C-reactive protein and prognosis after percutaneous coronary intervention and bypass graft surgery for left main coronary artery disease: Analysis from the EXCEL trial

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Abstract Background The prognostic impact of high-sensitivity C-reactive protein (CRP) levels in patients with left main coronary artery disease (LMCAD) treated with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) is unknown. We sought to determine the effect of elevated baseline CRP levels on the 3-year outcomes after LMCAD revascularization and to examine whether CRP influenced the relative outcomes of PCI versus CABG.

Methods In the EXCEL trial, patients with LMCAD and Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) scores ≤32 were randomized to PCI versus CABG. The primary composite outcome of death, myocardial infarction (MI), or stroke was analyzed according to baseline CRP levels.

Results Among 999 patients with available CRP levels, median CRP was 3.10 mg/L (interquartile range 1.12-6.40 mg/L). The rate of the primary composite end point of death, MI, or stroke at 3 years steadily increased with greater baseline CRP levels. The adjusted relationship between the 3-year composite rate of death, MI, or stroke and baseline CRP modeled as a continuous log-transformed variable demonstrated steadily increasing event rates with greater CRP levels (adjusted hazard ratio, 1.26, 95% CI 1.10-1.44, $P = .0008$). Similarly, patients with CRP ≥10 mg/L had a 3-fold higher risk of the 3-year primary end point compared to patients with lower CRP levels (adjusted hazard ratio 2.92, 95% CI 1.88-4.54, $P < .0001$). The association between an elevated CRP level and the adjusted 3-year risk of the primary composite end point did not differ according to revascularization strategy ($P_{interaction} = .75$).

Conclusions In patients with LMCAD undergoing revascularization, elevated baseline CRP levels were strongly associated with subsequent death, MI, and stroke at 3 years, irrespective of the mode of revascularization. Further studies are warranted to determine whether anti-inflammatory therapies may improve the prognosis of high-risk patients with LMCAD following revascularization. (Am Heart J 2019;210:49-57.)

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Systemic inflammation, as assessed by serum levels of C-reactive protein (CRP), is associated with adverse cardiovascular outcomes in patients with coronary artery disease (CAD).[1,2] Elevated CRP levels portend worse angiographic and clinical outcomes after percutaneous coronary intervention (PCI)[3,4] and coronary artery bypass grafting (CABG)[5,6]; however, the extent to which systemic inflammation negatively influences prognosis in high-risk patients with left main coronary artery disease (LMCAD) is unknown. Furthermore, no prior study has examined whether CRP levels should affect the choice of revascularization modality in high-risk patients with ischemic heart disease.

In the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial, PCI with everolimus-eluting stents was noninferior to CABG for the treatment of patients with LMCAD and low or intermediate SYNTAX scores with respect to the rate of the composite end point of death, stroke, or myocardial infarction (MI) at 3 years.[7] We sought to determine the association between CRP and outcomes after revascularization in patients with LMCAD and to assess the relative efficacy of PCI versus CABG according to baseline levels of CRP.

Methods

Study design and study population

The study design and primary results of the EXCEL trial have been previously described in detail.[7,8] In brief, EXCEL was an international, multicenter, randomized trial that compared stenting with everolimus-eluting stents with CABG in patients with LMCAD and low or intermediate SYNTAX scores (≤32) in whom equipoise for revascularization with both techniques was present after local heart team review. Randomization was performed using an interactive voice-based or Web-based system in block sizes of 16, 24, or 32, with stratification according to diabetes (present vs absent), site-assessed SYNTAX score (≤22 vs ≥23), and study center. The goal of PCI was complete revascularization of all ischemic territories with fluoropolymer-based cobalt-chromium everolimus-eluting stents (XIENCE, Abbott Vascular, Santa Clara, CA). CABG was performed with or without cardiopulmonary bypass at the discretion of the operator, with the goal of complete anatomical revascularization of all vessels ≥1.5 mm in diameter with ≥50% diameter stenosis; the use of multiple arterial grafts was strongly recommended.

The primary end point was a composite of death from any cause, stroke, or MI at 3 years. Major powered secondary end points included the primary composite end point at 30 days, and the composite of death, stroke, MI, or ischemia-driven revascularization at 3 years. Additional secondary end points included the components of the primary and secondary end points at 30 days and 3 years, stent thrombosis and symptomatic graft stenosis or occlusion at 30 days and 3 years, and periprocedural major adverse events occurring within 30 days, all as previously defined.[7,8] The definitions for MI as well as other end points were provided in the original publication.[7] The investigation was approved by the institutional review board or ethics committee at each participating center, and all patients signed informed consent. Major end points were adjudicated by an independent clinical events committee (Cardiovascular Research Foundation, New York, NY). Angiographic analyses were performed at an angiographic core laboratory (Cardiovascular Research Foundation). Follow-up has been completed for all patients through 3 years (median follow-up 1,095 days; interquartile range 1,095-1,095 days).

A baseline high-sensitivity CRP level was recommended to be drawn in all patients. The present study included all subjects in EXCEL in whom baseline CRP was available and the assigned revascularization procedure was performed.

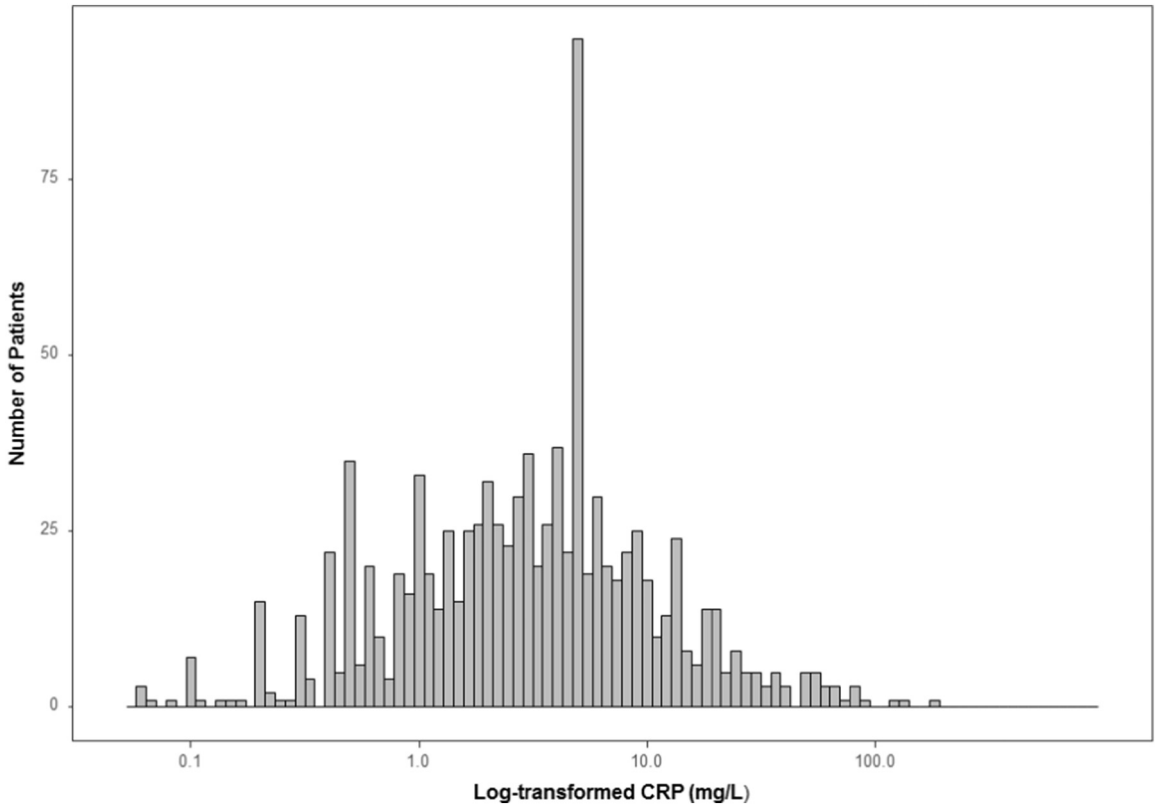
Statistical analysis

Primary analyses were based on CRP levels assessed as a continuous log-linear variable in adjusted models. Further analyses were performed with CRP categorized into 3 groups (low, intermediate, and high CRP levels defined as <3, 3-10, and ≥10 mg/L, respectively.) based on prior studies[9-12] or at the binary CRP cutoff level of 3 mg/L.

Comparisons of baseline and procedural characteristics and clinical events were conducted by χ^2 test or Fisher exact test for binary variables, analysis of variance for continuous variables, and the log-rank test for time-to-event variables. Adjusted comparisons were conducted using multivariable Cox proportional hazards regression. The association between CRP and adverse outcomes was adjusted for the following baseline covariates, which were defined a priori based on clinical relevance: age, sex, diabetes, hypertension, congestive heart failure, recent MI, body mass index, renal insufficiency (creatinine clearance <60 mL/min, calculated using the Cockcroft-Gault equation), anemia (hemoglobin level <13 mg/dL in men and <12 mg/dL in women), left ventricular ejection fraction (LVEF), SYNTAX score (angiographic core laboratory-assessed), distal left main bifurcation lesion, anemia, and randomized treatment. To explore the relationship between CRP and the risk of adverse outcomes, multivariable Cox proportional hazards regression was performed using a spline function to model log(CRP) as a continuous variable for the primary composite end point. Alternative models were also performed using CRP levels assessed in 3 groups (low, intermediate, high) or at the binary cutoff of 3 mg/L. As a further sensitivity analysis, we accounted for missing data using multiple imputation by generating 10 imputed data sets. The same covariates from the adjusted models were included in the imputation model.[13] Because acute MI is associated with acutely increased CRP levels, we further examined the impact of CRP in patients with versus without a recent MI (within 7 days of presentation). Lastly, the relative efficacy of PCI versus CABG according to increasing CRP levels was assessed by including an interaction term between treatment modality and CRP category in the multivariable models. All tests were 2-sided, and P values < .05 were considered statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

The EXCEL trial was sponsored by Abbott Vascular. The first and senior authors are responsible for the design and conduct of the present study, all study analyses, and the drafting of the manuscript.

Figure 1



Distribution of baseline high-sensitivity CRP within the study cohort.

Results

Study population and patient characteristics

The assigned revascularization was performed as the first procedure in 1,882 of 1,905 (98.8%) randomized patients with LMCAD in EXCEL, among whom 999 patients (53.1%) had available baseline CRP levels (509 and 490 patients randomized to PCI and CABG, respectively), comprising the present study cohort. Median CRP was 3.10 mg/L (interquartile range 1.12-6.40 mg/L) (Figure 1). CRP was <3 mg/L in 475 patients (47.5%), between 3 and 10 mg/L in 364 patients (36.4%), and ≥10 mg/L in 160 patients (16.0%). Baseline and procedural characteristics are presented for the 3 groups in Table I. Patients with high CRP levels had lower LVEF and were more likely to have baseline renal insufficiency and anemia compared to those with low and intermediate CRP levels. Medication use throughout the 3-year study period according to CRP level categorized in 3 groups is presented in Supplemental Table I.

Clinical outcomes

A primary composite end point event of death, MI, or stroke within 3 years occurred in 147/999 patients (14.7%). Patients who suffered from a primary end point event had higher baseline CRP levels compared to patients who did not (9.72 ± 2.1 vs 6.29 ± 1.6 mg/L, respectively, P = .003). Unadjusted clinical outcomes according to CRP levels assessed in 3 groups (low, intermediate, or high) (Table II) or at the binary cutoff of 3 mg/L (Supplemental Table II) were consistent and showed increasing event rates with higher baseline CRP levels. The adjusted relationship between the 3-year composite rate of death, MI, or stroke and baseline CRP modeled as a continuous log-linear variable demonstrated steadily increasing event rates with greater CRP levels (Figure 2 and Table III). Results were consistent when the association between log-linear CRP and the primary composite outcome was assessed in a multiple imputation model to account for missing data (Supplemental Table III). Furthermore, in alternative models, CRP was also associated with higher adjusted risk of the primary end point when modeled in 3 groups (<3, 3-10, and ≥10 mg/L) or at the binary cutoff of ≥3 versus <3 mg/L (Table IV). Sensitivity models assessing the effect of recent MI on the prognostic impact of CRP demonstrated no statistically significant interaction between recent MI and CRP modeled as a continuous log-linear variable ($P_{interaction}$ = .10) (Table III) or alternatively when CRP was assessed at a cutoff of ≥3 versus <3 mg/L (Table IV). However, the 3-year adjusted risk of the primary composite

Table I. Clinical and procedural characteristics according to baseline CRP level

Variable	CRP <3 mg/L (n = 475)	CRP 3-10 mg/L (n = 364)	CRP ≥10 mg/L (n = 160)	*P* value
Age (y)	66.0 ± 9.4 (475)	65.6 ± 9.4 (364)	66.5 ± 10.2 (160)	.56
Men	382/475 (80.4%)	277/364 (76.1%)	119/160 (74.4%)	.17
Diabetes	119/475 (25.1%)	101/364 (27.7%)	53/160 (33.1%)	.14
Hypertension	352/475 (74.1%)	252/364 (69.2%)	122/160 (76.3%)	.16
Hyperlipidemia	346/474 (73.0%)	237/364 (65.1%)	107/160 (66.9%)	.04
Current smoker	93/472 (19.7%)	81/363 (22.3%)	42/158 (26.6%)	.18
Prior MI	67/473 (14.2%)	66/363 (18.2%)	25/160 (15.6%)	.29
Prior PCI	69/474 (14.6%)	50/363 (13.8%)	13/160 (8.1%)	.11
Prior cardiac surgery	2/475 (0.4%)	1/364 (0.3%)	1/160 (0.6%)	.84
Congestive heart failure	38/474 (8.0%)	21/363 (5.8%)	15/158 (9.5%)	.27
Prior stroke or TIA	31/475 (6.5%)	27/364 (7.4%)	7/159 (4.4%)	.44
Peripheral vascular disease	34/473 (7.2%)	36/363 (9.9%)	18/159 (11.3%)	.19
COPD	24/474 (5.1%)	20/363 (5.5%)	14/160 (8.8%)	.22
Clinical presentation				
Recent MI*	34/471 (7.2%)	53/362 (14.6%)	44/160 (27.5%)	<.0001
Unstable angina	123/471 (26.1%)	102/362 (28.2%)	39/160 (24.4%)	.63
Stable angina	274/471 (58.2%)	186/362 (51.4%)	64/160 (40.0%)	.0003
Silent ischemia	35/471 (7.4%)	19/362 (5.2%)	11/160 (6.9%)	.44
Body mass index (kg/m^2)	27.7 ± 4.2 (475)	28.6 ± 4.6 (364)	28.6 ± 4.9 (160)	.009
Hemoglobin (g/dL)	13.9 ± 1.5 (474)	13.8 ± 1.4 (363)	13.1 ± 1.8 (160)	<.0001
Anemia‡	84/474 (17.7%)	72/363 (19.8%)	59/160 (36.9%)	<.0001
White blood cell count (×10^9/L)	7.4 ± 2.0 (474)	7.9 ± 2.1 (364)	8.2 ± 2.5 (160)	<.0001
Creatinine clearance (mL/min)	88.1 ± 28.8 (468)	86.3 ± 26.9 (360)	82.7 ± 35.5 (158)	.13
Renal insufficiency‖	72/468 (15.4%)	52/360 (14.4%)	48/158 (30.4%)	<.0001
Brain natriuretic peptide (pg/mL)	163.7 ± 426.5 (373)†	233.3 ± 496.9 (280)	406.9 ± 902.3 (120)	.0002
LVEF (%)	58.5 ± 9.5 (443)	57.3 ± 8.8 (335)	55.5 ± 10.8 (151)	.003
SYNTAX score	27.0 ± 9.4 (458)	26.3 ± 8.8 (355)	26.7 ± 9.6 (156)	.58
PCI data				
Staged procedure(s) planned	17/261 (6.5%)	17/196 (8.7%)	7/82 (8.5%)	.65
Number of LM stents	1.5 ± 0.8 (245)	1.4 ± 0.7 (179)	1.5 ± 0.8 (76)	.61
Procedure duration (min)	73.6 ± 36.3 (259)	71.5 ± 38.8 (191)	74.0 ± 36.6 (81)	.80
CABG data				
Off-pump CABG	89/226 (39.4%)	53/182 (29.1%)	30/79 (38.0%)	.08
Bypass duration (min)	89.2 ± 50.1 (130)	84.9 ± 51.4 (127)	87.3 ± 42.5 (47)	.79
Cross-clamp duration (min)	58.0 ± 28.9 (128)	54.8 ± 25.2 (124)	60.6 ± 36.8 (46)	.45
Procedure duration (min)	240.2 ± 65.9 (225)	242.5 ± 64.8 (174)	249.8 ± 71.8 (76)	.55

Data presented as n/N (%) or mean ± standard deviation (n).
TIA, transient ischemic attack; *COPD*, chronic obstructive pulmonary disease.
*Within 7 days of randomization.
‡Defined according to the World Health Organization criteria (hematocrit value at initial presentation <39% for men and <36% for women).
‖<60 mL/min as calculated by the Cockcroft-Gault equation.

end point was increased in those with high CRP levels compared to low or intermediate CRP levels among the 863 patients without a recent MI but not among the 132 patients with a recent MI (Table IV).

The relative 3-year risk of the primary composite end point did not differ significantly between PCI and CABG depending on baseline CRP level ($P_{interaction}$ = .75) (Figure 3).

Discussion

In the present analysis from the EXCEL trial, among patients with LMCAD undergoing percutaneous or surgical revascularization, higher baseline CRP levels prior to revascularization were associated with an increased adjusted 3-year risk of the primary composite end point of death, MI, or stroke, as well as each of these measures individually. The prognostic impact of an elevated baseline CRP was consistent regardless of LM revascularization by PCI or CABG.

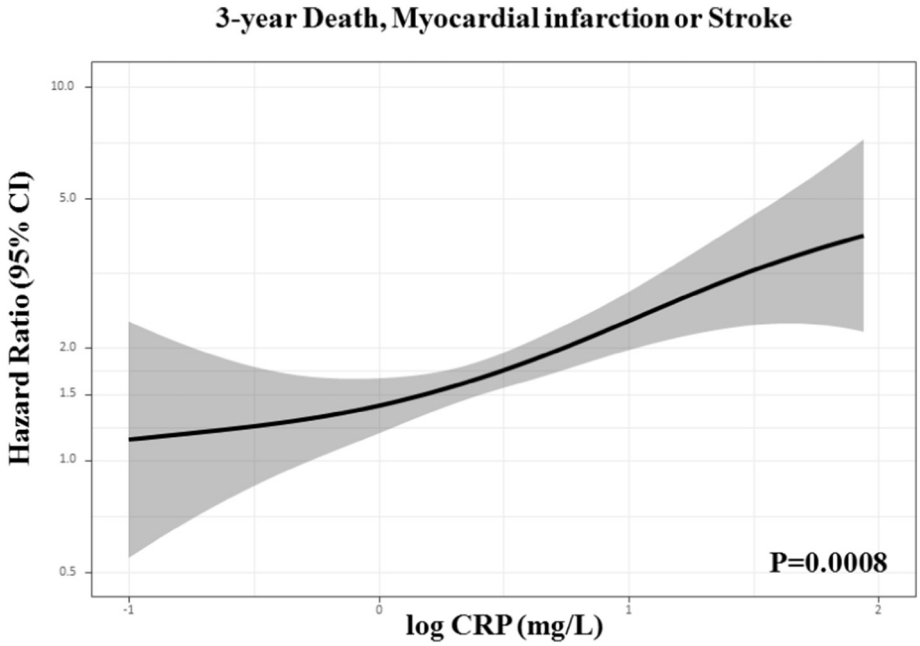
Despite compelling evidence suggesting a major role for inflammation in atherogenesis, until recently, the clinical utility of inflammatory biomarker assessment for prognostication and management of CAD has been uncertain.[14,15] The recent CANTOS trial[2] demonstrated that in patients with a history of MI and elevated CRP levels, canakinumab, a humanized monoclonal antibody to interleukin-1β, reduces CRP and major adverse cardiovascular events without affecting LDL levels, thus supporting a causative link between systemic inflammation and cardiovascular outcomes and the potential for

Table II. Three-year clinical outcomes according to baseline CRP level

Event	CRP <3 mg/L (n = 475)	CRP 3-10 mg/L (n = 364)	CRP ≥10 mg/L (n = 160)	*P* value
Death, MI, or stroke (primary end point)	11.0% (52)	13.8% (50)	28.3% (45)	<.0001
Death, MI, stroke, or IDR	17.6% (83)	19.7% (71)	32.0% (51)	.0002
All-cause death	5.1% (24)	5.0% (18)	16.4% (26)	<.0001
Cardiovascular	2.8% (13)	2.5% (9)	8.5% (13)	.002
Noncardiovascular	2.4% (11)	2.6% (9)	8.6% (13)	.0005
MI	6.0% (28)	7.8% (28)	14.5% (22)	.005
Periprocedural	4.2% (20)	4.9% (18)	4.4% (7)	.89
Spontaneous	2.0% (9)	3.1% (11)	10.2% (15)	<.0001
STEMI	2.1% (10)	2.8% (10)	1.4% (2)	.57
NSTEMI	4.1% (19)	5.3% (19)	13.2% (20)	.0002
Stroke	1.3% (6)	3.1% (11)	8.4% (13)	<.0001
Ischemic	1.1% (5)	2.5% (9)	5.1% (8)	.009
Hemorrhagic	0.2% (1)	0.6% (2)	4.6% (7)	<.0001
IDR	9.5% (44)	9.9% (35)	11.5% (17)	.74
Symptomatic graft stenosis or occlusion	1.5% (7)	2.8% (10)	2.6% (4)	.40
Definite/probable stent thrombosis	0.4% (2)	1.1% (4)	1.4% (2)	.41

Values are % (n).
IDR, Ischemia-driven revascularization; *STEMI*, ST-segment elevation myocardial infarction; *NSTEMI*, non–ST-segment elevation myocardial infarction.

Figure 2



Adjusted association between CRP and the 3-year risk of the primary composite end point of all-cause death, stroke, or MI. Multivariable Cox proportional hazards regression was performed using a spline function to model log(CRP) as a continuous variable for the primary composite end point.

anti-inflammatory agents to benefit high-risk patients with CAD.

Previous reports had shown that even modestly elevated CRP levels prior to PCI are associated with an increased risk of adverse events[3,4,16]; however, the long-term prognostic relationship between CRP in patients with LMCAD undergoing revascularization had not been clearly established prior to the current report. The present substudy from the EXCEL trial extends these prior findings by demonstrating that baseline CRP

Table III. Multivariable model for the 3-year risk of the composite outcome of death, MI, or stroke and sensitivity analysis for the adjusted risk associated with elevated CRP in patients with versus without recent MI

Covariate	Hazard ratio (95% CI)	*P* value	$P_{interaction}$
Sensitivity model I			
Log-transformed CRP (per 10-fold increase)	1.26 (1.10-1.44)	.0008	
No recent MI†	1.32 (1.14-1.53)	.0002	.10
Recent MI	0.94 (0.65-1.36)	.76	
Age (per year)	1.00 (0.98-1.02)	.99	
Male sex	1.03 (0.67-1.58)	.91	
Diabetes*	1.60 (1.08-2.37)	.02	
Hypertension*	1.24 (0.80-1.94)	.34	
Congestive heart failure	1.20 (0.63-2.30)	.58	
Recent myocardial infarction†	0.87 (0.47-1.63)	.64	
Body mass index (per kg/m^2)	0.98 (0.94-1.02)	.28	
Renal insufficiency‡	1.22 (0.74-2.01)	.44	
LVEF (per %)	1.01 (0.99-1.03)	.52	
SYNTAX score (per unit)	1.01 (0.99-1.03)	.40	
Distal left main bifurcation lesion	0.85 (0.56-1.30)	.45	
Treatment modality (PCI vs CABG)	0.80 (0.56-1.14)	.22	
Anemia	1.34 (0.88-2.04)	.17	

*Medically treated.
†Within 7 days of randomization.
‡Defined as creatinine clearance <60 mL/min, calculated using the Cockcroft-Gault equation.

Table IV. Alternative models for the adjusted 3-year risk of the primary composite outcome of death, MI, or stroke (all patients and patients with vs without recent MI)

Covariate	Hazard ratio (95% CI)	*P* value	$P_{interaction}$
Alternative model I			
CRP 3-10 mg/L vs <3 mg/L	1.19 (0.78-1.82)	.42	
No recent MI†	1.12 (0.71-1.78)	.62	.87
Recent MI†	1.00 (0.28-3.58)	.99	
CRP ≥10 mg/L vs <3 mg/L	2.92 (1.88-4.54)	<.0001	
No recent MI†	3.18 (1.98-5.10)	<.0001	.046
Recent MI†	0.72 (0.18-2.88)	.64	
Diabetes*	1.56 (1.05-2.31)	.03	
Alternative model II			
CRP ≥3 mg/L vs <3 mg/L	1.55 (1.07-2.26)	.02	
No recent MI†	1.64 (1.11-2.43)	.01	.31
Recent MI†	0.87 (0.27-2.79)	.81	
Diabetes*	1.58 (1.07-2.34)	.02	

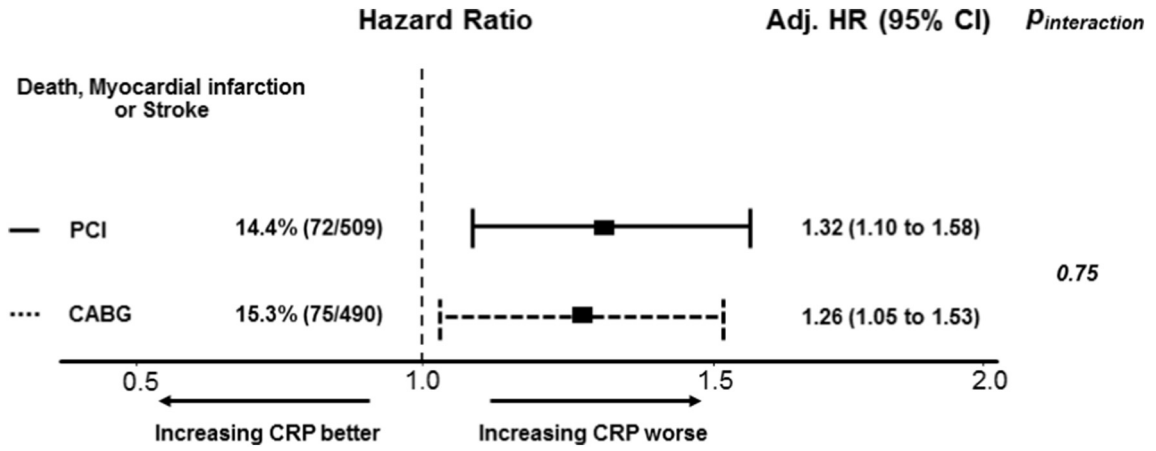
*Medically treated.
†Within 7 days of randomization.

elevation prior to revascularization of high-risk patients with LMCAD confers an increased risk for adverse cardiovascular events that is evident for at least 3 years.

In the present study, elevated CRP was associated with increased risk predominantly among patients without recent MI, possibly indicating that acutely elevated CRP levels in the setting of myonecrosis may not portend a worsened long-term prognosis after successful LMCAD revascularization, whereas a chronic proinflammatory state reflected by CRP elevation increases the long-term risk of recurrent cardiovascular adverse events. However, prior reports have demonstrated increased rates of adverse events in patients with unstable CAD and MI and high CRP levels.[17] Nevertheless, although a modest interaction between recent MI, high CRP ≥10 mg/L, and 3-year outcomes was observed in the multivariable model, when CRP was assessed as a continuous term, there was no interaction between MI, CRP, and outcomes; as such, further studies are required to examine whether elevated CRP levels in patients with recent MI confer an adverse prognosis after LM revascularization.

Prior studies have shown that patients with elevated CRP levels have greater mortality and worse event-free

Figure 3



Adjusted relationship between treatment modality and the composite primary outcome of death, MI, or stroke at 3 years according to CRP as a continuous log-linear variable.*HR*, hazard ratio.

survival compared to patients with lower CRP levels after non-LM PCI or CABG.[9,12,18] Elevated CRP has been correlated with reduced survival at 9 months in patients with LMCAD treated with PCI[19] or CABG[20]; however, to our knowledge, the present analysis is the first to directly assess whether the prognostic utility of systemic inflammation (as assessed by a surrogate biomarker) extends to 3 years in patients with LMCAD and whether it varies according to revascularization modality. In EXCEL, the association between an elevated baseline CRP level and long-term prognosis after both PCI and CABG were similar, implying that CRP level should not weigh heavily in the decision-making process between these 2 revascularization modalities. However, EXCEL excluded patients with high SYNTAX scores. It is possible that the results may vary in patients with extensive multivessel disease in whom CABG may provide more complete revascularization and protection against events associated with progressive native vessel atherosclerosis in patients with ongoing systemic inflammation.

In contrast to the relationship we observed between high CRP levels and the 3-year rates of death, MI, or stroke as well the individual end points of MI and stroke, no significant association between CRP levels and the risk of ischemia-driven revascularization, stent thrombosis, or symptomatic graft occlusion was observed. These findings may indicate that high levels of systemic inflammation impair prognosis primarily through effects on the untreated vasculature rather than by adversely affecting vascular responses to the treatments themselves (stents and bypass graft conduits).[21,22] Conversely, it is notable that elevated CRP was associated with increased rates of noncardiovascular as well as cardiovascular death, consistent with prior studies.[23-26] Several mechanisms have been proposed linking systemic inflammation to nonvascular disease (especially cancer), including induction of genomic instability, apoptosis, and aggressive tumor neovascularization driven by elevated levels of CRP inducers such as interleukin-1β and interleukin-6.[27] The white blood cell count was also higher in patients with elevated CRP levels, further supporting a link between inflammation[28,29] and coronary artery disease and consistent with prior studies indicating prognostic synergy between elevated white blood cell counts and CRP levels.[30] Nevertheless, we cannot exclude the possibility that CRP is merely a marker of risk for future noncardiovascular events in patients with low-grade chronic inflammation.

The benefits of aggressive statin therapy in patients with angiographically documented CAD are well known and are augmented in those with high CRP levels, reflecting their pleiotropic effects.[31-33] In this regard, >95% of patients in EXCEL were on statin therapy throughout the study duration. However, CRP is not often routinely assessed in patients with CAD undergoing revascularization, a practice which may warrant reevaluation. The demonstration in CANTOS that the anti-inflammatory agent canakinumab reduced MI and coronary revascularization rates in patients with baseline CRP levels >2 mg/L, with no effect on cholesterol metabolism, suggests that, in the future, the routine surveillance of systemic inflammation may direct the use of novel therapies to improve prognosis. The high cost of canakinumab for other conditions suggests that this treatment, if FDA indicated for secondary prevention and absent substantial cost reduction, will be relegated to high-risk patients. The present study suggests that CRP measurement may identify high-risk patients with LMCAD undergoing revascularization with PCI or CABG who may particularly benefit from aggressive anti-inflammatory

therapy. Repeated measures of CRP may be useful in monitoring the effect of such therapies.[2,26]

Study strengths and limitations

As the largest randomized trial to date of patients with LMCAD undergoing revascularization, EXCEL provides clinically relevant insights regarding the impact of preprocedure CRP levels on long-term cardiovascular outcomes after PCI or CABG. However, several limitations should be considered. First, the present analysis was post hoc and should thus be considered hypothesis generating. Second, high-sensitivity CRP levels were available in only ~55% of the EXCEL trial patient population. Although the results were similar when missing baseline data were imputed, our results may not be generalizable to patients with LMCAD not represented in the present study. Third, statin dosages were not captured in the EXCEL trial, and serial LDL levels were not measured during follow-up; as such, we are unable to examine the relationship between CRP level and effects of statin therapy. Fourth, CRP levels were not measured after revascularization, and therefore, residual inflammatory risk during follow-up, which may have prognostic significance,[2,16,34] was not assessed. However, the adverse effects of elevated baseline CRP levels in the present study were evidenced early after revascularization and persisted for 3 years, suggesting that such baseline measures may provide useful therapeutic guidance. Fifth, despite the strong predictive influence of high CRP levels on cardiovascular outcomes after multivariable adjustment for baseline covariates, we cannot exclude possible effects of unmeasured confounders. Finally, stent thrombosis and symptomatic graft occlusion occurred infrequently in the EXCEL trial; as such, our findings regarding the lack of an effect of elevated CRP on these outcomes cannot be considered conclusive.

Conclusions

In the randomized EXCEL trial, elevated baseline CRP levels in patients with LMCAD prior to revascularization with PCI or CABG were a powerful predictor of the composite outcome of death, MI, or stroke at 3 years. Further studies are needed to determine whether high-risk patients such as those in the present report with residual inflammatory risk despite statin therapy may benefit from the tailored use of anti-inflammatory therapies.

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Disclosures

Dr Lembo: fees for lectures and serving on advisory boards from Abbott Vascular, Boston Scientific, and Medtronic. Dr Kappetein: employee—Medtronic. Dr Sabik: consultant—Medtronic, Edwards, and Sorin; advisory board—Medtronic Cardiac Surgery. Dr Serruys: consultant—Abbott, Biosensors, Cardialysis, Micell Technologies, Medtronic, Sinomed Science Technologies, Stentys France, Svelte Medical Systems, Philips/Volcano, St Jude Medical, and Xeltis. Dr Stone's employer, Columbia University, receives royalties from sale of the Abbott Vascular–manufactured MitraClip. The rest of the authors have nothing to disclose.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.12.013.

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