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ORIGINAL RESEARCH ARTICLE

Residual Inflammatory Risk on Treatment With PCSK9 Inhibition and Statin Therapy

Editorial, see p 150

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BACKGROUND: The combination of statin therapy and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition markedly lowers low-density lipoprotein cholesterol (LDL-C) and reduces cardiovascular event rates. Whether residual inflammatory risk as measured by on-treatment high sensitivity C-reactive protein (hsCRP) remains an important clinical issue in such patients is uncertain.

METHODS: We evaluated residual inflammatory risk among 9738 patients participating in the SPIRE-1 and SPIRE-2 cardiovascular outcomes trials (Studies of PCSK9 Inhibition and the Reduction in Vascular Events), who were receiving both statin therapy and bococizumab, according to on-treatment levels of hsCRP (hsCRP$_{OT}$) and LDL-C$_{OT}$ measured 14 weeks after drug initiation. The primary end point was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death.

RESULTS: At 14 weeks, the mean percentage change in LDL-C among statin-treated patients who additionally received bococizumab was −60.5% (95% confidence interval [CI], −61.2 to −59.8; *P*<0.001; median change, −65.4%) as compared to 6.6% (95% CI, −1.0 to 14.1; *P*=0.09; median change, 0.0%) for hsCRP. Incidence rates for future cardiovascular events for patients treated with both statin therapy and bococizumab according to hsCRP$_{OT}$ <1, 1 to 3, and >3 mg/L were 1.96, 2.50, and 3.59 events per 100 person-years, respectively, corresponding to multivariable adjusted hazard ratios of 1.0, 1.16 (95% CI, 0.81–1.66), and 1.62 (95% CI, 1.14–2.30) (*P*-trend=0.001) after adjustment for traditional cardiovascular risk factors and LDL-C$_{OT}$. Comparable adjusted hazard ratios for LDL-C$_{OT}$ (<30, 30–50, >50 mg/dL) were 1.0, 0.87, and 1.21, respectively (*P*-trend=0.16). Relative risk reductions with bococizumab were similar across hsCRP$_{OT}$ groups (*P*-interaction=0.87).

CONCLUSIONS: In this post hoc analysis of the SPIRE trials of bococizumab in a stable outpatient population, evidence of residual inflammatory risk persisted among patients treated with both statin therapy and proprotein convertase subtilisin-kexin type 9 inhibition.

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Key Words: hsCRP ■ inflammation ■ LDL-C ■ PCSK9 inhibitor ■ PCSK9 ■ residual risk

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Clinical Perspective

What Is New?

- Among high-risk stable outpatients treated with moderate- or high-intensity statins and PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibition, roughly 1 in 2 had residual inflammatory risk defined by on-treatment high-sensitivity C-reactive protein (hsCRP) levels ≥2 mg/L, with roughly 1 in 3 having values >3 mg/L.
- Treatment with bococizumab was associated with a 60% mean reduction in low-density lipoprotein cholesterol (LDL-C) but little change in hsCRP.
- Levels of hsCRP >3 mg/L were associated with a 60% greater risk of future cardiovascular events, corresponding to a 3.6% annual event rate (3.6 per 100 person-years) even after accounting for on-treatment LDL-C.

What Are the Clinical Implications?

- PCSK9 inhibition added to statin therapy in stable outpatients does not lower hsCRP.
- Persistent elevations of hsCRP are associated with future cardiovascular risk in these patients even after low levels of LDL-C are achieved.
- If corroborated, these data suggest that inflammation modulation may yet have a role in primary and secondary prevention of cardiovascular disease when LDL-C is controlled.

Patients with residual inflammatory risk have high rates of recurrent cardiovascular events in association with persistently elevated levels of high-sensitivity C-reactive protein (hsCRP) despite aggressive use of statin therapy.[1–7] Such patients, commonly defined as those taking statin therapy who have hsCRP ≥2 mg/L and low-density lipoprotein cholesterol (LDL-C) <70 mg/dL,[8] comprise nearly 30% of patients in contemporary practice and are twice as common as those with residual cholesterol risk (defined by LDL-C levels ≥70 mg/dL and hsCRP <2 mg/L).[9] Recently, the CANTOS study (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) demonstrated that interleukin-1 inhibition with canakinumab significantly reduces both hsCRP and cardiovascular events in stable patients with prior myocardial infarction (MI) and elevated hsCRP,[10] data providing the first potential treatment for patients with residual inflammatory risk. Indeed, the magnitude of risk reduction with canakinumab in CANTOS, despite no change in LDL-C, was virtually identical to that achieved in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and SPIRE (Studies of PCSK9 Inhibition and the Reduction in Vascular Events) PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitor trials[11,12] of evolocumab and bococizumab, respectively, in stable high-risk populations. Table 1 provides a brief description of design elements of these trials as well as the recently completed ODYSSEY Outcomes trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab),[13] which tested the PCSK9 inhibitor alirocumab. Importantly, the absolute event rates of 5.3% and 9.1% at 1 year and 2 years on treatment with evolocumab in FOURIER inform us that many patients achieving very low LDL-C levels will continue to experience cardiovascular events. Whether residual inflammatory risk, that cardiovascular risk attributable to residual subclinical inflammation, remains an important clinical issue among statin-treated patients who additionally receive PCSK9 inhibition is unknown. We addressed this issue in the recently completed SPIRE-1 and SPIRE-2 trials.

METHODS

Data Availability

The data will not be made available to other researchers for purposes of reproducing the results. However, the methods used in the analysis are available on request.

Study Population and Procedures

The SPIRE bococizumab development program consisted of 2 parts: the 6 SPIRE lipid-lowering studies and the SPIRE-1 and SPIRE-2 event-driven cardiovascular trials. The design and primary findings of SPIRE-1 and SPIRE-2 have been previously published.[12,14] The virtually identical designs of the 2 trials permitted them to be combined according to an integrated statistical analysis plan. In brief, patients were eligible for enrollment if they had either a prior cardiovascular event (secondary prevention cohort) or a history of diabetes mellitus, chronic kidney disease, or peripheral vascular disease with additional cardiovascular risk conditions or a history of familial hypercholesterolemia (high-risk primary prevention cohort). All patients were required to have received ≥4 weeks of stable statin therapy (atorvastatin ≥40 mg/day, rosuvastatin ≥20 mg/day, or simvastatin ≥40 mg/day) unless they could not take those doses without side effects and were thus on lower intensity statin therapy or had complete statin intolerance (eligible for SPIRE-2 only). Patients were required to have a directly measured LDL-C level of ≥70 mg/dL in SPIRE-1 and ≥100 mg/dL in SPIRE-2. Patients were also eligible according to their non–high-density lipoprotein (non-HDL) cholesterol level at entry (≥100 mg/dL for SPIRE-1 and ≥130 mg/dL for SPIRE-2). In a double-blinded fashion, patients were randomized in a 1:1 ratio to treatment with subcutaneous bococizumab 150 mg every 2 weeks or matching placebo. The SPIRE program was sponsored by Pfizer.

The study population for the current analysis comprises the subgroup of SPIRE-1 and SPIRE-2 patients who were receiving moderate- or high-intensity statin therapy, were allocated to active bococizumab, and had available baseline and 14-week hsCRP measures available for analysis

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Table 1. Comparison of the CANTOS, SPIRE-1, SPIRE-2, FOURIER, and ODYSSEY Outcomes Clinical Trials

Variable	CANTOS[10]	SPIRE-1[12,14]	SPIRE-2[12,14]	FOURIER[11]	ODYSSEY Outcomes[13]
Monoclonal antibody	Canakinumab (human)	Bococizumab (humanized)	Bococizumab (humanized)	Evolocumab (human)	Alirocumab (human)
Entry LDL-C, mg/dL	No entry threshold	≥70	≥100	≥70	≥70
Statin requirement	No requirement; 91.1% taking statins, median (IQR) LDL-C: 82.0 (63.0–106.7)	Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, simvastatin 40 mg (or 80 mg if >1 y), or documented intolerance to high-intensity statin (SPIRE-1 and SPIRE 2) or documented complete statin intolerance (SPIRE-2)		High-intensity statin preferred, minimum dose atorvastatin 20 mg or equivalent	Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg or maximum tolerated dose of 1 of these agents
High-risk secondary prevention	Yes	Yes	Yes	Yes	Yes
High-risk primary prevention	No	Yes	Yes	No	No
Status	Completed	Prematurely terminated because of bococizumab immunogenicity	Prematurely terminated because of bococizumab immunogenicity	Completed	Completed

IQR indicates interquartile range; and LCL-C, low-density lipoprotein cholesterol.

(n=9738). Adherence to randomized treatment was high, with 89.9% and 88.8% of patients assigned to bococizumab having ≥80% compliance (≥80% of doses administered of doses planned) and 93.1% and 93.0% mean compliance (number of doses taken of number of doses planned) in SPIRE-1 and SPIRE-2, respectively. All patients provided written informed consent. Ethics committees at each center approved the protocol.

End Points

The prespecified primary end point of the 2 trials was a composite of adjudicated and confirmed nonfatal MI, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death. All incident events that were components of these end points were adjudicated by a committee in which the members were unaware of treatment assignments.

Statistical Analyses

Of 13 675 patients randomized to the active treatment arm, 12 711 (93.0%) were receiving moderate- or high-intensity statin therapy, and 9738 (71.2%) also had on-treatment hsCRP (hsCRP$_{OT}$) levels available at the 14-week time point. The corresponding proportion of patients randomized to placebo, receiving statin therapy, and having follow-up biomarker levels was 9785 (71.6%). Baseline characteristics of included versus excluded patients are shown in Table I in the online-only Data Supplement.

The study population was then restricted to individuals allocated to bococizumab and divided into 3 groups according to hsCRP$_{OT}$ level <1, 1 to 3, and >3 mg/dL comprising 30.4%, 34.8%, and 34.9% of patients, respectively. These cut points are consistent with the previously proposed Centers for Disease Control/American Heart Association classification scheme[15] and correspond to approximate tertiles of the population distribution. When cut points of <2 and ≥2 mg/dL were used, these percentages were 52.8% and 47.2%. Baseline characteristics according to the 3 primary hsCRP$_{OT}$ groups were summarized using percentages for categorical values and medians (interquartile ranges) for continuous variables. Trends in these characteristics across ordered hsCRP$_{OT}$ categories were assessed using the Cochran-Armitage trend test for differences in proportions and the Jonckheere-Terpstra test for differences in medians.

To evaluate the treatment effect of bococizumab on lipid levels and hsCRP, median on-treatment levels were determined at baseline and 14 weeks of therapy. Linear mixed-model repeated-measure analyses conditioning on the baseline value were used, with the independent value being the biomarker of interest after log transformation as deemed appropriate for nonnormal distributions. The mean percentage change and bococizumab treatment effect were estimated by fitting terms corresponding to the study drug assignment.

Percentage change in lipid levels in each hsCRP$_{OT}$ group among patients allocated to bococizumab was then estimated using mixed models as before, conditioning on the baseline value, and fitting a term corresponding to the hsCRP$_{OT}$ group.

Cox proportional hazards models were used to estimate hazard ratios (HRs) according to hsCRP$_{OT}$ group. Because the LDL-C–lowering effects of bococizumab emerge as early as 4 weeks after drug initiation,[12] all end points, including those occurring before 14 weeks, were used in the primary analysis. Sensitivity analyses were conducted after removing these events (Table II in the online-only Data Supplement). The 3 models presented are adjusted for (1) age and sex; (2) age, sex, traditional cardiovascular risk factors (including current smoking, diabetes mellitus, hypertension, and body mass index), plus statin intensity at enrollment (moderate or high); and (3) model 2 variables plus on-treatment LDL-C (LDL-C$_{OT}$). For each model, a test for trend across hsCRP$_{OT}$ categories was performed after assigning the median value to each group. All analyses were stratified by study (SPIRE-1 or SPIRE-2), region, and screening LDL-C threshold (≥70 or ≥100 mg/dL). We also assessed for heterogeneity in treatment effects

of bococizumab versus placebo according to $hsCRP_{OT}$ groups by use of an interaction term (bococizumab × $hsCRP_{OT}$ group).

To permit comparison to associations for on-treatment LDL-C measured at 14 weeks, the study population was additionally divided into $LDL\text{-}C_{OT}$ groups (approximate tertiles) using the categories of <30, 30 to 50, and >50 mg/dL, and comparable Cox models were used to estimate adjusted HRs in each of these groups. Cut points of <2 or ≥2 mg/L for hsCRP and <40 or ≥40 mg/dL for LDL-C were also used. Finally, to examine the risk association throughout the range of $hsCRP_{OT}$, we plotted the relationship between $hsCRP_{OT}$ and cardiovascular event rates using a smoothing function to the average of estimated event rates at each $hsCRP_{OT}$ level based on adjusted Cox models.

RESULTS

Study Population by $hsCRP_{OT}$ Levels

The study population comprised 2958 (30.4%) with $hsCRP_{OT}$ <1 mg/L, 3385 (34.8%) with $hsCRP_{OT}$ 1 to 3 mg/L, and 3395 (34.9%) with $hsCRP_{OT}$ >3 mg/L. Baseline characteristics according to $hsCRP_{OT}$ are shown in Table 2. Patients with higher $hsCRP_{OT}$ were more likely to be women, be obese, have diabetes mellitus or diagnosed hypertension, and be current smokers, but less likely to have prior cardiovascular disease. Several baseline lipid parameters were also significantly different across increasing hsCRP groups, including higher levels of LDL-C, total cholesterol (TC), non–HDL cholesterol (HDL-C), triglycerides, TC/HDL-C ratio, and apolipoprotein B, and lower levels of HDL-C.

Bococizumab Treatment Effects on Lipid Levels and hsCRP

When compared with placebo, bococizumab was associated with statistically significant reductions in LDL-C (−60.5%), TC (−37.6%), non–HDL-C (−54.9%), TC/HDL-C ratio (−41.1%), apolipoprotein B (−56.0%), and triglycerides (−19.9%) as well as an increase in HDL-C (+6.4%) (Table 3; all $P<0.001$). By contrast, there was no significant effect on hsCRP; mean percentage change was +6.6% (95% confidence interval [CI], −1.0 to 14.1; $P=0.09$; median change 0.0%) at 14 weeks and +6.7% (95% CI, −9.3% to 16.9%; $P=0.57$; median change 0.0%) at 52 weeks (n=3267). Percentage changes in lipid fractions were slightly lower in magnitude in higher $hsCRP_{OT}$ groups (Figure 1). Nonetheless, even among those with hsCRP >3 mg/L, the median $LDL\text{-}C_{OT}$ at 14 weeks was 41.7 (interquartile range, 25.9–67.0) mg/L. Bococizumab treatment effects by $hsCRP_{OT}$ were similar

Table 2. Baseline Characteristics According to $hsCRP_{OT}$ at 14 Weeks

Baseline Characteristic	$hsCRP_{OT}$ Group			
	<1 mg/L N=2958 (30.4%)	1–3 mg/L N=3385 (34.8%)	>3 mg/L N=3395 (34.9%)	*P* Value
Age, y	63 (56–69)	64 (57–70)	63 (57–69)	0.19
Female sex, %	28.0	29.4	31.4	<0.001
Body mass index, kg/m²	27.9 (25.5–30.9)	29.4 (26.6–32.7)	31.4 (27.9–35.9)	<0.001
Diabetes mellitus, %	37.4	47.2	60.2	<0.001
Hypertension, %	75.1	82.4	87.4	<0.001
Current smoking, %	19.0	23.8	30.0	<0.001
High-risk primary prevention, %	8.1	14.0	19.2	<0.001
United States/Canada, %	21.3	27.4	35.6	<0.001
Statin regimen, %				0.10
Moderate intensity	8.3	9.0	9.4	
High intensity	91.8	91.0	90.6	
LDL cholesterol, mg/dL	92.4 (80.5–110.4)	96.5 (82.4–118.0)	101.0 (85.1–125.5)	<0.001
Total cholesterol, mg/dL	161.8 (144.8–184.2)	166.2 (147.5–193.1)	171.5 (151.2–200.5)	<0.001
Non-HDL cholesterol, mg/dL	112.0 (97.1–132.2)	117.7 (101.2–143.8)	124.9 (105.5–153.9)	<0.001
HDL cholesterol, mg/dL	47.0 (40.0–56.0)	45.2 (38.4–53.5)	43.8 (37.0–52.5)	<0.001
Triglycerides, mg/dL	116.5 (87.6–160.2)	137.5 (101.3–192.5)	149.6 (108.0–210.6)	<0.001
Total/HDL cholesterol ratio	3.4 (2.9–4.1)	3.7 (3.1–4.4)	3.9 (3.2–4.7)	<0.001
Apolipoprotein B, mg/dL	78 (68–91)	82 (71–98)	87 (74–105)	<0.001
High-sensitivity CRP, mg/L	0.7 (0.4–1.2)	1.8 (1.1–2.9)	4.7 (2.7–7.6)	<0.001

Table entries are medians (interquartile range). Percentages may not add up to 100% because of rounding. CRP indicates C-reactive protein; HDL, high-density lipoprotein; $hsCRP_{OT}$, on-treatment levels of high-sensitivity C-reactive protein; and LDL, low-density lipoprotein.

Table 3. Median Lipid Levels and hsCRP at Baseline and 14 Weeks and Treatment Effect (Percentage Change) With Bococizumab

	Bococizumab		Placebo		Treatment Effect*		
Parameter	No.	Median (IQR)	No.	Median (IQR)	% Change	95% CI	*P*
LDL-C (mg/dL)							
Baseline	9662	96.5 (82.5–118.0)	9716	96.5 (82.6–117.5)	−60.5	(−61.2 to −59.8)	<0.001
14 wk	9662	34.7 (22.4–56.4)	9716	97.7 (82.0–120.3)			
Total cholesterol (mg/dL)							
Baseline	9670	166.5 (147.9–192.3)	9711	166.4 (148.0–191.9)	−37.6	(−38.1 to −37.1)	<0.001
14 wk	9670	102.7 (84.2–128.2)	9711	167.6 (146.7–195.0)			
Non-HDL cholesterol (mg/dL)							
Baseline	9648	118.0 (101.0–143.8)	9690	117.8 (101.4–142.7)	−54.9	(−55.1 to −53.7)	<0.001
14 wk	9648	50.0 (34.7–76.0)	9690	118.9 (100.0–146.3)			
HDL cholesterol (mg/dL)							
Baseline	9649	45.2 (38.2–54.0)	9694	45.6 (38.6–54.3)	6.4	(6.1 to 6.8)	<0.001
14 wk	9649	48.0 (40.9–57.9)	9694	45.9 (38.6–54.8)			
Triglycerides (mg/dL)							
Baseline	9699	134.5 (98.2–189.0)	9713	133.6 (98.5–187.2)	−19.9	(−21.0 to −18.8)	<0.001
14 wk	9699	107.0 (76.1–157.5)	9713	133.0 (96.0–189.4)			
Total cholesterol/HDL ratio							
Baseline	9648	3.6 (3.1–4.4)	9690	3.6 (2.1–4.4)	−41.1	(−41.7 to −40.6)	<0.001
14 wk	9648	2.0 (1.7–2.7)	9690	3.6 (3.0– 4.5)			
Apolipoprotein B (mg/dL)							
Baseline	9641	82.0 (71.0–99.0)	9678	82.0 (71.0–98.0)	−56.0	(−56.7 to −55.2)	<0.001
14 wk	9733	37.0 (17.5–56.0)	9782	82.5 (71.0–99.0)			
hsCRP (mg/L)							
Baseline	9738	1.88 (0.87–4.21)	9756	1.90 (0.85–4.08)	6.6	(−1.0 to 14.1)	0.09
14 wk	9738	1.84 (0.83–4.19)	9785	1.68 (0.78–3.88)			

CI indicates confidence interval; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; and LDL-C, low-density lipoprotein cholesterol.

*The percentage change is from baseline to 14 wk for the bococizumab group as compared with the placebo group.

in magnitude, and there was no evidence of heterogeneity across $hsCRP_{OT}$ groups (*P*-interaction=0.87).

Event Rates According to $hsCRP_{OT}$ and $LDL\text{-}C_{OT}$

Overall, a monotonic increase in adjusted event probabilities for the primary end point was observed with increasing $hsCRP_{OT}$ levels (Figure 2). Event rates in $hsCRP_{OT}$ groups were 1.96, 2.50, and 3.59 per 100 person-years for hsCRP <1, 1 to 2, and >3 mg/L, respectively (Table 4). In multivariable models that adjusted for age and sex (model 1), the corresponding HRs for CVD were 1.0 (reference), 1.23 (95% CI, 0.86–1.75), and 1.79 (95% CI, 1.28–2.50; *P*-trend<0.001). In models additionally adjusting for traditional cardiovascular risk factors and baseline intensity of statin therapy (model 2), the HR comparing highest to lowest $hsCRP_{OT}$ category (>3 versus <1 mg/L) was 1.67 (95% CI, 1.18–2.37; *P*=0.004). Further adjustment for $LDL\text{-}C_{OT}$ minimally attenuated this risk (model 3, Table 4, and Figure 3, left); adjusted HRs were 1.0 (reference), 1.16 (95% CI, 0.81–1.66), and 1.62 (95% CI, 1.14–2.30; *P*-trend=0.001).

Adjustments made for other potential confounding or mediating factors had minimal impact on these results. In models adjusting for on-treatment TC/HDL-C ratio (model 3 plus TC/HDL-C), adjusted HRs were 1.0 (reference), 1.13, and 1.58 (*P*-trend=0.002). In models adjusting for prior history of CVD (including peripheral vascular disease), adjusted HRs (model 3 plus prior CVD) were 1.0 (reference), 1.18, and 1.62 (*P*-trend=0.001). When adjusted for prior history of chronic kidney disease, HRs (model 3 plus prior chronic kidney disease) were 1.0 (reference), 1.16, and 1.60 (*P*-trend=0.001).

We found similar hazard ratios when analyses were restricted to the placebo group; adjusted HRs (model 3) were 1.0 (reference), 1.11, and 1.72 (*P*-trend<0.001) according to hsCRP values at 14 week categorized as <1, 1 to 3, and >3 mg/L, respectively. When individual components of the composite end point were exam-

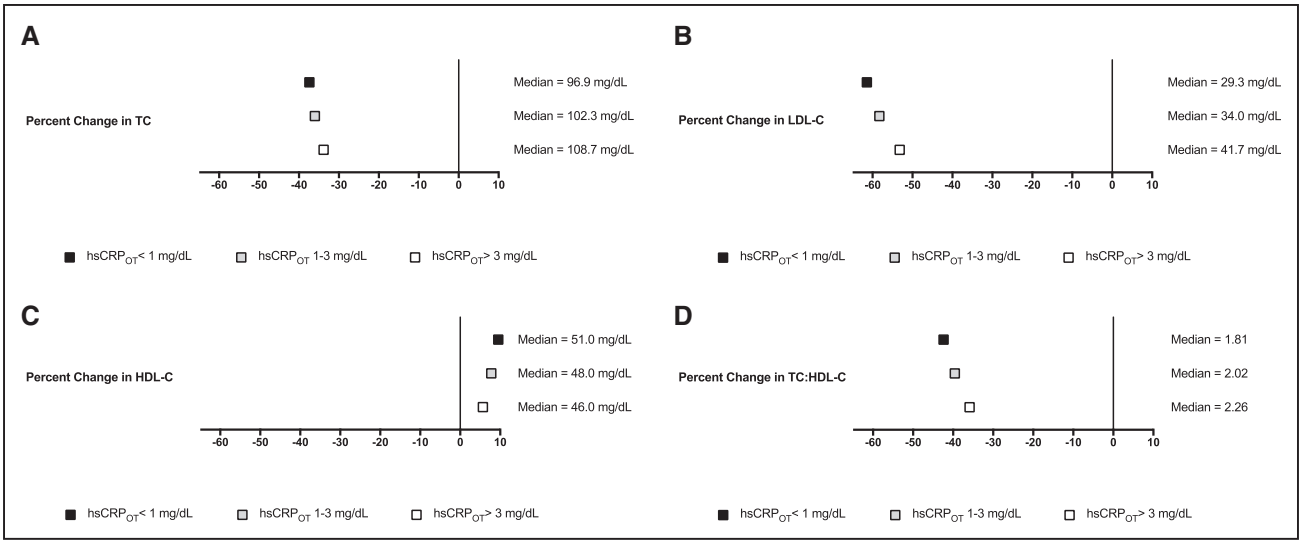

Figure 1. Mean percentage change in lipid levels from baseline to 14 weeks according to hsCRP$_{OT}$.
Median on-treatment lipid values (**A**, Total cholesterol; **B**, LDL cholesterol; **C**, HDL cholesterol; and **D**, TC:HDL-C ratio) in each hsCRP$_{OT}$ group are shown to the right of each plot. HDL-C indicates high-density lipoprotein cholesterol; hsCRP$_{OT}$, on-treatment levels of high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and TC, total cholesterol.

ined (model 3 adjustments), the hsCRP$_{OT}$ category was significantly associated with nonfatal MI (adjusted HRs, 1.0, 0.91, 1.46; *P*-trend=0.017), cardiovascular mortality (adjusted HRs, 1.0, 1.60, 3.76; *P*-trend=0.002), and total mortality (adjusted HRs, 1.0, 1.58, 3.45; *P*-trend<0.001) (Table 4). Similar but nonsignificant trends were noted for stroke and unstable angina requiring urgent coronary revascularization.

In parallel analyses in which patients were categorized according to LDL-C$_{OT}$ (<30, 30–50, >50 mg/dL), the HRs for the primary end point were 1.0 (reference), 0.87 (95% CI, 0.62–1.22), and 1.21 (95% CI, 0.87–1.68), with *P*-trend=0.16 in analyses adjusting for model 3 covariates and hsCRP$_{OT}$ instead of LDL-C$_{OT}$ (Figure 2, right, and Table III in the online-only Data Supplement). Similar findings were observed when the alternate cut points of ≥2 mg/L

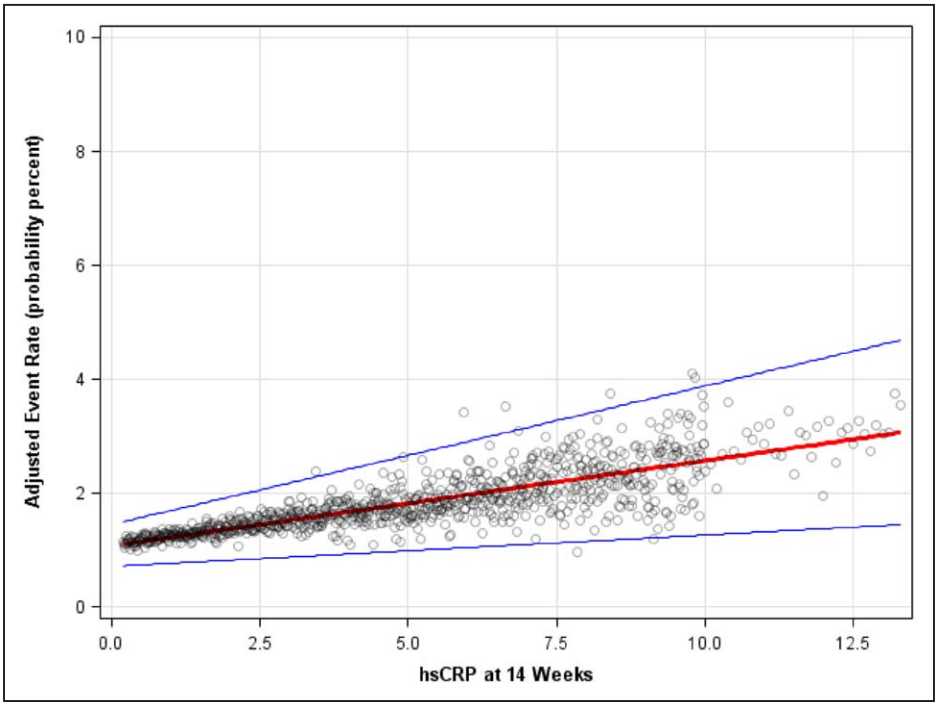

Figure 2. Relationship between hsCRP$_{OT}$ on a continuous scale and the adjusted event rate for the trial primary end point (myocardial infarction, stroke, unstable angina requiring urgent coronary revascularization, and cardiovascular death).
Model adjusts for age, sex, current smoking, diabetes mellitus, hypertension, body mass index, statin intensity at enrollment (moderate or high), and on-treatment levels of low-density lipoprotein cholesterol. Dots represent individual hsCRP$_{OT}$ values. The solid red line indicates the estimated event curve from adjusted models. hsCRP$_{OT}$ indicates on-treatment levels of high-sensitivity C-reactive protein.

Table 4. Hazard Ratios for Cardiovascular Events According to $hsCRP_{OT}$ at 14 Weeks

Variable	$hsCRP_{OT}$ Group			P
	<1 mg/L N=2958 (30.4%)	1–3 mg/L N=3385 (34.8%)	>3 mg/L N=3395 (34.9%)	
Primary end point* Events per 100 person-years	52 1.96	76 2.50	109 3.59	*P*-trend
Model 1	1 (ref)	1.23 (0.86–1.75) *P*=0.3	1.79 (1.28–2.50) *P*=0.001	<0.001
Model 2	1 (ref)	1.17 (0.82–1.68) *P*=0.4	1.67 (1.18–2.37) *P*=0.004	<0.001
Model 3	1 (ref)	1.16 (0.81–1.66) *P*=0.4	1.62 (1.14–2.30) *P*=0.007	0.001
Individual end points (model 3)				
Nonfatal myocardial infarction	N=31 1 (ref)	N=36 0.91 (0.56–1.49) *P*=0.7	N=61 1.46 (0.92–2.32) *P*=0.11	0.017
Nonfatal stroke	N=7 1 (ref)	N=14 1.62 (0.65–4.05) *P*=0.3	N=14 1.47 (0.56–3.85) *P*=0.4	0.4
Hospitalization for unstable angina requiring urgent revascularization	N=10 1 (ref)	N=16 1.33 (0.60–2.95) *P*=0.5	N=21 1.65 (0.74–3.68) *P*=0.2	0.2
Cardiovascular death	N=5 1 (ref)	N=11 1.60 (0.54–4.73) *P*=0.4	N=23 3.76 (1.38–10.2) *P*=0.009	0.002
Any death	N=10 1 (ref)	N=20 1.58 (0.73–3.41) *P*=0.3	N=38 3.45 (1.68–7.08) *P*=0.001	<0.001

Model 1, age- and sex-adjusted. Model 2, additionally adjusted for baseline smoking, diabetes mellitus, hypertension, body mass index, and baseline statin (moderate- or high-intensity). Model 3, additionally adjusted for on-treatment $LDL\text{-}C_{OT}$ (no. missing=76). All models stratified by study (SPIRE-1 or SPIRE-2), region, and LDL-C screening. $hsCRP_{OT}$ indicates on-treatment levels of high-sensitivity C-reactive protein; $LDL\text{-}C_{OT}$, on-treatment levels of low-density lipoprotein cholesterol; and ref, reference.

*The primary end point was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death.

for $hsCRP_{OT}$ and ≥40 mg/dL for $LDL\text{-}C_{OT}$ were used (Tables IV and V in the online-only Data Supplement).

DISCUSSION

In this population of 9738 high-risk patients concomitantly treated with statins and PSCK9 inhibition, 47.2% had residual inflammatory risk defined by $hsCRP_{OT}$ level ≥2 mg/L, with 34.9% having values >3 mg/L. Individuals with persistent hsCRP elevation tended to be those with multiple risk factors, including diabetes mellitus, obesity, hypertension, and mixed dyslipidemia, conditions known to correlate with, if not be driven by, a proinflammatory state. PCSK9 inhibition with bococizumab had no effect on hsCRP over time. Despite aggressive reduction of LDL-C, there was a continuous gradient in risk for future cardiovascular events according to $hsCRP_{OT}$. Compared to those without evidence of subclinical inflammation, those with $hsCRP_{OT}$ >3 mg/L (median $LDL\text{-}C_{OT}$, 41.7 mg/dL) had a 62% increase in risk of future cardiovascular events. Elevated hsCRP was significantly associated with increased rates of nonfatal MI, cardiovascular death, and all-cause mortality.

There is broad consensus that atherosclerosis is a disorder of both lipid accumulation and inflammation. From a clinical perspective, extensive prior work has found hsCRP to be an independent predictor of cardiovascular events in both primary prevention and high-risk secondary prevention settings. Further, among patients with residual inflammatory risk, randomized clinical trials have proven the efficacy of statin therapy in primary prevention[16] and anti-inflammatory therapy in secondary prevention.[10] It has been uncertain, however, whether residual inflammatory risk persists after the extremely aggressive reduction in LDL-C that can be achieved with the combination of statin therapy and PCSK9 inhibition. It is important to note that in an era when ever more specialized therapies in cardiovascular medicine continue to emerge, the call for biomarkers that inform clinicians about risk stratification, drug choice, dose-therapeutic responses and, ultimately, personalized interventions will only be amplified.

In this context, these data have several important implications. First, these data clarify that PCSK9 inhibition has no effect on plasma measures of hsCRP, despite large effects on atherogenic lipids. Second, the current data demonstrate that, despite the interrelationships between LDL oxidation and inflammation, the combination of high-intensity statin therapy and PCSK9 inhibition does not fully address inflammatory mechanisms of atherothrombosis that may be detected by elevated levels of hsCRP. In isolation, our post hoc findings are associative and could still be explained by underlying conditions that promote subclinical inflammation. As such, as we have argued elsewhere,[17] combination therapy with PCSK9 inhibition and anti-inflammatory therapy may provide the optimal method to address residual cardiovascular risk, a hypothesis that requires a prospective 2×2 factorial trial for adequate testing. Although canakinumab is currently the only anti-inflammatory agent proven to reduce cardiovascular events, clinical trials are currently in progress using colchicine and low-dose methotrexate.[18,19] Novel agents that inhibit the upstream NLRP3 inflammasome and downstream activation of interleukin-6 are also under consideration. It is important to note that our data do not pertain to the setting of acute coronary syndromes, where anti-inflammatory therapies have thus far failed to impart cardiovascular benefit.

The SPIRE cardiovascular outcomes trials were stopped early because of high rates of development of neutralizing antidrug antibodies.[20] Although bococizumab immunogenicity is associated with a less durable LDL reduction, treatment with bococizumab in the longer duration

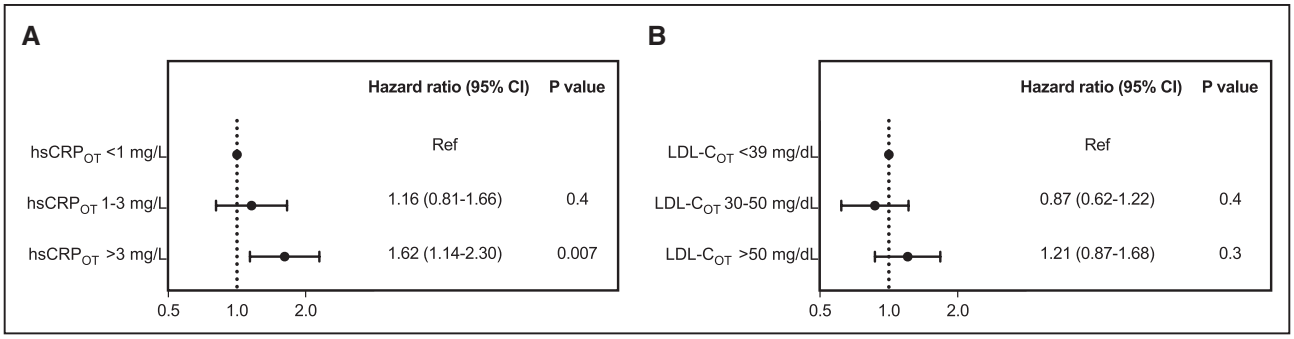

Figure 3. Risk association of hsCRP$_{OT}$ and LDL-C$_{OT}$ with incident cardiovascular events according to categories of each biomarker.
Adjusted for age, sex, current smoking, diabetes mellitus, hypertension, body mass index, statin intensity at enrollment (moderate or high), and hsCRP$_{OT}$ and LDL-C$_{OT}$ as appropriate. **A**, Models for hsCRP$_{OT}$. **B**, Models for LDL-C$_{OT}$. CI indicates confidence interval; hsCRP$_{OT}$, on-treatment levels of high-sensitivity C-reactive protein; LDL-C$_{OT}$, on-treatment levels of low-density lipoprotein cholesterol; and Ref, reference.

SPIRE-2 outcomes trial was nonetheless associated with a 21% (95% CI, 3–35; *P*=0.02) relative risk reduction in major cardiovascular events overall and a 14% (95% CI, −2 to −25) relative risk reduction per 1 mmol/L LDL-C. These data are fully in line with benefits observed in FOURIER[12,21] and preliminary data from the ODESSY Outcomes trial.[22] Thus, we believe our findings are unlikely to be explained by diminished bococizumab LDL-C–lowering efficacy and likely to apply more broadly to biological agents in this therapeutic class. As in any post hoc analysis, our findings may be susceptible to residual confounding. In particular, patients with persistent inflammatory risk were more likely to have cardiovascular risk factors and higher median on-treatment LDL-C$_{OT}$. However, our multivariable analyses adjusted for achieved LDL-C levels and showed minimal, if any, attenuation in risk. Furthermore, as shown in CANTOS, which enrolled on the basis of elevated hsCRP, this risk group is likely to benefit from anti-inflammatory therapy.[10] Consistent associations were noted for the individual trial end points of nonfatal MI, cardiovascular mortality, and all-cause mortality. However, it should be noted that the number of events was small. Thus, these findings must be interpreted with caution.

In summary, these contemporary randomized trial data demonstrate that elevated levels of hsCRP$_{OT}$ remain a significant predictor of future cardiovascular risk among patients with stable atherosclerosis concomitantly treated with statins and PCSK9 inhibition. This evidence of residual inflammatory risk despite maximal LDL-C lowering, if replicated in other cohorts, suggests that inflammation modulation may offer additional opportunities for cardiovascular risk reduction.

ARTICLE INFORMATION

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Residual Inflammatory Risk on Treatment With PCSK9 Inhibition and Statin Therapy

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Baseline Characteristics of Patients Included Versus Excluded from the Primary Analysis

Baseline Characteristic	Included N=9738	Excluded N=3947	P-value
Age, years	63 (57, 69)	64 (57, 70)	0.02
Female Sex, %	28.2	31.7	<0.001
Body-Mass Index, kg/m^2	29.6 (26.5, 33.3)	29.4 (26.3, 32.8)	<0.001
Diabetes, %	48.8	46.7	0.03
Hypertension, %	81.9	80.0	0.01
Current Smoking, %	24.4	24.7	0.83
High-Risk Primary Prevention, %	14.0	17.5	<0.001
US/Canada, %	28.4	29.4	0.25
LDL Cholesterol, mg/dL	96.5 (82.5, 118.0)	107.7 (86.5, 144.0)	<0.001
Total Cholesterol, mg/dL	166.6 (147.9, 192.5)	177.6 (152.0, 219.0)	<0.001
Non-HDL Cholesterol, mg/dL	118.0 (101.0, 144.0)	129.5 (104.8, 171.2)	<0.001
HDL Cholesterol, mg/dL	45.2 (38.2, 54.1)	45.0 (38.2, 53.9)	0.9
Triglycerides, mg/dL	134.5 (98.2, 189.0)	142.5 (103.1, 204.9)	<0.001
Total:HDL Cholesterol Ratio	3.6 (3.1, 4.4)	3.9 (3.2, 4.9)	<0.001
Apolipoprotein B, mg/dL	82 (71, 99)	90 (75, 113)	<0.001
High-Sensitivity CRP, mg/L	1.9 (0.9, 4.2)	2.2 (1.0, 4.7)	<0.001
Events, n (%)	237 (2.4)	115 (2.9)	0.11

* 13,675 patients randomized to the active treatment arm.
Minus 964 (7.0%) not on background statin
Minus 3090 (22.6%) of total randomized population without hsCRP$_{OT}$ levels available at the 14 week time point.

Values for continuous variables are median (IQR).

Supplemental Table 2. Hazard Ratios for Cardiovascular Events According to $hsCRP_{OT}$ (EXCLUDING 75 events occurring before 14 weeks)

	$hsCRP_{OT}$ Group			
	<1 mg/L N=2958 (30.4%)	1-3 mg/L N=3385 (34.8%)	>3 mg/L N=3395 (34.9%)	
Primary Endpoint*	35	49	78	P-trend
Events per 100 person-years	1.32	1.61	2.57	
Model 1	1 (ref)	1.16 (0.75 to 1.80) p=0.5	1.89 (1.26 to 2.83) p=0.002	<0.001
Model 2	1 (ref)	1.08 (0.70 to 1.69) p=0.7	1.72 (1.13 to 2.63) p=0.01	<0.001
Model 3	1 (ref)	1.08 (0.70 to 1.68) p=0.7	1.67 (1.09 to 2.56) P=0.02	0.001

* The primary endpoint was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death.

Model 1: age- and sex-adjusted

Model 2: additionally adjusted for baseline smoking, diabetes, hypertension, body-mass index, baseline statin (moderate- or high-intensity)

Model 3: additionally adjusted for on-treatment $hsCRP_{OT}$

All models stratified by study (SPIRE-1 or SPIRE-2), region, and screening LDL-C.

Supplemental Table 3. Hazard Ratios for the Cardiovascular Events According to LDL-C_{OT} at 14 Weeks

	LDL-C_{OT} Group			
	<30 mg/dL N=3979 (41.2%)	30-50 mg/dL N=2770 (28.7%)	>50 mg/dL N=2913 (30.1%)	
Primary Endpoint*	88	57	90	P-trend
Events per 100 person-years	2.50	2.28	3.40	
Model 1	1 (ref)	0.90 (0.64 to 1.27) p=0.6	1.36 (0.98 to 1.87) p=0.07	0.04
Model 2	1 (ref)	0.89 (0.63 to 1.25) p=0.5	1.28 (0.92 to 1.77) p=0.14	0.09
Model 3	1 (ref)	0.87 (0.62 to 1.22) p=0.4	1.21 (0.87 to 1.68) p=0.3	0.16

* The primary endpoint was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death.

* 76 patients excluded due to missing LDL-C_{OT}

Model 1: age- and sex-adjusted

Model 2: additionally adjusted for baseline smoking, diabetes, hypertension, body-mass index, baseline statin (moderate- or high-intensity)

Model 3: additionally adjusted for on-treatment $hsCRP_{OT}$

All models stratified by study (SPIRE-1 or SPIRE-2), region, and screening LDL-C.

Supplemental Table 4. Hazard Ratios for the Cardiovascular Events According to $hsCRP_{OT}$ at 14 weeks

	$hsCRP_{OT}$ Group	
	<2 mg/L N=5143 (52.8%)	≥2 mg/L N=4595 (47.2%)
Primary Endpoint*	104	133
Events per 100 person-years	2.25	3.23
Model 1	1.0 (ref)	1.40 (1.08 to 1.82) p=0.01
Model 2	1.0 (ref)	1.33 (1.01 to 1.74) p=0.04
Model 3	1.0 (ref)	1.29 (0.98 to 1.70) p=0.07

* The primary endpoint was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death.

Model 1: age- and sex-adjusted

Model 2: additionally adjusted for baseline smoking, diabetes, hypertension, body-mass index, baseline statin (moderate- or high-intensity)

Model 3: additionally adjusted for on-treatment LDL-C_{OT} (no. missing = 76)

All models stratified by study (SPIRE-1 or SPIRE-2), region, and screening LDL-C.

Supplemental Table 5. Hazard Ratios for the Cardiovascular Events According to LDL-C_{OT} at 14 weeks

	LDL-C_{OT} Group	
	<40 mg/dL N=5610 (58.1%)	≥40 mg/dL N=4052 (41.9%)
Primary Endpoint*	117	118
Events per 100 person-years	2.35	3.19
Model 1	1.0 (ref)	1.35 (1.03 to 1.78) p=0.03
Model 2	1.0 (ref)	1.29 (0.97 to 1.70) p=0.08
Model 3	1.0 (ref)	1.24 (0.93 to 1.64) p=0.14

* The primary endpoint was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death.

* 76 patients excluded due to missing LDL-C_{OT}

Model 1: age- and sex-adjusted

Model 2: additionally adjusted for baseline smoking, diabetes, hypertension, body-mass index, baseline statin (moderate- or high-intensity)

Model 3: additionally adjusted for on-treatment $hsCRP_{OT}$

All models stratified by study (SPIRE-1 or SPIRE-2), region, and screening LDL-C.