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JACC FOCUS SEMINAR: FUTURES OF CARDIOLOGY

JACC REVIEW TOPIC OF THE WEEK

Clinician's Guide to Reducing Inflammation to Reduce Atherothrombotic Risk

JACC Review Topic of the Week

Paul M Ridker, MD, MPH

ABSTRACT

Life-threatening cardiovascular events occur despite control of conventional risk factors. Inflammation, as measured by high-sensitivity C-reactive protein (hsCRP) concentration, is associated with future vascular events in both primary and secondary prevention, independent of usual risk markers. Statins are powerful lipid-lowering agents with clinically relevant anti-inflammatory effects. Recent data support targeting the interleukin (IL)-1-to-IL-6-to-CRP signaling pathway as an adjunctive method for atheroprotection. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial showed that reducing inflammation through IL-1β inhibition significantly reduced vascular risk, beyond that achievable with lipid lowering. CANTOS further demonstrated a 31% reduction in cardiovascular mortality and all-cause mortality among patients treated with canakinumab who achieved the largest reductions in hsCRP, as well as efficacy in high-risk patients with chronic kidney disease and diabetes. This review outlines the clinical implications of CANTOS for patients with "residual inflammatory risk," the potential benefits and risks associated with anti-inflammatory therapy, and the importance of CANTOS for future drug development. (J Am Coll Cardiol 2018;72:3320–31)

Smoking cessation, exercise, dietary discretion, blood pressure control, and aggressive reduction of low-density lipoprotein cholesterol (LDLC) are critical interventions in preventive cardiology; yet many patients experience life-threatening first and recurrent cardiovascular events despite control of conventional risk factors. Epidemiologic data from the mid 1990s indicated that inflammation, as measured either by high-sensitivity C-reactive protein (hsCRP) or interleukin (IL)-6, was strongly associated with future vascular events in both primary and secondary prevention, independent of usual risk markers (1-4). Immediately thereafter, statins were proven to be powerful lipid-lowering agents with clinically relevant anti-inflammatory effects (5,6).

Modern vascular biology now posits that both the innate and adaptive immune systems contribute importantly to the development and progression of atherothrombosis, along with lipid accumulation within plaque. Together, these findings implicate the IL-1-to-IL-6-to-CRP signaling pathway as at least 1 major target for vascular protection (7-9). The recent 10,000-patient CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) provides proof-of-principle in humans that reducing inflammation through IL-1β inhibition reduces vascular risk in the absence of any lipid-lowering effects (10). CANTOS has further demonstrated large and statistically significant reductions in cardiovascular and all-cause mortality among patients treated

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From the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, Massachusetts. Dr. Ridker has received research support for CANTOS from Novartis; has consulted for Novartis, Pfizer, Inflazome, and Corvidia; and holds patents assigned to Brigham and Women's Hospital, licensed to AstraZeneca and Siemens.

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with canakinumab who achieved the largest reductions in IL-6 or hsCRP, as well as efficacy in high-risk groups such as those with chronic kidney disease and diabetes.

This review describes the clinical implications of CANTOS for patients with "residual inflammatory risk," the potential benefits and risks associated with canakinumab, and the implications of CANTOS for the development of new anti-inflammatory agents which may serve as adjuncts to lipid-lowering therapy.

RESIDUAL RISK: WHY MEASURE BOTH LDLC AND hsCRP IN PATIENTS WITH KNOWN ATHEROSCLEROSIS?

In primary prevention, evaluation of the inflammatory biomarker hsCRP adds prognostic information to conventional measurements of cardiovascular risk with a magnitude of effect comparable to that of LDL or high-density lipoprotein cholesterol (HDLC) (**Figure 1A**) (11,12). Initial observations from the Physicians Health Study in 1997 (3) and the Women's Health Study in 2000 (13) indicated that hsCRP independently predicted future heart attacks, stroke, and cardiovascular death among apparently healthy individuals, data extending the observations made in unstable angina (2,4). These data have since been confirmed in >30 prospective epidemiologic cohorts worldwide. Current prevention guidelines suggest that use of hsCRP is most appropriate when clinical decisions to initiate statin therapy are uncertain (14). This recommendation is based largely on data from the 2008 JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) trial in which 20 g of rosuvastatin daily, compared to placebo, was found to reduce the rate of first myocardial infarction, stroke, or cardiovascular death by 47% when administered to patients with LDLC <130 mg/dl and hsCRP >2 mg/l (hazard ratio [HR]: 0.53; 95% confidence interval [CI]: 0.40 to 0.69; $p < 0.00001$) (15). Comparable data demonstrating the clinical relevance of reduced hsCRP after lipid lowering have been presented from the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy), A to Z (Aggrastat to Zocor), REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering), and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trials (16–19). Many preventive cardiologists additionally screen for hsCRP in primary prevention as a method of conveying risk and encouraging lifestyle changes related to diet, exercise, and smoking cessation (20,21). Contrary to common misperceptions, hsCRP levels are stable over time as long as they are not measured during acute infection. Among 8,901 patients followed over 4 years, variability and tracking results of hsCRP levels over time were virtually identical to those of LDLC and superior to those of blood pressure (22) (**Figures 1B and 1C**).

As also demonstrated in multiple cohorts, hsCRP predicts recurrent vascular events with at least as much fidelity as first events. hsCRP provides clinically relevant prognostic information for those with acute coronary ischemia, stable atherosclerosis, in the immediate post-angioplasty setting, following coronary artery bypass surgery, and in the setting of renal failure where LDLC no longer has predictive utility (23–26). Despite this evidence, screening for inflammation in secondary prevention has remained infrequent. This conservative approach partially reflects the fact that, at least until recently, no data were available proving that reducing hsCRP in the absence of lipid lowering would reduce rates of recurrent cardiovascular events.

This situation fundamentally changed with publication of the CANTOS trial (10). This multinational trial has proven that inflammation reduction in humans, at least by targeting IL-1β, significantly reduces vascular event rates in proportion to the magnitude of hsCRP reduction achieved and in the absence of any effects on atherogenic lipids. It is, thus, no longer appropriate to use the term "residual risk" to describe the high rate of recurrent cardiovascular events among those who experienced prior myocardial infarction. Rather, to provide best care, clinicians must now distinguish between patients with "residual cholesterol risk" and those with "residual inflammatory risk" (27).

In the first instance of "residual cholesterol risk" (such as when LDLC remains >100 mg/dl despite aggressive statin therapy), trial evidence indicates that ezetimibe and PCSK9 inhibitors can further lower vascular event rates by 6% to 15%, respectively (28–30); yet, the LDLC-lowering effects of PCSK9 inhibition vary widely for individual patients. Thus, one strategy for clinicians to consider for "residual cholesterol risk" is to give a short course of PCSK9 inhibition and then continue long-term treatment only among those who achieved large additional reductions in LDLC. This is a thoughtful approach, as the utility of PCSK9 inhibition among those with only a small adjunctive LDLC response is unlikely to justify costs.

In the second instance, "residual inflammatory risk," for example, when LDLC is already near 70 mg/dl after statin therapy, attention should turn to

ABBREVIATIONS AND ACRONYMS

HDLC = high-density lipoprotein cholesterol

hsCRP = high-sensitivity C-reactive protein

IL = interleukin

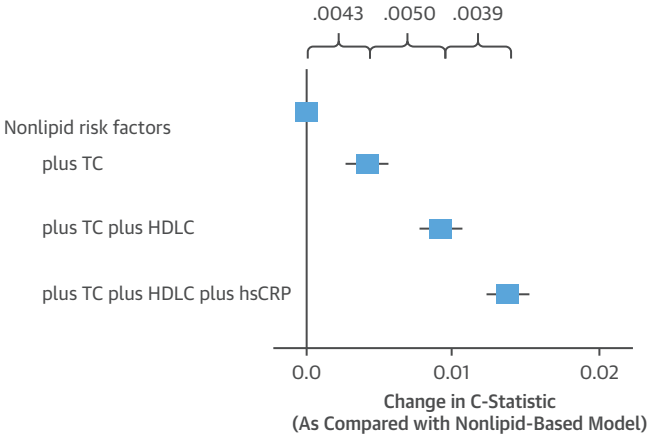
LDLC = low-density lipoprotein cholesterol

NLRP3 = NOD-like pyrin-containing 3 inflammasome

PCSK9 = proprotein convertase subtilisin/kexin type 9

FIGURE 1 Clinical Utility of Risk Prediction and Stability Over Time of hsCRP Are Virtually Identical to Those of LDLC

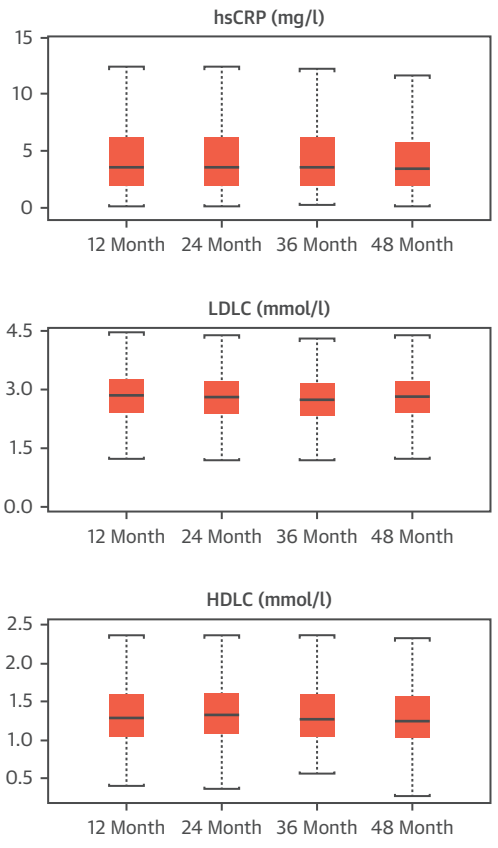
A



B

Variable	Intra-Class Correlation	95% CI
hsCRP	0.54	0.53-0.55
LDLC	0.57	0.56-0.58
BP (systolic)	0.49	0.43-0.54
BP (diastolic)	0.41	0.38-0.43

C



(A) The change in C-statistic for risk prediction models incrementally including hsCRP is virtually identical to that of models incrementally including total and HDLC. Data from Kaptoge et al. (11). **(B, C)** Intraclass correlations and stability tracking over time in 8,901 patients with repeated measurements of hsCRP, LDLC, HDLC, and BP over a 4-year period. Data from Glynn et al. (22). BP = blood pressure; HDLC = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDLC = low-density lipoprotein cholesterol; TC = total cholesterol.

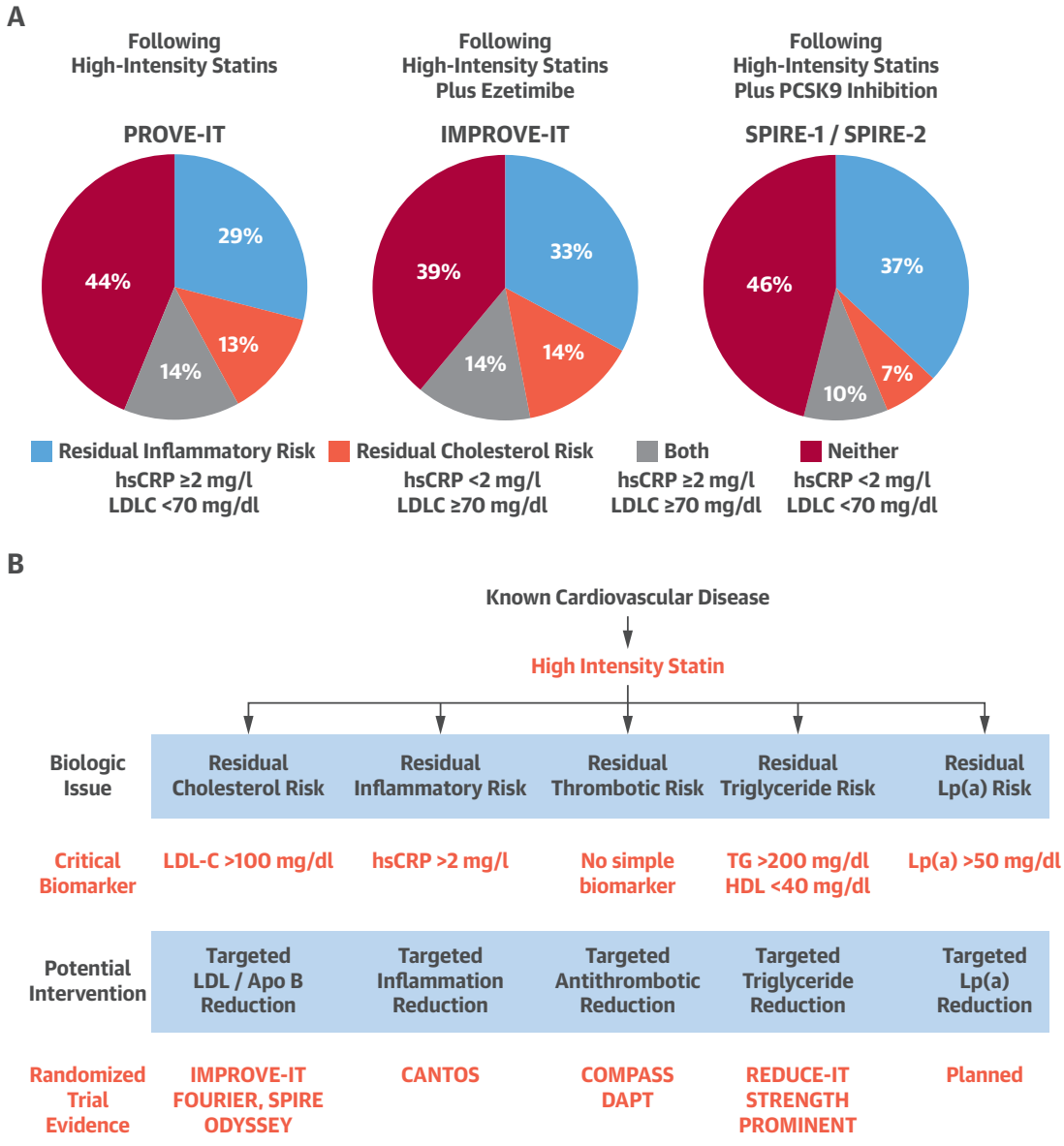
inflammation rather than hyperlipidemia as a potential biological process driving recurrent events. For patients with "residual inflammatory risk," defined as an hsCRP concentration remaining >2 mg/l despite aggressive LDLC lowering, recurrent event rates are high. Although it is often under-diagnosed by clinicians who do evaluate hsCRP in secondary prevention, high-risk patients with "residual inflammatory risk" are common; in the PROVE IT and IMPROVE-IT trials, one-third of all patients had post-statin hsCRP levels >2 mg/l, despite achieving LDLC concentrations <70 mg/dl (31) (**Central Illustration panel A**). As described below, a clinical strategy in which potentially eligible patients receive a single test dose of canakinumab to ascertain whether they achieve a robust reduction in hsCRP may, in a manner analogous to LDLC lowering, provide a thoughtful clinical approach to long-term inflammation inhibition.

Very recent data indicate that "residual inflammatory risk" remains even among those treated with both high-intensity statins and PCSK9 inhibitors; in both the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) and the SPIRE trials, hsCRP remained a common and strong predictor of future cardiovascular risk, despite LDLC levels as low as 20 to 30 mg/dl (32,33) (**Central Illustration panel A, Figure 2**).

WHY TARGET IL-1β RATHER THAN CRP?

CRP, a pentraxin derived hepatically, is a useful downstream clinical biomarker that integrates innate

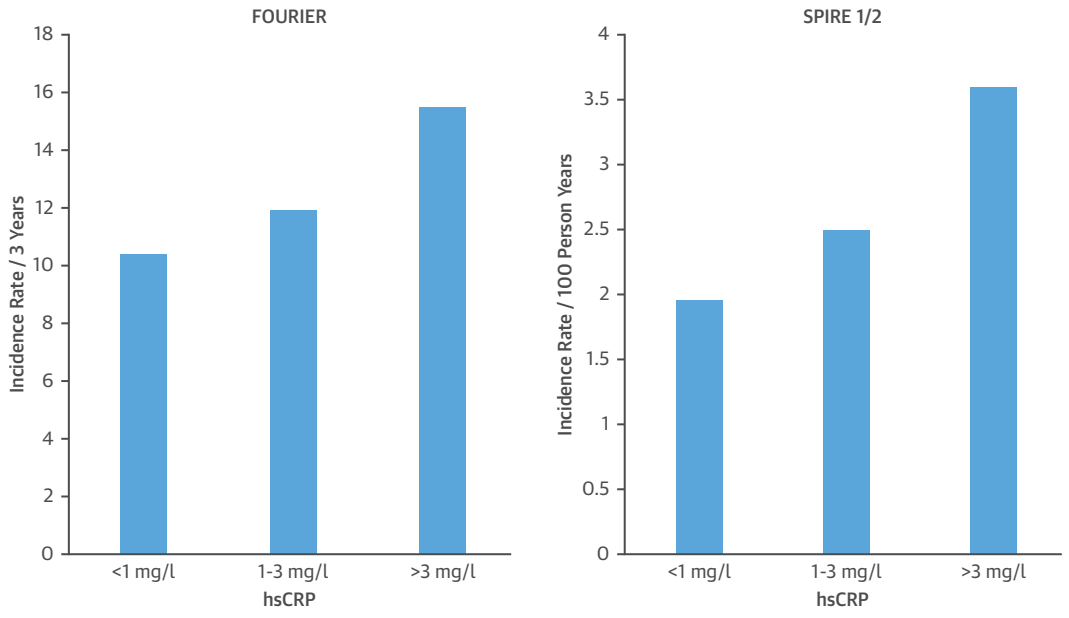
CENTRAL ILLUSTRATION Residual Risk and a Movement Toward Personalized Medicine



Ridker, P.M. J Am Coll Cardiol. 2018;72(25):3320–31.

(A) Atherosclerosis patients with "residual inflammatory risk" are more common than patients with "residual cholesterol risk." Plots show proportions of patients with hsCRP > or ≤2 mg/l and/or LDLC >70 mg/dl or <70 mg/dl after treatment with statins **(left)**, statins plus ezetimibe **(center)**, or statins plus PCSK9 inhibition **(right)**. Data from Ridker (31) and Pradhan et al. (33). **(B)** Redefining residual risk: moving towards personalized medicine for cardiovascular therapeutics. Following initiation of statin therapy, patients remain at high residual risk for recurrent cardiovascular events for different underlying pathophysiologic reasons, including "residual cholesterol risk," "residual inflammatory risk," "residual thrombotic risk," "residual triglyceride risk," and "residual Lp(a) risk," as examples. Relevant biomarkers to identify patient groups are provided as are completed, ongoing, or planned outcome trials for each group. CANTOS = Canakinumab Anti-inflammatory Thrombosis Outcomes Study; COMPASS = Cardiovascular Outcomes for People Using Anticoagulation; DAPT = Dual Antiplatelet Therapy; FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk; hsCRP = high-sensitivity C-reactive protein; IMPROVE-IT = Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDLC = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); ODDYSEY = ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab; PROMINENT = Pemefibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides In Patients with Diabetes; PROVE-IT = Pravastatin or Atorvastatin Evaluation an Infection Therapy; REDUCE-IT = Reduction of Cardiovascular Events with EPA - Intervention Trial; SPIRE = Studies of PCSK9 Inhibition and the Reduction of Vascular Events; STRENGTH = Outcomes Study to Assess Statin Residual Risk Reduction with EpaNova in High CV Risk Patients with Hypertriglyceridemia.

FIGURE 2 Residual Inflammatory Risk Is Present Even After Maximal Possible LDLC Lowering



Incidence rates of major cardiovascular events according to hsCRP levels among high-risk patients already treated with statins and PCSK9 inhibitors in the FOURIER **(left)** and SPIRE **(right)** trials. Data from Bohula et al. (32) and Pradhan et al. (33). FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk; SPIRE = Studies of PCSK9 Inhibition and the Reduction of Vascular Events; other abbreviations as in Figure 1.

immune function. However, CRP itself is unlikely to be an active participant in atherothrombosis (34-37). By contrast, experimental data and human genetic studies strongly suggest that the upstream cytokines IL-1 and IL-6 are likely to play causal roles in atherothrombosis (8,9).

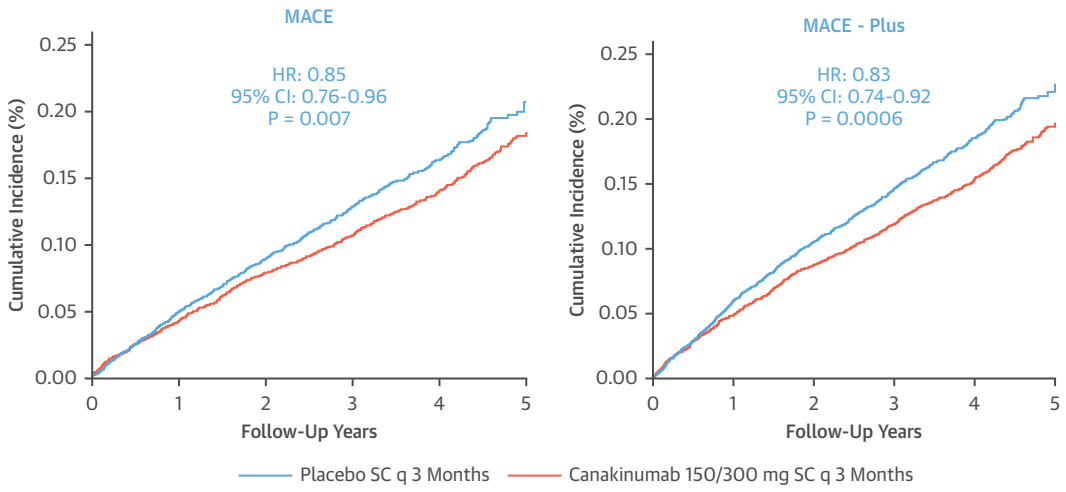
IL-1 was first cloned in 1984 in pioneering work related to fever (38). Two genetically encoded proteins, IL-1α and IL-1β, both bind to the IL-1 receptor. Of these, IL-1β is the dominant circulating form of IL-1 and is among the most powerful inducers of innate immunity (39). IL-1β is produced from pro-IL-1β through caspase cleavage and activation in the NLRP3 inflammasome, a group of intracellular proteins critical for pattern recognition in innate immunity (40). The NLRP3 inflammasome in turn is activated by several physiological processes including contact with crystalline structures, the most prominent of which for atherosclerosis is crystalline cholesterol (41). As recently reviewed, IL-1β plays multiple roles in atherogenesis, plaque growth, and subsequent rupture (8). IL-1 also induces IL-6 which in turn has additional direct vascular effects including leukocyte adhesion to endothelial cells, reduced smooth muscle proliferation, and production of collagenases (42). Furthermore, polymorphisms in the IL-6 signaling pathway are associated in Mendelian randomization studies with reduced lifelong vascular event rates and reduced levels of hsCRP (43,44).

Several agents that inhibit IL-1 are currently in use to treat rare inherited periodic fever syndromes and certain refractory arthritis cases. These agents include anakinra (an IL-1 receptor antagonist that blocks both IL-1α and IL-1β), rilonacept (an IL-1 trap that additionally inhibits the IL-1 receptor), and the monoclonal antibodies gevokizumab and canakinumab, which are highly specific for IL-1β. The latter of these two therapeutic monoclonal antibodies, canakinumab is currently approved by the U.S. Food and Drug Administration for cryopyrin-associated periodic syndromes and systemic juvenile idiopathic arthritis (45).

WHO WAS STUDIED IN CANTOS?

CANTOS randomized 10,061 stable post-myocardial infarction patients who had hsCRP levels ≥2 mg/l despite aggressive use of statins, anti-platelet agents, and renin-angiotensin inhibitors (10). Two-thirds of CANTOS participants had previously undergone coronary revascularization; 54% of the qualifying myocardial infarction events were ST-segment

FIGURE 3 **Reducing Inflammation to Reduce Cardiovascular Risk: CANTOS Trial Findings**



Cumulative incidence of MACE (e.g., myocardial infarction, stroke, or cardiovascular death) **(left)** or MACE-Plus (e.g., myocardial infarction, stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death) **(right)** in the CANTOS trial. Data are shown for the placebo and groups receiving 150 mg and 300 mg (SC every 3 months) of canakinumab. These dosage of canakinumab resulted in 35% to 40% reductions in hsCRP and IL-6 with no effect on LDLC. CANTOS = Canakinumab Anti-inflammatory Thrombosis Outcomes Study; IL = interleukin; MACE = major adverse cardiac event(s); SC = subcutaneous; other abbreviations as in Figure 1.

elevation myocardial infarctions, 34% were non-ST-segment elevation myocardial infarctions, and 12% were of unknown type. The mean age in CANTOS was 61 years old, 26% were women, 24% were current smokers, and 40% had diabetes. All of these characteristics are common in a high-risk atherosclerosis population.

What distinguished CANTOS from other contemporary trials was screening for hsCRP to ensure that all participants were at risk at least in part due to a persistent pro-inflammatory response. Due to this screening process, the median entry hsCRP in CANTOS was 4.2 mg/l, a value above the 85th percentile of the normal distribution. By contrast, the median LDLC level in CANTOS was only 82 mg/dl, lower than that in any of the major PCSK9 trials. The CANTOS trial was thus unique in that it focused specifically on atherosclerosis patients with "residual inflammatory risk" rather than "residual cholesterol risk."

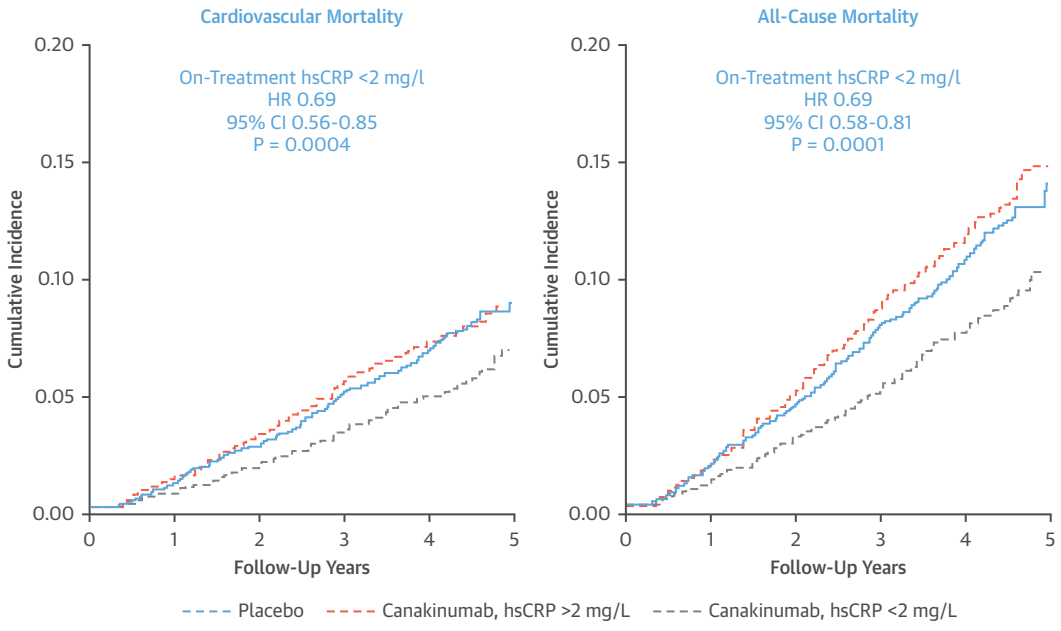
WHAT DID CANTOS SHOW?

CANTOS randomly allocated eligible participants to placebo or canakinumab at 1 of 3 doses (50, 150, or 300 mg) administered subcutaneously once every 3 months. As shown in the CANTOS pilot study, canakinumab is a fully human monoclonal antibody targeting IL-1β, which in turn will lower IL-6 and hsCRP but has no effect on LDLC (46). CANTOS patients were followed for incident major cardiovascular events, cancer, adverse events, and mortality over a 5-year period (median: 3.7 years). The trial was conducted in 39 countries. Of the >10,000 patients randomized, <30 were lost to follow-up.

An underappreciated but clinically important finding in CANTOS was that placebo event rates were high despite aggressive contemporary care. This demonstrates that "residual inflammatory risk" patients are a unique group with a substantially unmet clinical need.

The primary finding from CANTOS was of a statistically significant 15% reduction in nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death (major adverse cardiovascular events[MACE]) and a 17% reduction in this endpoint plus the addition of unstable angina requiring urgent coronary revascularization (MACE+), among those allocated to 150 mg of canakinumab administered subcutaneously (SC) once every 3 months. Virtually identical effect estimates were observed at the 300-mg dose level (Figure 3). By contrast, the 50-mg dose of canakinumab was associated with a nonsignificant reduction in risk of 7%. This suggestion of dose-dependency is of interest because it closely parallels the magnitude of hsCRP and IL-6 reduction achieved, which was

FIGURE 4 Lower is Better for Inflammation Reduction: CANTOS Trial On-Treatment Findings



Greater risk reductions were seen in CANTOS with greater hsCRP reduction, including 31% relative risk reductions in cardiovascular mortality **(left)** and all-cause mortality **(right)** for those treated with placebo or canakinumab who achieved hsCRP levels <2 mg/l after initiation of drug therap. Adapted with permission from Ridker (97). Abbreviations as in Figure 1.

between 35% and 40% at the 2 higher doses but only 25% at the lowest dose.

The relative risk reductions observed in CANTOS, which are virtually identical to those observed in the major PCSK9 trials, were achieved with no change in LDLC. Effects of canakinumab on risk were consistent across all pre-specified subgroups; it must be remembered, however, that all CANTOS participants had elevated levels of hsCRP at study entry.

One of the most intriguing cardiovascular aspects of CANTOS was the observation that coronary revascularization, an endpoint reflective of plaque progression and development of angina, was reduced by 30% with canakinumab ($p < 0.001$). This benefit of canakinumab was observed at all canakinumab doses.

Recent CANTOS analyses have affirmed the ability of canakinumab to reduce cardiovascular events among those with diabetes (47) and those with stage 3 kidney disease (baseline estimated glomerular filtration rate of 30 to 60 ml/min/1.73 m^2) (48). The latter data in moderate chronic kidney disease are important because few if any nonhemodynamic agents have demonstrated cardiovascular efficacy in this group. It is, thus, hoped that a trial of IL-1 or IL-6 inhibitors for cardiovascular protection in stage 4 renal failure (baseline estimated glomerular filtration rate of 15 to 30 ml/min/1.73 m^2) can soon commence.

WHY IS MEASUREMENT OF ON-TREATMENT hsCRP IMPORTANT?

Clinicians routinely measure on-treatment levels of blood pressure and on-treatment levels of LDLC as a method to monitor therapies for hypertension and hyperlipidemia. This practice has a firm biological basis as the efficacy of treatment in each case tracks with the magnitude of blood pressure and lipid reduction, respectively.

In parallel fashion, pre-specified analyses of CANTOS demonstrated that the benefits of inflammation reduction tracked directly with the magnitude of hsCRP lowering achieved, at least with canakinumab. Among CANTOS patients treated with canakinumab who achieved hsCRP levels <2 mg/l after the first dose, long-term rates of major cardiovascular events were reduced by 26%, whereas rates of both cardiovascular mortality and all-cause mortality were reduced by 31% (all $p < 0.001$) (49). In contrast, risk reductions were smaller and no longer significant for these endpoints among those treated with canakinumab who did not achieve hsCRP levels <2 mg/l after

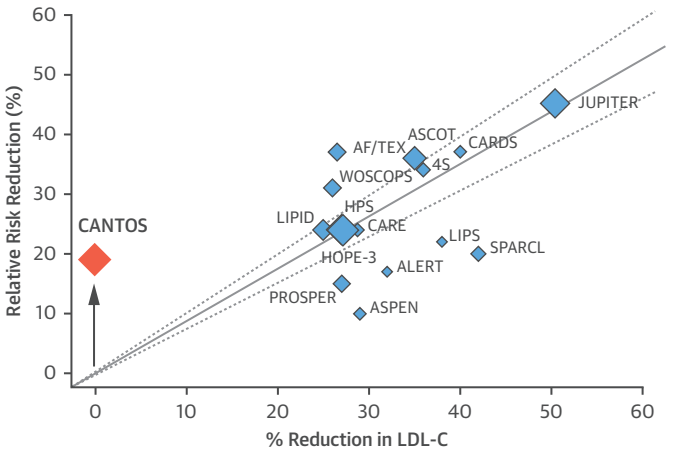
the initial dose (Figure 4). These differential effects according to biological response were robust to multivariate adjustment, were of similar magnitude using several alternative thresholds (including reductions in hsCRP of greater or lesser than 50%) and were virtually identical in causal inference analyses. All these sensitivity evaluations suggest that the physiological impact of canakinumab on hsCRP substantively outweighs residual confounding in these post-randomization analyses. The clinical strategy of sampling a single canakinumab dose in eligible patients and then treating on a long-term basis only those whose hsCRP is reduced by >50% or have on-treatment hsCRP levels <2 mg/l may provide a simple clinical method to predict long-term benefit; for example, the number needed to treat to prevent a major vascular event was 16 among "robust canakinumab responders" compared to 57 among "less robust responders."

On-treatment levels of IL-6 was also a potent method within CANTOS to predict efficacy of canakinumab (50). Those data suggest that novel agents that directly reduced IL-6 might be of further benefit in high-risk atherosclerosis patients. The highly concordant data for on-treatment hsCRP and on-treatment IL-6 support the hypothesis that "lower is better" for inflammation in a manner analogous to that of LDLC. IL-6 levels, like hsCRP, predict future cardiovascular events and efficacy of therapy in both primary prevention, acute coronary ischemia, and secondary prevention (51–53). However, measurement of IL-6 is not clinically available. As such, clinicians are currently limited to using hsCRP for baseline screening (to determine the presence of "residual inflammatory risk") and for on-treatment evaluation (to predict therapeutic efficacy).

WHAT WERE THE EFFECTS OF CANAKINUMAB ON INFECTION, CANCER, AND OTHER ADVERSE EVENTS? Compared to placebo, canakinumab allocation in CANTOS resulted in no significant adverse hepatic or renal effects. There were small dose-dependent reductions in platelet counts but no significant increase in bleeding. Injection site reactions were rare. Consistent with the role of IL-1 in multiple rheumatologic disorders, rates of incident arthritis, osteoarthritis, and gout were reduced by canakinumab (10).

Canakinumab was associated with mild leukopenia. The most important adverse effect of canakinumab was a small but statistically significant increase in fatal infection that occurred in approximately 1 in every 1,000 patents treated. Most of these events were due to common gram-positive organisms and were more prevalent in older diabetic patients (10).

FIGURE 5 Cardiovascular Event Reduction With No Change in LDLC: Additive Effects of Inflammation Inhibition to Lipid Lowering



Plot shows the relative risk reduction in cardiovascular events (y-axis) as a function of the percent of reduction in LDLC (x-axis) from completed placebo-controlled statin trials. **(Left)** Relative risk reduction were observed in CANTOS, with 0% reduction in LDLC but large reductions in hsCRP and IL-6. Virtually all CANTOS participants were already taking maximal doses of statin therapy, demonstrating the additive effects of inflammation inhibition to aggressive lipid lowering. 4S = Scandinavian Simvastatin Survival Study; AF/TEX = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT = Assessment of Lescol in Renal Transplantation; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints; CARDS = Cardiac and Renal Disease Study; CARE = Cholesterol and Recurrent Events; HOPE = Heart Outcomes Prevention Evaluation; HPS = Heart Protection Study; JUPITER = Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; LIPS = Lescol Intervention Prevention Study; PROSPER = Pravastatin in Elderly Individuals at Risk of Vascular Disease; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; WOSCOPS = West of Scotland Coronary Prevention Study; other abbreviations as in Figure 1.

Cardiologists considering the use of anti-inflammatory therapies, thus, need to ensure that patients who develop early signs or symptoms of infection receive early attention. There was no increase in opportunistic infections or reactivation of tuberculosis.

Rates of cancer mortality and incident lung cancer were significantly reduced with canakinumab. These beneficial effects were dose-dependent with relative hazard reductions of 67% ($p < 0.0001$) for total lung cancer and 77% ($p = 0.002$) for fatal lung cancer (54). New trials of canakinumab are being planned to evaluate whether these preventive effects on cancer can be exploited directly as adjunctive therapy in the treatment of certain tumors, particularly in non-small cell lung cancer. Evidence of reduced cancer incidence with canakinumab is consistent with experimental work indicating that cytokines such as IL-1β are involved in the growth, progression, and metastasis of certain inflammatory tumors (55–59).

WHAT ARE FUTURE DIRECTIONS FOR THE INFLAMMATION HYPOTHESIS OF ATHEROTHROMBOSIS?

Among patients with stable atherosclerosis, the CANTOS trial provides proof that IL-1β inhibition with canakinumab can reduce cardiovascular events beyond that achievable with lipid lowering. Whether IL-1α signaling is important for this process remains untested. Similarly, no current data address the utility of canakinumab during acute coronary ischemia (60). However, small studies with anakinra (an IL-1 receptor antagonist) and tocilizumab (a monoclonal antibody targeting IL-6) suggest potential benefits in this setting on remodeling and inflammatory biomarkers in the setting of heart failure and stroke (61–65).

Although CANTOS provided mechanistic evidence that targeting the IL-1-to-IL-6 pathway of innate immunity has a role in atherosclerosis treatment, it remains unknown whether inhibition of alternative inflammatory pathways will produce similar benefits. For example, the IL-1 pathway is not directly affected by low-dose methotrexate (which has been tested in the recently completed Cardiovascular Inflammation Reduction Trial) (66) or by nonsteroidal anti-inflammatory agents (agents which have not shown cardiovascular efficacy).

The NLRP3 inflammasome activates IL-1β and promotes induction of IL-18 (40,41). It is thus not surprising that oral NLRP3 inhibitors are being considered as potential future therapies for both chronic and acute coronary ischemia (67–69). NLRP3 inhibition could also have theoretical benefits for nonalcoholic steatohepatitis and severe kidney disease (70,71). Preliminary data support a role for colchicine in atheroprotection, an interesting observation as colchicine also has some NLRP3-inhibiting effects (72). Formal randomized placebo-controlled trials of colchicine are ongoing. It is important to recognize that agents targeting inflammation outside the IL-1-to-IL-6 pathway have failed to lower vascular event rates. As examples, neutral data have been reported in large-scale trials of the MAP-kinase inhibitor losmapimod and of the $LpPLA_2$ inhibitor darapladib (73,74).

Whereas NLRP3 inhibition represents a step upstream from direct IL-1 inhibition, agents such as tocilizumab and sirukumab that inhibit IL-6 represent a potential downstream form of inhibition (75). IL-6 may also represent a new target for vascular therapy; data from CANTOS indicate that the cardiovascular benefits of canakinumab relate directly to the magnitude of IL-6 reduction achieved (50).

Vaccination strategies designed to activate anti-inflammatory components of the adaptive immune response remain under investigation (76,77). Recent work in mice suggests that agents such as erlotinib, an agent that selectively inhibits epidermal growth factor receptor, may limit experimental atherosclerosis (78). As such, although CANTOS has demonstrated the effectiveness of inhibiting 1 critical component of the innate immune system, work will continue to address adaptive immunity as well (79).

Finally, recent evidence suggests that clonal hematopoiesis, a normal effect of aging in which certain white blood cell lines mutationally come to dominate others, is also associated with increased cardiovascular risk (80,81). At least 1 mutation associated with this process in the *Tet2* gene, which leads to both clonal hematopoiesis and activation of IL-1β inflammasomes in macrophages. *Tet2* in turn has been associated with accelerated atherosclerosis and heart failure in mouse models (82). Other data using parabiotic mouse models implicate IL-1β as a critical mediator of immune changes linking atherosclerosis, bone marrow, and splenic function (83), effects that can be seen following acute coronary syndromes by fluorodeoxyglucose-labeled positron-emission tomography (84). Modest but nonsignificant effects of canakinumab on measurements of vascular structure or function have been reported in cardiac magnetic resonance imaging studies of the carotid arteries and aorta (85). All these observations provide mechanistic insight into the success of CANTOS.

REDEFINING RESIDUAL RISK: LESSONS FROM CANTOS AND PERSONALIZED MEDICINE

Diet, exercise, and smoking cessation reduce systemic inflammation and are associated with reduced cardiovascular event rates. These interventions, along with blood pressure and aggressive lipid lowering, remain critical for atherosclerosis prevention (**Central Illustration panel B**).

Moving beyond basic preventive efforts, multiple commentators have noted that, in addition to providing proof-of-principle for the inflammation hypothesis of atherothrombosis, CANTOS is likely to open multiple new directions for therapeutic targeting (8,60,86–96). As principle investigator of CANTOS, this author agrees with this sentiment but believes there are 2 further major lessons to be gleaned.

First, the inflammation hypothesis of atherothrombosis neither conflicts nor competes with the lipid hypothesis. The exceptional success of lipid lowering in cardiovascular disease is among the most

important success stories of preventive medicine over the past 40 years, and a nearly linear relationship between LDLC reduction and cardiac risk has been repeatedly demonstrated. In CANTOS, a secondary prevention trial conducted in 39 countries, baseline levels of LDLC were only 82 mg/dl, a testament to aggressive and widespread pharmacologic interventions for LDL lowering. However, CANTOS also reported, for the first time, clear event reduction in the absence of any lowering of LDLC. This observation opens considerable optimism for a disease that continues to rank at the very top in terms of global burden of disease (**Figure 5**).

Second, CANTOS should open a clinical dialog about personalized medicine, based on the underlying biology affecting individual patients. The use of biomarker-targeted trials, of which JUPITER (15) and CANTOS (10) are examples, represents a break from the concept that all patents need all therapies; yet, just as there is "residual cholesterol risk" and "residual inflammatory risk," so too is there "residual thrombotic risk," "residual triglyceride risk," and "residual lipoprotein(a) risk," as well as fully unexplained disease. Each of these conditions has either a proven therapy or major trials underway or planned (**Central Illustration panel B**). From this perspective, the CANTOS trial also teaches that we must consider individual patients for specific therapies. The concept that "one size fits all" is no longer viable in the post-CANTOS and post-PCSK9 era. Rather, through judicious use of biomarker screening, we are now able to begin the process of "providing the right drug to the right patient at the right time."

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