

CLINICAL RESEARCH

Clinical Trial

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

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Objectives

The objective of this study was to determine whether colchicine 0.5 mg/day can reduce the risk of cardiovascular events in patients with clinically stable coronary disease.

Background

The presence of activated neutrophils in culprit atherosclerotic plaques of patients with unstable coronary disease raises the possibility that inhibition of neutrophil function with colchicine may reduce the risk of plaque instability and thereby improve clinical outcomes in patients with stable coronary disease.

Methods

In a clinical trial with a prospective, randomized, observer-blinded endpoint design, 532 patients with stable coronary disease receiving aspirin and/or clopidogrel (93%) and statins (95%) were randomly assigned colchicine 0.5 mg/day or no colchicine and followed for a median of 3 years. The primary outcome was the composite incidence of acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke. The primary analysis was by intention-to-treat.

Results

The primary outcome occurred in 15 of 282 patients (5.3%) who received colchicine and 40 of 250 patients (16.0%) assigned no colchicine (hazard ratio: 0.33; 95% confidence interval [CI] 0.18 to 0.59; $p < 0.001$; number needed to treat: 11). In a pre-specified secondary on-treatment analysis that excluded 32 patients (11%) assigned to colchicine who withdrew within 30 days due to intestinal intolerance and a further 7 patients (2%) who did not start treatment, the primary outcome occurred in 4.5% versus 16.0% (hazard ratio: 0.29; 95% CI: 0.15 to 0.56; $p < 0.001$).

Conclusions

Colchicine 0.5 mg/day administered in addition to statins and other standard secondary prevention therapies appeared effective for the prevention of cardiovascular events in patients with stable coronary disease. (J Am Coll Cardiol 2013;61:404–10) © 2013 by the American College of Cardiology Foundation

Despite routine use of antiplatelet and statin therapy, patients with coronary disease continue to be at risk of cardiovascular events, possibly because these treatments fail to target some of the inflammatory pathways implicated in the disease. The atherosclerotic wall is subject to injurious forces that promote plaque instability. The response to injury within the diseased vessel is dependent on the architecture and content of atherosclerotic plaques (1,2). Lipid-rich plaques with a neovascular base are particularly susceptible to the effect of injury, which may leave them

vulnerable to neutrophil infiltration (3). Neutrophils that enter the interstitial space may become activated upon exposure to the plaque contents, inciting an aggressive inflammatory response that may accelerate plaque instability, increasing the risk of plaque enlargement and rupture and hence increasing the risk of clinical events (3).

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This dynamic sequence of events raises the possibility that inhibition of neutrophil function may lead to a reduction in the risk of plaque instability and thereby reduction in the risk of disease progression. Colchicine has anti-inflammatory properties, including an antitubulin effect that inhibits neutrophil function (4), and this effect is believed to account for the efficacy of colchicine in the prevention of acute manifestations of gout and familial Mediterranean fever (FMF). Patients with FMF receive lifelong colchicine therapy at a dose of 1 to 2 mg/day, which is well tolerated (5,6). Although short-term use of low-dose colchicine has been found to have no effect on

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stent-related disease (7), no studies have been performed to determine whether long-term use of low-dose colchicine can be tolerated or can reduce the risk of de novo vascular events caused by disruption of native atherosclerotic plaques in patients with stable coronary disease.

We therefore conducted a prospective, randomized, observer-blinded endpoint (PROBE) trial to determine whether adding colchicine 0.5 mg/day to standard secondary prevention therapies including aspirin and high-dose statins reduces the risk of cardiovascular events in patients with objectively diagnosed and clinically stable coronary disease.

Methods

Study conduct and design. The LoDoCo (Low-Dose Colchicine) trial was conducted under the auspices of the Heart Research Institute of Western Australia. It was designed by the principal investigators, registered with the Australian Clinical Trial Registry (ACTRN 12610000293066), and received ethics approval from the Human Research Ethics Committee at Sir Charles Gairdner Hospital, Perth, Western Australia in July 2008. There was no external funding source.

We employed a PROBE design (8). Eligible consenting patients with established coronary disease presenting for routine clinical review were randomized to receive colchicine 0.5 mg/day or no colchicine without any other changes to their medical therapy. All outcomes were evaluated by an experienced adjudicator blinded to the treatment allocation.

Study size and eligibility. The study population was planned to include 250 patients randomized to the control group and 250 patients randomized to treatment who were tolerant of colchicine for at least 4 weeks after the date of their randomization.

Patients were eligible for inclusion if they met each of the following criteria: 1) angiographically proven coronary disease; 2) age 35 to 85 years; 3) clinically stable for at least 6 months; 4) no major competing comorbidities or contraindication to colchicine therapy; 5) considered to be compliant with therapy and attending routine cardiology follow-up appointments; and 6) willing to provide consent and be randomized into the study. Patients with a history of bypass surgery were only eligible if they had undergone bypass surgery more than 10 years before, had angiographic evidence of graft failure, or had undergone stenting since their bypass surgery. All patients signed informed consent before randomization.

Randomization. The randomization sequence was computer generated, concealed from the investigators at all times, and managed by a research assistant who had no involvement in the evaluation or management of study patients. Once the assistant received the consent form, the patients' demographic data were entered into the database, and the investigators and patients were advised in writing of the treatment group to which the patient had been assigned.

Despite use of the lowest dose of colchicine available, it was anticipated that a number of patients would withdraw

from therapy early after randomization because of gastrointestinal side effects. To ensure that the requisite number of patients in the treatment arm were actually tolerant of treatment, the protocol allowed for the research assistant to assign a newly recruited patient to treatment if a patient discontinued colchicine because of side effects in the first month. Patients who were intolerant of therapy remained in the study, were followed in the usual manner, and were included in the primary intent-to-treat analysis.

Intervention. Patients randomized to active treatment were given a prescription for colchicine 0.5 mg daily by their referring cardiologist. The drug was dispensed by their usual chemist, and if requested, patients were reimbursed for the cost of these prescriptions. All other treatments were continued as usual.

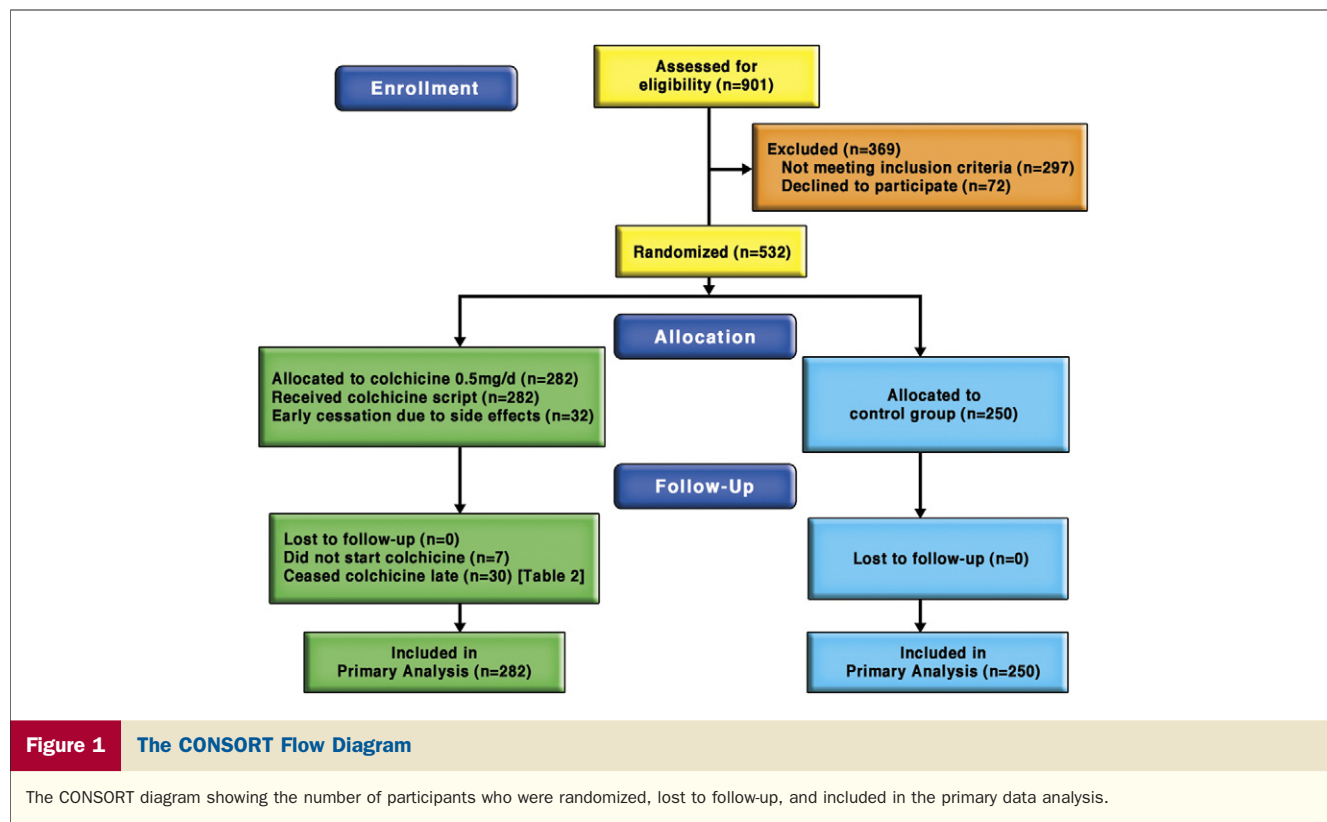
Follow-up and definition of clinical outcomes. Patient compliance with treatment and outcome data were collected at routine follow-up visits and at the time of any unplanned hospital admissions.

Acute coronary syndrome (ACS) was defined as either: 1) acute myocardial infarction (AMI), as evidenced by acute ischemic chest pain associated with a rise in serum troponin above the upper limit of normal (9); or 2) unstable angina (UA), as evidenced by a recent acceleration of angina unassociated with a rise in serum troponin but associated with angiographic evidence of a change in the patient's coronary anatomy (UA Braunwald classification types IB and IIB) (10). ACS was characterized as being stent related if there was evidence of significant in-stent stenosis or acute stent thrombosis. Out-of-hospital cardiac arrest was defined as: 1) a sudden death as evidenced on the patient's death certificate; or 2) a nonfatal out-of-hospital cardiac arrest, defined as a recovery from sudden collapse associated with documented asystole, ventricular tachycardia, or ventricular fibrillation. Noncardioembolic ischemic stroke was defined as computed tomography—or magnetic resonance imaging—proven ischemic stroke judged by the treating neurologist as not being due to atrial fibrillation or intracranial hemorrhage. The primary efficacy outcome was the composite of ACS, fatal or nonfatal out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke. Secondary outcomes were individual components of the primary outcome and the components of ACS unrelated to stent disease.

Timelines. The pre-specified study duration was a minimum follow-up of 2 years in all patients. Accordingly, the study was closed on May 31, 2012. During May, all living patients were contacted by phone to collect compliance and outcome data from the last date of follow-up. Final outcome

Abbreviations and Acronyms

ACS	= acute coronary syndrome(s)
AMI	= acute myocardial infarction
FMF	= familial Mediterranean fever
HR	= hazard ratio
MI	= myocardial infarction
PROBE	= prospective, randomized, observer-blinded endpoint
UA	= unstable angina



data were available for all patients, and no patients were lost to follow-up.

Statistical power. Assuming that the control group had a combined event rate (ACS, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) of 8% (11), an accrual interval of 2 years, and a follow-up after the accrual interval of 2 years, the planned sample size provided >80% power to detect a hazard ratio (HR) of ≤ 0.50 based on a 2-sided significance level of 5%.

Data analysis. Summary statistics, including mean and standard deviation, were calculated for all baseline characteristics by treatment arm. All time-to-event outcomes were calculated in days by subtracting the date of randomization from either the: 1) date of event or death; or 2) trial termination date for those patients not experiencing the defined event.

As pre-specified, the primary efficacy analysis was based on the intent-to-treat principle. The intent-to-treat analysis included all randomized patients and all events during the time from randomization to trial termination. The trial termination date was fixed as May 31, 2012. A secondary pre-specified on-treatment analysis was also performed, based on patients who were both tolerant and compliant to therapy beyond the first month of randomization. All events during the time from randomization until noncompliance with the colchicine treatment regime were included in this analysis.

The time to first event for all outcomes is presented using a Kaplan-Meier plot. The primary efficacy outcome was analyzed using a Cox proportional hazards model including

treatment group coded as control or colchicine. The secondary outcomes were analyzed similarly. In addition, the primary analysis was stratified by sex, age, diagnosis of diabetes, past myocardial infarction (MI), UA, coronary bypass surgery, coronary angioplasty, and therapy with aspirin, clopidogrel, or both; high-dose statin therapy (defined as a dose of statin equivalent to atorvastatin 40 mg or more); beta-blockers; calcium blockers; and angiotensin-converting enzyme inhibitors.

Results

Study population. Between August 2008 and May 2010, 901 patients with stable coronary disease attending routine outpatient cardiology appointments were assessed for eligibility for the study. Of these, 297 (33%) did not meet the entry criteria, 72 (8%) declined to participate, and 532 (59%) were enrolled into the study, 250 of whom were randomized to the control group and 282 to treatment. Of those randomized to treatment, 32 (11%) reported early intolerance due to gastrointestinal side effects and 7 patients subsequently reported that they chose to not start therapy (Fig. 1). All 532 randomized patients were followed for the duration of the study period, which ranged from a minimum of 24 to a maximum of 44 months. Median follow-up was 36 months. Baseline characteristics according to randomized treatment group are shown in Table 1. Both groups were well matched for important clinical characteristics, although more patients in the colchicine group were taking

Table 1 Study Population

	Control	Treatment
Total	250	282
Mean age, yrs	67 ± 9.2	66 ± 9.6
Male	222 (89)	251 (89)
Diabetes	69 (28)	92 (33)
Smoker	14 (6)	10 (4)
Past AMI or UA	61 (24)	64 (23)
CABG	39 (16)	62 (22)
PTCA	138 (55)	169 (60)
Aspirin and/or clopidogrel	235 (94)	262 (93)
DAPT	24 (10)	38 (13)
High-dose statin	235 (94)	271 (96)
Beta-blocker*	178 (71)	176 (62)
Calcium channel blocker†	25 (10)	52 (18)
ACE inhibitor	150 (60)	155 (55)

Values are n, mean ± SD, or n (%). *p < 0.05. †p < 0.01 for the comparison of the distribution between treatment and control.

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CABG = coronary artery bypass surgery; DAPT = dual antiplatelet therapy (aspirin and clopidogrel); PTCA = percutaneous coronary angioplasty; UA = unstable angina.

calcium channel blockers and fewer were on beta-blocker therapy. Almost all patients in each group were on antiplatelet therapy and high-dose statin therapy.

Late discontinuations. Thirty patients ceased colchicine therapy after a mean period of 2.36 years. Therapy was ceased due to an unrelated intercurrent illness in 11 patients, by choice in 5, and for a variety of possible drug-related effects in 14 patients (4.9%) as described in Table 2.

Outcomes. A primary outcome occurred in 55 of 532 patients, including 15 of 282 patients (5.3%) assigned to colchicine treatment and 40 of 250 patients (16%) assigned to the control group (HR: 0.33; 95% confidence interval [CI] 0.18 to 0.59; p < 0.001; number needed to treat: 11). A sensitivity analysis was performed for the primary outcome and adjusted for the usage of calcium channel blockers and beta-blocker therapy. These results were consistent with the primary analysis.

The time to first clinical event in each group by treatment is shown in Figure 2. The effect of colchicine on the primary outcome was evident early, and the benefits of colchicine

Table 2 Withdrawals From Therapy

Early withdrawals	32 (11)
Late withdrawals*	30 (11)
Unrelated intercurrent illness	11 (3.9)
Patient choice	5 (1.8)
Perceived side effects	
Intestinal upset	7 (2.5)
Myalgia	2 (0.90)
Myositis	1 (<0.5)
Rash	1 (<0.5)
Alopecia	1 (<0.5)
Itch	1 (<0.5)
Peripheral neuritis	1 (<0.5)

Values are n (%). *Withdrawals after 30 days; average time to withdrawal was 2.36 years.

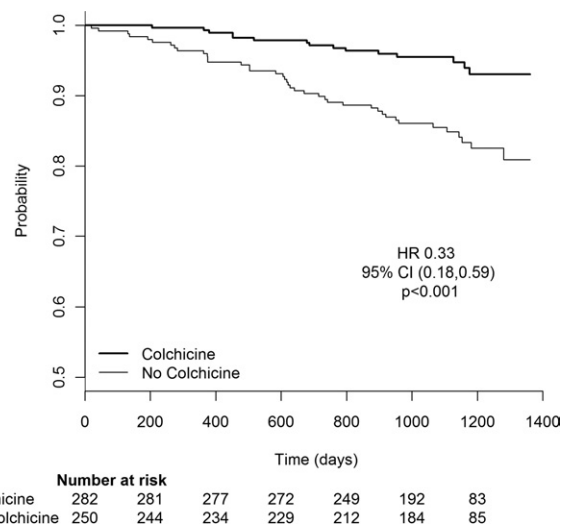


Figure 2 Freedom From the Primary Outcome

Freedom from the primary outcome (acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) by treatment. CI = confidence interval; HR = hazard ratio.

continued to accrue throughout the follow-up period. Results of the primary analysis were consistent in all subgroups examined (Fig. 3). There was no evidence of differential treatment effects based on any of the clinical or therapeutic variables.

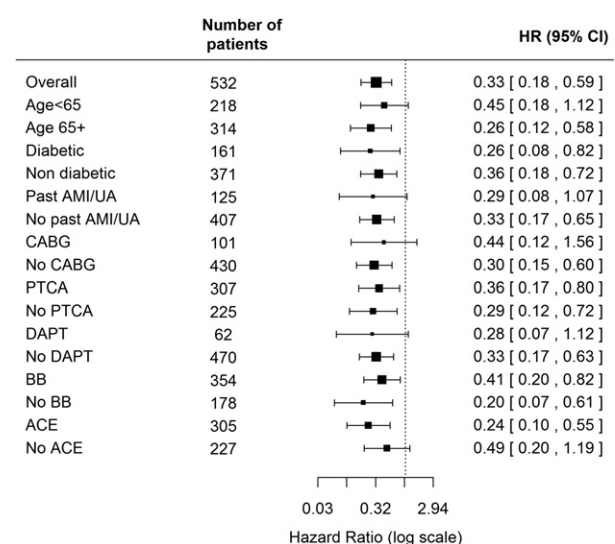


Figure 3 Forest Plot

The hazard ratios and 95% CI of the primary outcome in subgroups defined by patient demographics, past medical history, and concomitant treatments. ACE = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; BB = beta-blocker; CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; PTCA = percutaneous coronary angioplasty; UA = unstable angina; other abbreviations as in Figure 2.

Table 3 Primary Outcome and Its Components

	Control (n = 250)	Treatment (n = 282)	HR (95% CI)	p Value
Primary outcome	40 (16)	15 (5.3)	0.33 (0.18–0.59)	<0.001
Components of primary outcome				
Acute coronary syndrome	34 (13.6)	13 (4.6)	0.33 (0.18–0.63)	<0.001
OOH cardiac arrest	2 (0.8)	1 (0.35)*	0.47 (0.04–5.15)	0.534
Noncardioembolic stroke	4 (1.6)	1 (0.35)	0.23 (0.03–2.03)	0.184
Components of ACS				
Stent-related	4 (1.6)	4 (1.4)		NS
Nonstent-related	30 (12)	9 (3.2)	0.26 (0.12–0.55)	<0.001
Nonstent-related AMI	14 (5.6)	4 (1.6)	0.25 (0.08–0.76)	0.014
Nonstent-related UA	16 (12)	5 (2.4)	0.27 (0.10–0.75)	0.011

Values are n (%). *Nonfatal.

ACS = acute coronary syndrome; NS = nonsignificant; OOH = out of hospital; other abbreviations as in Table 1.

The reduction in the primary outcome was largely driven by the reduction in the number of patients presenting with ACS (13 of 282 [4.6%] vs. 34 of 250 [13.4%]; HR: 0.33; 95% CI: 0.18 to 0.63; $p < 0.001$). Out-of-hospital cardiac arrest and noncardioembolic ischemic stroke were infrequent, but their numbers were also reduced in the treatment group (Table 3).

Of the 47 patients who presented with ACS, the event was stent related in 8 (17%; 2 in each group had evidence of acute stent thrombosis, and 2 in each group had evidence of significant in-stent stenosis). Further analysis confirmed that patients randomized to treatment were less likely to present with ACS unrelated to stent disease (9 of 282 [3.2%] vs. 30 of 250 [12%]; HR: 0.26; 95% CI: 0.12 to 0.55; $p < 0.001$), be it associated with AMI (4 of 282 [1.4%] vs. 14 of 250 [5.6%]; HR: 0.25; 95% CI: 0.08 to 0.76; $p = 0.014$) or UA (5 of 282 [1.8%] vs. 16 of 250 [6.4%]; HR: 0.27; 95% CI: 0.10 to 0.75; $p = 0.011$) (Fig. 4, Table 3).

Of 39 patients randomized to treatment who did not receive therapy beyond the first month because of early intolerance or noncompliance, 4 (10%) presented with ACS due to acute stent thrombosis ($n = 1$) and UA ($n = 3$). Patients who were both compliant and tolerant to therapy beyond the first month of randomization had significantly fewer events than the control patients (11 of 243 [4.5%] vs. 40 of 250 [16%]; HR: 0.29; 95% CI: 0.15 to 0.56; $p < 0.001$). The results of all on-treatment analyses were consistent with those based on intent-to-treat analyses (Table 4).

Ten patients in the control group died compared with 4 patients in the colchicine group. Of the 10 control patients, 5 died of presumed cardiac cause, 2 following an out-of-hospital cardiac arrest, 2 from cardiogenic shock following AMI, and 1 following bypass surgery. All 4 patients in the colchicine group died of noncardiac causes.

Discussion

The LoDoCo trial demonstrated that the addition of colchicine 0.5 mg/day to standard therapy in patients with stable coronary disease significantly reduced the risk of a cardiovascular event, including ACS, out-of-hospital car-

diac arrest, and noncardioembolic ischemic stroke. The benefits of colchicine were achieved on a background of widespread use of effective secondary prevention strategies, including high-dose statins, as evidenced by the low event rate in the control group (11). The effect of adding colchicine became evident early, continued to accrue over time, and was largely driven by a reduction in ACS unrelated to stent disease.

These results are important because they suggest that colchicine, in contrast to its apparent lack of effect in the prevention of stent-related disease (7), may have a role in the prevention of cardiovascular events caused by instability of native atherosclerotic plaques in patients with stable coronary disease, possibly by inhibiting an inflammatory pathway that has been identified in unstable native coronary plaques (3).

The presence of activated neutrophils in the plaques of patients with unstable coronary syndromes (3) suggested that they may play a key role in the transformation of a stable, to an unstable plaque. Although the mechanism of benefit of colchicine was not the subject of this study, the drug is known to have protean effects that may be responsible for the improved clinical outcome of patients observed in this study, the best documented of which is the inhibition of neutrophil chemotaxis, ingress, and activation within a proinflammatory environment (12) such as may exist in an unstable plaque.

Indirect support for a beneficial effect of colchicine on cardiovascular disease comes from retrospective observations that continuous use of colchicine was associated with a lower than expected risk of AMI in patients with FMF (13) and gout (14), and the demonstration that low-dose colchicine can reduce levels of high-sensitivity C-reactive protein in patients with stable coronary disease (15).

Although most physicians are familiar with the short-term use of colchicine from its widespread use in gout and pericarditis (16), few will have prescribed it continuously to their patients. However, the long-term use of colchicine, at doses of 1 to 2 mg/day, has been well documented to be safe and reasonably well tolerated in patients with FMF (17).

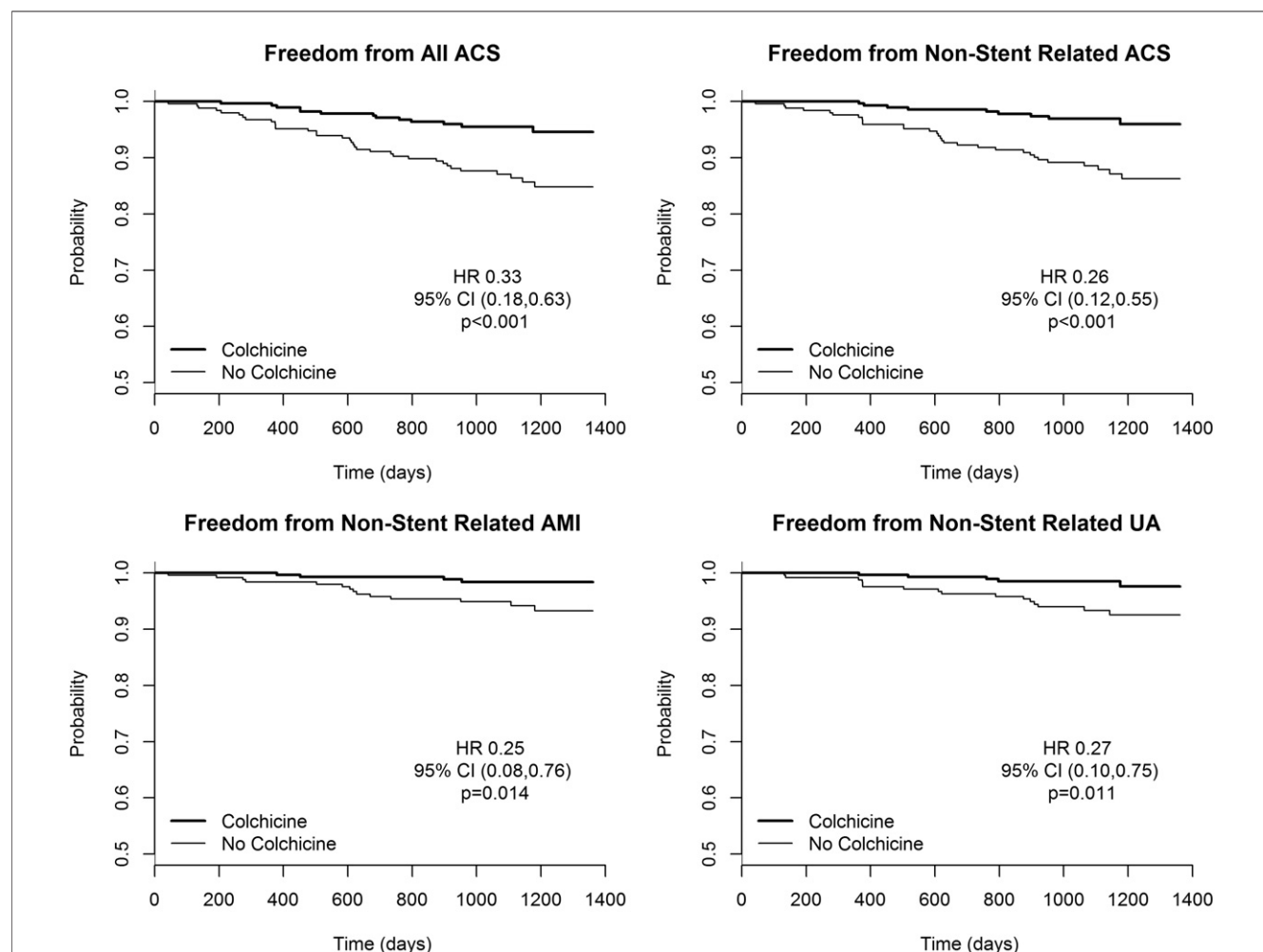


Figure 4 Freedom From Acute Coronary Syndrome

Freedom from acute coronary syndrome (ACS) and components of this outcome (AMI and UA) unrelated to stent disease. Abbreviations as in Figures 2 and 3.

In this study, despite use of the lowest available dose of colchicine, 11% of patients withdrew from therapy early due to intestinal intolerance, and a further 5% ceased therapy late due to a range of possible side effects, indicating that

widespread use of the drug may be limited by its side effects. In this regard, it is important to appreciate that combining colchicine with statin therapy has been reported to increase the risk of myalgia and rarely acute rhabdomyolysis in

Table 4 Primary Outcome and Its Components (On-Treatment Analysis)

	Control (n = 250)	Treatment (n = 243)	HR (95% CI)	p Value
Primary outcome	40 (16)	11 (5.3)	0.29 (0.15–0.56)	<0.001
Components of primary outcome				
Acute coronary syndrome	34 (13.6)	9 (4.6)	0.28 (0.13–0.58)	<0.001
OOH cardiac arrest	2 (0.8)	1 (0.35)*	0.55 (0.05–6.03)	0.622
Noncardioembolic stroke	4 (1.6)	1 (0.35)	0.27 (0.03–2.42)	0.242
Components of ACS				
Stent-related	4 (1.6)	3 (1.4)		NS
Nonstent-related	30 (12)	6 (3.2)	0.21 (0.09–0.50)	<0.001
Nonstent-related AMI	14 (5.6)	4 (1.6)	0.30 (0.10–0.91)	0.033
Nonstent-related UA	16 (12)	2 (2.4)	0.13 (0.03–0.57)	0.007

Values are n (%). *Nonfatal.
Abbreviations as in Tables 1 and 3.

patients with renal impairment (18). Further, because colchicine has a narrow therapeutic index, extreme care must be taken to avoid accidental overdoses, which may be fatal. Hence, patients receiving regular colchicine therapy require close clinical supervision.

Despite these caveats, colchicine may be an attractive therapy for secondary prevention of cardiovascular events because it is simple to use and inexpensive, it appears to be highly effective, and long-term use rarely leads to any major irreversible long-term toxicity. Before the drug is adopted clinically, however, it would be important for the findings of this hypothesis-generating study to be confirmed in larger studies of patients with coronary atherosclerosis.

Study limitations. This study has a number of limitations. The use of a PROBE design had the advantages of convenience, reduced cost, and fewer safety concerns; however, it may be subject to outcome ascertainment and reporting bias. Although the decision to allow the research assistant to assign additional patients to treatment if a patient reported early intolerance to therapy had the potential to introduce bias to the randomization process, this was largely avoided because at all times, the investigators remained unaware as to whether a newly recruited patient would be randomized to colchicine or control or would be replacing an intolerant patient. Further, because the treatment groups remained well matched at baseline, the primary events occurred over a 3- to 4-year period after randomization, all randomized patients were followed and included in the primary intent-to-treat analysis, and the results are extremely robust, it is extremely unlikely that our approach materially affected the results or conclusions.

The results of this study were almost entirely driven by an effect of colchicine on nonfatal cardiovascular events that disrupt patients' lives, portend their prognosis, and are responsible for a significant cost burden on the community. Although a favorable trend toward improved mortality was demonstrated, much larger studies are required to confirm whether colchicine may actually reduce the risk of fatal cardiac events. It would be of special interest to examine the value of initiating colchicine in patients recently hospitalized for ACS because they remain at particularly high risk of recurrent events for several months due to disruption of both culprit and nonculprit plaques (19).

Conclusions

In summary, colchicine 0.5 mg/day given in addition to high-dose statins and other standard secondary prevention therapies appeared effective for the prevention of cardiovascular events in patients with stable coronary disease. The major implications of these findings are that it may be possible to reduce the risk of cardiovascular events in patients with stable coronary disease by targeting an inflammatory pathway that has been identified in native unstable

atherosclerotic plaques using a low dose of colchicine. Despite the problems with early intolerance, it would appear that colchicine is a worthy candidate drug for future secondary prevention trials in patients with stable coronary disease.

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REFERENCES

1. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92:657–71.
2. van der Wal AC, Becker AE. Atherosclerotic plaque rupture—pathologic basis of plaque stability and instability. *Cardiovasc Res* 1999;41:334–44.
3. Naruko T, Ueda M, Haze K, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. *Circulation* 2002;106:2894–900.
4. Ben Chetrit E, Levy M. Colchicine: 1998 update. *Semin Arthritis Rheum* 1998;28:48–59.
5. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med* 1986;314:1001–5.
6. Cerquaglia C, Diaco M, Nucera G, La Regina M, Montalto M, Manna R. Pharmacological and clinical basis of treatment of familial Mediterranean fever (FMF) with colchicine or analogues: an update. *Curr Drug Targets Inflamm Allergy* 2005;4:117–24.
7. O'Keefe JH, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol* 1992;19:1597–600.
8. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Prospective Randomized Open Blinded End-Point. Blood Press* 1992;1: 113–9.
9. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007;50:2173–95.
10. Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation* 2000;102:118–22.
11. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010;304:1350–7.
12. Schattner A. Colchicine—expanding horizons. *Postgrad Med J* 1991; 67:223–6.
13. Langevitz P, Livneh A, Neumann L, et al. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. *Isr Med Assoc J* 2000;2:9–12.
14. 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;39:1458–64.
15. Nidorf SM, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. *Am J Cardiol* 2007;99:805–7.
16. Imazio M, Cecchi E, Demarie D, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the Colchicine for Acute Pericarditis (COPE) trial. *Circulation* 2005;112:2012–6.
17. Kallinich T, Haffner D, Niehues T, et al. Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. *Pediatrics* 2007;119:e474–83.
18. Alayli G, Cengiz K, Canturk F, Durmus D, Akyol Y, Menekse E. Acute myopathy in a patient with concomitant use of pravastatin and colchicine. *Ann Pharmacother* 2005;39:1358–61.
19. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226–35.

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