Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial

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Summary

Background Canakinumab, a monoclonal antibody targeting interleukin-1β, reduces inflammation and cardiovascular event rates with no effect on lipid concentrations. However, it is uncertain which patient groups benefit the most from treatment and whether reductions in the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) correlate with clinical benefits for individual patients.

Methods The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) used computer-generated codes to randomly allocate 10 061 men and women with a history of myocardial infarction to placebo or one of three doses of canakinumab (50 mg, 150 mg, or 300 mg) given subcutaneously once every 3 months. In a prespecified secondary analysis designed to address the relationship of hsCRP reduction to event reduction in CANTOS, we evaluated the effects of canakinumab on rates of major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality according to on-treatment concentrations of hsCRP. We used multivariable modelling to adjust for baseline factors associated with achieved hsCRP and multiple sensitivity analyses to address the magnitude of residual confounding. The median follow-up was 3·7 years. The trial is registered with ClinicalTrials.gov, number NCT01327846.

Findings Baseline clinical characteristics did not define patient groups with greater or lesser cardiovascular benefits when treated with canakinumab. However, trial participants allocated to canakinumab who achieved hsCRP concentrations less than 2 mg/L had a 25% reduction in major adverse cardiovascular events (multivariable adjusted hazard ratio [HR^{adj}]=0·75, 95% CI 0·66–0·85, p<0·0001), whereas no significant benefit was observed among those with on-treatment hsCRP concentrations of 2 mg/L or above (HR^{adj}=0·90, 0·79–1·02, p=0·11). For those treated with canakinumab who achieved on-treatment hsCRP concentrations less than 2 mg/L, cardiovascular mortality (HR^{adj}=0·69, 95% CI 0·56–0·85, p=0·0004) and all-cause mortality (HR^{adj}=0·69, 0·58–0·81, p<0·0001) were both reduced by 31%, whereas no significant reduction in these endpoints was observed among those treated with canakinumab who achieved hsCRP concentrations of 2 mg/L or above. Similar differential effects were found in analyses of the trial prespecified secondary cardiovascular endpoint (which additionally included hospitalisation for unstable angina requiring unplanned revascularisation) and in sensitivity analyses alternatively based on median reductions in hsCRP, on 50% or greater reductions in hsCRP, on the median percent reduction in hsCRP, in dose-specific analyses, and in analyses using a causal inference approach to estimate the effect of treatment among individuals who would achieve a targeted hsCRP concentration.

Interpretation The magnitude of hsCRP reduction following a single dose of canakinumab might provide a simple clinical method to identify individuals most likely to accrue the largest benefit from continued treatment. These data further suggest that lower is better for inflammation reduction with canakinumab.

Funding Novartis Pharmaceuticals.

Lancet 2018; 391: 319–28

Published Online November 13, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32814-3

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See Online for appendix

Introduction

Low-grade chronic inflammation contributes to all stages of the atherothrombotic process, spanning early plaque initiation, mature plaque growth, and acute plaque rupture preceding myocardial infarction, stroke, and cardiovascular death.[1,2] In the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), which enrolled 10 061 patients with a previous history of myocardial infarction, we recently demonstrated that canakinumab, a human therapeutic monoclonal antibody targeting interleukin-1β, significantly reduced major adverse cardiovascular event rates in the absence of lipid lowering.[3] Specifically, in CANTOS, random allocation to canakinumab at doses of either 150 mg or 300 mg subcutaneously once every 3 months resulted in a 39% reduction in high-sensitivity C-reactive protein (hsCRP) and a 15% reduction in major adverse cardiovascular events when compared with placebo, despite having no effect on LDL cholesterol. By contrast, random allocation to canakinumab 50 mg subcutaneously

Research in context

Evidence before this study

It is uncertain which patients gain the greatest cardiovascular benefit when treated with the anti-inflammatory agent canakinumab or if these benefits relate to the magnitude of inflammation reduction achieved for individual patients. We searched MEDLINE from inception until Aug 15, 2017, for the terms "cholesterol, LDL", "high sensitivity C-reactive protein, hsCRP", "residual risk", "myocardial infarction", "stroke", "interleukin-1", and "canakinumab" to identify previous publications in the English language describing the association of on-treatment high-sensitivity C-reactive protein (hsCRP) concentrations with cardiovascular outcomes in contemporary randomised trials of patients with or at risk for atherosclerotic cardiovascular disease. Whereas multiple previous analyses support the hypothesis that both on-treatment LDL cholesterol and on-treatment hsCRP define patient groups more or less likely to benefit from treatment, almost all of these previous analyses relate to statin therapy, which both lowers cholesterol and lowers inflammation. We found no previous outcome data for agents that only reduce inflammation without concomitant effects on cholesterol.

Added value of this study

CANTOS provides clinical trial evidence suggesting that patients who achieve lower concentrations of hsCRP after initiating canakinumab obtain greater cardiovascular benefits. Specifically, while baseline risk factors did not predict efficacy, individuals with robust reductions in hsCRP following a single dose of canakinumab had large, significant reductions in major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality with continued therapy. By contrast, clinical benefits were smaller among individuals who achieved less robust reductions of hsCRP after initiation of treatment.

Implications of all the available evidence

The use of a simple biological measure of inflammatory response might provide clinicians with a method to define patient groups most likely to benefit from long-term canakinumab treatment. These analyses have implications for patient selection, the number needed to treat, and cost-effectiveness of canakinumab among patients post myocardial infarction with residual inflammatory risk, as well as pathophysiological implications for future drug development. Studies of alternative anti-inflammatory therapies designed to target atherosclerosis will be needed to confirm and extend these findings.

once every 3 months resulted in a 26% reduction in hsCRP and a smaller non-significant 7% reduction in major cardiovascular events compared with placebo. While these data support the inflammation hypothesis of atherothrombosis, it is currently uncertain which patient groups benefit the most from treatment.

To address this issue, which has implications for pathophysiology, drug development, clinical practice, and cost-effectiveness, we sought to determine if the benefits of interleukin-1β inhibition with canakinumab on cardiovascular events in CANTOS related either to baseline clinical characteristics of the trial population or to the magnitude or level of hsCRP reduction achieved by individual trial participants. Performing on-treatment analyses of this type was prespecified in the CANTOS protocol and statistical analysis plan as exploratory outcomes relevant to understanding the biology of canakinumab.[4]

Methods

Study design and participants

CANTOS was a randomised, double-blind placebo-controlled trial that evaluated three doses of canakinumab (50 mg, 150 mg, or 300 mg) given subcutaneously once every 3 months as compared with matching subcutaneous placebo for the prevention of atherosclerotic events.[3,4] Overall, between April 11, 2011, and March 25, 2014, CANTOS enrolled 10 061 patients with a history of myocardial infarction and concentrations of hsCRP of 2 mg/L or above from over 1000 clinical sites in 39 countries. The study excluded patients with a history of chronic or recurrent infections, previous malignancy other than basal cell skin carcinoma, a suspected or known immunocompromised state, or a history of (or at high risk for) tuberculosis or HIV-related disease, and those using systemic anti-inflammatory treatments. All trial participants provided written informed consent to participate in the trial, which was overseen by an independent data and safety monitoring board.

Procedures

Blood samples were obtained from all trial participants in the canakinumab and placebo groups at randomisation and among 9534 participants (95%) at 3 months, just before repeat canakinumab (or placebo) injection. All baseline and 3 month samples were assayed for hsCRP and lipid concentrations in a central laboratory.

Outcomes

The primary endpoint was a composite of adjudicated recurrent myocardial infarction, stroke, or cardiovascular death. The key prespecified secondary cardiovascular efficacy endpoint included these events as well as adjudicated episodes of hospitalisation for unstable angina requiring urgent coronary revascularisation. Additional major endpoints adjudicated by the trial

endpoint committee included cardiovascular mortality, cancer mortality,[5] and all-cause mortality. Median follow-up was 3·7 years.

Statistical analysis

For the current analysis, we first ascertained whether the overall effect of canakinumab on future cardiovascular event rates was modified by common baseline clinical characteristics including age, sex, diabetes, smoking status, body-mass index (BMI), and hsCRP or lipid concentrations. We then divided trial participants allocated to canakinumab into two groups according to whether the concentration of hsCRP at 3 months was less than, or equal to or greater than 2 mg/L, a commonly used clinical cutpoint for hsCRP.[6] χ^2 tests were used to assess for significant differences between these two groups for categorical variables, and Wilcoxon rank-sum tests for continuous variables.

On a per-protocol prespecified basis, we used Cox proportional-hazards models stratified by time since index myocardial infarction to estimate relative hazards for major adverse cardiovascular events in these two groups, compared with those allocated placebo. Similar analyses compared the outcomes of cardiovascular mortality, all-cause mortality, and fatal infection. To address issues of confounding, multivariable modelling was used to adjust for baseline characteristics known to modestly affect hsCRP including age, sex, smoking status, hypertension, diabetes, and BMI. The multivariable models additionally adjusted for baseline hsCRP and LDL cholesterol. As an internal check to ensure the validity of this approach, we repeated the above process alternatively dividing the cohort according to whether the concentration of hsCRP at 3 months was less than, or equal to or greater than the study on-treatment median value of 1·8 mg/L; on the basis of tertiles of on-treatment hsCRP (rather than medians); on the basis of achieving reductions in hsCRP of greater than or less than 50%; and on the basis of achieving greater or less than the median percent reduction in hsCRP. Similar analyses were done at individual canakinumab dose concentrations to eliminate the potential for confounding on this basis.

In all instances, Cox proportional hazards models were used to estimate hazard ratios (HRs) comparing the different on-treatment canakinumab groups to placebo. p values for the test of trend were calculated across these

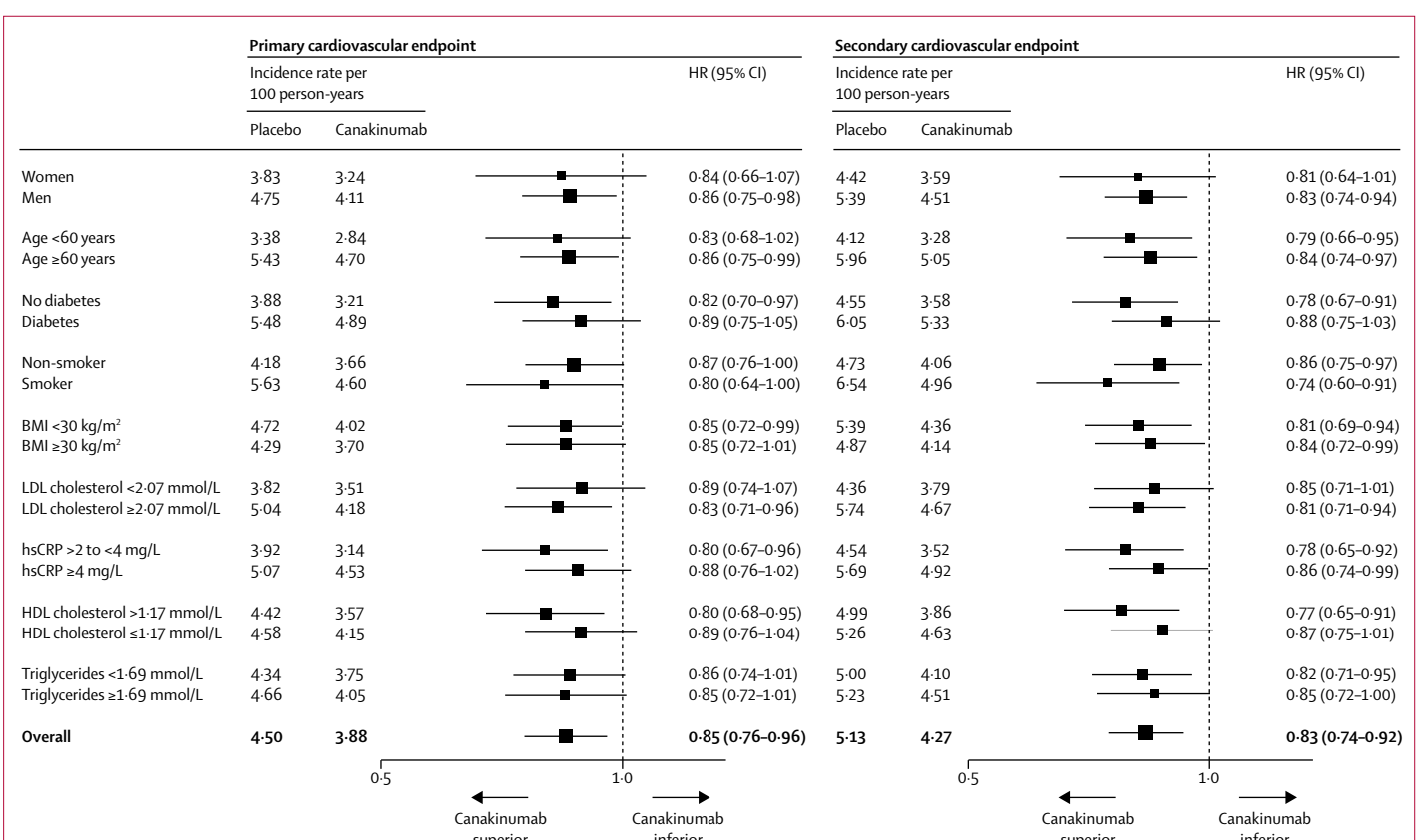

Figure 1: **Clinical efficacy of canakinumab as compared with placebo for the trial primary endpoint (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) and the trial secondary endpoint (non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina requiring unplanned revascularisation, or cardiovascular death) according to subgroups based upon baseline clinical characteristic**

Data are shown for the combined canakinumab 150 mg and 300 mg groups. HR=hazard ratio. BMI=body-mass index. hsCRP=high-sensitivity C-reactive protein.

three groups scored as 0, 1, or 2. Kaplan-Meier curves were constructed to visually evaluate any differences between groups.

As an alternative method to evaluate potential differences in on-treatment groups, we did a causal inference analysis which compared potential outcomes of individual participants treated with canakinumab had they counterfactually been treated with placebo. This latter analysis was again done at individual canakinumab dose concentrations to eliminate the potential for confounding on this basis.

To provide an overall assessment of clinical efficacy, the number needed to treat (NNT) over 5 years for the endpoint inclusive of myocardial infarction, stroke, coronary revascularisation, or death from any cause was computed as the reciprocal of the absolute difference between risks in patients treated with canakinumab versus patients treated with placebo based on Kaplan-Meier estimates of risk. Estimates were calculated for the cohort as a whole and separately among those who did or did not achieve hsCRP concentrations less than 2 mg/L.

All p values are two-sided and all CIs are at the 95% level. The trial is registered at ClinicalTrials.gov, number NCT01327846.

	Placebo (n=3182)	Canakinumab, hsCRP ≥2·0 mg/L at 3 months (n=2868)	Canakinumab, hsCRP <2·0 mg/L at 3 months (n=3484)
Age (years)	61·0 (54·0–68·0)	61·0 (55·0–68·0)	61·0 (54·0–68·0)
Sex			
Male	2365 (74%)	2115 (74%)	2620 (75%)
Female	817 (26%)	753 (26%)	864 (25%)
Current smoking	722 (23%)	795 (28%)	717 (21%)
Body-mass index (kg/m²)	29·7 (26·6–33·9)	30·5 (27·0–34·7)	29·6 (26·4–33·1)
Waist circumference (cm)	104·0 (96·0–114·3)	106·0 (97·0–116·8)	103·0 (95·0–112·0)
Hypertension	2514 (79%)	2328 (81%)	2747 (79%)
Diabetes	1265 (40%)	1229 (43%)	1307 (38%)
Qualifying myocardial infarction			
STEMI	1714 (54%)	1531 (53%)	1960 (56%)
Non-STEMI	1076 (34%)	983 (34%)	1143 (33%)
Unknown or missing	392 (12%)	354 (12%)	381 (11%)
History of PCI	2099 (66%)	1920 (67%)	2375 (68%)
History of CABG	453 (14%)	436 (15%)	458 (13%)
History of congestive heart failure	684 (21%)	662 (23%)	699 (20%)
Lipid-lowering therapy	2980 (94%)	2647 (92%)	3284 (94%)
Renin-angiotensin inhibitors	2527 (80%)	2263 (79%)	2787 (80%)
Anti-ischaemia agents*	2929 (92%)	2624 (92%)	3172 (91%)
hsCRP (mg/L)	4·10 (2·75–6·85)	5·55 (3·60–9·25)	3·40 (2·45–5·20)
Interleukin-6 (ng/L)	2·59 (1·79–4·03)	3·02 (2·02–4·86)	2·27 (1·59–3·43)
Total cholesterol (mmol/L)	4·15 (3·54–4·89)	4·19 (3·55–4·94)	4·08 (3·49–4·81)
LDL cholesterol (mmol/L)	2·14 (1·67–2·77)	2·16 (1·68–2·82)	2·10 (1·61–2·71)
HDL cholesterol (mmol/L)	1·15 (0·96–1·36)	1·11 (0·93–1·34)	1·14 (0·96–1·37)
Triglycerides (mmol/L)	1·57 (1·13–2·20)	1·60 (1·17–2·28)	1·54 (1·14–2·15)
eGFR (mL/min per 1·73 m²)	79·0 (65·0–93·0)	79·0 (64·0–93·0)	78·0 (65·0–92·0)
Randomised to canakinumab 50 mg	..	1155 (40%)	905 (26%)
Randomised to canakinumab 150 mg	..	977 (34%)	1186 (34%)
Randomised to canakinumab 300 mg	..	736 (26%)	1393 (40%)

Data are medians (IQR) for continuous variables and n (%) for categorical variables. STEMI=ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. eGFR=estimated glomerular filtration rate. hsCRP=high-sensitivity C-reactive protein. *Anti-ischaemia agents were defined as beta-blocking agents, nitrates, or calcium channel-blocking agents.

Table 1: **Baseline clinical characteristics of the placebo group and the canakinumab groups according to achieved concentrations of hsCRP above or below 2 mg/L at 3 months**

Role of the funding source

This trial was sponsored by Novartis Pharmaceuticals. Employees of the sponsor were involved in the design of the trial protocol, and the sponsor was responsible for data collection. The corresponding author had full access to all study data and was responsible for the decision to submit for publication.

Results

We initially addressed whether any baseline clinical characteristic of the CANTOS population might have modified the effect of canakinumab on clinical outcomes. However, all major clinical subgroups benefited from canakinumab for both the primary and secondary cardiovascular endpoints (figure 1). Canakinumab had similar efficacy among those with LDL cholesterol concentrations less than and greater than 80 mg/dL (2·06 mmol/L), the approximate trial median concentration at study entry. A similar lack of effect modification was observed for baseline hsCRP concentrations, although the range of hsCRP values was constrained by the trial protocol which required concentrations to be at least 2 mg/L at entry.

To begin our evaluation of whether on-treatment hsCRP concentrations predict clinical outcomes with canakinumab, we next examined how those who achieved lower concentrations differed from those who did not. Table 1 shows baseline characteristics of the study population in the placebo group and in the combined canakinumab groups according to whether the on-treatment hsCRP concentration was less than 2 mg/L versus 2 mg/L or higher when measured at 3 months (before receiving the next dose). As anticipated, hsCRP concentrations were lower at baseline among participants who subsequently achieved concentrations less than 2 mg/L at 3 months compared with those who did not. The proportions of individuals achieving on-treatment hsCRP concentrations less than 2 mg/L at 3 months were 701 (22%) of 3182 patients in the placebo group, 905 (44%) of 2060 in the canakinumab 50 mg group, 1186 (55%) of 2163 in the canakinumab 150 mg group, and 1393 (65%) of 2129 in the canakinumab 300 mg group (p<0·0001).

In univariable analyses, the magnitude of decrease in hsCRP with canakinumab related directly to the magnitude of clinical benefit associated with canakinumab treatment (table 2). Compared with placebo, participants allocated to

	n	Incidence rate* (n)	HR (95% CI); p value	HR^{adj}† (95% CI); p value
hsCRP by concentration threshold				
Placebo	3182	4·39 (500)	1 (ref)	1 (ref)
Canakinumab, hsCRP ≥2 mg/L	2868	4·20 (431)	0·95 (0·84–1·09); 0·48	0·90 (0·79–1·02); 0·11
Canakinumab, hsCRP <2 mg/L	3484	3·28 (421)	0·75 (0·66–0·85); <0·0001	0·75 (0·66–0·85); <0·0001
p_{trend} across categories	..	..	<0·0001	<0·0001
hsCRP by median concentration threshold				
Placebo	3182	4·39 (500)	1 (ref)	1 (ref)
Canakinumab, hsCRP ≥1·8 mg/L	3193	4·19 (480)	0·95 (0·84–1·08); 0·47	0·90 (0·79–1·02); 0·10
Canakinumab, hsCRP <1·8 mg/L	3159	3·19 (372)	0·73 (0·63–0·83); <0·0001	0·73 (0·64–0·84); <0·0001
p_{trend} across categories	..	..	<0·0001	<0·0001
hsCRP by tertile‡				
Placebo	3182	4·39 (500)	1 (ref)	1 (ref)
Canakinumab, hsCRP top tertile	2090	4·36 (325)	0·99 (0·86–1·14); 0·93	0·93 (0·80–1·07); 0·29
Canakinumab, hsCRP middle tertile	2044	3·66 (273)	0·83 (0·72–0·96); 0·014	0·80 (0·69–0·93); 0·004
Canakinumab, hsCRP lowest tertile	2218	3·09 (254)	0·71 (0·61–0·82); <0·0001	0·73 (0·62–0·85); <0·0001
p_{trend} across categories	..	..	<0·0001	<0·0001
hsCRP by 50% reduction threshold				
Placebo	3182	4·39 (500)	1 (ref)	1 (ref)
Canakinumab, hsCRP reduction <50%	2537	3·82 (347)	0·87 (0·76–1·00); 0·046	0·87 (0·76–1·00); 0·046
Canakinumab, hsCRP reduction ≥50%	3746	3·58 (494)	0·81 (0·72–0·92); 0·001	0·81(0·71–0·91); 0·0007
p_{trend} across categories	..	..	0·0013	0·0008
hsCRP by median percent reduction threshold§				
Placebo	3182	4·39 (500)	1 (ref)	1 (ref)
Canakinumab, hsCRP reduction <58·14%	3142	3·77 (426)	0·86 (0·75–0·98); 0·020	0·86 (0·75–0·98); 0·023
Canakinumab, hsCRP reduction ≥58·14%	3141	3·59 (415)	0·82 (0·72–0·93); 0·002	0·80 (0·70–0·92); 0·001
p_{trend} across categories	..	..	0·0019	0·001

HR=hazard ratio. hsCRP=high-sensitivity C-reactive protein. *Per 100 person-years of exposure. †Covariates included in the adjusted multivariable model include age, sex, smoking status, hypertension, diabetes, body-mass index, baseline concentration of hsCRP, and baseline concentration of LDL cholesterol. ‡Tertile cutpoints for on-treatment hsCRP concentration at 3 months were >2·6 mg/L, >1·2–2·6 mg/L, and ≤1·2 mg/L. §The median percent reduction in hsCRP at 3 months was 58·14%.

Table 2: **Incidence rates (per 100 person-years) and HRs for the primary prespecified cardiovascular endpoint of major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) in CANTOS, according to the magnitude or levels of on-treatment reduction in hsCRP achieved at 3 months among those allocated to canakinumab**

any dose of canakinumab who had hsCRP concentrations of 2 mg/L or higher at 3 months did not have a significant reduction in clinical events; for this group (n=2868), the HR compared with placebo for the trial primary endpoint was 0·95 (95% CI 0·84–1·09, p=0·48). By contrast, trial participants allocated to canakinumab who did achieve an hsCRP less than 2 mg/L at 3 months had a highly significant and much larger 25% reduction in risk (HR for the primary endpoint 0·75, 95% CI 0·66–0·85, p<0·0001; figure 2A). In this prespecified analysis, the p value for the test of trend across hsCRP strata was less than 0·0001. These data correspond to incidence rates for the primary endpoint of 4·39, 4·20, and 3·28 events per 100 person-years in the placebo group and in the combined canakinumab groups that did not and did achieve hsCRP concentrations less than 2 mg/L, respectively.

We did a series of sensitivity analyses to evaluate the robustness of these findings and to address whether any potential confounding factors had an effect on achieved hsCRP similar to that of canakinumab itself. First, we adjusted for baseline hsCRP and LDL cholesterol concentrations, as well as for clinical characteristics known to modestly impact on hsCRP (including age, sex, smoking status, hypertension, diabetes, and BMI). In these multivariable analyses, the calculated HRs for major adverse cardiovascular events among those treated with canakinumab who had hsCRP concentrations at 3 months less than or greater than 2 mg/L (adjusted HRs 0·75 and 0·90, respectively) were minimally changed from those observed in our univariable analysis (unadjusted HRs 0·75 and 0·95, respectively; table 2).

Second, we repeated our analysis using the trial prespecified secondary cardiovascular endpoint which included non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina requiring urgent revascularisation, or cardiovascular death. Compared with placebo, participants allocated to any dose of canakinumab who did not achieve a 3 month hsCRP less than 2 mg/L did not have a significant reduction in the secondary trial endpoint; for this group,

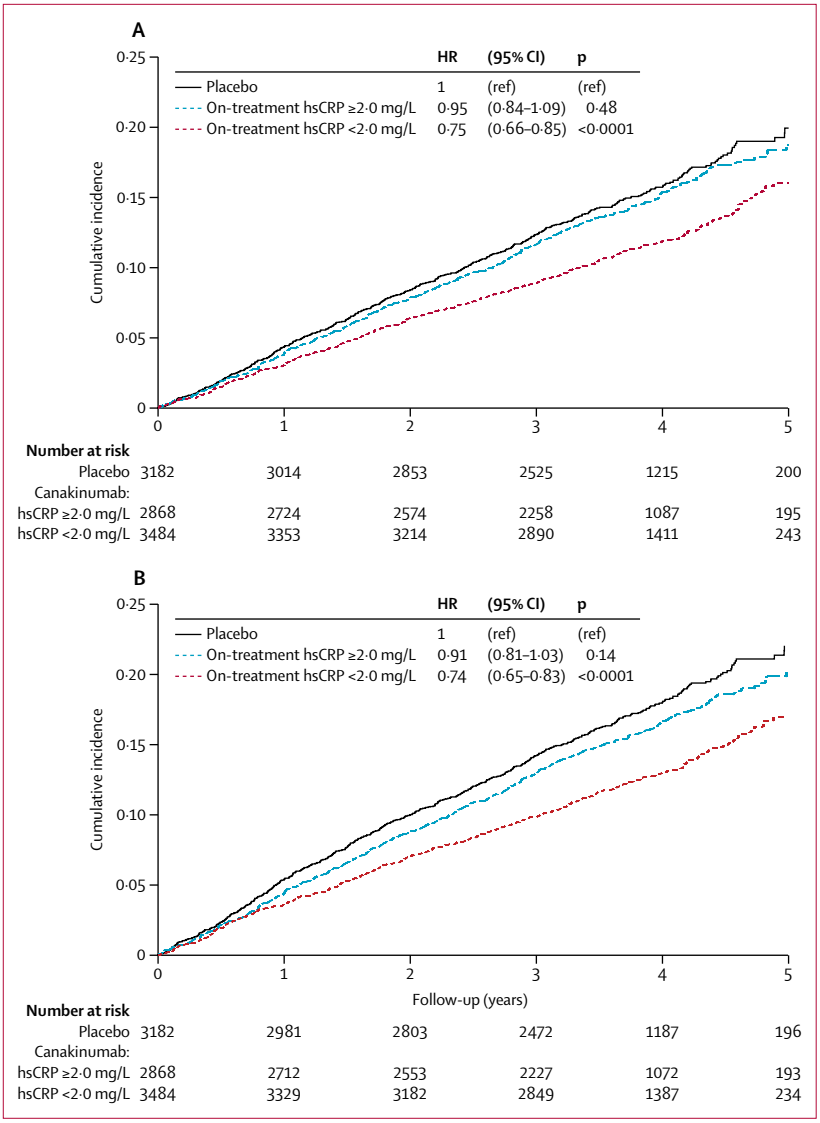

***Figure 2*: Cumulative incidence of cardiovascular events in the placebo group and in the combined canakinumab groups according to whether 3 month on-treatment high-sensitivity C-reactive protein (hsCRP) concentrations were above or below the commonly used clinical cutpoint of 2 mg/L**

Data are shown for (A) the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) and (B) the key prespecified secondary endpoint (non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina requiring unplanned revascularisation, or cardiovascular death).

the HR compared with placebo for the secondary trial endpoint was 0·91 (95% CI 0·81–1·03, p=0·14). By contrast, trial participants allocated to canakinumab who did achieve an hsCRP concentration of less than 2 mg/L at 3 months had a significant reduction in risk (HR for the primary endpoint of 0·74, 95% CI 0·65–0·83, p<0·0001; figure 2B). In this analysis, the p value for the test of trend across hsCRP strata was less than 0·0001 and the p value for the comparison between active treatment groups was 0·0010. These data correspond to incidence rates for the secondary trial endpoint of 5·02, 4·57, and 3·70 events per 100 person-years in the placebo group and in the combined canakinumab groups that did not and did achieve hsCRP concentrations less than 2 mg/L, respectively.

Third, we repeated our analysis using the median 3 month on-treatment concentration of hsCRP observed among those allocated to any dose of canakinumab (1·8 mg/L rather than the clinical cutpoint of 2 mg/L) and observed similar effects in both univariable and multivariable analyses (table 2).

Fourth, we repeated our analysis of the primary and secondary cardiovascular endpoints across tertiles of on-treatment hsCRP concentrations (rather than median concentrations) at 3 months. Effects were again similar in both univariable and multivariable analyses with the greatest reductions in risk for both the primary and secondary cardiovascular endpoints accruing among those with the greatest magnitude of hsCRP reduction (table 2, figure 3A, B).

Fifth, repeated analyses that used an on-treatment target of less than, or equal to or greater than a 50% reduction in hsCRP at 3 months yielded similar results (p_{trend} across groups 0·0008) albeit with mild attenuation between the two active groups (table 2).

Sixth, we repeated our analyses using an on-treatment target of less than, or equal to or greater than the median percent reduction in hsCRP and again observed similar results (p_{trend} across groups 0·001; table 2).

Seventh, we repeated our analyses for three additional cardiovascular endpoints prespecified in the CANTOS protocol. Cardiovascular death (fully adjusted HR 0·69, 95% CI 0·56–0·85, p=0·0004) and all-cause mortality (fully adjusted HR 0·69, 0·58–0·81, p<0·0001) both fell significantly among those who achieved on-treatment hsCRP less than 2 mg/L. A similar benefit was observed for the additional protocol prespecified endpoint of myocardial infarction, stroke, or death from any cause among those who achieved on-treatment hsCRP less than 2 mg/L (adjusted HR 0·73, 95% CI 0·65–0·82, p<0·0001). By contrast, no significant effects were observed for any of these additional endpoints among those treated with canakinumab who did not achieve hsCRP concentrations below this threshold (table 3).

Eighth, to assess the potential for residual confounding by randomised drug allocation, we did separate analyses for each individual canakinumab dose. Compared with placebo, the multivariable adjusted HRs for the primary endpoint among those who achieved 3 month on-treatment hsCRP concentrations less than 2 mg/L were 0·78 (95% CI 0·63–0·96, p=0·02) in the canakinumab 50 mg group, 0·75 (0·62–0·91, p=0·003) in the canakinumab 150 mg group, and 0·74 (0·62–0·88, p=0·0009) in the canakinumab 300 mg group. By contrast, no significant benefits of canakinumab were observed at any individual dose among those who did not achieve 3 month hsCRP concentrations less than 2 mg/L. In multivariable adjusted models further adjusted simultaneously for all three dose groups, the

adjusted HR for the primary endpoint among those who achieved 3 month on-treatment hsCRP concentrations less than 2 mg/L was 0·79 (95% CI 0·66–0·94, p=0·007), whereas those who did not achieve hsCRP concentrations at 3 months below this threshold had no significant benefit (HR=0·94, 0·80–1·10, p=0·41).

Additionally, a causal inference analysis was done in which we modelled potential outcomes using baseline covariates (age, sex, BMI, smoking status, diabetes, blood pressure, hsCRP, total and HDL cholesterol, glomerular filtration rate, history, and timing of vascular disease) for individual patients treated with canakinumab had they counterfactually been allocated to placebo, and then compared the modelled effects to observed effects. In this alternative analysis approach designed to address the estimation of treatment effect of canakinumab in patients who had achieved target concentrations of hsCRP, we again saw similar results at individual doses of canakinumab. For example, for those treated with 150 mg canakinumab who achieved an hsCRP less than the trial median concentration of 2 mg/L at 3 months, the relative HR for major adverse cardiovascular events compared with their outcome had they counterfactually been assigned to placebo was 0·76 (95% CI 0·64–0·91), whereas for those who achieved an hsCRP concentration of 2 mg/L or above at 3 months, the comparable relative HR was 0·90 (0·75–1·07). Similarly, for those treated with 300 mg canakinumab who achieved an hsCRP concentration of less than 2 mg/L at 3 months, the relative HR for major adverse cardiovascular events compared with their outcome had they counterfactually been assigned to placebo was 0·80 (95% CI 0·69–0·96), whereas for those who achieved hsCRP of 2 mg/L or above at 3 months, the comparable relative HR was 0·93 (0·74–1·04).

The calculated NNT over 5 years for myocardial infarction, stroke, coronary revascularisation, or death from any cause for the CANTOS cohort as a whole was 24. Among those with on-treatment hsCRP concentrations less than 2 mg/L, the 5 year NNT estimate was 16. The 5 year NNT estimate was 57 for those who did not achieve on-treatment hsCRP concentrations below this threshold.

Virtually identical results were obtained for the above analyses using on-treatment concentrations of interleukin-6 rather than on-treatment concentrations of hsCRP.

As previously reported, canakinumab did not associate with any adverse hepatic, renal, or haemorrhagic effects. Overall in CANTOS, canakinumab was associated with an increase in fatal infection, but this latter effect was not dose-dependent.[3] In on-treatment analyses, the incidence rate of fatal infection among patients treated with canakinumab whose hsCRP was less than 2 mg/L at 3 months was 0·27 per 100 person-years and the incidence rate of fatal infection among patients treated with canakinumab who did not achieve this concentration of hsCRP was 0·35 per 100 person-years. Although these rates were both higher than the placebo rate of 0·18 per 100 person-years, there was no significant difference in incidence rates for fatal infection comparing the two canakinumab groups defined by on-treatment concentrations of hsCRP at 3 months (p=0·33). Power was limited to detect differences, however, as the total number of fatal infections was small.

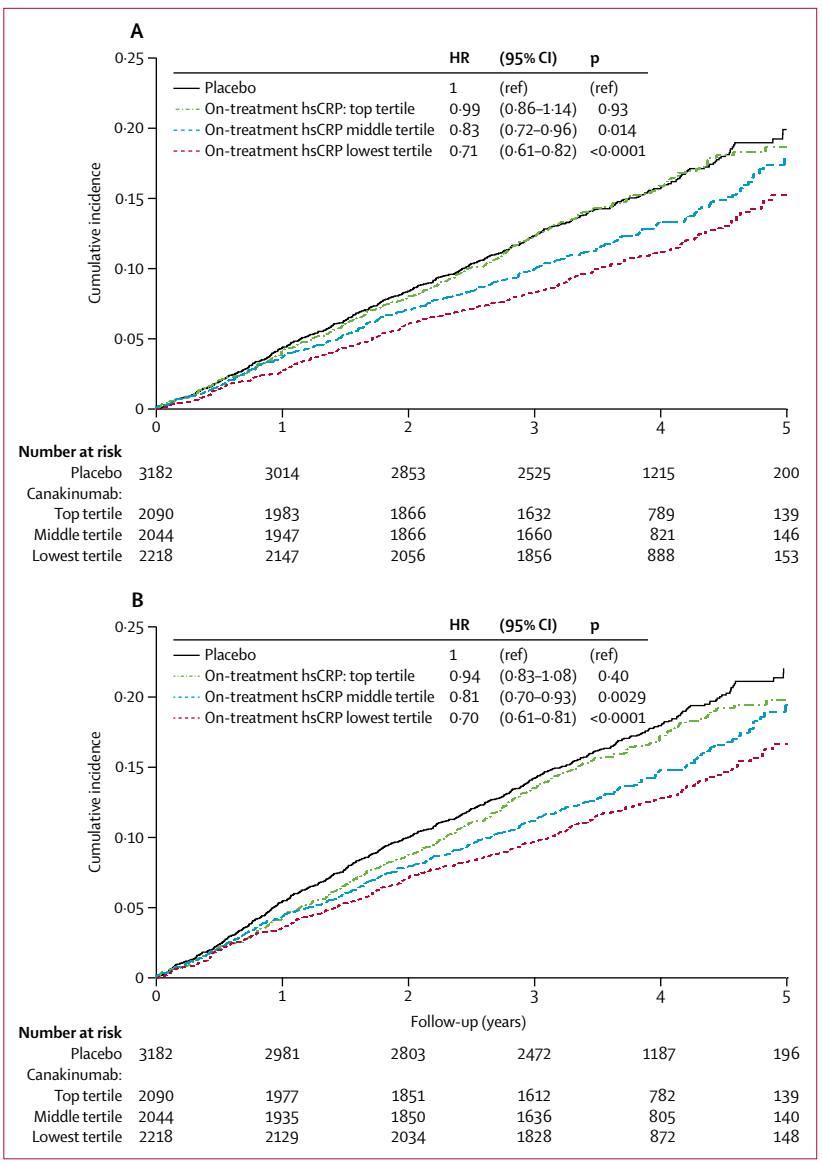

Figure 3: **Cumulative incidence of cardiovascular events in the placebo group and in the combined canakinumab groups according to tertiles of on-treatment high-sensitivity C-reactive protein (hsCRP) achieved at 3 months after the initial dose of canakinumab**

Tertile cutpoints are listed in the footnote of table 2. Data are shown for (A) the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) and (B) the key prespecified secondary cardiovascular endpoint (non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina requiring unplanned revascularisation, or cardiovascular death).

Discussion

This analysis of 9534 post-myocardial infarction patients in CANTOS shows that the magnitude of reduction in hsCRP following the first dose of canakinumab relates

	Placebo (n=3182)	Canakinumab, hsCRP ≥2 mg/L at 3 months (n=2868)	Canakinumab, hsCRP <2 mg/L at 3 months (n=3484)	p_{trend} across categories
Myocardial infarction, stroke, or death from any cause				
Incidence rate (n)	5·39 (614)	5·38 (553)	3·96 (508)	..
HR^{adj} (95% CI)	1 (ref)	0·93 (0·83–1·05)	0·73 (0·65–0·82)	..
p value	Ref	0·25	<0·0001	<0·0001
Cardiovascular death				
Incidence rate (n)	1·74 (211)	1·83 (198)	1·22 (164)	..
HR^{adj} (95% CI)	1 (ref)	0·99 (0·82–1·21)	0·69 (0·56–0·85)	..
p value	Ref	0·95	0·0004	0·0004
All-cause mortality				
Incidence rate (n)	2·79 (338)	3·14 (339)	1·96 (264)	..
HR^{adj} (95% CI)	1 (ref)	1·05 (0·90–1·22)	0·69 (0·58–0·81)	..
p value	Ref	0·56	<0·0001	<0·0001

Incidence rates are calculated per 100 person-years of exposure. Covariates included in the adjusted multivariable model include age, sex, smoking status, hypertension, diabetes, body-mass index, baseline concentration of hsCRP, and baseline concentration of LDL cholesterol. HR^{adj}=adjusted hazard ratio. hsCRP=high-sensitivity C-reactive protein.

Table 3: **Incidence rates and adjusted hazard ratios for additional prespecified cardiovascular endpoints in CANTOS, according to on-treatment hsCRP concentrations at 3 months, <2 mg/L or ≥2 mg/L**

directly to the magnitude of long-term clinical benefit for incident cardiovascular events, cardiovascular death, and all-cause mortality. The differential outcomes observed in CANTOS on the basis of achieved hsCRP concentration were robust to the choice of on-treatment measures (values above or below thresholds defined by medians, tertiles, percentage reductions, or commonly used clinical cutpoints), were minimally affected by adjustment for baseline clinical characteristics known to alter hsCRP concentrations, were observed at all individual dose concentrations, and were additionally observed in a causal inference analysis. Conversely, this analysis indicated no substantial differences between achieved hsCRP concentration and safety outcomes, including for rates of infection.

We believe these findings to be of interest for several reasons. First, our data for canakinumab and on-treatment concentrations of hsCRP are analogous to previous lipid-lowering trials and on-treatment concentrations of LDL cholesterol.[7,8] Indeed, the data presented here for hsCRP as a target for canakinumab (a therapy with major effects on inflammation but negligible effect on LDL cholesterol) are fully analogous to recent data for LDL cholesterol as a target for PCSK9 inhibition (a therapy with major effects on LDL cholesterol but no effect on inflammation).[9–11] Further, as most CANTOS participants were already on high-intensity statin therapy, the current data provide independent support for the general concept that achieving the dual goals of inflammation reduction as well as cholesterol reduction provides the greatest clinical benefits with regard to atherothrombotic prevention.

For example, many prospective clinical trials have shown that the benefits of lipid-lowering are maximised when low concentrations of both LDL cholesterol and hsCRP are achieved with statins.[12–19] Recently, Bohula and colleagues[20] have shown similar findings for the addition of ezetimibe to statin therapy, a combination treatment that further reduces both LDL cholesterol and hsCRP. Thus, from a pathophysiological perspective, the current data strongly suggest that lower is better for hsCRP and inflammation, at least following canakinumab. Our data also agree with findings from the REVERSAL trial in which plaque regression after initiation of statin therapy occurred only when both LDL cholesterol and hsCRP were reduced.[14]

Second, our data have practical implications for the potential use of canakinumab as an adjunctive post-myocardial infarction therapy. Like other monoclonal antibodies, the cost of canakinumab must be considered, so finding patient populations where benefits are maximised is important.[21] As shown in figure 1, all common clinical subgroups achieved similar relative risk reductions with canakinumab with no evidence of significant heterogeneity. Thus, other than high absolute risk, there does not appear to be a simple way to maximise canakinumab efficacy using baseline clinical characteristics of the CANTOS cohort.

The benefit associated with canakinumab for cardiovascular events (as well as all-cause mortality) related directly to the size of hsCRP reduction achieved after a single dose. Indeed, those who did not achieve substantial reductions in hsCRP had only small and non-significant benefits (figures 2 and 3). These data support the use of an on-treatment measure of hsCRP as a simple clinical mechanism to differentiate between candidates for sustained canakinumab treatment and individuals much less likely to benefit from continued treatment.

Application of this clinical strategy would ensure a favourable benefit-to-risk ratio for canakinumab and simultaneously improve cost-effectiveness. For example, the overall 5 year NNT in CANTOS for the endpoint inclusive of myocardial infarction, stroke, any coronary revascularisation, or death from any cause is 24. However, if only those with on-treatment hsCRP concentration less than 2 mg/L are analysed, the 5 year NNT is 16. This contrasts with a 5 year NNT of 57 for those who do not achieve hsCRP concentration less than 2 mg/L. The use of an on-treatment hsCRP value to ascertain canakinumab effectiveness should feel familiar to clinicians who already routinely assess on-treatment LDL cholesterol to ascertain the effectiveness of lipid-lowering therapy and who already routinely assess on-treatment blood pressure levels to determine the effectiveness of antihypertensive therapy.

Although derived from a large-scale placebo-controlled trial, our analysis has limitations. First, like any on-treatment analysis, the observations made here are no longer formally randomised and could reflect, in part, differences in baseline clinical characteristics

that associate with reduced on-treatment hsCRP concentrations. However, such differences in our data appeared to be modest as multivariate adjustment for a large range of baseline clinical characteristics including hsCRP concentration and canakinumab dose had minimal impact on our findings. We also observed almost identical differential effects in a causal inference analysis in which those treated with canakinumab were modelled as having counterfactually been treated with placebo. While no analysis can fully eliminate residual confounding, the fact that different forms of adjustment led to similar results and had relatively small impact on our overall finding is consistent with the hypothesis that the direct biological effect of canakinumab on hsCRP is far larger than the effect associated with other potential clinical variables.

Second, our data only apply to canakinumab; at least for now, there is no evidence that other therapies that reduce hsCRP also reduce clinical events. Reflecting the trial protocol, our data are also limited to those with elevated hsCRP at study entry.

Finally, the CANTOS protocol and statistical analysis plan used a conservative multiplicity-adjusted hierarchical approach to define thresholds for statistical significance that was formally met in our primary trial analysis only by the 150 mg dose of canakinumab, even though the magnitude of risk reductions and p values were virtually identical for the 300 mg dose.[3] However, as shown in the current prespecified on-treatment analyses, a greater proportion of individuals allocated to 300 mg canakinumab than to 150 mg canakinumab achieved hsCRP reductions at 3 months below thresholds associated with the greatest clinical benefit. Thus, for individual patients where variability in drug response might exist, the availability of both a 150 mg and a 300 mg dose might broaden the clinical use of canakinumab.

In sum, in these prespecified analyses from the multinational CANTOS trial, the magnitude of reduction in hsCRP, in the absence of any change in LDL cholesterol, was strongly related to cardiovascular event reduction and all-cause mortality reduction following canakinumab therapy. As such, the use of a simple biological measure of inflammatory response might provide clinicians with a method to define patient groups most likely to benefit from long-term canakinumab treatment. These data reinforce the clinical and pathophysiological concepts not only that lower is better for inflammation in a manner analogous to LDL cholesterol, but also that patients with residual inflammatory risk represent a separate and distinct group from patients with residual cholesterol risk who probably require different personalised approaches to treatment.[22] Last, we believe the clinical approach of targeting treatment to those who truly benefit on the basis of biological response represents a major step toward personalised medicine and rational resource utilisation.

Contributors

PMR was the trial's principal investigator and trial chairman, ran all investigator meetings, oversaw all daily trial activities, and wrote and edited the primary manuscript. JGM was the primary trial programmer and did all initial and subsequent analyses. BME chaired the Clinical Endpoints Committee and made logistic contributions. PL assisted in all investigator meetings and executive committee meetings. TT assisted with trial logistics. RJG was the academic trial statistician, designed and did the primary statistical analyses, and was the statistical liaison to the data and safety monitoring board. All authors additionally assisted in study design and data interpretation, and provided comments on the final Article.

Declaration of interests

PMR and RJG received research grant support from Novartis Pharmaceuticals to conduct the CANTOS trial. PMR has served as a consultant to Novartis and is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens. TT is an employee of, and holds stock in, Novartis Pharmaceuticals. All other authors declare no competing interests.

Acknowledgments

This study was funded by Novartis Pharmaceuticals.

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