

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

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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



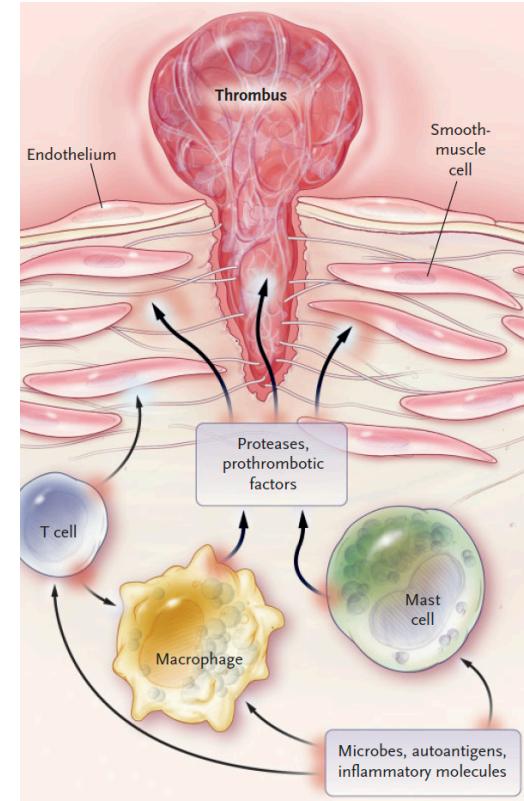
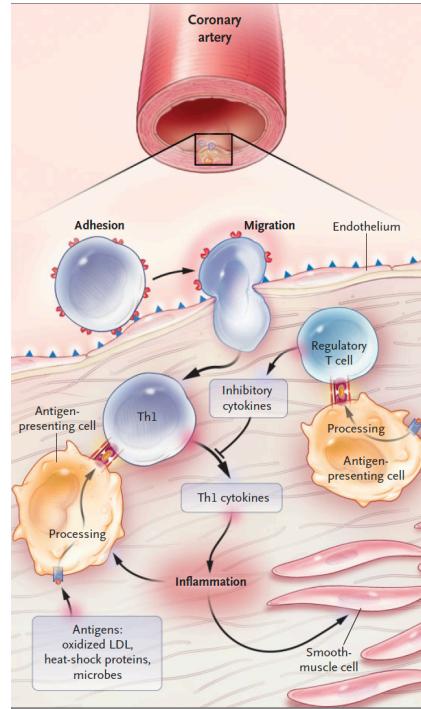
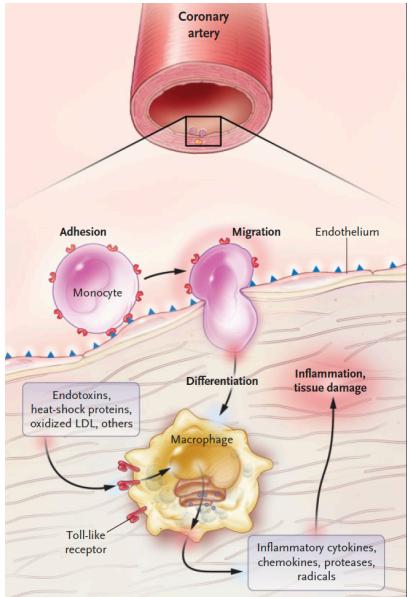
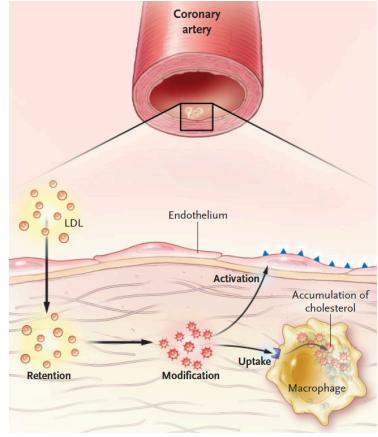
<http://www.nofreelunch.org/>

# 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.

# Anti-inflammatory CV trials

CANTOS	Stable CAD, persistent elevation of hsCRP (>2 mg/l)	Canakinumab (IL-1 $\beta$ 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
	<b>5600 pts, no effect on mortality, \$64K / treatment</b> <b>NNT = 180 for non-fatal MI, FDA refused approval</b>		
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-1 $\beta$ , IL-6 and hsCRP No reduction in cardiovascular events
	<b>4786 pts</b>		
LATITUDE-TIMI 60	Patients hospitalized with acute myocardial infarction	Losmapimod (a selective inhibitor of p38 $\alpha/\beta$ mitogen-activated protein kinases) twice per day vs placebo	No reduction in major ischaemic cardiovascular events
	<b>3503 pts</b>		

# Colchicine clinical trials in CAD

# LoDoCo - 2013

CLINICAL RESEARCH	Clinical Trial
<b>Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease</b>	

	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

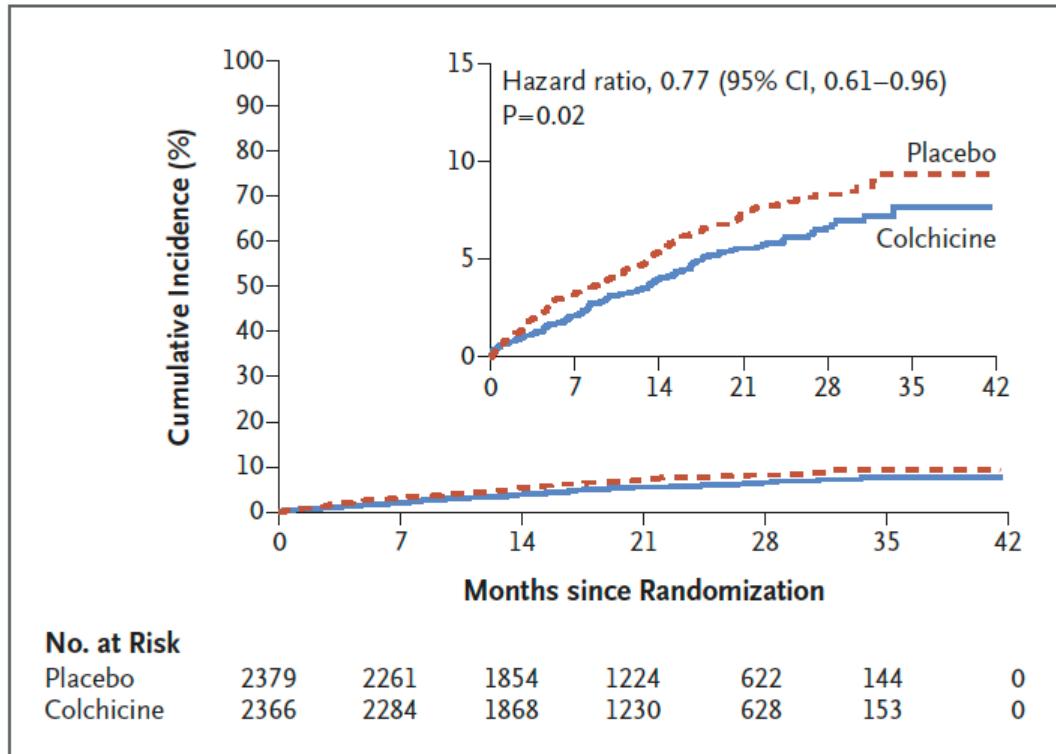
- Randomized (?) but protocol allowed RA to assign a newly recruited patient to treatment !!!, No placebo!
- Run-in only for colchicine group -> selection / survivor bias
- Unblinded (Open) label - outcome soft endpoint (UA)

# COLCOT - Dec 2019



Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

<sup>10</sup> 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)	1220/1844 (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).\*

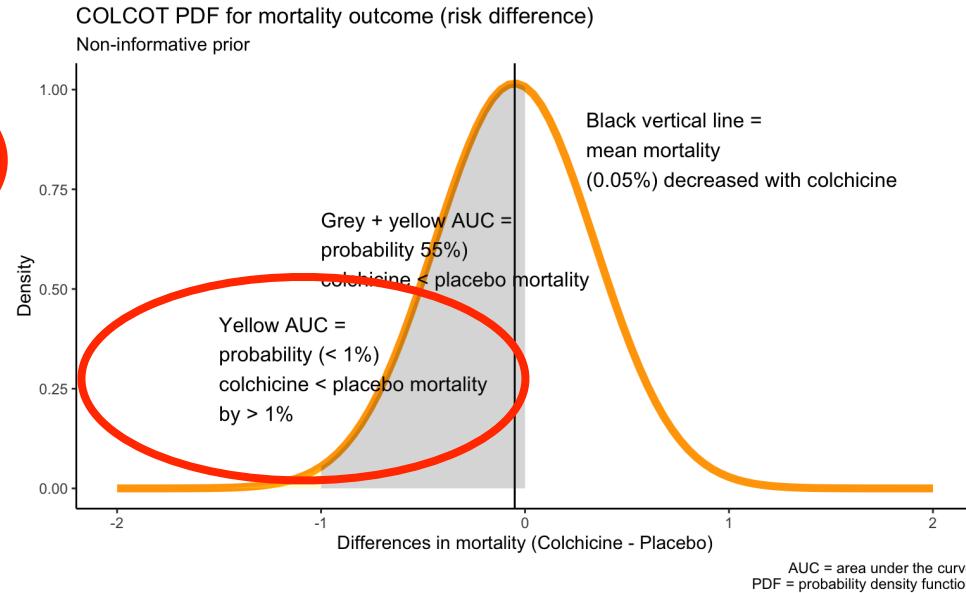
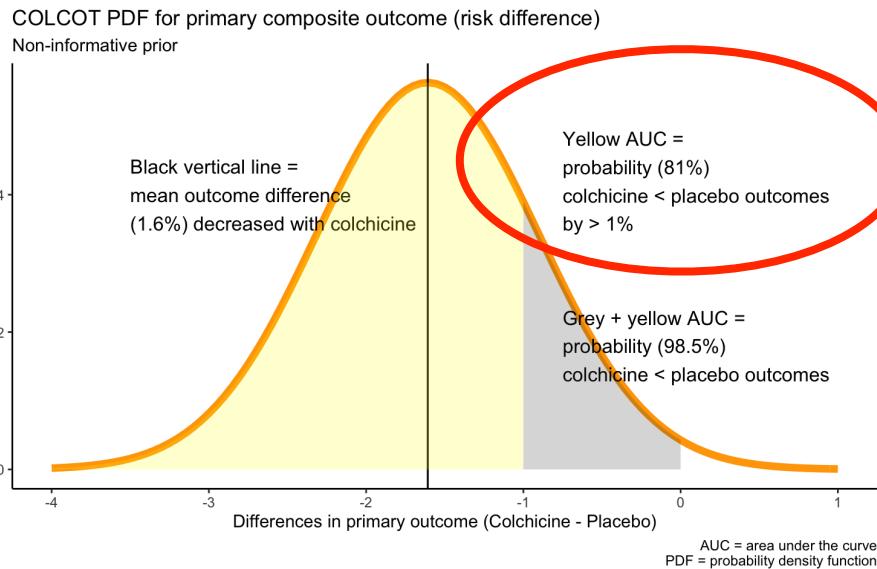
End Point	Colchicine (N=2366)	Placebo (N=2379)	Hazard Ratio (95% CI)	P Value
<i>number (percent)</i>				
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac 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 (7.1-5.5%) for 22 mo (avg) to prevent 1 composite outcome (most likely 1 PCI avoided)
- Fragility index = 5 # colchicine pts if switched from not having to having 1<sup>o</sup> 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 the definition of 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 ↓ 1° 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

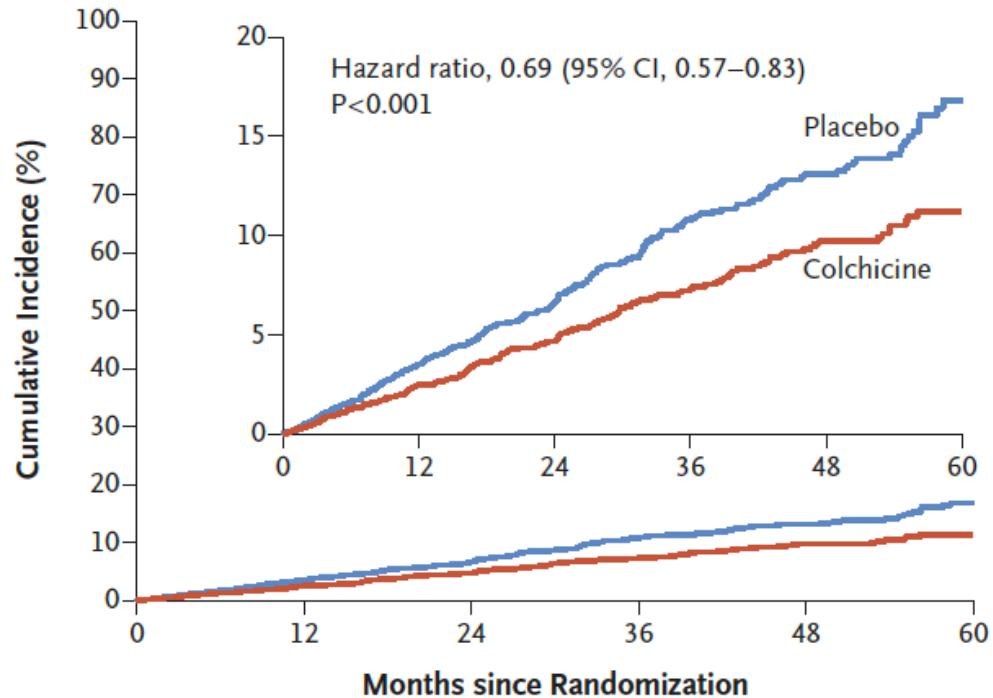
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Colchicine in Patients with Chronic Coronary Disease

1<sup>o</sup> end point composite of CV death, spontaneous (nonprocedural) MI, ischemic stroke, or ischemia-driven revascularization

### A Primary End Point



#### No. at Risk

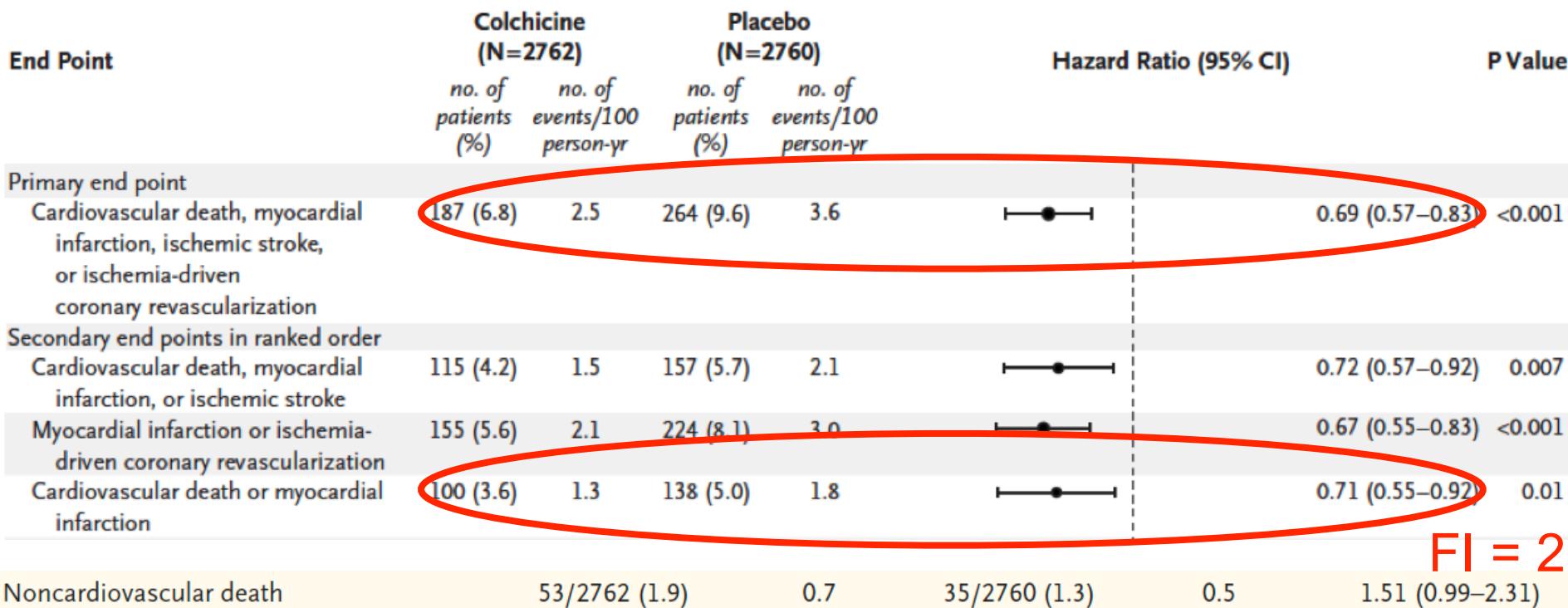
Placebo	2760	2655	1703	821	590	161
Colchicine	2762	2685	1761	890	629	166

## CONCLUSIONS

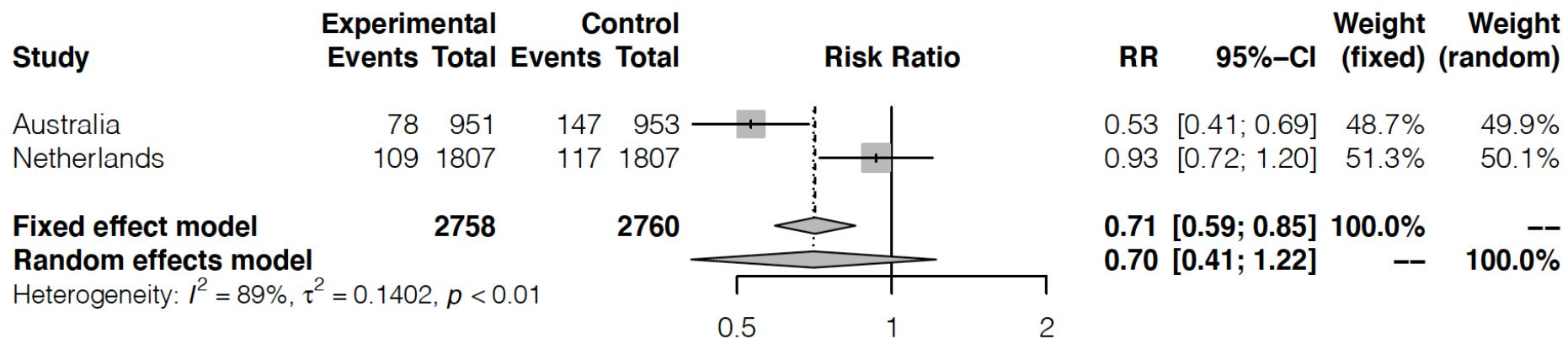
In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo. (Funded by the National Institutes of Health.)

# 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<sup>o</sup> end point, revised several times during the trial - 580 stopped Rx prematurely



# LoDoCo2 Trial - Which country?



- Large  $\Delta$  in results between countries, which statistical model to use
- Accounting btw country variation, 1<sup>0</sup> end point RR not statistically significant
- Non CV death ↑ colchicine (HR 1.51, 0.99-2.31)

# Synthesis of trial evidence

# Synthesizing the data - 1° outcome

Study  
LoDoCo1

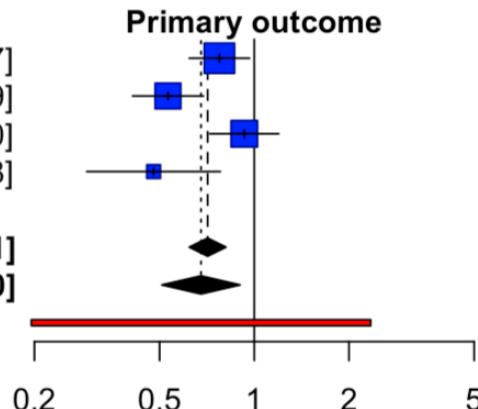
Experimental	Control	Weight (fixed)	Weight (random)	RR [95% CI]	Primary outcome
Events	Total	Events	Total		
14	282	40	250	5.0%	14.0% 0.31 [0.17; 0.56]

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

Study  
COLCOT  
LoDoCo2-A  
LoDoCo2-N  
COPS

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

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

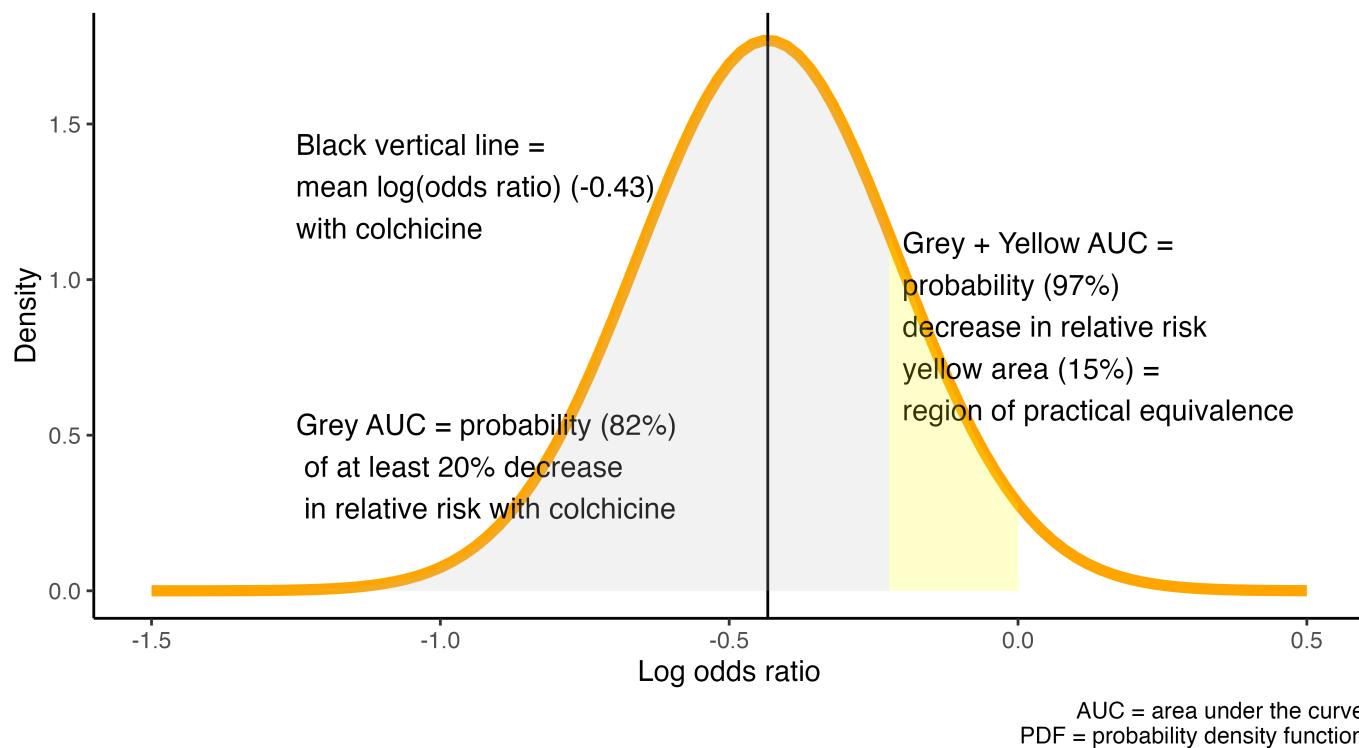


- Point estimate (PE) 32% reduction (95% CI 0.51 - 0.90)
- PE statistically significant but what about clinical significance?
- Prediction interval for next study remains wide & uncertain

# Synthesizing the data - 1° outcome

Colchicine trials PDF - log( odds ratio) primary outcome - excluding LoDoCo

Non-informative mean prior and vaguely informative heterogeneity prior



- $P(\text{fewer composite endpoints}) = 97\%$
- $P(\text{meaningful } \Delta \text{ fewer composite endpoints}) = 82\%$
- Includes soft outcomes - UA, revascularizations

# Synthesizing the data - total mortality

Study  
LoDoCo1

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

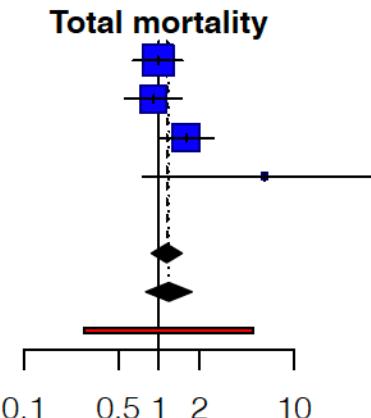
- LoDoCo1 excluded, no placebo, no blinding lack of randomization

Study

COLCOT  
LoDoCo2-A  
LoDoCo2-N  
COPS

Study	Experimental		Control		Weight (fixed)	Weight (random)	RR [95% CI]	Total mortality
	Events	Total	Events	Total				
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]	
<b>Total (fixed effect, 95% CI)</b>	<b>5524</b>		<b>5439</b>	<b>100.0%</b>	—	—	<b>1.14 [0.88; 1.49]</b>	
<b>Total (random effects, 95% CI)</b>					—	100.0%	<b>1.19 [0.80; 1.76]</b>	
<b>Prediction interval</b>							<b>[0.28; 4.98]</b>	

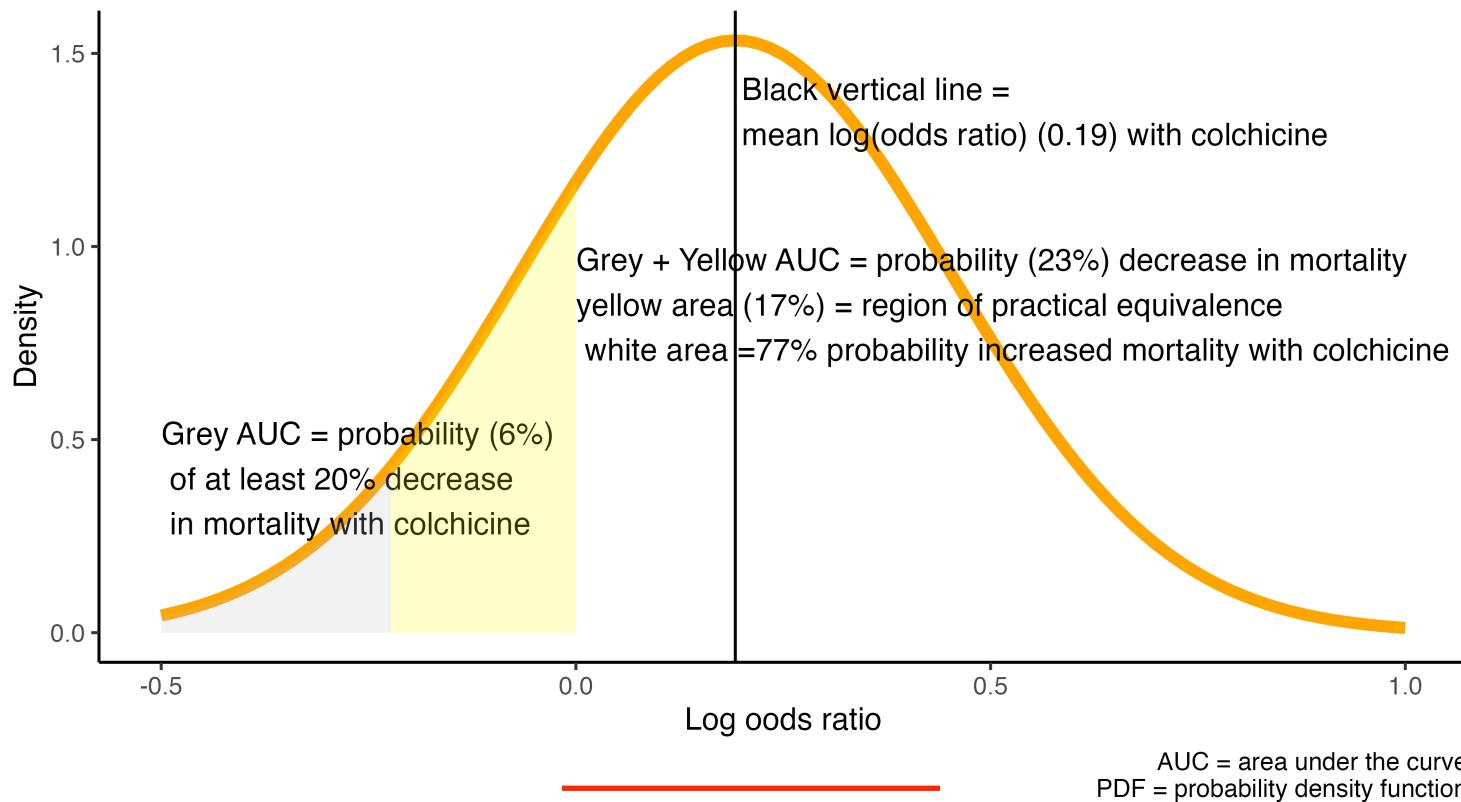
Heterogeneity:  $\tau^2 = 0.0707$ ;  $\chi^2 = 5.66$ , df = 3 ( $P = 0.13$ );  $I^2 = 47\%$



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

# Synthesizing the data - mortality

Colchicine trials PDF - log( odds ratio) total mortality outcome - excluding LoDoCo  
Non-informative mean prior and vaguely informative heterogeneity prior



- $P(\uparrow \text{mortality}) = 77\%$  (white area under the curve)
- $P(\downarrow \text{mortality}) = 23\%$  (grey and yellow area under the curve)
- $P(\text{meaningful } \downarrow \Delta \text{ in mortality}) = 6\%$  (grey area under the curve)

# 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
- In my opinion, the use of an anti-inflammatory treatment for CAD with colchicine is worthy of consideration
- But given the residual uncertainties, routine use seems premature

# Critical Reading References

## • Critical Reading

- Diamond GA, Forrester JS. Clinical trials and statistical verdicts: probable grounds for appeal. Ann Intern Med. 1983;98(3):385-94.
- Ioannidis JP. Why most published research findings are false. PLoS Med. 2005;2(8):e124
- Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928
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*Merci Beaucoup*