“Qu'est-ce que la goutte a à voir avec ceci? Colchicine et la maladie coronarienne”

James Brophy M Eng MD FRCP FACC FCCS FAHS PhD
Professor, McGill University
Dept. Medicine & EBOH

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Conflicts of Interest

I have no known conflicts associated with this presentation and to, the best of my knowledge, am equally disliked by all pharmaceutical and device companies

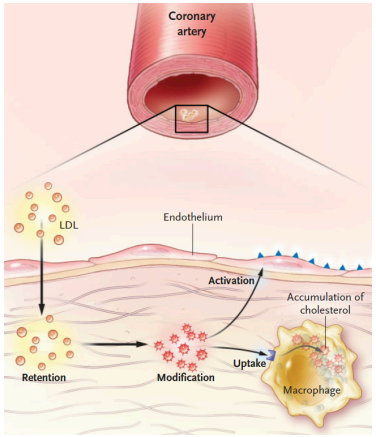
http://www.nofreelunch.org/

Objectifs

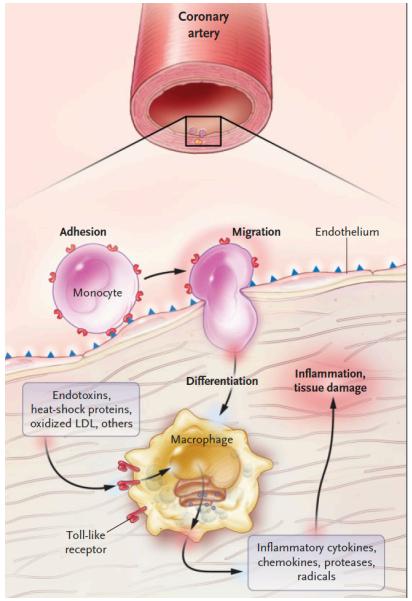
1. Examen de l'inflammation dans la maladie coronarienne
2. Examen critique d’études récentes sur la colchicine
3. Comment traduire les résultats de la recherche en pratique clinique (synthèse des résultats)

Inflammation in CAD

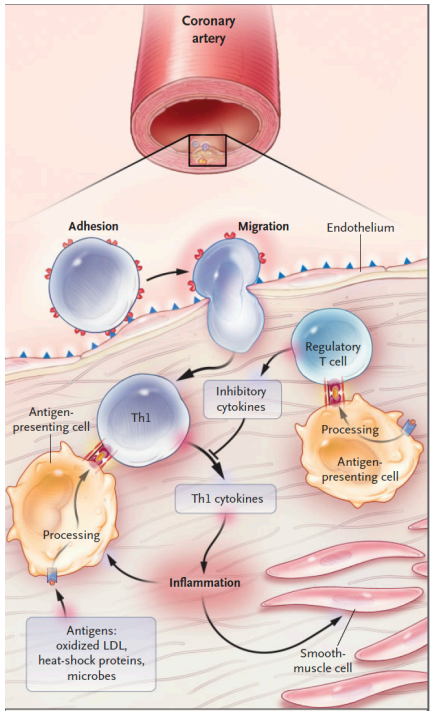
Inflammation in CAD



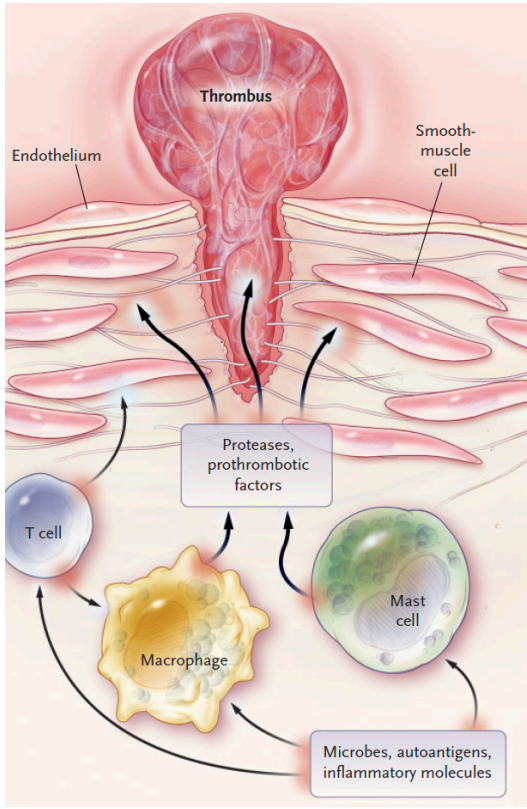
LDL Infiltration
-> Inflammation



Monocytes activated endothelium -> macrophage -> ^^ inflammation & tissue damage



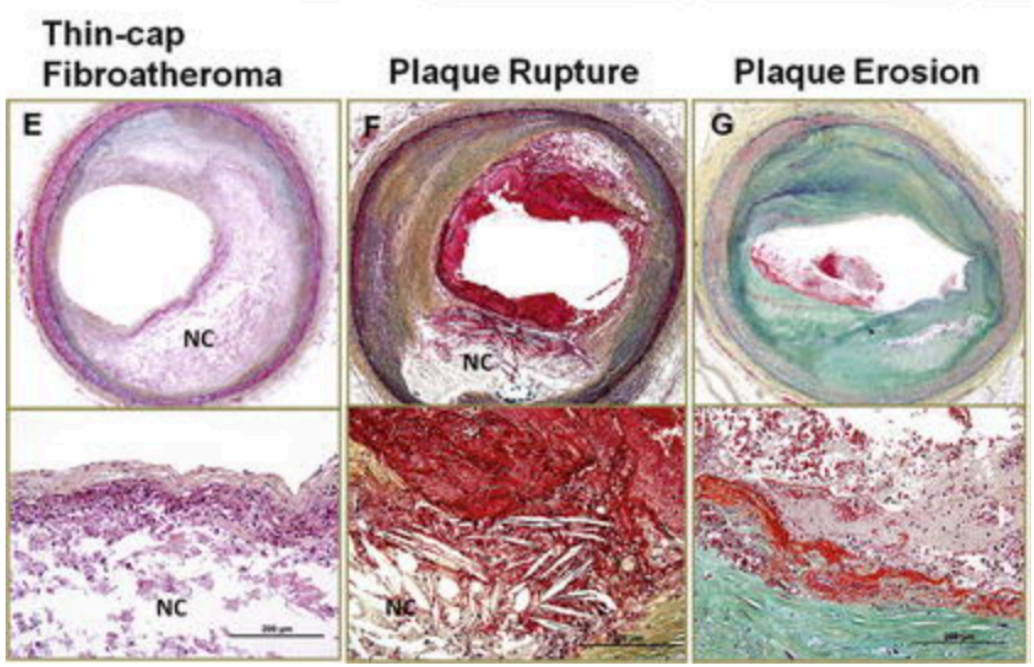
Antigens from macrophages -> ^ trigger T cells -> ^^^ inflammation



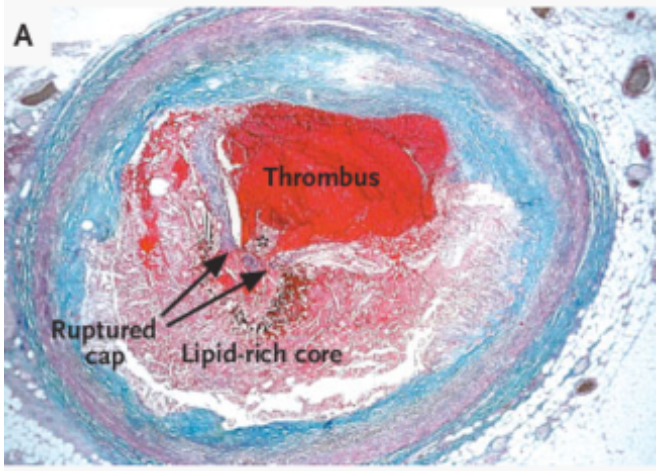
Inflammation -> reduction of plaque stability

N Engl J Med 2005;352:1685-95.

Inflammation in CAD

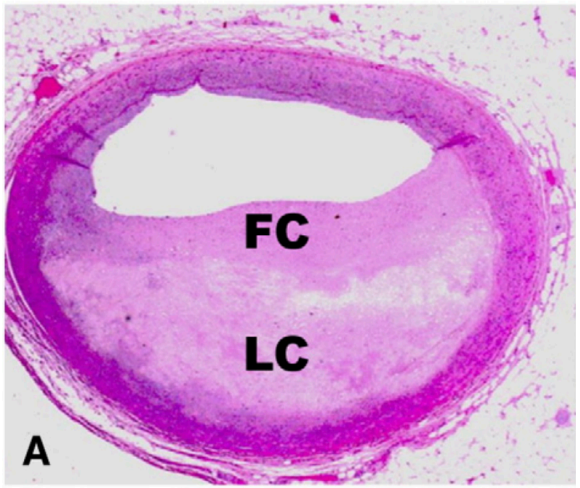


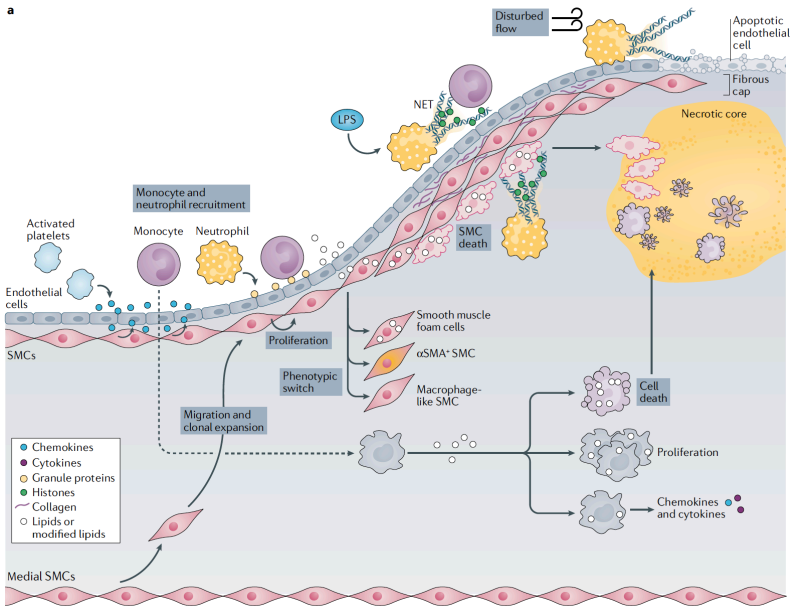
Complete occlusion



Inflammation in CAD

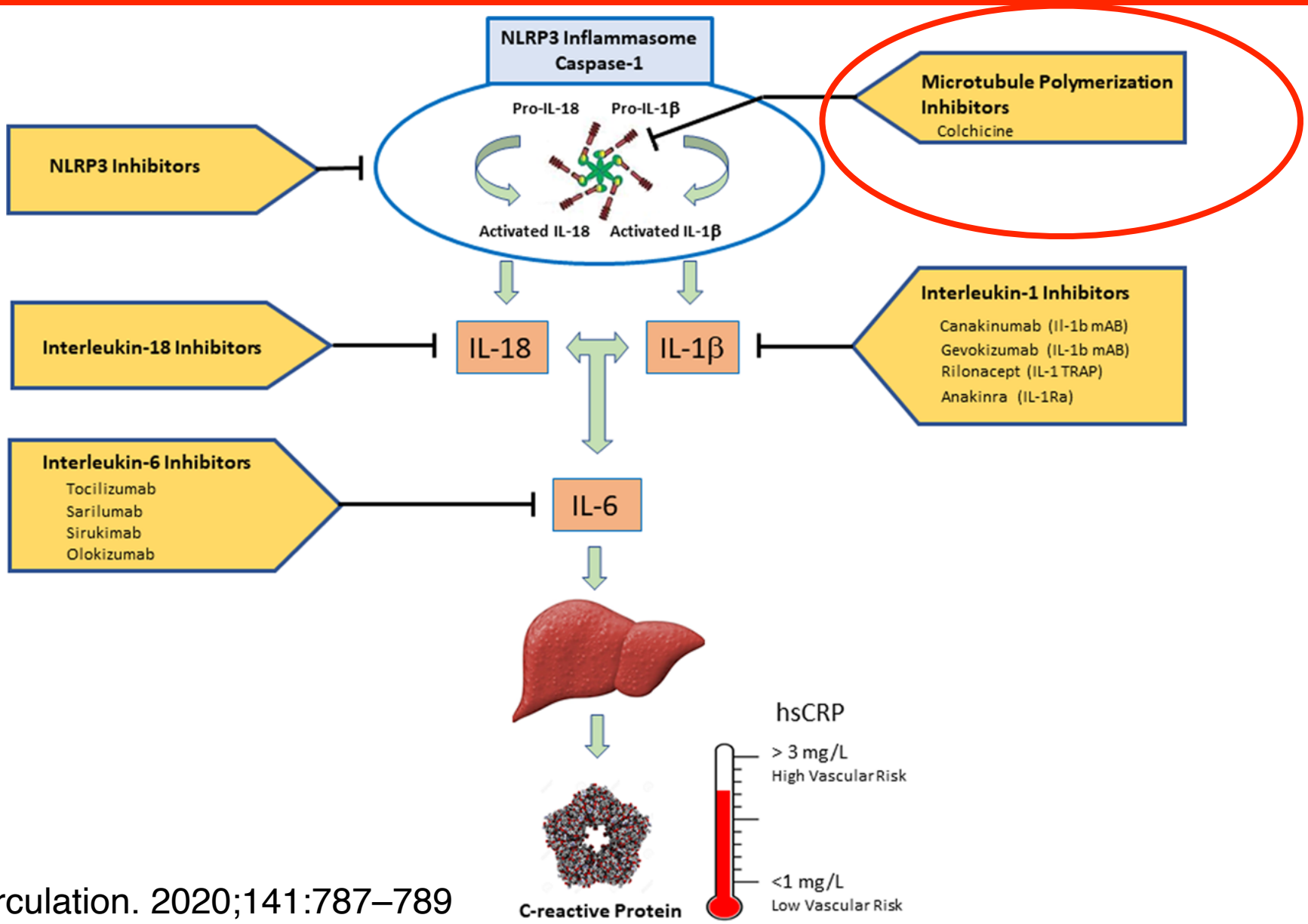
- In the past, atherosclerosis viewed as a lipid storage disease
- Inflammation doesn't replace traditional RF
- But may be partial driver of atherosclerosis and ACS
- Provides another set of potential pathways for novel therapeutics





NatuRe Revlews August 2021

Potential therapeutic inflammasome targets



Circulation. 2020;141:787–789

Anti-inflammatory CV trials

CANTOS	Stable CAD, persistent elevation of hsCRP (>2 mg/l)	Canakinumab (IL-1β antibody) subcutaneously vs placebo	Canakinumab lowered plasma CRP, IL-1 and IL-6 Reduction in cardiovascular events, cancer and gout attacks Small increase in fatal infections

5600 pts, no effect on mortality, $64K / treatment
NNT = 180 for non-fatal MI, FDA refused approval

CIRT	Stable CAD and persistent evidence of inflammation, type 2 diabetes or metabolic syndrome	Low-dose (15–20 mg) methotrexate (a purine metabolism inhibitor) once per week vs placebo	Halted prematurely for futility No change in plasma IL-1β, IL-6 and hsCRP No reduction in cardiovascular events

4786 pts

LATITUDE-TIMI 60	Patients hospitalized with acute myocardial infarction	Losmapimod (a selective inhibitor of p38α/β mitogen-activated protein kinases) twice per day vs placebo	No reduction in major ischaemic cardiovascular events

3503 pts

Colchicine clinical trials in CAD

LoDoCo - 2013

CLINICAL RESEARCH — Clinical Trial

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

	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

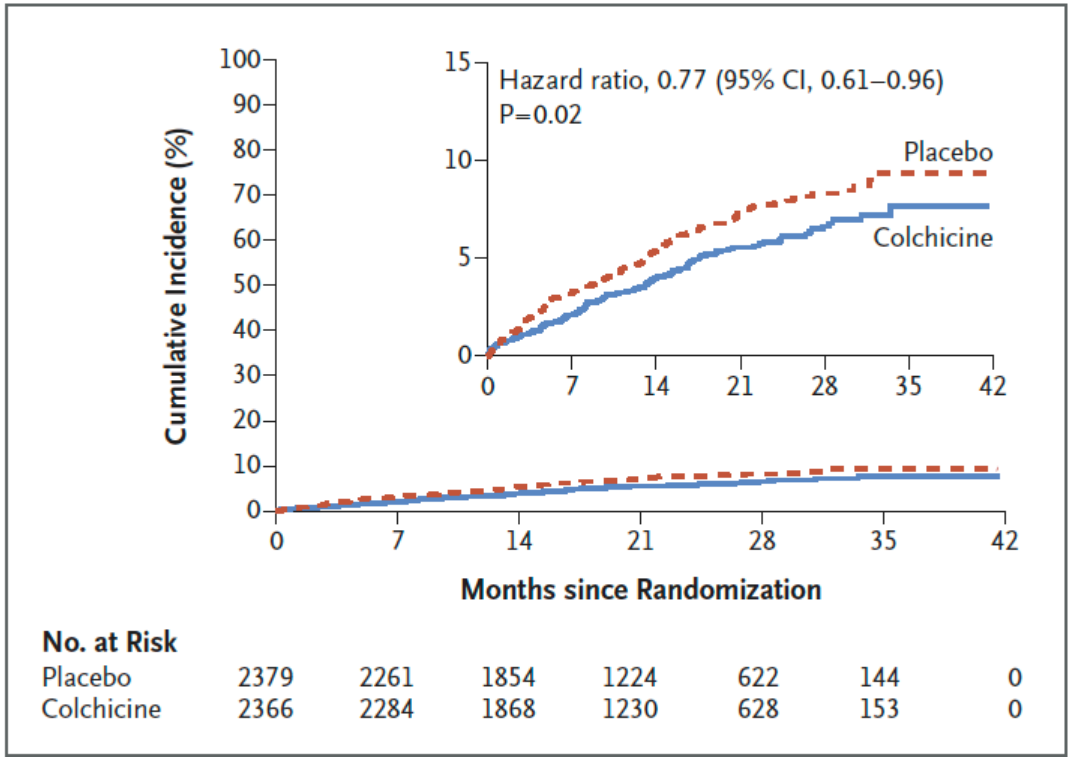
- Serious methodology questions
  - Randomized (?) but protocol allowed RA to assign a newly recruited patient to treatment !!!, No placebo!
  - Run-in only for colchicine group -> selection / survivor bias
  - Unblinded (Open) label - outcome soft endpoint (UA)

COLCOT - Dec 2019

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 26, 2019 VOL. 381 NO. 26

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

1⁰ end point composite of CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization



CONCLUSIONS

Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo. (Funded by the Government of Quebec and others; COLCOT ClinicalTrials.gov num-

COLCOT - Dec 2019

Table 1. Characteristics of the Patients.*

Characteristic	Colchicine (N=2366)	Placebo (N=2379)
Age — yr	60.6±10.7	60.5±10.6
Female sex — no. (%)	472 (19.9)	437 (18.4)
White race — no./total no. (%)†	1350/1850 (73.0)	1329/1844 (72.1)
Body-mass index	28.2±4.8	28.4±4.7
Current smoking — no./total no. (%)	708/2366 (29.9)	708/2377 (29.8)
Hypertension — no. (%)	1185 (50.1)	1236 (52.0)
Diabetes — no. (%)	462 (19.5)	497 (20.9)
History of myocardial infarction — no. (%)	370 (15.6)	397 (16.7)
History of PCI — no. (%)	392 (16.6)	406 (17.1)
History of CABG — no. (%)	69 (2.9)	81 (3.4)
History of heart failure — no. (%)	48 (2.0)	42 (1.8)
History of stroke or TIA — no. (%)	55 (2.3)	67 (2.8)
Time from index myocardial infarction to randomization — days	13.4±10.2	13.5±10.1
PCI for index myocardial infarction — no./total no. (%)	2192/2364 (92.7)	2216/2375 (93.3)
Medication use — no. (%)		
Aspirin	2334 (98.6)	2352 (98.9)
Other antiplatelet agent	2310 (97.6)	2337 (98.2)
Statin	2339 (98.9)	2357 (99.1)
Beta-blocker	2116 (89.4)	2101 (88.3)

COLCOT - Dec 2019

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

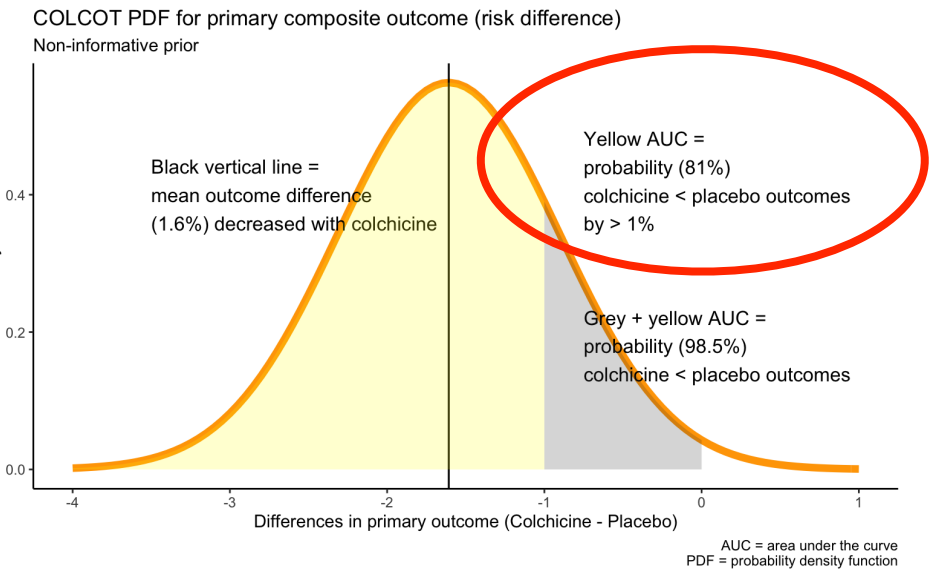
End Point	Colchicine (N=2366)	Placebo (N=2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	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)	

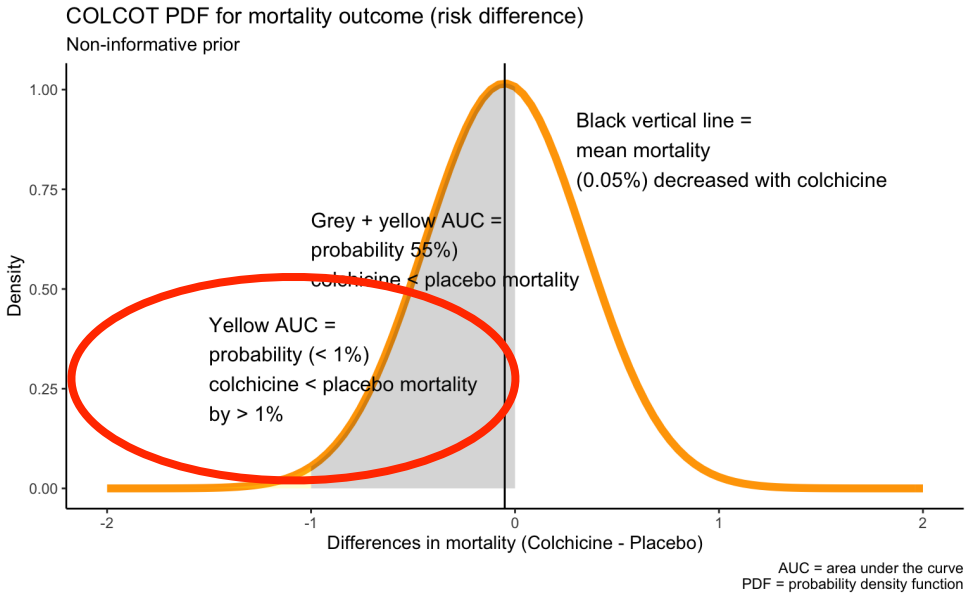
COLCOT - How strong is the evidence?

- NNT = 62 for 22 mo (avg) to prevent 1 composite outcome (most likely it is 1 PCI avoided)
- Fragility index = 5 # colchicine pts if switched from not having to having 1^0 endpoint -> p> 0.05
- 89 pts lost to follow-up >> FI (5), robustness?
- No mortality benefit
- Really want to know what is the probability that colchicine benefit is clinically meaningful
- What is clinically meaningful?

COLCOT - Dec 2019

- What is clinically meaningful?
- COLCOT powered -> 1.8% absolute reduction
- Consider 1% decrease to be clinically meaningful





- 81% probability clinically meaningful ↓ 1º outcome
- No mortality effect

COLCOT - Dec 2019

CONCLUSIONS

Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo. (Funded by the Government of Quebec and others; COLCOT ClinicalTrials.gov num-

Alternative conclusion

"In this trial, although there were no mortality differences, there was a moderate probability (>80%) of a clinically meaningful reduction in the composite CV outcome compared to placebo."

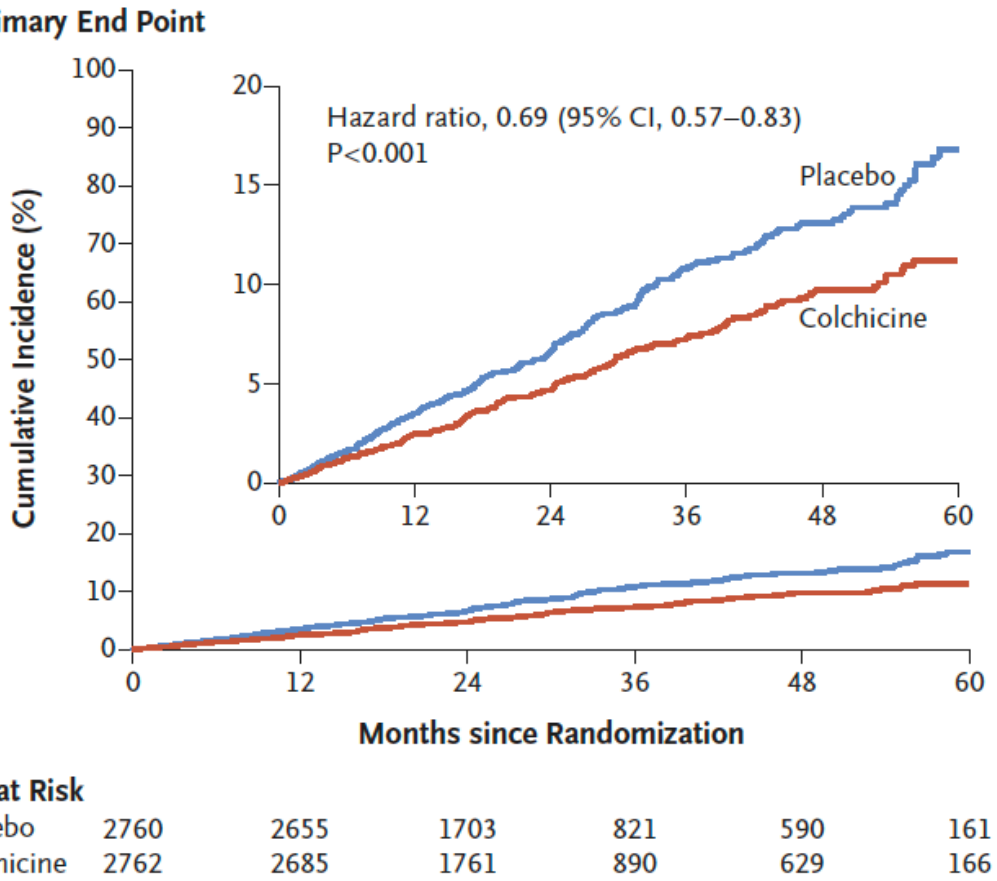
LoDoCo2 Trial - August 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

1[0] end point composite of CV death, spontaneous (nonprocedural) MI, ischemic stroke, or ischemia-driven revascularization



CONCLUSIONS

In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo. (Funded by the Na-

LoDoCo2 Trial - August 2020

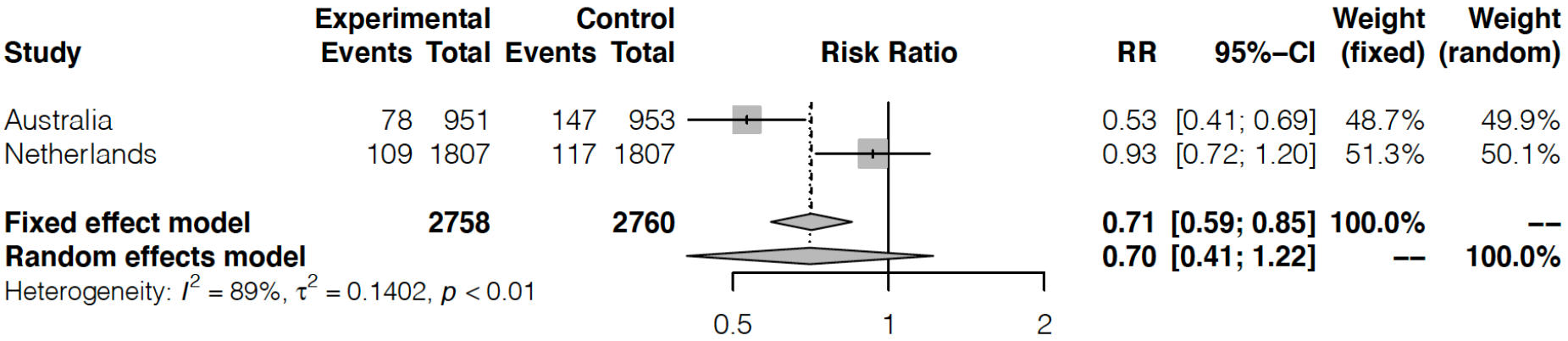
- Patients 35 to 82 with stable CAD (>6 mo) from 13 Australian and 30 Dutch centers
- Open label 1 mo run-in, FU average 28 months
- End points, including 1^0 end point, revised several times during the trial - 580 stopped Rx prematurely

End Point	Colchicine (N=2762) no. of patients (%)	Colchicine (N=2762) no. of events/100 person-yr	Placebo (N=2760) no. of patients (%)	Placebo (N=2760) no. of events/100 person-yr	Hazard Ratio (95% CI)	P Value
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
Noncardiovascular death	53/2762 (1.9)	0.7	35/2760 (1.3)	0.5	1.51 (0.99–2.31)	

FI = 8

FI = 2

LoDoCo2 Trial - Which country?

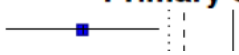


- Large Δ in results between countries, which statistical model to use
- Accounting btw country variation, 1^0 end point RR not statistically significant
- Non CV death ↑ colchicine (HR 1.51, 0.99-2.31)

Synthesis of trial evidence

Synthesizing the data - 1º outcome

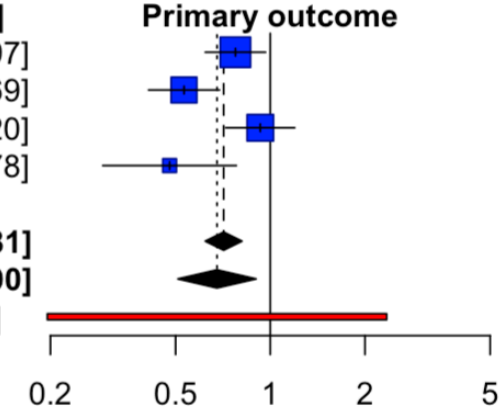
Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight (fixed)	Weight (random)	RR [95% CI]
LoDoCo1	14	282	40	250	5.0%	14.0%	0.31 [0.17; 0.56]



- LoDoCo1 excluded, no placebo, no blinding lack of randomization

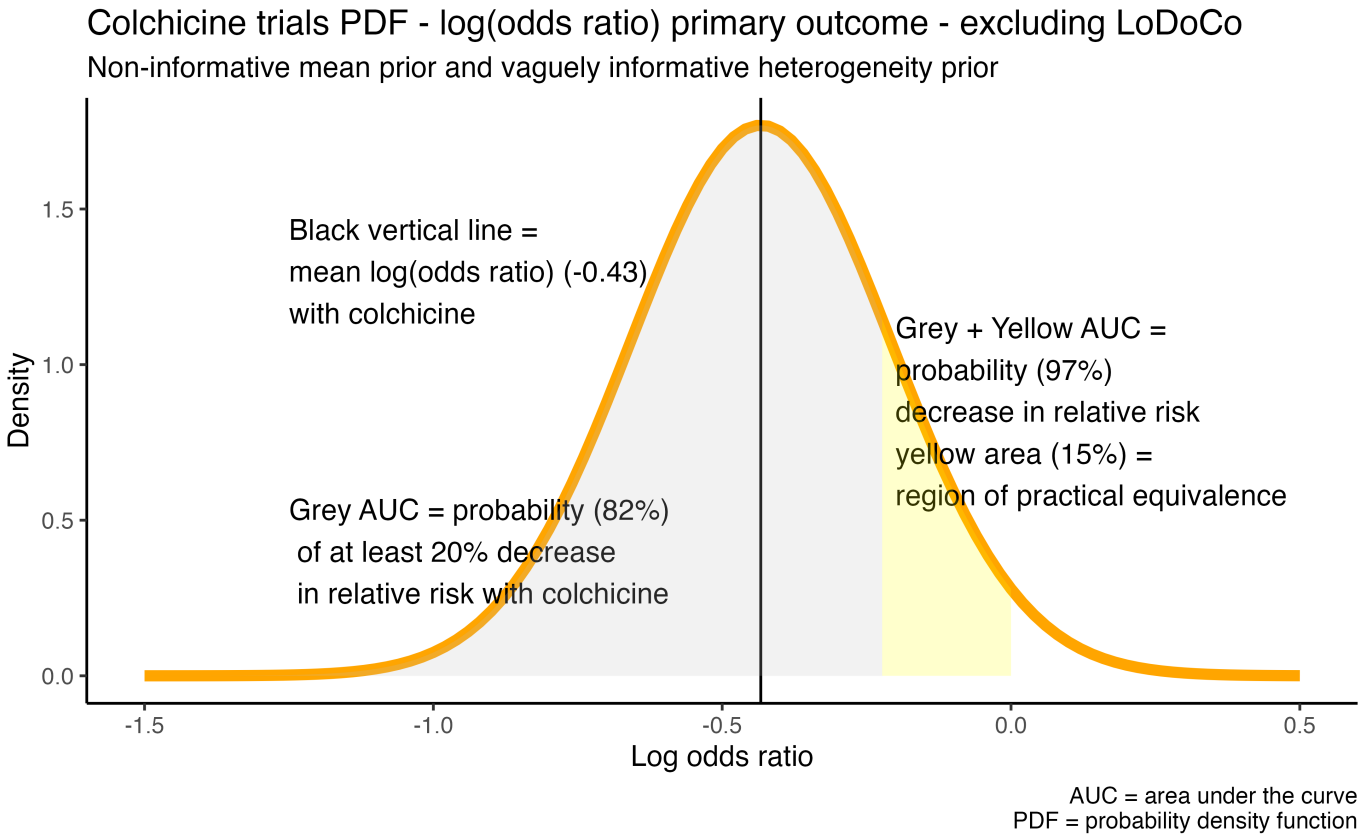
Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight (fixed)	Weight (random)	RR [95% CI]
COLCOT	131	2366	170	2379	37.2%	28.7%	0.77 [0.62; 0.97]
LoDoCo2-A	78	951	147	953	26.9%	26.9%	0.53 [0.41; 0.69]
LoDoCo2-N	109	1811	117	1807	28.4%	27.2%	0.93 [0.72; 1.20]
COPS	24	396	38	300	7.6%	17.2%	0.48 [0.29; 0.78]
Total (fixed effect, 95% CI)		**5524**		**5439**	**100.0%**	--	**0.71 [0.62; 0.81]**
Total (random effects, 95% CI)					--	**100.0%**	**0.68 [0.51; 0.90]**
Prediction interval							**[0.20; 2.34]**

Heterogeneity: $Tau^2 = 0.0620$; $Chi^2 = 12.25$, df = 3 ($P < 0.01$); $I^2 = 76\%$



- Point estimate (PE) 32% reduction (95% CI 0.51 - 0.90)
- PE statistically significant but what about clinical significance?
- Prediction interval for next study remains wide & uncertain

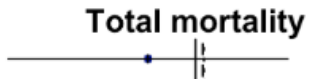
Synthesizing the data - 1º outcome



- P(fewer composite endpoints) = 97%
- P(meaningful Δ fewer composite endpoints) = 82%
- Includes soft outcomes - UA, revascularizations

Synthesizing the data - total mortality

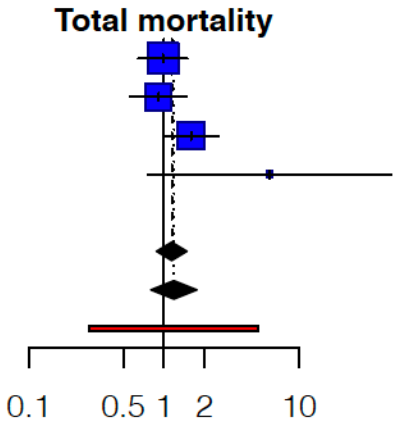
Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight (fixed)	Weight (random)	RR [95% CI]
LoDoCo1	1	282	2	250	1.2%	2.3%	0.44 [0.04; 4.86]



- LoDoCo1 excluded, no placebo, no blinding lack of randomization

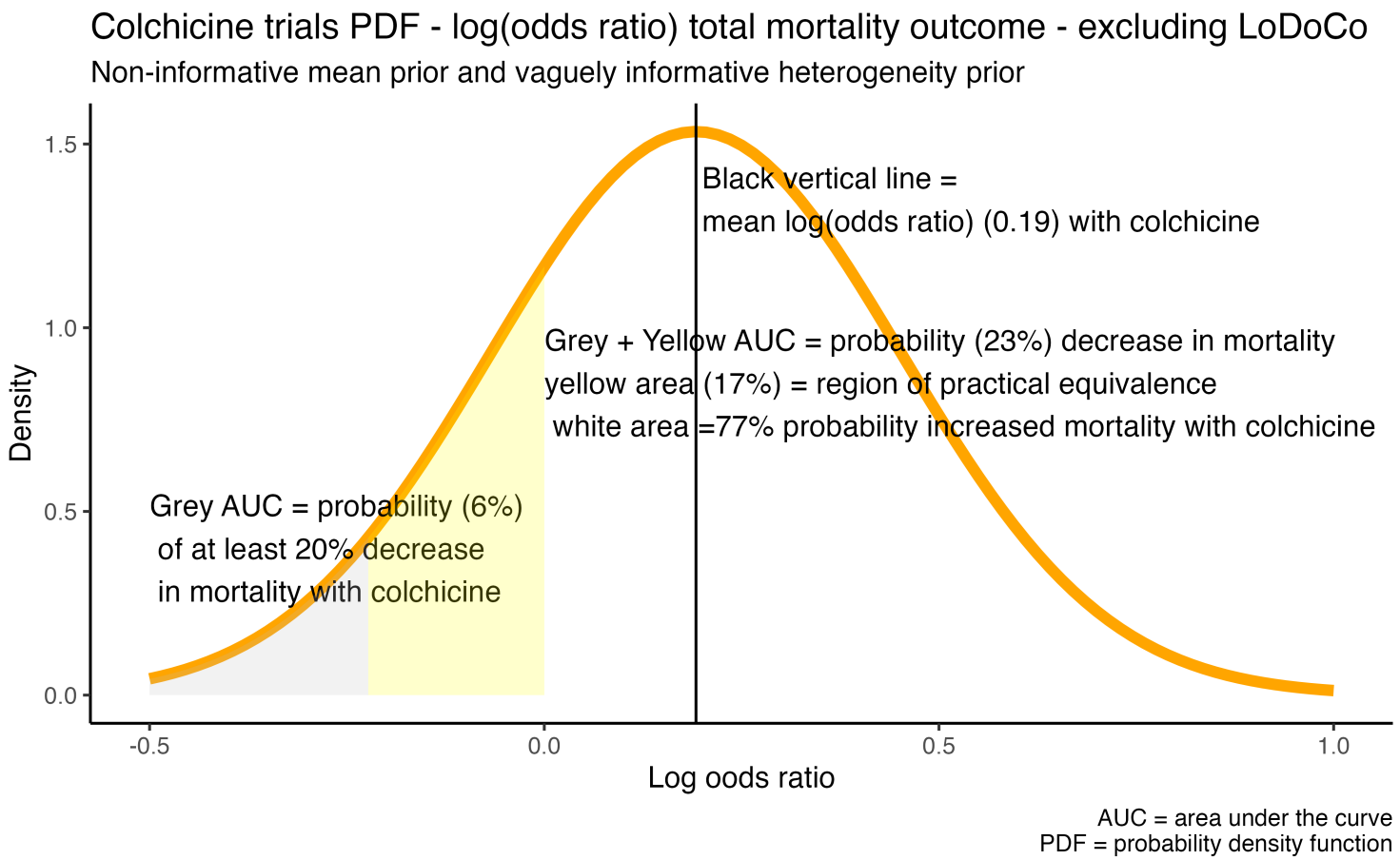
Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight (fixed)	Weight (random)	RR [95% CI]
COLCOT	43	2366	44	2379	39.4%	34.9%	0.98 [0.65; 1.49]
LoDoCo2–A	30	951	33	953	28.9%	30.6%	0.91 [0.56; 1.48]
LoDoCo2–N	43	1811	27	1807	30.1%	31.1%	1.59 [0.99; 2.56]
COPS	8	396	1	300	1.6%	3.4%	6.06 [0.76; 48.19]
Total (fixed effect, 95% CI)		**5524**		**5439**	**100.0%**		**1.14 [0.88; 1.49]**
Total (random effects, 95% CI)						**100.0%**	**1.19 [0.80; 1.76]**
Prediction interval							**[0.28; 4.98]**

Heterogeneity: $Tau^2 = 0.0707$; $Chi^2 = 5.66$, df = 3 (P = 0.13); $I^2 = 47\%$



- Point estimate 19% increase (95% CI 0.80 - 1.76)
- Probability of a clinically meaningful Δ in mortality?
- Wide interval for next study

Synthesizing the data - mortality



- P(↑ mortality) = 74%%
- P(meaningful Δ in mortality) = 6%

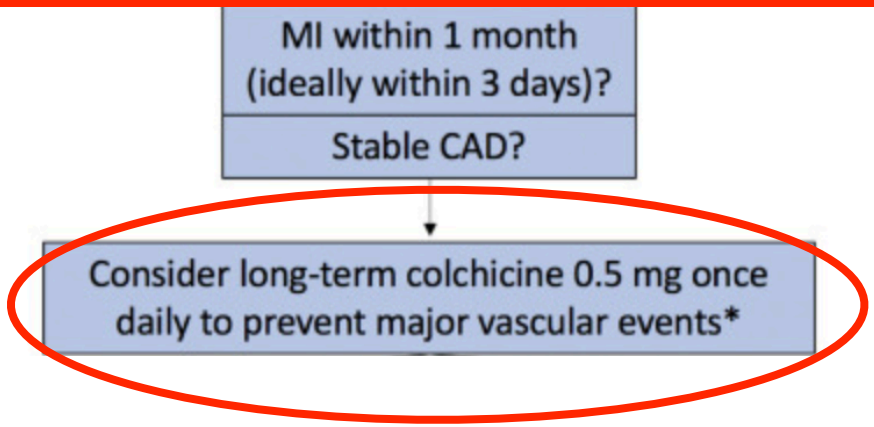
Colchicine as a 3rd pillar

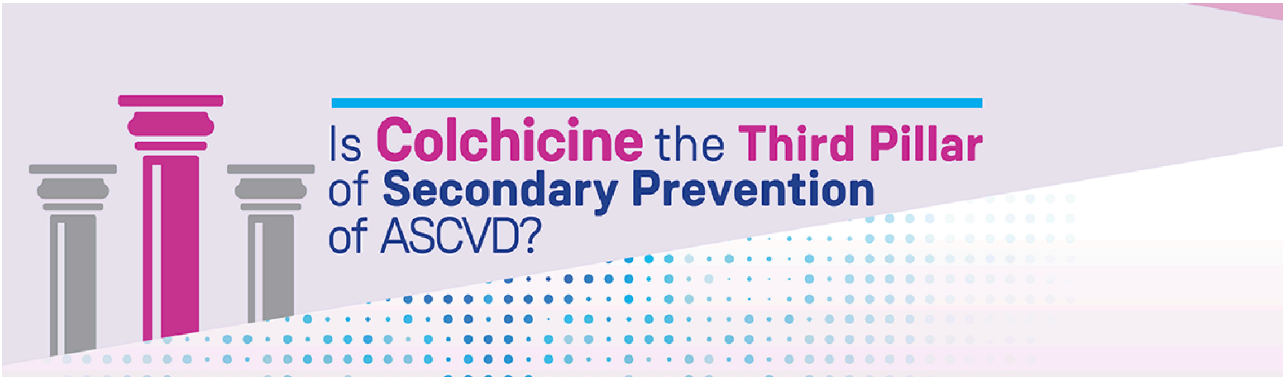
REVIEW | ARTICLES IN PRESS

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 • ...
Robert C Welsh, MD • Graham Wong, MD, MPH • Jean-Claude Tardif, MD • Show all authors

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





Third pillar?

ASA 27 trials (40,000)
BMJ 2002
15% CV mortality reduction

Statins 18 trials (170,000)
Lancet 2010
20% CV mortality reduction

Critical summary of the colchicine evidence

- 2 large colchicine CAD trials -> statistical significant reductions in composite CV endpoints

- But some questions remain
  - robustness of the data
  - moderate probability of clinically significant effect
  - no decrease in total mortality (trend ↑nonCV mortality)
  - ignores side /adverse effects , extra cost & inconvenience of another pill
  - other anti-inflammatory trials -> no success

My bottom line

- There is histological evidence about the role of inflammation in CAD
- There are 2 large “positive” colchicine RCTs
- In my opinion, the routine use of an anti-inflammatory treatment for CAD with colchicine is worthy of consideration
- But given the residual uncertainties speaking of a “Third Pillar” with its implication of a quasi-mandatory treatment seems premature

Critical Reading References

"The published conclusions of many clinical trials are ill-founded, and may be wrong."

Diamond GA, Forrester JS 1983

- Critical Reading

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Merci Beaucoup