Impact of estimated HDL particle size via the ratio of HDL-C and apoprotein A-I on short-term prognosis of diabetic patients with stable coronary artery disease

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Abstract

Background  Revascularization and statin therapy are routinely used in the management of stable coronary artery disease. However, it is unclear whether the estimated high-density lipoprotein (HDL) particle size (eHDL-S), the ratio of HDL cholesterol (HDL-C) to apoprotein A-I (apoA-I), is associated with the clinical outcomes of diabetic patients with stable coronary artery disease (CAD).

Methods  We performed a prospective cohort study of 328 patients diagnosed with stable CAD by coronary angiography. Patients were followed up for a mean duration of 12 months. The patients were divided into three groups by the tertiles of eHDL-S: low eHDL-S (< 0.71, n = 118); intermediate eHDL-S (0.71–0.79, n = 111); and high eHDL-S (> 0.79, n = 99). The associations between the baseline eHDL-S and short-term outcomes were evaluated using the Kaplan–Meier method and Cox proportional regression.

Results  The low eHDL-S group had higher triglyceride, hemoglobin A1c, uric acid, and leukocyte count than the other groups. During the follow-up period, 47/328 patients experienced a prespecified outcome. According to the Kaplan–Meier analysis, the incidence of prespecified outcomes was lower in the high eHDL-S group (P = 0.04). However, eHDL-S was not independently associated with adverse outcomes in Cox proportional hazards regression (hazard ratio (HR): 0.23, 95% confidence interval (95% CI): 0.01–1.24, P = 0.493).

Conclusion  Although the eHDL-S was associated with inflammatory biomarkers, it was not independently associated with the short-term prognosis of diabetic patients with stable CAD in the era of revascularization and potent statin therapy.

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Keywords: High-density lipoprotein; Apoprotein A-I; Diabetes mellitus; Coronary artery disease; Outcome

1 Introduction

There is abundant evidence showing an inverse association between high-density lipoprotein cholesterol (HDL-C) and the risk of coronary artery disease (CAD).[1-4] However, inconsistent findings have been reported and there may be paradoxical effects of HDL-C. For example, increases in serum HDL concentrations were not observed, despite pharmacological manipulations beyond optimal lipid-lowering therapy for secondary prevention, but some unpleasant side effects were noted, including hypertension, and the retention of sodium and water.[5,6] Moreover, some studies have suggested that the optimal HDL-C concentration should be tailored to the patients age and sex, and that the need to maintain HDL-C at “normal” or “very high” concentrations should be considered based on the presence or absence of other disorders, including dyslipidemia, hyperglycemia, and nonspecific inflammatory or pre-inflammatory conditions.[7,8] The conclusions of multiple cohort studies attributed the underlying mechanisms of HDL to the particle size or composition because of the variations among individuals and associations with the risk of cardiovascular diseases and diabetic mellitus.[10] The number of HDL particles might also be associated with its functionality and a better marker for residual risk than the actual HDL-C or apoprotein A-I (apoA-I) concentrations. Consequently, some hypotheses have been developed for a novel therapeutic concept, which aims to improve HDL functionality.
rather than simply increasing the cholesterol cargo in the modern era of potent statin therapy. Nevertheless, accurate measurement of the HDL-C concentration in a variety of clinical settings requires proper and regular external quality evaluation, and there are concentration-dependent differences between direct HDL-C testing methods. These issues may lead to misclassification of the cardiovascular risk assessment of individual patients. Furthermore, HDL particles are heterogeneous in size and composition, and a number of separation and analytical methods are used to determine the numbers of discrete HDL particles. Therefore, the determination of HDL particle size requires advanced instrumentation, is time-consuming, and is not routinely requested by clinicians. Fortunately, some investigators have proposed several theoretical equations relating HDL particle size to HDL composition. These theoretical formulas were mainly based on the spherical model of lipoprotein structure, and included the ratio of HDL-C to apoA-I, to predict HDL particle size.

Although prior researches have demonstrated that the ratio of HDL-C to apoA-I is correlated with HDL particle size, there is limited evidence to show whether or not the eHDL-S, the ratio of HDL-C to apoA-I, could provide useful prognostic information for diabetic patients with stable CAD. Additionally, the relationships between the eHDL-S and inflammatory biomarkers, lipid levels, and the severity of coronary lesions have not been established in which patients routinely receive potent statin therapy and revascularization. Therefore, the aim of this prospective study was to determine the whether the baseline eHDL-S is associated with the short-term prognosis of Chinese Han diabetic patients with stable CAD diagnosed by coronary angiography (CAG).

2 Methods

2.1 Subjects

Between June 2011 and March 2012, we prospectively enrolled 328 patients (73.3% males) aged 34–82 years (mean age 59.4 years) at our institute. All of the patients were diagnosed with type II diabetes and stable CAD, which was diagnosed by CAG. Patients without obstructive coronary lesions and patients with type I diabetes mellitus, acute coronary syndrome (ACS), significant hematologic disorders (white blood cell count \( \leq 3.5 \times 10^9/L \) or \( \geq 20 \times 10^9/L \)), infectious or inflammatory diseases, tumors, or severe liver and/or renal insufficiency were excluded from the study. All of the patients underwent extensive clinical, hematologic, and angiographic examinations to assess cardiac status. The patients were also asked about current or past history of traditional risk factors for CAD, including smoking habits, hypertension, hyperlipidemia, obesity, diabetes mellitus, previous stroke, peripheral vascular disease, family history of CAD, and non-cardiovascular diseases.

Hypertension was defined as repeated blood pressure measurement \( \geq 140/90 \) mmHg or current use of antihypertensive drugs. Diabetes mellitus was defined as fasting serum glucose concentrations of \( \geq 6.99 \) mmol/L at multiple times or current treatment with insulin or oral hypoglycemic agents. Hyperlipidemia was defined as fasting total cholesterol (TC) concentrations of \( \geq 5.2 \) mmol/L or triglyceride concentrations of \( \geq 1.7 \) mmol/L. CAD was defined as the presence of significant obstructive stenosis, of \( \geq 50\% \) of the vessel lumen diameter, in any of the main coronary arteries based on quantitative CAG images, which were interpreted by at least two independent senior interventional cardiologists. The severity of CAD was evaluated using the revised Gensini scoring system. Stent implantation, periprocedural medical treatment and care were performed according to standard criteria when there were indicative of revascularization. Post-interventional antiplatelet therapy consisted of clopidogrel and aspirin at standard dose. Drug-eluting stents were implanted in the majority of patients. The left ventricular ejection fraction was evaluated by the echocardiographer using the area length method according to the modified Simpson rule.

The study complied with the Declaration of Helsinki, and was approved by the ethical review board at Fuwai Hospital and National Center for Cardiovascular Diseases, Beijing, China. Written informed consent was obtained from all of the patients included in this study.

2.2 Measurements of biomarkers

Venous blood samples were obtained from each patient upon admission (baseline). Plasma TC and triglyceride concentrations were measured using enzymatic methods and HDL-C was determined using a direct method (Roche Diagnostics, Basel, Switzerland). Low-density cholesterol (LDL-C) was determined by Friedewald’s formula (if the fasting triglyceride concentration was \( < 3.39 \) mmol/L) or by ultracentrifugation. ApoA-I and apolipoprotein B (ApoB) were measured using an immunoturbidimetric method (Tina-quant; Roche Diagnostics) calibrated against the World Health Organization/International Federation of Clinical Chemistry reference standard SP3–07. The eHDL-S was calculated as the ratio of fasting HDL-C to apoA-I. Hemoglobin A1c (HbA1c) concentrations were measured using a
Tosoh G7 Automate HPLC Analyzer (TOSOH Bioscience, Japan). High-sensitivity C-reactive protein (hsCRP) concentrations were determined using an immunoturbidimetric method (Beckmann Assay 360; Beckmann, Brea, CA, USA). The median normal value for hsCRP is 0.8 mg/L, with 90% of normal values < 0.3 mg/L, and a lower detection limit of 0.2 mg/L. The inter-assay and intra-assay coefficients of variation were < 5%. All of the other biomarkers were measured using standard hematological and biochemical tests.

### 2.3 Follow-up and study endpoints

After discharge, the patients were followed up by telephone or clinical visits. The mean follow-up duration was 12 months. All of the patients were followed up; none of the patients was lost to follow-up. The prespecified clinical endpoints were defined as cardiac-related death or cardiac death, nonfatal myocardial infarction, revascularization, and re-hospitalization for acute coronary syndrome.

### 2.4 Statistical analysis

Quantitative variables are expressed as mean ± SD, and qualitative variables are expressed as the numbers of patients and percentages. Patients were divided into three groups according to tertiles of eHDL-S at baseline: low eHDL-S (< 0.71, n = 118), intermediate eHDL-S (0.71–0.79, n = 111), or high eHDL-S (> 0.79, n = 99). Continuous variables and categorical variables were analyzed using analysis of variance or χ² tests, as appropriate. Pearson’s and Spearman’s correlation tests were used to evaluate the relationships of eHDL-S with inflammatory biomarkers and the Gensini score. To determine whether eHDL-S could provide prognostic information for diabetic patients with stable CAD, we plotted event-free survival curves using the Kaplan–Meier methods and compared the curves using the log-rank test. The association between eHDL-S and clinical outcomes at 12 months was assessed using the Cox proportional hazards regression model with the forced entry method. In all analyses, P < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 19.0, SPSS, Chicago, IL, USA).

### 3 Results

#### 3.1 Baseline characteristics

The study population comprised 328 diabetic patients who underwent coronary angiography and were followed up for a mean duration of 12 months (range 20–448 days). The baseline demographic, clinical characteristics, and laboratory findings of the patients divided into tertiles of eHDL-S, which are presented in Table 1 and Figure 1. Of note, the inflammatory and oxidative stress biomarkers, especially the leukocyte count, uric acid, and Hba1c, were lower in patients with larger eHDL-S. The eHDL-S on admission was correlated with the fasting triglyceride concentrations. Similar proportions of patients in each of the three groups underwent secondary prevention and/or were implanted with drug-eluting stents. Regarding the severity of coronary lesions, although the Gensini score was greatest in the intermediate eHDL-S group, the χ² revealed a positive trend among the groups.

#### 3.2 Correlations between eHDL-S and inflammatory biomarkers, other lipids, and the Gensini score

According to the results of the Pearson’s and Spearman’s correlation tests, there were negative correlations among circulating Hba1c, leukocyte count, hsCRP, and fibrinogen (all P < 0.05; Table 2). As expected, the LDL-C concentrations were correlated with the Gensini scores. The χ² tests showed that the trends in Hba1c, leukocyte count, and Gensini scores among the three groups were significant, whereas the trend in fibrinogen and hsCRP were not significant (Figure 2). Although eHDL-S, HDL-C, and apoA-I were not uniformly correlated with inflammatory biomarkers, with some slight differences, the correlations between these variables and the Gensini scores were highly consistent.

#### 3.3 Utility of eHDL-S for predicting short-term prognosis

During the mean follow-up period of 12 months, 47 out of the 328 patients (14.3%) experienced an adverse clinical outcome. As showed in Figure 3, the incidence of the prespecified outcomes did was not significantly different among the three groups of patients. However, the Kaplan–Meier curves for the cumulative event-free survival revealed that the incidence of adverse outcomes was lower in the high eHDL-S group (Figure 4). Multivariate analysis using Cox proportional hazards regression model (Table 3) indicated that, other than the Gensini score and serum Hba1c, the eHDL-S was not independent associated with the overall incidence of the prespecified outcomes in this cohort of diabetic patients with stable CAD (hazard ratio (HR): 0.23, 95% confidence interval (95% CI): 0.01–11.24, P = 0.493).
### Table 1. Baseline characteristics of patients divided by tertiles of eHDL-S on admission.

| Variables                      | Low eHDL-S (< 0.71, n = 118) | Intermediate eHDL-S (0.71–0.79, n = 111) | High eHDL-S (> 0.79, n = 99) | P     |
|--------------------------------|-------------------------------|------------------------------------------|------------------------------|-------|
| Age, yrs                       | 58.1 ± 8.9                    | 59.8 ± 9.4                               | 60.4 ± 9.4                   | 0.148 |
| Male gender                    | 93 (78.8)                     | 79 (71.2)                                | 68 (68.7)                    | 0.209 |
| BMI, kg/m²                     | 25.9 ± 2.7                    | 24.9 ± 2.9                               | 25.6 ± 3.5                   | 0.067 |
| Current smoking                | 66 (55.9)                     | 64 (57.7)                                | 51 (51.5)                    | 0.666 |
| Hypertension                   | 80 (67.8)                     | 79 (71.2)                                | 61 (61.6)                    | 0.335 |
| Hyperlipidemia                 | 95 (80.5)                     | 90 (81.1)                                | 77 (77.8)                    | 0.830 |
| PVD                            | 1 (0.8)                       | 3 (2.7)                                  | 2 (2.0)                      | 0.600 |
| Prior stroke                   | 4 (3.4)                       | 6 (5.4)                                  | 3 (3.0)                      | 0.641 |
| Family history of CAD          | 13 (11.0)                     | 9 (8.1)                                  | 13 (13.1)                    | 0.492 |
| Laboratory test                |                               |                                          |                              |       |
| Leukocyte, 10⁹/L               | 6.8 ± 1.7                     | 6.5 ± 1.5                                | 6.0 ± 1.4                    | 0.002 |
| hsCRP, mg/L                    | 3.6 ± 3.8                     | 3.3 ± 4.6                                | 2.6 ± 3.8                    | 0.180 |
| Hemoglobin, g/L                | 138.9 ± 16.6                  | 138.6 ± 15.5                             | 137.2 ± 14.6                 | 0.699 |
| HbA1c, %                       | 7.1 ± 1.5                     | 6.9 ± 1.4                                | 6.6 ± 1.3                    | 0.029 |
| Platelet count, 10⁹/L          | 210.7 ± 60.9                  | 201.4 ± 54.3                             | 189.9 ± 50.3                 | 0.024 |
| Fibrinogen, g/L                | 3.2 ± 0.8                     | 3.1 ± 0.9                                | 3.0 ± 0.7                    | 0.126 |
| D-dimer, mg/dL                 | 0.3 ± 0.2                     | 0.4 ± 0.5                                | 0.5 ± 0.7                    | 0.032 |
| ALP, IU/L                      | 64.0 ± 18.0                   | 63.4 ± 17.9                              | 63.0 ± 20.2                  | 0.925 |
| Creatinine, mmol/L             | 77.8 ± 16.5                   | 77.0 ± 15.2                              | 74.0 ± 14.7                  | 0.185 |
| Uric acid, mmol/L              | 355.2 ± 80.5                  | 337.2 ± 75.5                             | 319.8 ± 77.3                 | 0.004 |
| NT-pro-BNP, fmol/mL            | 678.3 ± 486.8                 | 846.7 ± 780.2                            | 688.5 ± 406.2                | 0.057 |
| LVEF, %                        | 62.7 ± 7.3                    | 60.8 ± 9.5                               | 62.6 ± 8.0                   | 0.151 |
| Lipid profile                  |                               |                                          |                              |       |
| Triglycerides, mmol/L          | 2.3 ± 1.1                     | 1.6 ± 0.8                                | 1.2 ± 0.5                    | 0.000 |
| TC, mmol/L                     | 3.9 ± 1.0                     | 4.0 ± 0.9                                | 4.1 ± 1.1                    | 0.124 |
| LDL-C, mmol/L                  | 2.3 ± 0.8                     | 2.4 ± 0.8                                | 2.5 ± 0.9                    | 0.150 |
| HDL-C, mmol/L                  | 0.9 ± 0.2                     | 1.1 ± 0.2                                | 1.3 ± 0.3                    | 0.000 |
| Lipoprotein (a), mg/L          | 241.9 ± 259.0                 | 236.1 ± 240.9                            | 257.8 ± 233.1                | 0.805 |
| ApoA-I, g/L                    | 1.3 ± 0.2                     | 1.4 ± 0.3                                | 1.5 ± 0.3                    | 0.018 |
| ApoB, g/L                      | 1.1 ± 0.3                     | 1.0 ± 0.3                                | 1.1 ± 0.3                    | 0.109 |
| Gensini score                  | 26.8 ± 22.7                   | 30.2 ± 25.0                              | 20.8 ± 20.2                  | 0.012 |
| DES implantation               | 22 (18.6)                     | 26 (23.4)                                | 19 (19.2)                    | 0.639 |
| Medications                    |                               |                                          |                              |       |
| Aspirin                        | 116 (98.3)                    | 108 (97.3)                               | 96 (97.0)                    | 0.822 |
| Beta-blocker                   | 102 (86.4)                    | 89 (80.2)                                | 80 (80.8)                    | 0.383 |
| ACE-I/ARB                      | 33 (28.0)                     | 38 (34.2)                                | 14 (14.1)                    | 0.003 |
| Statin                         | 114 (96.6)                    | 108 (97.3)                               | 97 (98.0)                    | 0.914 |

Data are presented as mean ± SD or n (%). ACE-I: angiotensin converting enzyme inhibitors; ALP: alkaline phosphatase; Apo: apolipoprotein; ARB: angiotensin receptor blocker; BMI: body mass index; CAD: coronary artery disease; DES: drug-eluting stent; eHDL-S: estimated high density lipoprotein particle size; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycated hemoglobin A1c; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; PVD: peripheral vascular disease; TC: total cholesterol.
4 Discussion

To the best of our knowledge, this was the first study to determine whether eHDL-S is a useful predictor for adverse outcomes independent of other traditional prognostic variables of Chinese patients with type II diabetes and stable CAD in the modern era of revascularization and potent statin treatment. There are several important findings of our study. First, according to the baseline characteristics, patients with smaller eHDL-S had higher fasting triglyceride concentrations, consistent with the typical profile of lipid disorders in diabetic patients. Meanwhile, eHDL-S was negatively correlated with several biomarkers of inflammation and glucose metabolism, including the leukocyte count, fibrinogen, HbA1c, and Gensini score.

Table 2. Pearson’s and Spearman’s correlation between eHDL-S and inflammatory biomarkers and Gensini score.

| Variables     | Pearson’s correlations | Spearman’s correlations |
|---------------|------------------------|-------------------------|
| hs-CRP        | -0.099; *P = 0.073     | -0.293; *P = 0.000      |
| Leukocyte count | -0.192; *P = 0.000    | -0.202; *P = 0.000      |
| Fibrinogen    | -0.109; *P = 0.049     | -0.173; *P = 0.027      |
| HbA1c         | -0.125; *P = 0.024     | -0.09; *P = 0.152       |
| Gensini Score | -0.066; *P = 0.234     | -0.076; *P = 0.018      |

Apo: apolipoprotein; eHDL-S: estimated high-density lipoprotein particle size; HbA1c: glycosylated hemoglobin A1c; HDL-C: high density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; LDL-C: low density lipoprotein cholesterol.

Figure 2. (A): Correlations between eHDL-S on admission with hsCRP; (B): leukocyte count; (C): fibrinogen; (D): HbA1c; (E): Gensini score. eHDL-S: estimated high-density lipoprotein particle size; HbA1c: glycosylated hemoglobin A1c; hsCRP: high-sensitivity C-reactive protein.

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Figure 3. Correlations between eHDL-S on admission with clinical outcomes over a mean follow-up of 12 months. eHDL-S: estimated high-density lipoprotein particle size.

Figure 4. Kaplan–Meier curves for 12-month cumulative event-free survival according to tertiles of eHDL-S. eHDL-S: estimated high-density lipoprotein particle size.

Table 3 Cox proportional regression analysis of factors associated with the short-term risk of cardiovascular events

| Variable         | HR   | 95% CI    | P-value |
|------------------|------|-----------|---------|
| Age              | 0.98 | 0.95–1.02 | 0.226   |
| Sex              | 0.74 | 0.35–1.58 | 0.437   |
| BMI              | 1.05 | 0.96–1.16 | 0.300   |
| Current smoking  | 1.52 | 0.76–3.04 | 0.240   |
| Hypertension     | 0.85 | 0.43–1.70 | 0.651   |
| LVEF             | 1.00 | 0.97–1.04 | 0.841   |
| hsCRP            | 0.96 | 0.87–1.07 | 0.447   |
| Leukocyte count  | 1.01 | 0.83–1.23 | 0.905   |
| Fibrinogen       | 1.29 | 0.81–2.05 | 0.286   |
| HbA1C            | 1.38 | 1.14–1.67 | 0.001   |
| LDL-C            | 1.07 | 0.76–1.51 | 0.698   |
| eHDL-S           | 0.37 | 0.15–0.81 | 0.016   |
| Triglycerides    | 1.13 | 0.82–1.57 | 0.459   |
| Lipoprotein (a)  | 1.00 | 0.99–1.00 | 0.968   |
| Gensini score    | 1.01 | 1.00–1.03 | 0.043   |

BMI: body mass index; eHDL-S: estimated high-density lipoprotein particle size; HbA1c: glycated hemoglobin A1c; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction.

Although there has been considerable progress in this field, the interrelationships among HDL particle size, constituents, functionality, and inflammation are still not completely understood.[16–18] Nevertheless, several lines of evidence have established the basic theoretical foundation and the necessity for assessing HDL particle size. This evidence led to the introduction of a formula for estimating HDL particle size as the ratio of HDL-C to apoA-I rather than relying on direct measurements. Similar to a prior study that measured the actual HDL particle size, eHDL-S used here was negatively correlated with inflammatory markers, such as the leukocyte count, hsCRP, and HbA1c.[19] Moreover, unlike HDL-C and apoA-I, which were inversely associated with the Gensini scores, the eHDL-S displayed an inverse U-shaped relationship with the Gensini scores as an index of CAD severity.[20] According to a recent study, these results suggest that the protective effects of higher serum HDL-C or larger HDL particle size against CAD might be attenuated by greater inflammatory responses.[21,22] Numerous studies have demonstrated the cardioprotective effects of HDL-C or HDL particles.[23–28] In our study, although the Kaplan–Meier curves suggested that larger eHDL-S was associated with a lower incidence of adverse outcomes, the results of the multivariate analysis showed that the eHDL-S was not independently associated with the short-term prognosis of diabetic patients with stable CAD. There are some possible explanations for the present results. First, the eHDL-S might be influenced by differences in ethnicity, genetics, gender, age, inflammatory status, and metabolic disorders through changes in the concentrations and functionalities of HDL and apoA-I in patients of CAD. Because the cardioprotective effects of high HDL-C concentrations...
could be attenuated by serious inflammation, thus attenuating the secondary prevention of cardiovascular events. Additionally, the majority of patients in our study underwent percutaneous coronary intervention and 97.5% of patients received statin therapy for secondary prevention. Thus, the lipid profiles improved significantly after baseline, especially plasma LDL-C, and the specified outcomes were mainly related to revascularization. Furthermore, it must be stated that the eHDL-S, like HDL-C and apoA-I, is a surrogate marker for so-called “hard” cardiovascular endpoints. HDL particles show significant heterogeneity in terms of size, composition, and subtypes, might be influenced by genetic polymorphisms, and are modified by lifestyle interventions, it is effective separation and analytical methods are needed to accurately quantify HDL particles. Meanwhile, a prior study suggested that increases in apoA-I and the ratio of apoA-I to HDL-C, but not the actual HDL-C concentration, were associated with a reduced risk of cardiovascular events. Furthermore, results of the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study suggested that the number of HDL particles, but not particle size, might be a better marker of residual risk than chemically measured HDL-C or apoA-I in patients treated with a potent statin. Therefore, our study confirms and extends these earlier findings demonstrating a role of eHDL-S in predicting the short-term prognosis of diabetic patients with stable CAD.

There are several limitations of our study. First, the sample size was relatively small and all of the patients were Chinese Han. Second, the duration of follow-up was comparatively short, which might introduce some bias regarding the incidence of the cardiovascular outcomes. Finally, we did not include a control group with which to compare the predictive power of the number of size of HDL particles, or the eHDL-S.

In conclusion, the results of our study suggest that eHDL-S, the ratio of HDL-C to apoA-I, was associated with inflammatory biomarkers but it was not independently associated with the short-term prognosis of diabetic patients with stable CAD in the modern era of revascularization and potent statin therapy. Further studies with a larger sample size are needed to compare the predictive value of the number or size of HDL particles with eHDL-S in various patient populations and settings.

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