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EXERCER ET ENSEIGNER LA MÉDECINE GÉNÉRALE

Strasbourg
Palais de la musique et des congrès
20 • 21 • 22 NOVEMBRE 2024

De la colchicine en prévention secondaire à l'étude COLCOT-T2D

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UdeM endowed research chair in atherosclerosis
Professor of medicine
Montreal Heart Institute
University of Montreal

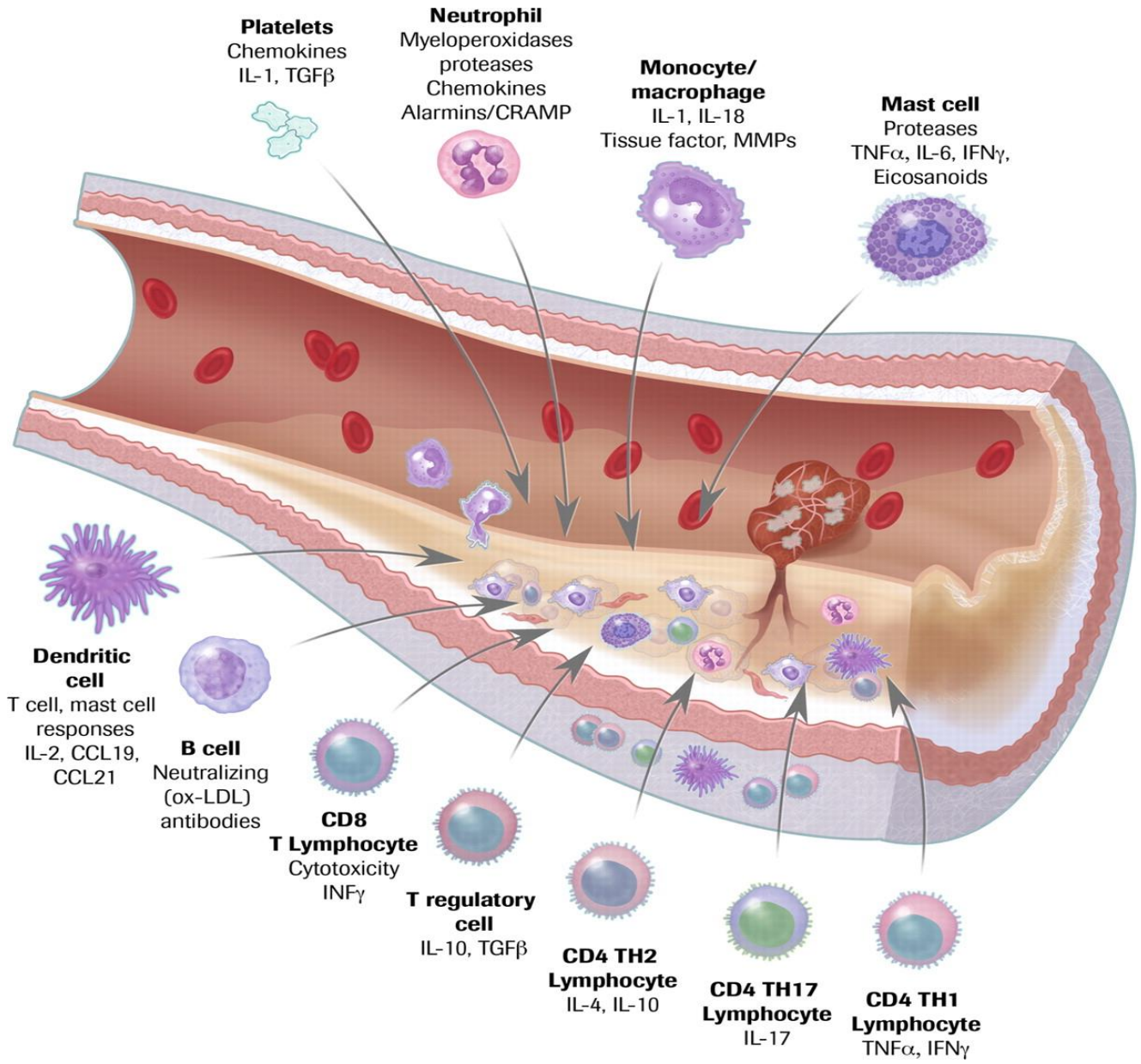
Novembre 2024

Divulgations d’intérêts

Subventions:	Boehringer-Ingelheim, Ceapro, DalCor Phamaceuticals, Esperion, Ionis, Merck, Novartis, Novo-Nordisk, Pfizer
Honoraires:	DalCor Pharmaceuticals, Pfizer
Actionnariat (mineur):	DalCor Pharmaceuticals
Brevets:	Pharmacogenomics-guided CETP inhibition Pharmacogenomics of responses to colchicine* Use of colchicine after myocardial infarction*

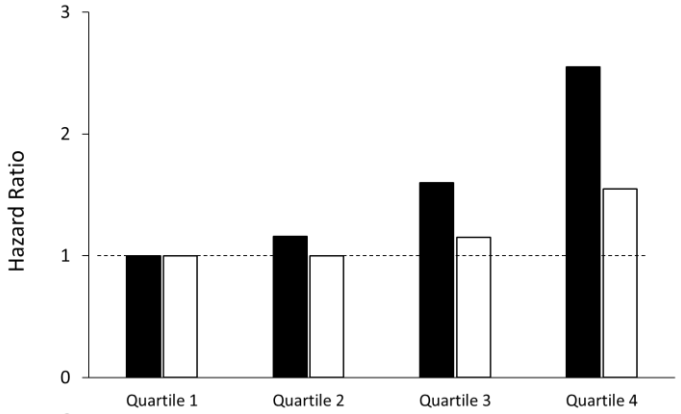
* Dr. Tardif a renoncé à ses droits dans ces brevets et ne peut ainsi pas en bénéficier financièrement.

Inflammation and immunity in atherosclerosis

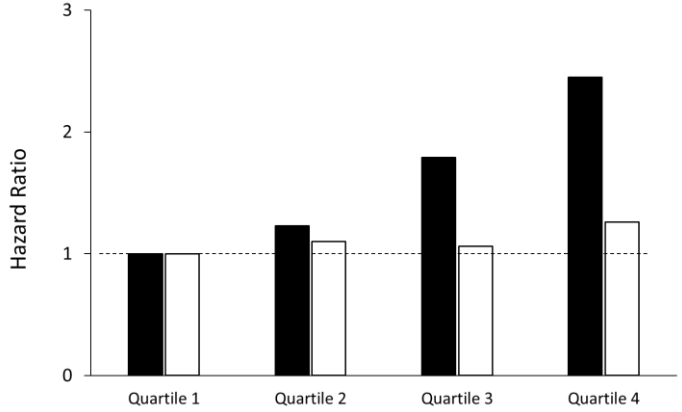


Results – IV Hazard Ratios for Cardiovascular Death Among 31,245 Statin Treated Patients

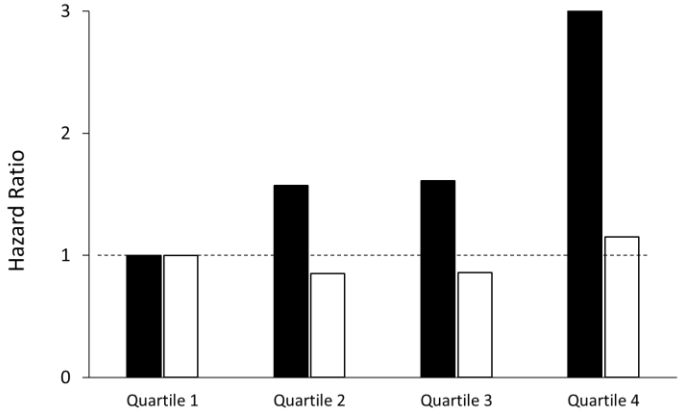
PROMINENT
(N = 9,988)



REDUCE-IT
(N = 8,179)

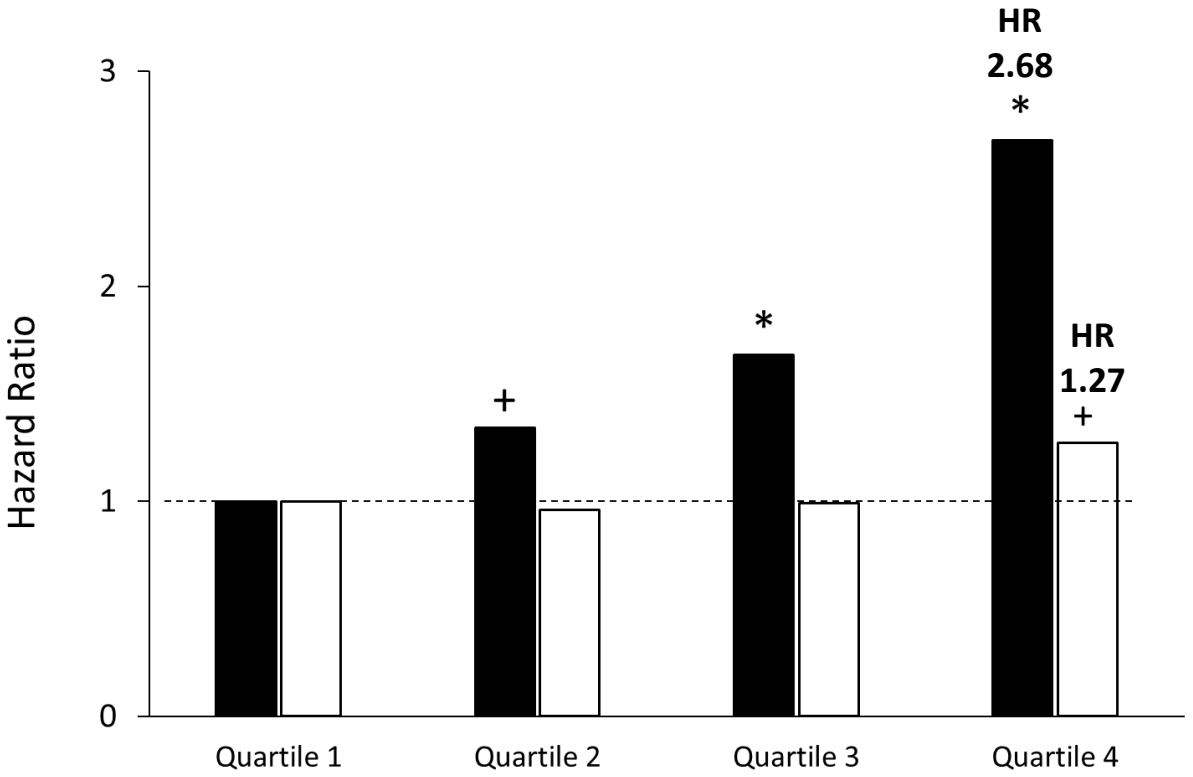


STRENGTH
(N = 13,078)



Pooled Data (N = 31,245)

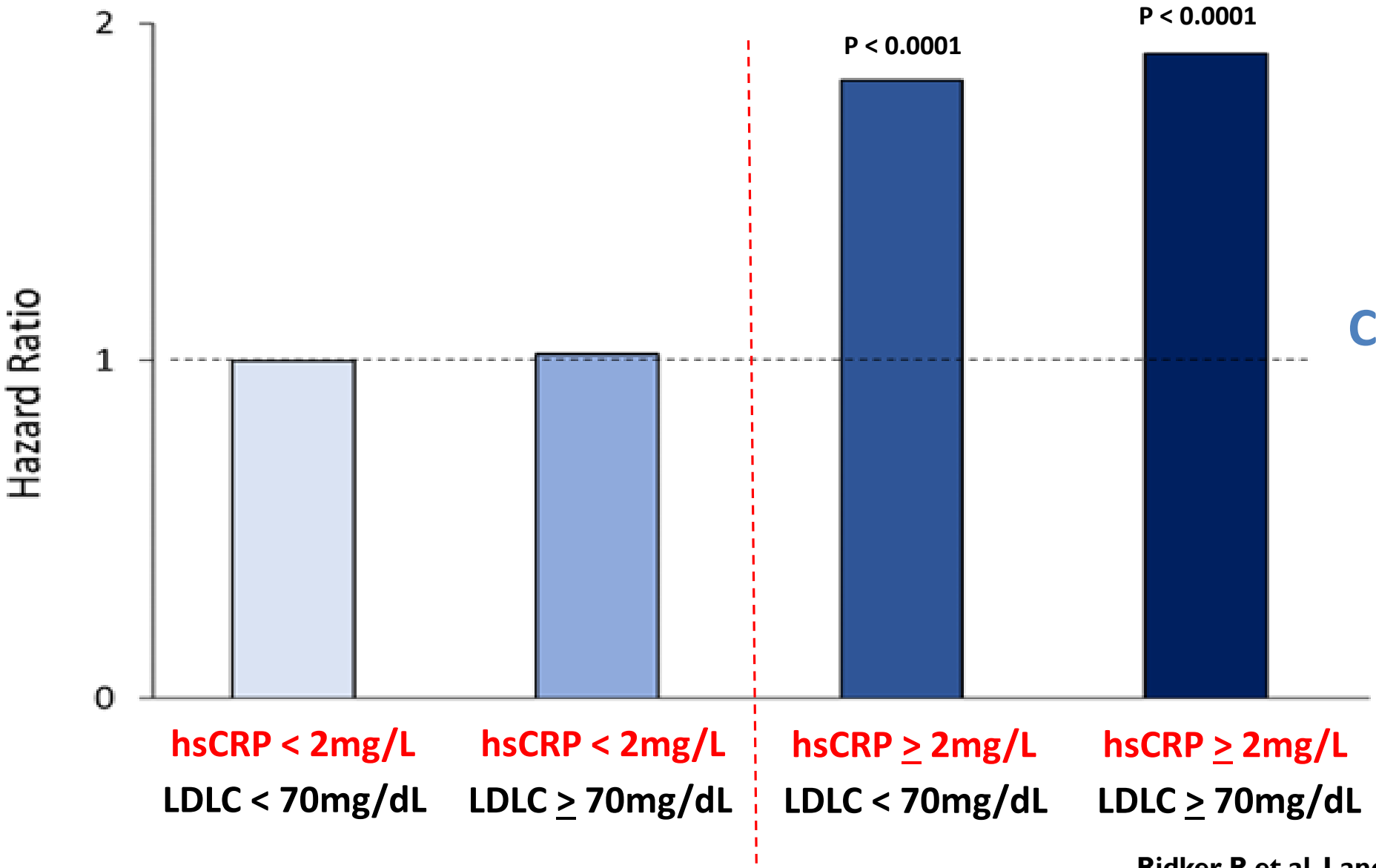
Cardiovascular Death



* P < 0.0001 + P < 0.05

Ridker P et al. Lancet 2023 March 6

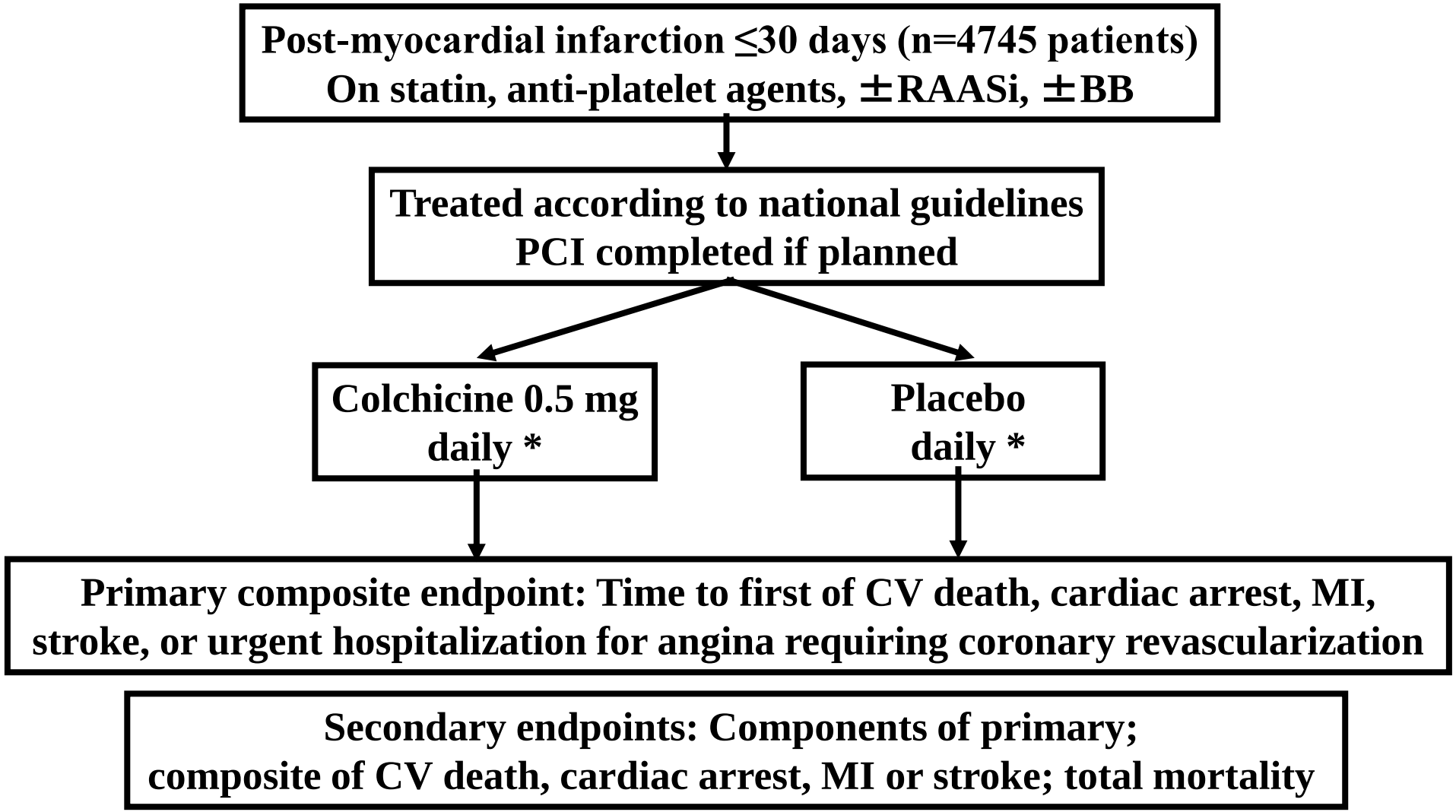
Results – VI Interaction Analyses - hsCRP < or ≥2 mg/L and/or LDLC < or ≥ 70 mg/dL



Cardiovascular Death

Ridker P et al. Lancet 2023 March 6

Study design



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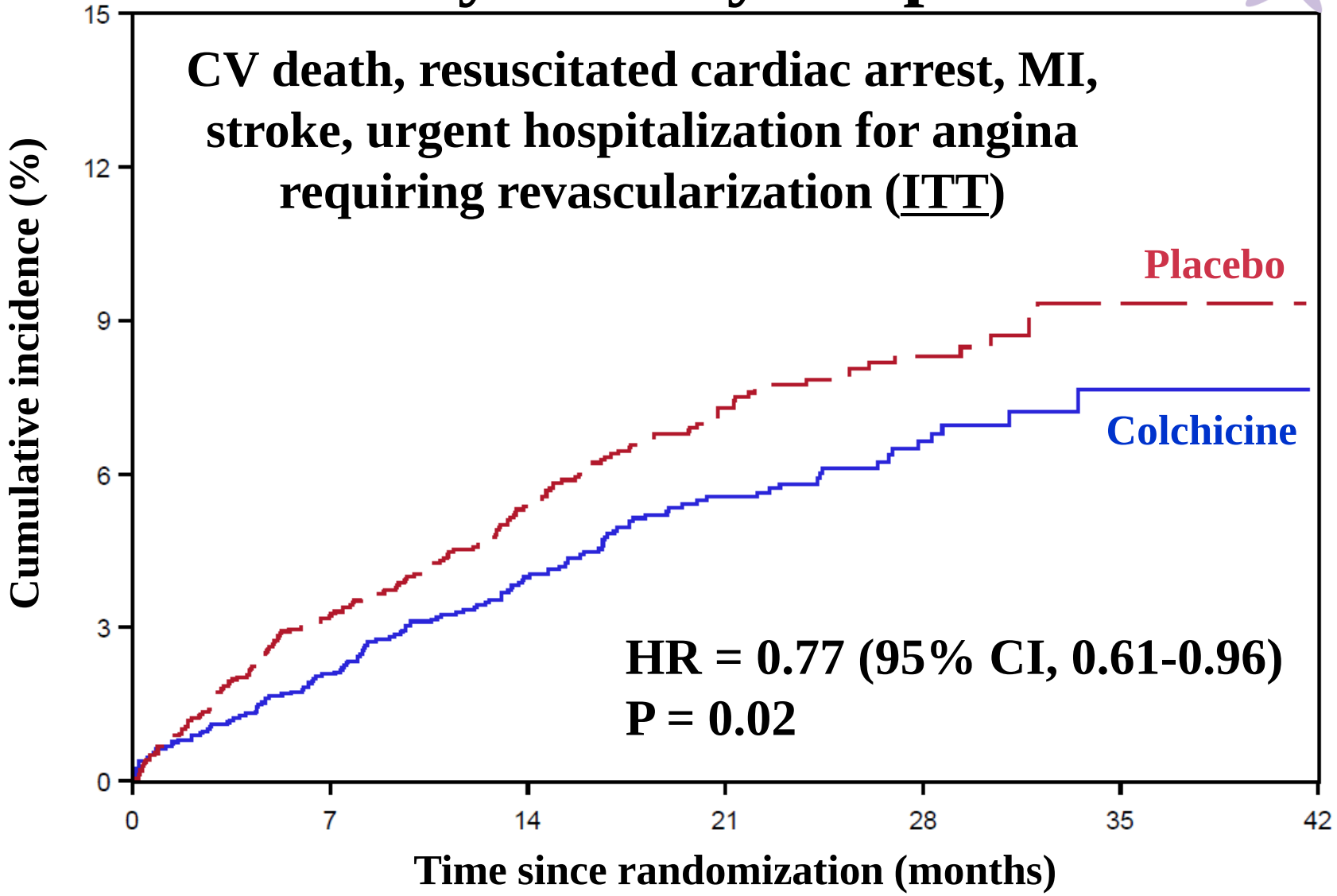
*provided by Pharmascience (Montreal)

Primary efficacy endpoint



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

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

Total (First + Recurrent) Primary Endpoint Events (ITT)

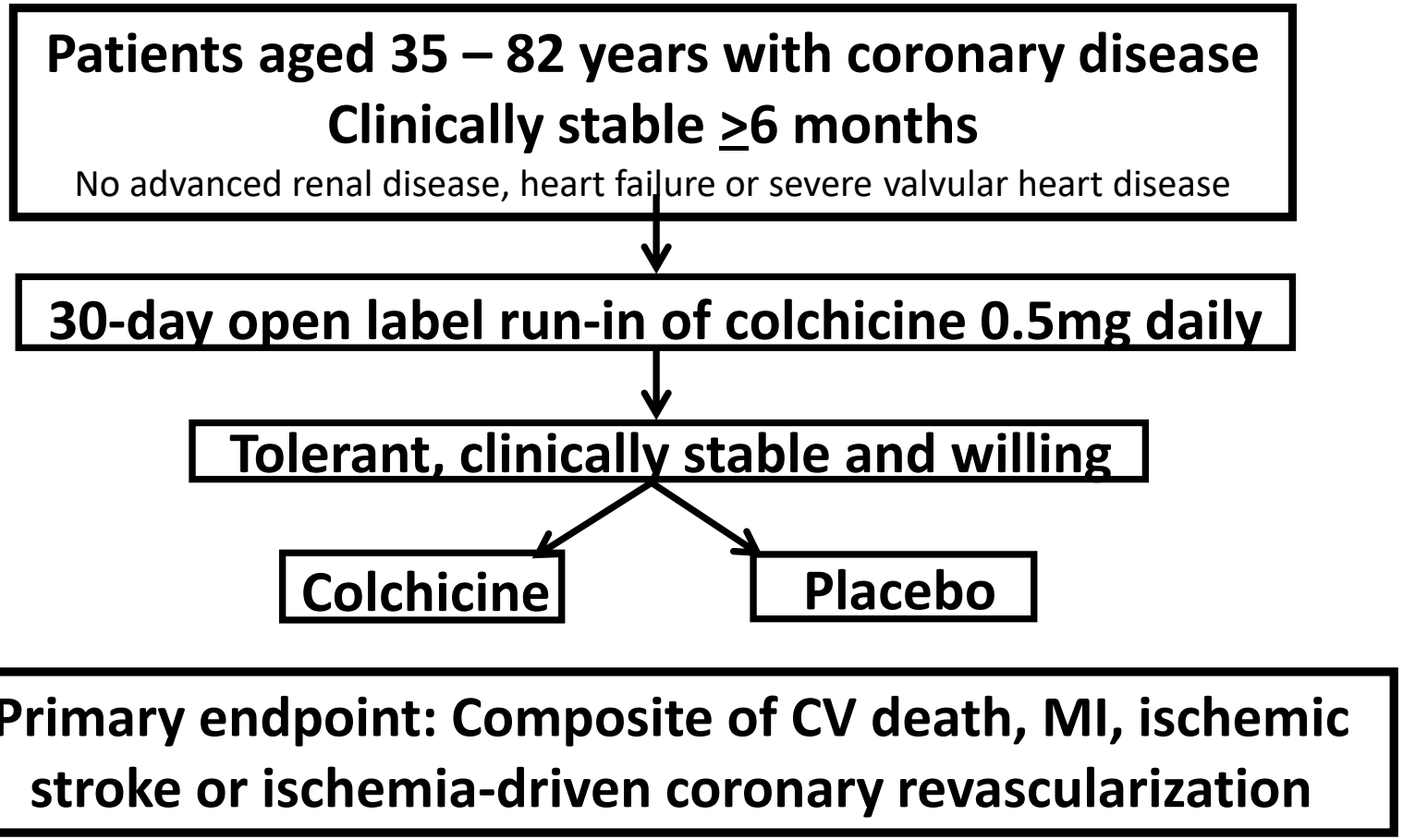
Endpoint / Model		Colchicine N=2366	Placebo N=2379	Hazard / Rate Ratio (95% CI)
Total number of primary endpoint events		154	223	
Rate of primary endpoint events per 100 patient-months		0.29	0.42	
Negative binomial model				0.66 (0.51; 0.86)
Andersen-Gill model				0.69 (0.54; 0.88)
Wei-Lin-Wessfeld model	1st event			0.77 (0.61; 0.96)
Wei-Lin-Wessfeld model	2nd event			0.73 (0.48; 1.11)
Wei-Lin-Wessfeld model	3rd event			0.64 (0.37; 1.10)
Wei-Lin-Wessfeld model	Average			0.77 (0.61; 0.96)

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

Adverse events

Safety population	Colchicine (N=2330)	Placebo (N=2346)	P Value
Any related AE - no. (%)	372 (16.0%)	371 (15.8%)	0.89
Any SAE - no. (%)	383 (16.4%)	404 (17.2%)	0.47
Gastro-intestinal AE - no. (%)	408 (17.5%)	414 (17.6%)	0.90
Gastro-intestinal SAE – no. (%)	46 (2.0%)	36 (1.5%)	0.25
Diarrhea AE - no. (%)	225 (9.7%)	208 (8.9%)	0.35
Nausea AE - no. (%)	43 (1.8%)	24 (1.0%)	0.02
Flatulence AE - no. (%)	15 (0.6%)	5 (0.2%)	0.02
GI haemorrhage AE - no. (%)	7 (0.3%)	5 (0.2%)	0.56
Infection SAE - no. (%)	51 (2.2%)	38 (1.6%)	0.15
Pneumonia SAE - no. (%)	21 (0.9%)	9 (0.4%)	0.03
Septic shock SAE - no. (%)	2 (0.1%)	2 (0.1%)	0.99
HF hospitalization - no. (%)	25 (1.1%)	17 (0.7%)	0.21
Cancer - no. (%)	43 (1.8%)	46 (2.0%)	0.77
Anemia - no. (%)	14 (0.6%)	10 (0.4%)	0.40
Leukopenia - no. (%)	2 (0.1%)	3 (0.1%)	0.66
Thrombocytopenia - no. (%)	3 (0.1%)	7 (0.3%)	0.21

Protocol



Planned to begin close-out 12 months after the last participant had been randomized*

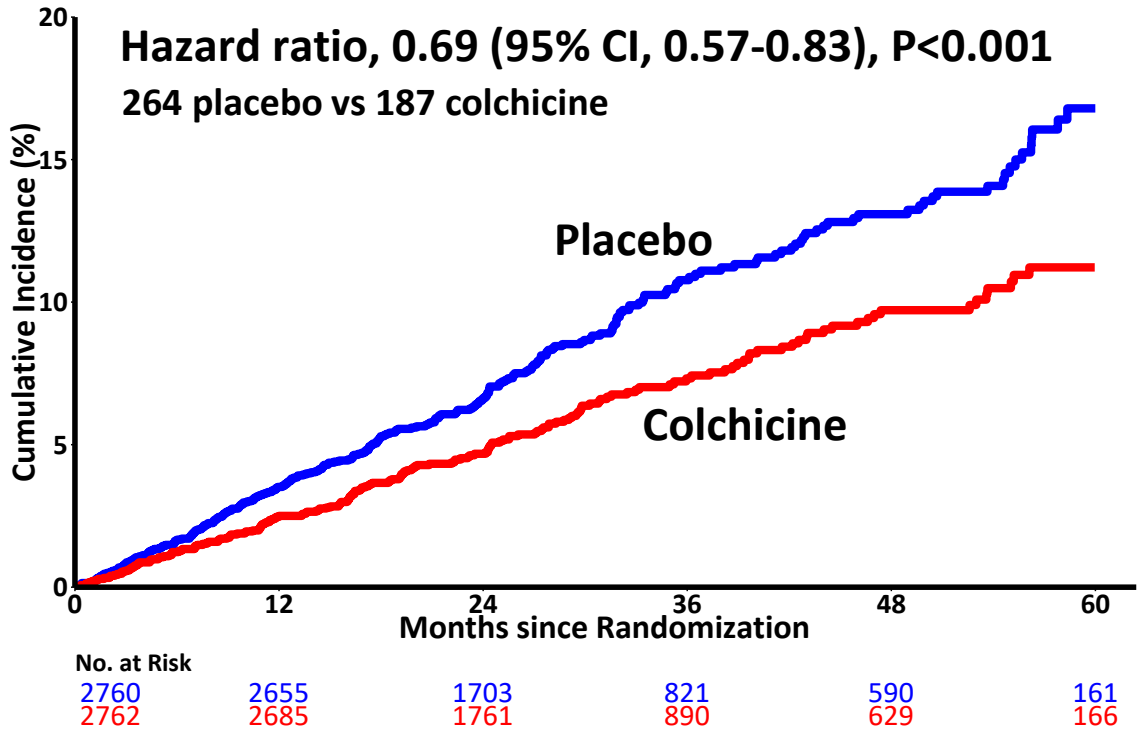
** If 331 primary events had accrued – sufficient to detect a 30% effect of therapy with 90% power*

Nidorf SM et al. N Engl J Med 2020 Aug 31

LODOCO2

Primary endpoint

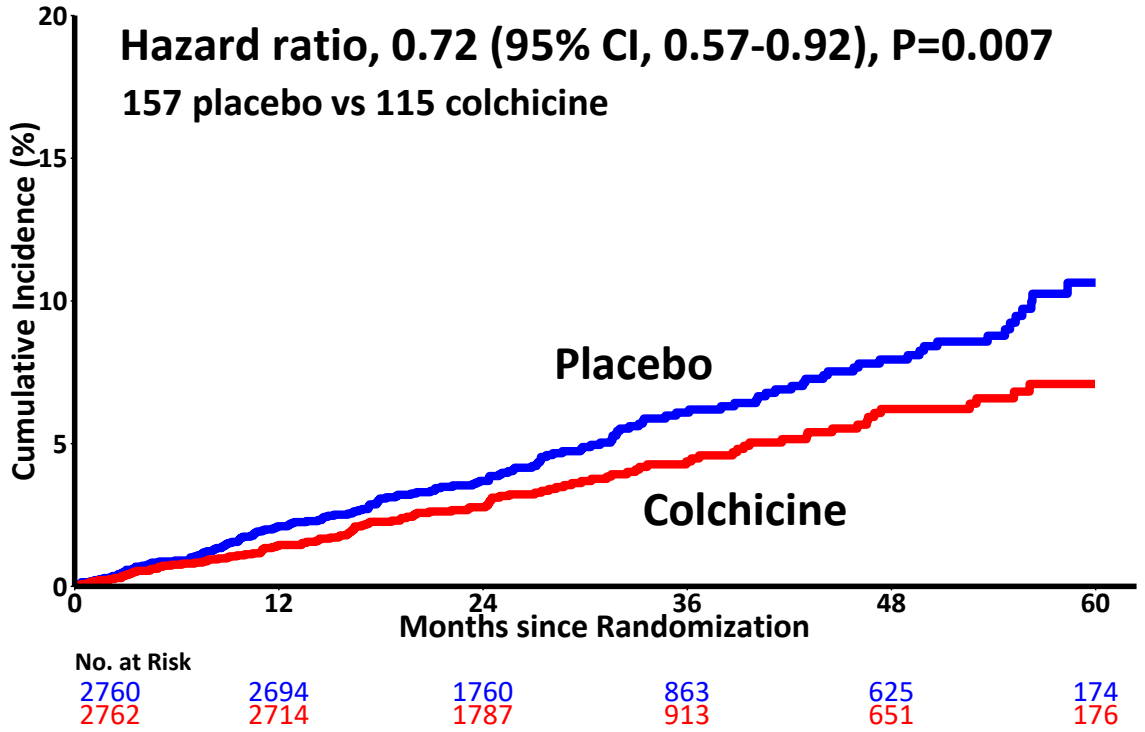
Cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization



Nidorf SM et al. N Engl J Med 2020 Aug 31

Key secondary endpoint

Cardiovascular death, myocardial infarction, or ischemic stroke



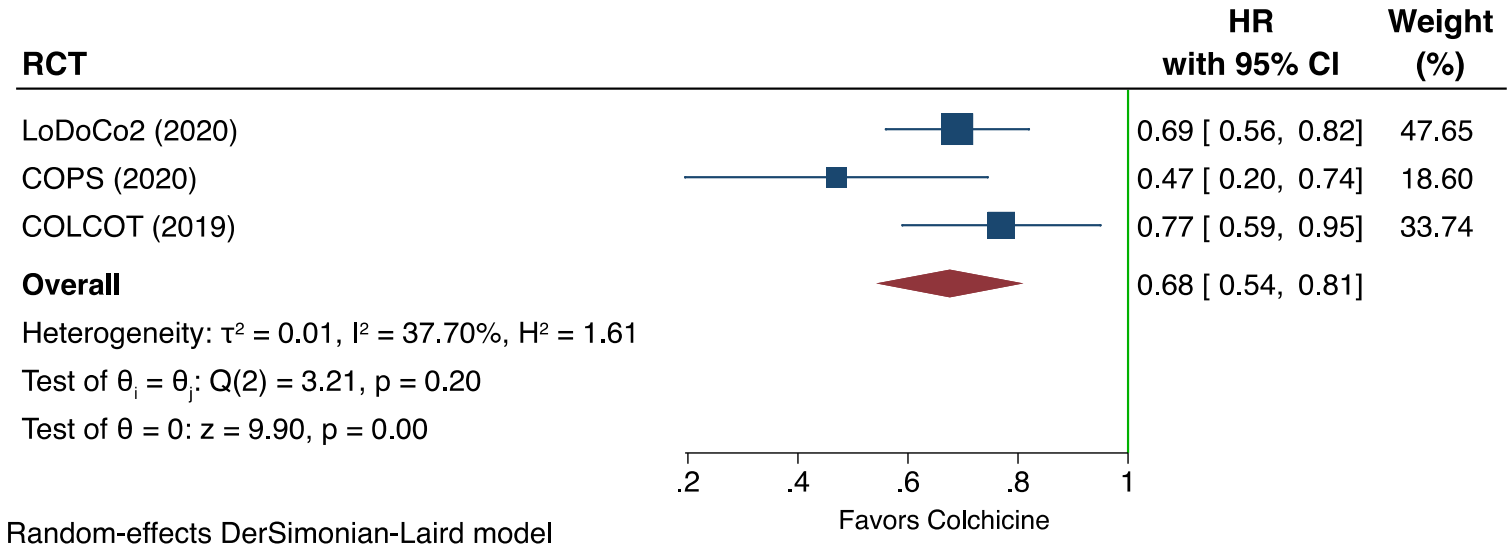
Nidorf SM et al. N Engl J Med 2020 Aug 31

Serious adverse events

	Colchicine (N = 2762)	Placebo (N = 2760)
Non-cardiovascular death	53(1.9)	35(1.3)
Diagnosis of new cancer	120(4.3)	122(4.4)
Hospitalization for infection	137(5.0)	144(5.2)
Hospitalization for pneumonia	46(1.7)	55(2.0)
Hospitalization for gastro-intestinal reason	53(1.9)	50(1.8)
Neutropenia	3(0.1)	3(0.1)
Myotoxicity	4(0.1)	3(0.1)

Nidorf SM et al. N Engl J Med 2020 Aug 31

Meta-analysis of colchicine studies in CAD
Primary composite endpoint



*Primary composite endpoint includes cardiovascular mortality, myocardial infarction, ischemic stroke, and urgent coronary revascularization

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Samuel M, Tardif JC, et al. Can J Cardiol 2021;37:776-785.

Approval of colchicine by US FDA for cardiovascular use in June 2023

- **"LODOCO (colchicine 0.5 mg once daily) is indicated to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease."**

- **"Concurrent use of strong CYP3A4 inhibitors or P-gp inhibitors with colchicine is contraindicated, including in patients with hepatic or renal impairment."**

- **"Colchicine is contraindicated in patients with pre-existing blood dyscrasias, renal failure, and severe hepatic impairment."**

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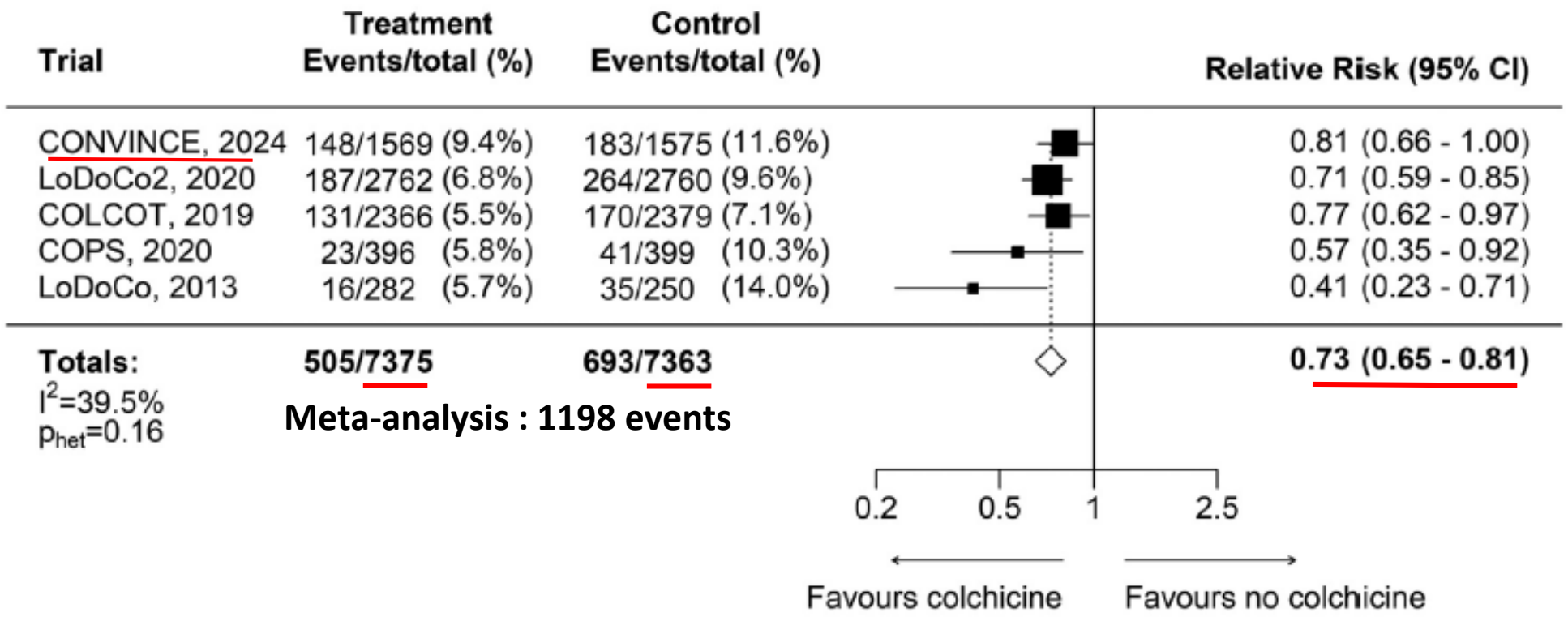
Meta-analysis estimate effect of colchicine on CV death, MI, ischemic stroke, and coronary revasc.



Colchicine Cardiovascular Trialists Collaboration. eClinical Medicine 2024;76:102835

Inflammation reduction therapy in 2024
Guidelines and regulatory agencies

FDA: "LODOCO (colchicine 0.5 mg once daily) is indicated to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease."

HC: "MYINFLA (colchicine extended-release tablets) is indicated for the reduction of atherothrombotic events in adult patients with existing coronary artery disease, in addition to standard therapies, including LDL-C lowering and antithrombotic drug treatment."

ESC 2024:

Recommendation Table 20 — Recommendations for anti-inflammatory drugs in patients with chronic coronary syndrome (see also Evidence Table 20)

Recommendation	Class[a]	Level[b]
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.[714–716]	IIa	A

Why were CLEAR-SYNERGY results neutral?

The outlier study

- **The inverted relationship between the incidence of non-fatal MI and all-cause deaths in CLEAR (MI/all-cause death ratio: 0.62) is consistent with the published impact of COVID-19 on cardiovascular clinical care and under-reporting of non-fatal events.**

- **Dal-GenE-1, IRONMAN and GUIDE-HF are other published trial results that were affected by COVID-19, with loss of statistical significance during the pandemic.**

- **Inflammation was not controlled in the colchicine arm of CLEAR with a least-squares mean hs-CRP of 3.0 mg/L (95% CI: 2.6-3.5 mg/L), in contrast to the on-treatment median values of 1.12 mg/L (IQR: 0.77, 2.10) in COLCOT and 0.94 mg/L (IQR: 0.53-1.93) in LoDoCo2.**

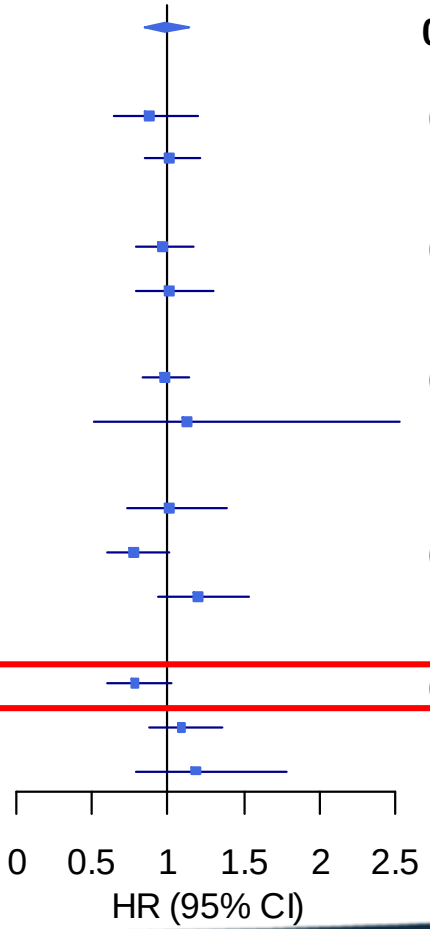
- **There was no benefit of colchicine on pericarditis in CLEAR.**

- **The neutral results of the spironolactone arm of CLEAR differ greatly from previous studies.**

Tardif JC, Kouz S. Eur Heart J: Acute Cardiovascular Care 2024 Nov. Jolly SS et al. N Engl J Med 2024 Nov 17.
Dal-GenE-1: Tardif JC et al. Eur Heart J 2022;43:3947-3956. IRONMAN: Kalra PR et al. Lancet 2022;400:2199-2209.
GUIDE-HF: Zile MR et al. Eur Heart J 2022;43:2603-2618.

CLEAR - Forest Plot of Primary Outcome in Pre-Specified Subgroups (II)

	Colchicine Count/Total (%)	Placebo Count/Total (%)	Hazard Ratio (95% CI)	P value for Interaction
Outcomes				
CVD/MI/Stroke/Revas	**322/3528(9.1)**	**327/3534(9.3)**	**0.98 (0.84-1.15)**	
Diabetes				**0.432**
Yes	79/658(12.0)	85/645(13.2)	0.88 (0.65-1.20)	
No	243/2870(8.5)	242/2889(8.4)	1.01 (0.85-1.21)	
Single/Multi-vessel status				**0.745**
Multi	192/1735(11.1)	200/1742(11.5)	0.97 (0.79-1.18)	
Single	130/1793(7.3)	127/1792(7.1)	1.02 (0.80-1.30)	
MI Type				**0.741**
STEMI	310/3363(9.2)	315/3350(9.4)	0.98 (0.84-1.15)	
NSTEMI	12/165(7.3)	12/184(6.5)	1.13 (0.51-2.52)	
Dosing				**0.054**
Once daily (<70Kg)	74/721(10.3)	72/697(10.3)	1.01 (0.73-1.40)	
Twice daily (>=70kg)	110/1161(9.5)	136/1137(12.0)	0.78 (0.61-1.00)	
Once daily (>=70kg)	138/1646(8.4)	119/1700(7.0)	1.20 (0.94-1.54)	
Covid Phase				**0.098**
Pre-covid	100/998(10.0)	125/991(12.6)	0.78 (0.60-1.02)	
During covid	170/1773(9.6)	159/1799(8.8)	1.09 (0.88-1.35)	
Post- covid	52/757(6.9)	43/744(5.8)	1.19 (0.79-1.78)	



CLEAR - Primary Outcome

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

	Colchicine (N=3528) (%)	Placebo (N=3534) (%)	HR	95% CI	p
CV death, MI, stroke or ischemia driven revascularization	9.1%	9.3%	0.99	0.85-1.16	0.93
CV death	3.3%	3.2%	1.03	0.80-1.34	
MI	2.9%	3.1%	0.88	0.66-1.17	
Stroke	1.4%	1.2%	1.15	0.72-1.84	
Ischemia driven revascularization	4.6%	4.7%	1.01	0.81-1.17	
CV death, MI or stroke	6.8%	7.1%	0.98	0.82-1.17	
All cause death	4.6%	5.1%	0.90	0.73-1.12	
Non-CV death	1.3%	1.9%	0.68	0.46-0.99	

COMPLETE TRIAL

Efficacy Outcomes

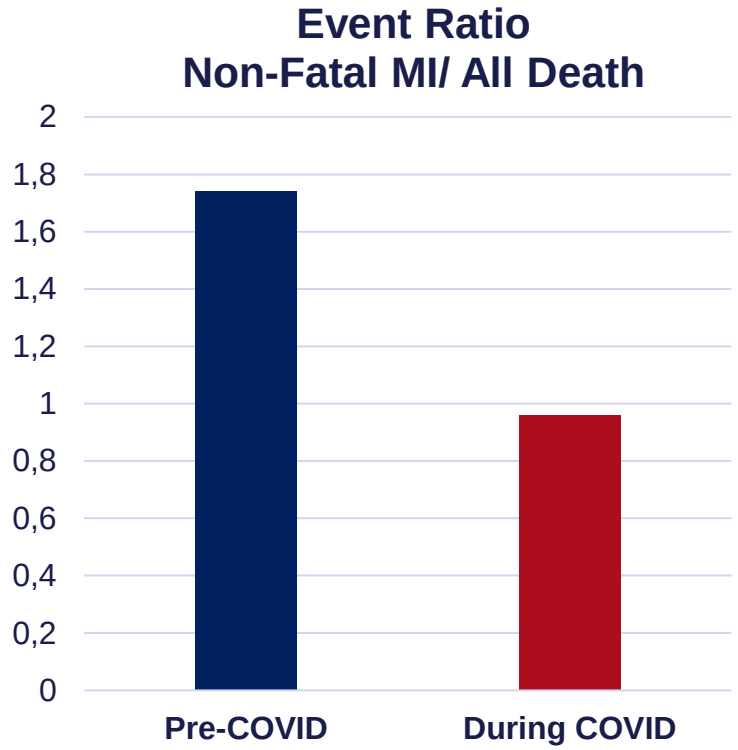
	Complete Revasc. N=2016		Culprit Lesion Only N=2025		HR (95% CI)	P value
	N (%)	%/year	N (%)	%/year		
Co-Primary Outcomes						
CV death or MI	**158 (7.8)**	**2.7**	**213 (10.5)**	**3.7**	**0.74 (0.60-0.91)**	**0.004**
CV death, MI or IDR	**179 (8.9)**	**3.1**	**339 (16.7)**	**6.2**	**0.51 (0.43-0.61)**	**<0.001**
Key Secondary Outcome						
CV death, MI, IDR, unstable angina or class IV HF	272 (13.5)	4.9	426 (21.0)	8.1	0.62 (0.53-0.72)	<0.001
Other Secondary Outcomes						
MI	109 (5.4)	1.9	160 (7.9)	2.8	0.68 (0.53-0.86)	0.002
IDR	29 (1.4)	0.5	160 (7.9)	2.8	0.18 (0.12-0.26)	<0.001
Unstable Angina	70 (3.5)	1.2	130 (6.4)	2.2	0.53 (0.40-0.71)	<0.001
CV death	59 (2.9)	1.0	64 (3.2)	1.0	0.93 (0.65-1.32)	0.68
All-cause Death	96 (4.8)	1.6	106 (5.2)	1.7	0.91 (0.69-1.20)	0.51

Mehta SR et al. *N Engl J Med* 2019; 381:1411-1421

Dal-GenE-1: Change in the expected relationship between fatal and non-fatal events during COVID-19

- The ratio of adjudicated non-fatal MI to all-cause death was higher pre-COVID than during-COVID because of the reduction of reported non-fatal MIs, combined with an increase in non-CV deaths.

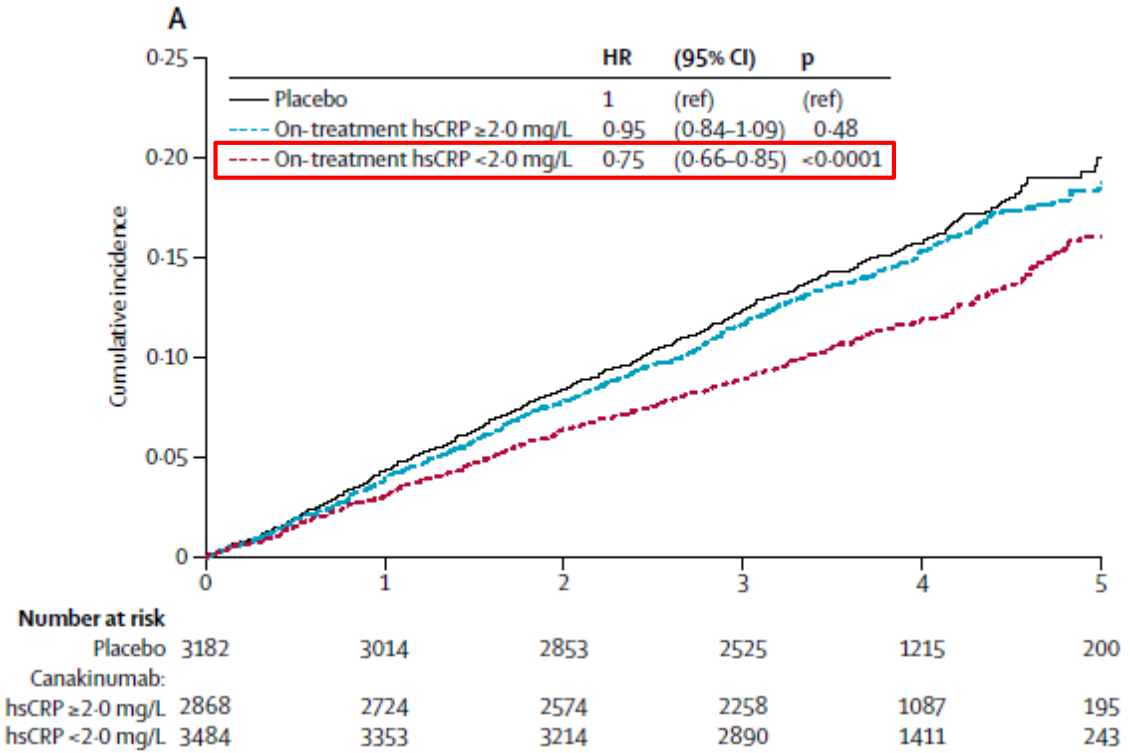
- This abrupt change in the relationship between deaths and non-fatal MIs is consistent with the published impact of COVID-19 on CV clinical care with under-reporting of non-fatal CV events.



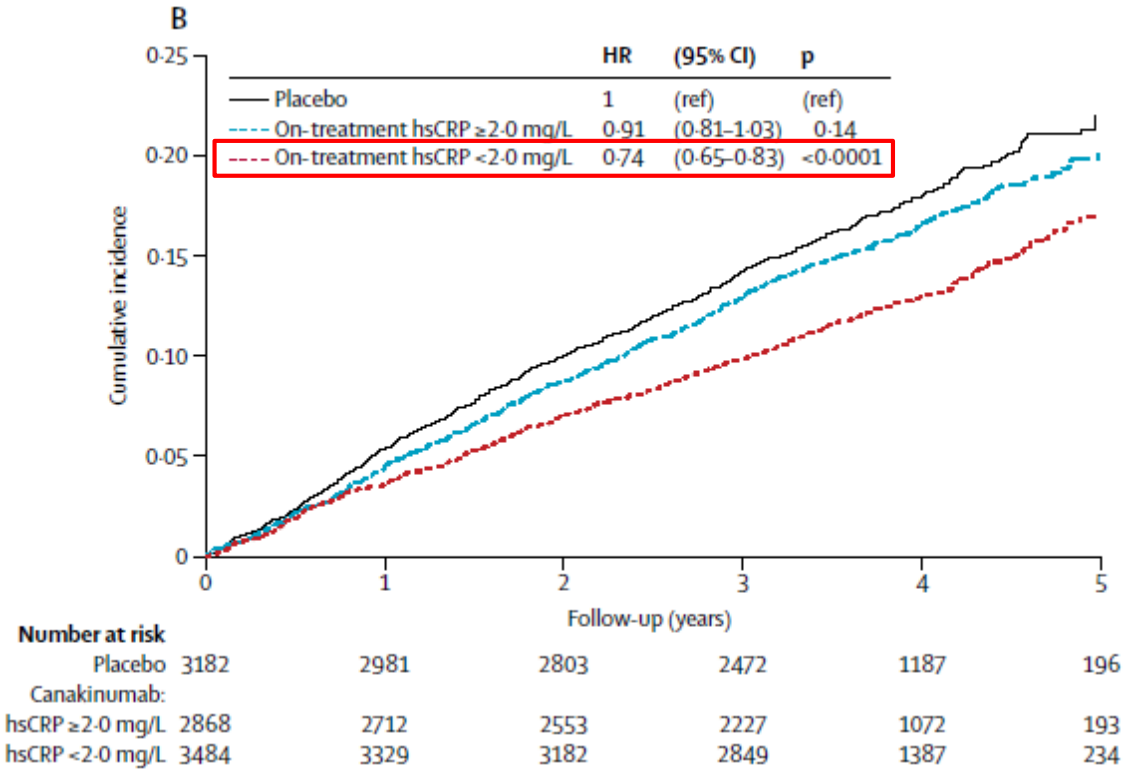
Tardif JC et al. Eur Heart J 2022;43:3947-3956

CANTOS: Greater CV risk reduction with greater inflammation reduction

CV death, MI, stroke



CV death, MI, stroke, USA requiring revasc.



Ridker P et al. Lancet 2018;391:319-328.

Inflammation contributes to cardiovascular risk in patients receiving statin therapy

The issue of polypharmacy is sometimes mentioned by physicians as the reason for having to choose between further lipid-lowering treatment or inflammation-reducing therapy in patients receiving statin therapy. It is time to reconsider our answer to this apparent problem considering the worldwide burden of atherosclerotic cardiovascular disease and the cost-effectiveness of colchicine.[13] Serious consideration should be given to applying the successful model of four treatment pillars in heart failure to the multifaceted prevention of atherothrombotic events in patients with coronary artery disease. Physicians should no longer consider intensive lipid lowering and inflammation reduction as mutually exclusive, but rather as complementary approaches in patients with atherosclerotic cardiovascular disease who are already receiving statin therapy. The large-scale COLCOT-T2D trial (NCT05633810) is extending this concept to primary prevention and testing whether inflammation reduction with low-dose colchicine is associated with improved cardiovascular outcomes in 10 000 patients with type 2 diabetes who are already receiving intensive therapy to reduce LDLC according to national guidelines.

Tardif JC, Samuel M. Lancet 2023;401:1245-1247

Désign de l'étude

COLCOT-T2D

Diabète de type 2 sans maladie coronarienne (n=10,000 patients)

Bras anti-inflammatoire

Bras anti-thrombotique	Colchicine (n=5000)	Pas de colchicine (n=5000)
Aspirin (n=2500)	Colchicine + Aspirin* (n=1250)	Placebo colchicine + Aspirin (n=1250)
Pas aspirin (n=2500)	Colchicine + Placebo aspirin (n=1250)	Placebo colchicine + Placebo aspirin (n=1250)
Non éligible à aspirin (n=5000)	Colchicine (n=2500)	Placebo colchicine (n=2500)

*Colchicine 0.5 mg une fois par jour
+ Aspirin sans enrobage entérique 40 mg 2 fois par jour

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Critères d'inclusion

COLCOT-T2D

- **Hommes et femmes âgés de 55-80 ans**
- **Diabète de type 2 traité selon les guides thérapeutiques nationaux**
- **Pas d'antécédent d'évènement clinique lié à la maladie coronarienne**
- **Au moins une caractéristique de haut risque**
- **Femmes avec potentiel de procréer doivent avoir un test urinaire de grossesse négatif au screening et accepter d'utiliser une méthode efficace de contraception**

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Critères d'efficacité

COLCOT-T2D

<u>Critère primaire</u>:

• Temps au premier évènement de décès CV, arrêt cardiaque, infarctus, AVC, ou hospitalisation urgente pour angine requérant revascularisation coronarienne

<u>Critères secondaires</u>:

• Trouble cognitif (MOCA) et démence

• Temps à chaque composante du critère primaire

• Temps au premier évènement de décès CV, arrêt cardiaque, infarctus ou AVC

• Fardeau total des évènements initiaux et subséquents du critère primaire

<u>Critères exploratoires</u>:

• Temps à la fibrillation atriale, à l'hospitalisation pour insuffisance cardiaque, et à toute revascularisation coronarienne (urgente ou élective)

• Biomarqueurs génétiques; protéines sanguines et concentrations de méds

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Désign de l'étude

COLCOT-T2D

Diabète de type 2 sans maladie coronarienne (n=10,000 patients)

Bras anti-inflammatoire

Bras anti-thrombotique	Colchicine (n=5000)	Pas de colchicine (n=5000)
Aspirin (n=2500)	Colchicine + Aspirin* (n=1250)	Placebo colchicine + Aspirin (n=1250)
Pas aspirin (n=2500)	Colchicine + Placebo aspirin (n=1250)	Placebo colchicine + Placebo aspirin (n=1250)
Non éligible à aspirin (n=5000)	Colchicine (n=2500)	Placebo colchicine (n=2500)

*Colchicine 0.5 mg une fois par jour
+ Aspirin sans enrobage entérique 40 mg 2 fois par jour

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