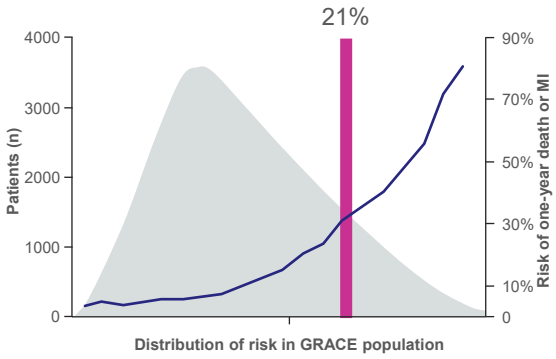
Is Colchicine the Third Pillar of Secondary Prevention of ASCVD?

1

GRACE ACS Risk Score 2.0

Age		69
Heart rate		100–109
Systolic blood pressure		140–159
CHF		Killip Class I
Diuretic usage		No
Creatinine		1.6–1.99 / 141–176
Renal failure		No
ST-segment deviation		Yes
Elevated troponin*		Yes
Cardiac arrest at admission		No

Number of patients by risk group for one-year death or MI



Calculated risk: 21%

*Or other necrosis cardiac biomarkers
ACS, acute coronary syndrome; CHF, congestive heart failure; MI, myocardial infarction
https://www.outcomes-umassmed.org/grace/acs_risk2/index.html

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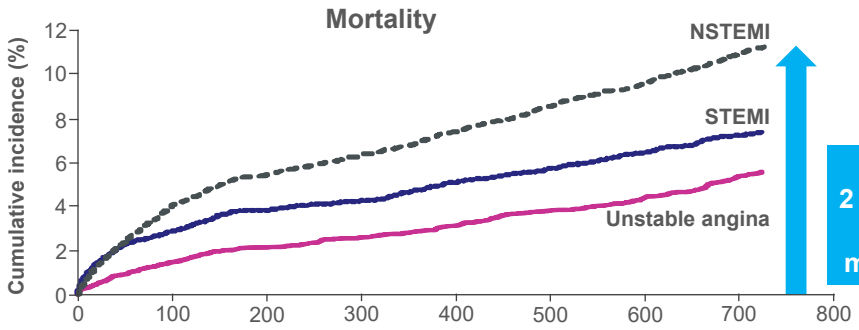
Late Consequences of ACS

GRACE

Two-year prospective follow-up (median 728 [212, 730] days) in patients with ACS discharge diagnosis (2004–2007; 57 sites where ethics approval, patient consent and logistics allowed)



7.1% mortality within 2 yrs after discharge, and 4.4% experienced a myocardial (re)infarction

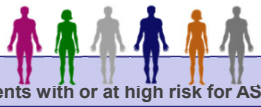
No. at risk:								
Non–ST-elevation MI	6974	6678	5390	4475	4225	4072	3968	3764
ST-elevation MI	6688	6491	5107	4352	4102	3985	3903	3709
Unstable angina	5384	5299	4470	3861	3677	3573	3512	3372

ACS, acute coronary syndrome; (N)STEMI, non–St-elevation myocardial infarction

Alnasser SM et al *Am J Med.* 2015;128:766-75.

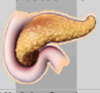
3

Residual Risk Pathways in Secondary Prevention



Patients with or at high risk for ASCVD

Despite contemporary evidence-based therapies*, residual risk of ASCVD events persists

	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
Biological Issue						
Critical Biomarker	LDL-C ≥2.6 mmol/L	Hs-CRP ≥2mg/L	No simple biomarker	TG ≥1.69 mmol/L	Lp(a) ≥50 mg/dL	HbA1c fasting glucose
Potential Intervention	Targeted LDL/Apo B reduction	Targeted inflammation reduction	Targeted antithrombotic reduction	Targeted triglyceride reduction	Targeted Lp(a) reduction	SGLT2 inhibitors GLP-1 agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT *PROMINENT*	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

*In addition to standard evidence-based therapies, more aggressive blood pressure targets may be considered

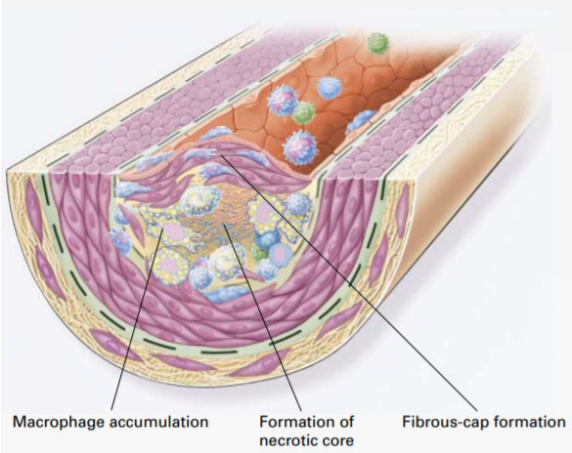
APO B, apolipoprotein B; ASVD, atrioventricular septal defect; GLP-1, glucagon-like peptide 1; HbA1c, hemoglobin A1c; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a); lipoprotein(a); TG, triglycerides; SGLT2, sodium-glucose cotransporter 2

Lawler RR et al *Eur Heart J.* 2021;42:113-31.

4

Atherosclerosis: An inflammatory disease

- Because high plasma concentrations of LDL-C is one of the principal risk factors for atherosclerosis, atherogenesis has been considered by many to consist largely of accumulation of lipids within the artery walls
- However, lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can best be described as an inflammatory disease



LDL-C, low-density lipoprotein cholesterol
Ross R. *N Engl J Med.* 1999;340:115-26.

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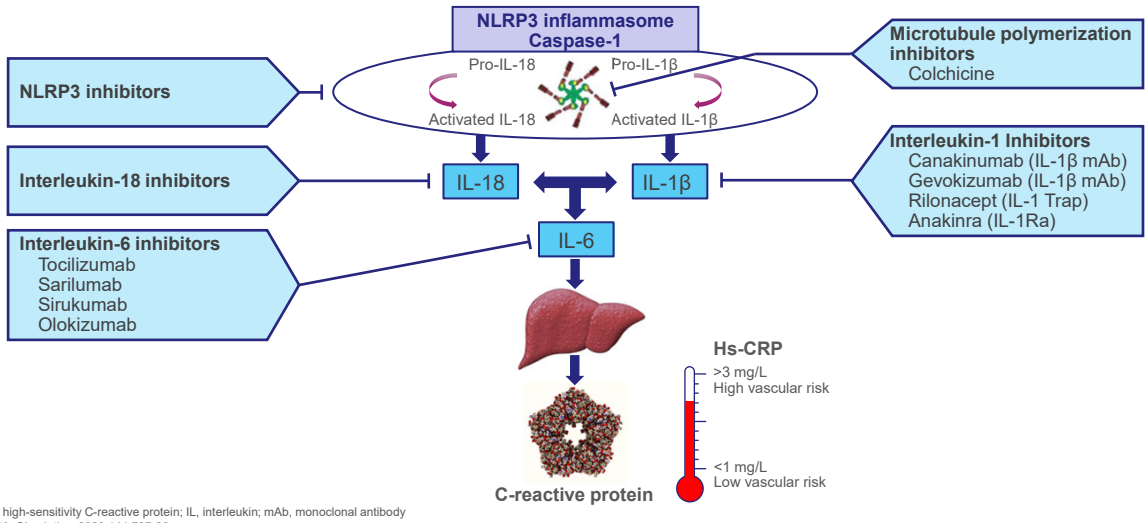
Potential Therapeutic Targets in the NLRP3 Inflammasome to Interleukin-1 to -6 to CRP Signalling Pathway



Hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; mAb, monoclonal antibody
Ridker PM. *Circulation.* 2020;141:787-89.

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6

Key Clinical Trials of Anti-inflammatory Therapy in Secondary Prevention

Trial	Drug	Target
CANTOS	Canakinumab	IL-1β
CIRT	Methotrexate	Purigenic signalling
COLCOT	Colchicine	Microtubule assembly
LoDoCo2	Colchicine	Microtubule assembly

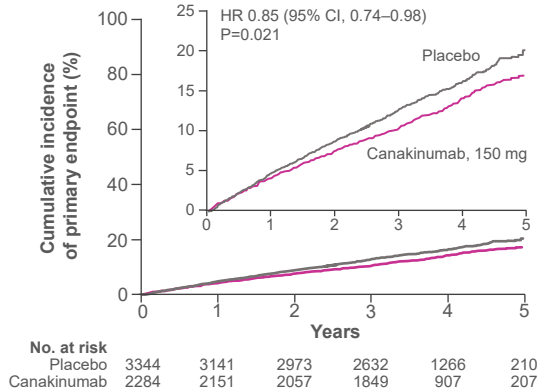
IL, interleukin
Liberal L et al. *Eur Heart J.* 2020;41:2974-82.

7

7

CANTOS: Canakinumab

- **Patients (n=10,061)**
  - MI history
  - Hs-CRP ≥2 mg/L
- **Intervention**
  - Canakinumab 50 mg,100 mg or 150 mg SC every 3 months vs. placebo
- **Primary composite MACE endpoint**
  - MI, stroke or CVD
- **Result**
  - 15% RR reduction in MACE with 150 mg dose
- **Risks**
  - Higher incidence of fatal infection and sepsis with canakinumab



CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio; Hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; RR, relative risk; SC, subcutaneous
Ridker PM et al. *N Engl J Med.* 2017;377:1119-31.

8

8

CANTOS: Conclusion

- **Canakinumab 150 mg ↓ risk of recurrent CV events but did not impact CV mortality**

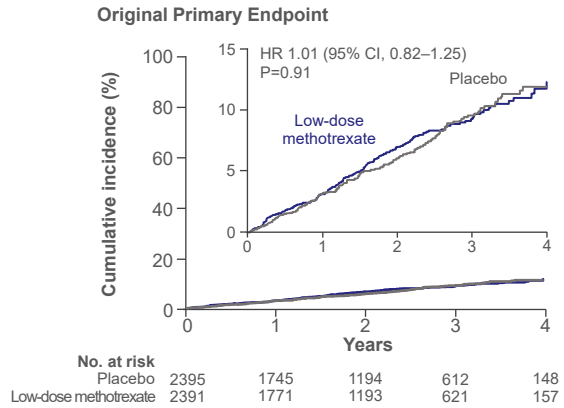
CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio; Hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; RR, relative risk; SC, subcutaneous
Ridker PM et al. *N Engl J Med*. 2017;377:1119-31.

9

9

CIRT: Methotrexate

- **Patients (n=4786)**
  - MI history or multivessel CAD and either type 2 diabetes or metabolic syndrome
- **Intervention**
  - Methotrexate 15–20 mg PO weekly with folic acid 1 mg daily vs. placebo
- **Primary composite MACE endpoint**
  - MI, stroke or CVD
- **Result**
  - No impact on MACE, IL-1β, IL-6 or CRP levels
  - Trial stopped early (median follow-up 2.3 years)
- **Risks**
  - ↑ liver-enzyme levels, ↓ leukocyte count, ↓ hematocrit, ↑non–basal-cell skin cancers



CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular death; CRP, C-reactive protein; HR, hazard ratio; IL, interleukin; MACE, major adverse cardiac events; MI, myocardial infarction PO, by mouth
Ridker PM et al. *N Eng J Med*. 2019;380:752-62.

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10

CIRT: Conclusion

- **METHOTREXATE had no impact on MACE, inflammatory cytokine or CRP levels**

CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular death; CRP, C-reactive protein; HR, hazard ratio; IL, interleukin; MACE, major adverse cardiac events; MI, myocardial infarction PO, by mouth
Ridker PM et al. *N Eng J Med*. 2019;380:752-62.

11

11

Colchicine Trials

12

Trials of Low-dose Colchicine for the Prevention of MACE

- **LoDoCo:** Patients with stable coronary disease
- **COPS:** ACS and evidence of CAD managed with PCI or medical therapy
- **COLCOT:** Patients with MI in the last 30 days
- **LoDoCo2:** Patients with chronic coronary disease

ACS, acute coronary syndrome; CAD, coronary artery disease; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention

13

13

COLCOT: Colchicine

- **Patients (n=4745)**
  - MI within 30 days, had completed any planned PCI, high-intensity statin
- **Intervention**
  - Colchicine 0.5 mg once daily vs. placebo
- **Primary composite endpoint**
  - CVD, resuscitated cardiac arrest, MI, stroke, unstable anginal hospitalization requiring revascularization

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., Petr Ostadal, M.D., Ph.D., Wolfgang Koenig, M.D., Denis Angoulvant, M.D., Jean C. Grégoire, M.D., Marc-André Lavoie, M.D., Marie-Pierre Dubé, Ph.D., David Rhainds, Ph.D., Mylène Provencher, Ph.D., Lucie Blondeau, M.Sc., Andreas Orfanos, M.B., B.Ch., Philippe L. L'Allier, M.D., Marie-Claude Guertin, Ph.D., and François Roubille, M.D., Ph.D.

CVD, cardiovascular death; MI, myocardial infarction; PCI, percutaneous coronary intervention
Tardif JC et al. *N Engl J Med.* 2019;381:2497-505.

14

14

COLCOT: Selected patient characteristics

	Colchicine (N=2366)	Placebo (N=2379)
Age – years	60.6 ± 10.7	60.5 ± 10.6
Female sex – no. (%)	20%	18%
Caucasian – no. (%)	1350/1850 (73%)	1329/1844 (72%)
BMI – kg/m^2	28.2 ± 4.8	28.4 ± 4.7
Smoking – no. (%)	30%	30%
Hypertension – no. (%)	50%	52%
Diabetes – no. (%)	20%	21%
Prior MI – no. (%)	16%	17%
Prior PCI – no. (%)	17%	17%
Prior CABG – no. (%)	3%	3%
Prior heart failure – no. (%)	2%	2%
Prior stroke/TIA – no. (%)	2%	3%
Index MI to randomization – days	13.4 ± 10.2	13.5 ± 10.1
PCI for index MI – no. (%)	93%	93%
Aspirin – no. (%)	99%	99%
P2Y12 receptor inhibitor – no. (%)	98%	98%
Statin – no. (%)	99%	99%
Beta blocker – no. (%)	89%	88%

BMI, body mass index; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack
Tardif JC et al. *N Engl J Med.* 2019;381:2497-505.

15

15

Polling Question No. 2

When would be the ideal time to initiate low-dose colchicine for Bob?

A. Within the first 3 days of STEMI

B. Two weeks post event

C. One month post event

Medication

- ASA 81 mg daily
- Ticagrelor 90 mg bid
- Ramipril 10 mg daily
- Amlodipine 10 mg daily
- Atorvastatin 40 mg daily

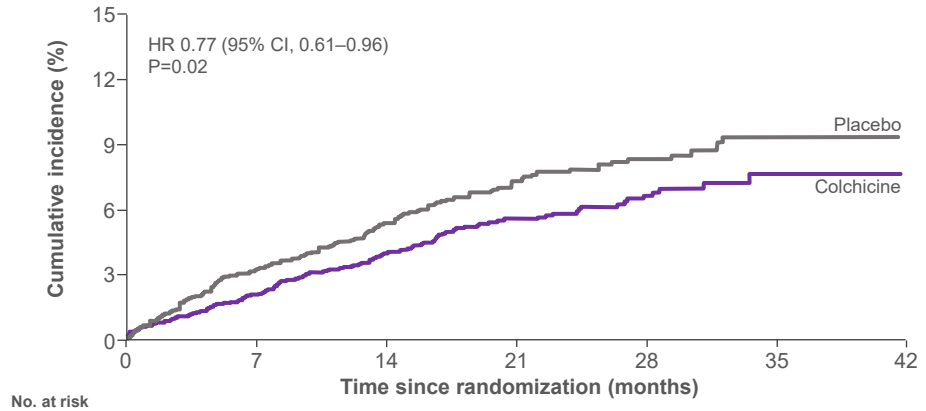
ASA, acetylsalicylic acid; bid, twice a day; STEMI, St-elevation myocardial infarction

16

16

COLCOT: Primary efficacy endpoint

CVD, resuscitated cardiac arrest, MI, stroke, urgent hospitalization for angina requiring revascularization (ITT)



No. at risk							
Colchicine	2366	2284	1868	1230	628	153	0
Placebo	2379	2261	1854	1224	622	144	0

CV, cardiovascular; CVD, cardiovascular death; HR, hazard ratio; ITT, intention-to-treat; MI, myocardial infarction
Tardif JC et al. *N Engl J Med*. 2019;381:2497-505.

17

17

COLCOT: Conclusion

- **Low-dose colchicine daily reduced the risk of ischemic CV events by 23% compared with placebo, when initiated within the <u>first 30 days after MI</u>**

CV, cardiovascular; CVD, cardiovascular death; HR, hazard ratio; ITT, intention-to-treat; MI, myocardial infarction
Tardif JC et al. *N Engl J Med*. 2019;381:2497-505.

18

18

COLCOT: Major clinical outcomes

Clinical Outcome Intent-to-treat population	Colchicine N=2366	Placebo N=2379	HR (95% CI)	P Value
Primary composite endpoint – no. (%)	131 (5.5%)	170 (7.1%)	0.77 (0.61–0.96)	0.02
CVD – no. (%)	20 (0.8%)	24 (1.0%)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest – no. (%)	5 (0.2%)	6 (0.3%)	0.83 (0.25–2.73)	
MI – no. (%)	89 (3.8%)	98 (4.1%)	0.91 (0.68–1.21)	
Stroke – no. (%)	5 (0.2%)	19 (0.8%)	0.26 (0.10–0.70)	
Urgent hospitalization for angina requiring revascularization – no. (%)	25 (1.1%)	50 (2.1%)	0.50 (0.31–0.81)	
Secondary composite endpoint – no. (%)	111 (4.7%)	130 (5.5%)	0.85 (0.66–1.10)	
Death – no. (%)	43 (1.8%)	44 (1.8%)	0.98 (0.64–1.49)	
DVT or pulmonary embolus – no. (%)	10 (0.4%)	7 (0.3%)	1.43 (0.54–3.75)	
Atrial fibrillation – no. (%)	36 (1.5%)	40 (1.7%)	0.93 (0.59–1.46)	

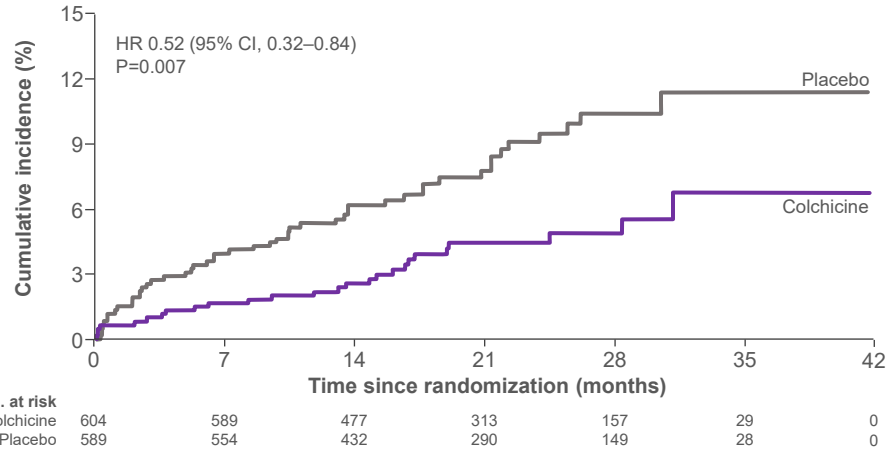
CI, confidence interval; CVD, cardiovascular death; DVT, deep vein thrombosis; HR, hazard ratio; MI, myocardial infarction

19

19

COLCOT Time-to-Treatment 0–3 Days: Primary efficacy endpoint

CVD, resuscitated cardiac arrest, MI, stroke, urgent hospitalization for angina requiring revascularization (TTI: 0–3 days)



CVD, cardiovascular death; MI, myocardial infarction; HR, hazard ratio, TTI, time to treatment initiation
Bouabdallaoui N et al. *Eur Heart J.* 2020;41:4092-99.

20

20

COLCOT Time-to-Treatment 0–3 Days: Conclusion

- **Early initiation of colchicine 0.5 mg within the first 3 days reduced risk by 48% compared with placebo**

CVD, cardiovascular death; MI, myocardial infarction; HR, hazard ratio, TTI, time to treatment initiation
Bouabdallaoui N et al. *Eur Heart J.* 2020;41:4092-99.

21

21

Time-to-Treatment Initiation 0–3 days: Major outcomes

Clinical Outcome TTI 0–3 days	Colchicine	Placebo	HR (95% CI)	P Value
Primary composite endpoint – no. (%)	4.3%	8.3%	0.52 (0.32–0.84)	0.007
CVD – no. (%)	0.3%	0.3%	1.04 (0.15–7.37)	
Resuscitated cardiac arrest – no. (%)	0.2%	0.5%	0.33 (0.03–3.20)	
MI – no. (%)	2.8%	4.9%	0.58 (0.32–1.05)	
Stroke – no. (%)	0.2%	0.8%	0.21 (0.02–1.81)	
Urgent hospitalization for angina requiring revascularization – no. (%)	1.0%	2.9%	0.35 (0.14–0.88)	
Secondary composite endpoint – no. (%)	3.3%	6.1%	0.55 (0.32–0.95)	0.031
All coronary revascularizations – no. (%)	5.5%	8.7%	0.63 (0.40-0.97)	

CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio; MI, myocardial infarction; TTI, time to treatment initiation
Bouabdallaoui N et al. *Eur Heart J.* 2020;41:4092-99.

22

22

COLCOT: Adverse events

	Colchicine (N=2330)	Placebo (N=2346)	P Value
Any related adverse event	16.0%	15.8%	0.89
Adverse events			
GI event	17.5%	17.6%	0.90
Diarrhea	9.7%	8.9%	0.35
Nausea	1.8%	1.0%	**0.02**
Flatulence	0.6%	0.2%	**0.02**
GI hemorrhage	0.3%	0.2%	0.56
Anemia	0.6%	0.4%	0.40
Leukopenia	0.1%	0.1%	0.66
Thrombocytopenia	0.1%	0.3%	0.21
Serious adverse events			
Any serious adverse event	16.4%	17.2%	0.47
GI event	2.0%	1.5%	0.25
Infection	2.2%	1.6%	0.15
Pneumonia	0.9%	0.4%	**0.03**
Septic shock	0.1%	0.1%	0.99
Hospitalization for heart failure	1.1%	0.7%	0.21
Cancer	1.8%	2.0%	0.77

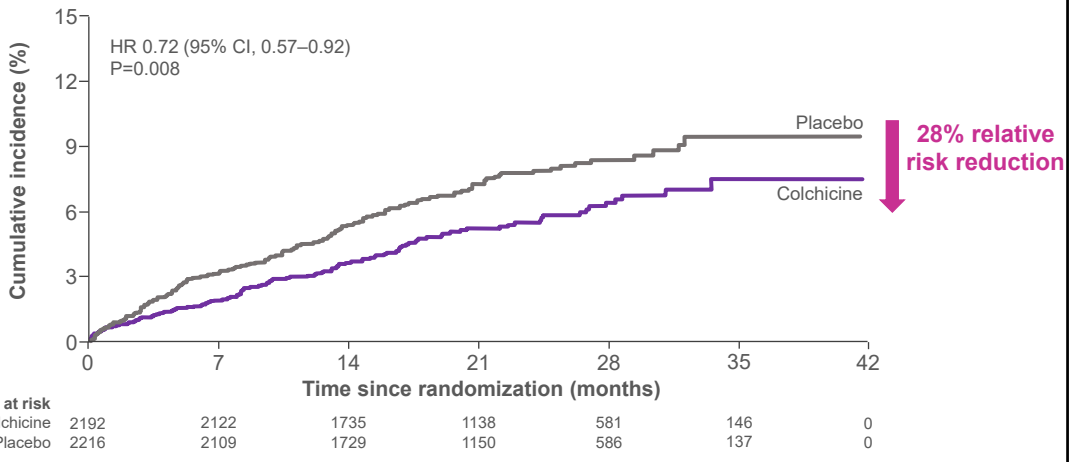
GI, gastrointestinal
Nidorf SM et al. *N Engl J Med.* 2020;383:1838-47.

23

23

COLCOT-PCI: Primary efficacy endpoint
Subgroup from COLCOT trial

CVD, resuscitated cardiac arrest, MI, stroke, urgent hospitalization for angina requiring revascularization (ITT)



CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio; ITT, intention-to-treat; MI, myocardial infarction
Tardif JC et al. *N Engl J Med.* 2019;381:2497-505.

24

24

COLCOT: Conclusion

- Colchicine 0.5 mg daily vs. placebo when added within 30 days post MI to patients on standard of care was associated with:
  - **23% ↓ in first ischemic CV event**
  - **34% ↓ in combined first and recurrent ischemic CV events**
- **Benefits were seen in addition to standard of care** (99% on Aspirin, 98% on P2Y12 receptor inhibitor, 99% on statin)
  - Confirms inflammation management ↓ CV risk
- **Ideally start colchicine 0.5 mg within 3 days of index event**, but is still efficacious if initiated later after MI
- Colchicine ↓ risk of ischemic CV events in patients treated with PCI for their index MI

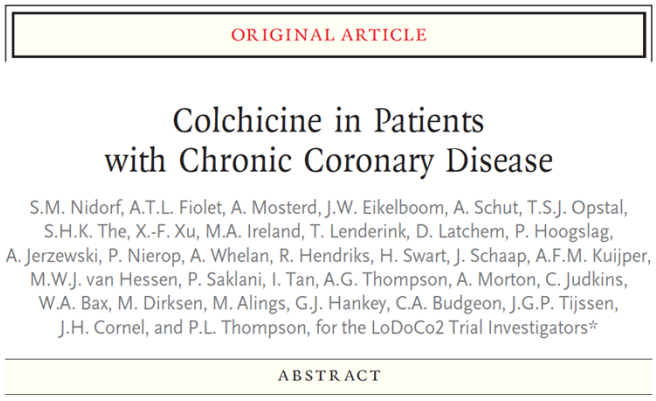
CV, cardiovascular death; MI, myocardial infarction; PCI, percutaneous coronary intervention

25

25

LoDoCo2: Colchicine

- **Patients (n=5522)**
  - Any evidence of coronary disease on angiography or CAC score ≥400
  - Clinically stable ≥6 months
- **Intervention**
  - Colchicine 0.5 mg once daily vs. placebo
- **Primary composite endpoint**
  - CVD, spontaneous (nonprocedural) MI, ischemic stroke or ischemia-driven coronary revascularization



ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, J.W. Eikelboom, A. Schut, T.S.J. Opstal, S.H.K. The, X.-F. Xu, M.A. Ireland, T. Lenderink, D. Latchem, P. Hoogslag, A. Jerzewski, P. Nierop, A. Whelan, R. Hendriks, H. Swart, J. Schaap, A.F.M. Kuijper, M.W.J. van Hessen, P. Saklani, I. Tan, A.G. Thompson, A. Morton, C. Judkins, W.A. Bax, M. Dirksen, M. Alings, G.J. Hankey, C.A. Budgeon, J.G.P. Tijssen, J.H. Cornel, and P.L. Thompson, for the LoDoCo2 Trial Investigators*

ABSTRACT

CAC, coronary artery calcium; CVD, cardiovascular death; MI, myocardial infarction
Nidorf SM et al. *N Engl J Med*. 2020;383:1838-47.

26

26

LoDoCo2

Baseline characteristics

	Colchicine N=2762	Placebo N=2760
Age, years	65.8 ± 8.4	65.9 ± 8.7
Male	84%	86%
Risk factors and history		
Current smoker	12%	12%
Hypertension	51%	50%
Diabetes	18%	19%
Prior revascularization	83%	84%
Prior ACS	84%	85%
Last ACS >24m	68%	69%

Medication use at baseline

	Colchicine N=2762	Placebo N=2760
Single antiplatelet therapy	67%	67%
Dual antiplatelet therapy	23%	23%
Anticoagulant	12%	12%
Statin	94%	94%
Any lipid-lowering agent	97%	97%
Renin angiotensin inhibitor	72%	71%
Beta blocker	61%	63%
Calcium channel blocker	23%	22%

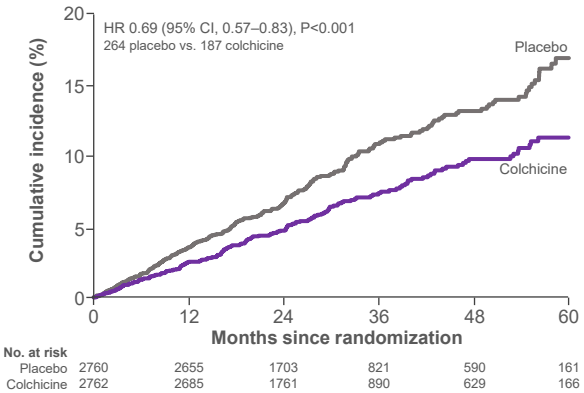
ACS, acute coronary syndrome
Nidorf SM et al. *N Engl J Med.* 2020;383:1838-47.

27

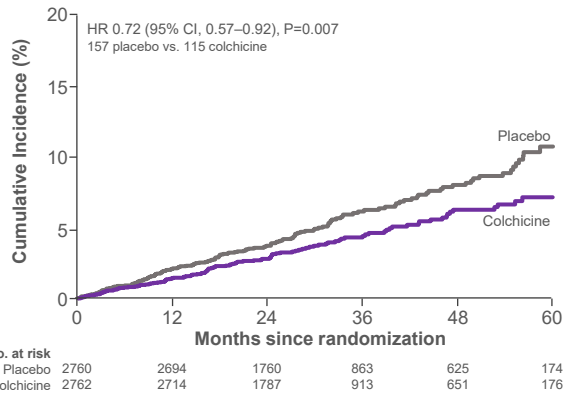
27

LoDoCo2: Primary and secondary endpoints

Primary endpoint: CVD, MI, ischemic stroke or ischemia-driven coronary revascularization



Key secondary endpoint: CVD, MI or ischemic stroke



28

CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention
Nidorf SM et al. *N Engl J Med.* 2020;383:1838-47.

28

LoDoCo2: Ranked secondary endpoints

	Colchicine (N=2762)	Placebo (N=2760)	HR (95% CI)	P Value
CVD, MI or ischemic stroke	4.2%	5.7%	0.72 (0.57–0.92)	**0.007**
MI or ischemia-driven coronary revascularization	5.6%	8.1%	0.67 (0.55–0.83)	**<0.001**
CVD or MI	3.6%	5.0%	0.71 (0.55–0.92)	**0.010**
Ischemia-driven coronary revascularization	4.9%	6.4%	0.75 (0.60–0.94)	**0.012**
MI	3.0%	4.2%	0.70 (0.53–0.93)	**0.014**
Ischemic stroke	0.6%	0.9%	0.66 (0.35–1.25)	0.198
Death from any cause	2.6%	2.2%	1.21 (0.86–1.71)	
CVD	0.7%	0.9%	0.80 (0.44–1.44)	

CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio; MI, myocardial infarction
Nidorf SM et al. *N Engl J Med.* 2020;383:1838-47.

29

29

LoDoCo2: Serious adverse events

	Colchicine (N=2762)	Placebo (N=2760)
Non-CVD	1.9%	1.3%
Diagnosis of new cancer	4.3%	4.4%
Hospitalization for infection	5.0%	5.2%
Hospitalization for pneumonia	1.7%	2.0%
Hospitalization for gastrointestinal reason	1.9%	1.8%
Neutropenia	0.1%	0.1%
Myotoxicity	0.1%	0.1%

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

30

30

LoDoCo2: Conclusion

- **Colchicine 0.5 mg daily ↓ CV events in chronic CAD** compared to placebo
  - 31% ↓ risk of CVD, MI, ischemic stroke or ischemia-driven coronary revascularization
  - 28% ↓ risk of CVD, MI, ischemic stroke
  - 30% ↓ risk of fatal or non-fatal MI
- The benefits of colchicine 0.5 mg daily were:
  - Observed early on
  - Increased over time
  - Occurred in patients on standard medical therapy for second prevention
- Important to discuss the benefits with patients; some are resistant to adding new therapy
- **Colchicine can help reduce the risk of another MACE**

CAD, coronary artery disease; CVD, cardiovascular death; MACE, major adverse cardiac events; MI, myocardial infarction

31

31

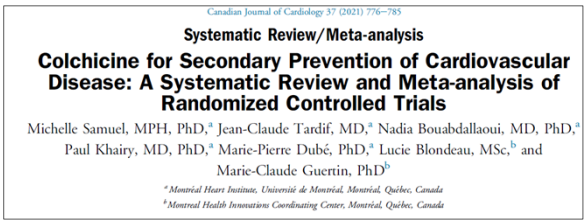
Meta-Analyses of Colchicine in Reducing Secondary MACE Risk

MACE, major adverse cardiac events

32

Systemic Review and Meta-analysis for Secondary Prevention of CVD

- Search identified 79 studies
  - Four RCTs were retained for use
- Primary efficacy endpoint
  - Composite CVD, MI, ischemic stroke and urgent coronary revascularization
- Secondary efficacy endpoint
  - Components of primary endpoint
  - Composite of CVD, MI, ischemic stroke, DVT/PE, AF



Canadian Journal of Cardiology 37 (2021) 776–785

Systematic Review/Meta-analysis

Colchicine for Secondary Prevention of Cardiovascular Disease: A Systematic Review and Meta-analysis of Randomized Controlled Trials

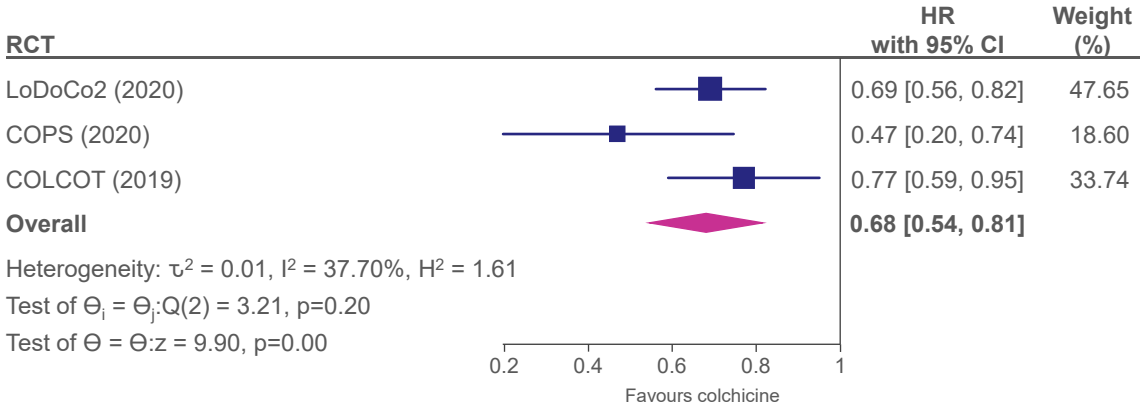
Michelle Samuel, MPH, PhD,[a] Jean-Claude Tardif, MD,[a] Nadia Bouabdallaoui, MD, PhD,[a] Paul Khairy, MD, PhD,[a] Marie-Pierre Dubé, PhD,[a] Lucie Blondeau, MSc,[b] and Marie-Claude Guertin, PhD[b]

[a] Montréal Heart Institute, Université de Montréal, Montréal, Québec, Canada
[b] Montreal Health Innovations Coordinating Center, Montréal, Québec, Canada

AF, atrial fibrillation; CVD, cardiovascular death; MI, myocardial infarction; PE, pulmonary embolism
RCT, randomized control trial
Samuel M et al. *Can J Cardiol.* 2021;37:776-85.

33

Meta-analysis of Colchicine Studies in CAD: Primary composite endpoint



Random-effects DerSimonian-Laird Model

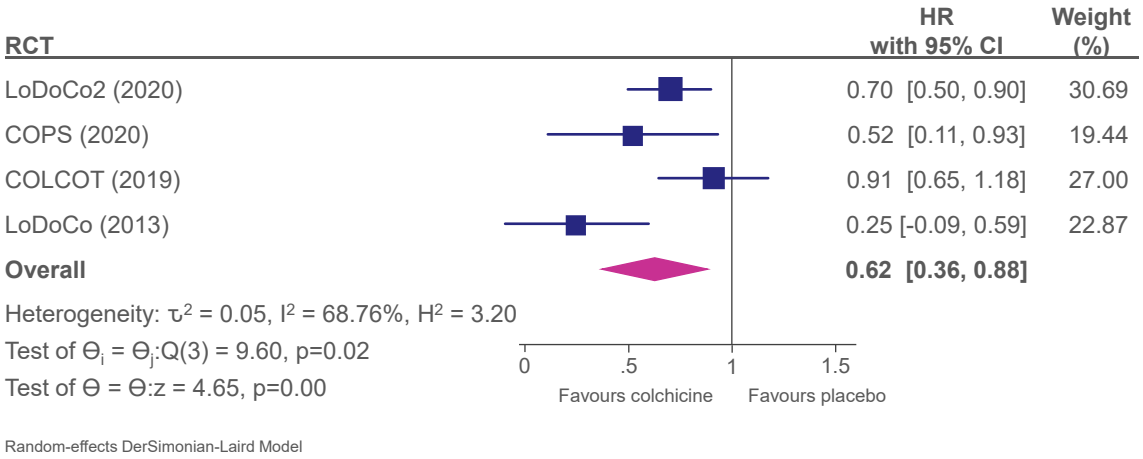
Primary composite endpoint includes cardiovascular mortality, MI, ischemic stroke and urgent coronary revascularization

CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction
Samuel M et al. *Can J Cardiol.* 2021;37:776-85.

34

34

Meta-analysis of Colchicine Studies in CAD: Myocardial infarction



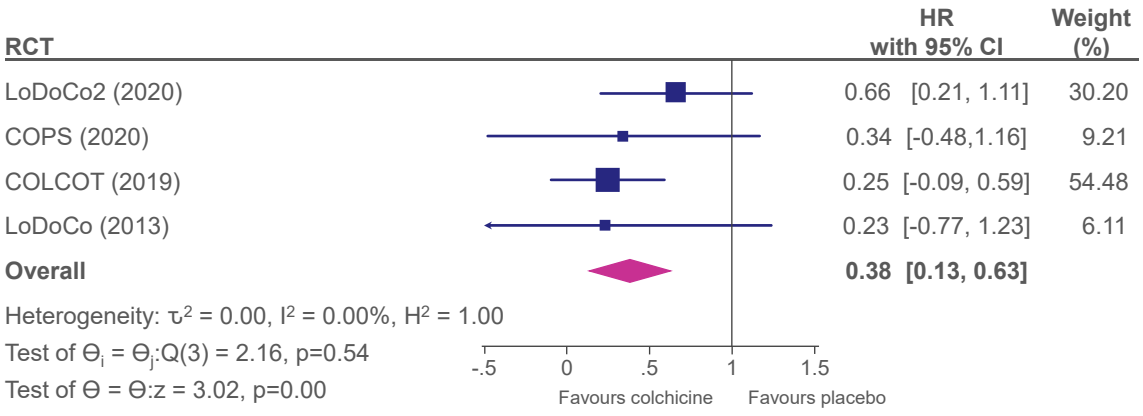
Random-effects DerSimonian-Laird Model

CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; RCT, randomized control trial
Samuel M et al. *Can J Cardiol.* 2021;37:776-85.

35

35

Meta-analysis of Colchicine Studies in CAD: Ischemic stroke



Random-effects DerSimonian-Laird Model

CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; RCT, randomized control trial
Samuel M et al. *Can J Cardiol.* 2021;37:776-85.

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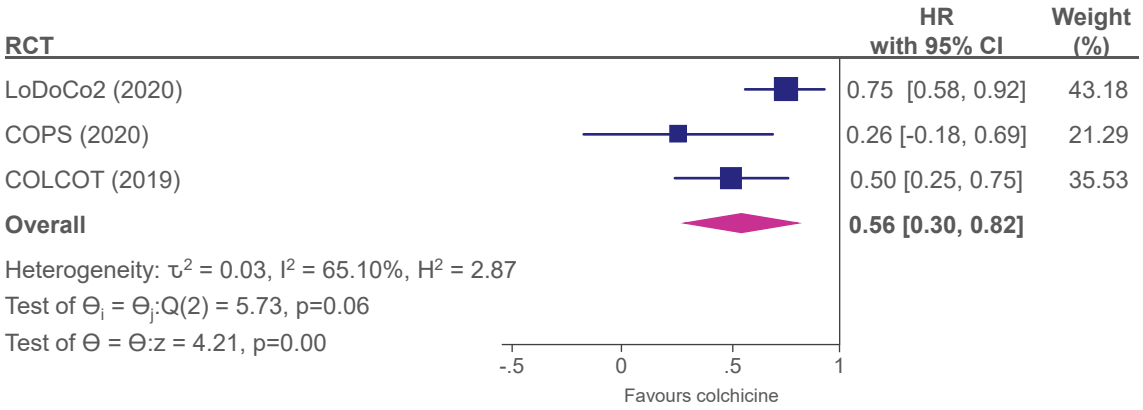
36

Meta-analysis of Colchicine Studies in CAD: Urgent coronary revascularization



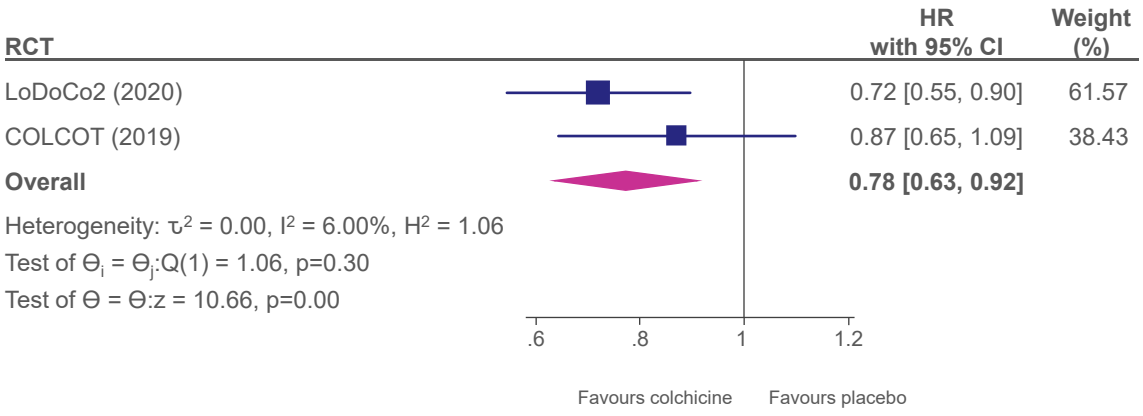
Random-effects DerSimonian-Laird Model

CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; RCT, randomized control trial
Samuel M et al. *Can J Cardiol.* 2021;37:776-85.

37

37

Meta-analysis of Colchicine Studies in CAD: CVD, MI and ischemic stroke



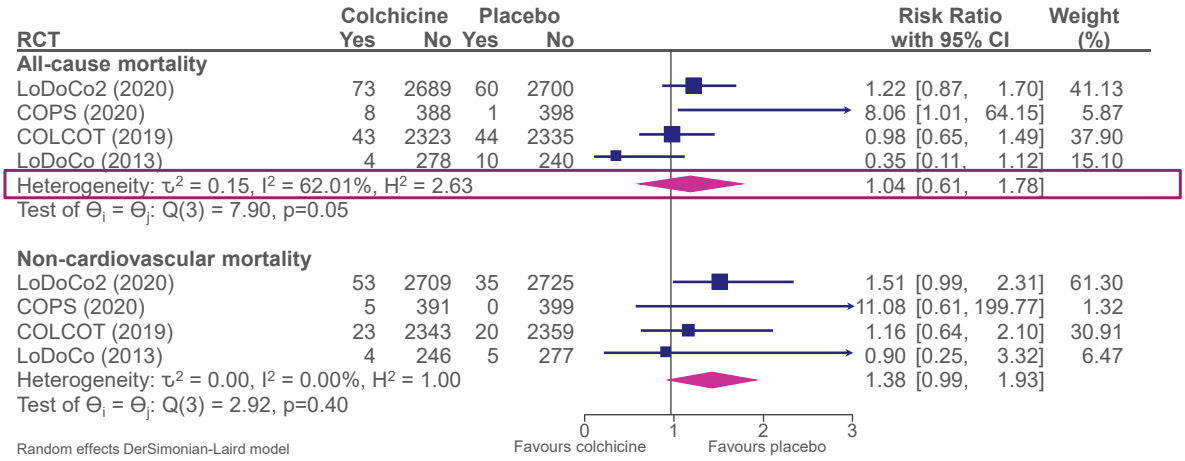
Random-effects DerSimonian-Laird Model

CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio; MI, myocardial infarction, RCT, randomized control trial
Samuel M et al. *Can J Cardiol.* 2021;37:776-85.

38

38

Meta-analysis of Colchicine Studies in CAD: All-cause and non-CV mortality

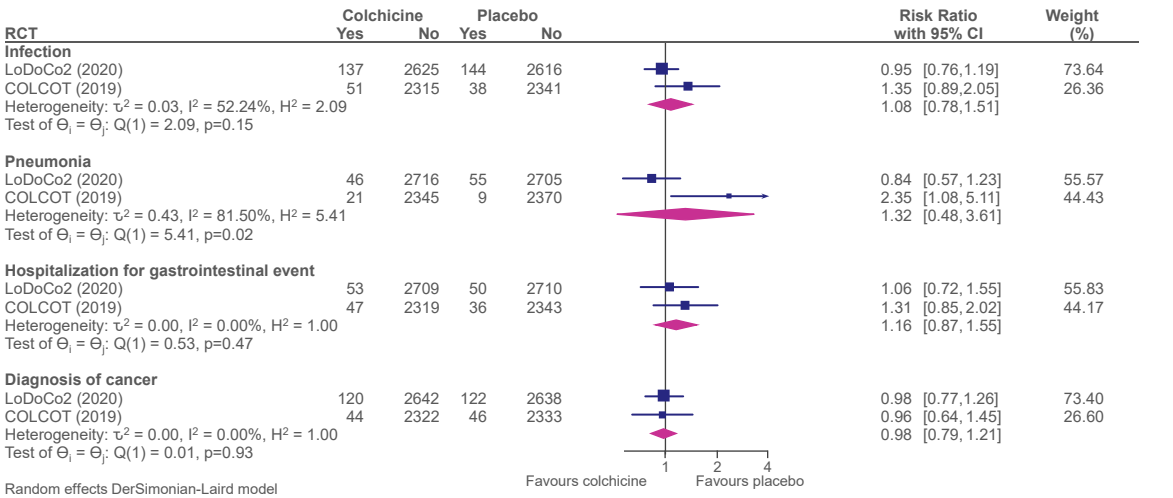


CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular death; RCT, randomized control trial
Samuel M et al. *Can J Cardiol.* 2021;37:776-85.

39

39

Meta-analysis of Colchicine Studies in CAD: Safety outcomes



CAD, coronary artery disease; RCT, randomized control trial
Samuel M et al. *Can J Cardiol.* 2021;37:776-85.

40

40

Colchicine in Coronary Disease: A meta-analysis of five studies

MACE

MI, stroke or CVD

Colchicine 0.5 mg
4.2%
250/5806

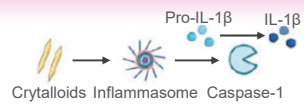
Placebo or no colchicine
5.7%
328/5788

Pooled relative risk reduction 25%
(RR 0.75, 95% CI, 0.61 to 0.92)

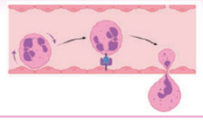
Myocardial infarction	Stroke	Coronary revascularization	Cardiovascular death
Significant relative risk reduction	Significant relative risk reduction	Significant relative risk reduction	No significant relative risk reduction
↓22%	↓46%	↓23%	
RR 0.78 (95% CI, 0.64 to 0.94)	RR 0.54 (95% CI, 0.34 to 0.86)	RR 0.77 (95% CI, 0.66 to 0.90)	RR 0.82 (95% CI, 0.55 to 1.23)

Potential mechanisms

1. Inhibiting inflammasome activation



2. Inhibiting neutrophil chemotaxis, adhesion and activation



3. Inhibiting neutrophil-platelet, interaction

CI, confidence interval; CVD, cardiovascular death; MACE, major adverse cardiac events; MI, myocardial infarction; RR, relative risk
Fiolet ATL, et al. *Eur Heart J*. 2021;42:2765-75.

41

41

Practical Approach to Colchicine in Secondary Prevention of CAD

CJC Canadian Journal of Cardiology / Journal canadien de cardiologie

REVIEW | ARTICLES IN PRESS

Colchicine for Prevention of Atherothrombotic Events in Patients with Coronary Artery Disease: Review and Practical Approach for Clinicians

Guillaume Marquis-Gravel, MD, MSc • Shaun G. Goodman, MD, MSc • Todd J. Anderson, MD • Alan D. Bell, MD • David Bewick, MD • Jafna Cox, BA, MD • Jean C. Grégoire, MD • Anil Gupta, MD • Thao Huynh, MD, MScPhD • Heather Kertland, PharmD • Simon Kouz, MD • Philippe L. L'Allier, MD • Mina Madan, MD • G. B. John Mancini, MD • Ruth McPherson, MD, PhD • Derek Y.F. So, MD, MSc • Robert C Welsh, MD • Graham Wong, MD, MPH • Jean-Claude Tardif, MD • Show less

Published: August 18, 2021 • DOI: https://doi.org/10.1016/j.cjca.2021.08.009

MI within 1 month (ideally within 3 days)?

Stable CAD?

Consider long-term colchicine 0.5 mg daily

Patient on strong CYP3A4 or Pgp inhibitors

Consider ↓ colchicine dose (0.3 mg q2d)

- Administer with water, with/without meals
- Avoid grapefruit juice
- Monitor for GI adverse effects
- Annual CBC monitoring
- Don't use in patients with severe hepatic disease or renal disease (eGFR<30 mL/min) due to risk of severe toxicity

CAD, coronary artery disease; CBC, complete blood count; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; MI, myocardial infarction; MI, myocardial infarction; Pgp, P-glycoprotein; Q2D, every other day
Adapted from: Marquis-Gravel G et al. *Can J Cardiol*. 2021 Aug 18:S0828-282X(21)00654-1. doi: 10.1016/j.cjca.2021.08.009. [Epub ahead of print]

42

42

Practical Colchicine Information

- **Colchicine should be added to the standard of care post-CV event** (e.g., ASA, statin, second antiplatelet)
- There is **no clinically meaningful interaction between colchicine and statin** (99% of patients were taking statins in COLCOT)
- **Significant caution** is needed in using colchicine in patients with **severe CKD** (eGFR <30 mL/min)
- Colchicine should be used **with caution** in patients using **strong CYP 3A4 inhibitors** (e.g., clarithromycin, ketoconazole) and **P-gp inhibitors** (e.g., cyclosporine)
- Most side effects related to colchicine (e.g., for treatment of gout) are related to higher dose and are uncommon with the 0.5 mg/day dose
  - Most commonly **GI-related**, and can be minimized by taking colchicine with a full glass of water and with food
- **Monitoring (baseline and at 1 month)** – CBC, liver enzymes, CK, creatinine/eGFR

ASA, acetylsalicylic acid; CBC, complete blood count; CK, creatine kinase; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; P-gp, P-glycoprotein
Sadiq NM et al. StatPearls Publishing; 2021. 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431102/

43

43

Planned and Ongoing Clinical Trials with Colchicine

Trial	Patient Population	Intervention vs. Placebo	Outcome
CLEAR Synergy (https://clinicaltrials.gov/ct2/show/NCT03048825)	Post-PCI treatment of MI	Colchicine 0.5 mg bid Spironolactone SYNERGY DES	MACE CVD or new/worsening heart failure
CONVINCE (https://clinicaltrials.gov/ct2/show/NCT02898610)	Ischemic stroke or TIA	Colchicine 0.5 mg/day X 60 months	Recurrent non-fatal ischemic stroke Non-fatal MACE Vascular death
COLCOT-T2D	T2D without documented CVD	Colchicine 0.5 mg/day	Composite of CV death, MI, stroke and urgent hospitalization for angina requiring coronary revascularization

bid, twice a day; CVD, cardiovascular death; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; T2D, Type 2 diabetes; TIA, transient ischemic attack

44

44

Summary: Colchicine in secondary prevention

- The use of **low-dose colchicine** for secondary prevention was associated with:
  - A **32% ↓ in the risk of major CV events** compared to placebo
  - Significantly **fewer MIs, ischemic strokes and urgent coronary revascularizations** were the primary drivers for the overall decrease in CV events
- The protective treatment effect was relatively **consistent across most subgroups studied** (age, gender, smoker, diabetes, hypertension, prior PCI/CABG, AF)
- The **safety profile** of colchicine in this population **is favourable**
- No difference in the incidence of CV or all-cause mortality

- **In patients with CAD, the addition of low-dose colchicine to standard medical therapy consistently and significantly reduces the incidence of major CV events compared with standard medical therapy alone[1]**

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention

1. Samuel M et al. *Can J Cardiol.* 2021;37:776-85.