Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31. DOI: 10.1056/NEJMoa1707914

Supplemental Materials

Ridker et al,

Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease

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A. Lists of Investigators

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Data and Safety Monitoring Board: Rory Collins (Chair), Kent Bailey, Roger Blumenthal, Helen Colhoun, Bernard Gersh, Robert J Glynn (non-voting).

B. Inclusion and Exclusion Criteria for CANTOS

Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.

2. Male, or Female of non-child-bearing potential

3. Age ≥ 18 years at Visit 1.

4. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before randomization. (1)

- Diagnosis of the qualifying MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin) OR development of new pathological Q waves regardless of symptoms. For details, refer to the Universal Definition of MI (1).

- Please see below for documentation requirements.

a. Acute MI (hospitalization records): requires documentation of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) or above criteria diagnostic for MI and evidence of myocardial ischemia as demonstrated by at least one of the following :

i. Symptoms of ischemia

ii. ECG changes indicative of new ischemia (new ST-T changes or new LBBB)

iii. Development of pathologic Q waves

iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

b. Prior MI (no hospital records for acute event available): requires documentation of any one of the following:

i. Development of pathological Q waves, with or without symptoms

ii. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause

iii. Pathologic findings of a healed or healing MI

- Patients with MI resulting from PCI or CABG will not be eligible

5. Have an hsCRP ≥ 2 mg/L (collected less than 60 days prior to Visit 2 and performed at the central laboratory, which is a minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long term (cardiovascular) medications.

Exclusion criteria

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test

2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are

a. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone or partial or total hysterectomy, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[For Croatia only]

[In Croatia, women who are < 50 years of age must have >2 years of amenorrhea or minimum of 1 year of amenorrhea with FSH levels of ≥40 IU determined on 2 or more occasions at least one month apart]

3. Any of the following concomitant conditions or diseases:

a. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure.

b. Major non-cardiac surgical or major endoscopic procedure within the past 6 months prior to Visit 1

c. Multi-vessel CABG surgery within the past 3 years

d. Symptomatic patients with Class IV heart failure (HF) (New York Heart Association).

e. Uncontrolled hypertension (defined as an average SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg at Visit 1. Patients are allowed to be re-evaluated, at the discretion of investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure above these limits (2).

f. Uncontrolled diabetes as defined by the investigator

g. Nephrotic syndrome or eGFR < 30 mL/min/1.73 m2 per MDRD formula or kidney transplant (regardless of renal function), at Visit 1

h. Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C (positive or indeterminate central laboratory results), or alanine aminotransferase/ aspartate aminotransferase (ALT/AST) levels > 3 times ULN or total bilirubin > 2 times ULN) at Visit 1

i. Prior malignancy other than basal cell skin carcinoma

4. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial

5. History or evidence of tuberculosis (TB) (active or latent) infection or one of the risk factors for tuberculosis such as but not limited or exclusive to:

a. History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection) health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient

b. Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last 12 months.

c. Evidence of TB infection (active or latent), at Visit 1, determined by purified protein derivative (PPD) skin test and/or QuantiFERON®-TB Gold (QFT-g) assay as defined by country guidelines.

i. If presence of TB (active or latent) is established then treatment (according to country guidelines for TB treatment or TB treatment with immunomodulating drugs) must have been initiated or completed prior to randomization per country guidelines.

ii. In the absence of country TB (active or latent) guidelines, the following has been demonstrated: TB has been treated adequately with antibiotics, cure can be demonstrated, and risk factors resulting in TB exposure and contracting TB have been removed (e.g. the patient does not live anymore in high TB exposure setting).

6. History of ongoing, chronic or recurrent infectious disease

7. Patients with suspected or proven immunocompromised state, including (a) those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded (b) those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy; or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g. high dose oral or intravenous steroids (> 20 mg prednisone orally daily for > 14 days, > 5 mg prednisone orally daily or equivalent dose of intravenous steroid) or high dose methotrexate (> 15 mg weekly). Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.

8. Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.

9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.

10. Patients who have received an investigational drug or device within 30 days (inclusive) of Visit 1, or who are expected to participate in any other investigational drug or device study during the conduct of this trial, except for patients who have an investigational drug eluting stent (DES), provided that they have completed the DES trial. FDA/country-specific drug regulatory authority approved DES devices are permitted.

11. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)

12. Any life threatening condition with life expectancy < 5 years, other than vascular disease that might prevent the patient from completing the study

Determination of tuberculosis status

Determination of tuberculosis (active or latent) status, either by performing the PPD skin test or the QFT-g assay will be required before administration of study drug and should be performed as defined by country guidelines. Patients need to have given written informed consent before any of these assessments are initiated. Patients who have had a negative PPD skin test or negative QFT-g assay performed within 30 days of screening (Visit 1) will not need repeat testing performed to determine eligibility. All other patients will need tuberculosis (active or latent) status determined at Visit 1.

Any significant findings will be recorded in the “Medical History” section of the eCRF as necessary.

Patients with either a positive PPD or positive or indeterminate QFT-g test may still participate in the study if

1. Treatment of tuberculosis (active or latent) (according to country guidelines) has been initiated or completed prior to randomization

or

2. Patients with a history of TB who were treated must demonstrate that treatment has been received and further work up (according to country practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

or

3. The repeat QFT-g test is negative in patients with an indeterminate QFT-g result at Visit 1.

PPD skin test

A PPD skin test may be initiated to evaluate for an occult infection with TB. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD usually injected intradermally into the volar surface of

the forearm. The injection site will be cleansed and the PPD extract will then be injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

A reaction will be measured in millimeters of indurations (hard swelling) after 48h – 72h. A PPD skin induration > 5 mm is interpreted as positive result. This will determine whether the patients have had a significant reaction to the PPD skin test. In case of a positive PPD skin test, the patient may be further screened for latent TB infection by performing the QFT-g test.

The investigator will either obtain PPD skin tests on his own and be reimbursed by Novartis for its cost or be supplied with them by the Novartis affiliate, depending on the local Novartis policy.

QuantiFERON-TB Gold Assay

A QuantiFERON®-TB Gold (QFT-g) assay may be performed to assess the TB (active or latent) status at baseline on patients as needed.

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin (BCG) vaccination or exposure to other Mycobacteria species. This test, in contrast to the PPD skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and puts it into relation to a negative and a positive control sample.

C. Trial Structure and Data Analysis Plan

CANTOS was designed as a proof-of-concept trial to directly test the inflammatory hypothesis of atherothrombosis. The primary aim of CANTOS was to evaluate whether long-term treatment with canakinumab as compared to placebo would reduce rates of recurrent cardiovascular events among stable post-myocardial infarction patients who remained at increased vascular risk due to persistently elevated levels of hsCRP ($\geq$ 2 mg/L) despite usual care including lipid lowering therapy.

The pre-specified primary endpoint of CANTOS was the time to first occurrence of a major adverse cardiovascular event (MACE), which is a composite including non-fatal MI, non-fatal stroke (including hemorrhagic stroke), and cardiovascular death. Endpoints are counted only if confirmed upon review by an independent adjudication committee masked to treatment assignment.

The trial had two key secondary efficacy variables: time to first occurrence of a composite cardiovascular event consisting of the components of the primary endpoint plus hospitalization for unstable angina requiring urgentrevascularization; and time to new onset of type 2 diabetes among those with pre-diabetes at baseline. These endpoints also required confirmation by the endpoints committee masked to treatment assignment. Findings for the diabetes endpoint will be presented in a subsequent report that also includes the results of a 6-month wash-out evaluation after the end of the trial.

All-cause mortality was a pre-specified secondary efficacy endpoint. Deaths for which the endpoints committee could not determine a cause were classified as cardiovascular deaths, and therefore included in the primary endpoint. Time to first post-randomization coronary revascularization procedure was specified as an exploratory endpoint, not evaluated by the endpoints committee. Supportive analyses included separate consideration of the individual components of the primary endpoint (MI, stroke, and cardiovascular death).

Based on experience with canakinumab in the setting of Muckle-Wells Syndrome and related IL-1 over-expression disorders, on pharmacokinetic/pharmacodynamic (free IL-1β suppression) modeling in studies of canakinumab performed in rheumatoid arthritis and gout, and on hsCRP lowering from a phase IIb study in diabetic patients at high vascular risk, an “anchor dose” was initially selected for canakinumab of 150 mg SC every three months. In addition, a higher dose of 300 mg given twice over a two week period and then every three months was also initially selected to address theoretical concerns regarding IL-1β auto-induction. As such, when the first patient was screened on April 11, 2011, CANTOS was initiated as a three arm trial comparing standard of care plus placebo to either standard of care plus canakinumab 150 mg or canakinumab 300 mg with participants allocated to each study arm in a 1:1:1 ratio. However, following health authority feedback requesting broader dose-response data and consideration of whether a lower dose would have a favorable risk benefit ratio, a lower dose canakinumab arm was introduced into the trial (50 mg sc every three months). The three doses of canakinumab implemented in the final amended protocol are thus

intended to allow for explorations of dose-response effects related to both efficacy and safety. As such, the protocol was amended and a formal four arm structure was approved centrally in July of 2011 but varied in the timing of its adoption by region and site as it further required individual IRB approval.

To accommodate this structural change and maintain study power, the proportion of individuals who ultimately would be allocated to placebo was increased as was the proportion moving forward who would be randomly allocated to the 50 mg dose. Thus, the treatment allocation ratios for CANTOS were altered from 1:1:1 for placebo:150 mg canakinumab: 300 mg canakinumab for the first 741 participants recruited to 2:1.4:1.3:1.3 for placebo: 50 mg canakinumab: 150 mg canakinumab: 300 mg canakinumab, respectively, for the remaining 9,320 participants. Randomization was stratified by time since index myocardial infarction (30 days to < 6 months and ≥ 6 months). In addition, on December 10, 2013, the Executive Committee accepted a request from the sponsor to reduce the study sample size from 17,200 to approximately 10,000 for reasons largely related to portfolio and budgetary optimization. The change was not based on safety or efficacy concerns. The study objectives and the requirement to accrue 1,400 confirmed primary endpoints for specified power were unchanged by this reduction in total sample size; estimated follow-up was increased by approximately one year so that the trial would still accrue the stipulated number of primary endpoints.

The first CANTOS participant was screened in April 2011. Between April 28, 2011 and March 3, 2014, CANTOS randomized 10,105 individuals. However, 44 were randomized erroneously or enrolled at sites that were closed owing to serious Good Clinical Practice violations. These subjects were prospectively omitted from all analyses before the end of the trial, resulting in 10,061 subjects included in the Full Analysis Set used for intention-to-treat analyses. All participants were followed until death, withdrawal of consent or their end of study visit, which occurred between January 9, 2017 and June 2, 2017. For intention-to-treat analyses of the primary efficacy endpoint, median follow-up was 3.70 years; minimum, maximum and interquartile range were 0.01, 5.77, 3.12, and 4.39 years, respectively. The regional distribution of trial participants was Asia (11.1%), Central Europe (24.7%), Western Europe (24.4%), Latin America/South America (14.2%), North America (24.0%), and Other (1.5%).

Distributions of percent changes in hs-CRP and lipid levels from baseline to specific follow-up time points (3, 12, 24, 36 and 48-months post randomization) on specific doses of canakinumab were compared to percent changes in the placebo group during the same interval with Wilcoxon rank sum tests. At each specific follow-up time, the difference in the median percent change observed in a given dose group minus the median percent change in the placebo group at that time was used to summarize the treatment effect. Similar comparisons of percent changes in IL-6 levels between specific dose groups and placebo during the first year of treatment used the same approach.

CANTOS was designed to test three formal primary statistical null hypotheses:

H11: The hazard rate for first adjudication committee confirmed primary vascular events in the canakinumab 300 mg group is greater than or equal to the hazard rate of the placebo group;

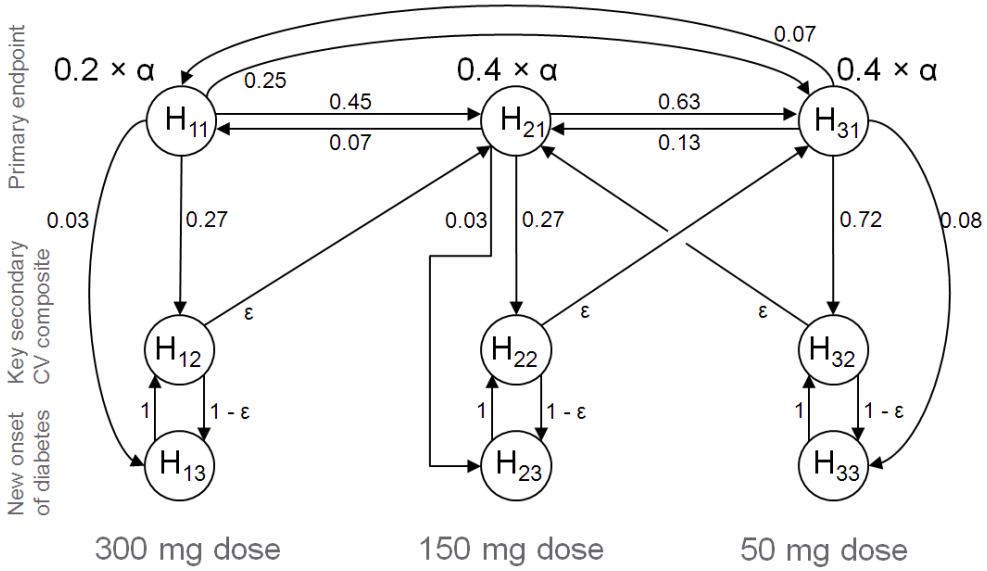
H21: The hazard rate for first adjudication committee confirmed primary vascular events in the canakinumab 150 mg group is greater than or equal to the hazard rate of the placebo group;

H31: The hazard rate for first adjudication committee confirmed primary vascular events in the canakinumab 50 mg group is greater than or equal to the hazard rate of the placebo group.

These hypotheses were tested by comparing each active dose to placebo with a log-rank test (3) stratified by time since index MI (30 days to < 6 months and ≥ 6 months) and by trial part (before versus after inclusion of the 50 mg dose) using the Full Analysis Set according to the intention-to-treat principle. Point estimates and confidence intervals for estimated relative hazards in treated versus placebo subjects were obtained from proportional hazards models with the exact method for tied failure times (4), stratified by time since index MI (30 days to < 6 months and ≥ 6 months) and by trial part (before versus after inclusion of the 50 mg dose), again using the Full Analysis Set according to the intention-to-treat principle.

For regulatory purposes, the family-wise error rate was controlled across the primary and two key secondary efficacy endpoints and the two interim analyses with the final analysis using the multiple testing procedure described below (5). For proof-of-concept purposes, for academic publication, and consistent with analyses conducted throughout the trial for all Data and Safety Monitoring Board meetings, unadjusted two-sided P-values and confidence intervals were reported. These analyses compared each active dose separately with placebo, trends in hazard rates across ascending canakinumab doses with scores 0, 1, 3, and 6 proportional to dose, and the combined active canakinumab treatment groups versus placebo. Parallel analyses were used for key secondary endpoints, exploratory cardiovascular endpoints, all-cause mortality, and adverse events.

Within the formal regulatory structure, we have adopted a sequentially rejective multiple test procedure to cap the familywise error rate (the probability of erroneously rejecting at least one true null hypothesis) at 0.025 (one-sided) accounting for the two interim efficacy analyses and the final analysis. Specifically, each null hypothesis was tested against the one-sided alternative that the hazard rate is smaller for the respective active dose group than for the placebo group. These hypotheses were tested by comparing each dose to placebo with a log-rank test stratified by time since index myocardial infarction (30 days to < 6 months and ≥ 6 months) and whether randomization was under the original 1:1.1 scheme or not.



Based on this testing procedure, if the primary null hypothesis for a dose has been rejected the key secondary endpoints for that dose are tested using a weighted Bonferroni-Holm test (6) at the available local significance level for the key secondary endpoints for that dose. The weighting of this Bonferroni-Holm procedure will be 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint.

Intersection null hypotheses involving the primary null hypotheses for the 300 mg, 150 mg or 50 mg doses were tested using a weighted version of Dunnett's test (7). Specifically, for any intersection hypothesis from the full closure that contains at least two of H11, H21 and H31, a weighted Dunnett test amongst the primary null hypotheses is performed with the overall significance level for that test and the weighting chosen according to the weights assigned to these null hypotheses by the update algorithm of the graphical method. The nominal adjusted significance levels based on the weighted Dunnett test are always slightly larger than the corresponding Bonferroni levels.

During the course of the trial, two interim analyses were conducted after 50% and 75%, respectively, of the target number of 1,400 participants had experienced a primary cardiovascular endpoint. To conserve alpha for the final analysis and to limit the possibility of a chance positive interim finding, each interim analysis followed the same closed testing procedure, with a one-sided significance level of 0.01% allotted to the first efficacy interim analysis, and a one-sided significance level of 0.04% allotted to the second efficacy interim analysis, and thus a one-sided significance level of 2.45% retained for the final analysis. Each interim analysis used a fixed Bonferroni split of the available one sided significance level. In this fashion the familywise type I error rate was controlled at the overall (one-sided) significance level α = 2.5% (functionally equivalent to a two-sided α = 5.0%).

Although the protocol specified the critical values for multiplicity-adjusted significance of any dose versus placebo in terms of one-sided tests, these are detailed here with respect to the two-sided P-values shown throughout the text. The trial spent 0.001 of its overall alpha of 0.05 on two interim analyses, and thus had remaining alpha of 0.049

at the final analysis (this is twice the one-sided remaining alpha of .0245 specified in the protocol). For reasons discussed in the protocol, 20% of this alpha (i.e. alpha of 0.098) was allocated to the test of the 300 mg dose versus placebo, 40% (i.e. alpha of 0.0196) to the test of the 150 mg dose versus placebo, and 40% (i.e. alpha of 0.0196) to the test of the 50 mg dose versus placebo. Importantly, because the three primary comparisons involved the common placebo group, the tests are correlated, so the primary analyses used a weighted Dunnett test to account for this correlation. While the protocol specified the approach to obtain the critical values, the final calculation of the critical values was performed at the time of database lock using the numbers of subjects in each treatment group and the correlations in the full analysis dataset. Thus, for the primary hypothesis tests, the two-sided critical values for the weighted Dunnett test are 0.01058 for the test of the 300 mg dose versus placebo, 0.02115 for the test of the 150 mg dose versus placebo, and 0.02115 for the test of the 50 mg dose versus placebo. Turning to the results shown in Table 2 of the paper, the 2-sided P-value from the log-rank test comparing the hazard of the primary endpoint between the 150 mg dose and placebo was 0.02074 which lies below the critical value of 0.02115 leading to rejection of the null hypothesis that the hazard rate of a confirmed primary endpoint was greater than or equal to the hazard rate in the placebo group. Neither of the log-rank P-values for the comparisons involving the 50 or the 300 mg doses were below their respective thresholds, so that no further formal testing of secondary endpoints was conducted.

Since the primary null hypothesis related to the 150 mg dose was rejected, the pre-specified procedure of Bretz et al was applied to test the key secondary endpoint of MACE plus unstable angina requiring urgentrevascularization. The protocol specified use of a Bonferroni-Holm procedure for this test. For this key secondary endpoint, the 2-sided critical value for significance was 0.00529. Since the observed 2-sided P-value for the comparison of the rate of the key secondary endpoint was 0.00525 (Table 2), the null hypothesis that the hazard of this endpoint in those assigned to the 150 mg dose was equal to or greater than the hazard in those assigned to placebo was rejected.

The validity of the proportional hazards assumption was tested for each model used for the pairwise comparison of an active dose of canakinumab versus placebo, separately for the primary and the key secondary endpoint. The evaluation used a Kolmogorov-type supremum test (8) implemented in Proc Phreg of SAS. The assumption of proportional hazards was not rejected for all models except one: for the comparison of the 50 mg dose versus placebo for the key secondary outcome of MACE plus hospitalization for unstable angina requiring urgent revascularization the test statistic was nominally significant (P=0.041). Consideration of the pattern of residuals, as well as separate analyses in the first 2 years of follow-up versus thereafter indicated that an apparent early benefit of the 50 mg dose on this outcome dissipated over time (Supplemental Figure S3).

With respect to power, CANTOS was designed such that if the trial accrued a confirmed primary endpoint in 1,400 randomized participants, and it was assumed that all three active doses reduced the primary event rate equally by 20%, there would be > 90% power to find a significant risk reduction in at least one canakinumab dose as compared to placebo. Depending on the exact distribution of endpoints across the three trial arms, either the 150 mg dose would

need to achieve a relative risk reduction of 15 to 16% versus placebo, or the 300 or 50 mg dose would need to achieve a relative risk reduction of 17 to 18% versus placebo in order for any dose to become significant.

Two simple one degree of freedom tests were used for exploratory purposes to aid in evaluation of associations of canakinumab with risks of primary outcomes and adverse effects relative to placebo: a test assuming a common effect of all doses of canakinumab on the relative hazard of the outcome, and a test assuming a linear trend across doses with scores 0, 1, 3, and 6. P-values came from likelihood ratio tests based on proportional hazards models stratified on time since index MI (30 days to < 6 months and ≥ 6 months) and whether randomization was under the original 1:1.1 scheme or not. P-values from these models are shown in the last two columns of Tables 2 and 3. Likelihood ratio goodness-of-fit tests were used to evaluate these models. Specifically, both of these one degree of freedom models are nested within a more general proportional hazards model that assumes distinct effects of each active dose versus placebo on the hazard of the outcome (i.e. includes an indicator variable for each of the three active treatment groups), with the same stratification variables as above. The two degree of freedom goodness of fit tests of the null hypothesis that the simple model adequately fits the data indicated that at least one of the two simple models provided an adequate fit (P>0.05) for each of the efficacy and side effect outcomes.

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D. Supplemental Table S1: Effects of 3-month treatment with canakinumab on hsCRP, IL-6, and lipid levels.

Biomarker		Placebo	Canakinumab Dose (SC q 3 months)			
			50mg	150mg	300mg	All Doses
hsCRP (mg/L)	Baseline median	4.10	4.20	4.20	4.13	4.15
	3-month median	3.50	2.20	1.80	1.30	1.80
	Change median, %	-17.1	-47.4	-59.2	-67.6	-58.6
	Interquartile range	-46.7,22.5	-67.7,-16.2	-75.4,-30.7	-80.7,-43.9	-76.0,-29.6
	P-value+		<0.001	<0.001	<0.001	<0.001
IL-6 (ng/L)	Baseline median	2.58	2.53	2.54	2.58	2.54
	3-month median	2.61	1.98	1.64	1.44	1.64
	Change median, %	0.00	-24.7	-36.3	-43.2	-35.2
	Interquartile range	-25.1,36.6	-45.8,2.6	-54.9,-8.2	-61.2,-21.1	-55.3,-8.5
	P-value+		<0.001	<0.001	<0.001	<0.001
LDLC (mg/dL)	Baseline median	82.8	81.2	82.0	83.1	82.0
	3-month median	82.0	82.4	84.0	83.1	83.1
	Change median, %	0.00	1.4	1.1	1.9	1.5
	Interquartile range	-13.6,14.9	-12.1,18.8	-12.3,17.6	-12.1,19.0	-12.1,18.5
	P-value+		0.002	0.015	0.001	<0.001
HDLC (mg/dL)	Baseline median	44.5	43.7	43.7	44.0	44.0
	3-month median	44.9	44.9	45.2	46.0	45.2
	Change median, %	0.00	2.9	3.7	3.8	3.5
	Interquartile range	-8.0,9.2	-6.42,11.8	-5.0,13.4	-5.0,15.2	-5.5,13.5
	P-value+		<0.001	<0.001	<0.001	<0.001
TG (mg/dL)	Baseline median	139.1	140.8	138.2	137.6	139.1
	3-month median	139.0	148.8	144.0	145.3	146.1
	Change median, %	-0.7	4.5	4.7	5.4	4.8
	Interquartile range	-19.0,23.3	-16.5,27.9	-15.4,30.1	-15.8,31.1	-15.9,29.8
	P-value+		<0.001	<0.001	<0.001	<0.001

+ Wilcoxon rank sum test for the % change from baseline in the canakinumab group as compared to the % change from baseline in the placebo group

E. Supplemental Table S2: Effects of 12-month treatment with canakinumab on hsCRP, IL-6, and lipid levels.

Biomarker		Placebo	Canakinumab Dose (SC q 3 months)			
			50mg	150mg	300mg	All Doses
hsCRP (mg/L)	Baseline median	4.05	4.20	4.15	4.10	4.15
	12-month median	3.40	2.20	1.80	1.50	1.80
	Change median, %	-18.4	-47.5	-57.1	-62.8	-56.4
	Interquartile range	-48.6,24.0	-69.3,-10.0	-76.1,-25.3	-79.0,-35.2	-75.7,-23.8
	P-value+		<0.001	<0.001	<0.001	<0.001
IL-6 (ng/L)	Baseline median	2.56	2.51	2.53	2.55	2.53
	12-month median	2.63	2.04	1.71	1.60	1.76
	Change median, %	3.49	-19.1	-33.8	-37.7	-30.9
	Interquartile range	-24.7,38.5	-44.0,14.7	-53.9,-6.0	-59,0,-4.1	-53.8,2.2
	P-value+		<0.001	<0.001	<0.001	<0.001
LDLC (mg/dL)	Baseline median	83.0	80.4	82.0	83.1	82.0
	12-month median	82.4	84.0	82.4	84.0	83.5
	Change median, %	0.00	1.53	0.81	0.00	0.88
	Interquartile range	-15.7,18.5	-14.5,22.6	-15.2,21.6	-16.2,20.8	-15.4,21.7
	P-value+		0.041	0.22	0.64	0.11
HDLC (mg/dL)	Baseline median	44.1	44.0	43.8	44.0	44.0
	12-month median	44.5	44.5	44.9	45.0	44.9
	Change median, %	0.00	1.06	2.67	2.75	2.22
	Interquartile range	-9.3,9.8	-8.1,11.8	-6.5,13.9	-7.1,13.6	-7.2,13.3
	P-value+		<0.001	<0.001	<0.001	<0.001
TG (mg/dL)	Baseline median	139.1	139.9	139.0	138.2	139.1
	12-month median	137.3	147.0	144.7	147.9	147.0
	Change median, %	-0.9	4.0	5.7	4.7	4.7
	Interquartile range	-21.6,25.5	-16.9,32.2	-17.2,35.2	-17.0,35.3	-17.0,34.2
	P-value+		<0.001	<0.001	<0.001	<0.001

+ Wilcoxon rank sum test for the % change from baseline in the canakinumab group as compared to the % change from baseline in the placebo group

F. Supplemental Table S3: Effects of 24-month treatment with canakinumab on hsCRP and lipid levels.

Biomarker		Placebo	Canakinumab Dose (SC q 3 months)			
			50mg	150mg	300mg	All Doses
hsCRP (mg/L)	Baseline median	4.05	4.15	4.10	4.08	4.10
	24-month median	3.40	2.30	1.80	1.60	1.90
	Change median, %	-20.6	-46.4	-56.5	-59.5	-54.6
	Interquartile range	-51.2,25.7	-69.5,-4.7	-75.3,-20.4	-77.9,-29.8	-74.8,-18.9
	P-value+		<0.001	<0.001	<0.001	<0.001
LDLC (mg/dL)	Baseline median	83.0	80.8	82.0	82.4	82.0
	24-month median	83.0	84.0	84.3	83.1	83.9
	Change median, %	0.0	2.2	2.1	1.5	1.9
	Interquartile range	-16.7,21.6	-15.4,24.5	-15.5,25.8	-17.3,23.5	-15.9,24.5
	P-value+		0.015	0.014	0.30	0.011
HDLC (mg/dL)	Baseline median	44.1	44.0	44.0	44.0	44.0
	24-month median	44.0	44.1	44.9	45.2	44.9
	Change median, %	0.00	0.76	1.92	2.45	1.90
	Interquartile range	-9.8,10.4	-9.3,12.3	-7.9,13.2	-8.1,14.0	-8.4,13.3
	P-value+		0.07	<0.001	<0.001	<0.001
TG (mg/dL)	Baseline median	139.1	139.9	139.0	138.2	139.1
	24-month median	136.0	142.6	146.1	146.0.	145.3
	Change median, %	-2.0	2.9	5.3	4.9	4.6
	Interquartile range	-23.4,25.0	-19.3,32.9	-18.3,35.1	-18.3,33.3	-18.7,34.0
	P-value+		<0.001	<0.001	<0.001	<0.001

+ Wilcoxon rank sum test for the % change from baseline in the canakinumab group as compared to the % change from baseline in the placebo group

G. Supplemental Table S4: Effects of 36-month treatment with canakinumab on hsCRP and lipid levels.

Biomarker		Placebo	Canakinumab Dose (SC q 3 months)			
			50mg	150mg	300mg	All Doses
hsCRP (mg/L)	Baseline median	4.05	4.10	4.15	4.05	4.10
	36-month median	3.50	2.40	2.00	1.70	2.00
	Change median, %	-18.8	-41.7	-53.9	-58.8	-52.2
	Interquartile range	-52.2,32.0	-67.7,-2.2	-73.7,-18.0	-77.5,-26.7	-73.6,-14.6
	P-value+		<0.001	<0.001	<0.001	<0.001
LDLC (mg/dL)	Baseline median	83.1	80.8	82.0	82.4	81.6
	36-month median	82.8	83.1	84.0	83.5	83.9
	Change median, %	-0.5	3.1	3.3	1.2	2.5
	Interquartile range	-17.8,22.4	-15.6,27.1	-16.7,28.7	-17.2,27.2	-16.5,27.7
	P-value+		0.002	<0.001	0.039	<0.001
HDLC (mg/dL)	Baseline median	44.1	44.0	43.7	44.0	44.0
	36-month median	44.0	44.0	44.5	45.0	44.5
	Change median, %	-1.3	0.00	1.6	2.1	1.3
	Interquartile range	-11.4,10.4	-10.6,11.8	-8.6,13.7	-9.1,14.1	-9.3,13.3
	P-value+		0.011	<0.001	<0.001	<0.001
TG (mg/dL)	Baseline median	139.1	140.8	139.9	138.2	139.5
	36-month median	134.6	142.3	147.0	144.4	145.0
	Change median, %	-0.6	2.4	4.5	6.3	3.9
	Interquartile range	-23.8,28.1	-21.4,33.3	-19.9,37.7	-18.3,37.1	-19.9,36.4
	P-value+		0.012	<0.001	<0.001	<0.001

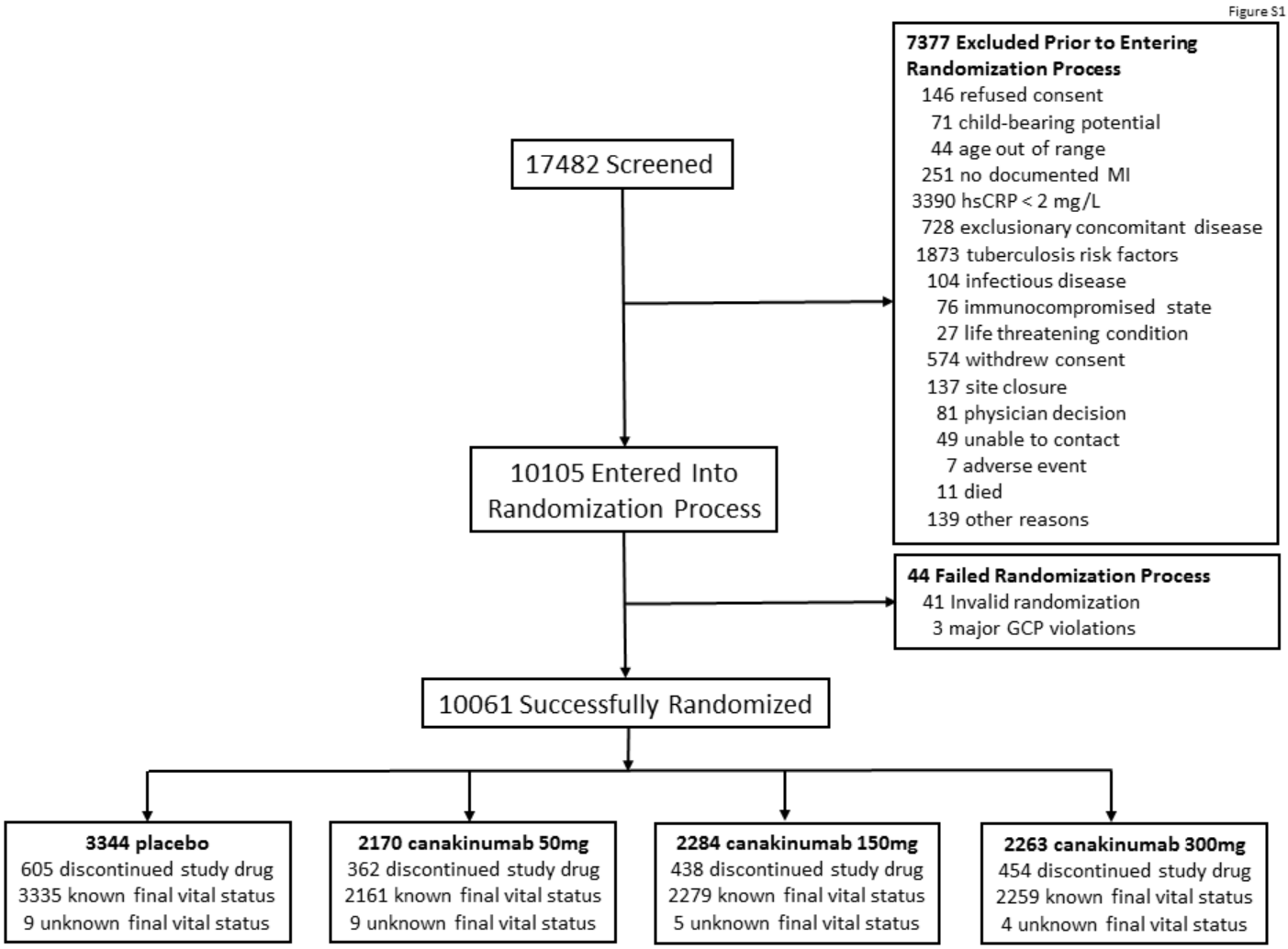
+ Wilcoxon rank sum test for the % change from baseline in the canakinumab group as compared to the % change from baseline in the placebo group

H. Supplemental Table S5: Effects of 48-month treatment with canakinumab on hsCRP and lipid levels.

Biomarker		Placebo	Canakinumab Dose (SC q 3 months)			
			50mg	150mg	300mg	All Doses
hsCRP (mg/L)	Baseline median	4.10	4.20	4.30	4.25	4.25
	48-month median	3.60	2.50	2.00	1.90	2.10
	Change median, %	-17.1	-43.4	-54.1	-57.8	-52.4
	Interquartile range	-51.7,29.4	-67.4,2.6	-74.4,-16.5	-76.9,-17.2	-73.3,-10.0
	P-value+		<0.001	<0.001	<0.001	<0.001
LDLC (mg/dL)	Baseline median	85.1	84.7	82.4	86.0	84.7
	48-month median	82.4	84.0	84.7	85.0	84.3
	Change median, %	-1.4	0.0	1.7	-2.8	0.0
	Interquartile range	-20.2,20.8	-18.9,24.3	-16.0,24.7	-20.6,24.9	-19.1,24.7
	P-value+		0.19	0.004	0.67	0.045
HDLC (mg/dL)	Baseline median	44.1	44.5	43.7	44.1	44.1
	48-month median	43.7	44.5	44.0	44.9	44.1
	Change median, %	-2.25	0.00	0.00	0.00	0.00
	Interquartile range	-12.8,10.0	-10.1,11.5	-10.3,13.7	-9.5,15.3	-10.0,13.6
	P-value+		0.008	<0.001	<0.001	<0.001
TG (mg/dL)	Baseline median	141.7	138.1	140.8	138.2	139.1
	48-month median	139.0	140.0	152.3	139.0	144.4
	Change median, %	-3.2	1.7	7.5	2.3	3.8
	Interquartile range	-25.0,26.8	-22.8,32.2	-18.9,39.4	-23.4,34.5	-21.7,36.3
	P-value+		0.026	<0.001	0.021	<0.001

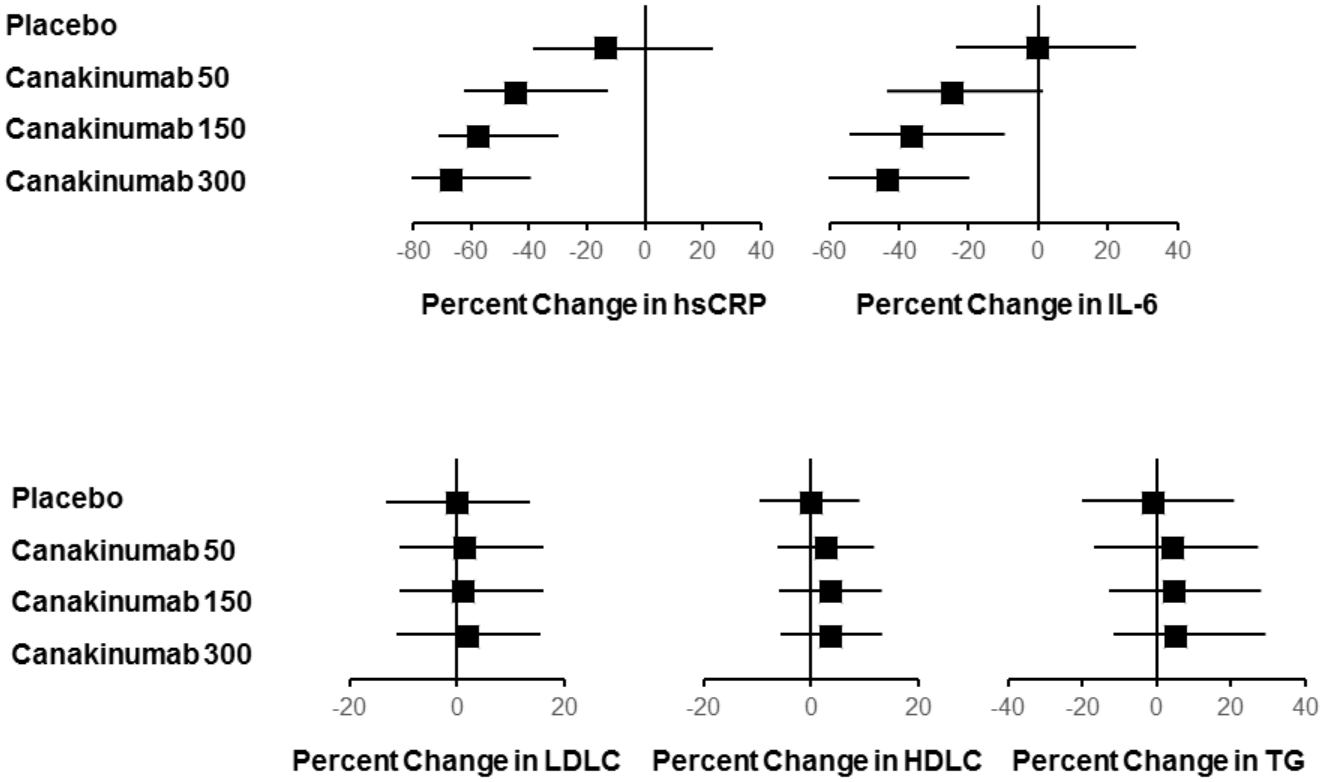
+ Wilcoxon rank sum test for the % change from baseline in the canakinumab group as compared to the % change from baseline in the placebo group

I. Supplemental Figure S1: CANTOS Consort Diagram

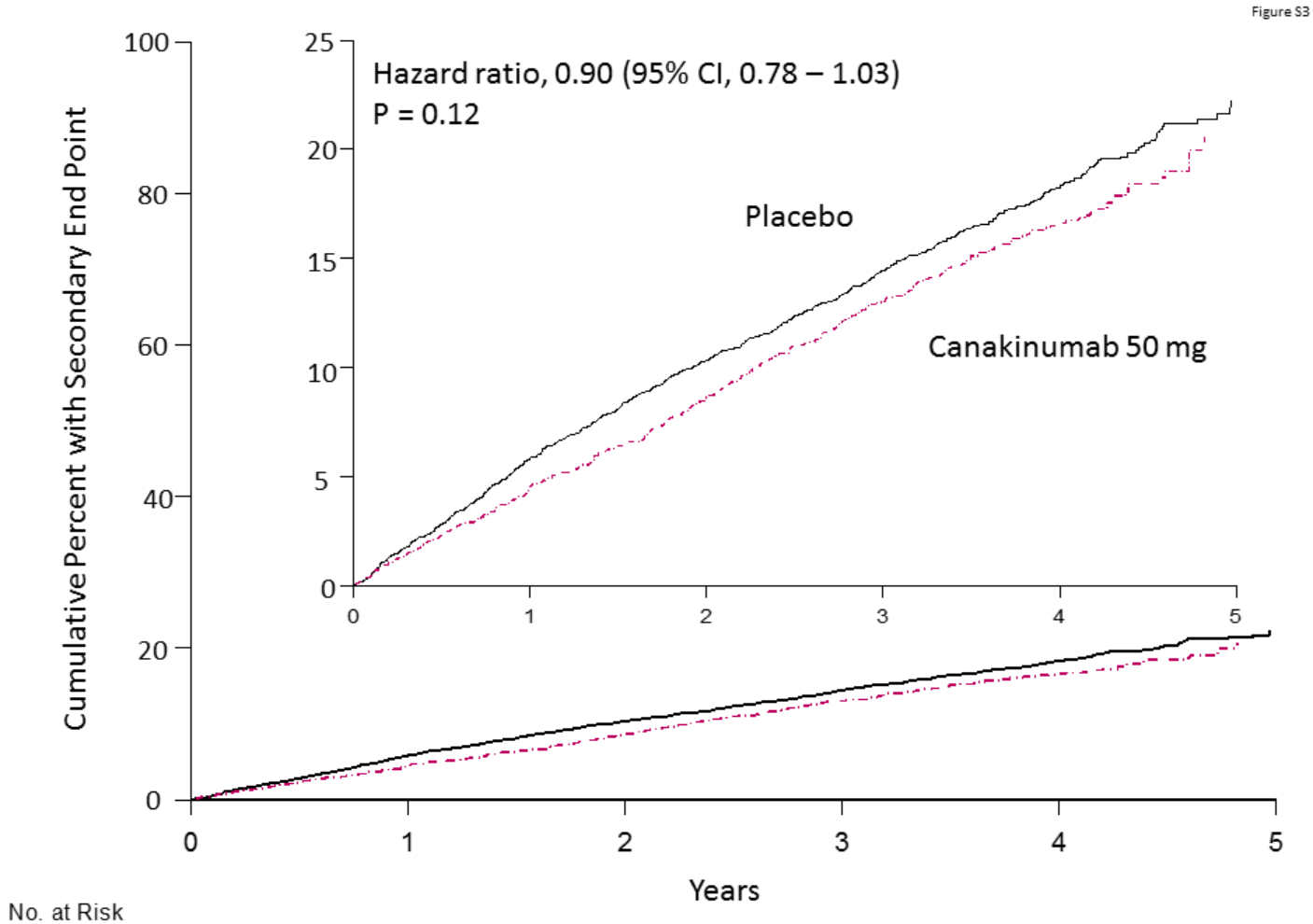


J. Supplemental Figure S2: 3-month effects of placebo and canakinumab on hsCRP, IL-6, and lipids

Figure S2



K. Supplemental Figure S3: Cumulative percent with the secondary end point of myocardial infarction, stroke, cardiovascular death and hospitalization for unstable angina requiring urgent revascularization in the 50mg canakinumab group



L. Supplemental Figure S4: Cumulative percent with the secondary endpoint of myocardial infarction, stroke, cardiovascular death and hospitalization for unstable angina requiring urgent revascularization in the 300mg canakinumab group