

discussed in the article and noted by the correspondents, this finding was contrasted to the absence of any imbalance in cardiovascular events in the larger placebo-controlled FRAME. These contrasting results have raised questions about the possible cardioprotective effect of alendronate or particular characteristics of the patients in our trial that may have made them more susceptible to cardiovascular events. We agree with Song and Lee that further investigation of this finding is warranted. We agree that osteoporosis treatment is generally intended to be long-term, but because of its time-limited bone-forming effect, romosozumab has been studied as a 1-year course of treatment and is not intended for continuous long-term use. As is good standard practice with all drugs, the benefits and potential risks of the product will have to be carefully assessed in order to make treatment decisions for individual patients.

Both the Prince and Hofbauer groups highlight the role of DKK1 on the vasculature and suggest further investigations to better understand the cardiovascular risk status of the patients in our trial. We have considered examining available spine images for aortic calcification in our trial. Although there is evidence of an association between aortic calcification and the risk of cardiac events in cross-sectional studies,¹ changes in aortic calcification during a time-limited pharmacologic intervention have not been shown to be predictive of a change in the risk of cardiovascular events.² As suggested by Hofbauer's

group, we measured DKK1 in response to romosozumab in ovariectomized cynomolgus monkeys³ but found no significant change, which appears to be consistent with earlier findings in a rat model of progressive renal osteodystrophy in which there also was no significant change in DKK1 levels in response to sclerostin antibody treatment.⁴ Thus, there is limited biologic plausibility to pursue this association further in humans.

Kenneth G. Saag, M.D.

University of Alabama
Birmingham, AL
ksaag@uab.edu

Jeffrey Petersen, M.D.

Andreas Grauer, M.D.

Amgen
Thousand Oaks, CA

Since publication of their article, the authors report no further potential conflict of interest.

1. Wilson PW, Kauppila LI, O'Donnell CJ, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation* 2001;103:1529-34.
2. Samelson EJ, Miller PD, Christiansen C, et al. RANKL inhibition with denosumab does not influence 3-year progression of aortic calcification or incidence of adverse cardiovascular events in postmenopausal women with osteoporosis and high cardiovascular risk. *J Bone Miner Res* 2014;29:450-7.
3. Ominsky MS, Boyd SK, Varela A, et al. Romosozumab improves bone mass and strength while maintaining bone quality in ovariectomized cynomolgus monkeys. *J Bone Miner Res* 2017; 32:788-801.
4. Moe SM, Chen NX, Newman CL, et al. Anti-sclerostin antibody treatment in a rat model of progressive renal osteodystrophy. *J Bone Miner Res* 2015;30:499-509.

DOI: 10.1056/NEJMc1714810

Canakinumab for Atherosclerotic Disease

TO THE EDITOR: Ridker et al. (Sept. 21 issue)¹ found in the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) that reduced inflammation was associated with reduced cardiovascular risk. Unfortunately, the opportunity to identify the precise point of action of canakinumab has not been exploited in this trial.

¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a validated molecular imaging technique that is widely used to non-invasively quantify plaque inflammation during treatment with therapeutic agents targeted at

reducing atherosclerotic inflammation.² Inflammatory activity that is detected by PET positively correlates with intraplaque macrophage infiltration.³ This trial could have used PET to verify that the observed reduction in the surrogate marker high-sensitivity C-reactive protein indeed correlates with reductions in plaque inflammation or that this effect can be primarily attributed to modification of extraarterial immunity,² as described for canakinumab.⁴ PET could have also been used to elucidate the systemic effects of targeting the interleukin-1 β innate immunity

pathway — for example, by assessment of the metabolic state of lymphoid organs and hematopoietic tissue.⁵ Finally, PET could have been used to identify the patients with marked plaque inflammation who will benefit most from this expensive therapeutic approach.

Thorsten Derlin, M.D.
Frank M. Bengel, M.D.

Hannover Medical School
Hannover, Germany
derlin.thorsten@mh-hannover.de

No potential conflict of interest relevant to this letter was reported.

1. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119-31.
2. Subramanian S, Emami H, Vucic E, et al. High-dose atorvastatin reduces periodontal inflammation: a novel pleiotropic effect of statins. *J Am Coll Cardiol* 2013;62:2382-91.
3. Rudd JH, Myers KS, Bansilal S, et al. (18)Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials. *J Am Coll Cardiol* 2007;50:892-6.
4. Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367:2396-406.
5. Emami H, Singh P, MacNabb M, et al. Splenic metabolic activity predicts risk of future cardiovascular events: demonstration of a cardiopleenic axis in humans. *JACC Cardiovasc Imaging* 2015;8:121-30.

DOI: 10.1056/NEJMc1714635

TO THE EDITOR: CANTOS showed that interleukin-1 β inhibition confers a significantly reduced risk of recurrent myocardial infarction. This finding implies that immune-mediated inflammatory diseases, including psoriasis, rheumatoid arthritis, and inflammatory bowel disease, are indeed independent risk factors for incident cardiovascular disease. Beneficial effects of antiinflammatory treatment on the progression of cardiovascular disease and on cardiovascular events have previously been shown among patients with psoriasis in registry-based and cardiovascular imaging studies.^{1,2} For clinicians treating inflammation-driven diseases, CANTOS provides arguments for tight disease control through early and aggressive dampening of systemic inflammation to prevent premature development of cardiovascular disease.³ Although the upstream inhibition of the proinflammatory cascade with canakinumab, in combination with potential safety aspects of interleukin-1 inhibition, could make this particular cytokine target problematic

for primary and secondary prevention of cardiovascular disease, the early indications from CANTOS may lead to a radical shift in the management of immunoinflammatory diseases across a wide range of medical specialties.

Kasper F. Hjulter, M.D., Ph.D.

Aarhus University Hospital
Aarhus, Denmark
kasperd@rm.dk

Alexander Egeberg, M.D., Ph.D.

Herlev and Gentofte Hospital
Hellerup, Denmark

Dr. Hjulter reports receiving research funding and consulting fees from AbbVie, lecture fees from AbbVie, Eli Lilly, LEO Pharma, and Novartis, and travel grants from AbbVie, LEO Pharma, and Novartis; and Dr. Egeberg, receiving research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation, and the Kongelig Hofbundtmager Aage Bang Foundation, consulting fees from LEO Pharma, Samsung Bioepis, Pfizer, Eli Lilly, and Janssen Pharmaceuticals, and speaking fees from Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals. No other potential conflict of interest relevant to this letter was reported.

1. Hjulter KF, Böttcher M, Vestergaard C, Bøtker HE, Iversen L, Kragballe K. Association between changes in coronary artery disease progression and treatment with biologic agents for severe psoriasis. *JAMA Dermatol* 2016;152:1114-21.
2. Wu JJ, Guérin A, Sundaram M, Dea K, Cloutier M, Mulani P. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor- α inhibitors versus methotrexate. *J Am Acad Dermatol* 2017;76:81-90.
3. Egeberg A, Skov L, Joshi AA, et al. The relationship between duration of psoriasis, vascular inflammation, and cardiovascular events. *J Am Acad Dermatol* 2017;77(4):650-656.e3.

DOI: 10.1056/NEJMc1714635

TO THE EDITOR: CANTOS showed that inhibition of interleukin-1 β reduced high-sensitivity C-reactive protein levels and improved clinical outcomes in patients with stable coronary artery disease, indicating that high-sensitivity C-reactive protein is a biomarker of cardiovascular risk and that interleukin-1 β is a driver of vascular inflammation. The hazard ratios for the primary end point were 0.93 in the group that received the 50-mg dose of canakinumab, 0.85 in the 150-mg group, and 0.86 in the 300-mg group, but were 0.90, 0.83, and 0.79, respectively, among adherent patients.

The MRC-ILA Heart Study¹ showed effective suppression of high-sensitivity C-reactive protein in non-ST-segment elevation acute coronary syndromes after 14 days of treatment with an interleukin-1 receptor antagonist. However, after

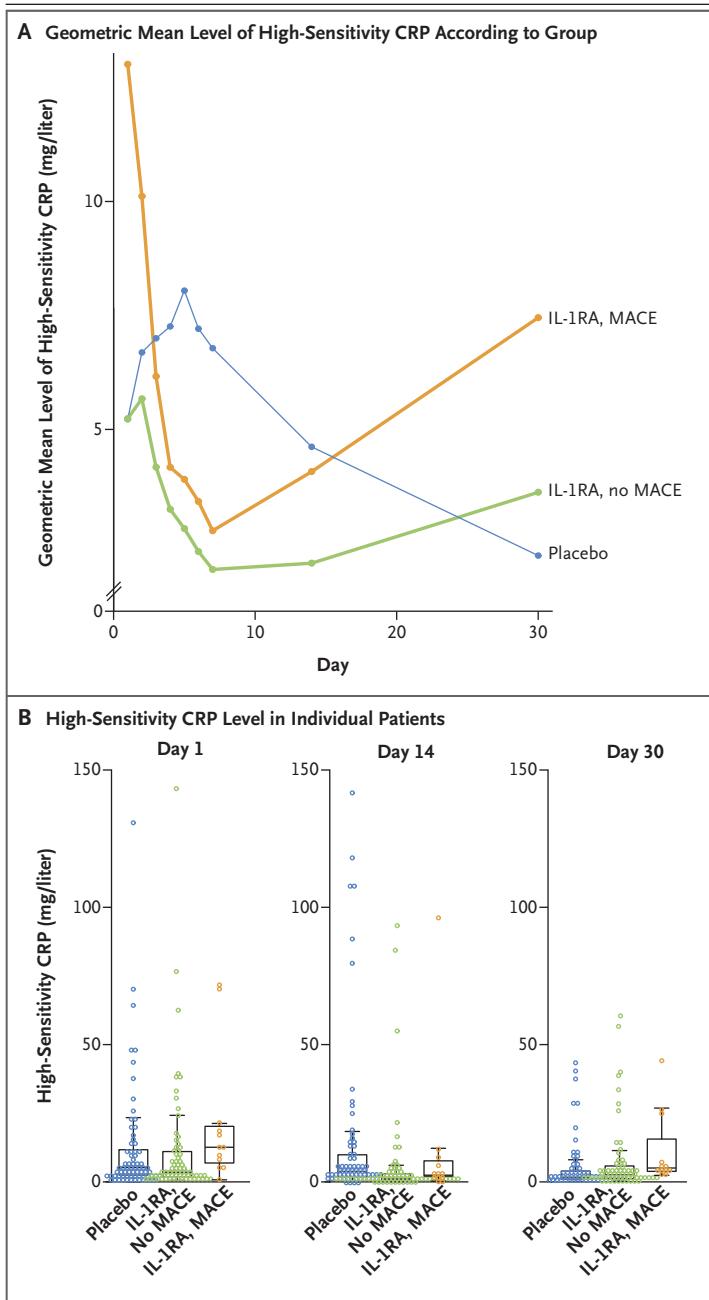


Figure 1. High-Sensitivity C-Reactive Protein (CRP) Levels in Patients with Non–ST-Segment Elevation Acute Coronary Syndromes.

Panel A shows the geometric mean level of high-sensitivity CRP according to group at days 1 through 7, 14, and 30. Patients who received an interleukin-1 receptor antagonist (IL-1RA) for 14 days had lower levels of high-sensitivity CRP at day 14 than those who had received placebo. However, at day 30 (16 days after the intervention period), those who had received IL-1RA had higher levels of high-sensitivity CRP than those who had received placebo. Among patients who received IL-1RA, those who had major adverse cardiac events (MACE) had higher levels of high-sensitivity CRP at days 1, 14, and 30 than those who did not have MACE. Panel B shows the high-sensitivity CRP level in individual patients (circles) at days 1, 14, and 30. In the box plots, the horizontal line inside the box indicates the median, the top and bottom of the box indicate the interquartile range, and the I bars indicate the 5th and 95th percentiles.

protein at day 1 (baseline), day 14 (end of treatment), and day 30 than those who did not have major adverse cardiac events (Fig. 1). Clinical and biologic data from nonadherent patients in CANTOS would be informative when physicians consider withdrawal from therapies that target interleukin-1.

Alexander M.K. Rothman, M.D., Ph.D.

University of Sheffield
Sheffield, United Kingdom

Allison C. Morton, M.D., Ph.D.

HeartCare Western Australia
Bunbury, WA, Australia

David C. Crossman, M.D.

University of St. Andrews
Fife, United Kingdom
dcc7@st-andrews.ac.uk

for the MRC-ILA Heart investigators

No potential conflict of interest relevant to this letter was reported.

discontinuation of the agent, these patients had a higher level of high-sensitivity C-reactive protein at day 30 than patients who had received placebo and a higher rate of major adverse cardiac events at 1 year. Unpublished data from the MRC-ILA Heart Study show that among patients who received the interleukin-1 receptor antagonist, those who had major adverse cardiac events had higher levels of high-sensitivity C-reactive

1. Morton AC, Rothman AMK, Greenwood JP, et al. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *Eur Heart J* 2015;36:377-84.

DOI: 10.1056/NEJMc1714635

TO THE EDITOR: In CANTOS, blocking interleukin-1 β reduced the incidence of atherothrombosis and nonfatal stroke, and an additional analysis

showed that patients who received the 300-mg dose of canakinumab had a total cancer mortality that was lower by 51% than those who received placebo and a lung-cancer mortality that was lower by 77%.¹ The incidence of fatal infection was nearly twice as high in the pooled canakinumab groups as in the placebo group, a finding similar to that observed with the interleukin-1 receptor antagonist anakinra.² The accompanying editorial by Harrington³ discussed the safety risk of interleukin-1 β blockade.

Interleukin-1 β is driven by multiple inflammasomes. As an alternative to inhibition of interleukin-1 β , precise inhibition of a single inflammasome, NLRP3, is likely to be safer. NLRP3 is implicated in diseases of aging, such as atherosclerosis and neurodegenerative disorders. Selective NLRP3 inhibition will leave other inflammasomes to respond to infection. In addition, at the onset of severe infection, an orally available small molecule could be withdrawn, whereas canakinumab cannot. NLRP3 activation also drives interleukin-18, the clinical targeting of which is also safe.⁴

CANTOS has advanced our understanding of the clinical relevance of interleukin-1 β and the NLRP3 inflammasome. This trial will drive the development and commercialization of an entirely new class of drugs.

Luke A. O'Neill, Ph.D., F.R.S.

Trinity College Dublin
Dublin, Ireland
laoneill@tcd.ie

Matthew A. Cooper, Ph.D.

University of Queensland
Brisbane, QLD, Australia

Dr. O'Neill reports being the co-founder, the chief scientific officer, and a shareholder of Inflazome, which is developing drugs that target inflammasomes; and Dr. Cooper, being the co-founder, the chief executive officer, and a shareholder of Inflazome. No other potential conflict of interest relevant to this letter was reported.

1. Ridker PM, MacFadyen JG, Thuren T, et al. Effect of interleukin-1 β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:1833-42.

2. Cabral VP, Andrade CA, Passos SR, Martins MF, Hkerberg YH. Severe infection in patients with rheumatoid arthritis taking anakinra, rituximab, or abatacept: a systematic review of observational studies. *Rev Bras Reumatol Engl Ed* 2016;56:543-50.

3. Harrington RA. Targeting inflammation in coronary artery disease. *N Engl J Med* 2017;377:1197-8.

4. McKie EA, Reid JL, Mistry PC, et al. A study to investigate the efficacy and safety of an anti-interleukin-18 monoclonal antibody in the treatment of type 2 diabetes mellitus. *PLoS One* 2016;11(3):e0150018.

DOI: 10.1056/NEJMc1714635

TO THE EDITOR: The trial by Ridker et al. examined canakinumab in a cohort of patients with established coronary artery disease. Although the reduction in cardiovascular events was significant (hazard ratio, 0.85), the disconcerting results included an increased risk of fatal infection and no mortality benefit. In addition, the drug is expensive (\$200,000 per year). The accompanying editorial calls for alternative, more cost-effective antiinflammatory agents without the associated risk of fatal infection.

In a prospective, randomized, secondary-prevention trial, colchicine, an ancient¹ but inexpensive antiinflammatory drug with pleiotropic effects including the targeting of neutrophils, resulted in a reduced rate of recurrent cardiovascular events (hazard ratio, 0.29) without an increase in fatal infection.² In light of this finding, it is surprising that this agent was not acknowledged by the authors, because at face value, it seems to fulfill the requirements suggested in the editorial. Although studies of colchicine thus far have been predominantly investigator-initiated and smaller in size, it is to be hoped that ongoing research will confirm the initial promising results with this drug.

Nitesh Nerlekar, M.B., B.S., M.P.H.

Richard W. Harper, M.B., B.S.

Monash University
Melbourne, VIC, Australia
nitesh.nerlekar@monash.edu

No potential conflict of interest relevant to this letter was reported.

1. Nerlekar N, Beale A, Harper RW. Colchicine — a short history of an ancient drug. *Med J Aust* 2014;201:687-8.

2. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;61:404-10.

DOI: 10.1056/NEJMc1714635

THE EDITORIALIST REPLIES: O'Neill and Cooper as well as Nerlekar and Harper provide commentary on the recent report on CANTOS and the accompanying editorial. Both letters point to the observation of an increased risk of serious

or fatal infections in the trial and note that perhaps alternative antiinflammatory agents might provide the clinical cardiovascular benefit observed with canakinumab but with a better safety profile. O'Neill and Cooper present the hypothesis that a more specific inhibitor of interleukin-1 β , perhaps through inhibition of NLRP3, might prove safer than canakinumab. Certainly, this is a reasonable concept to consider for future investigation.

Nerlekar and Harper express surprise that colchicine was not mentioned in my editorial as an antiinflammatory agent worthy of further investigation, given the findings from a small study (involving 532 patients) that suggested a possible clinical cardiovascular benefit from colchicine among patients with stable coronary artery disease.¹ This trial also showed that 11% of the patients who received colchicine discontinued the treatment in the first 30 days owing to gastrointestinal intolerance. A better understanding of the balance between risks and benefits requires a much larger clinical trial, powered appropriately for the clinical cardiovascular outcomes and with sufficient monitoring for an assessment of safety.

A recent Cochrane meta-analysis on colchicine in heart disease concluded that there was uncertainty regarding its risks and benefits in patients with heart disease but that it was worthy of further investigation.² This seems to be a reasonable conclusion. My editorial noted that "CANTOS has helped move the inflammatory hypothesis of coronary artery disease forward scientifically." Further investigation with alternative antiinflammatory agents that conserve or even accentuate the cardiovascular benefits of canakinumab while improving on its safety and cost characteristics would be welcomed.

Robert A. Harrington, M.D.

Stanford University
Stanford, CA

Since publication of his editorial, the author reports no further potential conflict of interest.

1. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;61:404-10.

2. Hemkens LG, Ewald H, Gloy VL, et al. Effects and safety of long-term use of colchicine on heart disease. London: Cochrane Collaboration, January 27, 2016 (http://www.cochrane.org/CD011047/VASC_effects-and-safety-long-term-use-colchicine-heart-disease).

DOI: 10.1056/NEJMc1714635

Oxygen Therapy in Suspected Acute Myocardial Infarction

TO THE EDITOR: Hofmann et al. (Sept. 28 issue)¹ found that oxygen supplementation in patients with suspected myocardial infarction who did not have hypoxemia at baseline did not affect 1-year mortality or the incidence of rehospitalization after 30 days. The trial outcome measures did not include any related to neurologic function or quality of life, despite the fact that cognitive deficits and functional disability often occur after myocardial infarction.²

It is unknown whether myocardial infarction, particularly in patients who have chronic hypertension or who are elderly, compromises cerebral perfusion at values that would be considered normotensive in most patients, because monitoring of brain-tissue oxygenation has not been performed in patients with normal oxygen levels during myocardial infarction. Cerebral hypoxia can occur in the absence of peripheral hypoxemia in

particular clinical scenarios.^{3,4} The DETO2X-AMI (Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction) trial was conducted predominantly in Swedes, whose vulnerability to cerebral hypoperfusion may differ from that of other ethnic groups, potentially limiting generalizability. Post hoc analysis of neurologic function in DETO2X-AMI participants, or a sufficiently powered subgroup of them, could be performed to determine whether oxygen supplementation decreases the risk of neurologic compromise in myocardial infarction.

Uzma Samadani, M.D., Ph.D.

Clementine K. Affana, M.D.

Hennepin County Medical Center
Minneapolis, MN
uzma@samadani.com

Dr. Samadani reports receiving lecture fees from the North American Brain Injury Society, the National Neurotrauma Soci-