High Sensitivity C-Reactive Protein, Low-Density Cholesterol, and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Acute Coronary Syndrome From the EXAMINE Trial

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Introduction

- High-sensitivity C-reactive protein (hsCRP) level is known to be an independent predictor for future development of cardiovascular disease[1,2]
- EXAMINE was a multicenter, randomized, double-blind study that evaluated the efficacy and safety of the dipeptidyl peptidase 4 inhibitor alogliptin in 5380 patients diagnosed with type 2 diabetes and an acute coronary syndrome within 15 to 90 days before randomization[3,4]
- The aim of this study was to assess the risk of major adverse cardiovascular events (MACE) according to baseline hsCRP levels in patients with type 2 diabetes and recent cardiovascular events enrolled in the EXAMINE trial

Methods

- As part of the EXAMINE protocol, venous blood samples were obtained at study entry. The hsCRP levels were measured at baseline in all available plasma samples (n=5380) using a validated latex-enhanced turbidimetric immunoassay (Hitachi 747 analyzer)
- The composite MACE end point consisted of cardiovascular death, non-fatal acute myocardial infarction (MI), and non-fatal stroke
  - Cardiovascular events and all deaths were adjudicated by members of an independent cardiovascular end points committee who were blinded to treatment assignment
- Study participants were stratified by baseline hsCRP values using established decision limits (<1, 1–3, and >3 mg/L) for prediction of cardiovascular outcomes
- Study participants were also divided into 4 groups according to both baseline hsCRP levels (≤3 mg/L or >3 mg/L) and achieved low-density lipoprotein cholesterol (LDL-C) levels (<70 mg/dL or ≥70 mg/dL)
- Multivariate Cox proportional hazards models were used to analyze the independent association between baseline hsCRP level and MACE, as well as urgent revascularization due to unstable angina, hospitalization for heart failure, and death from any cause

Results

Baseline Characteristics

- The key baseline characteristics of study participants according to baseline hsCRP concentrations (<1, 1–3, and >3 mg/L) are shown in Table 1

Table 1. Key Baseline Characteristics According to hsCRP Concentrations

	hsCRP stratification			
	<1 mg/L (n=1278)	1–3 mg/L (n=1963)	>3 mg/L (n=2139)	P-value
hsCRP (mg/L)	0.6 (0.4–0.8)	1.7 (1.3–2.3)	6.2 (4.2–11.9)	<0.001
Age (years)	61.4 (9.7)	60.9 (10.0)	60.5 (10.0)	0.022
Male (%)	75.7 (968)	68.0 (1334)	63.1 (1349)	<0.001
Body mass index (kg/m²)	27.3 (4.5)	29.3 (5.0)	30.9 (6.2)	<0.001
Cardiovascular risk factors and history (%)				
Current smoker	11.0 (141)	12.2 (239)	16.5 (354)	<0.001
Hypertension	78.5 (1003)	82.9 (1628)	85.9 (1838)	<0.001
Dyslipidemia	28.1 (359)	27.7 (543)	25.7 (550)	0.22
Myocardial infarction	87.6 (1119)	88.1 (1729)	88.2 (1886)	0.86
Glycated hemoglobin (%)	7.9 (1.1)	8.0 (1.1)	8.1 (1.1)	<0.001
Total cholesterol (mg/dL)	139.0 (119.0–166.0)	148.0 (125.0–178.0)	151.0 (126.0–184.0)	<0.001
HDL cholesterol (mg/dL)	43.0 (37.0–51.0)	42.0 (36.0–49.0)	41.0 (35.0–48.0)	<0.001
LDL-C (mg/dL)	67.0 (50.0–88.0)	72.0 (55.0–97.0)	76.0 (57.0–102.0)	<0.001
Triglyceride (mg/dL)	127.0 (93.0–171.0)	145.0 (107.0–200.0)	146.0 (106.0–205.0)	<0.001

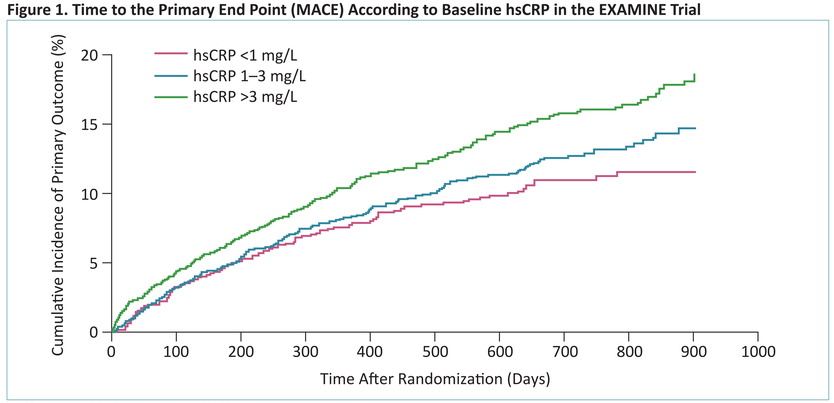
Data are expressed as percentage (number), mean (SD), or median (interquartile range).
hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein; SD, standard deviation.

Cardiovascular Outcomes by Baseline hsCRP Levels

- Cumulative MACE incidence rates were related to baseline hsCRP levels and were highest in patients with hsCRP >3 mg/L (P<0.001; Figure 1)
- Similarly, cumulative incidence rates of hospitalization for heart failure (Figure 2A) or death from any cause (Figure 2B) were related to both baseline hsCRP and achieved LDL-C levels (both P<0.001)
- Patients with baseline hsCRP >3 mg/L showed independent associations with future MACE, non-fatal MI, hospitalization for heart failure, and death from any cause compared to patients with baseline hsCRP <1 mg/L (Table 2)

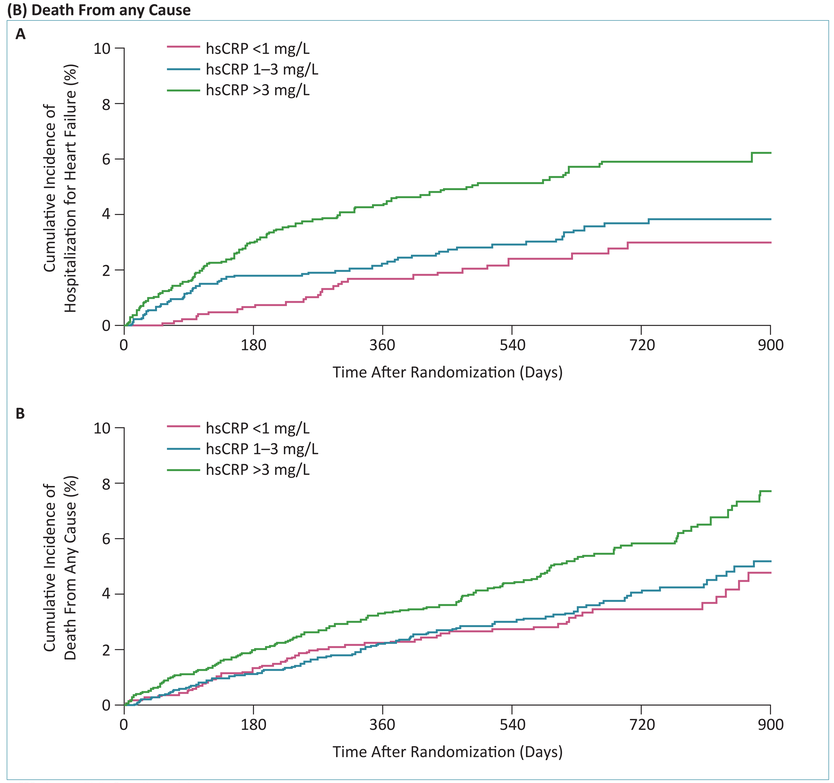
Results (continued)

Figure 1. Time to the Primary End Point (MACE) According to Baseline hsCRP in the EXAMINE Trial



hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular event.

Figure 2. Cumulative Incidence by Baseline hsCRP Category for (A) Hospitalization for Heart Failure and (B) Death From any Cause



hsCRP, high-sensitivity C-reactive protein.

Table 2. Hazard Ratios (95% Confidence Interval) for Cardiovascular Outcomes According to Baseline hsCRP Concentration in EXAMINE

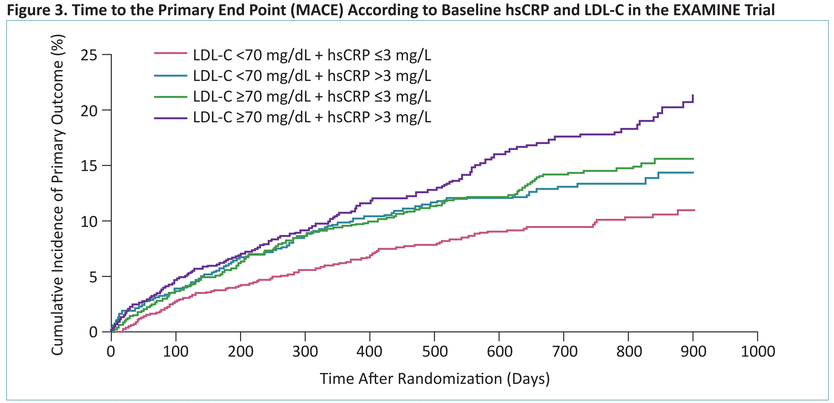
	hsCRP stratification			
	<1 mg/L (n=1278)	1–3 mg/L (n=1963)	>3 mg/L (n=2139)	P-value
Major adverse cardiovascular events	Reference	1.11 (0.88, 1.40)	1.42 (1.13, 1.78)	0.002
Death from cardiovascular causes		0.97 (0.67, 1.40)	1.40 (0.98, 2.00)	0.06
Non-fatal myocardial infarction		1.14 (0.85, 1.54)	1.40 (1.04, 1.89)	0.025
Non-fatal stroke		1.62 (0.81, 3.22)	1.57 (0.79, 3.13)	0.20
Urgent revascularization due to unstable angina		1.22 (0.72, 2.08)	0.91 (0.52, 1.61)	0.75
Hospitalization for heart failure		1.30 (0.83, 2.04)	2.04 (1.34, 3.11)	<0.001
Death from any cause		1.12 (0.80, 1.55)	1.77 (1.29, 2.42)	<0.001

hsCRP, high-sensitivity C-reactive protein.
Data are expressed as hazard ratio (95% confidence interval).
Data were adjusted for treatment group, age, sex, body mass index, current smoking, total cholesterol, estimated glomerular filtration rate, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, and diabetes duration.

Cardiovascular Outcomes by Baseline hsCRP and Achieved LDL-C Levels

- Rates of MACE for the groups evaluated according to both baseline hsCRP (≤3 or >3 mg/L) and achieved LDL-C (<70 or ≥70 mg/dL) are shown in Figure 3
  - Rates of MACE were different among the 4 groups (P<0.001)
- The rates of hospitalization for heart failure and death from any cause were also related to both baseline hsCRP and achieved LDL-C levels (both P<0.001)

Figure 3. Time to the Primary End Point (MACE) According to Baseline hsCRP and LDL-C in the EXAMINE Trial



hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major cardiovascular adverse event.

Conclusions

- Levels of hsCRP were associated with recurrent cardiovascular events in patients with type 2 diabetes and recent acute coronary syndrome
  - This association appeared to be independent of and additive to the achieved level of LDL-C
- The results indicate that patients achieving goal LDL-C targets of <70 mg/dL with statin therapy may benefit from the measurement of both hsCRP and LDL-C to assess residual cardiovascular risk

Disclosures

WBW is chair of the EXAMINE Steering Committee and has received personal fees from Takeda Development Center, Deerfield, IL; CM, GLB, WC, SH, RB, and FZ are members of the EXAMINE Steering Committee and have received personal fees from Takeda Development Center, Deerfield, IL; DM has received research grant support from Takeda; YL and CPC are employees of the Baim Clinical Research Institute, Boston, MA.

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