

A tale of two therapies lipid-lowering vs. anti-inflammatory therapy: a false dichotomy?

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The concept of atherosclerotic cardiovascular disease (ASCVD) as a cholesterol storage condition dates back to the 19th century. Beyond cholesterol, local inflammation consisting of accumulation of inflammatory cells (macrophages, T cells, and mast cells), proliferation of collagen-secreting smooth muscle cells with ensuing accumulation of extracellular matrix also contribute to the growth of an atherosclerotic lesion.¹ The lesion may evolve into an advanced atherosclerotic plaque in which cholesterol-filled macrophage foam cells die and contribute to the formation of a necrotic lipid core. Ultimately, the collagenous cap which typically separates the necrotic lipid core from the circulating blood may become thin, thereby rendering the plaque susceptible to rupture and provoking an arterial thrombus.² Non-lipid risk factors such as smoking, hypertension, and diabetes, as well as non-traditional risk factors also contribute to the multifactorial pathogenesis of atherothrombosis.

A large body of evidence supports the role of low-density lipoprotein (LDL) particles in atherogenesis.³ First, inherited variations that lead to a life-long high LDL-cholesterol (LDL-C) level promote atherosclerotic events [e.g. the well-known LDL-receptor defects in familial hypercholesterolaemia among others].³ Second, despite the prevalence of other major risk factors, populations such as Japanese men with very low levels of serum cholesterol have little coronary artery disease (CAD).⁴ Third, populations in some low-income countries may have very low LDL-C levels, and despite a burden of inflammation due to chronic infections, as reflected in high C-reactive protein (CRP) levels, have a low prevalence of ASCVD.⁵ Fourth, individuals with a life-long history of reduced LDL-C levels due to nonsense mutations in the gene encoding the proprotein convertase subtilisin/kexin-type 9 (PCSK9), also have minimal CAD risk even in the presence of multiple other ASCVD risk factors.⁶ Finally, the reduction of ASCVD events with therapeutic lowering of LDL-C has validated the essential role of LDL-C in atherogenesis and its clinical sequelae.³ Low-density lipoprotein thus fulfils modified Koch's postulates for causality.

However, some have construed the more recent interest in inflammation in atherosclerosis, reviving the ideas of Rudolf Virchow from the 19th century, as somehow overshadowing the importance of LDL-C in the pathogenesis of this disease. Indeed, inflammation's contribution to atherosclerosis derived support from the observation that statins exert anti-inflammatory effects on atherosclerotic plaques, and that part of their reduction in atherosclerotic events may derive from muting inflammation independent of LDL-C lowering.⁷ Yet, even sophisticated statistical deconvolution cannot rigorously distinguish the benefits due to direct anti-inflammatory effects of statins from their ability to lower LDL-C.

An analogy from traumatology may inform the debate regarding the relative importance of LDL and inflammation in ASCVD. If a foreign body, like a splinter, intrudes one's skin, a chronic inflammatory reaction ensues, unless the foreign body is removed. The addition of an anti-inflammatory therapy could, in turn, quell the response to the foreign body. In ASCVD, LDL-C lowering can limit the stimulus, similar to removal of a foreign body, and an anti-inflammatory therapy can mute the response to the stimulus. Thus, although lowering LDL-C level has a high priority, in selected patients lipid-lowering and anti-inflammatory treatment in tandem might optimize outcomes. Selection of the mode of the intensification of therapy can depend on indicators of residual risk. For those with LDL concentrations above target despite statin therapy, the addition of ezetimibe or of a PCSK9 inhibitor is most appropriate. For those with residual inflammation (high sensitivity C-reactive protein >2 mg/L) after adequate LDL lowering—an add-on anti-inflammatory therapy might be preferred, a proposition tested formally in the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS).^{8–10}

The CANTOS was a placebo-controlled, randomized trial that used canakinumab—a monoclonal antibody that neutralizes interleukin-1 beta but does not lower LDL-C. Compared with guideline-directed management including strict control of LDL-C, canakinumab reduced ASCVD events in patients with previous myocardial infarction⁸ providing unequivocal trial evidence that a targeted anti-inflammatory drug regimen further reduces ASCVD—despite

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Table 1 Summaries of five trials comparing either anti-inflammation or intensive low-density lipoprotein-cholesterol lowering with placebo^a

	CANTOS⁸ (n = 10,061)	FOURIER¹⁵ (n = 27,564)	LoDoCo2¹² (n = 5522)	COLCOT¹¹ (n = 4745)	ODYSEY¹⁶ (n = 18,924)
Focus of therapy					
Characteristics	Anti-inflammation	Intensive LDL-cholesterol lowering	Anti-inflammation	Anti-inflammation	Intensive LDL-cholesterol lowering
Trial population	History of MI	History of ASCVD	Chronic coronary disease	Recent MI	Recent ACS
Trial length, year	3.7	2.2	2.4	0.4	2.8
Age, year	61	63	66	61	59
Female sex, %	26	25	15	19	25
Current smokers, %	23	28	12	30	24
Body mass index, kg/m ² , or weight, kg	30	85 (mean weight)	NA	28	29
Hypertension, %	79	80	51	51	66
Diabetes, %	40	37	18	20	29
Heart failure, %	22	NR	NA	2	14
Myocardial infarction, %					
History	100	81	84	16	19
Recent	NA	NA	NA	100	83
Statin during trial, %	91	100	94	99	100
LDL-cholesterol, mg/dL	82	92	NA	NA	92
At baseline					
During trial	No change	Decrease by 59%	NA	NA	Decrease by 55%
HDL-cholesterol at baseline, mg/dL	45	44	NA	NA	43
Triglycerides at baseline, mg/dL	139	134	NA	NA	129
High sensitivity C-reactive protein at baseline, mg/L	4.2	NA	NA	4.3 (subgroup)	in 42% > 2 mg/L
During trial	Decrease by 60%	NA	NA	Net decrease by 10.1%	NA
Primary endpoint, hazard ratio (95% confidence interval)	0.85 (0.74–0.98)	0.85 (0.79–0.92)	0.69 (0.57–0.83)	0.77 (0.61–0.96)	0.85 (0.78–0.93)

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NA, data not available.

^aTo convert the values for cholesterol to millimoles per litre, multiply by 0.02586. To convert the values for triglycerides to millimoles per litre, multiply by 0.01129.

concomitant statin treatment. The independent preventive role of an anti-inflammatory drug therapy derived further support from the Colchicine Cardiovascular Outcomes Trial (COLCOT¹¹) in individuals with recent myocardial infarction and low-dose colchicine 2 trial (LoDoCo2¹²) in individuals with chronic stable coronary disease. These two large studies compared low-dose colchicine to placebo, on top of effective statin treatment. However, both the type of anti-inflammatory therapy and patient selection are probably important because treatment with low-dose methotrexate did not prevent ASCVD events in a high-risk patient population with stable CAD in the Cardiovascular Inflammation Reduction Trial (CIRT¹³). Although statins prevent ASCVD events, considerable residual risk often remains. Hence the need for more effective treatments. But, beyond statins, should one intensify LDL-C lowering or add an anti-inflammatory drug, and do these two types of interventions confer similar benefits?

The introduction of the PCSK9 inhibitors evolocumab and alirocicab into the clinic ushered in a new era in LDL lowering. These agents profoundly lower LDL-C, and when added to atorvastatin (80 mg) treatment, they more than halve the LDL-C levels, even below 1 mmol/L (38.6 mg/dL). Proprotein convertase subtilisin/kexin-type 9 has a role in inflammation,¹⁴ but PCSK9-inhibitors do not seem to have clinically relevant anti-inflammatory actions, as reflected by a lack of reductions in CRP. In the FOURIER¹⁵ and ODYSSEY¹⁶ trials, the PCSK9-inhibitors significantly reduced the risk of recurrent ASCVD events. The FOURIER trial and the Studies of PCSK9 Inhibition and the Reduction in Vascular Events (SPIRE) 1 and 2 trials showed that despite receiving both statin therapy and bococizumab (a PCSK9 inhibitor abandoned because of an unanticipated attenuation of LDL-C lowering effect over time) the patients had a residual inflammatory risk, so leaving room for improvement beyond LDL-C lowering.^{11,17}

To compare the effect of more effective LDL-C lowering or anti-inflammation on clinical outcomes, we tabulate here summaries of five trials, three comparing anti-inflammatory drugs^{8,11,12} with placebo and two comparing PCSK9 inhibitors^{15,16} with placebo (Table 1). These trials are all sizable, randomised, double-blind, and placebo-controlled. Participants in all trials received effective statin treatment and the baseline LDL-C levels were similar. Two (ODYSSEY and COLCOT) included patients with a recent CAD event, and three (FOURIER, CANTOS, and LoDoCo2) included stable patients with a history of ASCVD. Atherosclerotic cardiovascular disease risk factors and comorbidities differed, but were comparable between the populations having either chronic ASCVD or more recent qualifying events. The trials all showed significant treatment effects on the hazard ratio of the primary endpoint, although COLCOT was substantially shorter than the other trials.

These recent trials provide evidence that two apparently competing hypotheses of the pathogenesis of atherosclerosis—lipids or inflammation—actually operate in tandem. Low-density lipoprotein-lowering vs. targeting inflammation presents a false dichotomy. However, it is worth noting that in CANTOS average LDL-C level remained at 82 mg/dL (2.12 mmol/L) while in PCSK9 inhibitor trials LDL-C level was much lower at end of the trial [e.g. in FOURIER, median LDL was 30 mg/dL (0.78 mmol/L)¹⁵]. In practice, therefore,

although not yet evidence based, before considering the addition of an anti-inflammatory drug, LDL-C might be reduced to a level below 55 mg/dL (1.42 mmol/L), the new target for very high-risk patients in the ESC guidelines.¹⁸

What does the future hold and what is needed to further optimize the treatment of ASCVD? Detailed presentation of the myriad of novel treatment options currently being under investigation (e.g. gene and stem cell therapy, mechanical replacements, anti-ageing drugs) exceeds the scope of this short opinion paper. Because current treatments for ASCVD usually commence late in life when atherogenesis has already advanced, one approach merits consideration and testing: start treatments earlier, more effectively, and secure adherence for individuals with high future risk during the subclinical stage of atherosclerosis including risk determined by polygenic risk scores that may provide a crystal ball into future propensity for events.¹⁹ New treatment options of dyslipidaemia and inflammation in ASCVD prevention may help in this regard.^{9,20} The introduction of bempedoic acid (an ATP citrate lyase inhibitor) adds to the armamentarium of non-statin LDL-C lowering agents. The availability of inclisiran (an siRNA that limits the production of PCSK9) provides a remarkable duration of action and could be administered twice or even once a year.

Large-scale clinical trials are examining the abilities of the above novel LDL-C lowering therapies on cardiovascular outcomes. An antisense RNA therapeutic currently investigated in a sizeable outcome trial targets lipoprotein (a), a particularly atherothrombotic LDL variant. Beyond LDL, a cardiovascular endpoint study is evaluating a novel selective peroxisome proliferation activation receptor alpha modulator in individuals with high triglycerides and low HDL-C levels. REDUCE-IT revealed that prescription-grade eicosapentaenoic acid can substantially reduce events in individuals with hypertriglyceridaemia. Some, but probably not all of this benefit results from the lowering of triglycerides, and some may actually accrue from an anti-inflammatory action. Also, development and testing of new therapies targeting proinflammatory cytokines or blocking their activation by NLRP3 inflammasome inhibitors merit testing.

We conclude that in reality the lipid-lowering and anti-inflammatory therapies do not compete. Both approaches, when appropriately targeted according to the entry criteria of the rich portfolio of recent trials, have a place in the ongoing battle against the residual risk of atherosclerosis. There is no contest between the two approaches; there are only winners: our patients and public health.

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References

- Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011;**473**:317–325.
- Libby P. Editorial commentary: arson in the artery: who set the atheroma aflame? *Trends Cardiovasc Med* 2019;**29**:473–475.
- Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen M-R, Tokgözoğlu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;**38**:2459–2472.
- Keys A, ed. *Seven Countries*. Cambridge, MA: Harvard University Press; 1980. p1–381.
- Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, Frohlich B, Sutherland ML, Sutherland JD, Stieglitz J, Rodriguez DE, Michalik DE, Rowan CJ, Lombardi GP, Bedi R, Garcia AR, Min JK, Narula J, Finch CE, Gurven M, Thomas GS. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet* 2017;**389**:1730–1739.
- Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;**354**:1264–1272.
- Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;**352**:20–28.
- Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kotalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–1131.
- Pradhan AD, Aday AW, Rose LM, Ridker PM. Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. *Circulation* 2018;**138**:141–149.
- Ridker PM, MacFadyen JG, Thuren T, Libby P. Residual inflammatory risk associated with interleukin-18 and interleukin-6 after successful interleukin-1 β inhibition with canakinumab: further rationale for the development of targeted anti-cytokine therapies for the treatment of atherothrombosis. *Eur Heart J* 2020;**41**:2153–2163.
- Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie M-A, Dubé M-P, Rhoads D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin M-C, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;**381**:2497–2505.
- Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, for the LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary. *N Engl J Med* 2020;doi:10.1056/NEJMoa2021372.
- Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP, Glynn RJ. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;**380**:752–762.
- Ding Z, Pothineni NVK, Goel A, Lüscher TF, Mehta JL. PCSK9 and inflammation: role of shear stress, pro-inflammatory cytokines, and LOX-1. *Cardiovasc Res* 2020;**116**:908–915.
- Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–1722.
- Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby J-F, Tricoci P, White HD, Zeiher AM, ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–2107.
- Bohula E A, Giugliano R P, Leiter L A, Verma S, Park J-G, Sever P S, Lira Pineda A, Honarpour N, Wang H, Murphy S A, Keech A, Pedersen T R, Sabatine M S. Inflammatory and Cholesterol Risk in the FOURIER Trial. *Circulation* 2018;**138**:131–140. doi:10.1161/CIRCULATIONAHA.118.034032
- Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglul L, Wiklund O, ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
- Natarajan P, Aragam K. Polygenic scores to assess atherosclerotic cardiovascular disease risk. Clinical perspectives and basic implications. *Circ Res* 2020;doi:10.1161/CIRCRESAHA.120.315928.
- Ray KK, Corral P, Morales E, Nicholls SJ. Pharmacological lipid-modification therapies for prevention of ischaemic heart disease: current and future options. *Lancet* 2019;**394**:697–708.