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Inflammatory and Cholesterol Risk in the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk)

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BACKGROUND: In the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk), the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor evolocumab reduced low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk. It is not known whether the efficacy of evolocumab is modified by baseline inflammatory risk. We explored the efficacy of evolocumab stratified by baseline high-sensitivity C-reactive protein (hsCRP). We also assessed the importance of inflammatory and residual cholesterol risk across the range of on-treatment LDL-C concentrations.

METHODS: Patients (n=27 564) with stable atherosclerotic cardiovascular disease and LDL-C ≥70 mg/dL on a statin were randomly assigned to evolocumab versus placebo and followed for a median of 2.2 years (1.8–2.5). The effects of evolocumab on the primary end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization, and the key secondary end point of cardiovascular death, myocardial infarction, or stroke were compared across strata of baseline hsCRP (<1, 1–3, and >3 mg/dL). Outcomes were also assessed across values for baseline hsCRP and 1-month LDL-C in the entire trial population. Multivariable models adjusted for variables associated with hsCRP and 1-month LDL-C were evaluated.

RESULTS: A total of 7981 (29%) patients had a baseline hsCRP<1 mg/L, 11 177 (41%) had a hsCRP 1 to 3 mg/L, and 8337 (30%) had a hsCRP >3 mg/L. Median (interquartile range) baseline hsCRP was 1.8 (0.9–3.6) mg/L and levels were not altered by evolocumab (change at 48 weeks of –0.2 mg/dL [–1.0 to 0.4] in both treatment arms). In the placebo arm, patients in higher baseline hsCRP categories experienced significantly higher 3-year Kaplan-Meier rates of the primary and key secondary end points: 12.0%, 13.7%, and 18.1% for the primary end point (P_{trend}<0.0001) and 7.4%, 9.1%, and 13.2% for the key secondary end point (P_{trend}<0.0001) for categories of <1, 1 to 3, and >3 mg/dL, respectively. The relative risk reductions for the primary end point and key secondary end point with evolocumab were consistent across hsCRP strata (*P*-interactions>0.15 for both). In contrast, the absolute risk reductions with evolocumab tended to be greater in patients with higher hsCRP: 1.6%, 1.8%, and 2.6% and 0.8%, 2.0%, and 3.0%, respectively, for the primary and key secondary end points across hsCRP strata. In adjusted analyses of the association between LDL-C and hsCRP levels and cardiovascular risk, both LDL-C and hsCRP were independently associated with the primary outcome (*P*<0.0001 for each).

CONCLUSIONS: LDL-C reduction with evolocumab reduces cardiovascular events across hsCRP strata with greater absolute risk reductions in patients with higher-baseline hsCRP. Event rates were lowest in patients with the lowest hsCRP and LDL-C.

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Clinical Perspective

What Is New?

- We investigated the consistency of the benefit of evolocumab for prevention of cardiovascular events by baseline high-sensitivity C-reactive protein (hsCRP) in the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) of patients with stable atherosclerotic disease.
- The relative benefit of evolocumab for the prevention of adverse cardiovascular events was consistent irrespective of baseline hsCRP. However, because patients with higher hsCRP levels had higher rates of adverse cardiovascular events, they also tended to experience greater absolute benefit with evolocumab.
- In an analysis of baseline hsCRP and achieved low-density lipoprotein cholesterol, we found that adverse cardiovascular event rates were independently associated with both low-density lipoprotein cholesterol and hsCRP.

What Are the Clinical Implications?

- Low-density lipoprotein cholesterol reduction with evolocumab reduces cardiovascular events across hsCRP strata with greater absolute risk reductions in patients with higher baseline hsCRP.
- Event rates were lowest in patients with the lowest hsCRP and low-density lipoprotein cholesterol, supporting the relevance of both inflammatory and residual cholesterol risk.

Low-density lipoprotein cholesterol (LDL-C) has long been recognized as a risk factor for atherosclerotic cardiovascular disease.[1] To that end, the cardiovascular benefit of LDL-C lowering has been demonstrated with multiple agents, including statins and nonstatin agents (eg, ezetimibe).[2–4] Most recently, the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) showed that the anti-PCSK9 (proprotein convertase subtilisin-kexin type 9) monoclonal antibody evolocumab, when added to statin therapy, lowered LDL-C by an average of 59% and significantly reduced the risk of cardiovascular events in patients with stable atherosclerotic cardiovascular disease.[5]

Inflammation has also been shown to be associated with the risk of cardiovascular disease,[6] and a recent trial showed that it was a modifiable risk factor.[7] High-sensitivity C-reactive protein (hsCRP) has been used to identify patients at higher risk and who therefore may derive greater benefit from therapeutic interventions.[8] Furthermore, we and others have explored the prognostic value of LDL-C and hsCRP, but have not done so in the setting of extremely low LDL-C.[9–11]

In the present analysis of the FOURIER trial, our aim was to explore the consistency of benefit of evolocumab for the prevention of cardiovascular events by baseline hsCRP. In addition, we sought to investigate the importance of inflammatory and residual cholesterol risk as defined by LDL-C and hsCRP levels in the FOURIER trial.

METHODS

Study Population and Procedures

FOURIER was a randomized, double-blind placebo-controlled trial that enrolled 27 564 patients aged 40 to 85 years with clinically evident, stable atherosclerotic cardiovascular disease (prior myocardial infarction [MI], nonhemorrhagic stroke, or symptomatic peripheral artery disease) and additional risk factors placing them at increased cardiovascular risk, as previously described.[5,12] Eligible patients had an LDL-C ≥70 mg/dL or a non–high-density lipoprotein cholesterol (HDL-C) ≥100 mg/dL while taking an optimized regimen of lipid-lowering therapy (at least atorvastatin 20 mg daily or its equivalent, with or without ezetimibe). Key exclusions were recent MI or stroke within 4 weeks. Patients were randomly assigned in a 1:1 ratio to treatment with subcutaneous evolocumab (either 140 mg every 2 weeks or 420 mg every 4 weeks per patient preference) or matching placebo injections and were followed for a median of 2.2 years (interquartile range, 1.8–2.5 years). The earliest follow-up measurement of LDL-C was 4 weeks after randomization, and the earliest follow-up measurement of hsCRP was 48 weeks after randomization. High-sensitivity CRP was measured centrally using the Cobas particle-enhanced immunologic agglutination assay (Roche Diagnostics). All patients provided written informed consent. The protocol was approved by ethics committees at each center. We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

End Points

The FOURIER prespecified primary efficacy end point was a composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, MI, or stroke. All elements of these end points have been described previously and were adjudicated according to established definitions by the TIMI Study Group clinical events committee which was unaware of the treatment allocation.[5,12]

Statistical Analysis

Patients were categorized into 3 subgroups based on the baseline hsCRP according to the Centers for Disease Control/American Heart Association risk groups for low (<1 mg/L), intermediate (1–3 mg/L), and high (>3 mg/L) risk.[13] Patients (n=27 495, 99.7% of the trial population) were included in the subgroup analysis based on the availability of a baseline hsCRP measurement. We tested trends in baseline patient characteristics across hsCRP categories using the Jonckheere-Terpstra trend test for continuous variables and the Cochran-Armitage trend test for categorical variables.

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Median hsCRP values were determined at baseline and 48 weeks after randomization. The Wilcoxon rank sum test was used to evaluate differences in median hsCRP values by randomized treatment.

Cardiovascular event rates in patients allocated to the placebo arm and stratified by baseline hsCRP levels were estimated by using the Kaplan-Meier (KM) method and compared by using log-rank tests. Hazard ratios and 95% confidence intervals for the effect of evolocumab on cardiovascular outcomes in patients grouped according to baseline hsCRP were calculated using Cox proportional hazards modeling. Heterogeneity of treatment effect was evaluated by incorporating a treatment-by-baseline hsCRP subgroup interaction term in the Cox proportional hazards regression modeling by using a Wald χ^2 test. The 95% confidence intervals for the absolute risk reductions (ARRs) were calculated based on the assumption that the KM estimates for each treatment arm and the ARRs (ie, difference in KM estimates) between treatments for each end point follow a normal distribution. Because the 2 KM estimates are from independent groups, the variance of ARR was calculated from the variances of the KM estimates for the 2 treatment arms, which allowed the calculation of the 95% confidence intervals for ARR.

Variables independently associated with baseline hsCRP ($\log_2$-transformed) were identified first through univariate screens and then through stepwise model selection with the inclusion of variables with a significant association ($P<0.05$) with hsCRP levels. This strategy identified 16 variables (Table I in the online-only Data Supplement). Applying an analogous approach, 11 variables were identified that were independently associated with LDL-C at 1 month (Table II in the online-only Data Supplement). The union of the 2 sets yielded a total of 18 variables: age, body mass index, sex, white race, region, prior MI, history of stroke, peripheral artery disease, hypertension, diabetes mellitus, congestive heart failure, current smoking, renal dysfunction (estimated glomerular filtration rate of <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), high-intensity statin use at baseline, ezetimibe use at baseline, and baseline LDL-C, HDL-C, and log(triglycerides). These variables were incorporated as covariates in models examining the association of LDL-C and hsCRP with outcomes.

A time-to-event analysis was performed by using the landmark method, where outcomes were assessed beginning 1 month after randomization according to baseline hsCRP and 1-month achieved LDL-C concentrations in the pooled treatment group, excluding those patients with a cardiovascular event in the first month (n=84) or without a hsCRP (n=69) or LDL-C (n=1025) measurement. A total of 26 390 (96% of the total trial population) were included in this analysis based on the above-mentioned criteria. Primary and key secondary event rates were determined at 3 years according to (1) categorical subgroups defined by baseline hsCRP (<1, 1–3, >3 mg/L) and previously described subgroups based on LDL-C values 1 month after randomization (<20, 20–49, 50–69, 70–99, and ≥100 mg/dL) and (2) the continuous variables of $\log_2$-transformed baseline hsCRP and 1-month LDL-C values.[14] For the latter, patients with an hsCRP >10 mg/L (n=1637) were graphically excluded. Event rates were adjusted for variables independently associated with either baseline hsCRP or 1-month LDL-C, as detailed above.

All event rates are 3-year KM estimates, except where specified otherwise. All reported *P* values are 2-sided. $P<0.05$ was considered to signify nominal statistical significance with no adjustment for multiple comparisons. All analyses were conducted by using Stata/IC, version 13.1 (StataCorp LP) or SAS, version 9.4 (SAS Institute).

RESULTS

Study Population by hsCRP Levels

The primary analytic cohort was comprised of 27 495 patients (99.7% of trial population) with a baseline hsCRP value, with 7981 patients (29%) with a low-baseline hsCRP level (<1 mg/L), 11 177 (41%) with an intermediate hsCRP (1–3 mg/L), and 8337 (30%) with a high hsCRP (>3 mg/L; Table 1). Patients with higher baseline hsCRP had a greater prevalence of other cardiovascular risk factors including hypertension, diabetes mellitus, smoking, and renal dysfunction, and a higher rate of comorbid conditions including prior stroke and peripheral artery disease, as well (Table 1). Baseline LDL-C levels were higher and HDL-C levels were lower in those with higher baseline hsCRP. Baseline characteristics, in general, were well balanced between randomized treatment arms (evolocumab versus placebo) within each hsCRP stratum (Tables III through V in the online-only Data Supplement). Independent (multivariable) predictors of a higher-baseline hsCRP were the presence of certain comorbidities (smoking, peripheral artery disease, renal dysfunction, congestive heart failure, prior stroke, hypertension, increased body mass index), an abnormal lipid profile (higher-baseline LDL-C and triglycerides and lower HDL-C), female sex, lower rates of lipid-lowering therapy (high-intensity statin or ezetimibe), and lower rates of prior MI (Table I in the online-only Data Supplement).

The median and interquartile range for baseline hsCRP level was 1.7 mg/L (0.9–3.6) in the evolocumab arm and 1.8 mg/L (0.9–3.6) in the placebo arm (Table 2). The change in hsCRP at 48 weeks was –0.2 mg/L (–1.0 to 0.4) from baseline in both treatment arms with no significant difference in achieved hsCRP levels between evolocumab and placebo (median 48-week hsCRP level, 1.4 mg/L [0.7–3.1] for both treatments; Table 2). Likewise the change in hsCRP levels was similar between the evolocumab and placebo arms in subgroups defined by baseline hsCRP with a greater absolute decrease in hsCRP in patients with a higher baseline hsCRP consistent with a regression to the mean (Table VI in the online-only Data Supplement). In addition, in those achieving an on-treatment LDL-C of <20 mg/dL 1 month after randomization with a median absolute decrease in LDL-C of 64 mg/dL, there was no significant change in hsCRP at 48 weeks (–0.2 mg/L [–0.9 to 0.3]).

Table 1. Baseline Characteristics by hsCRP Subgroup

Baseline Characteristics	hsCRP <1 (n=7981, 29%)	hsCRP 1–3 (n=11 177, 41%)	hsCRP >3 (n=8337, 30%)	P_{trend}
hsCRP, mg/L	0.6 (0.4–0.8)	1.7 (1.3–2.3)	5.4 (3.9–8.8)	<0.0001
Age, y	64 (57–69)	63 (56–69)	62 (56–68)	<0.0001
Male	79	77	71	<0.0001
White	81	87	86	<0.0001
BMI, kg/m^2	27 (25–30)	29 (26–32)	30 (27–34)	<0.0001
Region				<0.0001
North America	14	16	19	
Europe	61	65	62	
Latin America	6	7	7	
Asia Pacific	19	12	12	
Prior myocardial infarction	84	82	78	<0.0001
Most recent MI, y	3.5 (1.0–8.0)	3.4 (1.0–7.5)	3.2 (0.9–7.1)	<0.0001
Prior stroke	18	19	21	<0.0001
Most recent stroke, y	3.4 (1.1–7.2)	3.1 (1.1–7.2)	3.4 (1.1–7.2)	0.65
Peripheral artery disease	9	13	17	<0.0001
Hypertension	76	81	84	<0.0001
Diabetes mellitus	31	36	43	<0.0001
Smoking	23	29	32	<0.0001
eGFR<60	15	19	23	<0.0001
Congestive heart failure	21	23	26	<0.0001
TRS 2P high risk (≥4)	33	40	48	<0.0001
Statin use*				0.037
High intensity	69	69	70	
Moderate intensity	31	31	30	
Ezetimibe	6.6	4.8	4.5	<0.0001
Aspirin	86	85	83	0.0003
P2Y12 inhibitor	39	39	40	0.15
β-Blocker	75	76	75	0.62
Baseline median values				
LDL-C, mg/dL	90 (79–105)	92 (80–109)	94 (81–112)	<0.0001
Total cholesterol, mg/dL	165 (150–184)	168 (152–189)	170 (153–192)	<0.0001
Triglycerides, mg/dL	120 (92–161)	136 (102–186)	144 (108–194)	<0.0001
HDL-C, mg/dL	46 (39–55)	44 (37–52)	42 (36–50)	<0.0001

Median and interquartile range or % represented. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and TRS 2P, TIMI Risk Score for Secondary Prevention.

*0.2%, 0.2%, 0.3% in the 3 groups were on other statin regimens (low-intensity, no statin) or had missing data.

There was minimal correlation between the hsCRP and LDL-C values achieved at 48 months after randomization (Spearman correlation coefficient=0.079).

Rates of Cardiovascular Outcomes by Baseline hsCRP

In patients randomly assigned to placebo in FOURIER (n=13 740), baseline hsCRP level was predictive of end points including the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina and coronary revascularization, and each of the individual end points, with the exception of unstable angina (P_{trend}<0.0001 across hsCRP strata for each end point, with the exception of unstable angina where P_{trend}=0.50; Figure 1). The largest gradient of risk was observed for the end points of death (cardiovascular and all-cause), stroke, and MI with a ≈3-, 2-, and 1.5-fold increased risk in patients, respectively, with an hsCRP >3 mg/L in comparison with those with an hsCRP <1 mg/L (Figure 1).

Table 2. Change in hsCRP Over Time by Randomized Treatment

	Evolocumab		Placebo		*P* Value*
	n	hsCRP, mg/L Median (IQR)	n	hsCRP, mg/L Median (IQR)	
Baseline	13755	1.7 (0.9 to 3.6)	13740	1.8 (0.9 to 3.6)	0.34
48 wk	13091	1.4 (0.7 to 3.1)	13054	1.4 (0.7 to 3.1)	0.72
Change from baseline to 48 wk	13062	–0.2 (–1.0 to 0.4)	13016	–0.2 (–1.0 to 0.4)	0.34

hsCRP indicates high-sensitivity C-reactive protein; change, change from baseline to 48 weeks; and IQR, interquartile rate.

**P* value for comparison of evolocumab versus placebo.

Benefit of Evolocumab Stratified by Baseline hsCRP Subgroup

The relative risk reduction with evolocumab versus placebo for the primary end point was consistent across baseline hsCRP strata (HR 0.82 [0.70–0.95] for hsCRP <1 mg/L, HR 0.93 [0.83–1.05] for hsCRP 1–3 mg/L, and HR 0.80 [0.71–0.90] for hsCRP >3 mg/L, *P*-interaction=0.17; Figure 2A). Similarly, the relative risk reduction for the key secondary end point was consistent across hsCRP subgroups (HR 0.81 [0.66–0.99] for hsCRP<1 mg/L, HR 0.87 [0.75–1.02] for hsCRP 1–3 mg/L, and HR 0.73 [0.63–0.85] for hsCRP >3 mg/L, *P*-interaction=0.26; Figure 2B).

However, given the increased absolute risk with increasing baseline hsCRP levels, the ARR for the primary end point with evolocumab tended to be higher: 1.6% (95% confidence interval, –0.5 to 3.7), 1.8% (0.0 to 3.5) and 2.6% (0.4 to 4.9), respectively, in those with baseline hsCRP levels of <1, 1 to 3, and >3 mg/L (Figure 2A). The corresponding numbers needed to treat were 56 and 38 in those with baseline hsCRP levels of 1 to 3 and >3 mg/L, respectively, to prevent a primary end point event at 3 years. Likewise, the ARR with evolocumab tended to increase for the secondary end point: ARR 0.8% (–1.1 to 2.7), 2.0%, (0.4 to 3.4), ARR 3.0% (1.0 to 5.0), respectively, in those with baseline hsCRP levels of <1, 1 to 3, and >3 mg/L with corresponding numbers needed to treat of 50 in the intermediate baseline hsCRP strata and 33 in the highest hsCRP strata to prevent a secondary end point event at 3 years (Figure 2B).

Cardiovascular Outcomes by hsCRP and LDL-C Levels

To evaluate the importance of cholesterol and inflammatory risk, 3-year event rates were assessed according to baseline hsCRP and LDL-C concentrations achieved at 1 month. Primary and key secondary event rates were adjusted for potential confounders, including variables independently associated with baseline hsCRP or on-treatment LDL-C: age, body mass index, sex, white race, region, prior MI, history of stroke, peripheral artery disease, hyper-

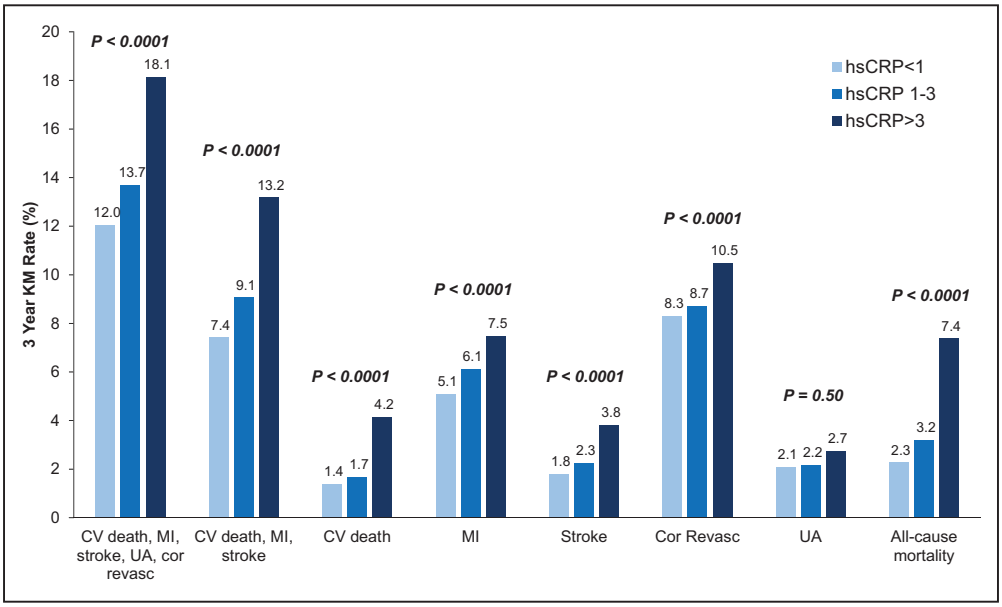

Figure 1. Gradient of cardiovascular risk by baseline hsCRP in the placebo arm.
Three-year Kaplan-Meier event rates stratified by low (<1 mg/L), intermediate (1–3 mg/L), and high (>3 mg/L) baseline hsCRP in subjects randomly assigned to placebo. The *P* value for trend across hsCRP subgroups is shown. Cor Revasc indicates coronary revascularization; CV, cardiovascular; hsCRP, high-sensitivity C-reactive protein; KM, Kaplan-Meier; MI, myocardial infarction; and UA, hospitalization for unstable angina.

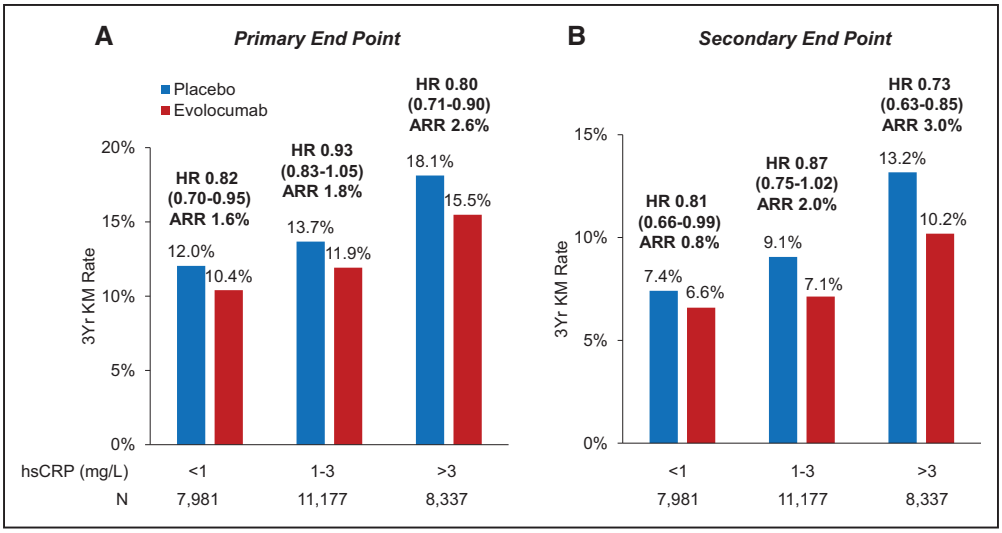

Figure 2. Rate of cardiovascular events by hsCRP and randomized treatment.
Three-year Kaplan-Meier event rates stratified by baseline hsCRP subgroup and randomization to evolocumab versus placebo for the primary composite end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (**A**) and the key secondary composite end point of cardiovascular death, MI, or stroke (MACE) (**B**). Hazard ratio (HR) and 95% confidence interval and the absolute risk reduction (ARR) shown for evolocumab versus placebo for each subgroup. Interaction *P* value for randomized treatment by hsCRP subgroup is 0.17 for the primary end point and 0.26 for the secondary end point. hsCRP indicates high-sensitivity C-reactive protein; KM, Kaplan-Meier; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

tension, diabetes mellitus, congestive heart failure, current smoking, renal dysfunction (estimated glomerular filtration rate of < 60 mL·min^{-1}·1.73 m^{-2}), high-intensity statin use at baseline, ezetimibe use at baseline, and baseline LDL-C, HDL-C, and triglycerides. After adjustment for confounders and hsCRP level, a higher 1-month LDL-C concentration was independently associated with higher rates of the primary and key secondary end points, with a 9% (hazard ratio [HR], 1.09; 1.05–1.14; *P*<0.0001) and 12% (HR, 1.12; 1.06–1.18; *P* <0.0001) increased relative risk, respectively, for every doubling in LDL-C (Figure 3). Likewise, after adjustment for confounders and achieved LDL-C, a higher hsCRP level was independently associated with higher rates of the primary and key secondary end points, with a 9% (HR, 1.09; 1.07–1.12; *P*<0.0001) and 13% (HR, 1.13; 1.09–1.17; *P*<0.0001) increased relative risk, respectively, for every doubling in hsCRP. Event rates were lowest in patients with the lowest levels of both LDL-C and hsCRP (Figure 3).

In an analysis by strata of hsCRP and achieved LDL-C values, even among patients achieving very low LDL-C values (<20 mg/dL) 1 month after randomization [n=2707]), the adjusted event rate varied by baseline hsCRP values where those with an hsCRP of 1, 1 to 3, and >3 mg/L had a 3-year primary event rate of 9.0% (95% confidence interval, 7.4%–10.6%), 10.8% (8.9%–12.6%), and 13.1% (10.8%–15.3%) and a key secondary event rate of 5.3% (4.1%–6.5%), 6.7% (5.2%–8.1%), and 8.9% (6.8%–10.8%), respectively (Figure 4).

DISCUSSION

In this analysis of the FOURIER trial, we explored the benefit of evolocumab, a potent LDL-C–lowering agent, for prevention of cardiovascular events by baseline hsCRP and investigated the prognostic significance of inflammatory and residual cholesterol risk. The relative benefit of evolocumab for prevention of adverse cardiovascular events was consistent irrespective of baseline hsCRP. However, as patients with higher hsCRP levels experienced higher rates of adverse cardiovascular events, they also tended to experience greater absolute benefit with evolocumab. In an analysis of baseline hsCRP and achieved LDL-C, we found that adverse cardiovascular event rates were independently associated with both LDL-C and hsCRP, supporting the relevance of both inflammatory and residual cholesterol risk.

Decades of epidemiological, experimental, and clinical research have supported the LDL hypothesis, which identifies LDL-C as a pathogenic mediator (ie, risk factor) of atherosclerotic disease, and have proven that lipid-lowering strategies improve cardiovascular outcomes for patients with atherosclerotic cardiovascular disease.[1,2] As a result, LDL-C–lowering therapy is a mainstay of secondary prevention for patients with

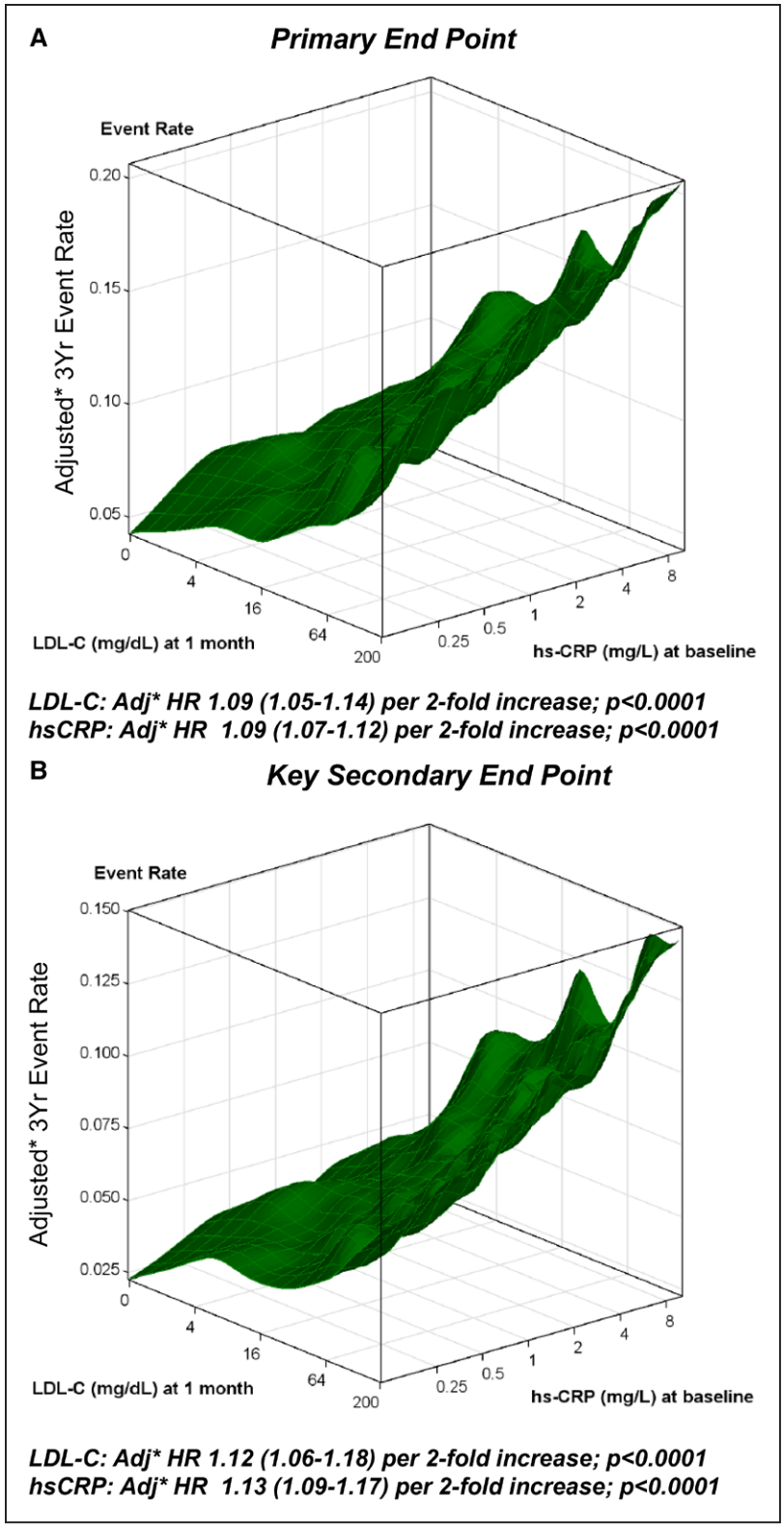

Figure 3. Association between LDL-C and hsCRP levels and cardiovascular risk.
Adjusted 3-year Kaplan-Meier event rates by baseline hsCRP and 1-month achieved LDL-C levels for the primary end point of CV death, MI, stroke, hospitalization for unstable angina and coronary revascularization (**A**) and the key secondary end point of MACE (**B**). Event rates were adjusted for variables independently associated with baseline hsCRP or 1-month LDL-C. Patients with an hsCRP>10 mg/L were graphically excluded. CV indicates cardiovascular; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

established cardiovascular disease using agents with proven cardiovascular benefit, including statins; the cholesterol absorption inhibitor, ezetimibe; and the PCSK9 inhibitor, evolocumab.[3,5,15] It is noteworthy that, in FOURIER, evolocumab lowered LDL-C by 59%, from a median baseline value of 92 mg/dL to 30 mg/dL at 48 weeks and reduced the risk of the primary end point of cardiovascular death, MI, stroke, hospitalization for unstable angina or coronary revascularization by 15%, and the risk of major adverse cardiovascular events by 20%, with an ARR of 2.0% and a number needed to treat of 50 over 3 years for the latter outcome.[5]

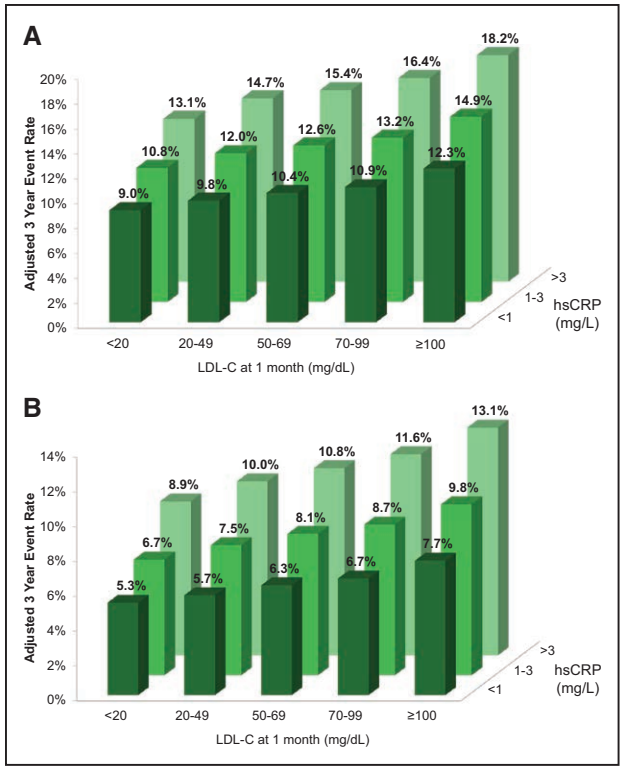

Figure 4. Primary and key secondary event rates by baseline hsCRP and Achieved 1-month LDL-C values. Primary (**A**) and key secondary (**B**) end point event rates were adjusted for variables independently associated with baseline hsCRP or 1month LDL-C. Adj HR, adjusted hazard ratio; hsCRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

These findings, however, raise 2 issues for consideration. First, given the current cost of PCSK9 inhibitors, can one identify subgroups of patients who derive greater ARRs? High-sensitivity CRP is a well-validated marker for the risk of future atherothrombotic events and cardiovascular mortality.[16] A similar relationship was seen in FOURIER, with an elevated hsCRP identifying patients who had almost twice the incidence of major adverse cardiovascular events. It is noteworthy that the relative benefit of evolocumab in comparison with placebo was maintained irrespective of the baseline hsCRP levels with a ≈15% to 20% reduction in the primary and key secondary end points (*P*-interactions >0.05 for each). However, given the increase in absolute risk in patients with higher hsCRP, those in the highest hsCRP stratum tended to have greater absolute benefit from aggressive LDL-C reduction, with the addition of evolocumab to a background of statin therapy resulting in an ARR in major adverse cardiovascular events of 3.0% and a number needed to treat of only 33 over 3 years.

The second issue is recognition that there remains important residual risk in patients treated with evolocumab, despite a median achieved LDL-C of 30 mg/dL. Indeed, the rate of the primary end point was 9.8% at 3 years in the patients treated with evolocumab in the overall trial, even in the setting of very low achieved LDL-C levels, and the current analysis showed that hsCRP levels did risk stratify patients at very low LDL-C levels.[5,14] These observations raise the question of whether additional risk factors, such as inflammation, may indeed be important targets for therapy beyond the achievement of ultralow LDL-C.

Basic research into the role of vascular inflammation in the pathogenesis of atherothrombosis has led to the conceptual framework that both abnormal lipid and abnormal inflammatory profiles independently drive cardiovascular risk.[17] Accordingly, residual cardiovascular risk will persist in the face of suboptimal control of cholesterol or inflammation. Consequently, it is proposed that both axes should be intentionally targeted with secondary preventative therapies. Supporting this notion, in the CANTOS trial (Canakinumab Antiinflammatory Thrombosis Outcome Study) of patients with prior MI and an elevated hsCRP>2 mg/L, the anti–IL-1β monoclonal antibody canakinumab reduced hsCRP from a median of 4.1 mg/L to 1.3 to 1.8 mg/L (59%– 68%) for the 2 highest doses with no change in LDL-C (median LDL-C of 83 mg/dL) and reduced the risk of cardiovascular death, MI, or stroke by 15%.[7]

We have previously shown the simultaneous predictive ability of both LDL-C and hsCRP levels in the PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22), A-to-Z (Aggrastat to Zocor [AtoZ]: the Use of Two Approved Drugs to Treat Patients Who Have Experienced Chest Pain or a Heart Attack), and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trials.[9–11] However, in these analyses, only 14 and 204 patients achieved an LDL-C<20 mg/dL in PROVE-IT TIMI 22 and IMPROVE-IT, respectively, unlike the 2707 patients who achieved an LDL-C<20 mg/dL in FOURIER. As a result, with FOURIER, we are able to investigate whether the association between inflammation and cardiovascular risk persists even with extremely low LDL-C levels. When evaluated as continuous variables across the range of baseline hsCRP and achieved LDL-C, we find that both variables are independent predictors of outcomes. Moreover, even in patients with an LDL-C<20 mg/dL 1 month after randomization, there remained a gradient of risk where those with an hsCRP of <1, 1 to 3, and >3 mg/L had a 3-year primary event rate of 9.0%, 10.8%, and 13.1%, respectively. Our data, therefore, support the concept of inflammatory risk regardless of LDL-C levels in patients with preexisting atherosclerotic cardiovascular disease. Coupling the findings from FOURIER and CANTOS, our observations raise consideration for

a targeted approach of lowest is best for both cholesterol and inflammation.

Limitations

Several limitations of our study should be considered. The analyses using on-treatment LDL-C concentrations were not randomized, because patients were classified based on a postrandomization measurement of LDL-C. We used multivariable adjustment to limit confounding attributed to differences in baseline characteristics across the groups of achieved LDL-C, but recognize that residual confounding may remain. In addition, hsCRP was not measured at 1 month and, therefore, a simultaneous assessment of achieved values for LDL-C and hsCRP was not possible. We instead used the baseline hsCRP value which we felt was reasonable based on the lack of change in hsCRP over 48 weeks and the fact that the trial participants had stable atherosclerotic cardiovascular disease with a median time of >3 years from the last atherothrombotic event (eg, stroke, MI). It is important to note that, because patients were already receiving statin treatment at randomization, the baseline hsCRP levels reflect residual risk after standard LDL-C lowering therapy. Finally, FOURIER is a study of stable patients with established cardiovascular disease. As such, we are not able to comment on whether the degree of inflammation is related to the initial development of atherosclerotic vascular disease in patients with long-standing very low levels of LDL-C.

Conclusions

LDL-C reduction with evolocumab is beneficial across hsCRP strata with greater absolute benefit in patients with higher hsCRP. hsCRP is a risk predictor even in patients with very low levels of LDL-C and, accordingly, cardiovascular event rates were lowest in patients with the lowest inflammatory and residual cholesterol risk.

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Inflammatory and Cholesterol Risk in the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk)

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SUPPLEMENTAL MATERIAL

Supplementary Table 1: Independent Predictors of log_2 transformed hsCRP

	T-statistic	p-value
BMI (kg/m^2)	29.3	<0.0001
Baseline HDL-C (mg/dL)	-16.1	<0.0001
Current Smoker	15.3	<0.0001
Baseline LDL-C (mg/dL)	12.9	<0.0001
Peripheral arterial disease	12.4	<0.0001
Male	-10.7	<0.0001
eGFR <60 ml/min/1.73 m^2	9.9	<0.0001
Region		
Europe	8.3	<0.0001
North America	7.1	<0.0001
South America	5.2	<0.0001
Ezetimibe Use at Baseline	-7.7	<0.0001
Congestive heart failure	5.2	<0.0001
Diabetes	5.2	<0.0001
Log(baseline triglycerides)	4.4	<0.0001
Prior stroke	3.3	0.0008
High-intensity statin at Baseline	-2.9	0.0039
Hypertension	2.7	0.0065
Prior MI	-2.0	0.047

BMI denotes body mass index; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol. In addition to those listed above, candidate variables included age and Caucasian.

Supplementary Table 2: Independent Predictors of log_2 transformed 1 month LDL-C

	T-statistic	p-value
Baseline LDL-C (mg/dL)	52.4	<0.0001
BMI (kg/m^2)	11.1	<0.0001
Log(baseline triglycerides)	-9.0	<0.0001
Male	-8.5	<0.0001
Age (yrs)	-5.2	<0.0001
Log_2(baseline hsCRP)	4.8	<0.0001
Congestive heart failure	4.6	<0.0001
Caucasian	3.3	0.0009
North America	2.5	0.0112
Current smoker	2.3	0.020
High-intensity statin at baseline	2.2	0.030

BMI denotes body mass index;LDL-C, low-density lipoprotein-cholesterol. In addition to those listed above, candidate variables included prior MI, prior stroke, peripheral artery disease, hypertension, diabetes, renal dysfunction, ezetimibe use at baseline, and baseline HDL-C.

Supplementary Table 3: Baseline Characteristics by Randomized Treatment within hsCRP <1 mg/L Subgroup

Baseline characteristics	Evolocumab (N=4,014)	Placebo (N=3,967)	P-value
hsCRP, mg/L	0.6 [0.4, 0.8]	0.6 [0.4, 0.8]	0.85
Age, years	64 [57, 70]	64 [57, 69]	0.51
Male	78	80	0.019
Caucasian	82	80	0.052
BMI, kg/m^2	27 [25, 30]	28 [25, 30]	0.35
Region			0.51
North America	14	14	
Europe	61	60	
Latin America	6	6	
Asia Pacific	19	19	
Prior myocardial infarction	84	84	0.64
Most recent MI, years	3.5 [1.1, 7.9]	3.4 [1.0, 8.1]	0.48
Prior stroke	18	18	0.42
Most recent stroke, years	3.5 [1.1, 7.3]	3.2 [1.1, 6.9]	0.88
Peripheral arterial disease	10	9	0.35
Hypertension	76	75	0.86
Diabetes mellitus	32	31	0.23
Smoking	22	24	0.051
eGFR<60	15	14	0.17
Congestive heart failure	21	20	0.07
TRS 2P High Risk (≥4)	33	32	0.48
Statin Use*			0.60
High intensity	69	68	
Moderate intensity	31	32	
Ezetimibe	6.9	6.2	0.21
Aspirin	87	85	0.037
P2Y12 inhibitor	38	40	0.10
Beta blocker	76	74	0.050
Baseline median values			
LDL-C, mg/dL	90 [79, 105]	90 [79, 105]	0.92
Total cholesterol, mg/dL	165 [150, 185]	164 [149, 184]	0.11
Triglycerides, mg/dL	122 [94, 163]	118 [91, 160]	0.012
HDL-C, mg/dL	46 [39, 55]	46 [39, 55]	0.45

*Median and interquartile range or % represented. BMI denotes body mass index; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; TRS 2P, TIMI Risk Score for Secondary Prevention; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol. *0.2% of patients in each group were on other statin regimens (low-intensity, no statin) or had missing data.*

Supplementary Table 4: Baseline Characteristics by Randomized Treatment within hsCRP 1-3 mg/L Subgroup

Baseline characteristics	Evolocumab (N=5,576)	Placebo (N=5,601)	P-value
hsCRP, mg/L	1.7 [1.3, 2.2]	1.7 [1.3, 2.3]	0.17
Age, years	63 [56, 69]	63 [56, 68]	0.83
Male	77	76	0.61
Caucasian	87	88	0.44
BMI, kg/m^2	29 [26, 32]	29 [26, 32]	0.37
Region			0.27
North America	17	16	
Europe	64	66	
Latin America	7	7	
Asia Pacific	12	12	
Prior myocardial infarction	82	82	0.70
Most recent MI, years	3.4 [1.0, 7.4]	3.3 [1.0, 7.6]	0.79
Prior stroke	18	19	0.20
Most recent stroke, years	3.0 [1.0, 7.1]	3.3 [1.1, 7.3]	0.25
Peripheral arterial disease	13	12	0.047
Hypertension	81	81	0.52
Diabetes mellitus	36	36	0.69
Smoking	29	28	0.40
eGFR<60	19	19	0.27
Congestive heart failure	23	23	0.57
TRS 2P High Risk (≥4)	40	40	0.76
Statin Use*			0.48
High intensity	69	69	
Moderate intensity	31	30	
Ezetimibe	4.5	5.1	0.17
Aspirin	86	85	0.27
P2Y12 inhibitor	39	38	0.39
Beta blocker	76	76	0.65
Baseline median values			
LDL-C, mg/dL	92 [80, 108]	92 [80, 109]	0.16
Total cholesterol, mg/dL	168 [151, 189]	169 [152, 189]	0.21
Triglycerides, mg/dL	136 [102, 189]	136 [102, 185]	0.33
HDL-C, mg/dL	44 [37, 53]	44 [37, 53]	0.50

*Median and interquartile range or % represented. BMI denotes body mass index; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; TRS 2P, TIMI Risk Score for Secondary Prevention; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol. *0.3% and 0.2% of patients in each group were on other statin regimens (low-intensity, no statin) or had missing data.*

Supplementary Table 5: Baseline Characteristics by Randomized Treatment within hsCRP >3mg/L Subgroup

Baseline characteristics	Evolocumab (N=4,165)	Placebo (N=4,172)	P-value
hsCRP, mg/L	5.3 [3.8, 8.7]	5.4 [3.9, 9.0]	0.16
Age, years	62 [56, 68]	62 [56, 68]	0.62
Male	72	70	0.14
Caucasian	86	86	0.88
BMI, kg/m^2	30 [27, 34]	30 [27, 34]	0.044
Region			0.36
North America	19	20	
Europe	63	62	
Latin America	7	7	
Asia Pacific	12	11	
Prior myocardial infarction	77	78	0.35
Most recent MI, years	3.2 [0.9, 7.1]	3.1 [0.8, 7.2]	0.32
Prior stroke	22	21	0.10
Most recent stroke, years	3.4 [1.1, 6.8]	3.5 [1.1, 7.5]	0.54
Peripheral arterial disease	18	17	0.32
Hypertension	84	84	0.86
Diabetes mellitus	43	44	0.39
Smoking	32	33	0.54
eGFR<60	23	22	0.19
Congestive heart failure	26	26	0.75
TRS 2P High Risk (≥4)	48	48	0.92
Statin Use*			0.20
High intensity	71	69	
Moderate intensity	29	31	
Ezetimibe	4.6	4.3	0.48
Aspirin	84	83	0.51
P2Y12 inhibitor	41	39	0.17
Beta blocker	75	76	0.40
Baseline median values			
LDL-C, mg/dL	94 [81, 113]	94 [81, 112]	0.78
Total cholesterol, mg/dL	169 [153, 192]	170 [152, 192]	0.90
Triglycerides, mg/dL	142 [108, 195]	145 [107, 194]	0.99
HDL-C, mg/dL	42 [36, 50]	42 [36, 51]	0.50

*Median and interquartile range or % represented. BMI denotes body mass index; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; TRS 2P, TIMI Risk Score for Secondary Prevention; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol. *0.3% and 0.4% of patients in each group were on other statin regimens (low-intensity, no statin) or had missing data.*

Supplementary Table 6: Change in hsCRP over time by randomized treatment stratified by baseline hsCRP

	Evolocumab		Placebo		
	n	hsCRP Median (IQR)	n	hsCRP Median (IQR)	p-value for Evolocumab vs Placebo
hsCRP <1 mg/L					
Baseline	4014	0.6 [0.4, 0.8]	3967	0.6 [0.4, 0.8]	0.85
48 week	3871	0.60 [0.37, 1.00]	3808	0.57 [0.35, 0.95]	0.0064
Change (baseline to 48 weeks)	3871	0.02 [-0.15, 0.32]	3808	-0.01 [-0.18, 0.30]	0.0011
hsCRP 1-3 mg/L					
Baseline	5576	1.7 [1.3, 2.2]	5601	1.7 [1.3, 2.3]	0.17
48 week	5307	1.4 [0.9, 2.5]	5330	1.5 [0.9, 2.5]	0.18
Change (baseline to 48 weeks)	5307	-0.3 [-0.8, 0.6]	5330	-0.2 [-0.8, 0.6]	0.76
hsCRP >3 mg/L					
Baseline	4165	5.4 [3.9, 8.7]	4172	5.4 [3.9, 9.0]	0.16
48 week	3884	3.4 [1.8, 6.0]	3878	3.4 [1.8, 6.0]	0.68
Change (baseline to 48 weeks)	3884	-1.9 [-4.2, 0.1]	3878	-2.0 [-4.5, 0.1]	0.49