secondary and Sensitivity Analyses

In the main sensitivity analysis, HR was 0.65 (95% CI, 0.38–1.09; $P=0.10$), in a time to end point event Cox regression with group as the independent variable. This result remained stable in a further sensitivity analysis (HR, 0.64 [95% CI, 0.37–1.09]; $P=0.10$) when adjusted for age, sex, diabetes status, hypertension, hypercholesterolemia, previous MI, and smoking status, and clustered over individual. Both models satisfied the proportional hazards assumption.

Individual components of the primary end point are highlighted in [Table 2](#). There were differences observed in rates of total death (8 versus 1; $P=0.018$), particularly noncardiovascular death (5 versus 0; $P=0.023$), between treatment groups. A comprehensive summary of the causes of death is listed in [Table 3](#). A total of 5 of the 8 patients who died were still taking colchicine at the time of their death. In other components of the primary end point, there were numeric differences in favor of colchicine and a difference in urgent revascularization (HR, 0.26 [95% CI, 0.07–0.92]; $P=0.037$). An exploratory analysis comparing the effect of colchicine in particular patient subgroups is shown in [Figure 3](#).

Table 2. Clinical End Points (Intention-to-Treat Population)*

End point	Colchicine	Placebo	Hazard ratio (95% CI)	P value
At 365 days				

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Primary composite end point	24	38	0.65 (0.38–1.09)	0.10
Components of primary end point				
Deaths from any cause	8	1	8.20 (1.03, 65.61)	0.047
Cardiovascular death	3	1	3.09 (0.32, 29.71)	0.33
Acute coronary syndrome	11	20	0.56 (0.27–1.18)	0.13
STEMI	3	3		
NSTEMI	4	7		
UA	4	10		
Stroke	2	5	0.41 (0.08–2.10)	0.28
Urgent revascularization	3	12	0.26 (0.07–0.92)	0.037
Hospitalization for chest pain	7	11	0.34 (0.04–3.31)	0.36
At 400 days				
Primary composite end point	24	41	0.60 (0.36–1.01)	0.053
Components of primary end point				
Deaths from any cause	8	1	8.20 (1.03, 65.61)	0.047
Cardiovascular death	3	1	3.09 (0.32, 29.71)	0.33
Acute coronary syndrome	11	22	0.52 (0.25–1.07)	0.08
STEMI	3	3		
NSTEMI	4	8		
UA	4	11		

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Stroke	2	6	0.34 (0.07–1.70)	0.19
Urgent revascularization	3	12	0.26 (0.07–0.92)	0.037
Hospitalization for chest pain	7	11	0.34 (0.04–3.31)	0.36
<p>NSTEMI indicates non-ST–segment elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.</p> <p>* Cox regression model clustered over multiple events with an individual and adjusted for group assignment.</p>				

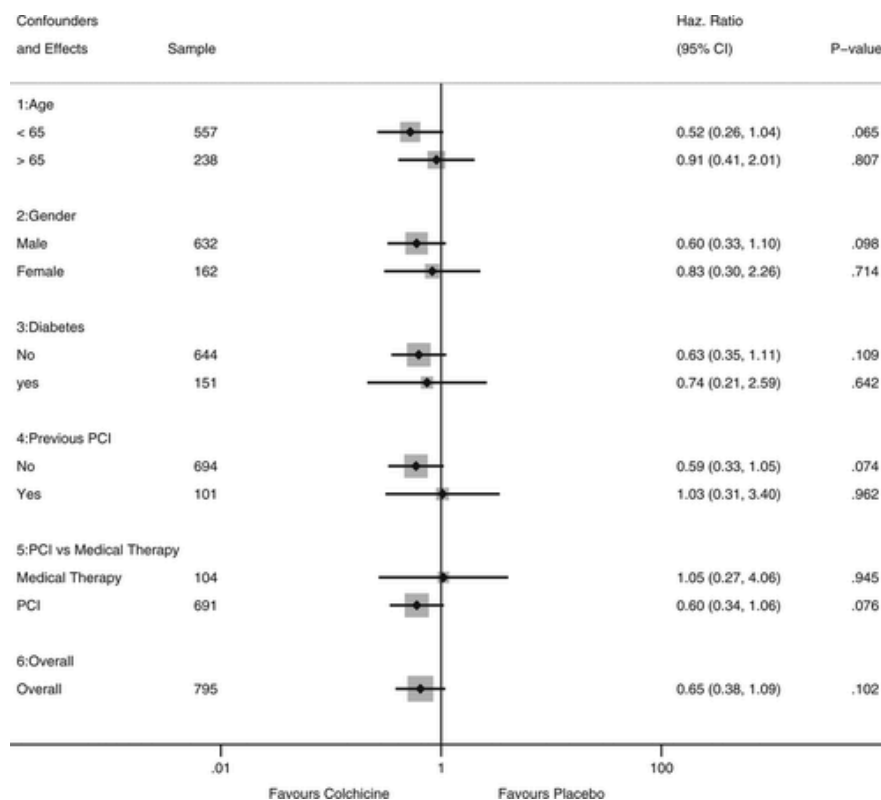
Table 3. Causes of Death

Patient number	Treatment group	Cardiovascular or noncardiovascular death	Early discontinuation (within first 30 days)	Clinical information
1	Colchicine	Cardiovascular death	No	Unconscious collapse with cardiac arrest; CPR performed but unable to be resuscitated; previous angiogram demonstrated occluded RCA with 50% mid-LAD lesion; medically managed
2	Colchicine	Cardiovascular death	No	Found dead in car after morning run; presented with inferior STEMI and PCI to RCA 8 months before death
3	Colchicine	Cardiovascular death	No	Found unresponsive by family; had limb weakness noted the day before; death from stroke
4	Placebo	Cardiovascular death	No	Culprit PCI performed at time of STEMI but severe LCx lesion initially managed medically; represented with STEMI, cardiogenic shock, and PEA/VF arrest; unable to revive
5	Colchicine	Noncardiovascular death	Early discontinuation owing to nausea	Severe community-acquired pneumonia at 11 mo after enrollment
6	Colchicine	Noncardiovascular death	No	Metastatic cancer; developed microangiopathic hemolytic anemia

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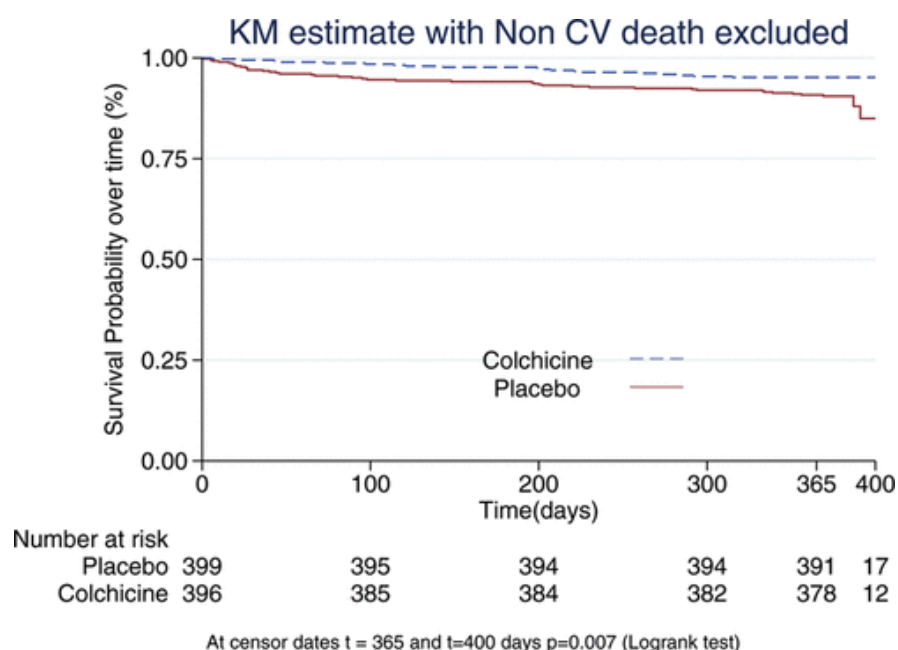
number	group	noncardiovascular death	(within first 30 days)	Clinical information
7	Colchicine	Noncardiovascular death	Early discontinuation owing to diarrhea	Severe community-acquired pneumonia at 11 mo after enrollment
8	Colchicine	Noncardiovascular death	No	Had fever and productive cough for several days but did not seek medical attention; found unresponsive by family; presumed death attributable to sepsis (no autopsy performed)
9	Colchicine	Noncardiovascular death	Early discontinuation owing to personal choice	Acute myeloid leukemia; developed severe sepsis

CPR indicates cardiopulmonary resuscitation; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; RCA, right coronary artery; STEMI, ST-segment–elevation myocardial infarction; and VF, ventricular fibrillation.


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In a post hoc analysis of the composite end point using only cardiovascular death rather than total death (cardiovascular death, stroke, ACS, and urgent revascularization) over the 12-month follow-up there was a significant reduction in events in favor of colchicine (5.0% versus 9.5%; HR, 0.51 [95% CI, 0.29–0.89]; $P=0.019$; [Figure 4](#)).



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Figure 4. Kaplan-Meier (KM) survival for composite end point using cardiovascular (CV) death in the intention-to-treat population at 365 days and 400 days. Kaplan-Meier event curves for the composite end point of death from cardiovascular causes, acute coronary syndrome, stroke, and urgent revascularization in the colchicine group and placebo group in a time-to-event analysis.

Patients who were adherent to the study medication were included in the per protocol on-treatment analysis. The primary outcome occurred in 20 patients in the colchicine group versus 33 patients in the placebo group (5.4% versus 8.5%; HR, 0.67 [95% CI, 0.37–1.18]; $P=0.17$).

At 400 days, there was a statistically significant difference between groups for the primary outcome (ACS, stroke, death, and urgent revascularization), with 24 events in the colchicine group compared with 41 events in the placebo group ($P=0.047$, log-rank test). There was a nominally significant reduction in events using cardiovascular death in the post hoc analysis of the composite end point at 400 days (HR, 0.47 [95% CI, 0.27–0.82]; $P=0.008$).

Safety and Adverse Events

[< back](#)**Table 4. Adverse Events Related to Study Medication**

Event	Colchicine (n=396)	Placebo (n=399)
Any related adverse effect	91 (23.0)	99 (24.8)
Gastrointestinal symptoms including diarrhea, flatulence, and abdominal discomfort*	91 (23.0)	83 (20.8)
Skin rashes	0 (0)	10 (2.6)
Alopecia	0 (0)	1 (0.3)
Paresthesia	0 (0)	2 (0.5)
Myalgia	0 (0)	8 (2.0)
Myelosuppression	0 (0)	0 (0)
Values are n (%).		
* <i>P</i> value for the difference in gastrointestinal symptoms between groups is 0.46.		

Discussion

This study demonstrated that in patients presenting with an ACS, the addition of low-dose oral colchicine to standard medical therapy during hospitalization and continued for 12 months did not affect the rate of the primary composite outcome of death, ACS, ischemia-driven urgent revascularization, and stroke compared with standard medical therapy alone. There was a signal to higher total mortality in the colchicine group.

Recent clinical data have highlighted the therapeutic role of targeting inflammatory pathways to improve outcomes among patients with ACS.¹³ CANTOS demonstrated a reduction of recurrent cardiovascular events in patients with increased high-sensitivity C-reactive protein levels treated with the IL-1 β antagonist canakinumab.⁶ However, because of the modest effect size, cost, subcutaneous administration, and increase in fatal infections seen in the study, generalized use of this drug seems unlikely.

Colchicine is widely prescribed and has a known safety and side effect profile. Although expensive in the United States, colchicine is widely regarded as a low-cost drug. Colchicine has a broad anti-inflammatory action, not only targeting the NLRP3 (NLR family pyrin domain containing 3) inflammasome, whose activation leads to downstream IL-1 β and IL-6 upregulation, but also disrupting microtubules and having

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crystals are known to promote local inflammation and incite plaque instability.^{15–17} Moreover, Martínez et al¹⁰ demonstrated that increased local cardiac production of inflammatory cytokines such as IL-1, IL-18, and IL-6 in patients with ACS was significantly suppressed by oral colchicine (1 mg followed by 0.5 mg an hour later) 6 to 24 hours before cardiac catheterization.

The recently published COLCOT demonstrated the clinical efficacy of using once-daily colchicine among patients with recent ACS in improving the combined end point of cardiovascular death, resuscitated cardiac arrest, stroke, MI, and unplanned hospitalization for unstable angina requiring revascularization.⁸ In addition to medical therapy, colchicine had an HR of 0.77 for reducing this primary end point that was predominantly driven by reductions in stroke and urgent revascularization. These results echo our data but with important differences. These included differences in the inclusion criteria and management of nonculprit vessel disease together with a different dosing schedule. We began all treatment during the index hospitalization, whereas the COLCOT investigators began at a median of 14 days after the initial ACS (although treatment during index admission was allowed). Moreover, we adopted a higher dose of colchicine (0.5 mg twice daily) in the first month, in accordance with previously published data that colchicine administered in this fashion can effectively reduce high-sensitivity C-reactive protein level independent of aspirin and statins in patients with CAD¹⁸ and that once-daily colchicine failed to suppress high-sensitivity C-reactive protein in ACS (LoDoCo-MI study [Low Dose Colchicine After Myocardial Infarction]).¹⁹ In addition, there is evidence of heightened inflammation and increased risk of adverse cardiovascular events in the early phases after an ACS event.²⁰

The LoDoCo trial, which included 23% patients with a previous ACS, demonstrated a significant reduction in the composite incidence of ACS, out-of-hospital cardiac arrest, and noncardioembolic ischemic stroke in patients with stable coronary disease who received 0.5 mg/d colchicine (HR, 0.33; number need to treat, 11; $P<0.001$).⁹ The significance of the results of this trial are uncertain because of its open, single-blinded design.

Our post hoc analyses that included 400-day follow-up as well as using only cardiovascular death rather than total death demonstrated that there was a significant reduction in the primary outcome between groups in favor of colchicine. The extended analysis also suggests that there is an early sustained effect from colchicine that increases over the course of treatment. This may be as a result of both the anti-inflammatory properties and the plaque-modulating effects of colchicine²¹ and may explain the effect on the rates of urgent revascularization.

These results are hypothesis-generating and should be interpreted with caution given the nature of post hoc analyses and the higher mortality signal in the trial.

In our study, the rate of all-cause death and in particular noncardiovascular death was higher in the colchicine group compared with placebo. As shown in [Table 3](#), the cause of noncardiovascular death was related to sepsis in 4 out of the 5 events. A total of 3 out of 4 patients with sepsis-related deaths in the colchicine group discontinued study medication early in the trial (within the first 30 days) and were not taking colchicine at the time of death.

Despite its widely perceived “immunosuppressive” effect, contradictory data suggest colchicine is associated with increased risk of infections. One population-based cohort study in Taiwan involving 24 410

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randomized, controlled trials with a total of 8659 pooled participants) demonstrated no significant difference in infectious events in the colchicine group compared with the noncolchicine group (0.4% versus 2.1%).²³ Another UK-based retrospective large cohort study demonstrated variable risks of contracting respiratory and urinary tract infections with colchicine use in patients with gout, but no difference in risk of infection-related mortality in this cohort.²⁴ This was supported by a systematic review conducted by Hemkens et al²⁵ that showed that continuous long-term colchicine (at least 6 months of treatment for a wide range of inflammatory diseases) versus no or any other treatment not containing colchicine in adult populations did not have any significant association with all-cause mortality (relative risk, 0.94 [95% CI, 0.82–1.09]; 4174 participants, 30 studies; $I^2=27\%$).

Although the higher rates of noncardiovascular deaths seen in our study may reflect type 1 error attributable to imprecision based on the few events for analysis, this finding cannot be ignored and requires further investigation. In the recently published COLCOT, there was a higher risk of pneumonia in the colchicine group compared with the placebo group (0.9% versus 0.4%; $P=0.03$), but no difference in cardiovascular or all-cause mortality.⁸ Our trial used a higher colchicine dose in the first month (0.5 mg twice-daily dosing compared with once-daily dosing in COLCOT) and this may have contributed to the observed higher total death rates in the colchicine group compared with the placebo group. Similarly, CANTOS demonstrated a higher incidence of fatal infection in the canakimumab-treated group compared with placebo but no significant difference in all-cause mortality.⁶ The findings of both COLCOT and CANTOS perhaps indicate that immunomodulating therapy in ACS may bring about cardiovascular benefit at a cost of fatal or nonfatal infections. Future larger studies are warranted to evaluate the safety of colchicine in the ACS population, in particular noncardiovascular deaths and serious infections.

Limitations

There are several limitations to our study. This was an Australian, multicenter trial; unlike COLCOT, it was not international. We had much slower than anticipated recruitment, with a failure to reach the target study number. There were many potential reasons for this but a lack of remuneration for patient recruitment was a major factor. As such, this may have affected the overall generalizability of the trial. We may therefore have lacked the power to demonstrate the true benefit of colchicine. Despite this lower number of recruited patients, we achieved a higher than expected event rate. This may have resulted because of our broad real-world study with minimal restrictions on inclusion criteria resulting in a higher-risk population than studied in other randomized trials.

This was an investigator-initiated study with limited funding and as such we had limited staff performing phone follow-up. This sometimes meant that there were difficulties contacting patients at 12 months despite efforts to do so. Even though follow-up occurred within the 365-day window, a large proportion of patients were followed up outside this time frame (median 371 days), and so to allow as complete follow-up as possible we decided to extend follow-up and censor at 400 days, particularly because more events appeared later.

Because the follow-up was performed over the phone, there is the potential of reporting bias, with patients omitting clinical events. We attempted to minimize this wherever possible by contacting all primary health care providers and reviewing all hospital records during the study period.

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Tolerability of Colchicine

As observed in previous studies, gastrointestinal symptoms were common (up to 20%) in patients treated with colchicine.^{9,23} Intriguingly, the rates of gastrointestinal adverse effects in our study were similar between colchicine and placebo groups, and this was also reported in COLCOT (17.5% colchicine versus 17.6% placebo). A total of 39 (5%) patients discontinued study medications within the first 30 days because of gastrointestinal intolerance (28 [7%] in the colchicine group versus 11 [3%] in the placebo group), which may influence the conduct and planning of a future colchicine study.

Colchicine stands out as a promising therapy for cardiovascular disease. Its known long-term safety profile and efficacy in dampening inflammation make it an attractive agent for further research in patients with CAD, who remain at heightened risk for adverse cardiovascular outcomes after their index events. Despite the Australian COPS trial (Colchicine in Patients With Acute Coronary Syndromes) being negative, there are elements of the trial that when taken together with COLCOT provide evidence supporting the use of colchicine in ACS, but further trials are needed to evaluate the safety and efficacy of colchicine in an ACS population, in particular the higher rates of noncardiovascular death seen in our study. If proven clinically beneficial, colchicine may have an enormous impact on cardiovascular patients globally, owing to its widespread availability and ease of administration.

Conclusions

In patients presenting with ACS, addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months and was associated with a higher rate of mortality.

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Disclosures

None.

Supplemental Materials

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Data Supplement Table

List of participating sites, principal investigators, and committee members

Footnotes

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