Sesión bibliográfica: RCV

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02/02/2024

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Review Article

Residual cardiovascular risk: When should we treat it?

Francisco Gomez-Delgado [a,b], Manuel Raya-Cruz [a], Niki Katsiki [c,d], Javier Delgado-Lista [b,e,1], Pablo Perez-Martinez [b,e,1,*]

European Journal of Internal Medicine, https://doi.org/10.1016/j.ejim.2023.10.013

El RCV residual se define como el exceso de complicaciones cardiovasculares en pacientes con buen control de los FRCV clásicos.

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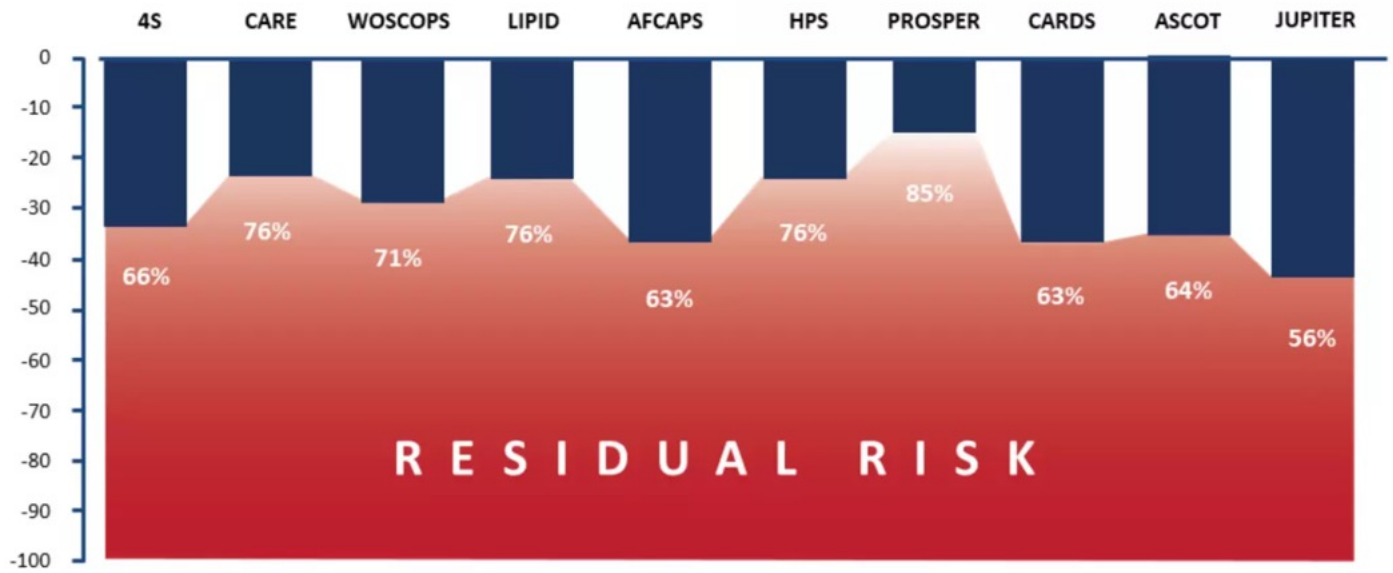
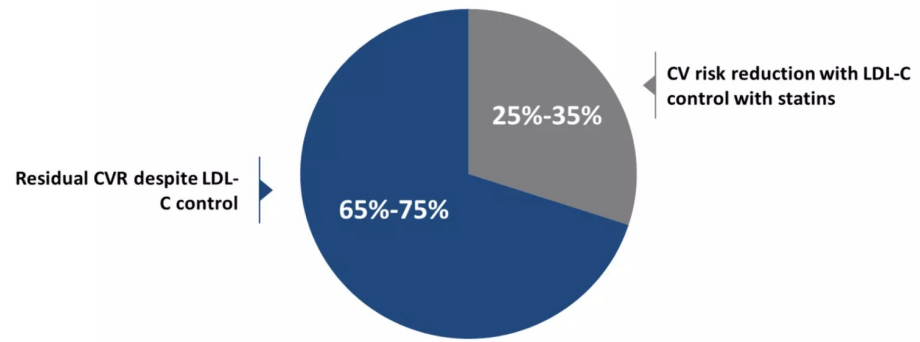
Landmark Trials With Statin Monotherapy



Despite the CV Benefit of LDL-C Lowering, Significant Residual Risk Remains



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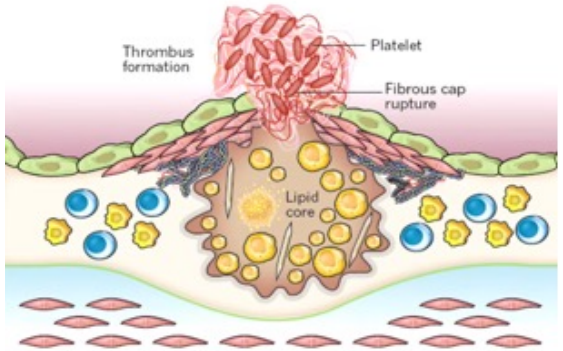

Riesgo residual inflamatorio
¿ Dónde estamos ?

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ORIGINAL RESEARCH ARTICLE

Inflammation and Cholesterol as Predictors of Cardiovascular Events Among 13970 Contemporary High-Risk Patients With Statin Intolerance

Paul M Ridker, MD; Lei Lei, PhD; Michael J. Louie, MD; Tariq Haddad, MD; Stephen J. Nicholls, MD; A. Michael Lincoff, MD; Peter Libby, MD; Steven E. Nissen, MD; on behalf of the CLEAR Outcomes Investigators

PROMINENT	Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial
STRENGTH	Long-term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patents with Hypertriglyceridemia

13970 statin-intolerant patients to 180 mg of oral bempedoic acid daily or placebo

Table 1. Predictive Value of Baseline High-Sensitivity C-Reactive Protein for Incident Major Adverse Cardiovascular Events, Cardiovascular Death, and All-Cause Mortality in the CLEAR-Outcomes Trial

	Quartile of baseline high-sensitivity C-reactive protein			
Values	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Range, mg/L	<1.15	1.15–2.30	2.31–4.46	>4.46
Median, mg/L	0.74	1.65	3.16	7.08
Major adverse cardiovascular event				
n/N	349/3440	427/3456	445/3473	511/3459
$HR_{adjusted}$	1.0	1.19	1.24	1.43
95% CI	referent	1.03–1.37	1.07–1.43	1.24–1.65
P value	NA	0.02	0.004	<0.0001
Cardiovascular death				
n/N	85/3440	117/3456	143/3473	178/3459
$HR_{adjusted}$	1.0	1.31	1.58	2.00
95% CI	referent	0.99–1.73	1.20–2.07	1.53–2.61
P value	NA	0.06	0.001	<0.0001
All death				
n/N	131/3440	182/3456	235/3473	301/3459
$HR_{adjusted}$	1.0	1.33	1.70	2.21
95% CI	referent	1.06–1.66	1.37–2.11	1.79–2.73
P value	NA	0.01	<0.0001	<0.0001

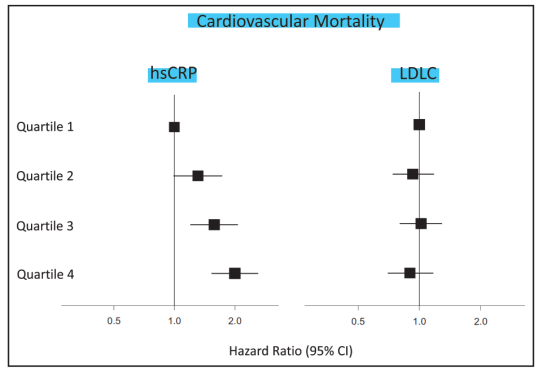


Figure 1. Relative impact of inflammation and cholesterol as independent determinants of risk for cardiovascular death. Increasing quartiles of inflammatory risk (as assessed by hsCRP; **left**) and increasing quartiles of cholesterol risk (as assessed by LDLC; **right**) as predictors of cardiovascular death among 13970 statin-intolerant patients. Hazard ratios and 95% CIs adjusted for age, sex, ethnicity, region, diabetes, body mass index, estimated glomerular filtration rate, blood pressure, alcohol use, smoking status, known atherosclerotic disease, and randomized treatment assignment. hsCRP indicates high-sensitivity C-reactive protein; and LDLC, low-density lipoprotein cholesterol.

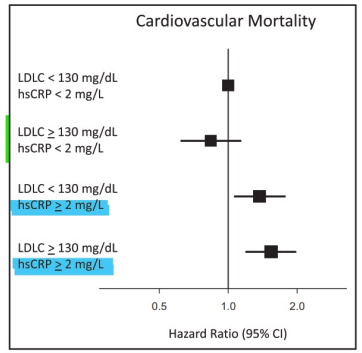
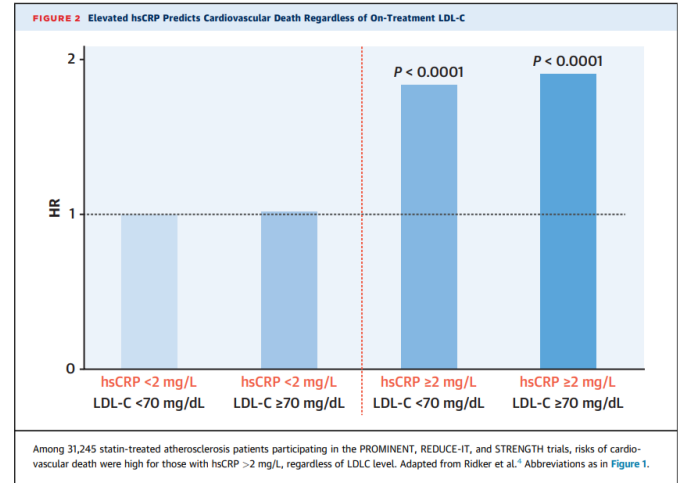


Figure 2. Inflammation determines risk of cardiovascular death at both high and low levels of LDLC. Joint analysis of hsCRP (≥ or <2 mg/L) and LDLC (≥ or <130 mg/dL) as predictors of cardiovascular death among 13970 statin-intolerant patients. Hazard ratios and 95% CIs adjusted for age, sex, ethnicity, region, diabetes, body mass index, estimated glomerular filtration rate, blood pressure, alcohol use, smoking status, known atherosclerotic disease, and randomized treatment assignment. hsCRP indicates high-sensitivity C-reactive protein; and LDLC, low-density lipoprotein cholesterol.



Circulation. 2024;149:28–35. DOI: 10.1161/CIRCULATIONAHA.123.066213

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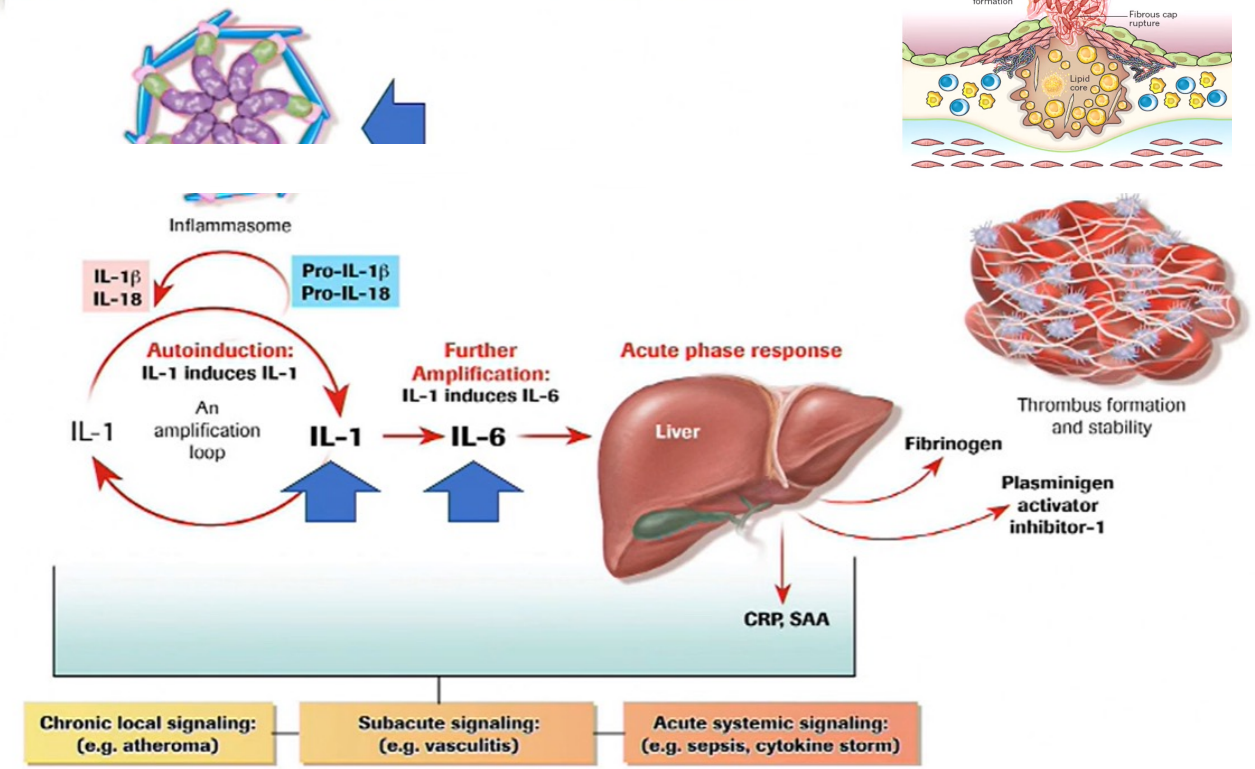
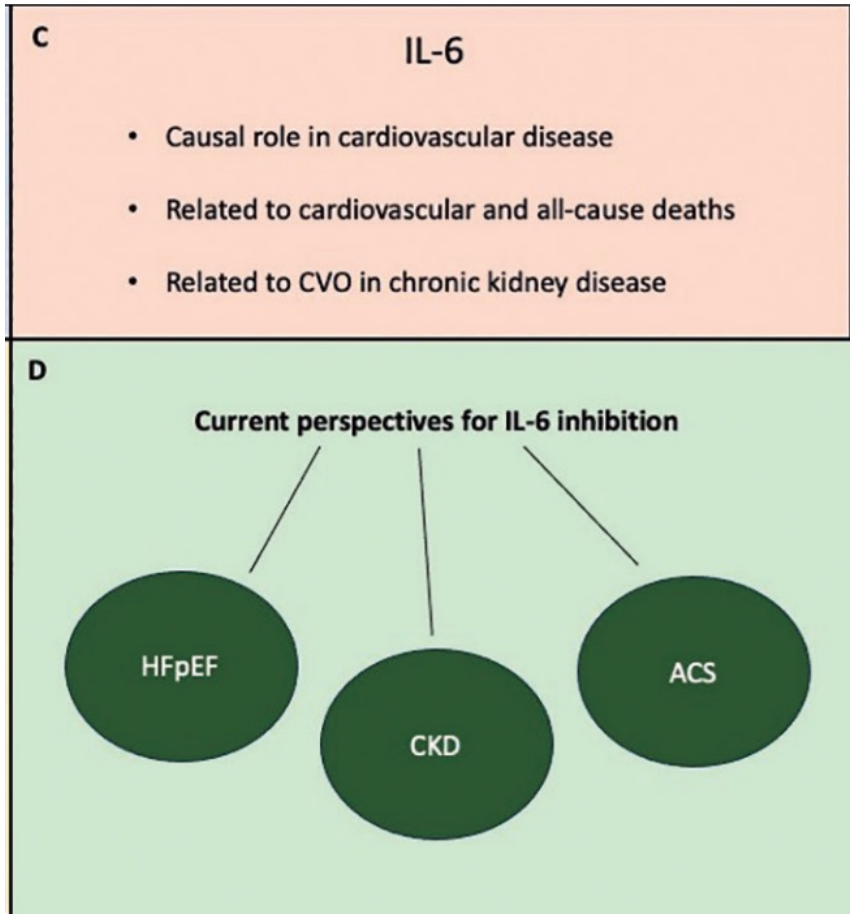
Vías de señalización: Inflamasoma y citocinas



6. En ocasiones la cápsula fibrosa es insuficiente y se produce la rotura de la lesión que conlleva agregación plaquetar y trombosis.
EPISODIO CLÍNICO

Thrombus formation and stability



Int J Cardiovasc Sci. 2023;36:e20230072

Review Article

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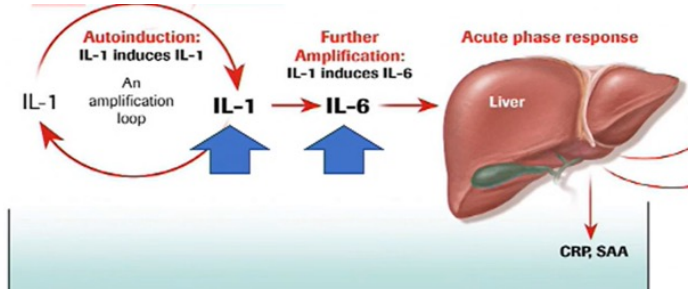
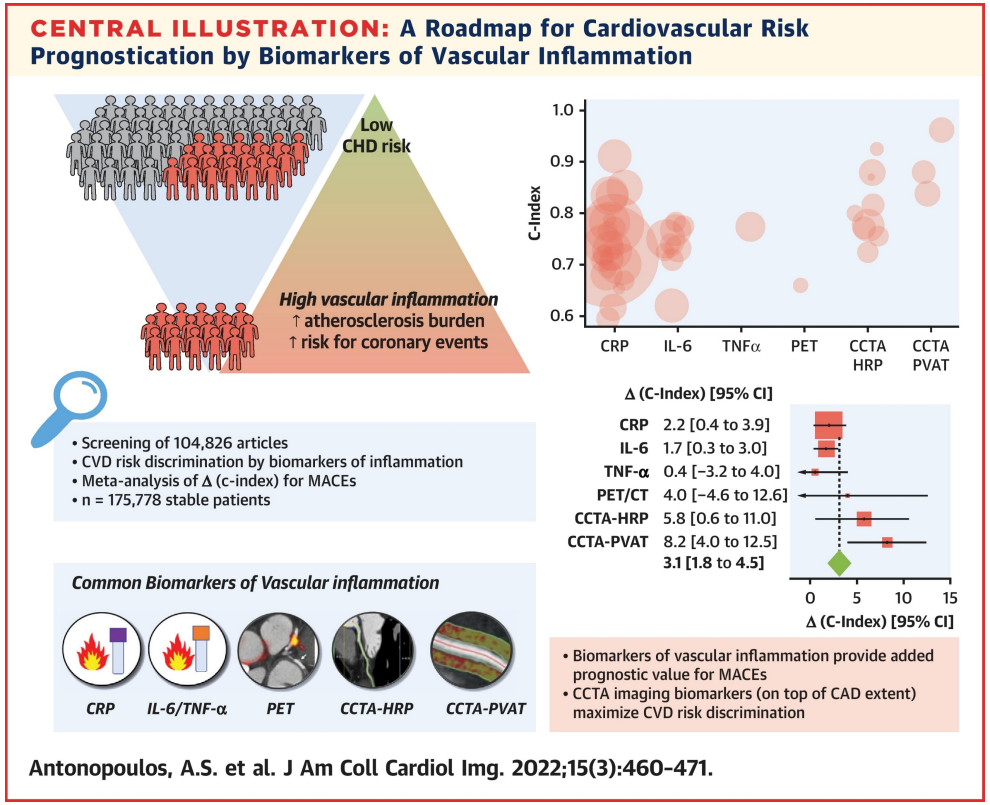
Measuring inflammation

- **PCRus.** **(≥ 2 mg/dl)**
- **IL-6/TNF-α**
- **MPO (Mieloperoxidasa).**
- Lipoprotein-associated phospholipase-A2 (Lp-PLA2).
- Trimethylamine-N-oxide (TMAO).





American Journal of Preventive Cardiology 4 (2020) 100130

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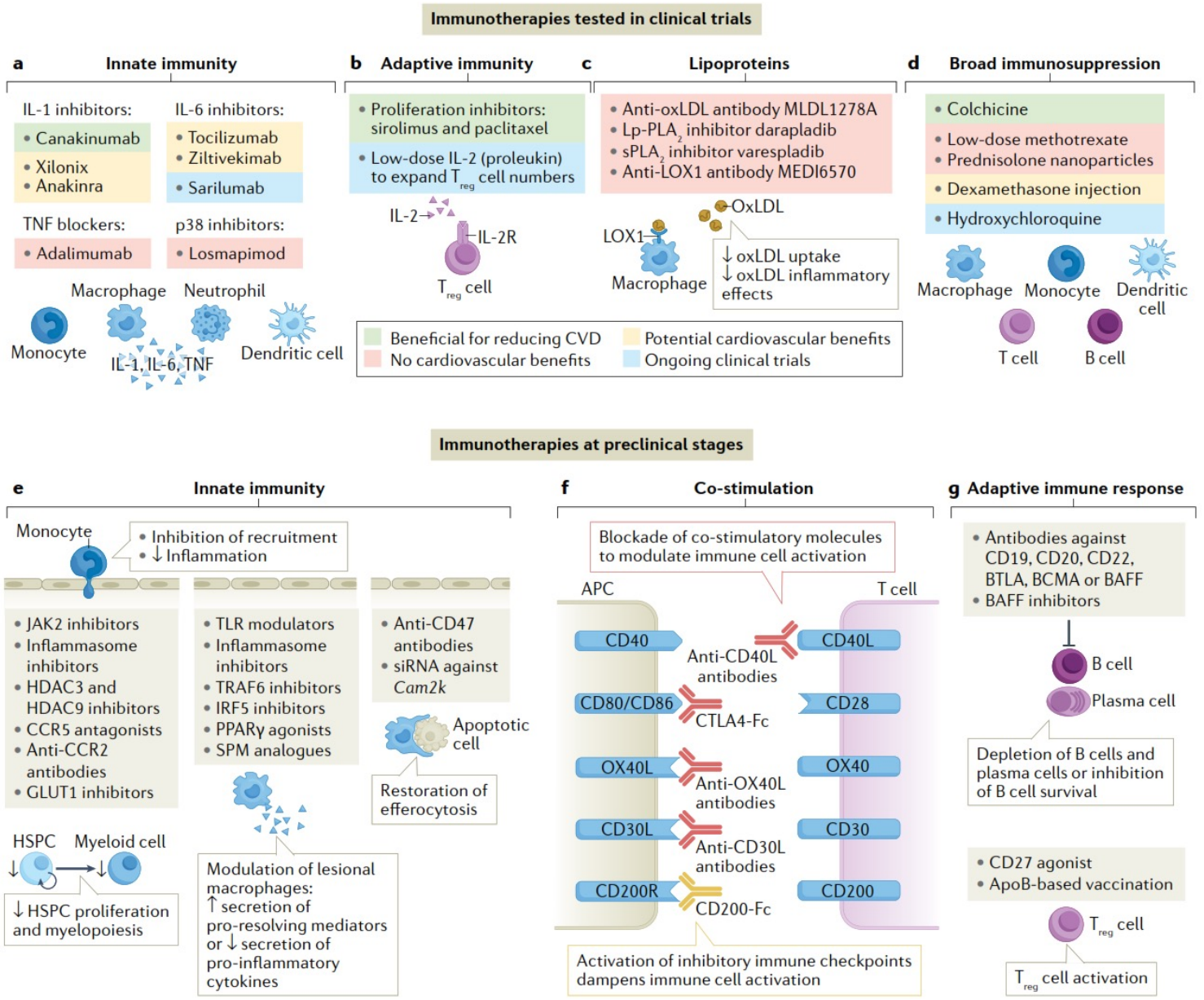


Relevant Trials				
Randomized Control Trial	**Population**	**Medication**	**Primary Outcome**	**Results**
LoDoCo (2013)	532 patients with stable CAD	0.5 mg of colchicine daily	Composite of acute coronary syndrome, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke	10.7% absolute reduction in primary endpoint driven primarily by a reduction in acute coronary syndrome
CANTOS (2017) Anti (IL-1 beta)	10,061 patients with previous MI and hs-CRP >2 mg/L	Canakinumab 50 mg, 150 mg, or 300 mg every 3 months	Composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death	15% relative reduction in the primary endpoint for the 150 mg group primarily driven by a reduction in nonfatal myocardial infarction
CIRT (2019)	4786 patients with previous MI or multivessel CAD with either type 2 diabetes or metabolic syndrome	15-20 mg of methotrexate weekly	Composite of nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, or hospitalization for unstable angina that led to urgent revascularization	No difference in the primary outcome, IL-1β, or CRP levels compared to placebo
COLCOT (2019)	4745 patients within 30 days after a MI who had a preserved EF	0.5 mg of colchicine daily	Composite of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization	1.6% absolute reduction in the primary endpoint driven primary by a reduction in the incidence of stroke or urgent hospitalization for angina leading to coronary revascularization

Anti (IL-1 beta)

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

the Canakinumab Anti inflammatory Thrombosis Outcomes Study

Inhibition of interleukin-1β by the injectable monoclonal antibody canakinumab led to a 15% lower risk of cardiovascular events than was observed with Placebo, also led to a slightly higher incidence of fatal infections.

CIRT

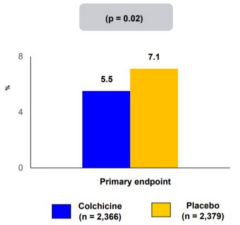
CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

the Cardiovascular Inflammation Reduction Trial

Methotrexate did not affect cardiovascular outcomes or plasma markers of inflammation

COLCOT (2019)

Trial Description: Patients who suffered a myocardial infarction within the last 30 days were randomized to colchicine 0.5 mg daily vs. placebo.



RESULTS

- Primary efficacy endpoint: CV death, MI, stroke, resuscitated cardiac arrest, or urgent hospitalization for unstable angina leading to revascularization at 22.6 months, occurred in 5.5% of the colchicine group vs. 7.1% of the placebo group (p = 0.02)
- Stroke: 0.2% of the colchicine group vs. 0.8% of the placebo group (p < 0.05)
- Urgent hospitalization for unstable angina leading to revascularization: 1.1% of the colchicine group vs. 2.1% of the placebo group (p < 0.05)

CONCLUSIONS

- Among patients who suffered a recent myocardial infarction, low-dose colchicine was effective at preventing major adverse cardiovascular events compared with placebo; benefit was primarily due to a reduction in the incidence of stroke and urgent hospitalization for unstable angina leading to revascularization

Tardif JC, et al. N Engl J Med 2019;Nov 16:[Epub]

Table 2. Major Clinical End Points (Intention-to-Treat Population).☆ Duración: 28 meses

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)	

LoDoCo 2

Nidorf, SM, et al. Colchicine in Patients with Chronic Coronary Disease. The New England Journal of Medicine. 2020. 383(19):1838-1847.

QUESTION
In patients with chronic CAD, does colchicine improve CV outcomes?

INCLUSION CRITERIA
35-82 years old
CAD
Clinically stable for ≥6 months

EXCLUSION CRITERIA
eGFR <50 mL/min/1.73 m2
NYHA class ≥3
Mod or severe heart valve disease
Functional CABG
Need for long-term colchicine tx

N = 5522

Colchicine N = 2762

OR

Placebo N = 2760

1° Outcome
New MI + CV mortality + CVA+ Ischemia-driven revascularization

Colchicine 187 (6.8%) | Placebo 264 (9.6%)
HR 0.69; P < 0.001
95% CI = 0.57-0.83
NNT = 36

2° Outcome
New MI + CV mortality + CVA

Colchicine 115 (4.2%) | Placebo 157 (5.7%)
HR 0.72; P = 0.007
95% CI = 0.57-0.92
NNT = 67

Colchicine associated with non-significant trend toward increased non-CV deaths
1.9% (colchicine) vs. 1.3% (placebo)
HR 1.51; 95% CI = 0.99 - 2.31

Conclusion
In chronic CAD, colchicine decreased composite outcome of CV death, MI, CVA, or ischemia-driven coronary revascularization.

Created by: @JulietePower44 | Edited by: @CBlumenthal2

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Colchicine in Patients with Chronic Coronary Disease

LoDoCo2 Trial Investigators*

Table S1 LoDoCo2 Key Trial Inclusion and Exclusion Criteria

Inclusion criteria	1. Age >35 and ≤82 years 2. Proven coronary artery disease; as evidenced by coronary angiography, CT coronary angiography or a Coronary Artery Calcium Score (Agatston score >400). Individuals with a history of bypass surgery are only eligible if they have undergone coronary artery bypass surgery more than 10 years before, or have angiographic evidence of graft failure or have undergone percutaneous intervention since their bypass surgery 3. Clinically stable for at least six months
Exclusion criteria	1. Women who are pregnant, breast feeding or may be considering pregnancy during the study period 2. Renal impairment as evidenced by a serum creatinine >150 µmol/l or estimated glomerular filtration rate (eGFR) <50mL/min/1.73m2 3. Severe heart failure – systolic or diastolic New York Heart Association Functional classification 3 or 4 4. Moderate or severe valvular heart disease considered likely to require intervention 5. Dependency or frailty or an estimated life expectancy < 5 years 6. Peripheral neuritis, myositis or marked myo-sensitivity to statins 7. Requirement for long term colchicine therapy for any other reason 8. Current enrollment in another trial

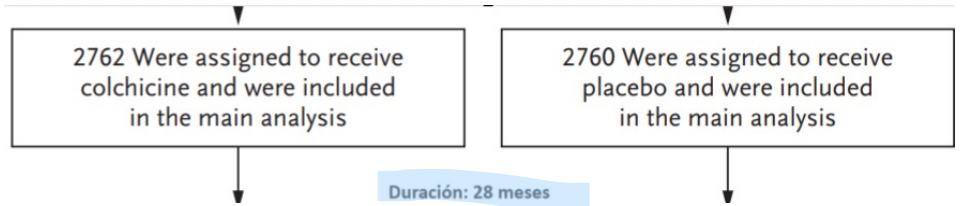

Table 2. Adverse Events in the Intention-to-Treat Population.*

Event	Colchicine (N=2762)		Placebo (N=2760)		Hazard Ratio or Cumulative Incidence Ratio (95% CI)
	no. of patients/ total no. (%)	*no. of events/100 person-yrs*	*no. of patients/ total no. (%)*	*no. of events/100 person-yrs*	
Noncardiovascular death	53/2762 (1.9)	0.7	35/2760 (1.3)	0.5	1.51 (0.99–2.31)
Diagnosis of cancer	120/2762 (4.3)	1.6	122/2760 (4.4)	1.6	0.98 (0.76–1.26)
Hospitalization for infection	137/2762 (5.0)	1.8	144/2760 (5.2)	1.9	0.95 (0.75–1.20)
Hospitalization for pneumonia	46/2762 (1.7)	0.6	55/2760 (2.0)	0.7	0.84 (0.56–1.24)
Hospitalization for gastrointestinal reason	53/2762 (1.9)	0.7	50/2760 (1.8)	0.7	1.06 (0.72–1.56)
Gout	38/2762 (1.4)	—	95/2760 (3.4)	—	0.40 (0.28–0.58)
Neutropenia	4/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myotoxic effects†	3/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myalgia‡	384/1811 (21.2)	—	334/1807 (18.5)	—	1.15 (1.01–1.31)
Dysesthesia: numbness or tingling‡	143/1811 (7.9)	—	150/1807 (8.3)	—	0.95 (0.76–1.18)

Table S7 Noncardiovascular deaths

	Colchicine (N = 2762)	Placebo (N = 2760)
	no.	*no.*
Cancer	26	22
Infection	4	4
Respiratory failure	9	4
Multi-organ failure	3	2
Dementia	4	1
Accidental	2	2
Progressive renal failure	1	-
Suicide	1	-
Cerebral vasculitis	1	-
Intestinal ischemia	1	-
Unknown	1	-
Total	53	35

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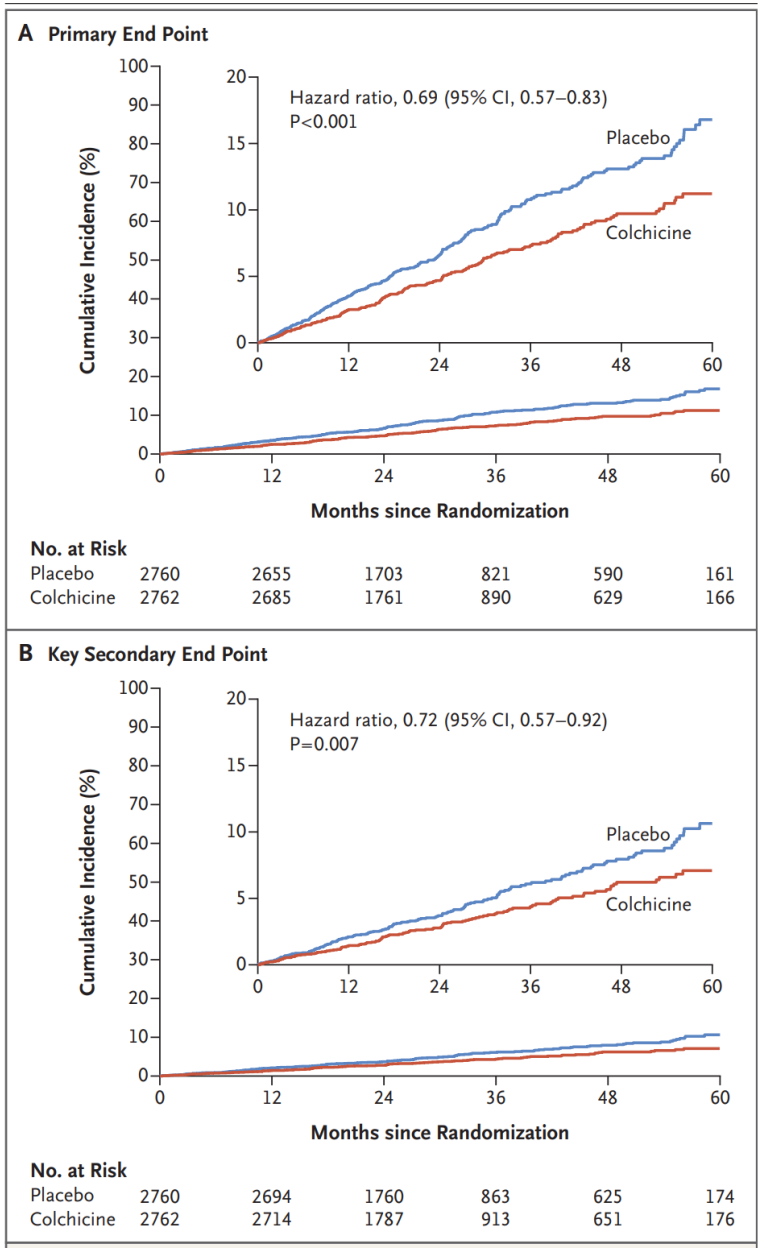
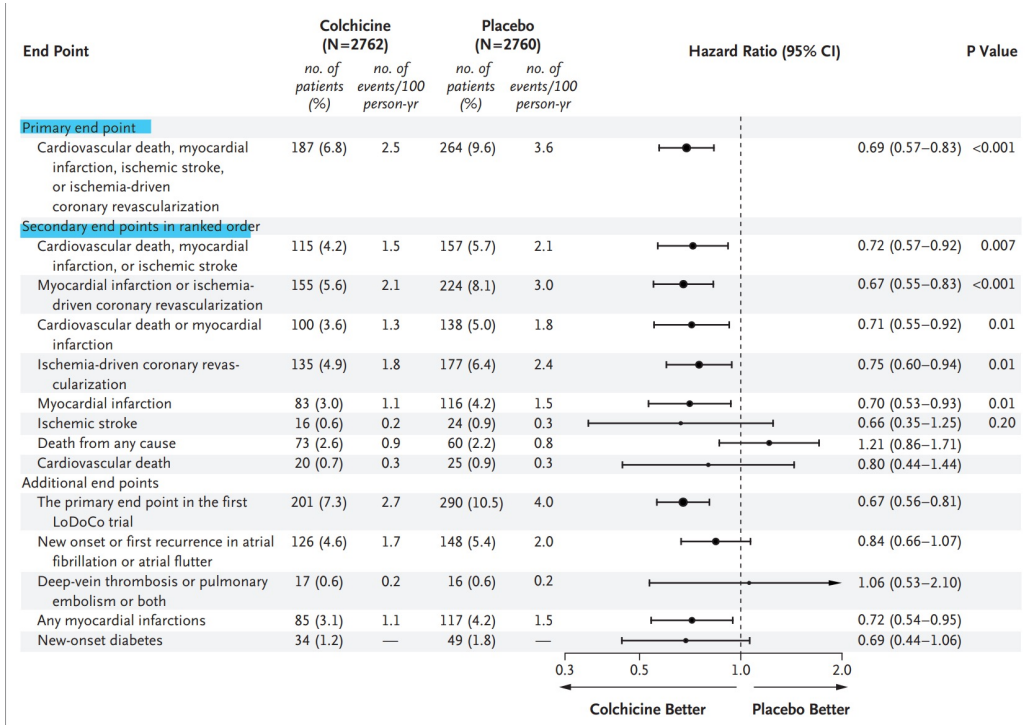


(6.8%) in the colchicine group
(9.6%) in the placebo group
NNT: 36



Medication use — no. (%)		
Single antiplatelet therapy	1849 (66.9)	1852 (67.1)
Dual antiplatelet therapy	638 (23.1)	642 (23.3)
Anticoagulant	342 (12.4)	330 (12.0)
No antiplatelet agent or anticoagulant	4 (0.1)	11 (0.4)
Statin	2594 (93.9)	2594 (94.0)
Ezetimibe	551 (19.9)	522 (18.9)
Any lipid-lowering agent	2670 (96.7)	2665 (96.6)

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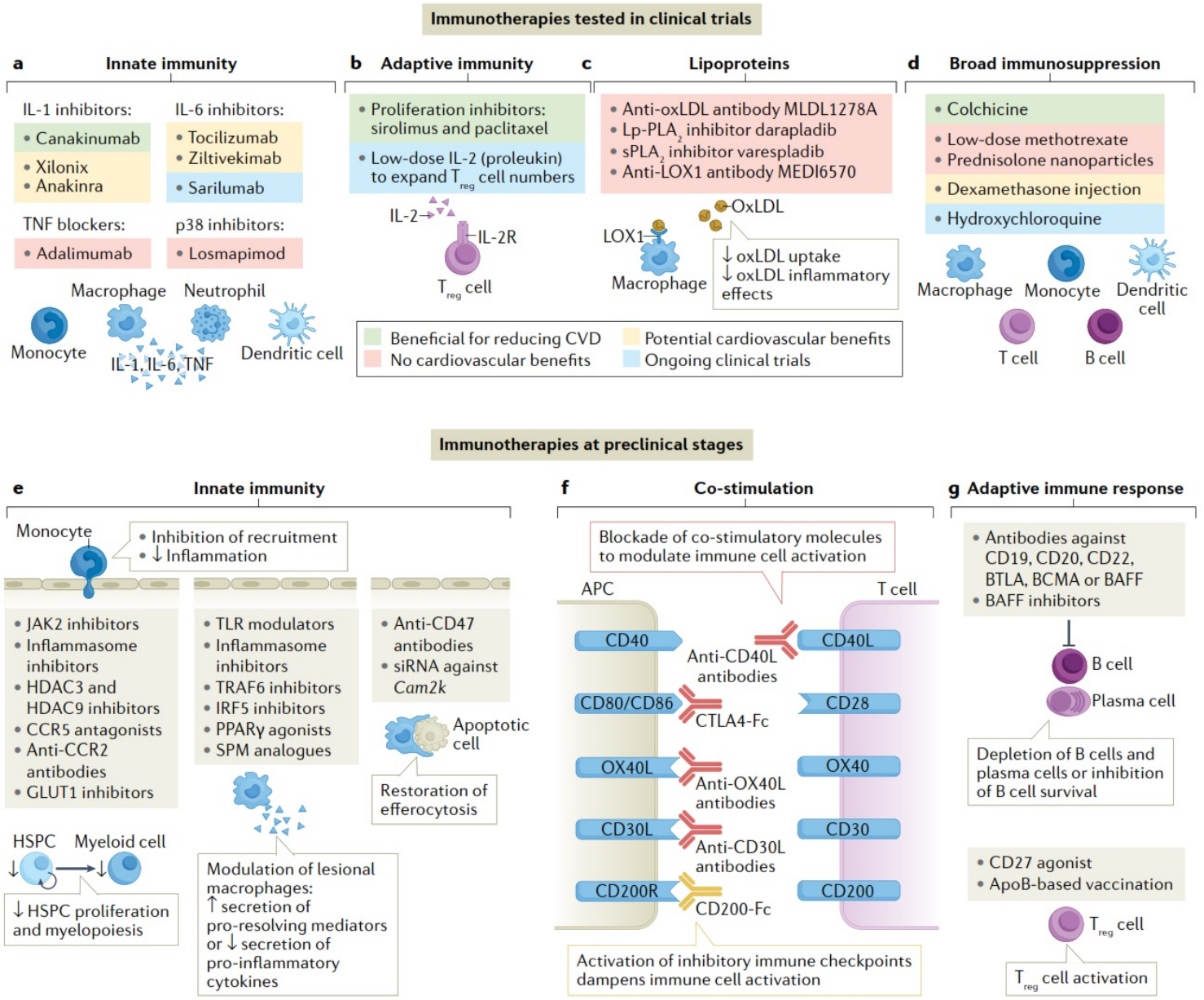


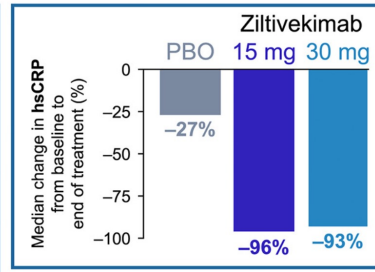
Table 2 | **Potentially effective immunotherapies in phase II clinical trials in cardiovascular disease**

Study (year)	Agent	Drug target	Study design	Patient cohort	Primary end point	Main outcomes	Ref.
El Sayed et al. (2016)	Xilonix	Monoclonal antibody specifically targeting IL-1α	Randomized, placebo-controlled	43 patients undergoing percutaneous SFA revascularization	Clinically significant target vessel restenosis, time to restenosis and incidence of major adverse cardiovascular events	At 12 months of follow-up, no difference between Xilonix and placebo; at 3 months, trend towards decreased restenosis (0% versus 10%) and cardiovascular events (9% versus 24%) in the Xilonix versus placebo groups	112
MRC-ILA heart study (2015)	Anakinra	IL-1 receptor antagonist	Randomized, double-blind, placebo-controlled	182 patients with NSTE–ACS presenting <48 h from onset of chest pain	hsCRP AUC over the first 7 days after treatment initiation	Decrease in hsCRP levels after 14 days of treatment with anakinra; similar risk of MACE at 30 days and 3 months but significant increase in MACE at 1 year in the anakinra group compared with the placebo group	111
VCU-ART3 (2020)	Anakinra	IL-1 receptor antagonist	Randomized, double-blind, placebo-controlled	99 patients with STEMI	hsCRP AUC at baseline and at 72 h and 14 days after treatment initiation	Decrease in hsCRP AUC after 14 days of treatment with anakinra; reduced incidence of new-onset heart failure, death and hospitalization for heart failure in the anakinra group compared with the placebo group	110
DANCE (2018)	Dexamethasone delivered to the adventitial tissue surrounding target lesions	Broad anti-inflammatory effect	Prospective, single-group, open-label; data compared with findings from contemporary trials	262 patients with symptomatic PAD receiving PTA ($n = 124$) or atherectomy ($n = 159$)	12-month primary patency (composite of freedom from binary restenosis and clinically driven target-lesion revascularization)	Reduced restenosis after 12 months of follow-up	243
Kleveland et al. (2016)	Tocilizumab	Monoclonal antibody against IL-6 receptor	Randomized, double-blind, placebo-controlled	117 patients with NSTEMI, included in the randomization at a median of 2 days after symptom onset	hsCRP AUC at 1–3 days of treatment initiation	Tocilizumab reduced hsCRP levels compared with placebo	119
ASSAIL-MI (2021)	Tocilizumab	Monoclonal antibody against IL-6 receptor	Randomized, double-blind, placebo-controlled	199 patients within 6 h of STEMI and undergoing PCI	Myocardial salvage index measured by MRI 3–7 days after treatment initiation	Tocilizumab increased the myocardial salvage index and reduced CRP levels compared with placebo	118
RESCUE (2021)	Ziltivekimab	Monoclonal antibody against IL-6	Randomized, double-blind, placebo-controlled	264 patients with chronic kidney disease and hsCRP >2 mg/l	hsCRP measured 12 weeks after treatment initiation	Ziltivekimab reduced hsCRP levels at all doses compared with placebo	120

AUC, area under the curve; CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; MACE, mayor adverse cardiovascular events; MI, myocardial infarction; NSTE–ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty; SFA, superficial femoral artery; STEMI, ST-segment elevation myocardial infarction.

Ziltivekimab reduced markers of systemic inflammation in the phase 2 trial RESCUE-2 in patients at high risk of atherosclerotic events in Japan

- **Ziltivekimab** is a fully human monoclonal antibody directed against the **IL-6 ligand**, developed for the treatment of atherosclerosis.
- In the US phase 2 trial RESCUE, ziltivekimab significantly **reduced markers of inflammation** compared with placebo in patients at high atherosclerotic risk.



Key result

Over 12 weeks, **ziltivekimab significantly reduced levels of hsCRP, serum amyloid A and fibrinogen** versus placebo ($p < 0.01$).

Patients (≥ 20 years old, non-dialysis-dependent CKD stage 3–5, hsCRP ≥ 2 mg/L) were randomized to receive placebo (n = 13) or ziltivekimab 15 mg (n = 11) or 30 mg (n = 12) s.c. at Weeks 0, 4 and 8.

Methods

CKD, chronic kidney disease; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; PBO, placebo; s.c., subcutaneous.

Journal of Cardiology
Volume 82, Issue 4, October 2023, Pages 279-285

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Table 3 | **Ongoing randomized controlled trials targeting the immune system in atherosclerosis**

Trial name (number)	Agent	Drug target	Trial design	Patient cohort	Primary end point	Ref.
OXI (NCT02648464)	Hydroxychloroquine	Broad immunosuppression	Phase IV	125 patients with MI	Rate of cardiovascular adverse events (MI, death, hospitalization for unstable angina and heart failure)	252
CHANGAN (NCT02874287)	Hydroxychloroquine	Broad immunosuppression	Phase IV	35 patients with CAD and hsCRP >1 mg/l	Change in fasting hsCRP level	253
LILACS (NCT03113773)	Low-dose IL-2	Induces expansion of regulatory T cell numbers	Phase I–II	41 patients with a history of CAD or acute coronary syndrome	Safety, tolerability and circulating regulatory T cell levels	254
IVORY (NCT04241601)	Low-dose IL-2	Induces expansion of regulatory T cell numbers	Phase II	60 patients with ACS and hsCRP >2 mg/l	Change in vascular inflammation, as measured by FDG PET–CT	255
NCT04762472	Montelukast	Leukotriene receptor	Phase IV	200 adults asymptomatic for atherosclerotic disease and exposed to air pollution	Subclinical atherosclerosis (as measured by brachial flow-mediated dilatation, carotid intima–media thickness and blood inflammatory markers)	256
NCT04616872	Methotrexate delivered in LDL-like nanoparticles	Broad immunosuppression	Phase II–III	40 patients with multivessel CAD and hsCRP >2 mg/l	Reduction in plaque volume, measured by CTA	257
SARIPET (NCT04350216)	Sarilumab	Monoclonal antibody against IL-6 receptor	Phase IV	20 patients with active rheumatoid arthritis and CRP levels >1 mg/dl	Changes in carotid atheroma plaque assessed by ultrasonography	258
PAC-MAN (NCT04148833)	Paclitaxel	Proliferation	Phase II–III	40 patients with CAD	Low-attenuation plaque volume measured by CTA	259
GOLDILOX (NCT04610892)	MEDI6570	Antibody against LOX1 receptor (blocks uptake of oxidized LDL)	Phase IIb	792 patients with a history of MI	Non-calcified plaque volume measured by CTA	260
CLEAR-Synergy (NCT03048825)	Colchicine	Broad immunosuppression	Phase III	7,000 patients with MI	MACE	261
CONVINCE (NCT02898610)	Colchicine	Broad immunosuppression	Phase III	2,623 patients with ischaemic stroke or at high risk of transient ischaemic attack	Recurrence of non-fatal ischaemic stroke or non-fatal MACE, or vascular-related death	262
ZEUS (NCT05021835)	Ziltivekimab	Monoclonal antibody against IL-6	Phase III	6,200 patients with chronic kidney disease and CRP ≥2 mg/l	Time to first MACE	The ZEUS trial (2025)

ACS, acute coronary syndrome; CAD, coronary artery disease; CRP, C-reactive protein; CTA, computed tomography angiography; FDG, fluorodeoxyglucose; hsCRP, high-sensitivity C-reactive protein; LOX1, lectin-like oxidized LDL receptor 1; MACE, major adverse cardiovascular events; MI, myocardial infarction.

IL-6 inhibition:
HERMES: patients with heart failure and preserved ejection fraction (HERMES).
ARTEMIS: acute coronary syndromes.

Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke (CONVINCE)

Study Start (Actual)
2016-12-12

Primary Completion (Actual)
2022-11-21

Study Completion (Estimated)
2023-12-31

Enrollment (Actual)
3154

Study Type
Interventional

Phase
Phase 3

The Time to Initiate Anti-Inflammatory Therapy for Patients With Chronic Coronary Atherosclerosis Has Arrived

Paul M Ridker, MD, MPH

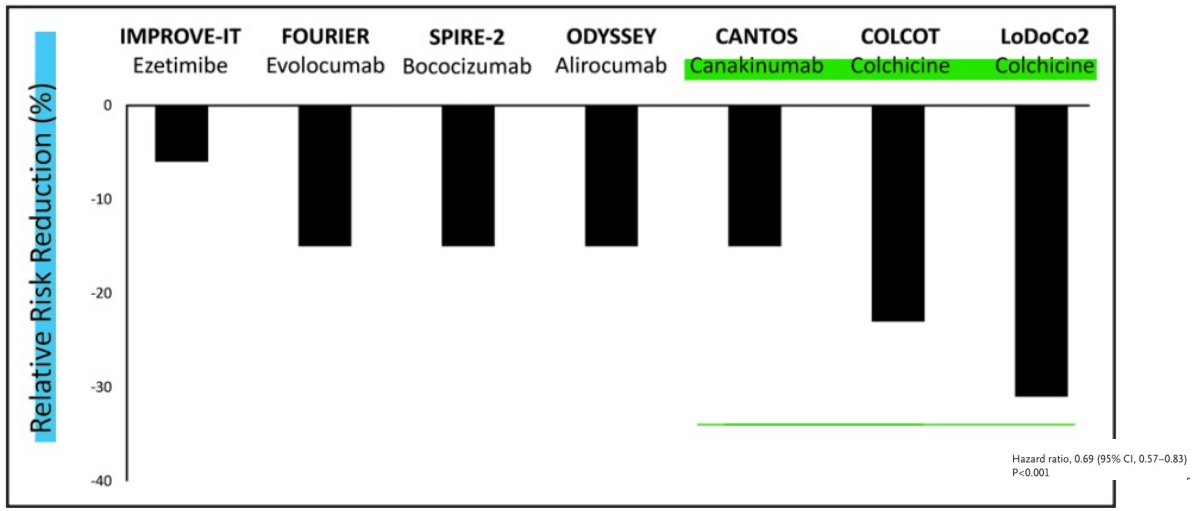
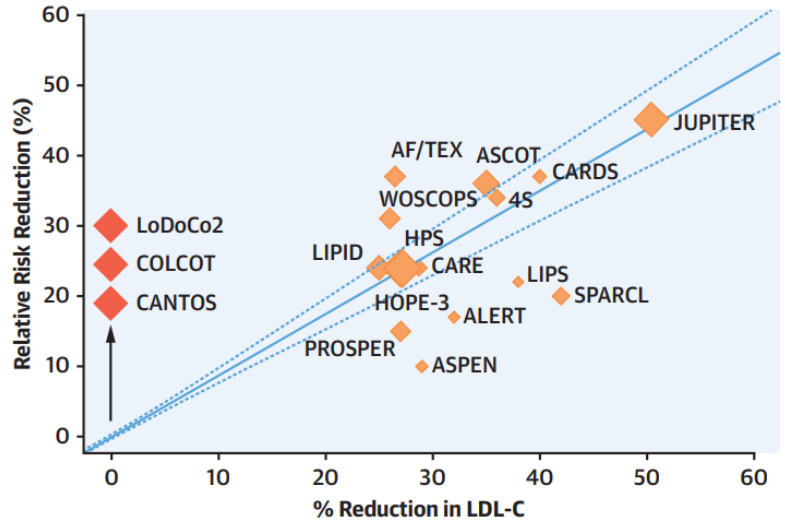


Figure. Relative risk reductions reported from double-blind placebo-controlled trials of ezetimibe, PCSK9 inhibition, canakinumab, and low-dose colchicine on the incidence of major adverse cardiovascular events when each randomly allocated agent was used as an adjunct to statin therapy.

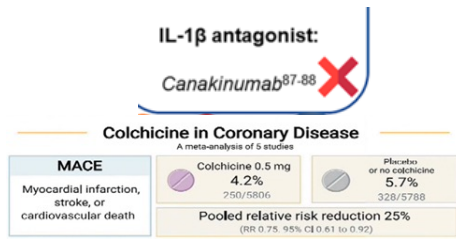
CANTOS indicates Canakinumab Anti-inflammatory Thrombosis Outcomes Study; COLCOT, Colchicine Cardiovascular Outcomes Trial; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LoDoCo2, Low Dose Colchicine Trial -2; ODYSSEY, Alirocumab and Cardiovascular Outcomes After Acute Coronary Syndrome; and SPIRE-2, Studies of PCSK9 Inhibition and the Reduction of Vascular Events -2.

Circulation. 2023;148:1071–1073. DOI: 10.1161/CIRCULATIONAHA.123.066510

FIGURE 5 Targeted Anti-Inflammatory Therapy Demonstrates Substantial Cardiovascular Risk Reduction Without Change in LDL-C



Trials of statin therapy compared with placebo demonstrate a consistent linear reduction in cardiovascular risk proportionate to reductions in LDL-C **(orange diamonds)**. Targeted anti-inflammatory therapy with subcutaneous canakinumab (as shown in the CANTOS [Canakinumab Anti-inflammatory Thrombosis Outcomes Study]) or oral colchicine (0.5 mg, as shown in LoDoCo2 [Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease] and COLCOT [Colchicine Cardiovascular Outcomes Trial]) also substantially lowers cardiovascular risk yet does so without lowering LDL-C **(red diamonds)**. LDL-C = low-density-lipoprotein cholesterol. From Ridker PM. Anti-inflammatory therapy for cardiovascular disease. In: Ballantyne CM. *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. Third ed. Elsevier; 2023: chapter 24.



JACC VOL. 82, NO. 7, 2023
AUGUST 15, 2023:648–660

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–111
doi:10.1093/eurheartj/ehab484

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

4.10. Anti-inflammatory therapy

Recommendation for anti-inflammatory therapy

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

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–107
https://doi.org/10.1093/eurheartj/ehad191

2023 ESC Guidelines for the management of acute coronary syndromes

Anti-inflammatory drugs		
Low-dose colchicine (0.5 mg once daily) may be considered, particularly if other risk factors are insufficiently controlled or if recurrent cardiovascular disease events occur under optimal therapy.[850,851]	IIb	A

Junta de Castilla y León Sacyl Complejo Asistencial Universitario de León

Low-Dose Colchicine for Secondary Prevention of Coronary Artery Disease

JACC Review Topic of the Week

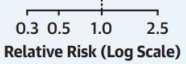
Kyle Nelson, MD,[a] Valentin Fuster, MD,[a,b] Paul M Ridker, MD, MPH[c]

FIGURE 3 Effects of Low-Dose Colchicine on Myocardial Infarction, Stroke, and Cardiovascular Death

Myocardial Infarction, Stroke, or Cardiovascular Death

Acronym	Colchicine Events/Total (%)	Comparator Events/Total (%)	Weight (GIV)	Relative Risk (95% CI)
LoDoCo2, 2020	115/2,762 (4.2%)	157/2,760 (5.7%)	43.4%	0.73 (0.58-0.93)
COPS, 2020	12/396 (3.0%)	16/399 (4.0%)	7.2%	0.76 (0.36-1.58)
COLCOT, 2019	111/2,366 (4.7%)	130/2,379 (5.5%)	40.9%	0.86 (0.67-1.10)
LoDoCo, 2013	12/282 (4.3%)	25/250 (10.0%)	8.6%	0.43 (0.22-0.83)
Totals	250/5,806	328/5,788	100%	0.75 (0.61-0.92)

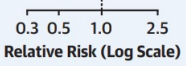
I^2 = 23.9%. Random effects model for overall effect, P = 0.005



Myocardial Infarction, Stroke, Coronary Revascularization, or Cardiovascular Death

Acronym	Colchicine Events/Total (%)	Comparator Events/Total (%)	Weight (GIV)	Relative Risk (95% CI)
LoDoCo2, 2020	187/2,762 (6.8%)	264/2,760 (9.6%)	43.0%	0.71 (0.59-0.85)
COPS, 2020	15/396 (3.8%)	28/399 (7.0%)	9.4%	0.54 (0.29-0.99)
COLCOT, 2019	131/2,366 (5.5%)	170/2,379 (7.1%)	36.8%	0.77 (0.62-0.97)
LoDoCo, 2013	16/282 (5.7%)	35/250 (14.0%)	10.8%	0.41 (0.23-0.71)
Totals	349/5,806	497/5,788	100%	0.67 (0.55-0.82)

I^2 = 41.2%. Random effects model for overall effect, P < 0.001



Meta-analysis of the effects of low dose colchicine (0.5 mg/d orally) on the composite endpoint of myocardial infarction, stroke, or cardiovascular death **(top)** and on the composite endpoint further including coronary revascularization **(bottom)** observed in the LoDoCo2, COPS, COLCOT, and LoDoCo1 trials. Adapted from Fiolet et al.[22]

https://doi.org/10.1016/j.jacc.2023.05.055

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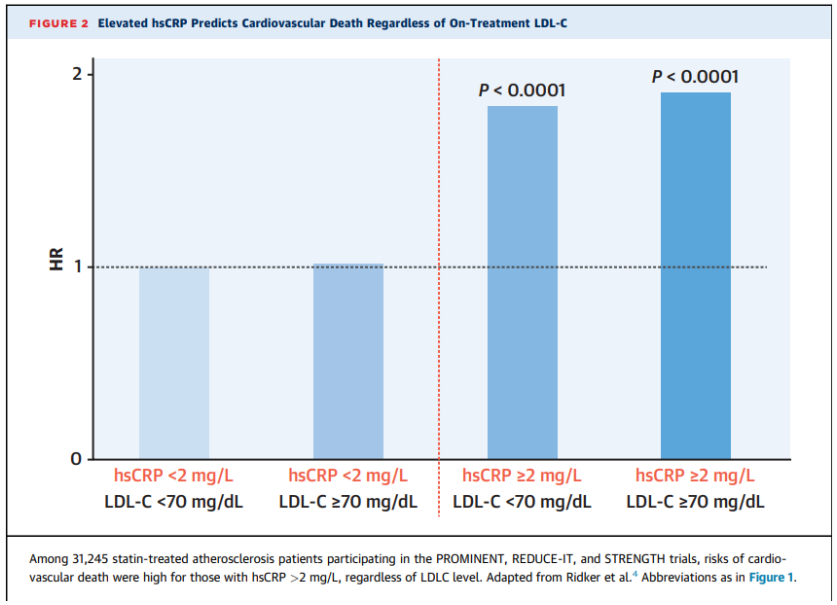
Low-Dose Colchicine for Secondary Prevention of Coronary Artery Disease

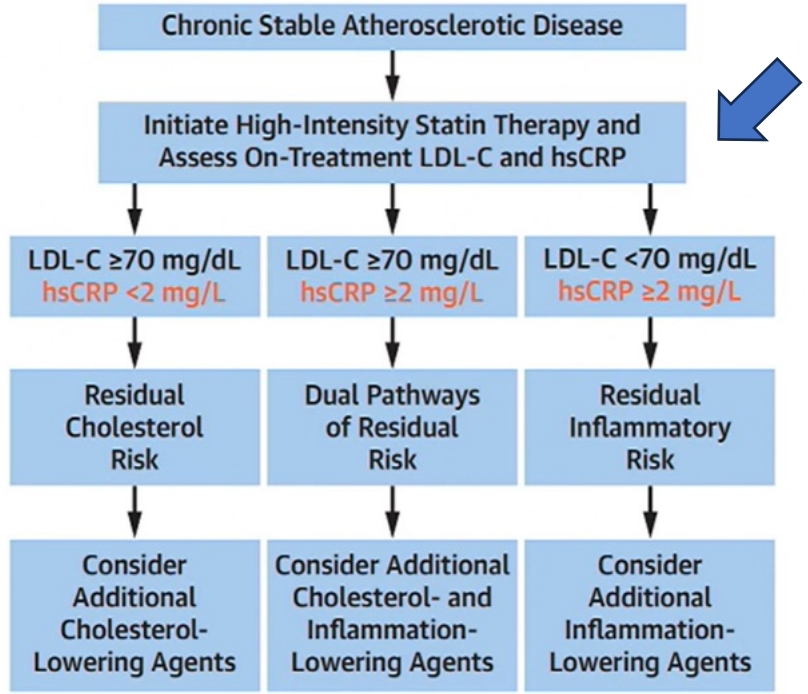
JACC Review Topic of the Week

Kyle Nelson, MD,[a] Valentin Fuster, MD,[a,b] Paul M Ridker, MD, MPH[c]

Manejo del riesgo residual inflamatorio/lipídico en la enfermedad aterosclerosa



Among 31,245 statin-treated atherosclerosis patients participating in the PROMINENT, REDUCE-IT, and STRENGTH trials, risks of cardiovascular death were high for those with hsCRP >2 mg/L, regardless of LDLC level. Adapted from Ridker et al.[4] Abbreviations as in Figure 1.



HIGHLIGHTS

- Low-dose (0.5 mg/d) colchicine, an anti-inflammatory drug, reduces cardiovascular events rates by 25% to 30% in patients with coronary atherosclerosis.
- Low-dose colchicine should be considered for patients with stable ischemic heart disease who, despite guideline-directed therapy, have high-sensitivity C-reactive protein concentrations >2 mg/L, but it should be avoided in patients with renal or hepatic impairment or those concomitantly taking CYP3A4/P-glycoprotein inhibitors.
- In the future, combination therapy with lipid-lowering and anti-inflammatory medications may be used more frequently for patients with atherosclerosis.

https://doi.org/10.1016/j.jacc.2023.05.055

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U.S. FDA Approves First Anti-Inflammatory Drug for Cardiovascular Disease

LODOCO®* (colchicine, 0.5 mg tablet) *Reduces Cardiac Event Risk in Adult Patients with Established Atherosclerotic Cardiovascular Disease (ASCVD) by an Additional 31% on Top of Standard of Care.

LODOCO Targets Residual Inflammation as an Underlying Cause of ASCVD and Can be Used Alone or in Combination with Cholesterol-Lowering Medications

LODOCO can reduce the risk of cardiac events in patients with established cardiovascular diseases by 31% on top of standard of care, will be available for prescription in the second half of 2023. (Photo: Business Wire)

FDA approves anti-inflammatory drug for patients with established or risk of CVD

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

The FDA has approved colchicine as the first anti-inflammatory drug for the treatment of CVD. Colchicine is indicated to reduce the risk of MI, stroke, coronary revascularization and CV mortality in adult patients with established ASCVD or with multiple CVD risk factors.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is 0.5 mg orally once daily.

If a dose of LODOCO is missed, the missed dose should be taken as soon as possible, and the patient should then return to the normal dosing schedule. If a dose is skipped, the patient should not double the next dose.

Revised: 06/2023

CLEAR-Synergy (NCT03048825)	Colchicine	Broad immunosuppression	Phase III	7,000 patients with MI	MACE	261
CONVINCE (NCT02898610)	Colchicine	Broad immunosuppression	Phase III	2,623 patients with ischaemic stroke or at high risk of transient ischaemic attack	Recurrence of non-fatal ischaemic stroke or non-fatal MACE, or vascular-related death	262

Cochrane Library

Cochrane Database of Systematic Reviews

Colchicine for the primary prevention of cardiovascular events (Protocol)

Martí-Carvajal AJ, De Sanctis JB, Hidalgo R, Martí-Amarista CE, Alegría E, Correa-Pérez A, Monge Martín D, Riera Lizardo RJ

2022

Cochrane Library

Cochrane Database of Systematic Reviews

Colchicine for the secondary prevention of cardiovascular events (Protocol)

Ebrahimi F, Hirt J, Schönenberger C, Ewald H, Briel M, Janiaud P, Hemkens LG

2023

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2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH)

Recommendations of antiplatelet therapy in hypertension

Recommendations and statements	CoR	LoE
Low-dose aspirin is not recommended for primary prevention in patients with hypertension.	III	A
Antiplatelet therapy is recommended for secondary prevention in hypertensive patients.	I	A
Use of a polypill containing low-dose aspirin can be considered in hypertensive patients for secondary prevention.	II	A

Arteriosclerosis, Thrombosis, and Vascular Biology
Volume 42, Issue 10, October 2022; Pages 1207-1216
https://doi.org/10.1161/ATVBAHA.122.318020

SPECIAL ARTICLE

Aspirin for the Primary Prevention of Cardiovascular Disease: Time for a Platelet-Guided Approach

See accompanying editorial on page 1217

April 26, 2022

Aspirin for Primary Prevention—Time to Rethink Our Approach

Jeffrey S. Berger, MD, MS[1]

» Author Affiliations | Article Information

JAMA Netw Open. 2022;5(4):e2210144. doi:10.1001/jamanetworkopen.2022.10144

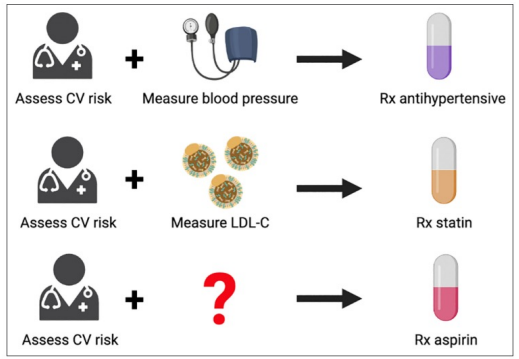
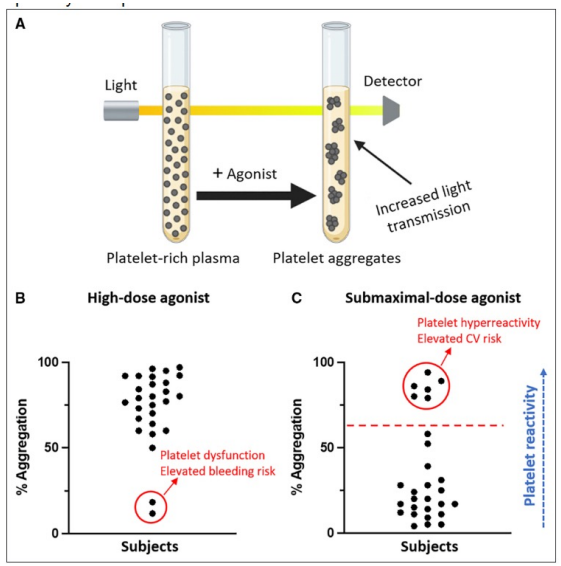
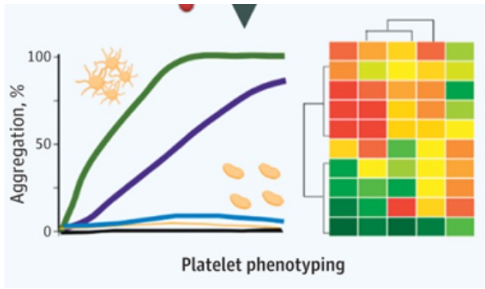
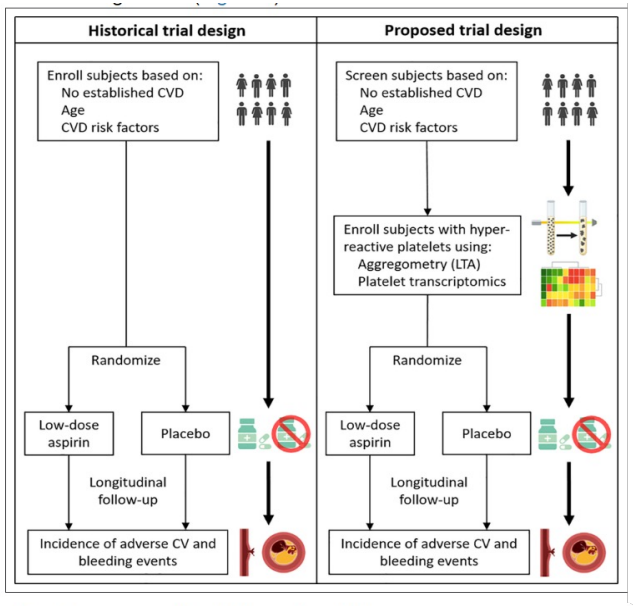


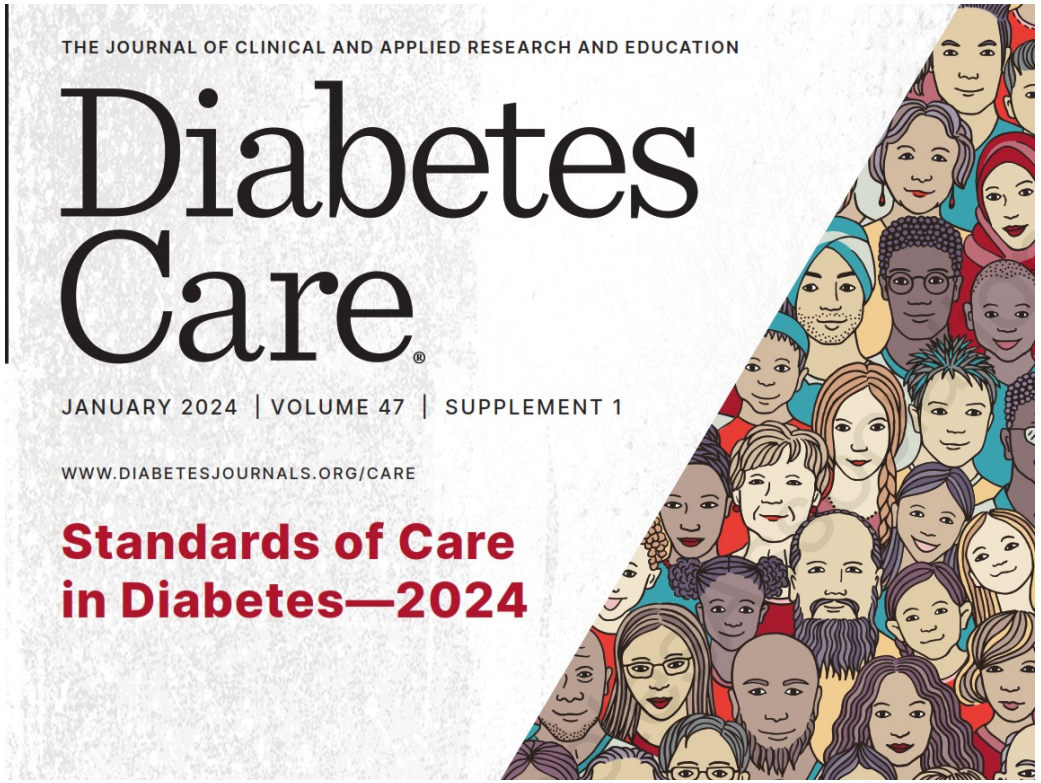
Figure 2. Approaches to pharmacological primary cardiovascular disease prevention.







spirin primary prevention trials: past and future.



ANTIPLATELET AGENTS

Recommendations

10.34 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. **A**

10.37 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the individual on the benefits versus the comparable increased risk of bleeding. **A**

" The main adverse effect is an increased risk of gastrointestinal bleeding ".

.. 50-70 años y otro FRCV
(family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria).

.. > 70 años: NO

Con la evidencia actual (ARRIVE, ASPREE, ASCEND y ADAPTABLE) en prevención primaria:
… el uso de la aspirina en general, puede no recomendarse.

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Summary of European guidelines for aspirin

August 2023

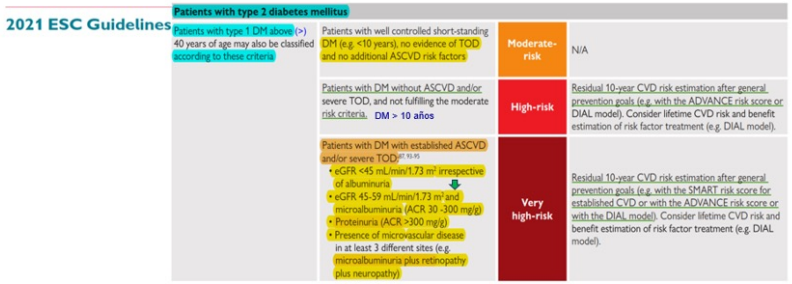
European guidelines make the following recommendations concerning aspirin and VTE prophylaxis:

- We recommend the use of aspirin as an option for venous thromboembolism (VTE) prevention after total hip arthroplasty, total knee arthroplasty and hip fracture surgery (Grade 1B).

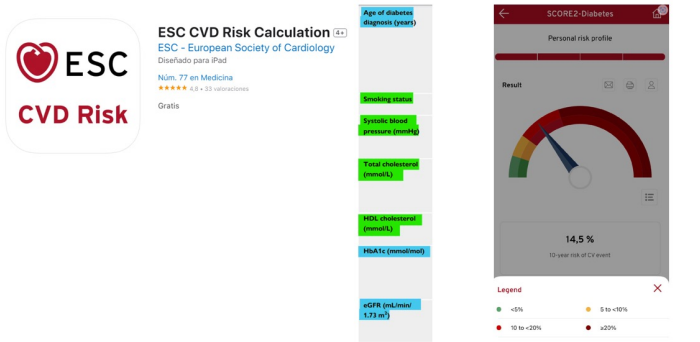
The ESC 2019 guidelines on diabetes (DM), pre-diabetes, and cardiovascular disease state:

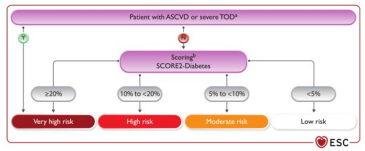
- “Patients with DM and symptomatic CVD should be treated no differently to patients without DM
- In patients with DM at moderate CV risk, aspirin for primary prevention is not recommended
- In patients with DM at high/very high risk, aspirin may be considered in primary prevention

Diabetes mellitus



DM en ESC 2023





Aspirin for the Primary Prevention of CV Events:

ASCEND
Diabetes

ARRIVE Aspirin (100 mg daily) vs placebo...

...in 12,546 adults without diabetes

Men ≥55 years with ≥ 2 CV risk factors

Women ≥60 years with ≥3 CV risk factors

Reduced myocardial infarctions ☑ Yes ☐ No

Reduced stroke risk ☐ Yes ☑ No

Increased risk of bleeding ☑ Yes ☐ No

Conclusions/Limitations:
No significant difference in primary EP (CV death, MI, stroke, UA, TIA). High rates of discontinuation in both arms. Event rate much lower than predicted.

ASCEND Aspirin (100 mg daily) vs placebo...

...in 15,480 patients ≥40 years with diabetes and free of CVD

Reduced risk of serious vascular events ☑ Yes ☐ No

Reduced risk of cancer ☐ Yes ☑ No

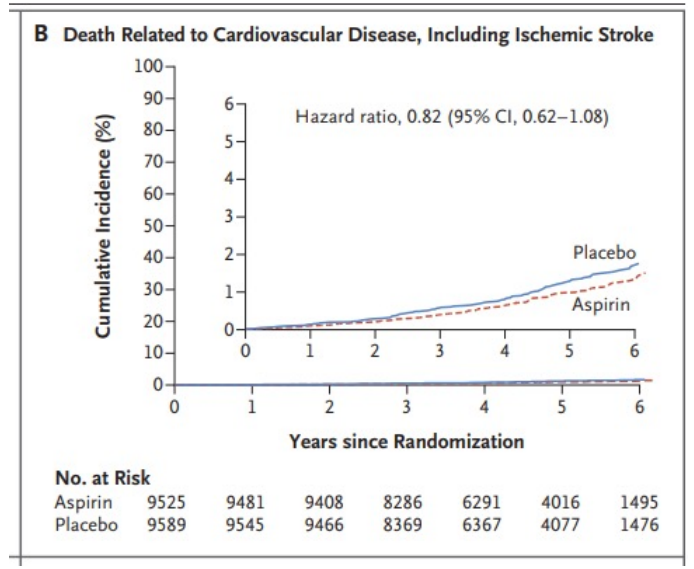
Increased risk of major bleeding ☑ Yes ☐ No

Conclusion:
Primary endpoint (MI, ischemic stroke, TIA, CV death excluding ICH) reduced 12% with aspirin, but counterbalanced by 29% increased risk of bleeding

> 70 años:

ESC
European Society of Cardiology

Not recommend aspirin for healthy people over 70 following results of the ASPREE trial.



70 years of age or older at trial entry

Aspirin Use to Prevent Cardiovascular Disease
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

Adults 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults 60 years or older.	D

N ENGL J MED 379;16 NEJM.ORG OCTOBER 18, 2018

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. 50 - 70 años:

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.. Valorar si alto/ muy alto RCV.

IIb

Aspirin Use to Prevent Cardiovascular Disease
US Preventive Services Task Force Recommendation Statement

Adults aged 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults aged 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.	C

NO PRECISA CALCULAR RCV

Paciente de MUY ALTO RCV