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ORIGINAL ARTICLE

High-sensitivity C-reactive protein, low-density lipoprotein cholesterol and cardiovascular outcomes in patients with type 2 diabetes in the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial

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Aims: We sought to assess the risk of major adverse cardiovascular events (MACE) by utilizing high-sensitivity C-reactive protein (hsCRP) level and low-density lipoprotein cholesterol (LDL-C) in patients with type 2 diabetes and recent acute coronary syndrome.

Materials and methods: Study participants enrolled in the EXAMINE trial (Clinical trials registration number: NCT00968708) and were stratified by baseline hsCRP levels (<1, 1-3 and >3 mg/L). They were also sub-divided into 4 groups according to baseline hsCRP (≤3 or >3 mg/L) and achieved LDL-C (<70 or ≥70 mg/dL) levels. Among 5380 patients, the MACE rate, a composite of cardiovascular death, non-fatal acute myocardial infarction and non-fatal stroke, was evaluated during the 30 months of follow-up.

Results: Cumulative incidence of MACE was 11.5% (119 events), 14.6% (209 events) and 18.4% (287 events) in patients with hsCRP levels of <1, 1 to 3 and >3 mg/L, respectively ($P < .001$). In patients with hsCRP >3 mg/L, the adjusted hazard ratio (95% confidence interval) was 1.42 (1.13, 1.78; $P = .002$) for MACE compared with patients with hsCRP <1 mg/L. MACE cumulative incidences were 11.0% (128 events), 14.4% (100 events), 15.6% (194 events) and 21.3% (182 events) in patients with low LDL-C and low hsCRP, low LDL-C and high hsCRP, high LDL-C and low hsCRP, and high LDL-C and high hsCRP levels, respectively ($P < .001$).

Conclusions: Levels of hsCRP were associated with recurrent cardiovascular events in patients with type 2 diabetes and recent acute coronary syndrome, and this association appears to be independent of and additive to the achieved LDL-C level.

KEYWORDS

acute coronary syndromes, cardiovascular outcomes, high-sensitivity C-reactive protein, LDL cholesterol, type 2 diabetes

1 | INTRODUCTION

Inflammation plays a key role in the pathogenesis of atherosclerosis.[1] There are numerous diverse markers for systemic inflammation, but among them, high-sensitivity C-reactive protein (hsCRP) is one of the best studied biomarkers for vascular risk in both primary and secondary prevention settings.[2,3] In primary prevention, cardiovascular (CV) risk predictions according to CRP concentration are comparable to

those according to systolic blood pressure, total cholesterol and non-high-density lipoprotein (HDL) cholesterol levels.[4] In a meta-analysis addressing secondary prevention, hsCRP concentrations measured within 72 hours from the onset of acute coronary syndrome (ACS) were associated with a higher long-term risk of recurrent CV events.[5] However, because hsCRP rises 5 to 8 times in the setting of ACS, the cut-points used in the acute setting differ from those used in a stable population.

To date, several prospective studies have examined the role of hsCRP in predicting future CV morbidity and mortality in stable patients with type 2 diabetes mellitus, with varying results.[6–12] The aim of our study was to determine whether the baseline hsCRP level is predictive of the risk of major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal myocardial infarction and stroke, in patients at high risk of CV disease, with type 2 diabetes and recent ACS, who were enrolled in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial.[13] In addition, we evaluated whether the associations between hsCRP level and future CV outcomes were independent of achieved low-density lipoprotein (LDL) cholesterol (LDL-C) levels.

2 | METHODS

2.1 | Study design and patients

The design of the EXAMINE study has been published previously.[13] EXAMINE was a multicenter, randomized, double-blind study that evaluated the efficacy and safety of the dipeptidyl peptidase 4 (DPP-4) inhibitor alogliptin in 5380 patients diagnosed with type 2 diabetes and ACS within 15 to 90 days before randomization. Other inclusion criteria required a glycated haemoglobin level of 6.5% to 11.0% at baseline or, if the antidiabetic regimen included insulin, a glycated haemoglobin level of 7.0% to 10.0%. Major exclusion criteria were diagnosis of type 1 diabetes; unstable cardiac disorders including New York Heart Association Functional Classification IV heart failure, refractory angina, uncontrolled arrhythmia, critical valvular heart disease or severe uncontrolled hypertension; and dialysis within 14 days before screening.

Patients were randomly assigned to receive alogliptin or placebo, administered in a double-blind fashion, in addition to standard-of-care treatment for type 2 diabetes. Throughout the study, patients were required to receive standard-of-care treatment for type 2 diabetes and CV risk factors according to regional guidelines. Because alogliptin is cleared by the kidney, alogliptin and matching placebo doses were modified according to the estimated glomerular filtration rate (GFR, MDRD) at baseline and after randomization.

2.2 | Cardiovascular adjudication

The composite MACE endpoint consisted of cardiovascular death, non-fatal acute myocardial infarction and non-fatal stroke. Cardiovascular death was defined as death from cardiac and cerebrovascular causes and any death without another known cause. Urgent revascularization because of unstable angina, hospitalization for heart failure, and death as a result of any cause were adjudicated also. CV events and all deaths were adjudicated by members of an independent cardiovascular endpoints committee who were blinded to treatment assignment (Cleveland Clinic Cardiovascular Endpoint Committee, Cleveland, Ohio).

2.3 | Measurement of hsCRP

Venous blood samples were obtained in EDTA-treated tubes at study entry as part of the study protocol. Plasma samples were refrigerated and transported overnight to the central laboratory, and were stored at −80°C or colder until analysed after a single freeze–thaw cycle. The hsCRP was measured at baseline in all available samples (n = 5380) using a validated latex-enhanced turbidimetric immunoassay (Hitachi 747 analyzer). All assays were performed by laboratory personnel blinded to treatment allocation and clinical outcome.

2.4 | Statistical analysis

Study participants were stratified by baseline hsCRP values using established decision limits (<1, 1-3 and >3 mg/L) for prediction of CV outcomes.[3] Data are expressed as mean ± SD or median and interquartile range for continuous measures, or as proportions for categorical variables. Differences between groups were tested by ANOVA or Wilcoxon rank-sum test for continuous variables and the χ^2-test or Fisher's exact test for categorical variables. Event rates through 30 months were calculated using the Kaplan–Meier method. Multivariate Cox proportional hazards models were used to analyse the time to the occurrence of CV outcomes in association with baseline hsCRP levels. The covariates included in the adjusted model were treatment group, age, sex, body mass index, current smoking status, total cholesterol, estimated GFR, blood pressure, glycated haemoglobin and duration of diabetes. Assessment of the treatment effect of alogliptin was performed on an intention-to-treat basis. To determine potential shared effects, study participants were divided into 4 groups according to both baseline hsCRP (≤3 or >3 mg/L) and achieved LDL-C (<70 or ≥70 mg/dL). With this combination, we determined whether the hsCRP level has an independent and additional role, to assess CV risk beyond that conveyed by the achieved LDL-C level, as defined by current guidelines.[14,15] A 2-sided *P* value of .05 was considered significant for all tests. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and were performed by the biometrics group at the Baim Clinical Research Institute (Boston, Massachusetts).

3 | RESULTS

The baseline characteristics of study participants according to baseline hsCRP concentrations (<1, 1-3, and >3 mg/L) are shown in Table 1. Of the 5380 subjects who had an hsCRP concentration measured at baseline, approximately 40% (n = 2139) had an hsCRP concentration of >3 mg/L. Patients with higher hsCRP levels (>3 mg/L) were more obese, and more likely to have higher blood pressure; had higher fasting glucose, glycated haemoglobin, LDL-C and triglyceride levels; and had lower HDL cholesterol levels than patients with

TABLE 1 Baseline characteristics according to high-sensitivity C-reactive protein concentrations

	High-sensitivity C-reactive protein stratification			
	<1 mg/L (n = 1278)	1 to 3 mg/L (n = 1963)	>3 mg/L (n = 2139)	*P* value
High-sensitivity C-reactive protein (mg/L)	0.6 (0.4-0.8)	1.7 (1.3-2.3)	6.2 (4.2-11.9)	<.001
Age (years)	61.4 (9.7)	60.9 (10.0)	60.5 (10.0)	.022
Male (%)	75.7 (968)	68.0 (1334)	63.1 (1349)	<.001
Body mass index (kg/m^2)	27.3 (4.5)	29.3 (5.0)	30.9 (6.2)	<.001
Cardiovascular risk factors and history (%)				
Current smoker	11.0 (141)	12.2 (239)	16.5 (354)	<.001
Hypertension	78.5 (1003)	82.9 (1628)	85.9 (1838)	<.001
Dyslipidaemia	28.1 (359)	27.7 (543)	25.7 (550)	.22
Myocardial infarction	87.6 (1119)	88.1 (1729)	88.2 (1886)	.86
Coronary bypass surgery	9.2 (118)	12.2 (240)	15.4 (330)	<.001
Percutaneous coronary intervention	67.0 (856)	61.7 (1211)	61.0 (1305)	.001
Congestive heart failure	22.8 (292)	27.0 (530)	31.7 (679)	<.001
Transient ischemic attack	1.8 (23)	2.8 (54)	3.2 (68)	.054
Peripheral arterial disease	6.8 (87)	9.6 (188)	11.2 (239)	<.001
Systolic blood pressure (mmHg)	127.8 (16.9)	129.1 (16.2)	129.5 (16.8)	.014
Diastolic blood pressure (mmHg)	75.5 (9.9)	76.5 (9.3)	76.8 (9.9)	<.001
Glycated haemoglobin (%)	7.9 (1.1)	8.0 (1.1)	8.1 (1.1)	<.001
Fasting glucose (mg/dL)	140.0 (116.0-173.0)	146.0 (121.0-185.0)	148.0 (122.0-189.0)	<.001
Total cholesterol (mg/dL)	139.0 (119.0-166.0)	148.0 (125.0-178.0)	151.0 (126.0-184.0)	<.001
HDL cholesterol (mg/dL)	43.0 (37.0-51.0)	42.0 (36.0-49.0)	41.0 (35.0-48.0)	<.001
LDL cholesterol (mg/dL)	67.0 (50.0-88.0)	72.0 (55.0-97.0)	76.0 (57.0-102.0)	<.001
Triglyceride (mg/dL)	127.0 (93.0-171.0)	145.0 (107.0-200.0)	146.0 (106.0-205.0)	<.001
Estimated GFR (ml/min/1.73 m^2)	71.7 (20.4)	71.9 (21.2)	69.6 (22.1)	<.001
Index ACS (%)				
Myocardial infarction	78.6 (1003)	76.3 (1494)	77.6 (1655)	.31
Unstable angina	21.4 (273)	23.7 (463)	22.4 (478)	.31
Time between index ACS and randomization (days)	48.0 (32.0-67.0)	44.0 (30.0-64.0)	43.0 (28.0-62.0)	<.001

Abbreviations: ACS, acute coronary syndrome; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data are expressed as percentage (number), mean (SD) or median (interquartile range). LDL cholesterol levels were measured in 1271, 1928 and 2111 patients, and index ACS cases were determined in 1276, 1957 and 2133 in patients, with hsCRP levels of <1, 1 to 3 and >3 mg/L, respectively. Body mass index was determined in 1277 patients with hsCRP levels <1 mg/L and HDL cholesterol was measured in 1962 patients with hsCRP levels 1–3 mg/L.

average to lower hsCRP levels (≤3 mg/L). The high hsCRP patients were also more likely to be current smokers and have a history of hypertension, coronary bypass surgery, congestive heart failure or peripheral artery disease, and were less likely to have a history of percutaneous coronary intervention.

During a median duration of 18 months of follow-up, cumulative incidences of MACE were 11.5% (119 events), 14.6% (209 events) and 18.4% (287 events) in patients with baseline hsCRP <1, 1 to 3 and >3 mg/L, respectively ($P < .001$) (Figure 1). Similarly, cumulative incidences of hospitalization for heart failure or death from any cause were related to baseline hsCRP levels (both $P < .001$). No differences in the rates of urgent revascularization for unstable angina were observed across the hsCRP concentrations (Figure S1).

In patients with baseline hsCRP >3 mg/L, the adjusted hazard ratio (HR) (95% confidence interval [CI]) was 1.42 (95% CI, 1.13, 1.78; $P = .002$) for MACE, 1.40 (95% CI, 1.04, 1.89; $P = .025$) for non-fatal myocardial infarction, 2.04 (95% CI, 1.34, 3.11; $P < .001$) for hospitalization following heart failure and 1.77 (95% CI, 1.29, 2.42; $P < .001$) for death from any cause, compared to patients with baseline hsCRP <1 mg/L, and were independent of treatment group, age, sex, body mass index, current smoking status, total cholesterol, estimated GFR, blood pressure, glycated haemoglobin and duration of diabetes. Baseline hsCRP concentrations did not show an independent association with the individual endpoints of death from cardiovascular causes, non-fatal stroke or urgent revascularization because of unstable angina. In addition, patients with average concentrations of hsCRP (1-3 mg/L) had a CV risk comparable to patients with lower baseline hsCRP concentrations (<1 mg/L) (Table 2).

Results for the groups evaluated according to both baseline hsCRP (≤3 or >3 mg/L) and achieved LDL-C (<70 or ≥70 mg/dL) levels are shown in Figure 2. Cumulative incidences of MACE were 11.0% (128 events), 14.4% (100 events), 15.6% (194 events) and 21.3% (182 events) in patients with low LDL-C and low hsCRP concentrations, low LDL-C and high hsCRP concentrations, high LDL-C and low hsCRP concentrations, and high LDL-C and high hsCRP concentrations, respectively ($P < .001$). Hospitalization for heart failure and death from any cause were also related to both baseline hsCRP and achieved LDL-C levels (both $P < .001$). Cumulative incidences of urgent revascularization for unstable angina were similar among the 4 groups (Figure S2).

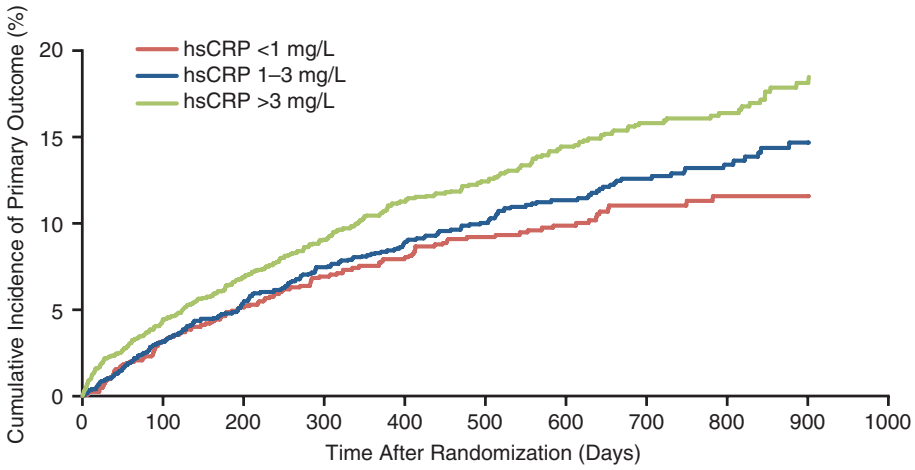

FIGURE 1 Time to the primary endpoint (major adverse cardiovascular events) according to baseline high-sensitivity C-reactive protein (hs-CRP) in the EXAMINE trial

TABLE 2 Cardiovascular outcomes according to baseline high-sensitivity C-reactive protein concentrations

	High-sensitivity C-reactive protein stratification			
	<1 mg/L (n = 1278)	1 to 3 mg/L (n = 1963)	>3 mg/L (n = 2139)	*P* value*
Major adverse cardiovascular events	**Reference**	1.11 (0.88, 1.40)	1.42 (1.13, 1.78)	.002
Death from cardiovascular causes		0.97 (0.67, 1.40)	1.40 (0.98, 2.00)	.06
Non-fatal myocardial infarction		1.14 (0.85, 1.54)	1.40 (1.04, 1.89)	.025
Non-fatal stroke		1.62 (0.81, 3.22)	1.57 (0.79, 3.13)	.20
Urgent revascularization because of unstable angina		1.22 (0.72, 2.08)	0.91 (0.52, 1.61)	.75
Hospitalization for heart failure		1.30 (0.83, 2.04)	2.04 (1.34, 3.11)	<.001
Death from any cause		1.12 (0.80, 1.55)	1.77 (1.29, 2.42)	<.001

Data are expressed as hazard ratio (95% confidence interval). Data were adjusted for treatment group, age, sex, body mass index, current smoking status, total cholesterol, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, glycated haemoglobin and diabetes duration. **P* value compares >3 mg/L to the reference group.

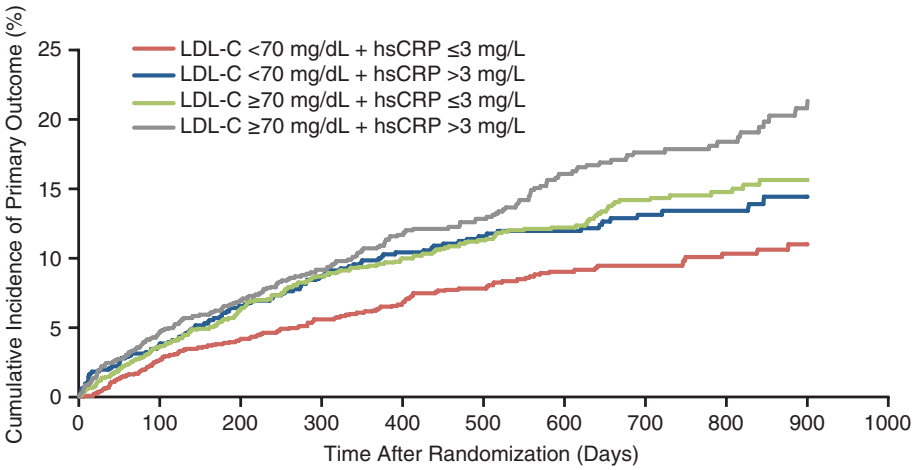

FIGURE 2 Time to the primary endpoint (major adverse cardiovascular events) according to baseline high-sensitivity C-reactive protein (hs-CRP) and low-density lipoprotein (LDL) cholesterol in the EXAMINE trial

4 | DISCUSSION

In patients with type 2 diabetes and recent ACS, we have determined that baseline hsCRP levels are predictive of developing recurrent MACE. Patients with a higher baseline hsCRP level (>3 mg/L) developed CV events regardless of the achieved LDL-C level, and this association persisted even in patients with an achieved LDL-C level of <70 mg/dL, a threshold value recommended by most current guidelines for patients with coronary disease.[14,15] Incorporating both hsCRP and LDL-C provided additional stratification of risk, with a more than 2-fold higher risk when both markers were elevated. The patterns are similar to those seen in other patient populations that did not have type 2 diabetes, or recent ACS. As such, use of these 2 simple and widely available tests could help to risk-stratify this group of patients.

It has been suggested that the association between hsCRP level and risk of CV disease is generally weaker in patients with type 2 diabetes compared with those without diabetes.[16–18] Type 2 diabetes is characterized by diverse CV risk factors including high triglycerides and low HDL cholesterol levels, hypertension and hyperglycaemia per se, and these multiple risk factors may partially mask the role of hsCRP as a risk factor for CV morbidity and mortality.[16–18] In an

analysis from the Collaborative Atorvastatin Diabetes Study (CARDS) trial, the baseline CRP level was not predictive of future CV disease. Moreover, the efficacy of statins was not different according to achieved CRP levels, and thus, the authors did not support the use of CRP as an indicator of statin efficacy in patients with type 2 diabetes.[10] Collectively, these data suggested that, in populations with increased inflammatory and vascular burden, the measurement of hsCRP may have limited clinical relevance in the assessment of future development of CV events.

In contrast, several prospective cohort studies have shown that individuals with higher CRP levels were at risk of future CV disease, including patients with type 2 diabetes.[6–9] In a population-based Italian cohort, followed for 5 years, higher CRP values (>3 mg/L) were associated with increased overall and CV mortality in patients with type 2 diabetes after adjusting for conventional CV risk factors.[6] Similarly, in a study involving 878 Finnish subjects with type 2 diabetes who were free of myocardial infarction at baseline, coronary heart disease mortality was increased in subjects with a higher CRP level (>3 mg/L).[7] Therefore, there is still equipoise regarding the usefulness of measuring the hsCRP level to assess CV risk in patients with a high vascular risk, including those with type 2 diabetes and previous CV disease from the ADVANCE study[11] and those with ACS.[12]

While there is a discrepancy between some of the above-referenced results and those from EXAMINE, there are substantial differences in the patient populations. Our study was comprised of patients with ACS, on average, 45 days before randomization, and most patients (>90%) were already receiving a statin at baseline. In ADVANCE, only one-third (34.8%) of patients had a history of previous CV disease and fewer patients had had statin treatment at baseline. Of note, among the 1345 patients (34.8%) who had a history of CV disease at baseline in ADVANCE,[11] the hsCRP level was not associated with recurrent vascular events (HR [95% CI], 1.09 [0.96, 1.23]).

In addition, subjects from the ADVANCE trial had a median hsCRP level of 1.8 mg/L at baseline. Despite the well-known reduction in hsCRP after treatment with statins, the EXAMINE patients had a higher on-treatment median hsCRP level of 2.2 mg/L. Therefore, EXAMINE patients may have a greater inflammatory burden than those in other study populations, which cannot be captured entirely by CV risk factors driven by type 2 diabetes and a history of CV disease. Our findings demonstrate that a higher hsCRP value can predict future secondary CV events in patients with established CV disease. In support of this notion is the finding that there was a graded increase in future CV risk across a full range of hsCRP values and risk scores from the Framingham study.[19]

Another key finding of our analysis is that the hsCRP value was independent of, and additive to, the achieved LDL-C level in predicting future CV events. There has been controversy regarding whether statins have non-lipid-lowering pleiotropic benefits. A meta-regression analysis showed a strong correlation between LDL-C reduction and hsCRP reduction ($r = 0.80$, $P < .001$), and at least 90% of the hsCRP reduction with lipid-lowering drugs may be explained by the reduction in LDL-C.[20] This would lead to the conclusion that the potential non-lipid-lowering effects of statins on inflammation might be modest in magnitude. In contrast, results from a secondary analysis from the JUPITER trial demonstrated that the correlation between the reduction in hsCRP and the reduction in LDL-C was relatively weak ($r = 0.15$) and relative risk for vascular events with rosuvastatin, 20 mg daily, was 0.45 in those who achieved an LDL-C level <70 mg/dL, 0.38 in those who achieved an hsCRP level <2.0 mg/L, and 0.35 in those who achieved both LDL-C and hsCRP targets together. Thus, the authors concluded that, not only LDL-C reduction, but also hsCRP reduction, could be induced by statin therapy.[21] Finally, the PROVE IT-TIMI 22 trial demonstrated that hsCRP reduction is beneficial in preventing vascular events, whether or not LDL-C levels were reduced to the target value of <70 mg/dL with statin treatment.[22]

In EXAMINE, the cumulative incidences of MACE, hospitalization for heart failure and death from any cause were the lowest in patients achieving both LDL-C <70 mg/dL and hsCRP <3.0 mg/L. However, there were mismatches in the LDL-C levels and hsCRP in EXAMINE. For example, low LDL-C (<70 mg/dL) but high hsCRP (>3.0 mg/L) values with statin treatment were observed in 47.1% (2503/5310) of the study patients. In addition, one-third of our patients (33.4%, 882/2640) had an hsCRP level ≥3.0 mg/L despite achieving an LDL-C target <70 mg/dL. This suggests that both the achieved LDL-C and the hsCRP levels had independent, as well as additive, effects in predicting future CV risk, and support the non-lipid-lowering benefits of statins, such as its anti-inflammatory properties.

Our analysis has some limitations. We had only a single measurement of hsCRP at the baseline period and, therefore, we cannot exclude the possibility of some variability in the hsCRP level from that of an acute-phase reaction. However, a non-CV inflammatory condition causing an hsCRP elevation is more likely to underestimate the true association between hsCRP value and CV outcome and not to falsely overestimate the risk relationship. Also, we did not have information regarding other risk factors that possibly affect future CV disease, including socioeconomic status, physical activity, dietary factors and family history of CV disease.

In conclusion, in patients with type 2 diabetes and high CV risk, with recent ACS, but under treatment with statins and with good glycaemic control, we have found a significant association between on-treatment hsCRP values and future CV outcomes. The results indicate that patients achieving LDL-C targets of <70 mg/dL with statin therapy, may benefit from the measurement of both hsCRP and LDL-C to assess residual CV risk.

Conflict of interest

W. B. W. is chair of the EXAMINE steering committee and has received personal fees from Takeda Development Center, Deerfield, Illinois. F. Z. is a member of the EXAMINE steering committee and has received personal fees from Takeda Development Center, Deerfield, Illinois. C. R. M. is a member of the EXAMINE steering committee has received personal fees from Takeda Development Center, Deerfield Illinois. Y. L. is an employee of Baim Clinical Research Group, Boston, Massachsetts. G. L. B. is a member of the EXAMINE steering committee and has received personal fees from Takeda Development Center, Deerfield, Illinois. W. C. C. is a member of the EXAMINE steering committee and has received personal fees from

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Author contributions

All authors take full responsibility for the work as a whole, including the study design, and the decision to submit and publish the manuscript. Y. C. H. wrote the initial draft of the manuscript and W. B. W. provided additional writing to complete the present draft. D. A. M. reviewed/edited the manuscript. C. P. C. reviewed/edited the manuscript. Y. L. performed analyses and assisted in drafting the statistical analysis section of the manuscript. R. M. B. reviewed/edited the manuscript. S. R. H. reviewed/edited the manuscript. C. R. M. reviewed/edited the manuscript. W. C. C. reviewed/edited the manuscript. G. L. B. reviewed/edited the manuscript. F. Z. reviewed/edited the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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