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# Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

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## ABSTRACT

**BACKGROUND**

Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherothrombosis has remained unproved.

**METHODS**

We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1$\beta$, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

**RESULTS**

At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median follow-up of 3.7 years, the incidence rate for the primary end point was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group. The hazard ratios as compared with placebo were as follows: in the 50-mg group, 0.93 (95% confidence interval [CI], 0.80 to 1.07; P=0.30); in the 150-mg group, 0.85 (95% CI, 0.74 to 0.98; P=0.021); and in the 300-mg group, 0.86 (95% CI, 0.75 to 0.99; P=0.031). The 150-mg dose, but not the other doses, met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; P=0.005). Canakinumab was associated with a higher incidence of fatal infection than was placebo. There was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P=0.31).

**CONCLUSIONS**

Antiinflammatory therapy targeting the interleukin-1$\beta$ innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)

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*A complete list of members of the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

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Current pharmaceutical interventions that are designed to slow the progression of atherosclerosis focus almost exclusively on reducing plasma levels of cholesterol. However, clinical and experimental data support an additional critical role for inflammation in atherothrombosis.[1-3] We previously found that downstream biomarkers of inflammation such as high-sensitivity C-reactive protein and interleukin-6 are associated with an increased risk of cardiovascular events, independent of the cholesterol level.[4,5] We have also found that statins reduce the levels of cholesterol and markers of inflammation,[6] and in a series of clinical trials we and others subsequently found that beneficial outcomes after statin therapy relate to both a reduction in cholesterol level and inflammation inhibition.[7-11] Yet, to date, no evidence has shown that reducing vascular inflammation in the absence of concomitant lipid lowering reduces the rates of cardiovascular events. As such, the inflammatory hypothesis of atherothrombosis has remained unproved.

Interleukin-1$\beta$ is a cytokine that is central to the inflammatory response and that drives the interleukin-6 signaling pathway. Canakinumab, a fully human monoclonal antibody targeting interleukin-1$\beta$, has antiinflammatory effects and has been approved for clinical use in rheumatologic disorders.[12,13] In a phase 2 trial involving patients with diabetes who were at high vascular risk, we found that interleukin-1$\beta$ inhibition with canakinumab markedly reduced plasma levels of interleukin-6 and high-sensitivity C-reactive protein without lowering the level of low-density lipoprotein (LDL) cholesterol.[14] Thus, we hypothesized that canakinumab could provide a critical proof-of-concept treatment to test the inflammatory hypothesis of atherothrombosis directly. The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), a randomized, double-blind, placebo-controlled trial involving stable patients with previous myocardial infarction, evaluated whether canakinumab could prevent recurrent vascular events in men and women who have a persistent proinflammatory response, defined as a high-sensitivity C-reactive protein level of 2 mg or more per liter.[15]

## METHODS

### TRIAL DESIGN AND OVERSIGHT

This investigator-driven clinical trial was sponsored by Novartis. The trial protocol, available with the full text of this article at NEJM.org, was designed by academic members of the executive committee with input from physician and statistician employees of the sponsor. The protocol was approved at participating centers by the responsible institutional review board or ethics committee, as applicable in the 39 countries involved. An independent data and safety monitoring committee oversaw the trial. The sponsor was responsible for data collection. The first author and an academic statistician at Brigham and Women's Hospital had full access to the trial databases, generated trial analyses, prepared the first draft of the manuscript, and made the decision to submit the manuscript for publication. The authors assume responsibility for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

### TRIAL POPULATION

Patients were eligible for enrollment if they had a history of myocardial infarction and had a blood level of high-sensitivity C-reactive protein of 2 mg or more per liter despite the use of aggressive secondary prevention strategies. The trial excluded from enrollment patients with a history of chronic or recurrent infection, previous cancer other than basal-cell skin carcinoma, a suspected or known immunocompromised state, a history or high risk of tuberculosis or disease related to the human immunodeficiency virus, or ongoing use of other systemic antiinflammatory treatments. Details of the inclusion and exclusion criteria are provided in Section B in the Supplementary Appendix, available at NEJM.org.

### RANDOMIZATION

Initially, patients were randomly assigned in a 1:1:1 ratio to receive placebo, canakinumab at a dose of 150 mg, or canakinumab at a dose of 300 mg. After the enrollment of 741 patients, a 50-mg dose of canakinumab was added at the request of a regulatory agency, and the randomization ratio was adjusted accordingly; we sought to achieve a final randomization ratio of 1.5 (placebo group):1:1:1 (Section C in the Supplementary Appendix). All doses of canakinumab and placebo were administered subcutaneously once every 3 months; for the 300-mg dose, the regimen was 300 mg every 2 weeks for the first two doses, then once every 3 months. Randomization was performed with the use of a centralized computer system, with stratification according



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to the time since the index myocardial infarction and according to trial part (before vs. after inclusion of the 50-mg dose group).

### END POINTS

The primary efficacy end point was the first occurrence of nonfatal myocardial infarction, any nonfatal stroke, or cardiovascular death in a time-to-event analysis. The trial had two key secondary efficacy end points. The first key secondary end point included the components of the primary end point as well as hospitalization for unstable angina that led to urgent revascularization. The second key secondary end point, the incidence of new-onset type 2 diabetes among patients with prediabetes at randomization in a time-to-event analysis, is not reported here. The two other prespecified secondary end points were death from any cause and the composite of nonfatal myocardial infarction, any nonfatal stroke, or death from any cause. All the components of these end points were adjudicated by an end-point adjudication committee, whose members were unaware of the trial-group assignments.

### STATISTICAL ANALYSIS

The trial was designed to accrue a total of 1400 primary end-point events across all the groups. Assuming that all three active doses would result in a primary event rate that was 20% lower than the rate with placebo, we calculated that the trial would have more than 90% power to detect a significantly lower risk with at least one canakinumab dose than with placebo. The investigators initially sought to enroll 17,200 patients in order to accrue 1400 events over a period of 5 years. In December 2013, at the request of the sponsor, the sample size was reduced to 10,000 patients. The planned follow-up was extended by 1 year to maintain the targeted number of events.

The distributions of the percentage change from baseline in the high-sensitivity C-reactive protein and lipid levels were compared between the placebo group and each canakinumab group at intervals up to 48 months. Similar comparisons were made for interleukin-6 levels up to 12 months. Log-rank tests and Cox proportional-hazards models, stratified according to the time since the index myocardial infarction and according to trial part, were used to analyze the prespecified primary and key secondary cardiovascular end points that occurred during trial follow-up, according to the intention-to-treat principle.

The formal evaluation of significance for individual doses, with adjustment for multiple comparisons, followed a closed testing procedure (Section C in the Supplementary Appendix). On the basis of the closed testing procedure, and with the use of the prespecified allocation of alpha error, the two-sided P value thresholds for statistical significance for the primary end point were 0.01058 for the test of the 300-mg dose of canakinumab versus placebo and 0.02115 for the tests of the other two doses versus placebo. The closed testing procedure also specified that formal significance testing for the key secondary end points would be performed for any given dose only if the significance threshold for the primary end point for that dose had been met.

Although the primary analysis strategy was based on pairwise comparisons of individual dose groups with the placebo group, comparisons were also made between the incidence rates in the placebo group and the incidence rates across the ascending canakinumab doses (using scores of 0, 1, 3, and 6 that were proportional to doses in a trend analysis) and in the combined canakinumab groups versus placebo. In addition, analyses that focused on patients who adhered to the trial regimen were performed, with follow-up for each patient being censored 119 days after the last injection was received. The significance thresholds for these tests were not adjusted for multiple comparisons. Similar analyses were used for adverse events. All P values are two-sided, and all confidence intervals were computed at the 95% level.

## RESULTS

### PATIENTS

Trial enrollment began in April 2011 and was completed in March 2014; the last trial visit was in June 2017. Of 17,482 patients who had previously had myocardial infarction and had undergone screening in the central laboratory, 10,061 (57.6%) underwent randomization correctly and received at least one dose of canakinumab or placebo (Fig. S1 in the Supplementary Appendix). The most common reasons for exclusion were a high-sensitivity C-reactive protein level of less than 2 mg per liter (46.0% of the excluded patients), active tuberculosis or tuberculosis risk factors (25.4%), and exclusionary concomitant disorders (9.9%).

The mean age of the participants who under-



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**Table 1. Characteristics of the Trial Participants.***

| Characteristic | Placebo Group (N=3344) | Canakinumab | | | |
|---|---|---|---|---|---|
| | | 50-mg Group (N=2170) | 150-mg Group (N=2284) | 300-mg Group (N=2263) | All Doses (N=6717) |
| Age — yr | 61.1±10.0 | 61.1±10.1 | 61.2±10.0 | 61.1±10.1 | 61.1±10.1 |
| Female sex — no. (%) | 865 (25.9) | 541 (24.9) | 575 (25.2) | 606 (26.8) | 1722 (25.6) |
| Current smoking — no. (%) | 765 (22.9) | 531 (24.5) | 534 (23.4) | 536 (23.7) | 1601 (23.8) |
| Median body-mass index (IQR) | 29.7 (26.6–33.8) | 29.9 (26.6–33.9) | 29.8 (26.5–33.7) | 29.8 (26.5–33.8) | 29.9 (26.6–33.8) |
| Hypertension — no. (%) | 2644 (79.1) | 1751 (80.7) | 1814 (79.4) | 1799 (79.5) | 5364 (79.9) |
| Diabetes — no. (%) | 1333 (39.9) | 854 (39.4) | 954 (41.8) | 888 (39.2) | 2696 (40.1) |
| Qualifying myocardial infarction — no. (%) | | | | | |
| STEMI | 1807 (54.0) | 1231 (56.7) | 1231 (53.9) | 1213 (53.6) | 3675 (54.7) |
| Non-STEMI | 1132 (33.9) | 710 (32.7) | 781 (34.2) | 761 (33.6) | 2252 (33.5) |
| Unknown type or missing data | 405 (12.1) | 229 (10.6) | 272 (11.9) | 289 (12.8) | 790 (11.8) |
| History of PCI — no. (%) | 2192 (65.6) | 1454 (67.0) | 1555 (68.1)† | 1509 (66.7) | 4518 (67.3) |
| History of CABG — no. (%) | 469 (14.0) | 302 (13.9) | 324 (14.2) | 316 (14.0) | 942 (14.0) |
| History of congestive heart failure — no. (%) | 721 (21.6) | 451 (20.8) | 478 (20.9) | 523 (23.1) | 1452 (21.6) |
| Lipid-lowering therapy — no./total no. (%) | 3132/3344 (93.7) | 2038/2169 (94.0) | 2114/2280 (92.7) | 2113/2259 (93.5) | 6265/6708 (93.4) |
| Statin — no./total no. (%) | 3045/3344 (91.1) | 1990/2169 (91.7) | 2065/2280 (90.6) | 2057/2259 (91.1) | 6112/6708 (91.1) |
| Renin–angiotensin inhibitor — no./total no. (%) | 2665/3338 (79.8) | 1718/2166 (79.3) | 1817/2277 (79.8) | 1792/2250 (79.6) | 5327/6693 (79.6) |
| Anti-ischemia agent — no./total no. (%)‡ | 3080/3344 (92.1) | 1974/2169 (91.0) | 2079/2280 (91.2) | 2058/2259 (91.1) | 6111/6708 (91.1) |
| Antithrombotic agent or anticoagulant — no./total no. (%) | 3188/3344 (95.3) | 2059/2169 (94.9) | 2157/2280 (94.6) | 2149/2259 (95.1) | 6365/6708 (94.9) |
| Median high-sensitivity CRP level (IQR) — mg/liter | 4.10 (2.75–6.85) | 4.25 (2.80–7.15) | 4.25 (2.85–7.05) | 4.15 (2.85–7.15) | 4.20 (2.80–7.10) |
| Median interleukin-6 level (IQR) — ng/liter | 2.61 (1.80–4.06) | 2.53 (1.80–4.17) | 2.56 (1.74–4.11) | 2.59 (1.79–4.08) | 2.56 (1.77–4.13) |
| Median total cholesterol level (IQR) — mg/dl | 161 (137–190) | 159 (136–189) | 159 (136–188) | 161 (137–189) | 160 (136–189) |
| Median LDL cholesterol level (IQR) — mg/dl | 82.8 (64.2–107.5) | 81.2 (62.3–106.0) | 82.4 (63.4–106.0) | 83.5 (64.0–108.0) | 82.0 (63.0–106.7) |
| Median HDL cholesterol level (IQR) — mg/dl | 44.5 (37.1–52.6) | 43.7 (37.0–52.2) | 43.7 (36.3–52.0)† | 44.0 (36.7–53.0) | 43.7 (36.7–52.2)† |
| Median triglyceride level (IQR) — mg/dl | 139 (100–194) | 140 (102–198) | 139 (101–196) | 138 (103–194) | 139 (102–196) |
| Median estimated GFR (IQR) — ml/min/1.73 $m^2$ | 79.0 (65.0–93.0) | 79.0 (64.0–92.0) | 79.0 (64.5–93.0) | 78.0 (64.0–93.0) | 78.5 (64.0–93.0) |
| Lost to follow-up — no. (%) | 9 (0.3) | 9 (0.4) | 5 (0.2) | 4 (0.2) | 18 (0.3) |

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline, except as noted. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. CABG denotes coronary-artery bypass grafting, CRP C-reactive protein, GFR glomerular filtration rate, HDL high-density lipoprotein, IQR interquartile range, LDL low-density lipoprotein, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

† P<0.05 for the comparison of canakinumab with placebo.

‡ Anti-ischemia agents were defined as beta-blocking agents, nitrates, or calcium-channel–blocking agents.



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went randomization was 61 years, 25.7% of the patients were women, and 40.0% had diabetes (Table 1). Most participants had undergone previous revascularization procedures (66.7% of the patients had undergone percutaneous coronary intervention, and 14.0% coronary-artery bypass grafting). At baseline, antithrombotic agents were taken by 95.0% of the patients, lipid-lowering agents by 93.4%, anti-ischemia agents by 91.4%, and inhibitors of the renin–angiotensin system by 79.7%. The median high-sensitivity C-reactive protein level at trial entry was 4.20 mg per liter, and the median LDL cholesterol level was 82.4 mg per deciliter (2.13 mmol per liter).

### EFFECTS ON INFLAMMATORY BIOMARKERS AND LIPID LEVELS

At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group (P<0.001 for all comparisons of the median percentage change in a canakinumab group with the placebo group) (Fig. 1, and Fig. S2 and Tables S1 through S5 in the Supplementary Appendix). Similar effects were observed for the interleukin-6 level (measured up to 12 months). By contrast, canakinumab use resulted in no significant reduction from baseline in the LDL cholesterol or HDL cholesterol level and in a 4 to 5% median increase in the triglyceride level.

### FOLLOW-UP AND EFFECTS ON CLINICAL END POINTS

By the end of follow-up, 18.1% of patients in the placebo group had discontinued the trial regimen, as compared with 18.7% of patients in the combined canakinumab groups (Fig. S1 in the Supplementary Appendix). At a median follow-up of 3.7 years, the incidence rate for the primary end point (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the group that received the 50-mg dose of canakinumab, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group (Table 2). No significant effect, as compared with placebo, was observed with regard to the primary end point in the 50-mg group (hazard ratio, 0.93; P=0.30) (Fig. 2A). By contrast, a significant effect for the primary end point was observed in the 150-mg group (hazard ratio vs. placebo, 0.85; P=0.02075, with a threshold P value of 0.02115) (Fig. 2B). In the 300-mg group, the hazard ratio was similar to that in the

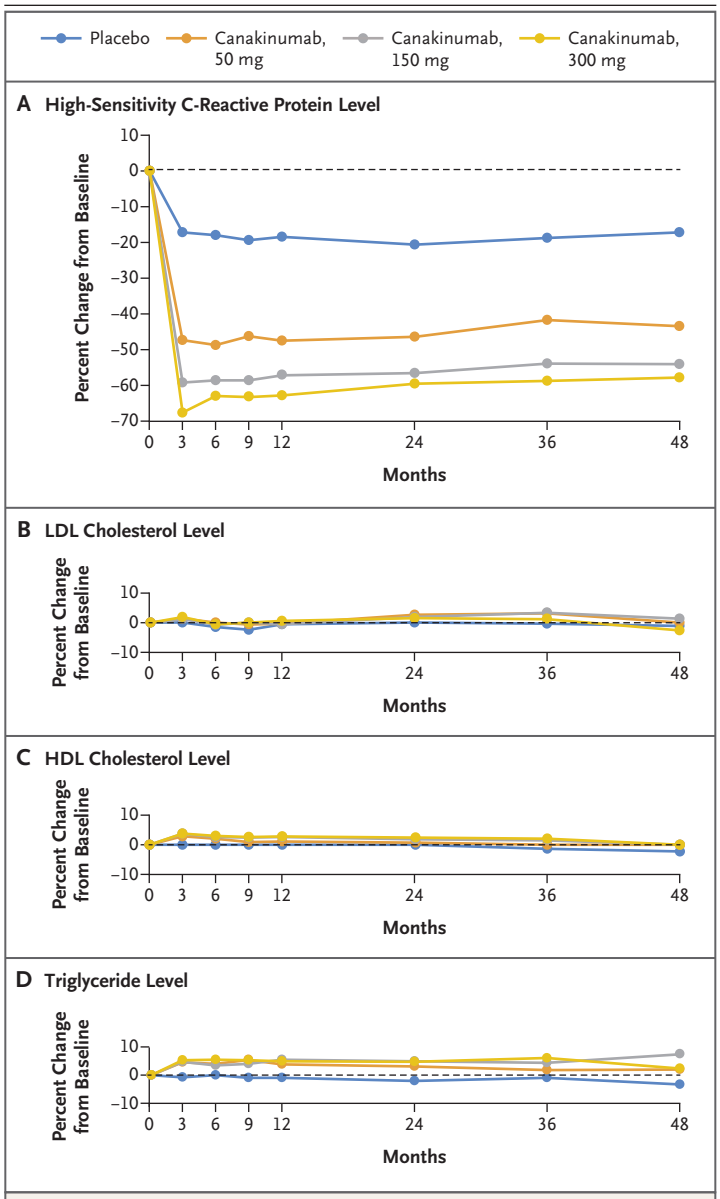


**Figure 1. Effects of Canakinumab, as Compared with Placebo, on Plasma Levels of High-Sensitivity C-Reactive Protein, Low-Density Lipoprotein (LDL) Cholesterol, High-Density Lipoprotein (HDL) Cholesterol, and Triglycerides.** Shown are the median percentage changes from baseline (dashed line). Specific data points, as well as data regarding interleukin-6 levels at 3 months and 12 months, are presented in Tables S1 through S5 in the Supplementary Appendix.



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**Table 2.** Incidence Rates and Hazard Ratios for Major Clinical Outcomes and All-Cause Mortality.*

| Clinical Outcome | Placebo Group (N=3344) | Canakinumab | | | | P Value for Trend across Doses vs. Placebo |
|---|---|---|---|---|---|---|
| | | 50-mg Group (N=2170) | 150-mg Group (N=2284) | 300-mg Group (N=2263) | All Doses (N=6717 ) | |
| Primary end point† | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 4.50 (535) | 4.11 (313) | 3.86 (320) | 3.90 (322) | 3.95 (955) | 0.02 |
| Hazard ratio (95% CI) | 1.00 | 0.93 (0.80–1.07) | 0.85 (0.74–0.98) | 0.86 (0.75–0.99) | 0.88 (0.79–0.97) | |
| P value | — | 0.30‡ | 0.021§ | 0.031‡ | 0.02 | |
| Key secondary cardiovascular end point¶ | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 5.13 (601) | 4.56 (344) | 4.29 (352) | 4.25 (348) | 4.36 (1044) | 0.003 |
| Hazard ratio (95% CI) | 1.00 | 0.90 (0.78–1.03) | 0.83 (0.73–0.95) | 0.83 (0.72–0.94) | 0.85 (0.77–0.94) | |
| P value | — | 0.12‖ | 0.005§ | 0.004‖ | 0.001 | |
| Myocardial infarction, stroke, or death from any cause | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 5.56 (661) | 5.17 (394) | 4.77 (395) | 4.88 (403) | 4.93 (1192) | 0.02 |
| Hazard ratio (95% CI) | 1.00 | 0.94 (0.83–1.07) | 0.85 (0.75–0.96) | 0.87 (0.77–0.99) | 0.89 (0.81–0.97) | |
| P value | — | 0.35 | 0.01 | 0.03 | 0.01 | |
| Myocardial infarction | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 2.43 (292) | 2.20 (169) | 1.90 (159) | 2.09 (174) | 2.06 (502) | 0.03 |
| Hazard ratio (95% CI) | 1.00 | 0.94 (0.78–1.15) | 0.76 (0.62–0.92) | 0.84 (0.70–1.02) | 0.84 (0.73–0.97) | |
| P value | — | 0.56 | 0.005 | 0.07 | 0.02 | |
| Hospitalization for unstable angina that led to urgent revascularization | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 0.69 (85) | 0.48 (38) | 0.44 (38) | 0.40 (34) | 0.44 (110) | 0.005 |
| Hazard ratio (95% CI) | 1.00 | 0.70 (0.47–1.03) | 0.64 (0.44–0.94) | 0.58 (0.39–0.86) | 0.64 (0.48–0.85) | |
| P value | — | 0.07 | 0.02 | 0.006 | 0.002 | |
| Any coronary revascularization | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 3.61 (421) | 2.53 (191) | 2.49 (205) | 2.56 (209) | 2.53 (605) | <0.001 |
| Hazard ratio (95% CI) | 1.00 | 0.72 (0.60–0.86) | 0.68 (0.58–0.81) | 0.70 (0.59–0.83) | 0.70 (0.62–0.79) | |
| P value | — | <0.001 | <0.001 | <0.001 | <0.001 | |
| Any stroke | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 0.74 (92) | 0.73 (58) | 0.74 (63) | 0.60 (51) | 0.69 (172) | 0.17 |
| Hazard ratio (95% CI) | 1.00 | 1.01 (0.72–1.41) | 0.98 (0.71–1.35) | 0.80 (0.57–1.13) | 0.93 (0.72–1.20) | |
| P value | — | 0.95 | 0.91 | 0.20 | 0.58 | |



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| | | | | | | |
|---|---|---|---|---|---|---|
| Cardiovascular death, confirmed | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 1.44 (182) | 1.18 (94) | 1.26 (110) | 1.33 (115) | 1.26 (319) | 0.76 |
| Hazard ratio (95% CI) | 1.00 | 0.80 (0.62–1.03) | 0.88 (0.70–1.12) | 0.93 (0.74–1.18) | 0.87 (0.73–1.05) | |
| P value | — | 0.083 | 0.30 | 0.55 | 0.15 | |
| Cardiovascular death or death of unknown cause | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 1.86 (235) | 1.71 (137) | 1.65 (144) | 1.74 (151) | 1.70 (432) | 0.62 |
| Hazard ratio (95% CI) | 1.00 | 0.89 (0.72–1.11) | 0.90 (0.73–1.10) | 0.94 (0.77–1.16) | 0.92 (0.78–1.07) | |
| P value | — | 0.30 | 0.30 | 0.59 | 0.28 | |
| Noncardiovascular death, confirmed | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 1.11 (140) | 1.14 (91) | 1.08 (94) | 1.02 (88) | 1.08 (273) | 0.45 |
| Hazard ratio (95% CI) | 1.00 | 1.02 (0.78–1.34) | 0.97 (0.74–1.26) | 0.92 (0.70–1.20) | 0.97 (0.79–1.19) | |
| P value | — | 0.87 | 0.81 | 0.54 | 0.79 | |
| Death from any cause | | | | | | |
| Incidence rate per 100 person-yr (no. of patients) | 2.97 (375) | 2.85 (228) | 2.73 (238) | 2.76 (239) | 2.78 (705) | 0.39 |
| Hazard ratio (95% CI) | 1.00 | 0.94 (0.80–1.11) | 0.92 (0.78–1.09) | 0.94 (0.80–1.10) | 0.94 (0.83–1.06) | |
| P value | — | 0.48 | 0.33 | 0.42 | 0.31 | |

* Data are shown as incidence rates per 100 person-years (with numbers of patients with event) to facilitate the comparison of rates between groups. P values for trend, P values for the combination of all doses as compared with placebo, and P values for all secondary end points other than the key secondary cardiovascular end point have not been adjusted for multiple comparisons. CI denotes confidence interval.

† The primary end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

‡ This result was not significant as compared with placebo according to the prespecified closed-testing procedure. The threshold P value for the primary end point for the 50-mg dose was 0.02115. The threshold P value for the primary end point for the 300-mg dose was 0.01058.

§ This result was significant as compared with placebo, with adjustment for multiple comparisons and with accounting for two efficacy interim analyses, in accordance with the prespecified closed-testing procedure (Section C in the Supplementary Appendix). The threshold P value for the primary end point for the 150-mg dose was 0.02115. The threshold P value for the key secondary cardiovascular end point for the 150-mg dose was 0.00529.

¶ The key secondary cardiovascular end point was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina that led to unplanned revascularization, or cardiovascular death.

‖ These analyses were considered to be exploratory.



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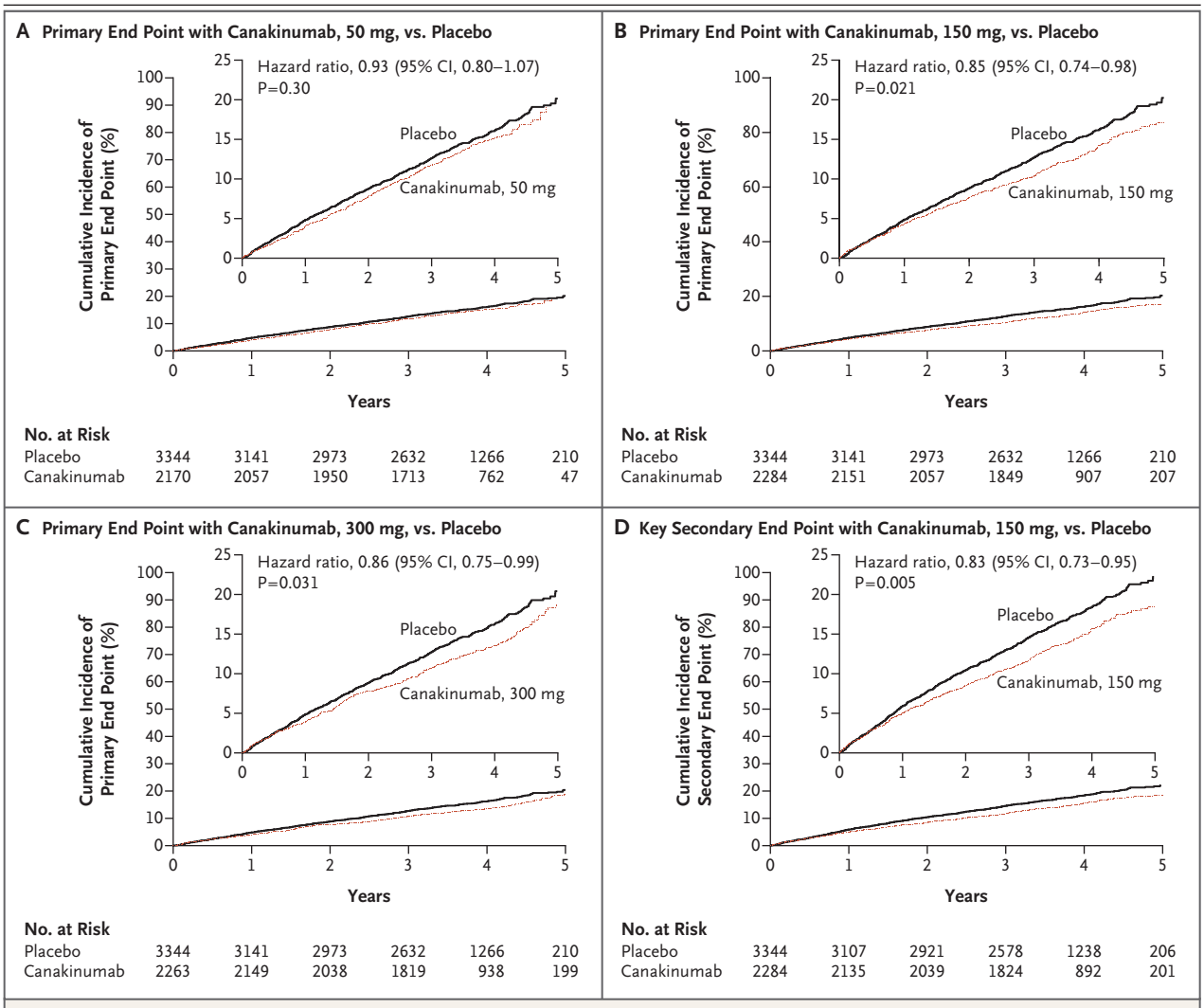


**Figure 2. Cumulative Incidence of the Primary End Point and the Key Secondary Cardiovascular End Point.**

Shown is the cumulative incidence of the primary end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in the placebo group versus the various canakinumab dose groups (Panels A through C). The insets show the same data on an enlarged y axis. The threshold P value for the primary end point was 0.02115 in the 150-mg group and 0.01058 in the 300-mg group. The group receiving the 150-mg dose of canakinumab met the prespecified multiplicity-adjusted threshold for statistical significance for the primary cardiovascular end point and for the key secondary cardiovascular end point that additionally included hospitalization for unstable angina that led to urgent revascularization (Panel D). The threshold P value for the key secondary cardiovascular end point in the 150-mg group was 0.00529.

150-mg group, but the P value did not meet the prespecified threshold for significance (hazard ratio vs. placebo, 0.86; P=0.0314, with a threshold P value of 0.01058) (Fig. 2C). The P value for trend across the canakinumab dose groups as compared with the placebo group was 0.02, and the P value for the comparison of all canakinumab doses combined with the placebo group was 0.02 (both results not adjusted for multiple testing).

For the key secondary cardiovascular end point (the components of the primary end point plus hospitalization for unstable angina that led to urgent revascularization), the incidence rate was 5.13 events per 100 person-years in the placebo group, 4.56 events per 100 person-years in the group that received the 50-mg dose of canakinumab, 4.29 events per 100 person-years in the 150-mg group, and 4.25 events per 100 person-



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years in the 300-mg group (Table 2). In the group that received the 150-mg dose of canakinumab (for which the P value met the significance threshold for the primary end point), the hazard ratio versus placebo for the secondary cardiovascular end point was 0.83 (P=0.00525, with a threshold P value of 0.00529) (Fig. 2D). According to the closed testing procedure, formal significance testing for the prespecified secondary end point was not performed for the 50-mg group and the 300-mg group. The hazard ratio versus placebo in the 50-mg group was 0.90, and the hazard ratio versus placebo in the 300-mg group was 0.83 (Figs. S3 and S4 in the Supplementary Appendix). The P value for trend across the canakinumab groups as compared with the placebo group was 0.003, and the P value for the comparison of all canakinumab doses combined with the placebo group was 0.001 (both results not adjusted for multiple testing).

Analyses of the additional secondary end points and of the components of the primary and secondary end points were not adjusted for multiple testing (Table 2). Nominally significantly lower rates than in the placebo group were seen with regard to myocardial infarction in the group that received the 150-mg dose of canakinumab; with regard to hospitalization for unstable angina that led to urgent revascularization in the 150-mg group and the 300-mg group; and with regard to any coronary revascularization in all three dose groups. All-cause mortality was neutral in the comparison of all canakinumab doses with placebo (hazard ratio, 0.94; 95% confidence interval, 0.83 to 1.06; P=0.31).

In analyses that focused on patients who adhered to the trial regimen, the observed hazard ratios were 1.00 in the placebo group, 0.90 in the group that received the 50-mg dose of canakinumab, 0.83 in the 150-mg group, and 0.79 in the 300-mg group (P=0.003 for trend across groups). In similar analyses for the key secondary cardiovascular end point, the corresponding hazard ratios were 1.00, 0.88, 0.80, and 0.77 (P<0.001 for trend across groups).

#### ADVERSE EVENTS AND OTHER CLINICAL OUTCOMES

Neutropenia was more common among patients who were assigned to receive canakinumab than among those in the placebo group, and significantly more deaths were attributed to infection or sepsis in the pooled canakinumab groups than in the placebo group (incidence rate, 0.31 vs. 0.18 events per 100 person-years; P=0.02) (Table 3). The patients who died from infection tended to be older and more likely to have diabetes than those who did not die from infection. Six confirmed cases of tuberculosis occurred during the trial, with similar rates in the pooled canakinumab group and the placebo group (0.06% in each group); five cases occurred in India and one in Taiwan.

Thrombocytopenia was more common among patients who were assigned to receive canakinumab than among those in the placebo group, but no significant difference in the incidence of hemorrhage was observed. The incidence rate of injection-site reaction did not differ significantly between any canakinumab group and the placebo group. In a finding that was consistent with known effects of interleukin-1$\beta$ inhibition, canakinumab resulted in significantly fewer reports of arthritis, gout, and osteoarthritis than did placebo (Table 3). Cancer mortality was significantly lower with canakinumab than with placebo.[16]

## DISCUSSION

CANTOS was designed to test directly the inflammatory hypothesis of atherothrombosis. In this trial, in patients with a history of myocardial infarction, the levels of high-sensitivity C-reactive protein and interleukin-6 were significantly reduced from baseline by canakinumab, as compared with placebo, with no significant reduction in lipid levels from baseline. Although the 50-mg dose of canakinumab did not have a significant effect on the primary cardiovascular end point as compared with placebo, patients in the 150-mg group had a risk of the primary end point that was 15% lower than the risk in the placebo group (3.86 vs. 4.50 events per 100 person-years) and a risk of the key secondary cardiovascular end point that was 17% lower than that in the placebo group (4.29 vs. 5.13 events per 100 person-years). The P values for both end points met the prespecified multiplicity-adjusted thresholds for statistical significance. Although the hazard ratios for the comparison of canakinumab with placebo in the 300-mg group were similar to those in the 150-mg group, the prespecified thresholds for significance were not met in this group. However,



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**Table 3.** Incidence Rates and Numbers of Serious Adverse Events and Selected Safety Laboratory Data During Treatment, Stratified According to Trial Group.*

| Adverse Event or Laboratory Variable | Placebo Group (N=3344) | Canakinumab | | | | P Value | |
|---|---|---|---|---|---|---|---|
| | | 50-mg Group (N=2170) | 150-mg Group (N=2284) | 300-mg Group (N=2263) | All Doses (N=6717) | For Trend across Doses vs. Placebo | For Combined Dose Groups vs. Placebo |
| Event — incidence rate per 100 person-yr (no. of patients with event) | | | | | | | |
| Any serious adverse event | 11.96 (1202) | 11.41 (741) | 11.71 (812) | 12.33 (836) | 11.82 (2389) | 0.43 | 0.79 |
| Any serious adverse event of infection | 2.86 (342) | 3.03 (230) | 3.13 (258) | 3.25 (265) | 3.14 (753) | 0.12 | 0.14 |
| Cellulitis | 0.24 (30) | 0.24 (19) | 0.37 (32) | 0.41 (35) | 0.34 (86) | 0.02 | 0.09 |
| Pneumonia | 0.90 (112) | 0.94 (74) | 0.94 (80) | 0.99 (84) | 0.95 (238) | 0.56 | 0.62 |
| Urinary tract infection | 0.22 (27) | 0.18 (14) | 0.24 (21) | 0.20 (17) | 0.21 (52) | 0.84 | 0.87 |
| Opportunistic infection† | 0.18 (23) | 0.16 (13) | 0.15 (13) | 0.20 (17) | 0.17 (43) | 0.97 | 0.78 |
| Pseudomembranous colitis | 0.03 (4) | 0.13 (10) | 0.05 (4) | 0.12 (10) | 0.10 (24) | 0.13 | 0.03 |
| Fatal infection or sepsis | 0.18 (23) | 0.31 (25) | 0.28 (24) | 0.34 (29) | 0.31 (78) | 0.09 | 0.02 |
| Any cancer‡ | 1.88 (231) | 1.85 (144) | 1.69 (143) | 1.72 (144) | 1.75 (431) | 0.31 | 0.38 |
| Fatal cancer‡ | 0.64 (81) | 0.55 (44) | 0.50 (44) | 0.31 (27) | 0.45 (115) | <0.001 | 0.02 |
| Other adverse event | | | | | | | |
| Injection-site reaction† | 0.23 (29) | 0.27 (21) | 0.28 (24) | 0.30 (26) | 0.28 (71) | 0.49 | 0.36 |
| Arthritis | 3.32 (385) | 2.15 (164) | 2.17 (180) | 2.47 (201) | 2.26 (545) | 0.002 | <0.001 |
| Osteoarthritis | 1.67 (202) | 1.21 (94) | 1.12 (95) | 1.30 (109) | 1.21 (298) | 0.04 | <0.001 |
| Gout | 0.80 (99) | 0.43 (34) | 0.35 (30) | 0.37 (32) | 0.38 (96) | <0.001 | <0.001 |
| Drug-induced liver injury† | 0.18 (23) | 0.15 (12) | 0.13 (11) | 0.05 (4) | 0.11 (27) | 0.004 | 0.05 |
| Leukopenia | 0.24 (30) | 0.30 (24) | 0.37 (32) | 0.52 (44) | 0.40 (100) | 0.002 | 0.01 |
| Neutropenia | 0.06 (7) | 0.05 (4) | 0.07 (6) | 0.18 (15) | 0.10 (25) | 0.01 | 0.17 |
| Any hemorrhage | 4.01 (462) | 3.33 (249) | 4.15 (327) | 3.82 (301) | 3.78 (877) | 0.94 | 0.31 |
| Thrombocytopenia | 0.43 (53) | 0.56 (44) | 0.54 (46) | 0.71 (60) | 0.60 (150) | 0.02 | 0.03 |
| Hepatic variable — percent of patients with condition (no.) | | | | | | | |
| Alanine aminotransferase >3× normal value | 1.4 (46) | 1.9 (42) | 1.9 (44) | 2.0 (45) | 2.0 (131) | 0.19 | 0.06 |
| Aspartate aminotransferase >3× normal value | 1.1 (36) | 1.5 (32) | 1.5 (35) | 1.5 (34) | 1.5 (101) | 0.30 | 0.11 |
| Alkaline phosphatase >3× normal value | 0.4 (15) | 0.5 (11) | 0.4 (10) | 0.5 (12) | 0.5 (33) | 0.67 | 0.82 |
| Bilirubin >2× normal value | 0.8 (26) | 1.0 (21) | 0.7 (15) | 0.7 (15) | 0.8 (51) | 0.34 | 0.83 |

* Data are shown as incidence rates per 100 person-years (with numbers of patients with event) for adverse events and as percentages of patients with the condition (with numbers of patients) for hepatic variables to facilitate the comparison of rates between groups. All adverse-event categories are based on standardized queries or classification levels in the *Medical Dictionary for Regulatory Activities*, version 20.0, except those otherwise indicated.

† These adverse events, including drug-induced liver injury as a serious adverse event, were considered by the sponsor to be adverse events of special interest.

‡ Included here are cancers that were adjudicated by the cancer end-point adjudication committee.



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both a pooled analysis of all canakinumab doses and a trend analysis suggested a beneficial effect of canakinumab with regard to cardiovascular outcomes.

The specific targeting of interleukin-1$\beta$ as a cytokine-based therapy for the secondary prevention of atherosclerotic events rests on several observations. The proinflammatory cytokine interleukin-1$\beta$ plays multiple roles in the development of atherothrombotic plaque, including the induction of procoagulant activity, the promotion of monocyte and leukocyte adhesion to vascular endothelial cells, and the growth of vascular smooth-muscle cells.[17-19] In mice, interleukin-1$\beta$ deficiency reduces lesion formation, whereas in cholesterol-fed pigs, exposure to exogenous interleukin-1$\beta$ increases intimal medial thickening.[20,21] The NOD-like receptor protein 3 (NLRP3) inflammasome activates interleukin-1$\beta$, a process promoted by cholesterol crystals, neutrophil extracellular traps, tissue hypoxia, and arterial flow patterns that are known to promote focal development of atherosclerosis within arteries.[22-25] This activation of interleukin-1$\beta$ stimulates the downstream interleukin-6–receptor signaling pathway, which has been implicated by mendelian randomization studies as a potential causal pathway for atherothrombosis.[26,27] More recently, studies in parabiotic mice[28] and studies of clonal hematopoiesis[29,30] have implicated interleukin-1$\beta$ in processes by which bone marrow activation accelerates atherosclerosis. Furthermore, the expression of specific inflammasome gene modules affecting interleukin-1$\beta$ has been associated with death from any cause and increased atherosclerosis in elderly patients.[31]

Although the patients in CANTOS had generally well-controlled levels of LDL cholesterol, rates of both the primary end point and the secondary cardiovascular end point in the placebo group were high, with cumulative incidences of more than 20% at 5 years. Our data thus affirm that statin-treated patients with residual inflammatory risk as assessed by means of a high-sensitivity C-reactive protein level of 2 mg or more per liter at baseline have future event rates that are at least as high as, if not higher than, those among statin-treated patients with a residual risk due to LDL cholesterol level. These two groups of patients may differ and may require personalized approaches to treatment.[32] Despite the fact that no significant reduction in cholesterol levels occurred in this trial, the magnitude of effect on cardiovascular events with canakinumab (given every 3 months) was similar to that associated with monoclonal antibodies targeting proprotein convertase subtilisin–kexin type 9 (PCSK9; given every 2 to 4 weeks).[33,34] Yet, inhibition of interleukin-1$\beta$ is a narrowly focused intervention that represents only one of many potential anti-inflammatory pathways that might serve as targets for atheroprotection.[35-37] Thus, our data suggest that other antiinflammatory interventions, such as those that directly inhibit NLRP3 function or that alter downstream interleukin-6 signaling, may also be beneficial in reducing cardiovascular risk.

We found a significantly higher incidence of fatal infection and sepsis with canakinumab than with placebo, as well as a reduction in platelet counts with no increase in bleeding risk. By contrast, cancer mortality was significantly lower among patients assigned to receive canakinumab than among those in the placebo group, a finding that is consistent with experimental data relating interleukin-1 to the progression and invasiveness of certain tumors, particularly lung cancer.[16,38,39] There was no significant difference between the canakinumab groups and the placebo group in all-cause mortality. No statistically or clinically significant hepatic toxic effect was noted. The beneficial effects of canakinumab that were observed with regard to arthritis, gout, and osteoarthritis are consistent with well-described effects of the interleukin-1 and interleukin-6 pathways in these disorders.

In conclusion, in CANTOS, patients with a history of myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter were randomly assigned to one of three doses of canakinumab or to placebo. Canakinumab significantly reduced high-sensitivity C-reactive protein levels from baseline, as compared with placebo, without reducing the LDL cholesterol level, and the 150-mg dose resulted in a significantly lower incidence of recurrent cardiovascular events than placebo.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article is dedicated to the memory of Arthur Eisner.



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## APPENDIX

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