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Inhibition of Interleukin-1β and Reduction in Atherothrombotic Cardiovascular Events in the CANTOS Trial

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ABSTRACT

BACKGROUND Inflammation reduction with the interleukin (IL)-1β inhibitor canakinumab significantly reduces the first major adverse cardiovascular event in patients with prior myocardial infarction (MI) and residual inflammatory risk (high-sensitivity C-reactive protein ≥ 2 mg/l). However, the effect of canakinumab on the total number of cardiovascular events, including recurrent events collected after a first event, is unknown.

OBJECTIVES This study sought to determine whether randomly allocated canakinumab would reduce the total burden of serious cardiovascular events.

METHODS We randomized 10,061 patients to placebo or canakinumab 50 mg, 150 mg, or 300 mg once every 3 months and compared the rates of the composite of all serious cardiovascular events (MI, stroke, coronary revascularization, and cardiovascular death) in active versus placebo groups. We used negative binomial regression to account for correlations among repeated events in the same person and to estimate rate ratios and 95% confidence intervals.

RESULTS During a median of 3.7 years of follow-up, 3,417 total serious cardiovascular events occurred in 2,003 individuals among the 10,061 unique patients randomized. Canakinumab reduced the rates of total serious cardiovascular events, with rates per 100 person-years in the placebo, 50 mg, 150 mg, and 300 mg canakinumab groups of 10.4, 8.4, 8.3, and 8.2, respectively. The corresponding rate ratios (95% confidence intervals) compared with placebo were 0.80 (0.69 to 0.93) for 50 mg, 0.79 (0.68 to 0.92) for 150 mg, and 0.78 (0.67 to 0.91) for 300 mg.

CONCLUSIONS Anti-inflammatory therapy with canakinumab significantly reduced the total number of cardiovascular events in patients with prior MI and evidence of residual inflammatory risk. (Cardiovascular Risk Reduction Study [Reduction in Recurrent Major CV Disease Events] (CANTOS); NCT01327846 (J Am Coll Cardiol 2020;76:1660–70)

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The primary analysis of the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial showed that the interleukin (IL)-1β inhibitor canakinumab reduces the risk of a first major adverse cardiovascular event in patients with prior myocardial infarction (MI) and evidence of ongoing subclinical inflammation (1). Recently, the COLCOT (Colchicine Cardiovascular Outcomes Trial) reported that the anti-inflammatory medication colchicine reduced the risk of the composite primary endpoint of nonfatal MI, nonfatal stroke, urgent hospitalization for angina leading to coronary revascularization, resuscitated cardiac arrest, or cardiovascular death (2). These studies establish that anti-inflammatory therapies can reduce the risk of the first recurrent atherothrombotic events.

However, patients enrolled in CANTOS, like other patients with established cardiovascular disease, not only have high risk for recurrent cardiovascular events, but remain at elevated risk for recurrent events over time. The approach of measuring just the first cardiovascular event often underestimates the burden of the disease on the patient, as well as on the health care system as a whole (3). Some contemporary trials have defined the total number of events as the trial primary endpoint (4), and others have reported the total burden of cardiovascular events to understand the residual cardiovascular risk that enrolled patients encounter (5–7).

Patients randomized in CANTOS were followed for the total duration of the trial, and those who incurred a trial endpoint were asked to remain on their assigned treatment for the duration of the trial. The initial and subsequent events were collected and adjudicated in the same fashion, allowing a broader assessment of the efficacy of canakinumab in preventing cardiovascular events. To address the extent to which randomly allocated IL-1β inhibition reduced the total number of cardiovascular events, we tested whether, when compared to placebo, canakinumab would reduce the total number of serious cardiovascular events, a composite of nonfatal MI, nonfatal stroke, coronary revascularization, and cardiovascular death.

SEE PAGE 1671

METHODS

The CANTOS study design and primary results have been published previously (1,8). Briefly, patients with a prior history of MI and a high-sensitivity C-reactive protein (hsCRP) ≥2 mg/l were eligible for random allocation to placebo, canakinumab 50 mg, 150 mg, or 300 mg given once every 3 months subcutaneously. Patients were followed prospectively for the occurrence of serious cardiovascular events, including nonfatal MI, nonfatal stroke, unstable angina requiring unplanned coronary revascularization, planned coronary revascularization, and cardiovascular death. An Institutional Review Board or ethics committee approved the protocol at all participating centers. A Clinical Endpoints Committee composed of cardiologists and neurologists blinded to randomized treatment allocation adjudicated all cases of MI, unstable angina requiring unplanned coronary revascularization, stroke, and cardiovascular death. For this analysis, all events were counted, including those that occurred on the same day. The clinical endpoint used for this study was the total number of serious cardiovascular events, a composite of nonfatal MI, nonfatal stroke, coronary revascularization, and cardiovascular death.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

hsCRP = high-sensitivity C-reactive protein

IL = interleukin

MACE = major adverse cardiovascular events (MI, stroke, cardiovascular death)

MACE+ = major adverse cardiovascular events plus unstable angina requiring unplanned coronary revascularization

MI = myocardial infarction

STATISTICAL ANALYSIS. Baseline characteristics of participants with no serious cardiovascular events, 1 serious cardiovascular event, or more than 1 serious cardiovascular event were compared using Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. This study used a composite endpoint of all serious cardiovascular events, which was the occurrence of a composite of nonfatal MI, nonfatal stroke, coronary revascularization, or cardiovascular death. We also evaluated the effect of canakinumab on the total number of CANTOS trial pre-specified primary endpoints (nonfatal MI, stroke, or cardiovascular death), and a CANTOS trial pre-specified secondary endpoint (nonfatal MI, stroke, unstable angina requiring unplanned coronary revascularization, or cardiovascular death), as well as the effect on MI plus all coronary revascularizations. We assessed the risk of a first serious cardiovascular event for each of the 3 active canakinumab groups (50 mg, 150 mg, 300 mg) as compared with placebo using Cox proportional hazards models. To test for an effect on the total number of serious cardiovascular events, and the total number of CANTOS primary and secondary endpoints, we calculated the incidence rate and rate ratios for the occurrence of the combined first and subsequent serious cardiovascular events in each of the treatment groups using negative binomial regression. As a sensitivity analysis to address the competing risk of all-cause mortality, we repeated the negative binomial

TABLE 1 Baseline Characteristics of the Study Population

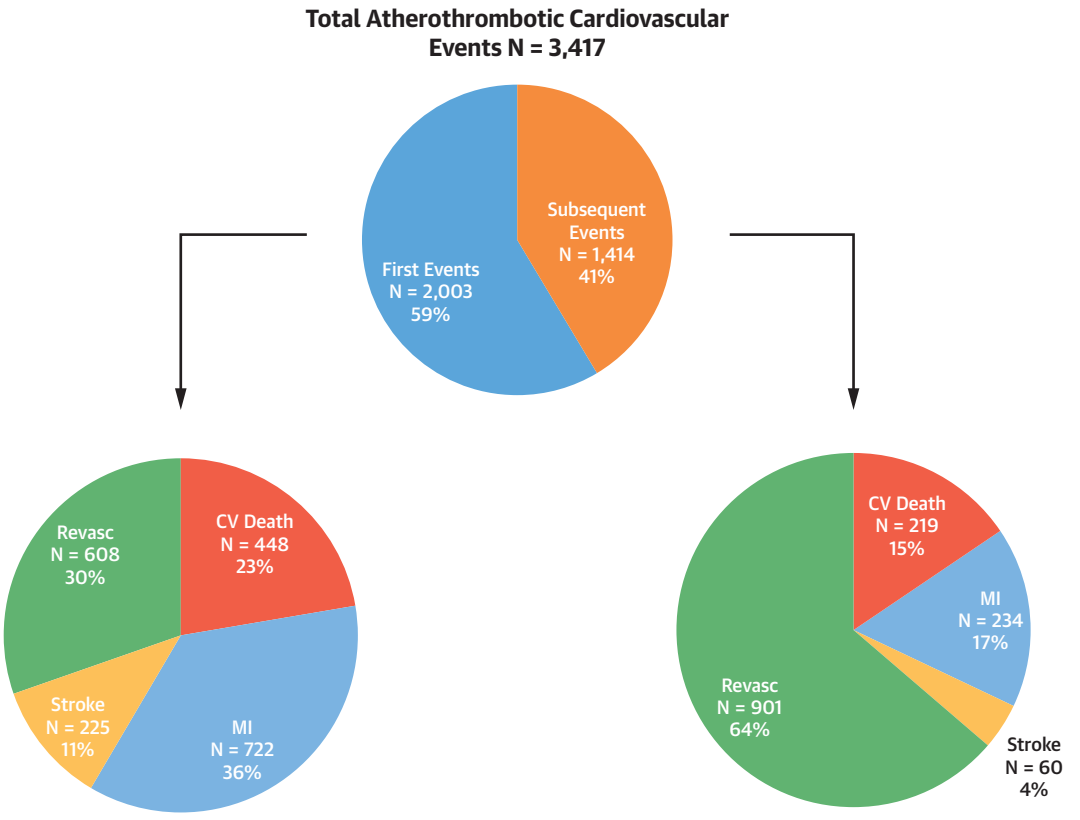
	None (n = 8,058)	Single (n = 1,093)	Multiple (n = 910)	p Value
Age, yrs	61 (54–68)	64 (56–71)	62 (55–68)	<0.0001
Female	2130 (26)	250 (23)	207 (23)	0.004
Smoking status				<0.0001
Current smoking	1,819 (23)	185 (26)	262 (29)	
Past smoking	3,831 (48)	505 (46)	417 (46)	
Never smoker	2,408 (30)	303 (28)	231 (25)	
Body mass index, kg/m^2	29.9 (26.6–33.8)	29.3 (26.0–33.5)	30.1 (26.7–34.3)	0.12
Hypertension	6,287 (78)	924 (85)	797 (88)	<0.0001
Diabetes	3,077 (38)	514 (47)	438 (48)	<0.0001
Qualifying MI				<0.0001
NSTEMI	2,667 (33)	558 (34)	159 (41)	
STEMI	4481 (56)	817 (50)	184 (48)	
Unknown type or missing	907 (11)	243 (15)	42 (11)	
History of PCI	5,361 (67)	690 (63)	659 (72)	<0.0001
History of CABG	1,013 (13)	222 (20)	176 (19)	<0.0001
History of congestive heart failure	1,564 (19)	368 (34)	241 (26)	<0.0001
History of COPD	645 (8)	151 (14)	124 (14)	<0.0001
History of AF	653 (8)	153 (14)	97 (11)	<0.0001
History of PAD	615 (8)	141 (13)	125 (14)	<0.0001
Lipid-lowering therapy	7,552 (94)	1001 (92)	844 (93)	0.02
Statin	7,361 (91)	982 (90)	814 (89)	0.06
Renin-angiotensin inhibitor	6,389 (80)	869 (80)	734 (81)	0.60
Antithrombotic agent or anticoagulant	7,644 (95)	1,526 (94)	361 (94)	0.44
Anticoagulant	548 (7)	141 (13)	72 (8)	<0.0001
Antiplatelet	2,244 (28)	300 (28)	260 (29)	0.86
Aspirin	7,122 (80)	922 (84)	793 (87)	0.0004
hsCRP, mg/l	4.1 (2.8–6.8)	4.7 (3.1–8.4)	4.5 (2.9–7.2)	<0.0001
Interleukin-6, ng/l	2.5 (1.7–4.0)	3.1 (2.0–5.0)	2.7 (1.9–4.3)	<0.0001
Total cholesterol, mg/dl	159 (135–186)	163 (139–197)	167 (141–203)	<0.0001
LDL cholesterol, mg/dl	91 (63–105)	86 (67–114)	89 (66–118)	<0.0001
HDL cholesterol, mg/dl	44 (37–53)	44 (37–53)	43 (36–51)	0.003
Triglycerides, mg/dl	138 (102–193)	136 (97–194)	147 (105–222)	<0.0001
Hemoglobin A1c	5.9 (5.6–6.6)	6.1 (5.7–7.1)	6.2 (5.7–7.3)	<0.0001
eGFR, ml/min per 1.73 m^2	79 (65–93)	74 (59–91)	76 (61–93)	<0.0001

Values are median (interquartile range) or n (%). The cohort is divided according to whether the participants had no serious cardiovascular events, a single serious cardiovascular event, or multiple serious cardiovascular events during follow-up.

AF = atrial fibrillation; CABG = coronary artery bypass grafting surgery; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

regression with an expanded composite endpoint of nonfatal MI, nonfatal stroke, coronary revascularization, or all-cause mortality. To be consistent with prior published work from CANTOS and to understand better the effect of canakinumab on the total number of cardiovascular events among those who achieved significant reductions in subclinical vascular inflammation, we stratified patients randomly allocated to canakinumab into 2 groups according to the robustness and magnitude of inflammation inhibition achieved after taking the initial dose of active therapy. Specifically, we assessed the risks of total serious cardiovascular events among those with hsCRP ≥ or <2 mg/l and IL-6 ≥ or <1.65 ng/l (the on-treatment median value) (9,10). Analyses were adjusted for a wide array of potential confounders, including age, sex, race, body mass index, hypertension, diabetes, baseline concentration of low-density lipoprotein cholesterol, hsCRP, hemoglobin A1c, estimated glomerular filtration rate, albumin, smoking status, history of percutaneous coronary intervention, heart failure, chronic obstructive pulmonary disease, atrial fibrillation, or peripheral artery disease, type of qualifying MI, and antiplatelet and lipid-lowering therapy. Finally, to estimate the total number of cardiovascular events prevented with canakinumab therapy, we calculated the rate

FIGURE 1 The Proportion and Type of First and Subsequent Serious CV Events in CANTOS



The data are based on the total number of nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, and cardiovascular (CV) death events in the trial. There were 3,417 events in 2,003 individuals. In total, 2,003 events were first events and 1,414 were subsequent events. Although MI was the most common first event, coronary revascularization was the most common subsequent event. CANTOS = Canakinumab Anti-Inflammatory Thrombosis Outcomes Study; Revasc = revascularization.

differences and 95% confidence interval (CI) between the treatment arms, defined as the difference in the incidence rates between treatment arms. This rate difference was then extrapolated to a hypothetical population of 1,000 patients treated for the median follow-up time of CANTOS (3.7 years).

RESULTS

Of the 10,061 patients enrolled in CANTOS, 8,058 experienced no serious cardiovascular events, 1,618 experienced a single serious cardiovascular event, and 385 experienced more than 1 serious

TABLE 2 Incidence Rates and Hazard Ratios for the First Serious Cardiovascular Event

		Canakinumab Dose			
	Placebo	50 mg	150 mg	300 mg	All Doses Combined
First serious cardiovascular event					
n events/n at risk	737/3,344	413/2,170	424/2,284	429/2,263	1,266/6,717
Incidence rate	6.42	5.57	5.24	5.34	5.38
Hazard ratio (95% CI)		0.88 (0.78–0.99)	0.81 (0.72–0.91)	0.83 (0.73–0.93)	0.84 (0.76–0.92)
p value		0.04	0.001	0.002	0.0001
p trend across doses				0.001	

A serious cardiovascular event was defined as the composite of myocardial infarction, stroke, coronary revascularization, and cardiovascular death. Data are presented by randomized treatment group: placebo, canakinumab 50 mg, canakinumab 150 mg, and canakinumab 300 mg.

TABLE 3 Incidence Rates and Rate Ratios for the Total Number of Serious Cardiovascular Events

		Canakinumab Dose			
All Serious Cardiovascular Events	**Placebo**	**50 mg**	**150 mg**	**300 mg**	**All Doses Combined**
n events/n at risk	1,311/3,344	670/2,170	723/2,284	713/2,263	2,106/6,717
Incidence rate	10.4	8.4	8.3	8.2	8.30
Rate ratio (95% CI)	Referent	0.80 (0.69–0.93)	0.79 (0.68–0.92)	0.78 (0.67–0.91)	0.79 (0.70–0.89)
p value	-	0.004	0.002	0.001	<0.0001
MACE					
n events/n at risk	702/3,344	388/2,170	409/2,284	409/2,263	1,206/6,717
Incidence rate	5.56	4.85	4.69	4.73	4.75
Rate ratio (95% CI)		0.88 (0.74–1.04)	0.83 (0.70–0.98)	0.84 (0.72–0.996)	0.85 (0.75–0.97)
p value		0.12	0.03	0.045	0.013
p-trend across doses				0.045	
MACE+					
n events/n at risk	797/3,344	432/2,170	453/2,284	446/2,263	1,331/6,717
Incidence rate	6.32	5.40	5.20	5.16	5.25
Rate ratio (95% CI)		0.86 (0.74–1.004)	0.81 (0.69–0.95)	0.81 (0.69–0.95)	0.83 (0.74–0.93)
p value		0.056	0.008	0.008	0.002
p trend across doses				0.008	
MI plus any revascularization					
n events/n at risk	976/3,344	471/2,170	509/2,284	509/2,263	1,489/6,717
Incidence rate	7.75	5.90	5.85	5.90	5.88
Rate ratio (95% CI)		0.77 (0.64–0.92)	0.74 (0.62–0.89)	0.73 (0.62–0.88)	0.75 (0.65–0.86)
p value		0.004	0.001	0.0006	<0.0001
p trend across doses				0.001	

A serious cardiovascular event was defined as the composite of myocardial infarction, stroke, coronary revascularization, and cardiovascular death. Data are presented by randomized treatment group: placebo, canakinumab 50 mg, canakinumab 150 mg, and canakinumab 300 mg.

CI = confidence interval; MACE = major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death); MACE+ = major adverse cardiovascular events plus unstable angina requiring unplanned coronary revascularization; MI = myocardial infarction.

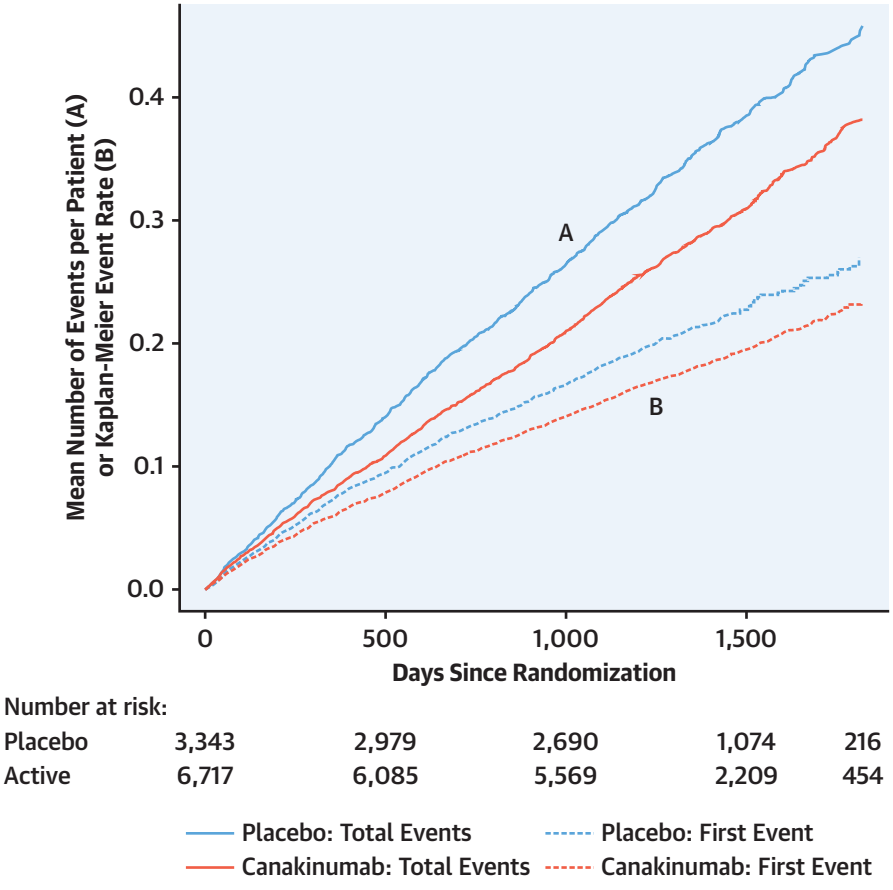
cardiovascular event. Seventy-three percent of all participants who survived their first serious cardiovascular event had at least 1 more injection of study drug. Table 1 displays the baseline characteristics of the study population, divided according to the number of serious cardiovascular events they experienced during follow-up. Those with multiple events were more likely to be current smokers; have type 2 diabetes or hypertension; or have higher concentrations of total cholesterol, triglycerides, or HbA1c at baseline. A prior history of percutaneous coronary intervention, chronic obstructive pulmonary disease, or peripheral artery disease was also more common among those with multiple serious cardiovascular events during follow-up.

FIRST AND RECURRENT EVENTS. During a median follow-up of 3.7 years, there were a total of 3,417 serious cardiovascular events (a composite of nonfatal MI, nonfatal stroke, unstable angina requiring unplanned coronary revascularization, planned coronary revascularization, and cardiovascular death) that occurred among the 10,061 patients randomized in CANTOS. These events occurred in 2,003 distinct patients who also incurred 1,414 subsequent events (Figure 1). Of the 2,003 first serious cardiovascular events, 36% were MI, 30% coronary revascularization, 23% cardiovascular death, and 11% stroke. Of the 1,414 subsequent serious cardiovascular events, the highest proportion was revascularization (64%). Seventeen percent of these subsequent events were MI, 15% cardiovascular death, and 4% stroke (Figure 1). The total number of pre-specified primary endpoints (nonfatal MI, nonfatal stroke, or cardiovascular death) are outlined in Supplemental Figure 1.

Seventy-three percent of all patients who survived their first event remained adherent to study medication. However, the rates of adherence appeared to be higher after coronary revascularization events (83%) than after MI (71%) or stroke (52%).

EFFICACY OF CANAKINUMAB FOR FIRST SERIOUS CARDIOVASCULAR EVENTS. The incidence of a first serious cardiovascular event in patients randomly allocated to placebo, 50 mg, 150 mg, or 300 mg of canakinumab was 6.42, 5.57, 5.24, and 5.34 events per 100 person-years, respectively (Table 2). Compared with placebo, each dose of canakinumab was associated with a significant reduction in the risk of a first

CENTRAL ILLUSTRATION **Time to the First Serious Cardiovascular Event and the Total (First and Subsequent) Serious Cardiovascular Events Over Time in the CANTOS Study**



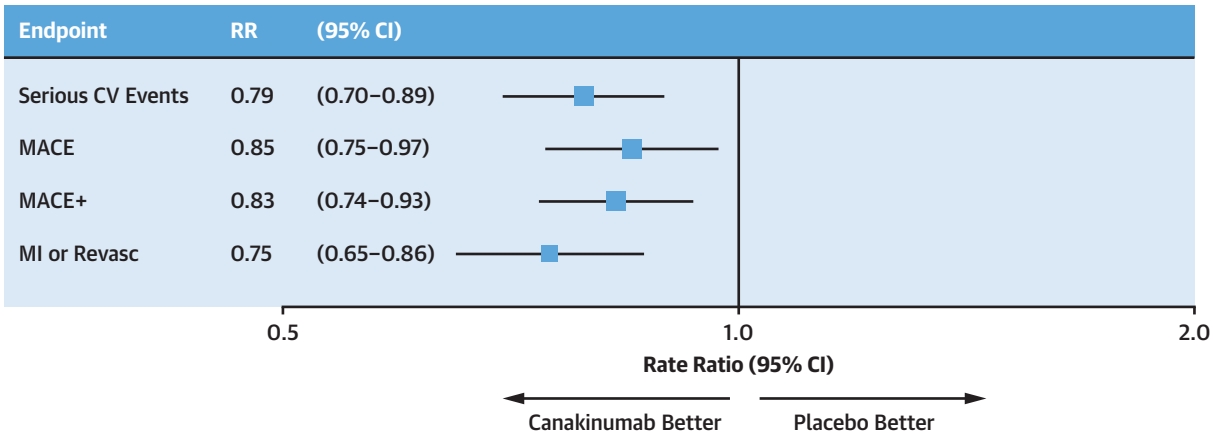
Everett, B.M. et al. J Am Coll Cardiol. 2020;76(14):1660–70.

(A) The mean number of serious cardiovascular events per patient, a measure of the cumulative total number of first and subsequent serious cardiovascular events in the study population, throughout the first 5 years of observation time of the study. **(B)** The Kaplan-Meier event rate for a first serious cardiovascular events per patient is also shown. Patients randomly allocated to placebo are shown in **blue**, whereas patients randomly allocated to all 3 canakinumab doses (50 mg, 150 mg, and 300 mg) have been combined and are shown in **red**. The number at risk are for the total events analysis. For both analyses, follow-up is truncated at 5 years.

serious cardiovascular event, with hazard ratios and 95% CIs ranging from 0.88 (0.78 to 0.99; p = 0.04) for the 50 mg dose to 0.83 (0.73 to 0.93; p = 0.002) for the 300 mg dose (Table 2).

EFFICACY FOR TOTAL CARDIOVASCULAR EVENTS. In addition to reducing rates of first serious cardiovascular events, canakinumab also limited the occurrence of the total number of serious cardiovascular events compared with placebo. The incidence rates of all serious cardiovascular events were 10.39, 8.38, 8.29, and 8.24 events per 100 person-years in the placebo, 50 mg, 150 mg, and 300 mg treatment groups, respectively. We observed significant reductions in the rate ratio for doses of canakinumab compared with placebo (Table 3). Specifically, the rate ratios for the total serious cardiovascular events for canakinumab 50 mg, 150 mg, and 300 mg as compared with placebo were 0.80 (0.69 to 0.93; p = 0.004), 0.79 (0.68 to 0.92; p = 0.002), and 0.78 (0.67 to 0.91; p = 0.001) (Table 3). An analysis for the endpoints of MACE, MACE+, and MI plus all coronary revascularizations yielded similar results (Table 3). In a sensitivity analysis that included all-cause mortality with MI, stroke, and coronary revascularization as a composite endpoint, no substantial changes in our results for the 50 mg (rate ratio: 0.90; 95% CI: 0.77 to

FIGURE 2 The Effect of Canakinumab as Compared With Placebo on the Rates of the Total (First and Subsequent) Events of 4 Different Cardiovascular Composite Endpoints



Rate ratios (RR) and 95% confidence intervals (CI) derived from negative binomial models for patients randomly allocated to placebo as compared with canakinumab (50 mg, 150 mg, and 300 mg doses combined). The results are displayed for the total number of serious cardiovascular (CV) events (the composite of myocardial infarction [MI], stroke, coronary revascularization, and cardiovascular death) for the total number of major adverse CV events (MACE, the CANTOS trial primary endpoint, a composite of MI, stroke, or CV death); the total number of major adverse CV events plus unstable angina requiring unplanned coronary revascularization (MACE+); and the total number of composite of MI or coronary revascularization. MACE = major adverse cardiovascular events (MI, stroke, cardiovascular death); MACE+ = major adverse cardiovascular events plus unstable angina requiring unplanned coronary revascularization; other abbreviations as in **Figure 1**.

1.04), 150 mg (rate ratio: 0.85; 95% CI: 0.73 to 0.99), or 300 mg (rate ratio: 0.86; 95% CI 0.74 to 0.99) doses of canakinumab versus placebo were observed. Outcomes for individual components of the composite endpoints are presented in Supplemental Table 1.

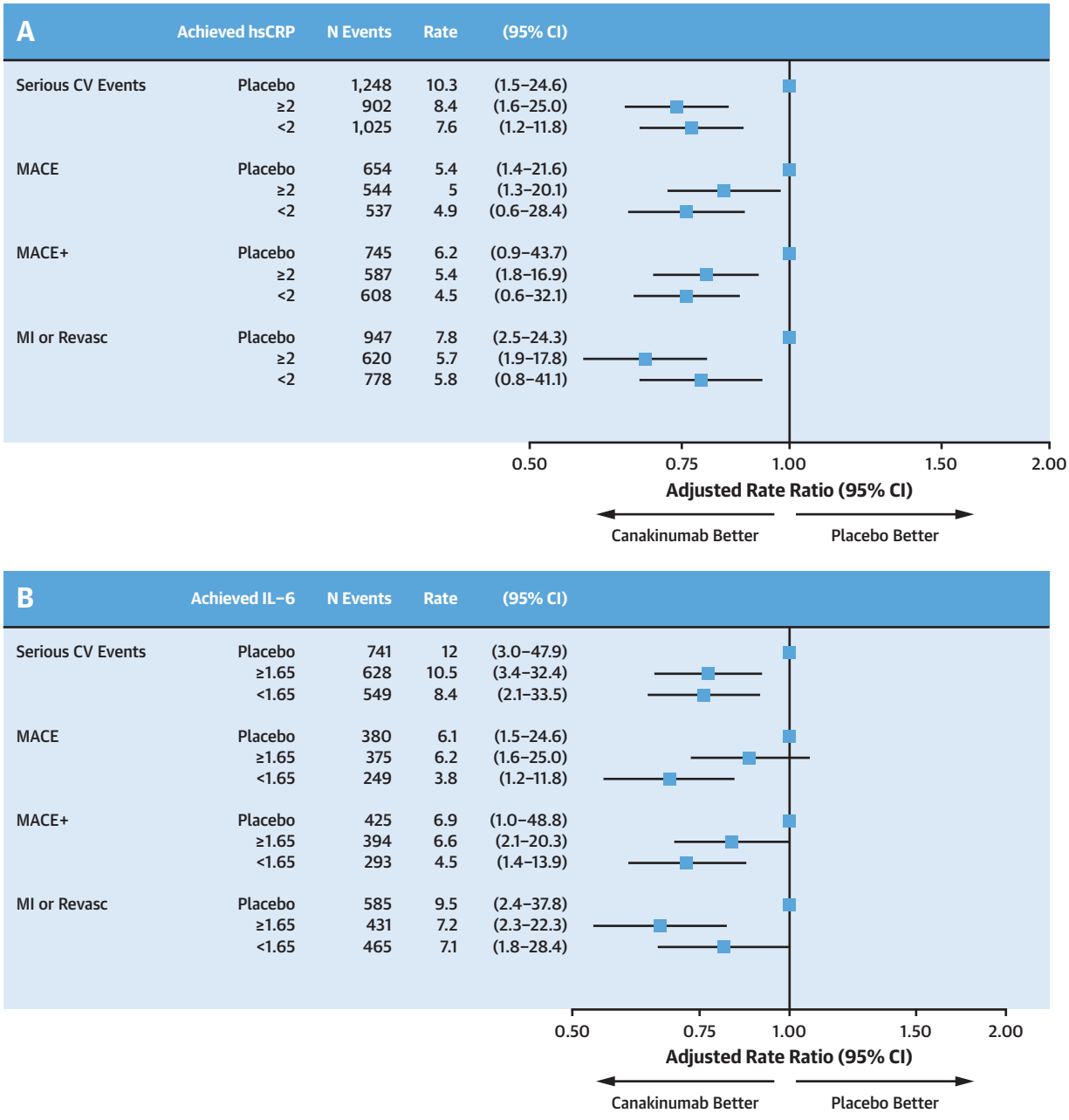
Combination of all canakinumab doses showed a difference in the mean cumulative number of events per patient in the active canakinumab as compared with the placebo canakinumab treatment groups, a measure of the effect of canakinumab across the total number of serious cardiovascular events (**Central Illustration**). We also observed a significant reduction in the time to a first serious cardiovascular event (the Kaplan-Meier event rate) (**Central Illustration**). The mean cumulative number of events per patient and the Kaplan-Meier event rate for the trial prespecified primary endpoint of MACE (the composite of MI, stroke, or cardiovascular death) are presented in Supplemental Figure 2. These figures demonstrate the extent to which the serious cardiovascular event rates are higher for individual patients when considering the total number of serious cardiovascular events, rather than just the first event. When all canakinumab doses were combined and compared with placebo, we observed consistent reductions in the rates of the pre-specified endpoint of the total number of serious cardiovascular events as well as the total number of MACE and MACE+ events, and the total number of MI plus all coronary revascularization events (**Figure 2**).

We then repeated these analyses and compared the rates and rate ratios of the total burden of cardiovascular events for those randomly allocated to canakinumab stratified according to achieved on-treatment hsCRP after adjustment for an array of potential confounders. Patients randomly allocated to canakinumab had significant reductions in the rate of the total number of serious cardiovascular events, MACE, MACE+, and for the composite of MI or coronary revascularization regardless of whether they achieved hsCRP <2 mg/l (**Figure 3A**, Supplemental Table 2).

We repeated this analysis among the 4,833 patients who had on-treatment IL-6 measurements available and observed similar results. Specifically, after adjustment for potential confounders, those randomly allocated to canakinumab who achieved on-treatment IL-6 concentrations less than the median value of 1.65 ng/l had similar reductions in the rates of the total number of serious cardiovascular events as those who did not achieve IL-6 concentrations <1.65 ng/l (**Figure 3B**, Supplemental Table 3). The rates of the total number of MACE, MACE+, and MI or coronary revascularization events showed similar results (**Figure 3B**).

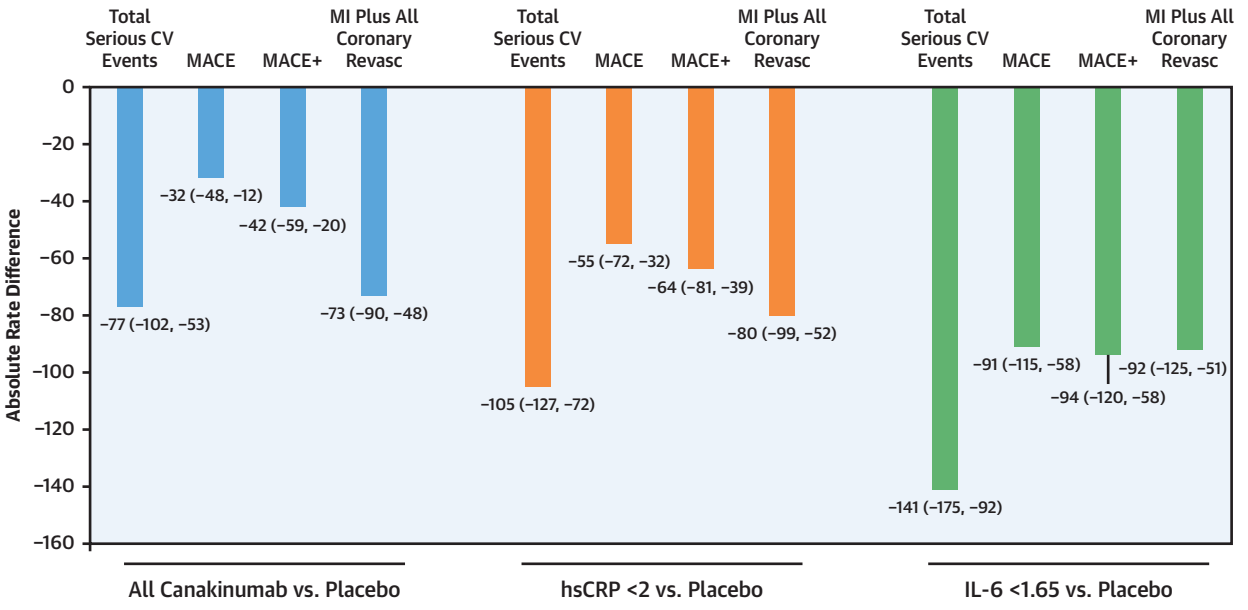
When the differences in first and subsequent cardiovascular event rates in patients who received

FIGURE 3 **The Effect of Canakinumab as Compared With Placebo on the Rates of Total (First and Subsequent) Cardiovascular Events, Stratified by Achieved Inflammatory Biomarker Concentration**



Adjusted rate ratios from negative binomial models for patients randomly allocated to active as compared to placebo canakinumab (50 mg, 150 mg, and 300 mg doses combined) for the total number of events for 4 different composite cardiovascular endpoints. **(A)** The results are stratified according to whether patients achieved high-sensitivity C-reactive protein (hsCRP) <2 mg/l or ≥2 mg/l on treatment. **(B)** The results are stratified according to whether patients achieved interleukin (IL)-6 <1.65 ng/l or ≥1.65 ng/l on treatment. For both biomarkers, patients randomly allocated to the placebo group are the referent group. Rate ratios are adjusted for age, sex, race, body mass index, hypertension, diabetes, baseline concentration of low-density lipoprotein cholesterol, hsCRP, hemoglobin A1c, estimated glomerular filtration rate, albumin, smoking status, history of percutaneous coronary intervention, heart failure, chronic obstructive pulmonary disease, atrial fibrillation, or peripheral artery disease, type of qualifying myocardial infarction, antiplatelet and lipid-lowering therapy. Abbreviations as in Figures 1 and 2.

FIGURE 4 Rate Difference in Total (First and Subsequent) Cardiovascular Events Per 1,000 Patients Treated With Canakinumab as Compared With Placebo



Rate differences and 95% CI (in parentheses) per 1,000 patients treated with canakinumab as compared with placebo for 3.7 years. **Blue bars** are for all patients treated with canakinumab. **Orange bars** are for those patients on canakinumab who achieved on-treatment hsCRP <2.0 mg/l. **Green bars** are for those patients who achieved on-treatment IL-6 <1.65 ng/l. Each panel includes the total serious CV events (a composite of MI, stroke, coronary revascularization, or cardiovascular death), the total MACE (MI, stroke, or cardiovascular death), the total MACE+ events (MI, stroke, unstable angina requiring unplanned coronary revascularization, or cardiovascular death), and MI or all coronary revascularization (revasc) events. Abbreviations as in Figures 1 to 3.

canakinumab were compared with those who received placebo were extrapolated to a population of 1,000 patients over the study median follow-up time (3.7 years), we observed 77 (95% CI: −102 to −53) fewer serious cardiovascular events. When the composite endpoint was narrowed to the trial primary MACE point, we calculated 32 (95% CI: −48 to −12) fewer events in the canakinumab-treated patients, as well as 42 (95% CI: −59 to −20) fewer MACE+ events in those receiving canakinumab (Figure 4).

We then repeated this analysis in the subset of canakinumab-allocated patients who achieved hsCRP <2 mg/l, compared with those allocated to placebo. Specifically, when extrapolated to 1,000 patients treated for the median study follow-up time (3.7 years), we observed 105 (95% CI: −127 to −72) fewer serious cardiovascular events, 55 (95% CI: −72 to −32) fewer MACE, 64 (95% CI: −81 to −39) fewer MACE+, and 80 (95% CI: −99 to −52) fewer MI or coronary revascularization procedures (Figure 4). When we compared those randomly allocated to canakinumab who achieved IL-6 concentrations less than the median of 1.65 ng/l with those allocated to placebo, we observed between 91 (95% CI: −115 to −58) and 105 (95% CI: −127 to −72) fewer serious cardiovascular events, MACE, MACE+, or MI or coronary revascularization events in a hypothetical population of 1,000 patients treated for 3.7 years (Figure 4).

DISCUSSION

This analysis of data from the CANTOS trial found that random allocation to IL-1β inhibition with canakinumab reduced the total number of serious cardiovascular events in patients with prior MI and evidence of ongoing subclinical inflammation at the time of randomization. The incidence of first and subsequent serious cardiovascular events fell from 10.4 events per 100 person-years to 8.3 events per 100 person-years in patients who received IL-1β inhibition with canakinumab. This represents a 21% relative reduction, and a 2.1 per 100 person-years absolute reduction, in the rate of the total number of serious cardiovascular events. These reductions occurred among all participants who were allocated to IL-1β inhibition with canakinumab, including among those randomized to the lowest dose (50 mg given every

3 months). These reductions indicate that inhibition of IL-1β in patients with established cardiovascular disease and subclinical vascular inflammation offers substantial benefits in reducing the burden of cardiovascular disease.

We believe that these data have clinical importance for a number of reasons. First, we are in the early phases of identifying and evaluating the role of anti-inflammatory therapy generally, and IL-1β inhibition in particular, for the treatment of atherosclerotic cardiovascular disease. Using a targeted approach of IL-1β inhibition with canakinumab, we observed a substantial reduction in the total number of cardiovascular events among those randomized to any dose of active therapy, including the lowest dose (50 mg given subcutaneously every 3 months). Although this dose did not lead to a statistically significant reduction in the rate of the first MACE, MACE+ (1), or first serious cardiovascular event for the 50-mg dose as compared with placebo, these data suggest that when the total burden of cardiovascular events is considered, the lowest tested dose does still offer cardiovascular benefit to patients. When considering the total number of serious cardiovascular events, we observed an approximate 20% reduction in the rate of serious cardiovascular events for all 3 canakinumab doses (rate ratio 0.80 for 50 mg, 0.79 for 150 mg, and 0.78 for 300 mg). Similar reductions applied to the more restrictive endpoints of MACE, MACE+, and MI or coronary revascularization. These data support the hypothesis that IL-1β inhibition would offer a substantial benefit in the overall morbidity associated with cardiovascular disease.

This study made the novel observation that canakinumab produced benefits on the total number of serious cardiovascular events regardless of whether patients receiving active therapy achieved reductions in hsCRP to <2 mg/l or reductions in IL-6 to <1.65 ng/l after adjusting for potential confounders. For example, compared with placebo, the reductions in the rates of serious cardiovascular events was 23% for those who achieved hsCRP <2 mg/l on canakinumab therapy, and 26% for those who received IL-1β inhibition with canakinumab but did not achieve an hsCRP <2 mg/l. These results differ from other published work from CANTOS (9,11), which showed that most of the benefit of canakinumab therapy applied to those patients who achieved reductions in hsCRP to <2 mg/l, or reductions in IL-6 to <1.65 ng/l. There are a number of possible explanations for these differences. In contrast to our first event analysis in which virtually all participants were on active therapy, 27% of the cohort did not continue canakinumab after their first event. As such, the hsCRP and IL-6 values measured at 3 months may not reflect the true state of anti-inflammatory therapy at the time of the second atherothrombotic event. Further, as second and third events in any given participant occurred by definition after the first event, they also occurred later in the trial when rates of nonadherence were higher and where the long-term biological effects of canakinumab may not be reflected in the concentrations of hsCRP or IL-6 measured soon after randomization. Another possible explanation for our results is that we have attenuated associations between achieved hsCRP and IL-6 concentrations and recurrent cardiovascular events by adjusting for baseline characteristics that may lie on the causal pathway between inflammation and those events.

Although IL-1β inhibition with canakinumab associated with reduced rates of gout, osteoarthritis, and fatal cancer, it also entailed an increased risk of fatal infection (1,12). Thus, understanding the benefit of IL-1β inhibition with canakinumab on the total number of identifying patients who are likely to benefit from the therapy can inform both patient and clinician understanding of the benefits and risks of a given therapy. The data published here provide a broader sense of the cardiovascular benefit, which can be balanced against the risks of canakinumab (1).

In addition, although IL-1β inhibition was among the first anti-inflammatory drugs to demonstrate efficacy in atherosclerotic cardiovascular disease, colchicine 0.5 mg daily was associated with a 23% reduction in the first occurrence of cardiovascular death, MI, stroke, resuscitated cardiovascular death, or urgent hospitalization for angina leading to coronary revascularization (hazard ratio: 0.77; 95% CI: 0.61 to 0.96) in a recently published trial (2). Thus, 2 medications with different pharmacologic properties can reduce residual risk in at-risk populations. Together, these observations suggest that inflammation inhibition, either with agents that target IL-1β or perhaps other pathways, has the opportunity to reduce the burden of cardiovascular illness in large numbers of patients. Future trials of other novel agents may help us further understand the role of inflammation reduction in the preventions of serous cardiovascular events in high-risk populations.

STUDY STRENGTHS LIMITATIONS. In addition to the strengths of a large, randomized, double-blind, placebo-controlled trial, patients continued on study drug (active or placebo) after a first cardiovascular event, lending validity to the observed differences in total events over time. More than 73% of participants remained on study drug after their first events. All MI, stroke, unstable angina requiring unplanned

coronary revascularization, and death events were centrally adjudicated by the Clinical Endpoints Committee. The analysis of achieved hsCRP and IL-6 concentrations, like those of achieved low-density lipoprotein cholesterol or blood pressure, are no longer formally randomized. However, they are adjusted for an array of potential confounders. Although the approach of counting all serious cardiovascular events provides a more accurate assessment of the health burden caused by cardiovascular disease than a first-event analysis, it can be challenging to determine which events are truly discrete events after the first event. The analysis also weights a number of different cardiovascular events as the same, which assumes that patients and clinicians weight each different type of event the same, when they may actually place a different value on preventing different types of serious cardiovascular events.

CONCLUSIONS

This analysis of the total burden of serious cardiovascular events in patients randomized in the CANTOS trial demonstrates that therapy with canakinumab leads to significant reductions in the rates of serious cardiovascular events in men and women with prior MI and evidence of residual inflammatory risk. These reductions were observed among all participants who were allocated to IL-1β inhibition with canakinumab, including among those randomized to the lowest dose, and were sustained throughout the trial. In the appropriate patient population, IL-1β inhibition may offer the opportunity to reduce the burden of cardiovascular events experienced by high-risk patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Inhibition of interleukin-1β with the monoclonal antibody canakinumab reduces first and subsequent cardiovascular events, a composite of nonfatal MI, nonfatal stroke, coronary revascularization, and cardiovascular death

TRANSLATIONAL OUTLOOK: Further research into the role of anti-inflammatory therapies may lead to novel strategies to reduce the burden of cardiovascular disease.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.