COLCHICINE

AN OLD ACQUAINTANCE IN NEW ATTIRE?

Presented by:

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OVERVIEW OF THIS PODCAST

- Pharmacologic properties
- Colchicine Toxicity
- Colchicine in Pericarditis
- Colchicine in Coronary artery disease
- Colchicine in Stroke
- Colchicine in COVID-19

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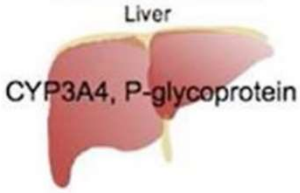
PHARMACOLOGIC PROPERTIES

- Colchicine is a tricyclic, lipid-soluble alkaloid with a long terminal half-life (20 to 40 hours) and bioavailability ranging from 24% to 88% . Within the bloodstream, ~40% of colchicine binds to albumin.
- Although peak plasma concentrations occur 1 hour after administration, maximal anti-inflammatory effects develop over 24 to 48 hours, based on intra-leukocyte accumulation. Colchicine reaches much higher concentrations within leukocytes than in plasma, and persists there for several days after ingestion, with concentrations ranging from 4 to 64 ng/1.
- CYP3A4 and P-glycoprotein are largely responsible for colchicine metabolism. CYP3A4 and P-glycoprotein are also largely responsible for colchicine's numerous drug-drug interactions, as each interacts with a range of other drugs. Because of CYP3A4 interactions, colchicine metabolism is impaired in patients taking clarithromycin, fluoxetine, paroxetine, nefazodone, indinavir and other protease inhibitors, tolbutamide and azole antifungals, cimetidine, and several non-dihydropyridine calcium channel blockers, each of which is metabolized through this pathway.

Chappey ON, Niel E, Wautier JL, et al. Colchicine disposition in human leukocytes after single and multiple oral administration. Clin Pharmacol Ther. 1993; 54(4):360–7

Metabolism



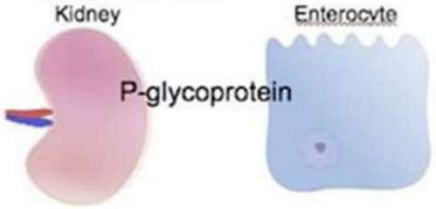
CYP3A4 inhibitors

Strong inhibitors

- Clarithromycin
- Telithromycin
- Nefazodone
- Indinavir
- Saquinavir
- Ritonavir
- Atazanavir
- Ketaconazole
- Itraconazole
- Grapefruit juice
- Erythromycin
- Fluconazole
- Verapamil
- Diltiazem
- Fluoxetine
- Paroxetine
- Cimetidine

Weak inhibitors

Excretion



P-glycoprotein inhibitors

- Cyclosporine
- Ketoconazole
- Tacrolimus
- Clarithromycin
- Verapamil
- Diltiazem
- Ranolazine
- Itraconazole
- Grapefruit juice
- Saquinavir
- Telapravir
- Lovastatin
- Simvastatin
- Budesonide
- Dexamethasone
- Hydrocortisone
- Erithromycin
- Atorvastatin

FDA prescribing information for colchicine. Available at: http://www.accessdata.fda.gov/scripts/ cder/drugsatfda/index.cfm

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COLCHICINE TOXICITY

- The commonest side effects of colchicine are gastrointestinal, with nausea, vomiting and particularly diarrhea occurring in five to ten percent of patients even at recommended doses. Dose reduction may permit resolution of these symptoms. Colchicine doses of 0.5 to 0.8 mg/kg are highly toxic, and doses of more than 0.8 mg/kg are typically lethal;
- to reduce the risk of irreversible bolus overdose, the FDA withdrew approval for intravenous colchicine.
- Acute overdose usually manifests as gastrointestinal symptoms within 24 hours of ingestion, widespread organ system dysfunction (renal failure, circulatory collapse, marrow failure, muscle weakness, rhabdomyolysis and respiratory failure) within seven days, and finally either resolution of symptoms or worsening organ dysfunction and death. Treatment for acute colchicine overdose is supportive.
- Chronic colchicine overdose can occur when daily colchicine doses are not adjusted for reduced renal function or interacting medications; colchicine neuromyopathy and cytopenias are classic features of chronic-type overdose.

Mullins ME, Carrico EA, Horowitz BZ. Fatal cardiovascular collapse following acute colchicine ingestion. J Toxicol Clin Toxicol. 2000; 38(1):51–4

Aghabiklooei A, Zamani N, Hassanian-Moghaddam H, Nasouhi S, Mashayekhian M. Acute colchicine overdose: report of three cases. Reumatismo. 2013; 65(6):307–11.

COLCHICINE IN PERICARDITIS

- The early years: prospective open-label cohorts (1987–2005)
- The use of colchicine for acute pericarditis was first proposed by Rodriguez de la Serna et al. in Barcelona in 1987 based on its efficacy in preventing polyserositis in patients with familial Mediterranean fever. He reported on three patients who had recurrent pericarditis (two idiopathic and one with systemic lupus erythematosus), despite adequate treatment with corticosteroids. All were treated with colchicine (1 mg/ day) with tapering of the corticosteroids over 2 months. There were no relapses throughout the follow-up period of 15– 35 months.

doi:10.1093/eurheartj/ehx246

COLCHICINE IN PERICARDITIS

- Randomized clinical trials (2005–14)
- Recurrent pericarditis:
- Three RCTs, all led by Imazio, have been published to date. The CORE (COlchicine for REcurrent pericarditis) trial in 2005, the CORP (COlchicine for Recurrent Pericarditis) trial in 2011; and the CORP-2 (efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis) trial in 2014 investigated the safety and efficacy of colchicine as an adjunct to conventional therapy for recurrent pericarditis.
- In the most recent and largest CORP-2 trial, the proportion of patients with recurrent pericarditis was 26 (21.6%) of 120 in the colchicine group and 51 (42.5%) of 120 in the placebo group (relative risk 0.49; 95% CI 0.24–0.65; P ¼ 0.0009; number needed to treat, 5).

doi:10.1093/eurheartj/ehx246

Acute pericarditis

- The COPE (Colchicine for acute PEricardtis) Trial in 2005 and the ICAP (Investigation on Colchicine for Acute Pericarditis) trial in 2013 aimed to verify the safety and efficacy of colchicine as an adjunct to conventional therapy for the first episode of acute pericarditis. These trials included 120 and 240 patients, respectively, all recruited in Italian centres. Similar to the data reported for recurrent pericarditis, both trials showed that colchicine, when added to conventional antiinflammatory therapy, significantly reduced the rate of incessant or recurrent pericarditis in patients with acute pericarditis.

Post-pericardiotomy syndrome

- Post-pericardiotomy syndrome (PPS) is a troublesome complication of cardiac surgery, occurring in 10–45% of cases. Three RCTs have evaluated the use of colchicine in this context.
- Imazio et al., once again performed two large RCTs to settle this issue, the COPPS (COlchicine for the Prevention of the Postpericardiotomy Syndrome) and the COPPS-2 trials published in 2010 and 2014, respectively, to test the efficacy and safety of colchicine for the primary prevention of PPS. Both studies enrolled 360 patients in multiple Italian sites. In COPPS, colchicine was initiated on the third post-operative day and significantly reduced the incidence of PPS at 12 months compared with placebo (8.9 vs. 21.1%, respectively; P¼ 0.002; number needed to treat, 8), without significant side effects.1

doi:10.1093/eurheartj/ehx246

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What do guidelines say?

The 2015 European Society of Cardiology (ESC) guidelines for the diagnosis and management of pericardial diseases gave colchicine a 1A recommendation for both acute and recurrent pericarditis as a first-line adjunct to aspirin/NSAIDs. The recommended treatment duration is 6 months in recurrent and 3 months in acute pericarditis, with dosing adjusted to body weight (0.5 mg once daily for patients 70 kg and 0.5 mg twice daily for patients contraindications and it is tolerated. Preventive administration of colchicine is recommended for 1 month.

Table 1 **Primary outcomes of the Cochrane database of systematic reviews (modified from ref. 23)**

	Risk of relapse without colchicine	Risk of relapse with colchicine over 18 months	Number of patients with adverse effects for 100 treated
Acute pericarditis	20–30%	8–15%	10
Recurrent pericarditis	40–50%	15–20%	10

Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lionis C, Maisch B, Mayosi B, Pavie A, Ristic AD, Sabaté Tenas M, Seferovic P, Swedberg K, Tomkowski W; ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015 Nov 7;36(42):2921-2964. doi: 10.1093/eurheartj/ehv318. Epub 2015 Aug 29. PMID: 26320112; PMCID: PMC7539677.

COLCHICINE FOR SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

- LODOCO trial
- LODOCO2 trial
- COLCOT trial
- COPS trial
- COLCHICINE-PCI trial

https://doi.org/10.1016/j.cjca.2020.10.006

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LODOCO
LOW-DOSE COLCHICINE FOR SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

Study Design
•Parallel
•Placebo Controlled
•Randomized
•Stratified
Patient Populations:
•Angiographic proof of CAD:
- Clinically stable for >6 months
- Patients with CABG included if surgery >10 years or graft failure or stenting
•Ages from 35-85 years
•No other major competing comorbidity or contraindication to colchicine
•Not taking colchicine for any other purpose
•Considered compliant with their usual therapy

Duration of follow-up: 3 years
Mean patient age: 66.5 years
Percentage female: 11%

Primary Endpoints:
•Primary outcome composite (time to first occurrence):
- ACS event
- Cardiac arrest with resuscitation
- Noncardioembolic ischemic stroke

Secondary Endpoints:
•The time to each component of the primary outcome
•The time to ACS and each of its components (acute myocardial infarction and unstable angina) unrelated to stent disease

Drug/Procedures Used:
Patients were randomized in a 1:1 fashion to either colchicine 0.5 mg/d or matching placebo.
Concomitant Medications:
High-dose statin (95%), aspirin and/or clopidogrel (94%), beta-blockers (67%), angiotensin-converting enzyme inhibitors (58%)

http://dx.doi.org/10.1016/j.jacc.2012.10.027

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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.

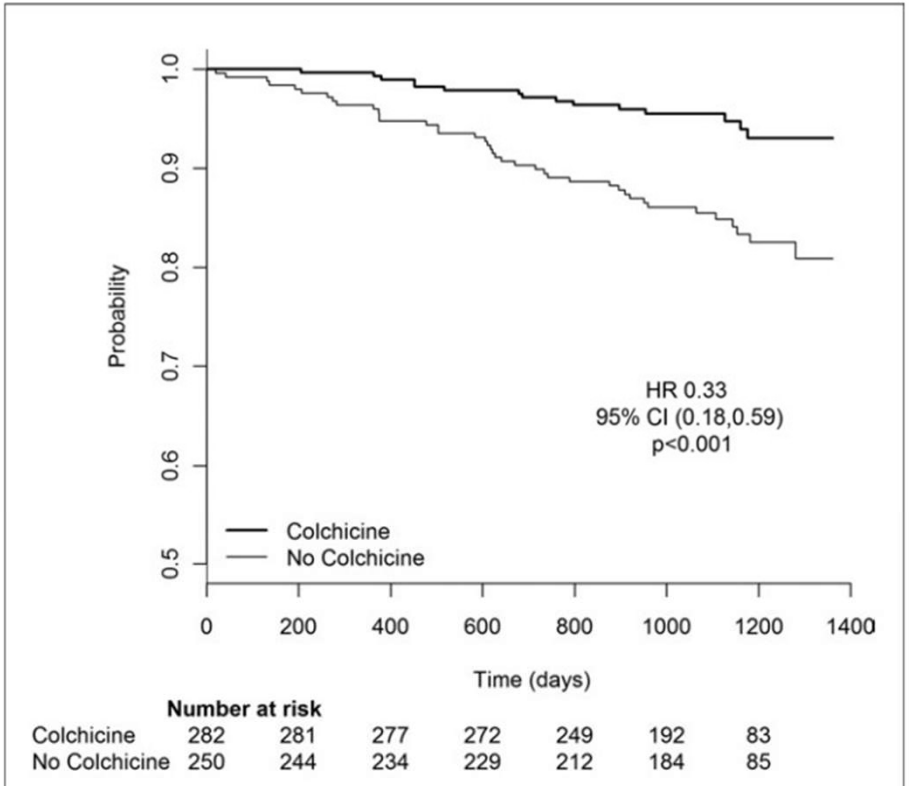


Figure 2 Freedom From the Primary Outcome

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.

http://dx.doi.org/10.1016/j.jacc.2012.10.027

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.

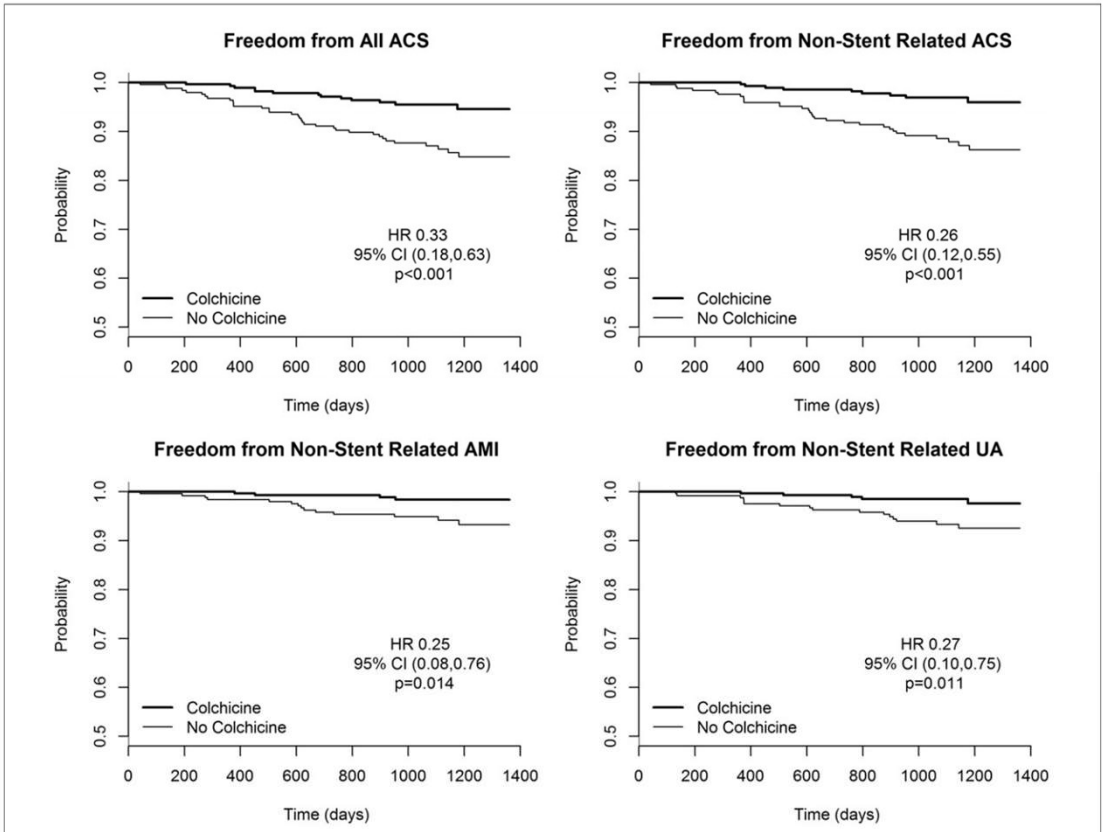


Figure 4 Freedom From Acute Coronary Syndrome

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.

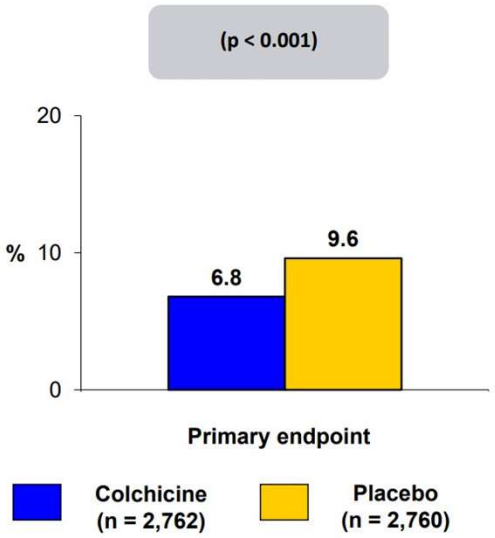
http://dx.doi.org/10.1016/j.jacc.2012.10.027

LoDoCo2

#ESCCongress

AMERICAN COLLEGE of CARDIOLOGY

Trial Description: Patients with stable ischemic heart disease (SIHD) were randomized in a 1:1 fashion to either colchicine 0.5 mg daily or placebo. Patients were followed for a median of 28.6 months.



RESULTS

- Primary endpoint, CV death, MI, stroke, ID-revascularization: colchicine vs. placebo: 6.8% vs. 9.6%; HR 0.69, 95% CI 0.57-0.83 ($p < 0.001$)
- CV death, MI, stroke: 4.2% vs. 5.7% ($p = 0.007$), all-cause mortality: 2.6% vs. 2.2% ($p > 0.05$), Non-CV mortality: 0.7 vs. 0.5 events/100-PY; HR 1.51, 95% CI 0.99-2.31
- MI: 3.0% vs. 4.2% ($p = 0.01$)

CONCLUSIONS

- Colchicine improves CV outcomes among patients with SIHD compared with placebo. Reductions were noted in MI and ID-revascularization; however, there was a signal towards higher non-CV mortality with colchicine
- Unclear if non-CV mortality finding is a true signal or a chance finding, but will need to be carefully assessed going forward; noted in COPS trial as well

Nidorf SM, et al. N Engl J Med 2020;383:1838-47

DOI: 10.1056/NEJMoa2021372

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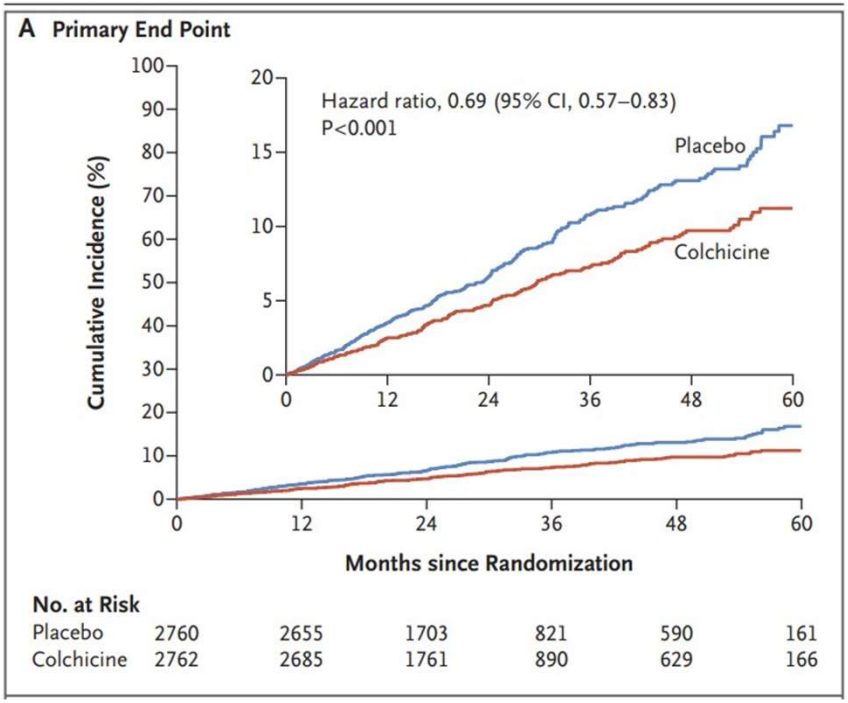

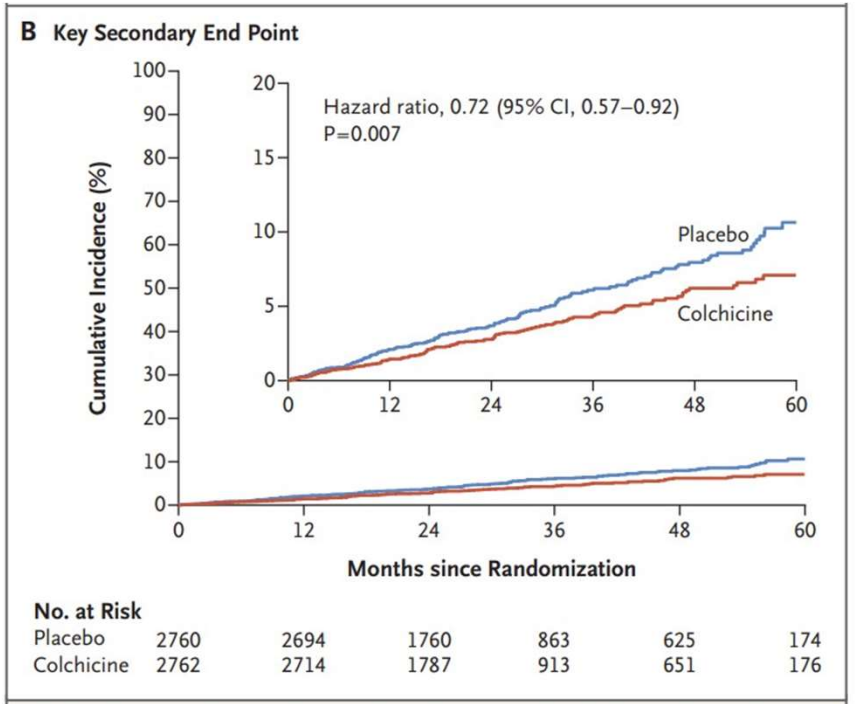

Figure 2. Cumulative Incidence of the Primary End Point and the Key Secondary End Point.

Panel A shows the cumulative incidence of the primary composite end point of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization, and Panel B shows the cumulative incidence of the key secondary composite end point of cardiovascular death, myocardial infarction, or ischemic stroke. The inset in each panel shows the same data on an enlarged y axis.

DOI: 10.1056/NEJMoa2021372

End Point	Colchicine (N=2762)		Placebo (N=2760)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/100 person-yr*	*no. of patients (%)*	*no. of events/100 person-yr*		
Primary end point						
Cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization	187 (6.8)	2.5	264 (9.6)	3.6	0.69 (0.57–0.83)	<0.001
Secondary end points in ranked order						
Cardiovascular death, myocardial infarction, or ischemic stroke	115 (4.2)	1.5	157 (5.7)	2.1	0.72 (0.57–0.92)	0.007
Myocardial infarction or ischemia-driven coronary revascularization	155 (5.6)	2.1	224 (8.1)	3.0	0.67 (0.55–0.83)	<0.001
Cardiovascular death or myocardial infarction	100 (3.6)	1.3	138 (5.0)	1.8	0.71 (0.55–0.92)	0.01
Ischemia-driven coronary revascularization	135 (4.9)	1.8	177 (6.4)	2.4	0.75 (0.60–0.94)	0.01
Myocardial infarction	83 (3.0)	1.1	116 (4.2)	1.5	0.70 (0.53–0.93)	0.01
Ischemic stroke	16 (0.6)	0.2	24 (0.9)	0.3	0.66 (0.35–1.25)	0.20
Death from any cause	73 (2.6)	0.9	60 (2.2)	0.8	1.21 (0.86–1.71)	
Cardiovascular death	20 (0.7)	0.3	25 (0.9)	0.3	0.80 (0.44–1.44)	
Additional end points						
The primary end point in the first LoDoCo trial	201 (7.3)	2.7	290 (10.5)	4.0	0.67 (0.56–0.81)	
New onset or first recurrence in atrial fibrillation or atrial flutter	126 (4.6)	1.7	148 (5.4)	2.0	0.84 (0.66–1.07)	
Deep-vein thrombosis or pulmonary embolism or both	17 (0.6)	0.2	16 (0.6)	0.2	1.06 (0.53–2.10)	
Any myocardial infarctions	85 (3.1)	1.1	117 (4.2)	1.5	0.72 (0.54–0.95)	
New-onset diabetes	34 (1.2)	—	49 (1.8)	—	0.69 (0.44–1.06)	

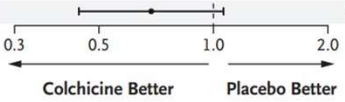

Figure 3. Key End Points and their Components.

The cause-specific hazard ratios were estimated from Cox proportional-hazard regression analysis with death from noncardiovascular causes or death from any cause as a competing risk event. Myocardial infarction refers to spontaneous (nonprocedural) myocardial infarction. The primary end point in the first low-dose colchicine (LoDoCo) trial was a composite of sudden cardiac death, nonfatal out-of-hospital cardiac arrest, acute coronary syndrome (myocardial infarction or unstable angina irrespective of revascularization), or atherosclerotic ischemic stroke. Any myocardial infarctions refers to either spontaneous or procedural myocardial infarctions. The ratio for new-onset diabetes is presented as a cumulative incidence ratio because time-to-event data were not collected. The size of the data points is inversely proportional to the precision (the standard error of the log of the hazard ratios or cumulative incidence ratio) of the estimates, with larger data points representing more precise estimates. The testing hierarchy for statistical significance was broken at the end point of ischemic stroke.

DOI: 10.1056/NEJMoa2021372

Cost-Effectiveness of Low-Dose Colchicine after Myocardial Infarction in the COLchicine Cardiovascular Outcomes Trial (COLCOT)

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Overview of COLCOT[1]

- Randomized, double-blind, placebo-controlled trial
- Patients who had a myocardial infarction ≤30 days were randomized 1:1 to low dose colchicine (0.5 mg per day) or placebo
- 4,745 randomized patients
  (Colchicine: N=2,366 and Placebo: N=2,379)
- Follow-up: 2 years
- Primary composite endpoint included:
  - Death from cardiovascular causes
  - Resuscitated cardiac arrest
  - Myocardial infarction
  - Stroke
  - Urgent hospitalization for angina leading to revascularization

[1]Tardif JC et al. *N Engl J Med.* 2019; 381:2497-2505.

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

End Point	Colchicine (N = 2366)	Placebo (N = 2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

* Only the initial event was counted in the analyses of time to first event for the primary composite end point and for the secondary composite end point. In the component analysis, the different types of events were counted separately.
† The log-rank test and the multivariable Cox proportional-hazards model including age, history of diabetes, previous coronary revascularization, and previous heart failure yielded similar P values.
‡ The secondary composite end point included death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, and stroke.

DOI: 10.1056/NEJMoa1912388

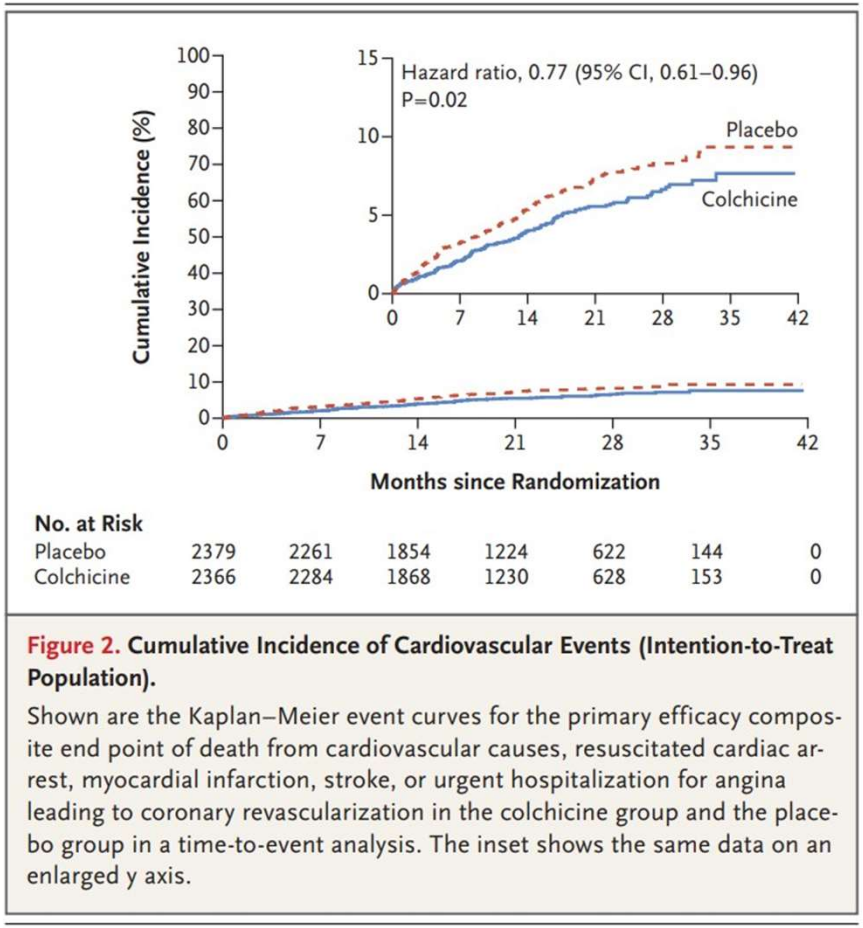


Figure 2. Cumulative Incidence of Cardiovascular Events (Intention-to-Treat Population).

Shown are the Kaplan–Meier event curves for the primary efficacy composite end point of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization in the colchicine group and the placebo group in a time-to-event analysis. The inset shows the same data on an enlarged y axis.

Table 3. Adverse Events (Safety Population).*

Event	Colchicine (N=2330)	Placebo (N=2346)	P Value
	number of patients (percent)		
Any related adverse event†	372 (16.0)	371 (15.8)	0.89
Adverse events			
Gastrointestinal event	408 (17.5)	414 (17.6)	0.90
Diarrhea	225 (9.7)	208 (8.9)	0.35
Nausea	43 (1.8)	24 (1.0)	0.02
Flatulence	15 (0.6)	5 (0.2)	0.02
Gastrointestinal hemorrhage	7 (0.3)	5 (0.2)	0.56
Anemia	14 (0.6)	10 (0.4)	0.40
Leukopenia	2 (0.1)	3 (0.1)	0.66
Thrombocytopenia	3 (0.1)	7 (0.3)	0.21
Serious adverse events			
Any serious adverse event‡	383 (16.4)	404 (17.2)	0.47
Gastrointestinal event	46 (2.0)	36 (1.5)	0.25
Infection	51 (2.2)	38 (1.6)	0.15
Pneumonia	21 (0.9)	9 (0.4)	0.03
Septic shock	2 (0.1)	2 (0.1)	0.99
Hospitalization for heart failure	25 (1.1)	17 (0.7)	0.21
Cancer§	43 (1.8)	46 (2.0)	0.77

DOI: 10.1056/NEJMoa1912388

COPS TRIAL

- 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

DOI: 10.1161/CIRCULATIONAHA.120.050771

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

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

NSTEMI indicates non-ST–segment elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.

*Cox regression model clustered over multiple events with an individual and adjusted for group assignment.

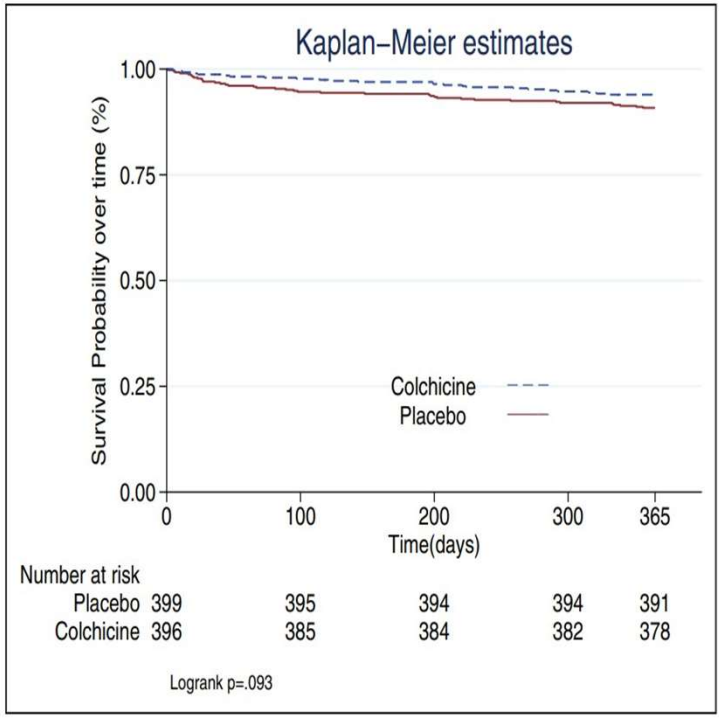


Figure 2. Kaplan-Meier survival for primary end point in the intention-to-treat population at 365 days.
Kaplan-Meier event curves for the primary composite end point of death from all causes, acute coronary syndrome, stroke, and urgent revascularization in the colchicine group and placebo group in a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

DOI: 10.1161/CIRCULATIONAHA.120.050771

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
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.

DOI: 10.1161/CIRCULATIONAHA.120.050771

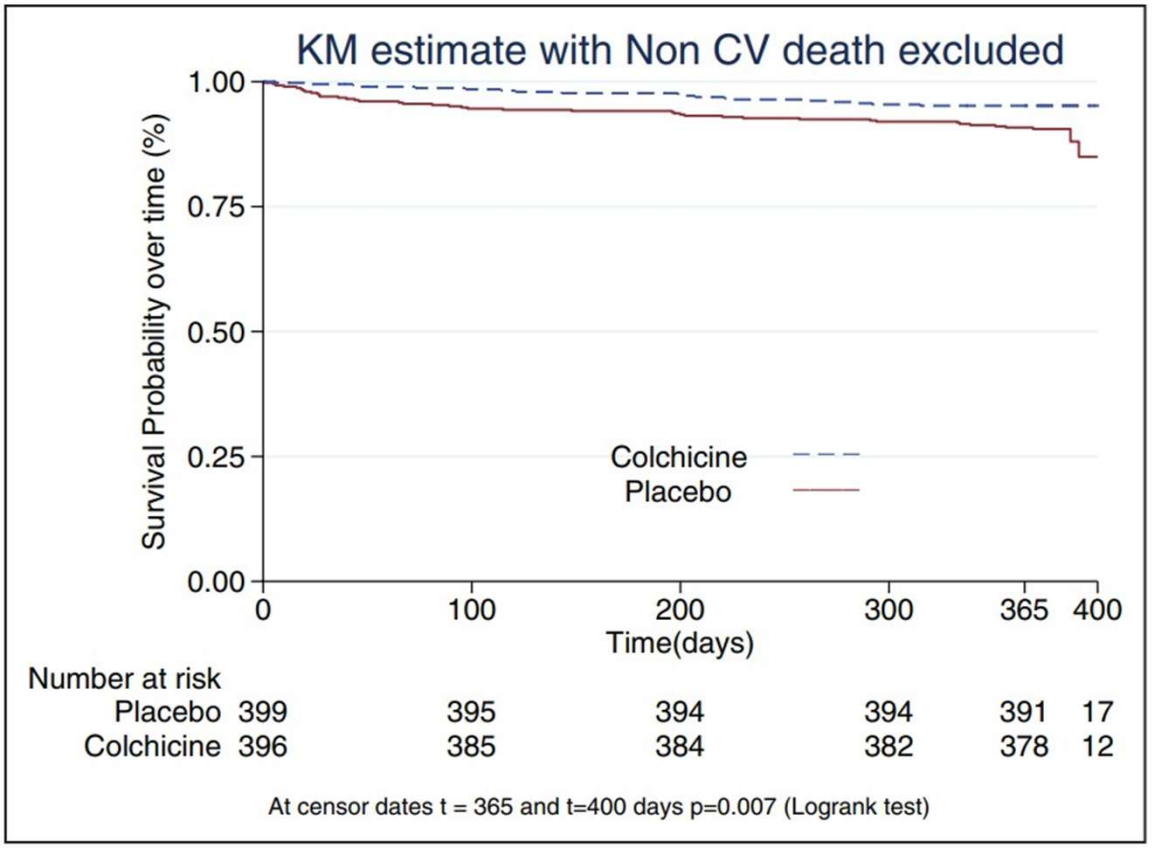


Figure 4. Kaplan-Meier (KM) survival for composite end point using cardiovascular (CV) death in the intention-to-treat population at 365 days and 400 days.
Kaplan-Meier event curves for the composite end point of death from cardiovascular causes, acute coronary syndrome, stroke, and urgent revascularization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

DOI: 10.1161/CIRCULATIONAHA.120.050771

THE COLCHICINE-PCI RANDOMIZED TRIAL

- The COLCHICINE-PCI study is a randomized, double-blind, placebo-controlled trial to determine the effects of acute pre-procedural oral administration of 1.8 mg of colchicine on PCI-related myocardial injury. A nested inflammatory biomarker substudy was performed to further delineate changes in inflammatory profiles associated with colchicine administration.
- Adults age 18 years or older with suspected ischemic heart disease or acute coronary syndromes referred for clinically indicated coronary angiography with possible PCI were eligible for inclusion. Subjects were excluded if they met any of the following criteria: 1) use of oral steroids or non-steroidal anti-inflammatory agents other than aspirin within the longer of 72 hours or three times the agent's half-life, 2) high-intensity statin treatment started within 24 hours of procedure, 3) glomerular filtration rate

doi:10.1161/CIRCINTERVENTIONS.119.008717.

Outcomes in patients undergoing percutaneous coronary intervention (PCI) randomized to an acute pre-procedural oral load of colchicine or placebo

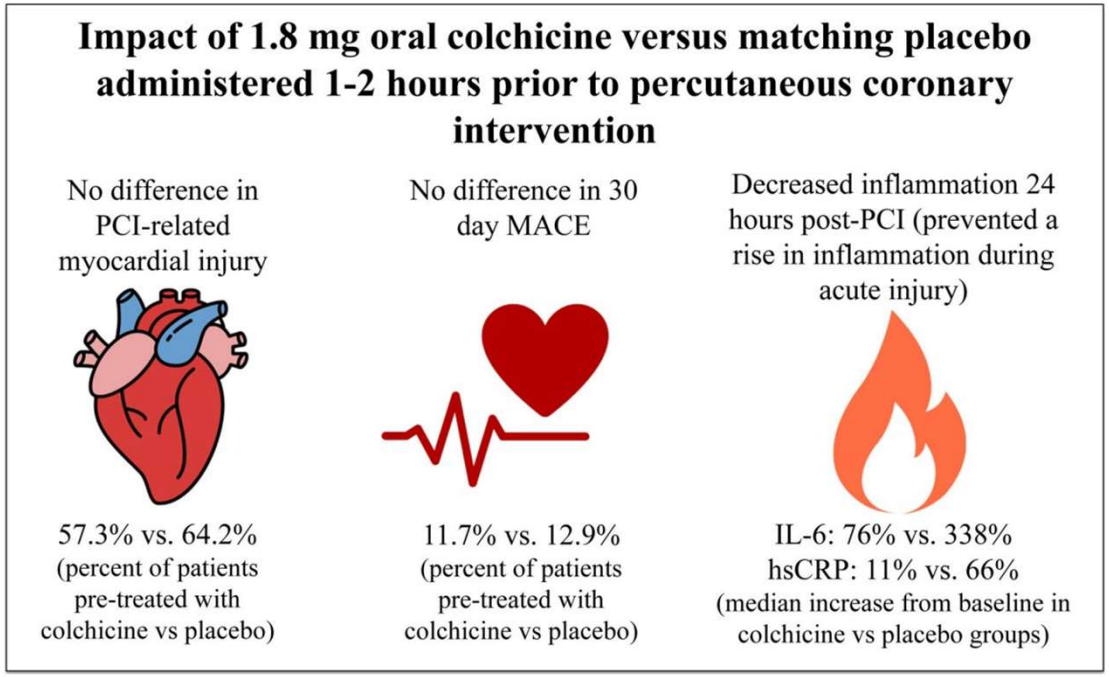
	Colchicine (n=206)	Placebo (n=194)	p-value
Primary outcome			
PCI-related myocardial injury	118 (57.3)	122 (64.2)	0.19
Secondary outcomes			
30-day major adverse cardiovascular events	24 (11.7)	25 (12.9)	0.82
Type 4a myocardial infarction (Universal Definition)	23 (11.2)	23 (12.1)	0.89
Type 1 myocardial infarction (Universal Definition)	0	1 (0.5)	0.49
Target vessel revascularization	0	0	--
All-cause mortality	1 (0.5)	1 (0.5)	0.99
PCI-related myocardial infarction (SCAI definition)	6 (2.9)	9 (4.7)	0.49

Data are presented as frequency (proportion) and compared using chi-square test, or fisher's exact test if the cell number is less than 5.

doi:10.1161/CIRCINTERVENTIONS.119.008717.

Adverse events

	Colchicine (n=366)	Placebo (n=348)	p-value
Chest pain, %	33 (9.0)	25 (7.2)	0.45
Gastrointestinal symptoms, %	34 (9.3)	11 (3.2)	0.001
Hypersensitivity reaction, %	4 (1.1)	4 (1.1)	0.99
Access site discomfort, %	4 (1.1)	4 (1.1)	0.99
Hemodynamic instability, %	0	5 (1.4)	0.03
Fever, %	0	2 (0.6)	0.24
Elevated creatinine, %	1 (0.3)	2 (0.6)	0.62
Ischemic stroke, %	1 (0.3)	0	0.99
Fluid overload, %	1 (0.3)	1 (0.3)	0.99
Urinary retention, %	2 (0.5)	0	0.50
Bleeding, %	1 (0.3)	2 (0.6)	0.62
Palpitations, %	0	1 (0.3)	0.49
Headache, %	1 (0.3)	0	0.99
Serious adverse events total, %	5 (1.4)	12 (3.4)	0.11



doi:10.1161/CIRCINTERVENTIONS.119.008717.

EFFECT OF LOW-DOSE COLCHICINE IN ACUTE AND CHRONIC CORONARY SYNDROMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

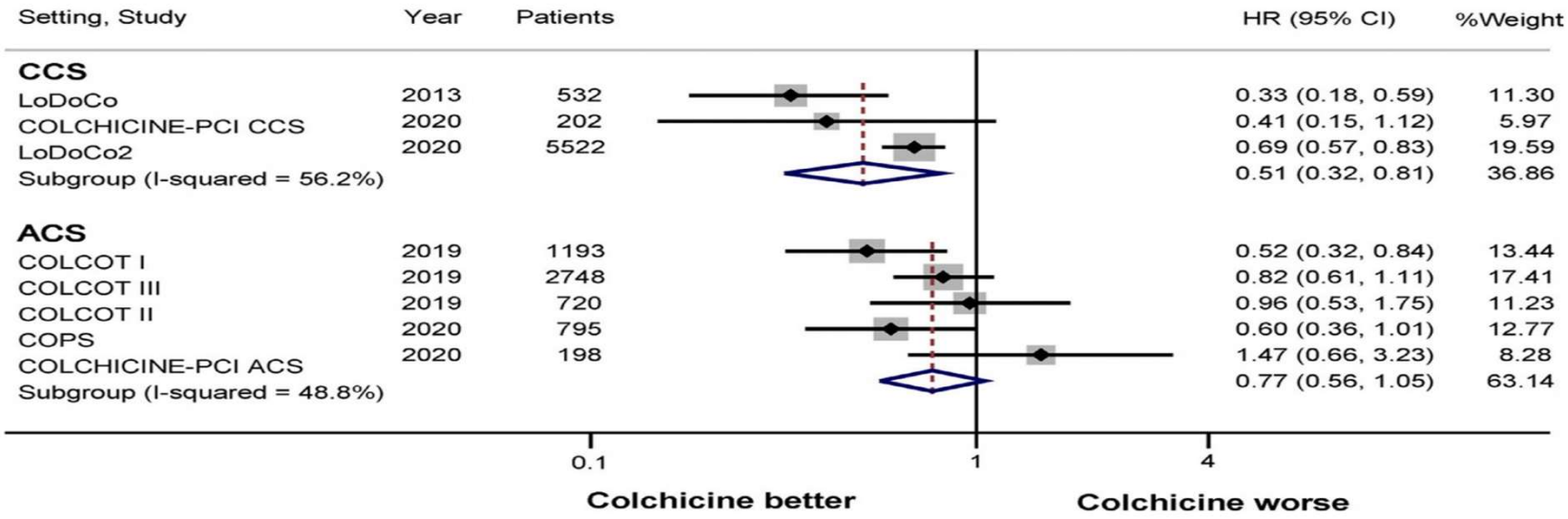


FIGURE 2 Effects of colchicine on cardiovascular outcomes in chronic and acute coronary syndromes (CCS/ACS). COLCOT I: time-to-treatment initiation (TTI) 0-3 days. COLCOT II: TTI 4-7 days. COLCOT III: TTI > 7 days. HR, hazard ratio; CI, confidence interval

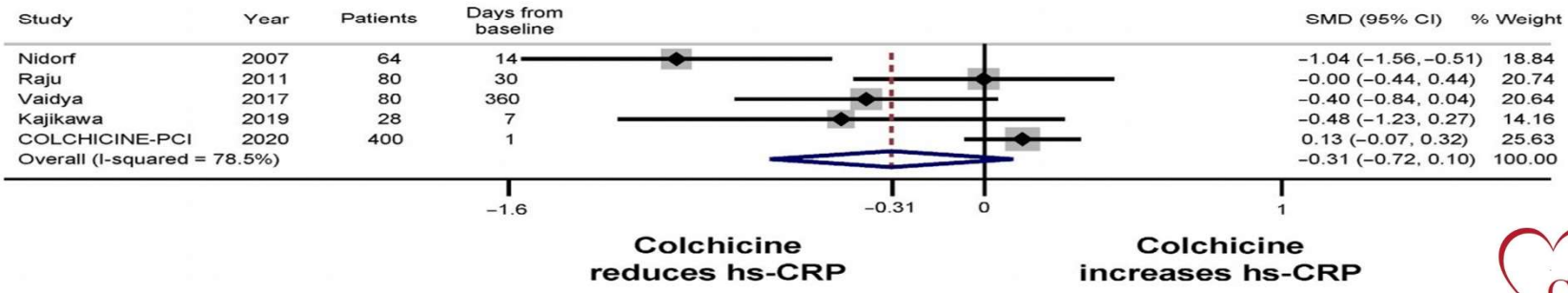


FIGURE 3 Effects of colchicine on high-sensitivity C-reactive protein (hs-CRP)

Eur J Clin Invest. 2021;51:e13464

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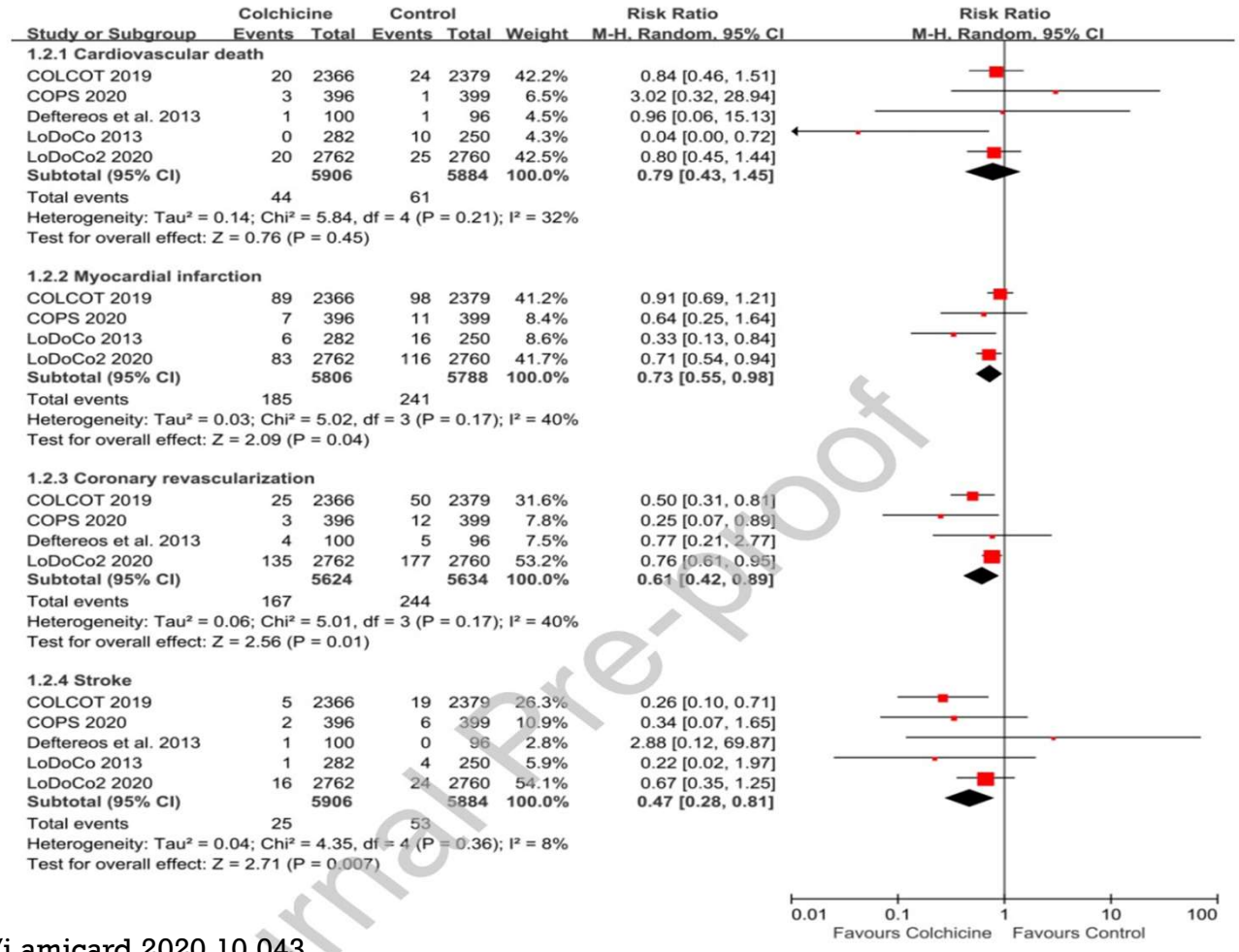
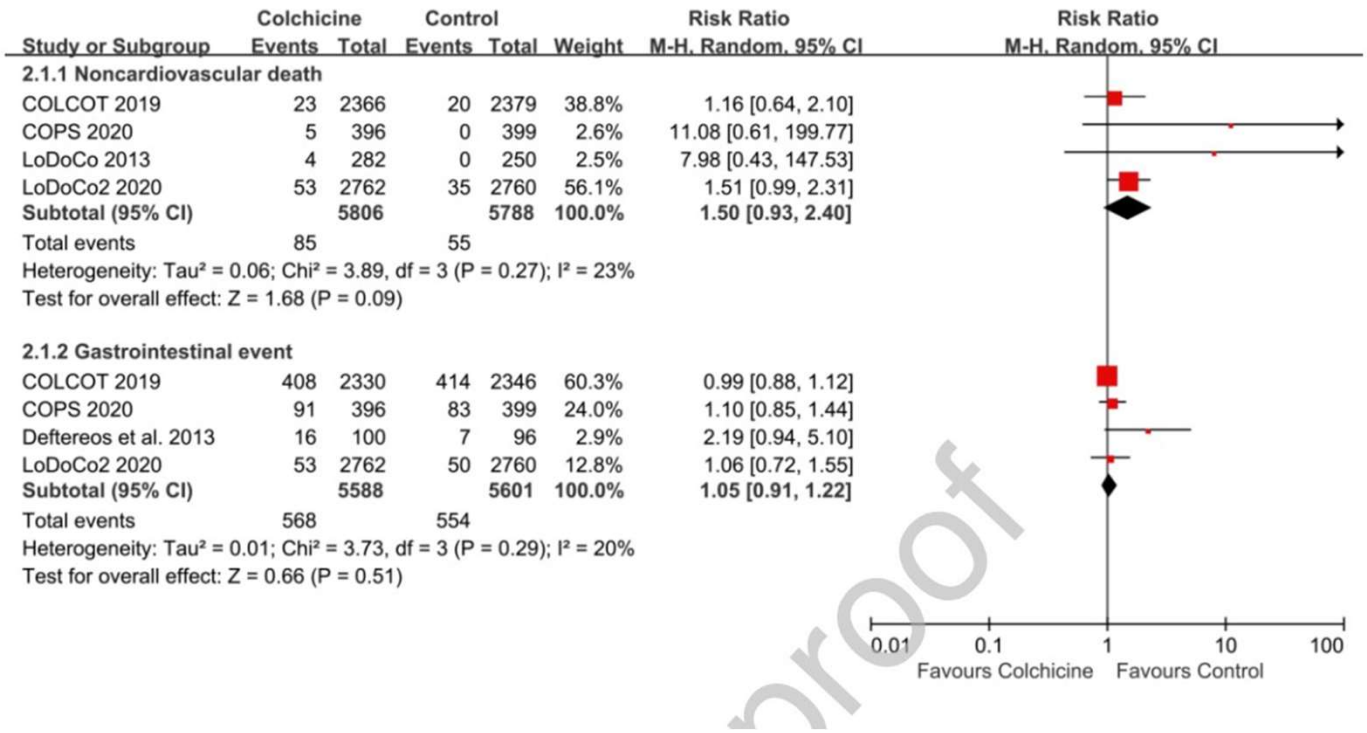
Figure 3. Meta-analysis for the risk of cardiovascular death, myocardial infarction, coronary revascularization and stroke. CI, confidence interval.



https://doi.org/10.1016/j.amjcard.2020.10.043

Figure 4. Meta-analysis for the risk of noncardiovascular death and gastrointestinal events. CI, confidence interval.



https://doi.org/10.1016/j.amjcard.2020.10.043

ROLE OF COLCHICINE IN STROKE PREVENTION: AN UPDATED META-ANALYSIS

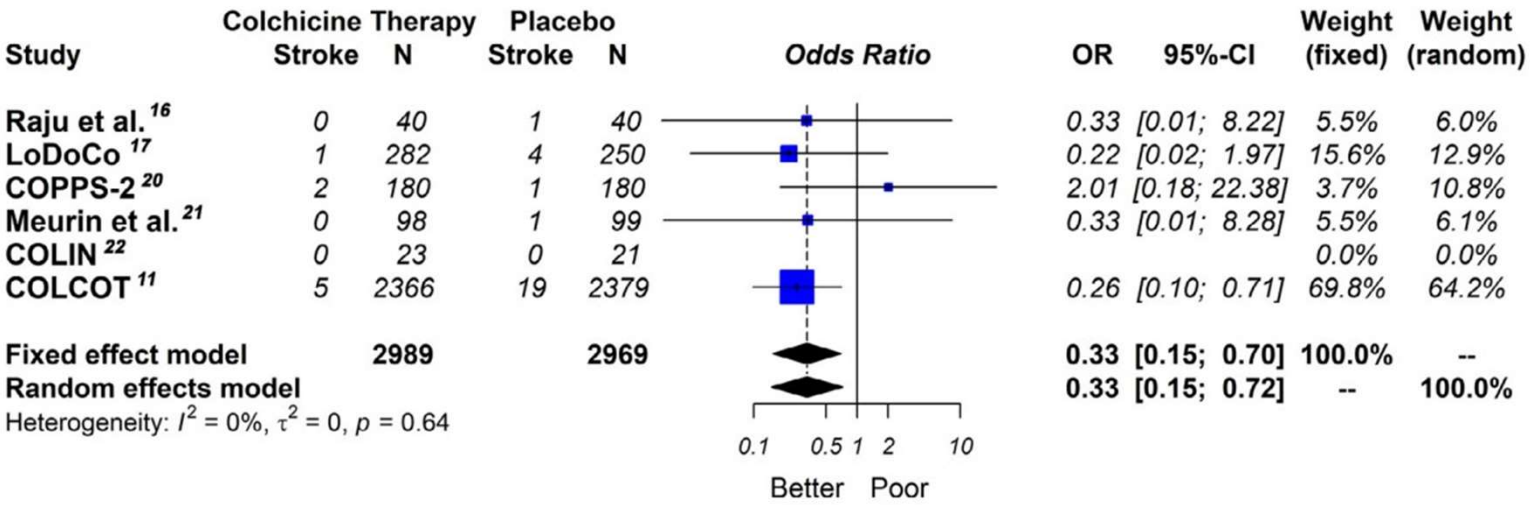


Figure 3. *Effect of colchicine therapy on stroke incidence. Random effects, odds ratio, 95% confidence intervals (CI) and I^2 statistics.*

https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104756

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IMPACT OF COLCHICINE ON MORTALITY IN PATIENTS WITH COVID-19: A META-ANALYSIS

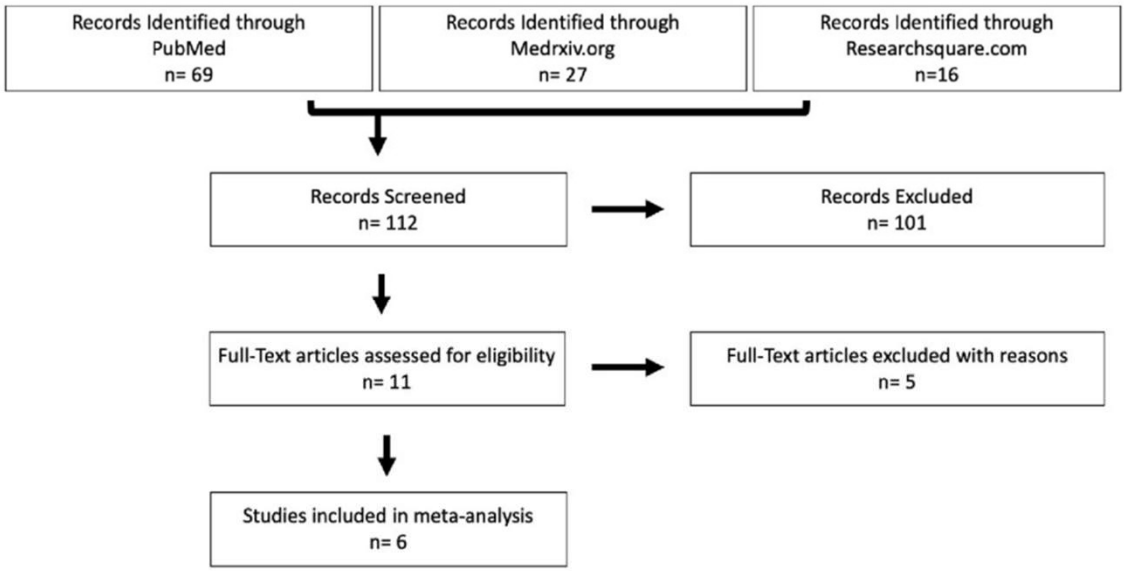

Fig. 1. Flow diagram of search and selection strategy.

https://doi.org/10.1016/j.hjc.2020.11.012

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Studies evaluating impact of colchicine on mortality in patients with COVID-19.

Study	Country	Colchicine/Control Group					
		Patients, N	Age (years)	Males (%)	DM (%)	HTN (%)	Known CAD (%)
Studies Published after Peer-Review							
Deftereos et al.[7]	Greece	55/50	63/65	56/60	16/24	40/50	16/10
Scarsi et al.[9]	Italy	122/140	10/14	64/64		----- 64/74* -----	
Brunetti et al.[10]	USA	33/33	62/64	64/67	21/21	61/36	12/6#
Sandhu et al.[11]	USA	34/78	68/66	62/51	32/51	53/72	6/8
Pre-prints							
Lopes et al.[12]	Brazil	17/18	48/54	53/28	29/33	---- 47/33§ ----	
Pinzón et al.[13]	Colombia	145/156	NR	NR	NR	NR	NR
Overall		406/475					

CAD: Coronary Artery Disease, DM = Diabetes Mellitus, HTN= Hypertension, NR=Not Reported.

* Reported as any cardiovascular comorbidity.

§ Reported as cardiovascular diseases.

\# Reported as previous myocardial infarction.

https://doi.org/10.1016/j.hjc.2020.11.012

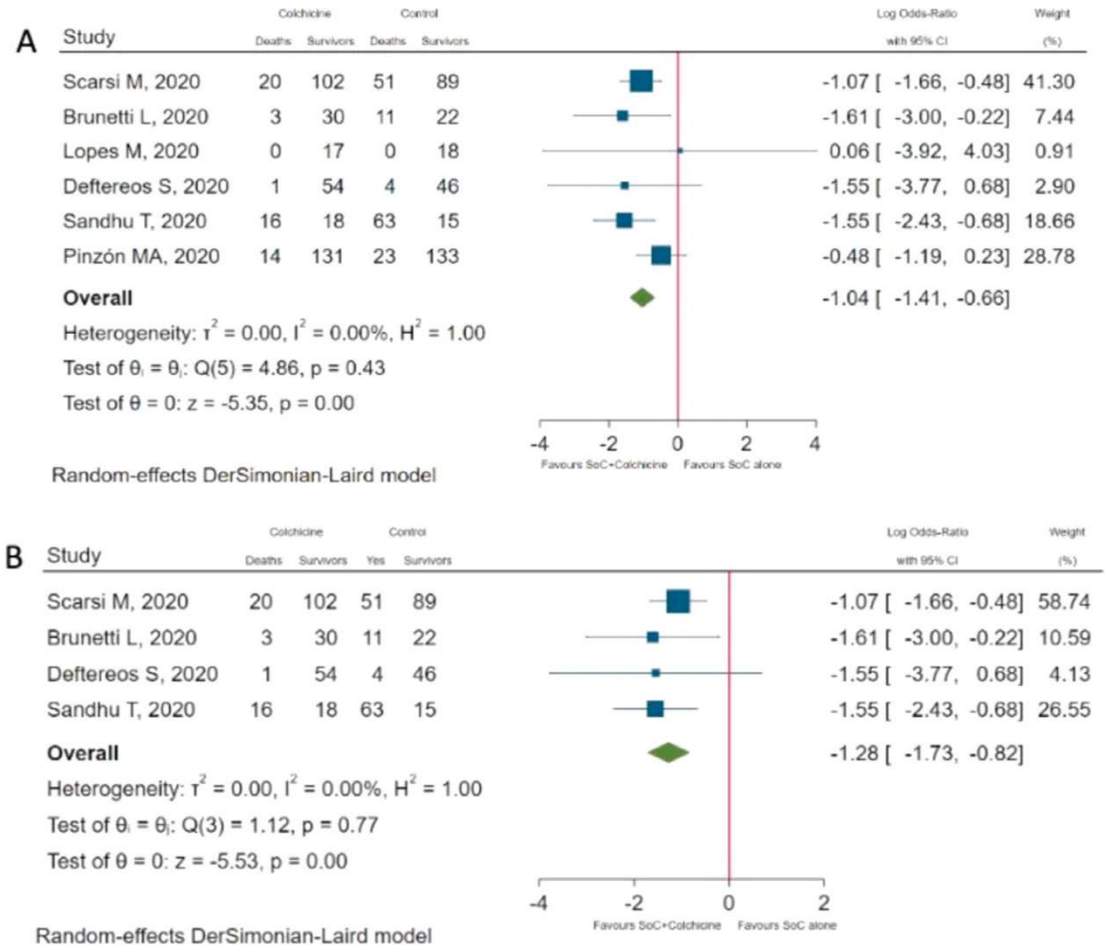

Fig. 2. Log-odds ratios for mortality between colchicine on top of standard-of-care and standard-of-care. Negative values suggest superiority of colchicine. (A) for all studies (peer-reviewed and preprints) (B) for only peer-reviewed studies.

https://doi.org/10.1016/j.hjc.2020.11.012

COLCORONA TRIAL

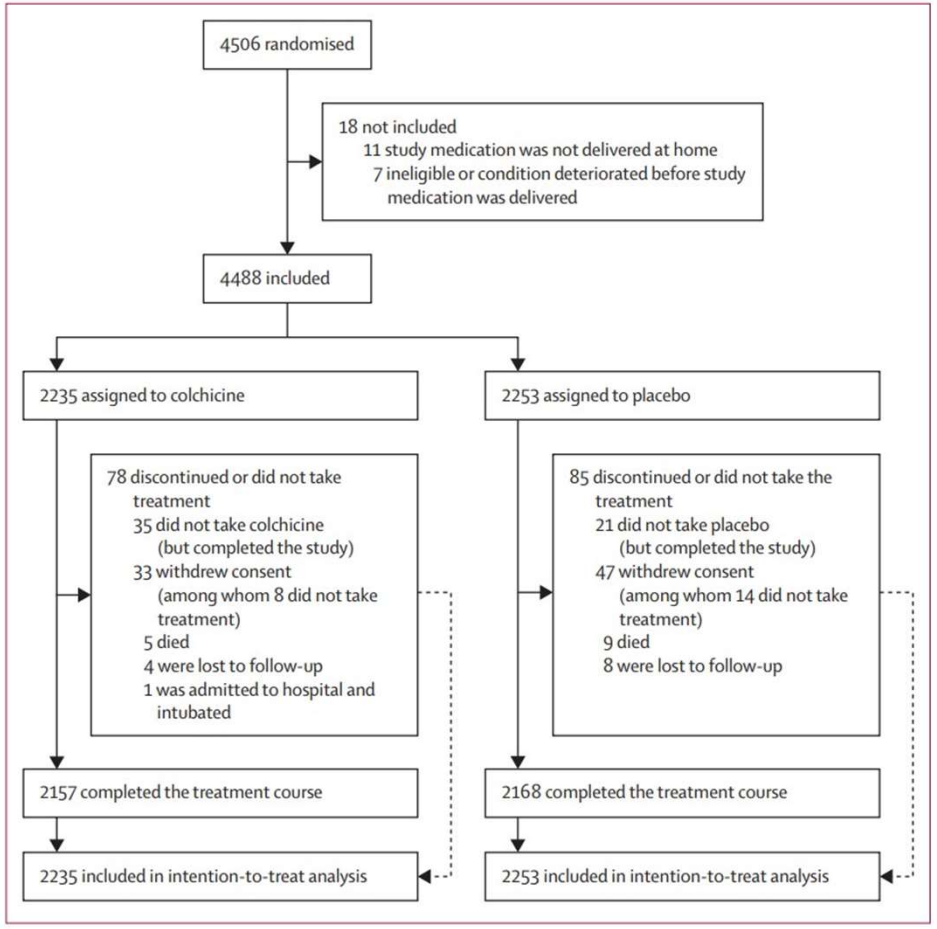

Figure: **Trial profile**
Of a sample of 5536 patients screened in Canada, 775 (14%) patients were randomly assigned to treatment, because 2392 (43%) patients did not have at least one high-risk characteristic (which was an inclusion criterion) or met at least one exclusion criterion, and 2369 (43%) patients declined participation. Note that information on screened individuals is only available for those recruited in Canada.

https://doi.org/10.1016/

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Summary

Background Evidence suggests a role for excessive inflammation in COVID-19 complications. Colchicine is an oral anti-inflammatory medication beneficial in gout, pericarditis, and coronary disease. We aimed to investigate the effect of colchicine on the composite of COVID-19-related death or hospital admission.

Methods The present study is a phase 3, randomised, double-blind, adaptive, placebo-controlled, multicentre trial. The study was done in Brazil, Canada, Greece, South Africa, Spain, and the USA, and was led by the Montreal Heart Institute. Patients with COVID-19 diagnosed by PCR testing or clinical criteria who were not being treated in hospital were eligible if they were at least 40 years old and had at least one high-risk characteristic. The randomisation list was computer-generated by an unmasked biostatistician, and masked randomisation was centralised and done electronically through an automated interactive web-response system. The allocation sequence was unstratified and used a 1:1 ratio with a blocking schema and block sizes of six. Patients were randomly assigned to receive orally administered colchicine (0·5 mg twice per day for 3 days and then once per day for 27 days thereafter) or matching placebo. The primary efficacy endpoint was the composite of death or hospital admission for COVID-19. Vital status at the end of the study was available for 97·9% of patients. The analyses were done according to the intention-to-treat principle. The COLCORONA trial is registered with ClinicalTrials.gov (NCT04322682) and is now closed to new participants.

Findings Trial enrolment began in March 23, 2020, and was completed in Dec 22, 2020. A total of 4488 patients (53·9% women; median age 54·0 years, IQR 47·0–61·0) were enrolled and 2235 patients were randomly assigned to colchicine and 2253 to placebo. The primary endpoint occurred in 104 (4·7%) of 2235 patients in the colchicine group and 131 (5·8%) of 2253 patients in the placebo group (odds ratio [OR] 0·79, 95·1% CI 0·61–1·03; p=0·081). Among the 4159 patients with PCR-confirmed COVID-19, the primary endpoint occurred in 96 (4·6%) of 2075 patients in the colchicine group and 126 (6·0%) of 2084 patients in the placebo group (OR 0·75, 0·57–0·99; p=0·042). Serious adverse events were reported in 108 (4·9%) of 2195 patients in the colchicine group and 139 (6·3%) of 2217 patients in the placebo group (p=0·051); pneumonia occurred in 63 (2·9%) of 2195 patients in the colchicine group and 92 (4·1%) of 2217 patients in the placebo group (p=0·021). Diarrhoea was reported in 300 (13·7%) of 2195 patients in the colchicine group and 161 (7·3%) of 2217 patients in the placebo group (p<0·0001).

Interpretation In community-treated patients including those without a mandatory diagnostic test, the effect of colchicine on COVID-19-related clinical events was not statistically significant. Among patients with PCR-confirmed COVID-19, colchicine led to a lower rate of the composite of death or hospital admission than placebo. Given the absence of orally administered therapies to prevent COVID-19 complications in community-treated patients and the benefit of colchicine in patients with PCR-proven COVID-19, this safe and inexpensive anti-inflammatory agent could be considered for use in those at risk of complications. Notwithstanding these considerations, replication in other studies of PCR-positive community-treated patients is recommended.

https://doi.org/10.1016/

COLCHICINE IN NEW ERA

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THANKS FOR BEING ATTENTIVE

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