SABATO 9 OTTOBRE

La terapia antinfiammatoria nella cardiopatia ischemica: dal canakinumab alla colchicina

Felicita Andreotti, *Roma*

CCC 7-10 ott 2021, Firenze, IT

La terapia antiinfiammatoria nella cardiopatia ischemica: dal canakinumab alla colchicina

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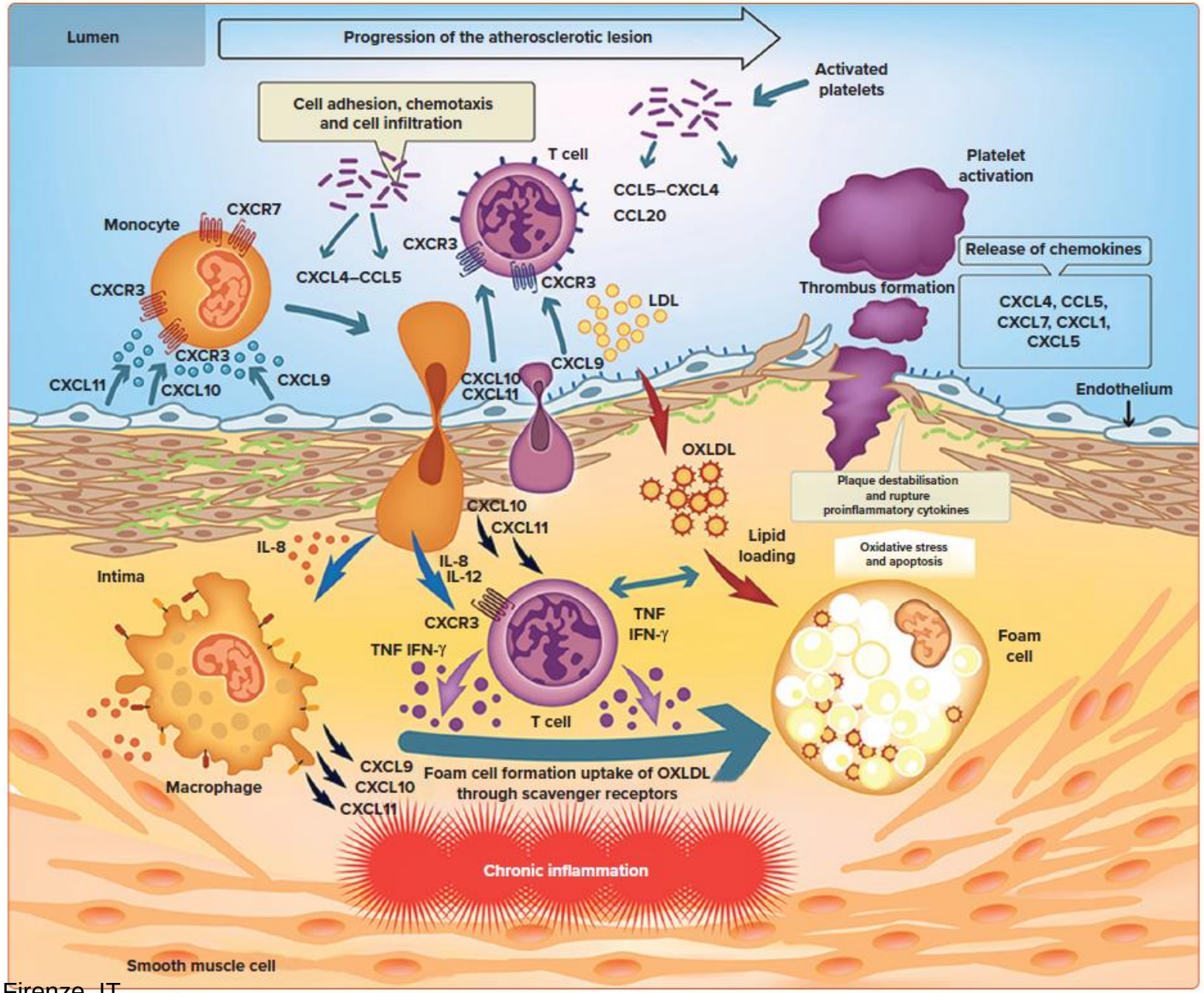
Potential conflicts

- Speaker, consultant or member of advisory boards for **Amgen, Bayer, BMS/Pfizer, Daiichi Sankyo, Medscape, Radcliffe** Cardiology
- Institutional grants or funding as Principal Investigator from **Wellcome Trust, British Heart Foundation, CNR** and Ministry of Italian University and Research (**MIUR** - national **PRIN** coordinator)

Outline

- **Inflammation and ischaemic heart disease (IHD)**
- **Mechanisms of anti-inflammatory drugs**
- **Phase 2 and 3 trials**
- **Implications and conclusions**

Figure 1: The Complex Process Involving Multiple Players in the Development and Progression of the Atherosclerotic Lesion



Source: Szentes et al. 2018.[20] Reproduced from Frontiers under a Creative Commons (CC BY 4.0) licence.

Neutrophils?

Prothrombotic factors?

Inflammation and IHD

Histopathology

- Atherosclerosis is a chronic vascular inflammatory process
- Unstable plaques contain a higher percentage of macrophages and neutrophils vs. stable plaques
- Arterial thrombi contain platelets, fibrin, erythrocytes and leukocytes

Molecular and experimental data

- Prothrombotic factors (fibrinogen, PAI-1 and VWF) are acute phase proteins
- Inhibition of IL1β or IL6 reduces circulating fibrinogen levels in humans
- Colchicine slows atherogenesis and hepatic secretion of fibrinogen in experimental models

Inflammation and IHD

Pathophysiology and prognostic data

- Traditional CV risk factors induce low grade systemic inflammation
- Low grade inflammation increases the risk of major CV events and inflammatory biomarkers predict the risk of CV events in patients with acute or chronic coronary syndromes
- Acute MI stimulates an acute phase response in proportion to the extent of necrosis
- Aspirin reduces the levels of inflammatory biomarkers and the risk of major CV events

Mechanisms of Disease

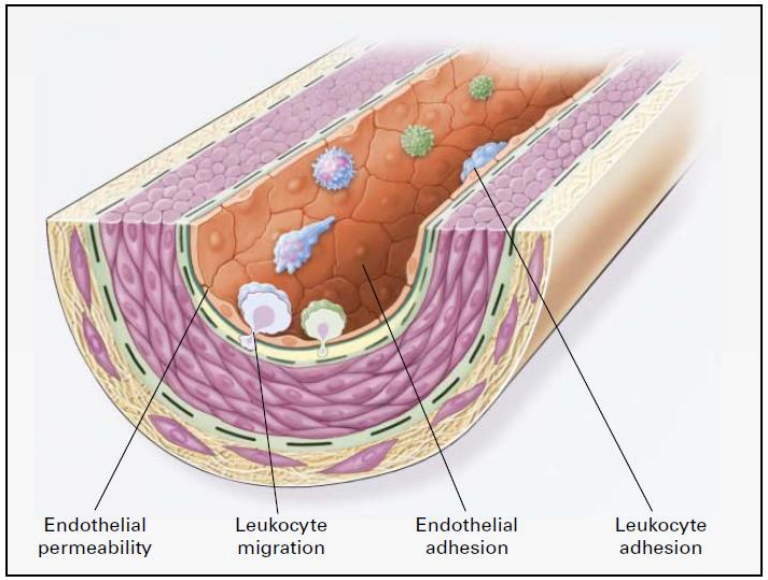
Review Article

ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

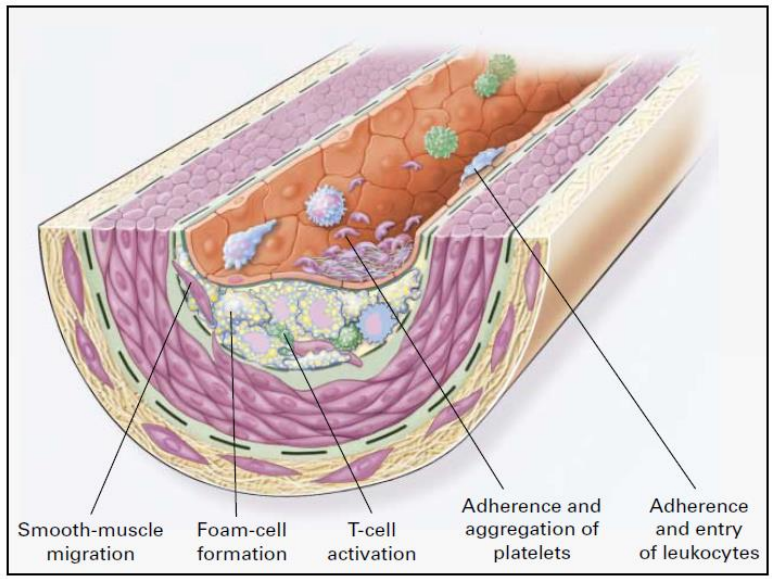
RUSSELL ROSS, PH.D.

The NEW ENGLAND JOURNAL of MEDICINE

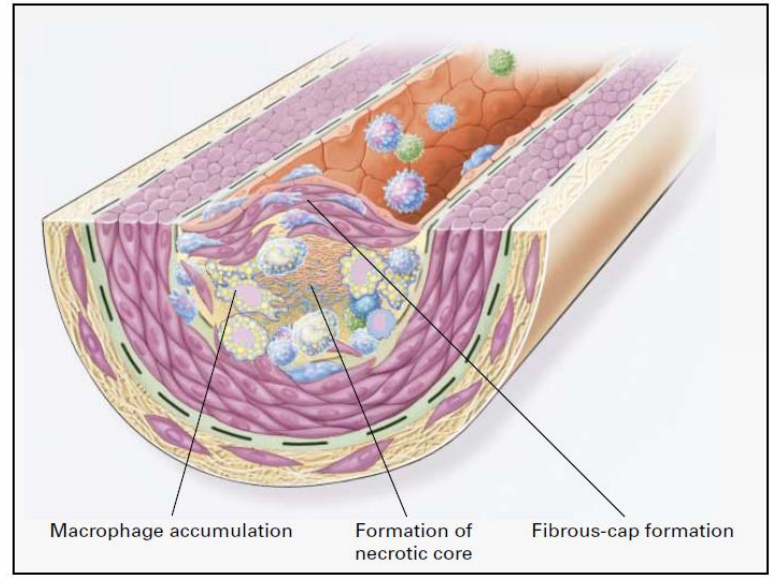
Endothelial Dysfunction



Fatty-Streak Formation



Advanced, Complicated Lesions



N Engl J Med 1999;340:115-26

The New England
Journal of Medicine

Volume 331 AUGUST 18, 1994 Number 7

THE PROGNOSTIC VALUE OF C-REACTIVE PROTEIN AND SERUM AMYLOID A PROTEIN IN SEVERE UNSTABLE ANGINA

GIOVANNA LIUZZO, M.D., LUIGI M. BIASUCCI, M.D., J. RUTH GALLIMORE, B.SC., RITA L. GRILLO, B.SC., ANTONIO G. REBUZZI, M.D., MARK B. PEPYS, M.D., PH.D., AND ATTILIO MASERI, M.D.

Conclusions. Elevation of C-reactive protein and serum amyloid A protein at the time of hospital admission predicts a poor outcome in patients with unstable angina and may reflect an important inflammatory component in the pathogenesis of this condition. (N Engl J Med 1994; 331:417-24.)

Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin

TABLE 2. Proinflammatory Cytokines and CRP in Patients With CSA vs Normal Controls

	Patients With CSA (n=60)	Normal Controls (n=24)	*P*
MCSF, pg/mL	800 (315–1415)	372 (265–770)	<0.01
IL-6, pg/mL	3.9 (2.7–5.4)	1.7 (1.3–2.5)	<0.01
CRP, mg/mL	1.29 (0.5–3.09)	0.23 (0.17–1.4)	<0.01
IL-1b, pg/mL	0.24 (0.18–0.5)	0.2 (0.17–0.47)	NS

Values are expressed as median and 25th and 75th percentile.

TABLE 3. Effects of Aspirin on Proinflammatory Cytokines and CRP Plasma Levels in Patients With CSA

	Placebo (40)	ASA (40)	*P*	Controls (24)	*P*
MCSF	991 (459–1476)	843 (501–1357)	<0.05	372 (265–770)	<0.05
IL-6	3.5 (3.2–4.6)	2.9 (2.5–3.4)	<0.05	1.7 (1.3–2.5)	<0.05
CRP	1.4 (0.54–4.05)	1 (0.5–3.1)	<0.05	0.23 (0.17–1.4)	<0.05

n=40 patients with ischemia at Holter randomized to aspirin (20) or placebo (20) and then crossed over. ASA indicates aspirin (300 mg).

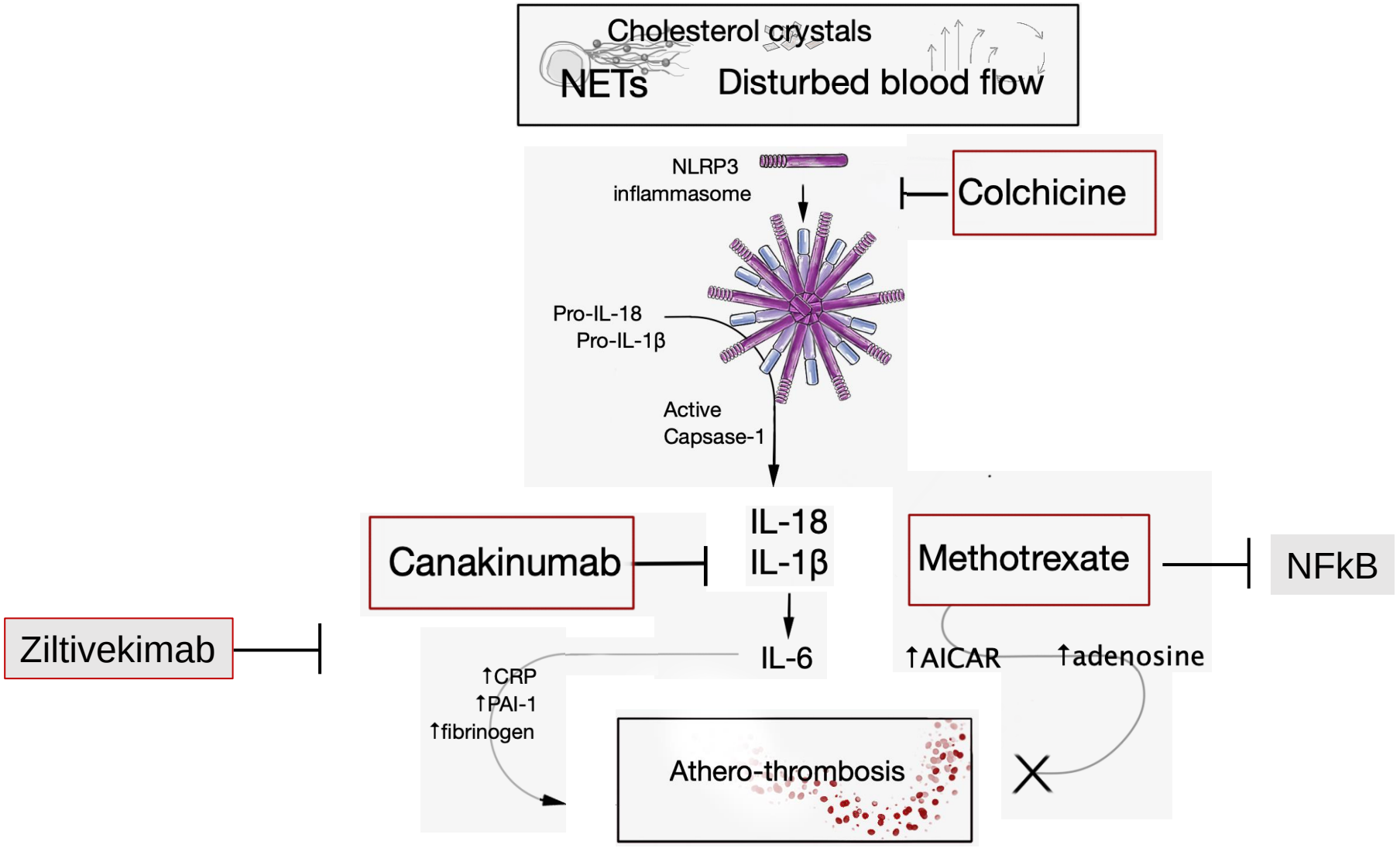
Values are expressed as median and 25th and 75th percentile.

Ikonomidis, Andreotti et al. – Circulation 1999;100:793-8

Outline

- Inflammation and ischaemic heart disease (IHD)
- Mechanisms of anti-inflammatory drugs
- Phase 2 and 3 trials
- Implications and conclusions

Mechanisms of anti-inflammatory drugs



Mod. From Maggioni AP, Iervolino A, Andreotti F. Vessel Plus 2021;5:14. DOI:10.20517/2574-1209.2021.05

Mechanisms of anti-inflammatory drugs

- **Low-dose aspirin:**
  COX-inhibition: < MCSF-IL6-CRP
- **Canakinumab:**
  anti-IL1: < IL-6, FBG, CRP
- **Methotrexate:**
  blocks NFkB-DNA/RNA synthesis-DHFR
- **Colchicine:**
  blocks tubulin polymerization: < plt-neutrophil-mast cell-monocyte activity, < superoxide, < FBG, < ATS
- **Ziltivekimab:**
  anti-IL6: < CRP-FBG-Lp(a)

Outline

- Inflammation and ischaemic heart disease (IHD)
- Mechanisms of anti-inflammatory drugs
- **Phase 2 and 3 trials**
- Implications and conclusions

Overview of anti-inflammatory trials in CVD

Table 1: Selected Clinical Trials Targeting Inflammatory Modulation in Atherosclerotic Cardiovascular Disease

Target/Pathway	Agent	Study	n	Results	Patient Group
Oxidised LDL	Succinobucol	ARISE[79]	6,144	No effect	Post ACS
sPLA2	Varespladib	VISTA-16[80]	5,145	No effect	Post ACS
LpPLA2	Darapladib	STABILITY[81]	15,828	No effect	Stable CAD
LpPLA2	Darapladib	SOLID-TIMI 52[82]	13,026	No effect	Post ACS
P-selectin	Inclacumab	SELECT-ACS[83]	544	No effect	ACS/PCI
IL-1 receptor	Anakinra	VCU-ART2[84]	30	No effect	ACS
P38 MAP kinase	Losmapimod	LATITUDE-TIMI 60[85]	3,503	No effect	ACS
Neutrophil chemotaxis/NLRP3 inflammasome	Colchicine	LoDoCo[71]	532	Positive	Stable CAD
IL-1β	Canakinumab	CANTOS[57]	10,061	Positive	Stable CAD
Tumour necrosis factor/IL-6	Etanercept versus tocilizumab	ENTRACTE[87]	3,080	No differences	Rheumatoid arthritis
Neutrophil chemotaxis/NLRP3 inflammasome	Colchicine	COLCOT[72]	4,500	Positive	Post ACS
IL-6, TNF	Methotrexate	CIRT[64]	4,786	No effect	CAD + diabetes/MS
Neutrophil chemotaxis/NLRP3 inflammasome	Colchicine	LoDoCo2[69]	5,522	Positive	Stable CAD

ACS = acute coronary syndrome; CAD = coronary artery disease; IL = interleukin; LDL = low-density lipoprotein; LpPLA2 = lipoprotein-associated phospholipase A2; MAPK = mitogen-activated protein kinase; MS = metabolic syndrome; NLRP3 = nucleotide-binding oligomerisation domain, leucine-rich repeat and pyrin domain containing protein 3; PCI = percutaneous coronary intervention; sPLA2 = secretory phospholipase A2 TNF = tumour necrosis factor.

The NEW ENGLAND JOURNAL of MEDICINE

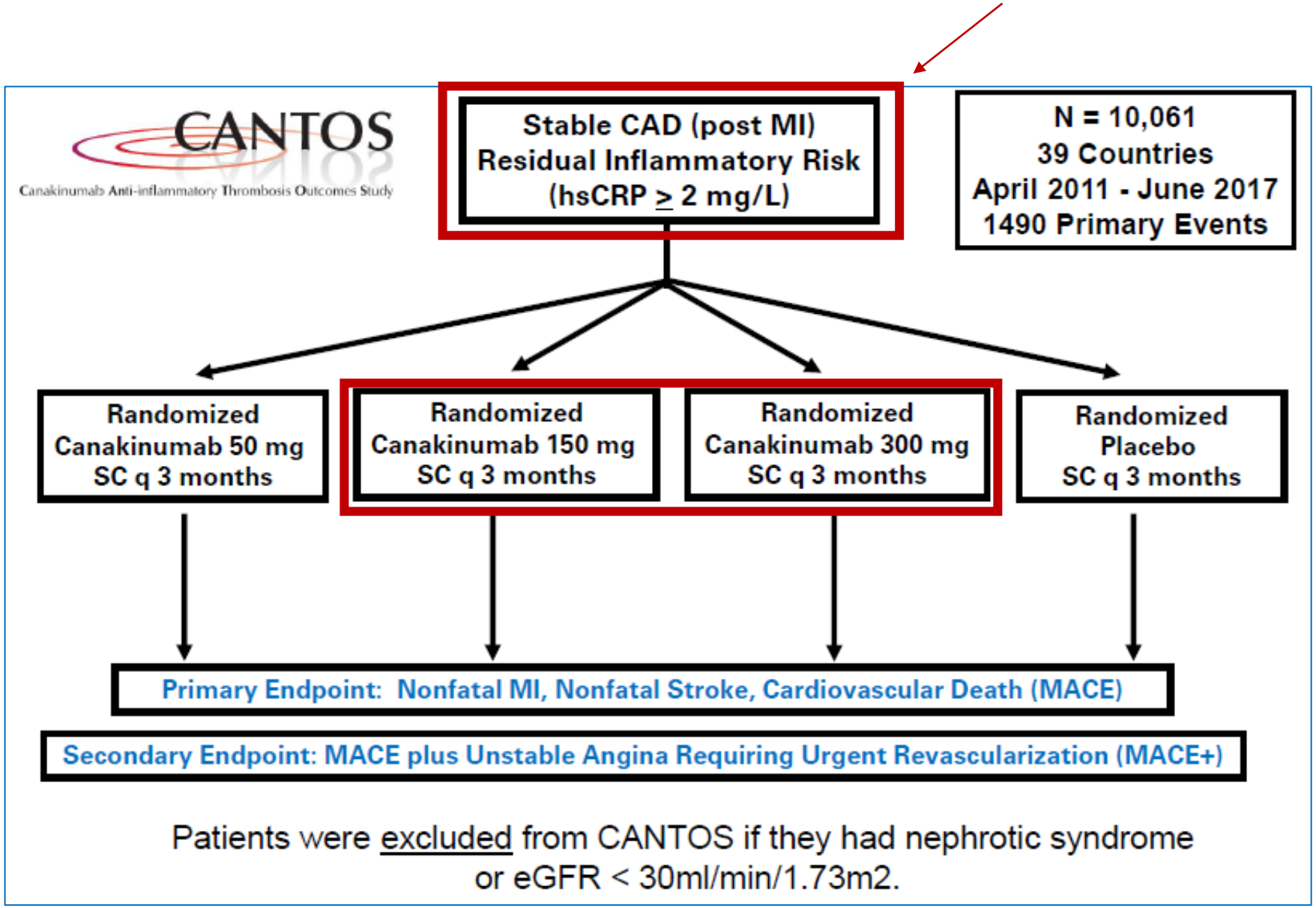
ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

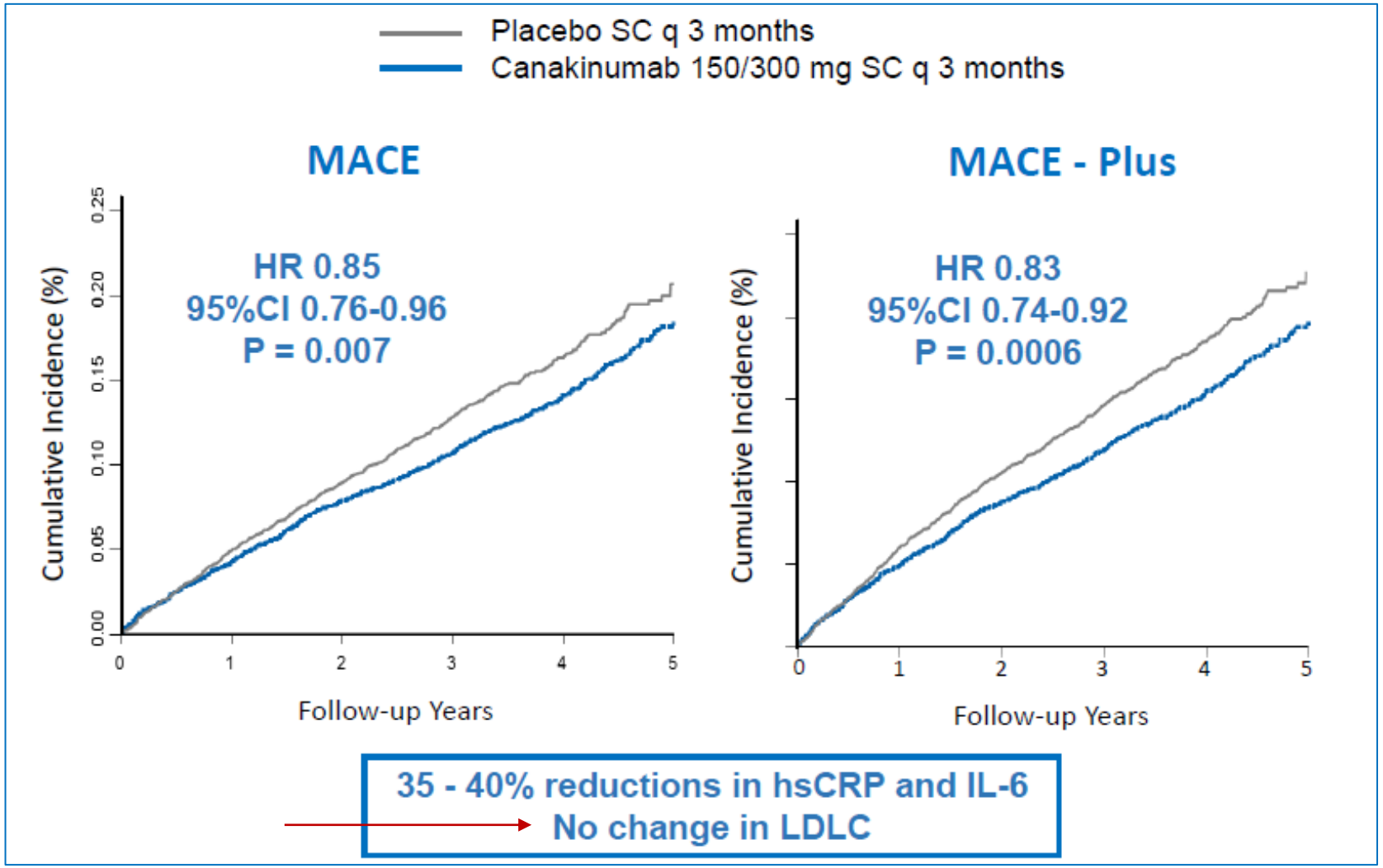
N Engl J Med. 2017 Sep 21;377(12):1119-1131

Canakinumab Anti-inflammatory Thrombosis Outcomes Study



Ridker PM et al. N Engl J Med 2017;377:1119-1131

CANTOS: Primary Cardiovascular Endpoints



Ridker PM et al. N Engl J Med 2017;377:1119-1131

The NEW ENGLAND JOURNAL of MEDICINE

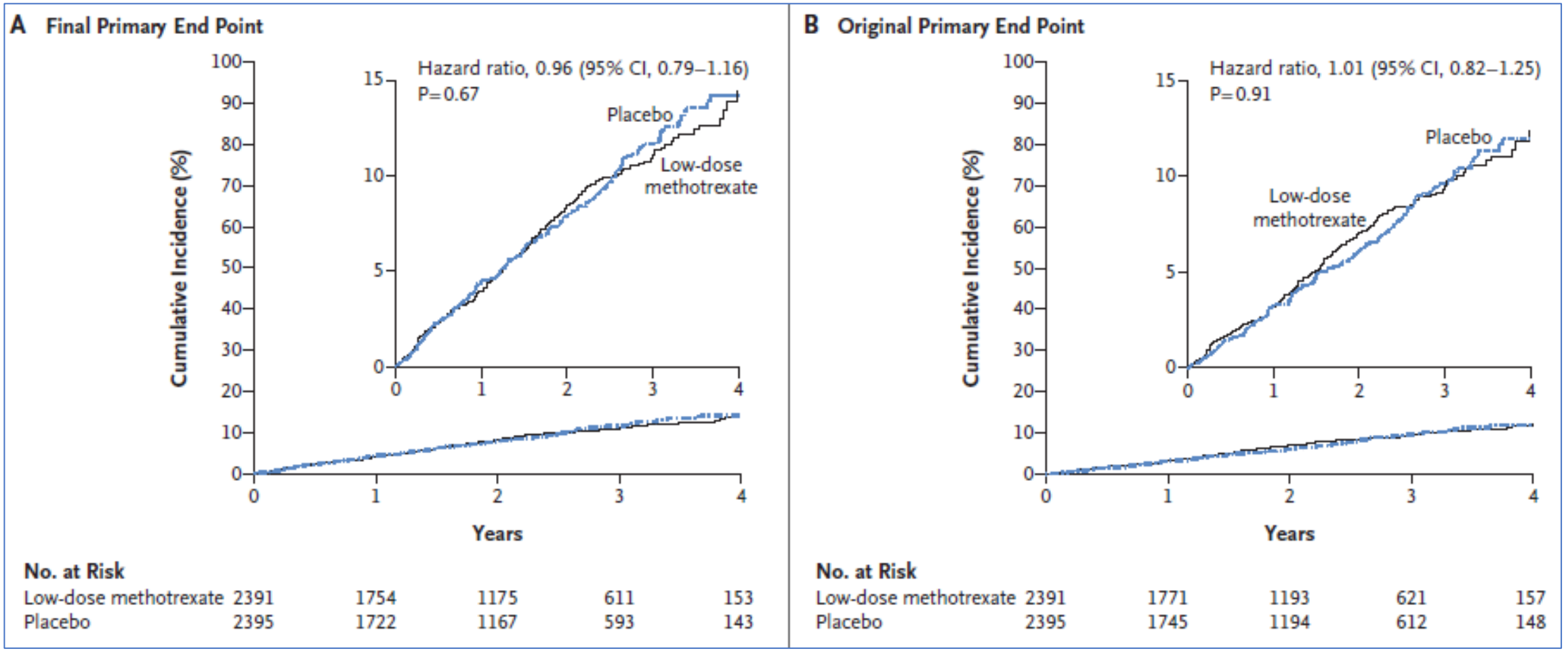
ORIGINAL ARTICLE

Low-Dose Methotrexate for the Prevention of Atherosclerotic Events

Paul M Ridker, M.D., Brendan M. Everett, M.D., Aruna Pradhan, M.D., Jean G. MacFadyen, B.A., Daniel H. Solomon, M.D., Elaine Zaharris, B.A., Virak Mam, B.S., Ahmed Hasan, M.D., Yves Rosenberg, M.D., Erin Iturriaga, M.S.N., Milan Gupta, M.D., Michelle Tsigoulis, Subodh Verma, M.D., Michael Clearfield, D.O., Peter Libby, M.D., Samuel Z. Goldhaber, M.D., Roger Seagle, M.D., Cyril Ofori, M.D., Mohammad Saklayen, M.D., Samuel Butman, M.D., Narendra Singh, M.D., Michel Le May, M.D., Olivier Bertrand, M.D., James Johnston, M.D., Nina P. Paynter, Ph.D., and Robert J. Glynn, Sc.D., for the CIRT Investigators*

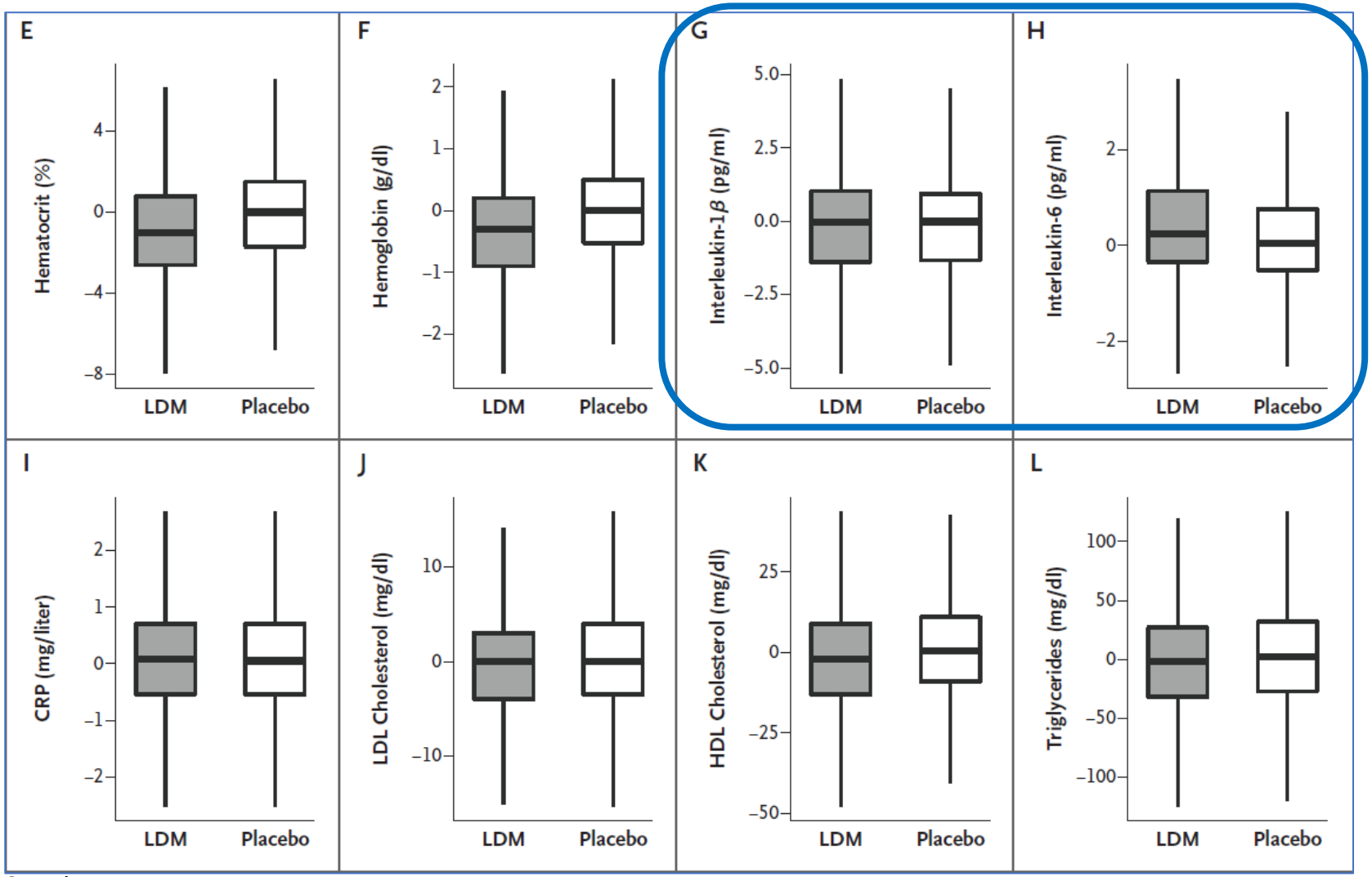
N Engl J Med. 2019 Feb 21;380(8):752-762

CIRT: main results



N Engl J Med. 2019 Feb 21;380(8):752-762

CIRT: Laboratory Findings



N Engl J Med. 2019 Feb 21;380(8):752-762

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

N Engl J Med. 2019 Dec 26;381(26):2497-2505.

Study design

Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute
MHICC

COLCOT

Post-myocardial infarction ≤30 days (n=4745 patients)
On statin, anti-platelet agents, ±RAASi, ±BB

Treated according to national guidelines
PCI completed if planned

Colchicine 0.5 mg daily *

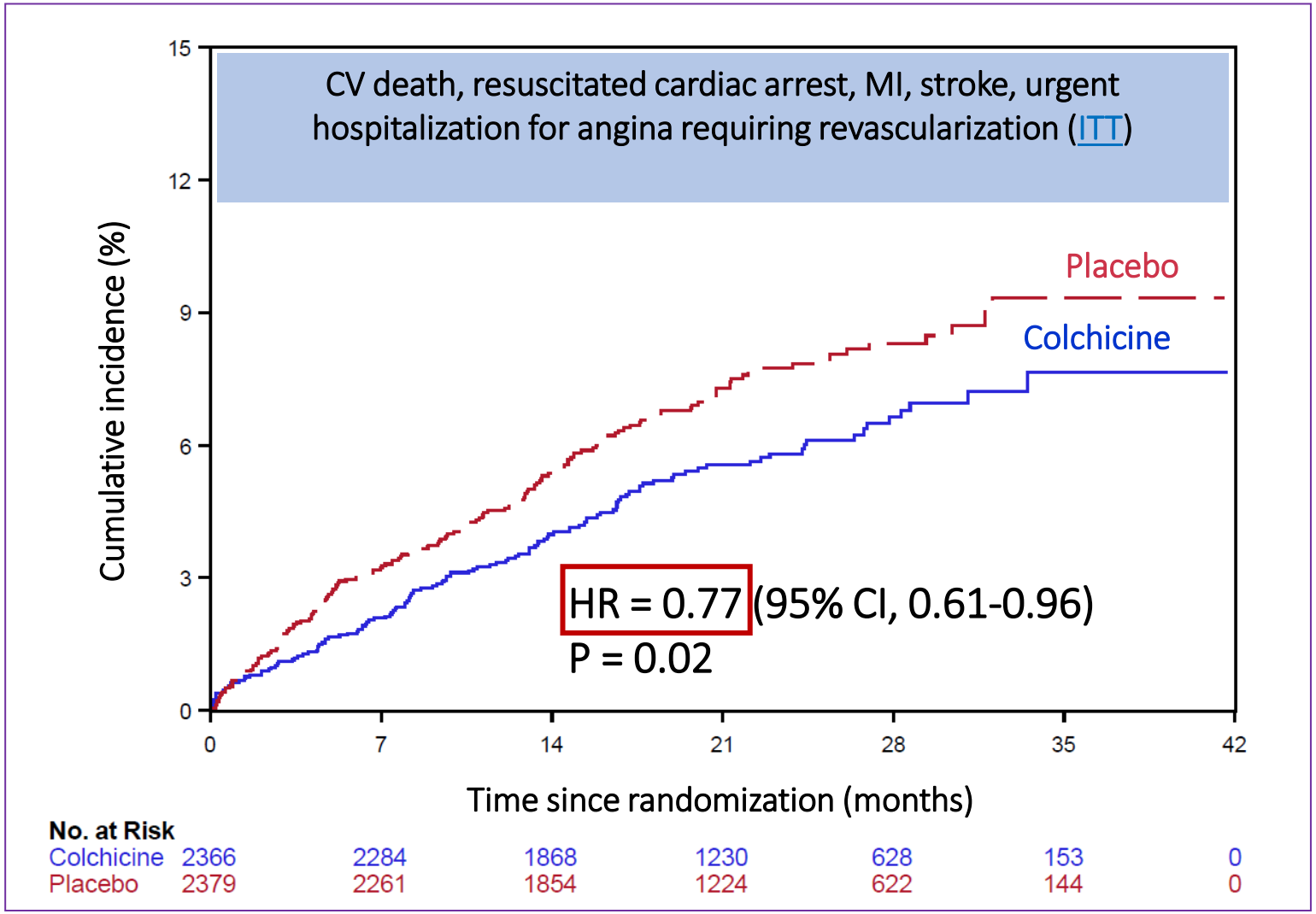
Placebo daily *

*provided by Pharmascience (Montreal)

Primary composite endpoint: Time to first of CV death, cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization

Secondary endpoints: Components of primary;
composite of CV death, cardiac arrest, MI or stroke; total mortality

Primary efficacy endpoint

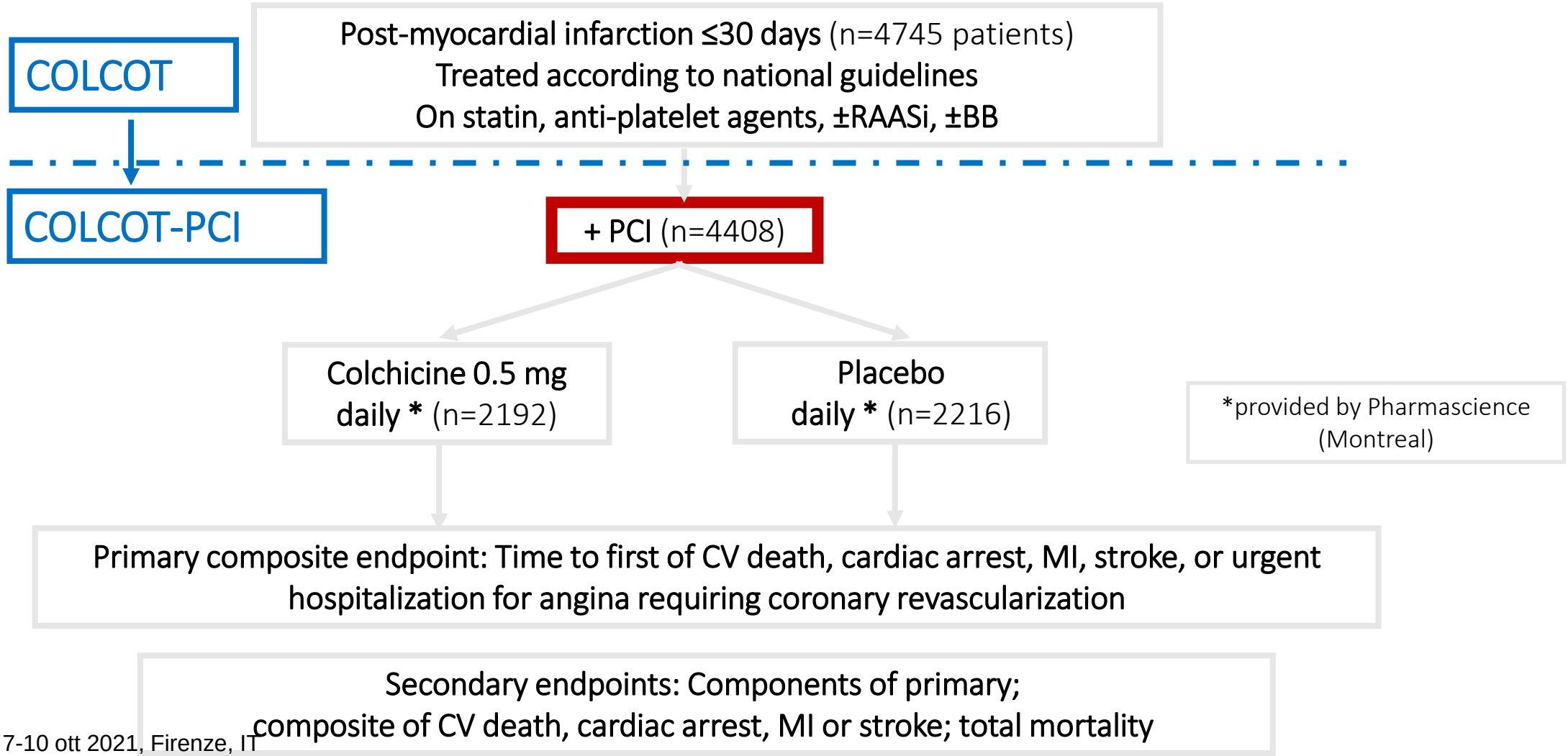


N Engl J Med. 2019 Dec 26;381(26):2497-2505

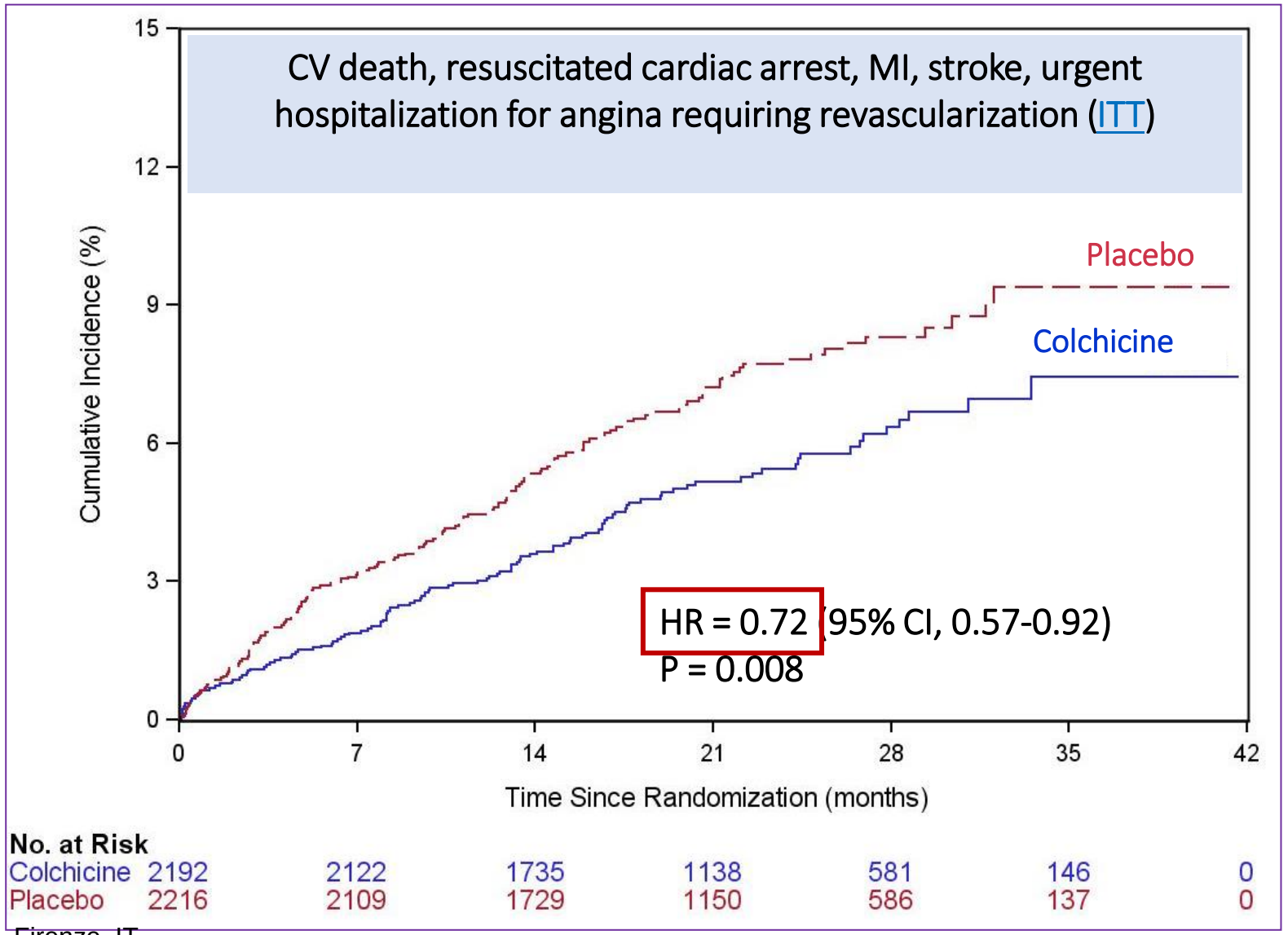
Study design

Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute
MHICC

COLCOT



Primary efficacy endpoint (COLCOT-PCI)



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

Major Clinical Outcomes

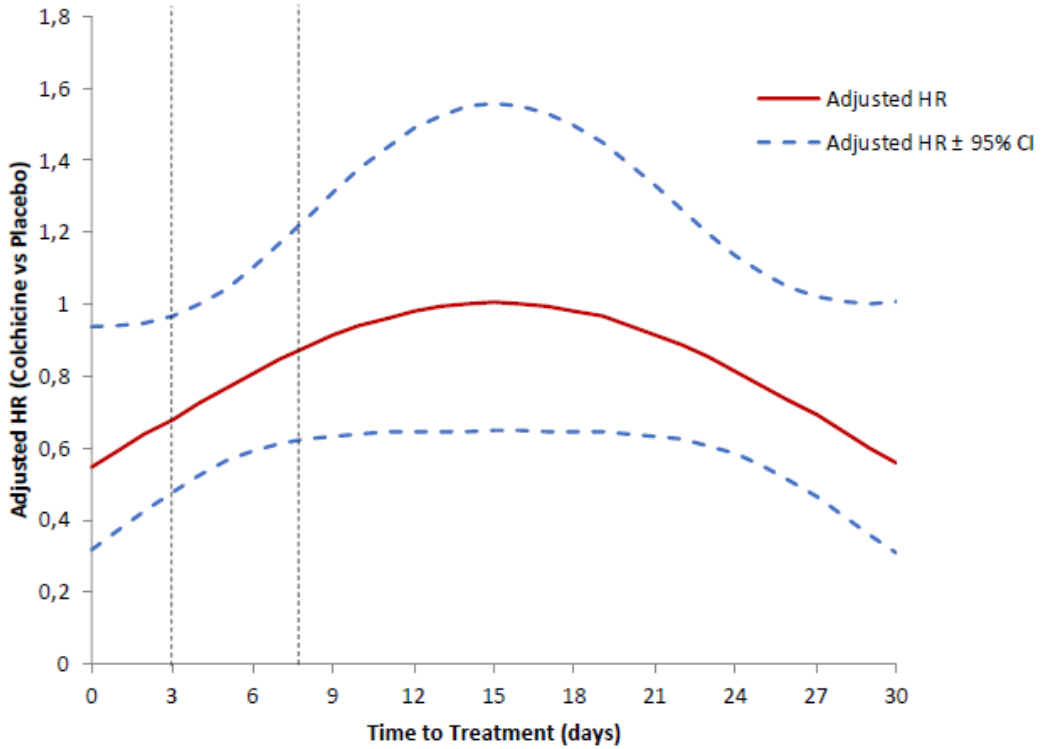
Clinical Outcome Intent-to-treat population	Colchicine N=2366	Placebo N=2379	Hazard Ratio (95% CI)	P Value
Primary composite endpoint - no. (%)	**131 (5.5%)**	**170 (7.1%)**	**0.77 (0.61-0.96)**	**0.02**
CV death - no. (%)	20 (0.8%)	24 (1.0%)	0.84 (0.46-1.52)	
Resuscitated cardiac arrest - no. (%)	5 (0.2%)	6 (0.3%)	0.83 (0.25-2.73)	
Myocardial infarction - 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)	

N Engl J Med. 2019 Dec 26;381(26):2497-2505

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

N Engl J Med. 2019 Dec 26;381(26):2497-2505

Time-to-treatment initiation of colchicine and cardiovascular outcomes



The incidence of the primary endpoint for patients in whom colchicine compared to placebo was initiated

<day 3 (HR=0.52, 95% CI 0.32-0.84),

in contrast to patients in whom colchicine was initiated between

days 4-7 (HR=0.96, 95% CI 0.53-1.75) or

>day 8 (HR=0.82, 95% CI 0.61-1.11)

Bouabdallaoui N, Tardif JC et al. Eur Heart J 2020;41(42):4092-4099

The NEW ENGLAND JOURNAL of MEDICINE

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.M.W. Alings, G.J. Hankey, C.A. Budgeon, J.G.P. Tijssen, J.H. Cornel, and P.L. Thompson, for the LoDoCo2 Trial Investigators*

N Engl J Med. 2020 Nov 5;383(19):1838-1847.

Protocol

Patients aged 35 – 82 years with proven coronary disease

Clinically stable ≥6 months

No advanced renal disease, heart failure or severe valvular heart disease

↓

30-day open label run-in of colchicine **0.5mg daily**

↓

Tolerant, clinically stable and willing

↙ ↘

Colchicine | Placebo

Primary endpoint: Composite of CV death, MI, ischemic stroke or ischemia-driven coronary revascularization

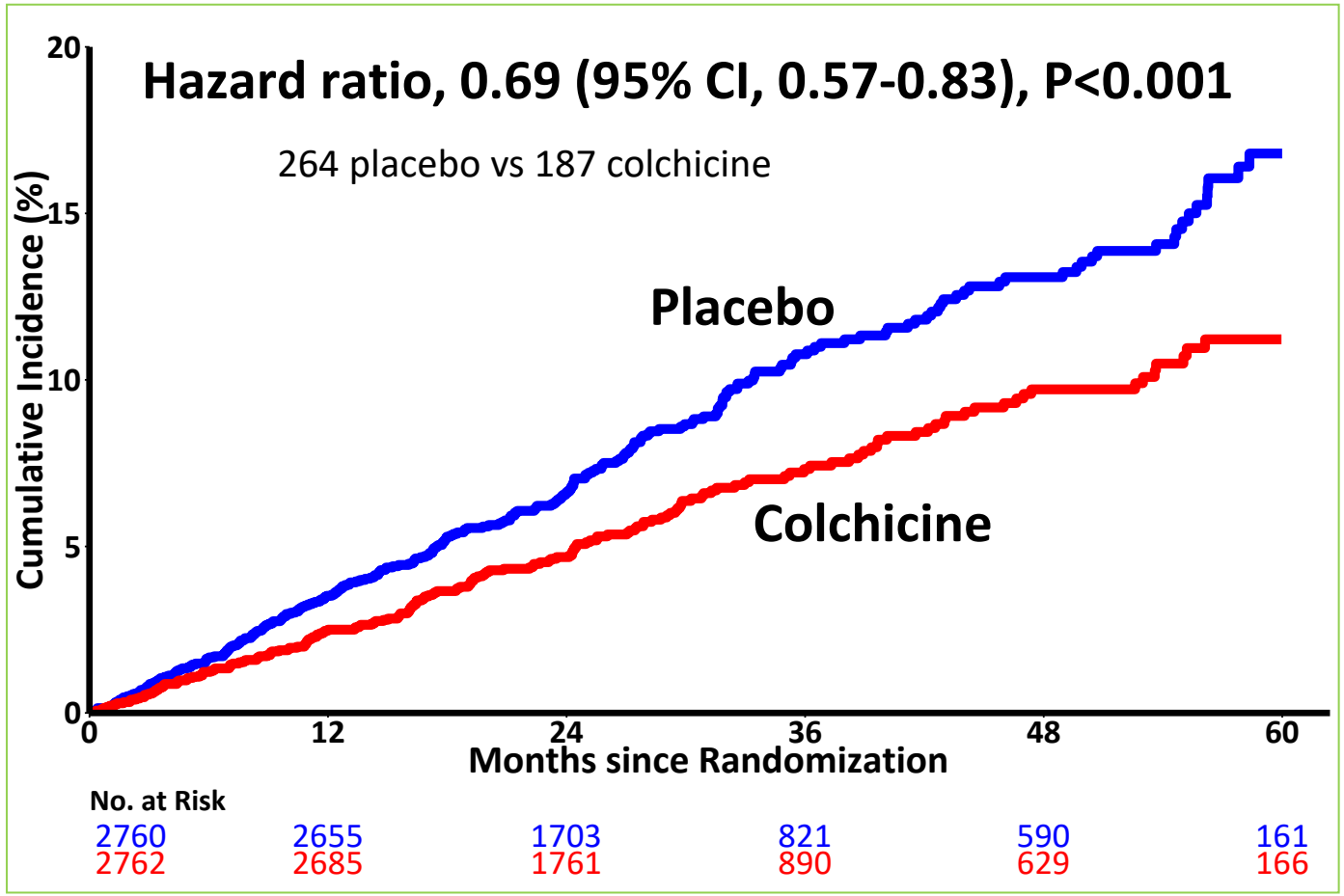
Planned to begin close-out 12 months after the last participant had been randomized*

** 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 Nov 5;383(19):1838-1847.

Primary endpoint

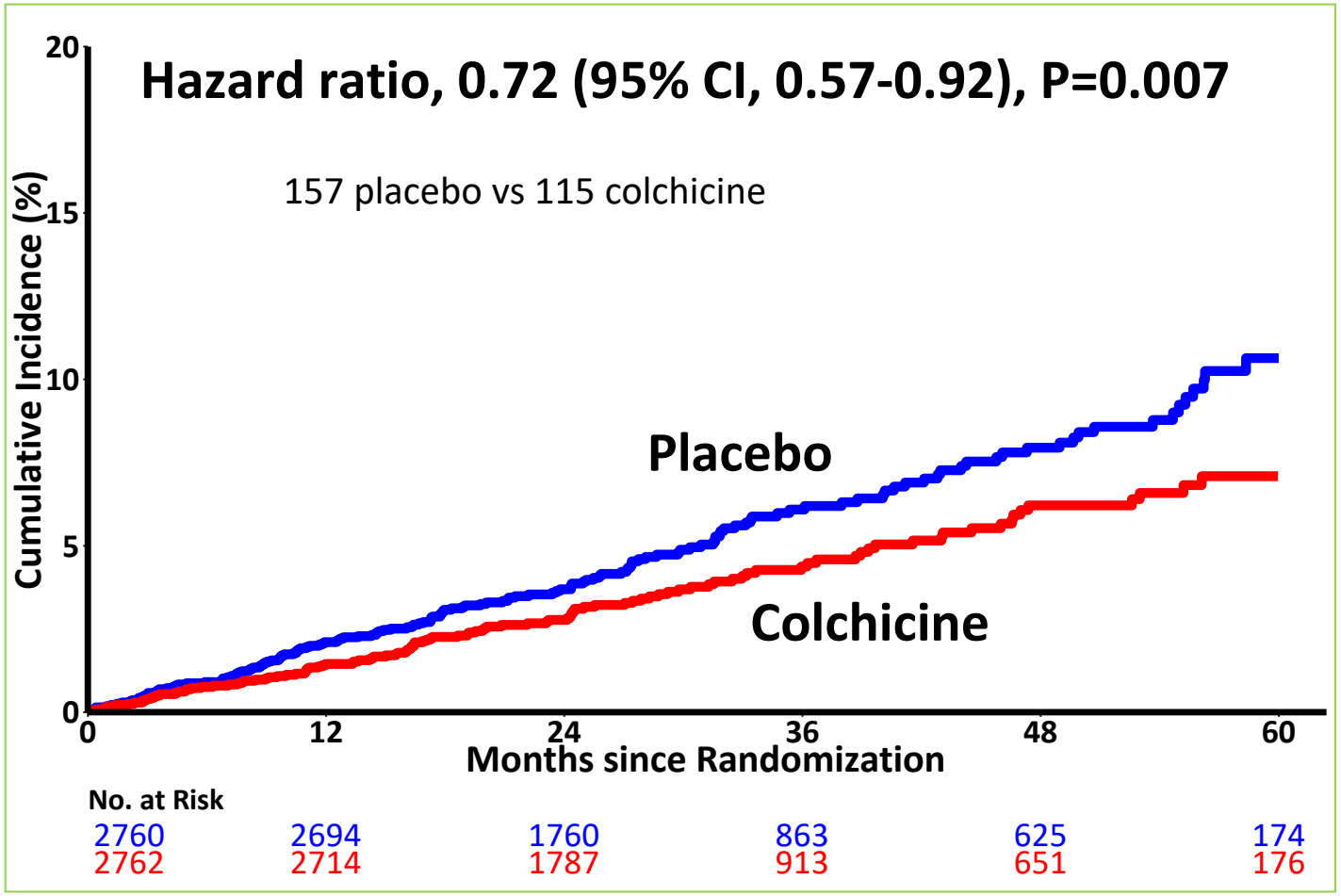
Cardiovascular death, MI, ischemic stroke or ischemia-driven coronary revascularization



Nidorf SM et al. N Engl J Med. 2020 Nov 5;383(19):1838-1847.

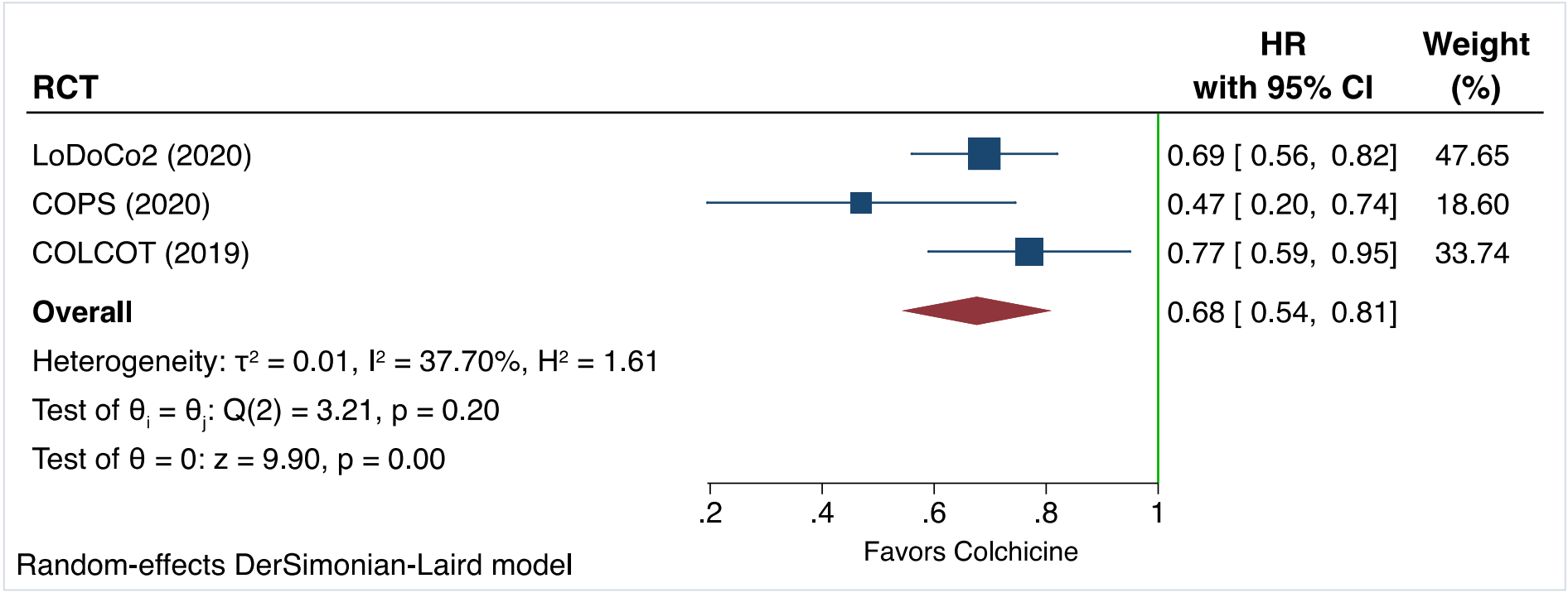
Key secondary endpoint

Cardiovascular death, MI, or ischemic stroke



Nidorf SM et al. N Engl J Med. 2020 Nov 5;383(19):1838-1847.

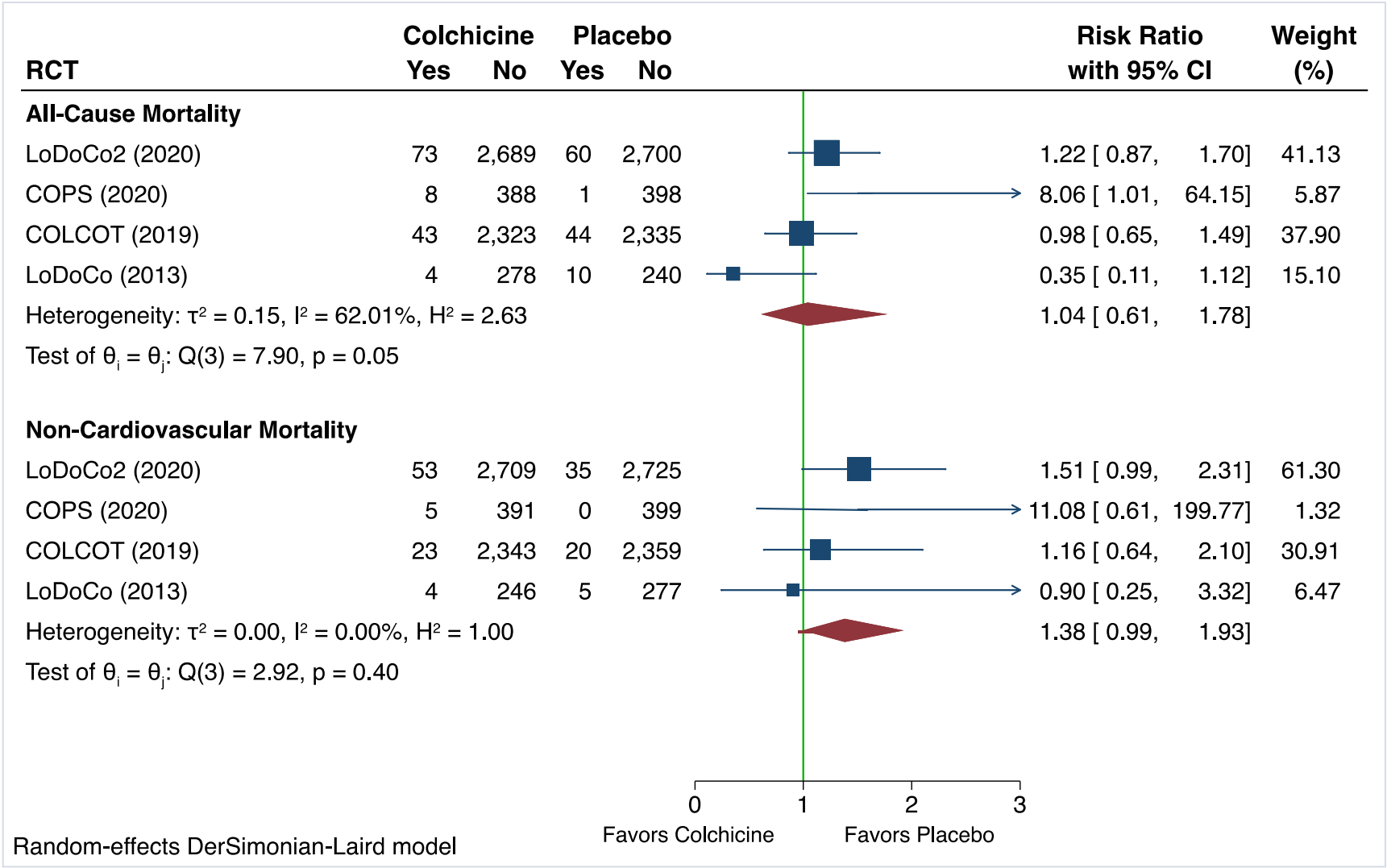
Meta-analysis of colchicine studies in CAD
Primary composite endpoint



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

Samuel M, Tardif JC et al. Can J Cardiol 2021;37(5):776-785. doi: 10.1016/j.cjca.2020.10.006.

Meta-analysis of colchicine studies in CAD
All-cause and non-CV mortality



Samuel M, Tardif JC et al. Can J Cardiol 2021;37(5):776-785. doi: 10.1016/j.cjca.2020.10.006.

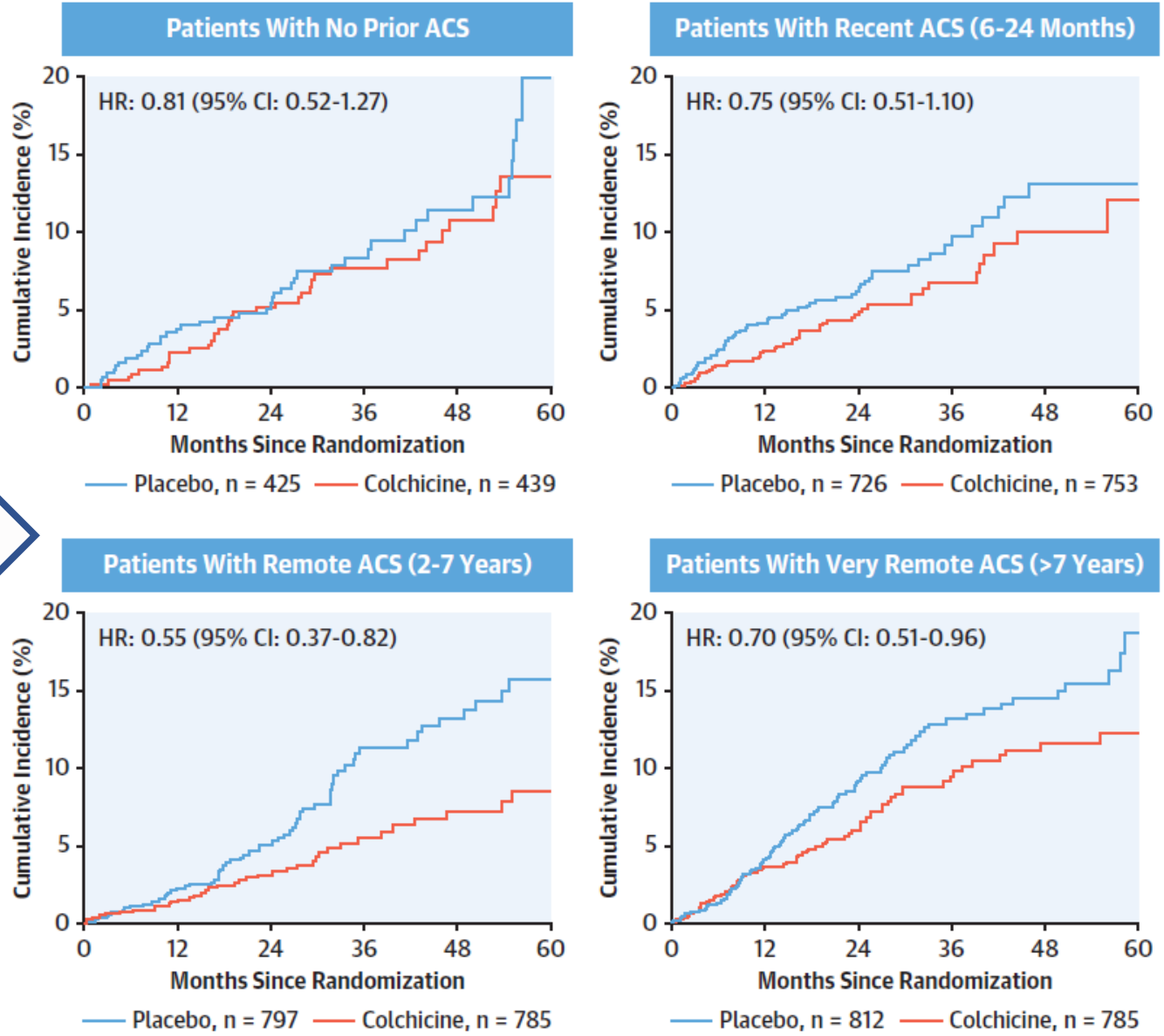
Colchicine in Patients With Chronic Coronary Disease in Relation to Prior Acute Coronary Syndrome

Tjerk S.J. Opstal, MD,[a,b] Aernoud T.L. Fiolet, MD,[c,d] Amber van Broekhoven, MD,[a] Arend Mosterd, MD, PhD,[d,e] John W. Eikelboom, MD, PhD,[f] Stefan M. Nidorf, MD, PhD,[g,h] Peter L. Thompson, MD, PhD,[g,i,j] Michiel Duyvendak, PharmD, PhD,[k,l] J.W. Martijn van Eck, MD, PhD,[m] Eugène A. van Beek, MD, PhD,[n] Frank den Hartog, MD, PhD,[o] Charley A. Budgeon, PhD,[j] Willem A. Bax, MD, PhD,[p] Jan G.P. Tijssen, PhD,[q,r] Saloua El Messaoudi, MD, PhD,[a] Jan H. Cornel, MD, PhD,[a,b,d] on behalf of the LoDoCo2 Trial Investigators

Composite of cardiovascular death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization

Conclusions

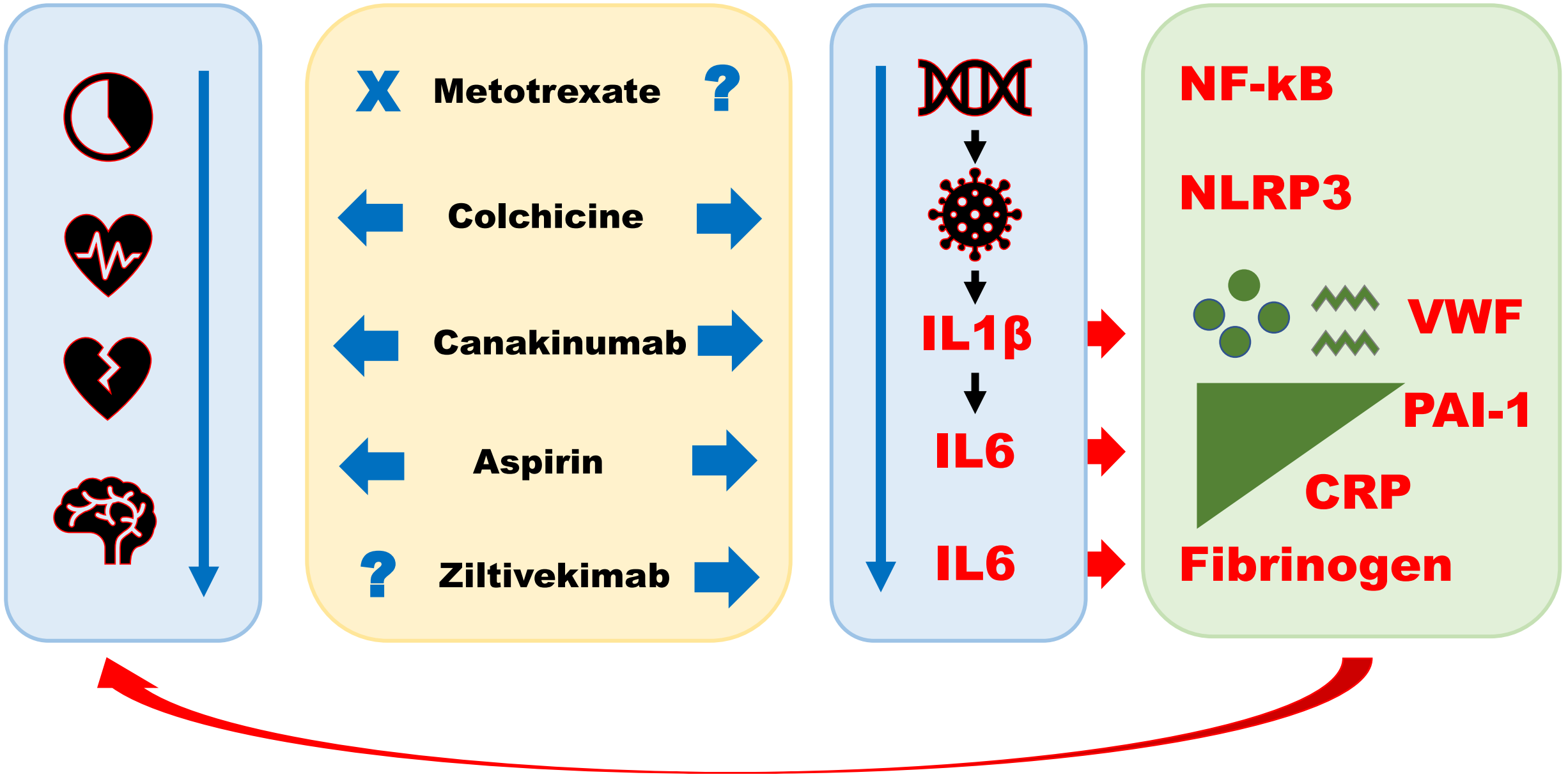
The benefits of colchicine are consistent irrespective of history and timing of prior ACS, thereby highlighting the importance of compliance with long-term secondary prevention therapies, including the use of anti-inflammatory therapy.



Opstal, T.S.J. et al. J Am Coll Cardiol. 2021;78(9):859–866.

Outline

- Inflammation and ischaemic heart disease (IHD)
- Mechanisms of anti-inflammatory drugs
- Phase 2 and 3 trials
- Implications and conclusions


X
Metotrexate
?
Colchicine
Canakinumab
Aspirin
?
Ziltivekimab
NF-kB
NLRP3
IL1β
IL6
IL6
VWF
PAI-1
CRP
Fibrinogen

- **Canakinumab e colchicina si sono dimostrati entrambi efficaci nel prevenire ECVM in pazienti coronaropatici ma solo la colchicina ha sicurezza e costi accettabili per l'uso in prevenzione cardiovascolare secondaria**

- **Si attendono risultati clinici con l'anti-IL6 ziltivekimab**

Secondary prevention strategies for patients with chronic coronary syndromes

Life style changes (smoking cessation, body weight control, heart-healthy diet, exercise), SBP <130 mmHg and HbA1c in diabetics <6.5%

Therapeutic targets

Neurohormonal system

All patients

ACE-I (ARBs if not tolerated)

Betablockers

Patients with LVD and HF

ACE-I (ARBs if not tolerated)

ARNI (if low EF)

Betablockers

MRAs

Lipid metabolism

All patients

High intensity statins

If LDL target not achievable or if statin intolerance

Ezetimibe

PCSK9-i

Thrombosis

All patients

ASA

High ischaemic risk and low bleeding risk

ASA+ADPi/P2Yi

or

ASA+low-dose rivaroxaban

Inflammation

All patients

Low-dose colchicine

Diabetic patients

As for non diabetics

plus

GLP1 RA

or

SGLT2-i

Maggioni AP, Iervolino A, Andreotti F. Vessel Plus 2021;5:14. DOI:10.20517/2574-1209.2021.05

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Figura 1 - Raccomandazioni per la terapia antinfiammatoria in prevenzione CV

Recommendation	Class[a]	Level[b]
Low-dose colchicine (0.5 mg *o.d.*) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy.[85,86]	IIb	A

COLCOT & LODOCO-2

Visseren FLI et al.. Eur Heart J 2021;42(:3227-3337