Journal of Geriatric Cardiology (2014) 11: 245–252

Research Article · Open Access ·

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 pre-specified outcome. According to the Kaplan–Meier analysis, the incidence of pre-specified 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): 0.01–11.24, 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.

J Geriatr Cardiol 2014; 11: 245–252. doi:10.11909/j.issn.1671-5411.2014.03.015

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.[2,7–9] 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

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Received: July 05, 2014 **Revised:** August 8, 2014
Accepted: August 30, 2014 **Published online:** September 18, 2014

rather than simply increasing the cholesterol cargo in the modern era of potent statin therapy.[11] 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.[4,12] 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.[13] 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.[14]

Although prior researches have demonstrated that the ratio of HDL-C to apoA-I is correlated with HDL particle size,[14] 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 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 ≥ 140/90 mmHg or current use of antihypertensive drugs. Diabetes mellitus was defined as fasting serum glucose concentrations of ≥ 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 ≥ 5.2 mmol/L or triglyceride concentrations of ≥ 1.7 mmol/L. CAD was defined as the presence of significant obstructive stenosis, of ≥ 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.[15] 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-1 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 χ^2 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 χ^2 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 χ^2 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/m^2	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, 10^9/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, 10^9/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, μmol/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: glycosylated 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.

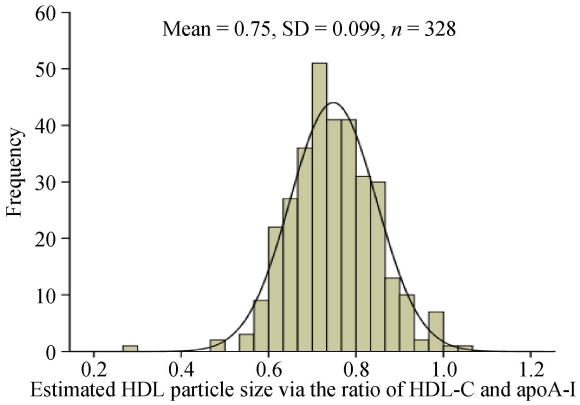

Figure 1. Distribution of eHDL-S in the study population. ApoA-I: apoprotein A-I; eHDL-S: the ratio of HDL-C to apoA-I; HDL-C: high-density lipoprotein cholesterol.

4 Discussion

To the best of our knowledge, this was the first study determine that 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,

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

Variables	eHDL-S	HDL-C	ApoA-I	LDL-C
Pearson's correlations				
hs-CRP	−0.099; *P* = 0.073	−0.228; *P* = 0.000	−0.226; *P* = 0.000	0.037; *P* = 0.504
Leukocyte count	−0.192; *P* = 0.000	−0.144; *P* = 0.009	−0.054; *P* = 0.327	0.075; *P* = 0.173
Fibrinogen	−0.109; *P* = 0.049	−0.171; *P* = 0.002	−0.148; *P* = 0.007	0.032; *P* = 0.565
HbA1c	−0.125; *P* = 0.024	−0.042; *P* = 0.445	−0.028; *P* = 0.614	0.061; *P* = 0.272
Gensini Score	−0.066; *P* = 0.234	−0.091; *P* = 0.100	−0.076; *P* = 0.168	0.136; *P* = 0.014
Spearman's correlations				
hs-CRP	−0.237; *P* = 0.000	−0.293; *P* = 0.000	−0.188; *P* = 0.001	0.067; *P* = 0.224
Leukocyte count	−0.180; *P* < 0.001	−0.193; *P* = 0.000	−0.088; *P* = 0.110	0.091; *P* = 0.101
Fibrinogen	−0.160; *P* < 0.004	−0.202; *P* = 0.000	−0.155; *P* = 0.005	−0.022; *P* = 0.694
HbA1c	−0.060; *P* = 0.004	−0.054; *P* = 0.329	−0.028; *P* = 0.611	0.040; *P* = 0.469
Gensini score	−0.059; *P* = 0.286	−0.079; *P* = 0.152	−0.073; *P* = 0.190	0.146; *P* = 0.008

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.

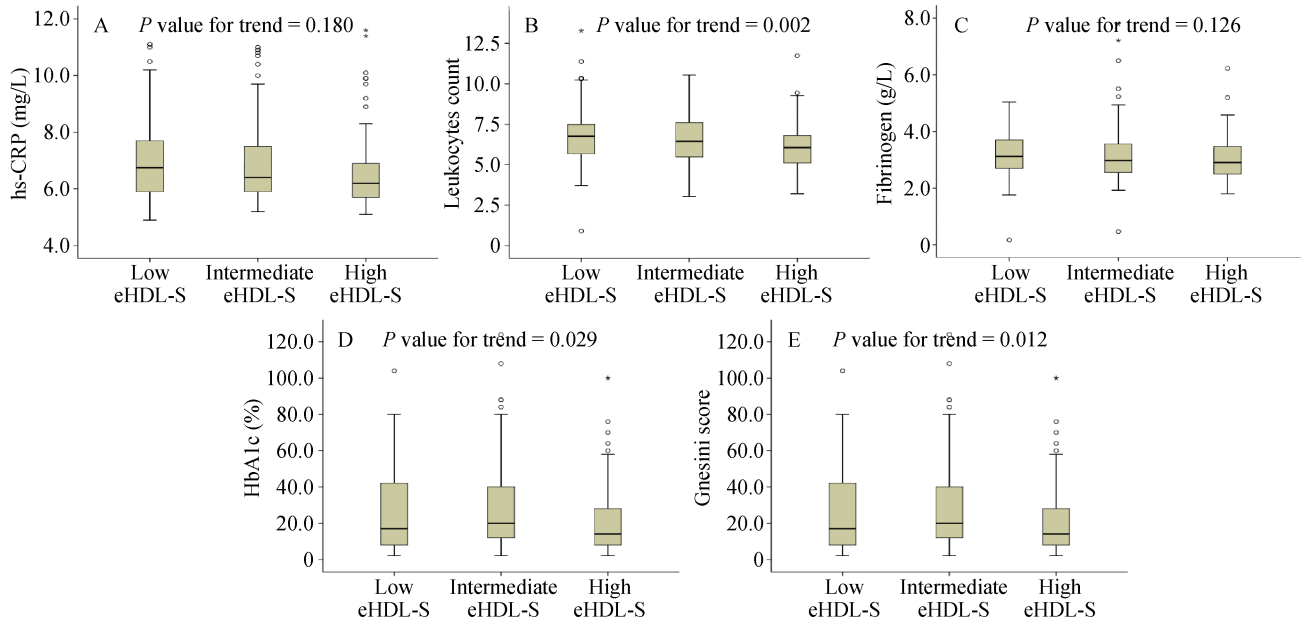

Figure 2. (A): Correlations between eHDL-S on admission with hsCRP; (B): leukocyte count; (C): fibrinogen; (D): HbA1c; (E): Gensini score. eHDL-S: estimated high-density lipoprotein particle size; HbA1c: glycosylated hemoglobin A1c; hsCRP: high-sensitivity C-reactive protein.

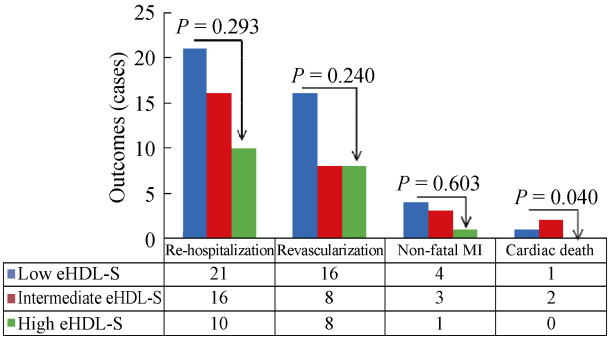

Figure 3. Correlations between eHDL-S on admission with clinical outcomes over a mean follow-up of 12 month. eHDL-S: estimated high-density lipoprotein particle size.

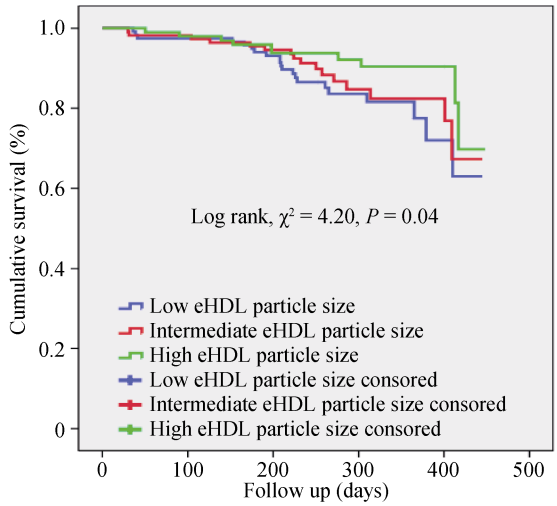

Figure 4. Kaplan–Meier curves for 12-month cumulative event-free survival according to tertiles of eHDL-S. eHDL-S: estimated high-density lipoprotein particle size.

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	0.27	0.01–11.24	0.493
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: glycosylated hemoglobin A1c; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction.

fibrinogen, hsCRP, and HbA1c. Second, the Gensini scores differed markedly among the three groups, and actually showed an inverse U-shaped curve with the eHDL-S. Third, although the incidence of the prespecified outcomes during the follow-up period was not significantly different among the three groups of patients, the Kaplan–Meier curves for cumulative event-free survival suggested that the incidence of early adverse events was lower in patients with high eHDL-S. However, multivariate analysis showed that the Gensini score and serum HbA1c were independently associated with the short-term prognosis of this cohort of diabetic patients with stable CAD, the eHDL-S was independently associated with these outcomes (HR: 0.23, 95% CI: 0.01–11.24, $P = 0.493$). Based on these findings, the current study not only confirmed the hypotheses proposed in earlier studies but also provided novel information regarding the role of the eHDL-S in predicting clinical outcomes in diabetic patients with stable CAD.

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 theoretic 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.[3,23–28] 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.[29] 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 particules.[30–32] 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.[26] 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.[11] 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.

References

1 Di Angelantonio E, Sarwar N, Perry P, *et al.* Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009; 302: 1993–2000.

2 Milwidsky A, Kivity S, Kopel E, *et al*. Time dependent changes in high density lipoprotein cholesterol and cardiovascular risk. *Int J Cardiol* 2014; 173: 295–299.

3 van de Woestijne AP, van der Graaf Y, Liem AH, *et al*. Low high-density lipoprotein cholesterol is not a risk factor for recurrent vascular events in patients with vascular disease on intensive lipid-lowering medication. *J Am Coll Cardiol* 2013; 62: 1834–1841.

4 Silbernagel G, Schottker B, Appelbaum S, *et al*. High-density lipoprotein cholesterol, coronary artery disease, and cardiovascular mortality. *Eur Heart J* 2013; 34: 3563–3571.

5 Kaur N, Pandey A, Negi H, *et al*. Effect of HDL-raising drugs on cardiovascular outcomes: A systematic review and meta-regression. *PLoS One* 2014; 9: e94585.

6 Kawamoto R, Tabara Y, Kohara K, *et al*. Increased high-density lipoprotein cholesterol is associated with a high prevalence of pre-hypertension and hypertension in community-dwelling persons. *Endocrine* 2012; 42: 321–328.

7 Wilkins JT, Ning H, Stone NJ, *et al.* Coronary heart disease risks associated with high levels of hdl cholesterol. *J Am Heart Assoc* 2014; 3: e000519.

8 de la Llera Moya M, McGillicuddy FC, Hinkle CC, *et al*. Inflammation modulates human hdl composition and function in vivo. *Atherosclerosis* 2012; 222: 390–394.

9 Yetukuri L, Soderlund S, Koivuniemi A, *et al*. Composition and lipid spatial distribution of hdl particles in subjects with low and high hdl-cholesterol. *J Lipid Res* 2010; 51: 2341–2351.

10 Schaefer EJ, Anthanont P, Asztalos BF. High-density lipoprotein metabolism, composition, function, and deficiency. *Curr Opin Lipidol* 2014; 25: 194–199.

11 Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation* 2013; 128: 1189–1197.

12 Leiviska J, Sundvall J, Alfthan G, *et al.* What have we learnt about high-density lipoprotein cholesterol measurements during 32 years? Experiences in finland 1980-2012. *Clin Chim Acta* 2013; 415: 118–123.

13 Mazer NA, Giulianini F, Paynter NP, *et al.* A comparison of the theoretical relationship between hdl size and the ratio of hdl cholesterol to apolipoprotein A-I with experimental results from the women's health study. *Clin Chem* 2013; 59: 949–958.

14 Chandra A, Rohatgi A. The role of advanced lipid testing in the prediction of cardiovascular disease. *Curr Atheroscler Rep* 2014; 16: 394.

15 Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol* 1983; 51: 606.

16 Landmesser U, von Eckardstein A, Kastelein J, *et al.* Increasing high-density lipoprotein cholesterol by cholesteryl ester transfer protein-inhibition: A rocky road and lessons

learned? The early demise of the dal-heart programme. *Eur Heart J* 2012; 33: 1712–1715.
17 Khera AV, Cuchel M, de la Llera-Moya M, *et al.* Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011; 364: 127–135.
18 Fisher EA, Feig JE, Hewing B, *et al*. High-density lipoprotein function, dysfunction, and reverse cholesterol transport. *Arterioscler Thromb Vasc Biol* 2012; 32: 2813–2820.
19 Laurila PP, Surakka I, Sarin AP, *et al.* Genomic, transcriptomic, and lipidomic profiling highlights the role of inflammation in individuals with low high-density lipoprotein cholesterol. *Arterioscler Thromb Vasc Biol* 2013; 33: 847–857.
20 Bilhorn KR, Luo Y, Lee BT, *et al*. High-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and cardiovascular disease in united states adults. *Am J Cardiol* 2012; 110: 1464–1467.
21 Tehrani DM, Gardin JM, Yanez D, *et al.* Impact of inflammatory biomarkers on relation of high density lipoprotein-cholesterol with incident coronary heart disease: Cardiovascular health study. *Atherosclerosis* 2013; 231: 246–251.
22 van der Steeg WA, Holme I, Boekholdt SM, *et al*. High- density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: Significance for cardiovascular risk: The ideal and epic-norfolk studies. *J Am Coll Cardiol* 2008; 51: 634–642.
23 Duffy D, Holmes DN, Roe MT, *et al.* The impact of high-density lipoprotein cholesterol levels on long-term outcomes after non-st-elevation myocardial infarction. *Am Heart J* 2012; 163: 705–713.
24 Lu Q, Tian G, Zhang Y, *et al*. Low HDL-C predicts risk and PCI outcomes in the Han Chinese population. *Atherosclerosis* 2013; 226: 193–197.
25 Acharjee S, Boden WE, Hartigan PM, *et al.* Low levels of high-density lipoprotein cholesterol and increased risk of cardiovascular events in stable ischemic heart disease patients: A post-hoc analysis from the courage trial (clinical outcomes utilizing revascularization and aggressive drug evaluation). *J Am Coll Cardiol* 2013; 62: 1826–1833.
26 Boekholdt SM, Arsenault BJ, Hovingh GK, *et al*. Levels and changes of hdl cholesterol and apolipoprotein A-I in relation to risk of cardiovascular events among statin-treated patients: A meta-analysis. *Circulation* 2013; 128: 1504–1512.
27 Xue H, Fu Z, Zhu H, *et al.* High-density lipoprotein cholesterol and risk of cardiovascular events in octogenarian patients with acute coronary syndrome: Long-term follow-up study. *Int J Cardiol* 2014; 174: 133–134.
28 Mackey RH, Greenland P, Goff DC, Jr., *et al.* High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: Mesa (multi-ethnic study of atherosclerosis). *J Am Coll Cardiol* 2012; 60: 508–516.
29 Elis A, Pereg D, Froom P, *et al.* HDL-C levels and revascularization procedures in coronary heart disease patients treated with statins to target LDL-C levels. *Clin Cardiol* 2011; 34: 572–576.
30 Jayaraman S, Cavigiolio G, Gursky O. Folded functional lipid-poor apolipoprotein a-i obtained by heating of high-density lipoproteins: Relevance to high-density lipoprotein biogenesis. *Biochem J* 2012; 442: 703–712.
31 Huggins GS, Papandonatos GD, Erar B, *et al.* Do genetic modifiers of high-density lipoprotein cholesterol and triglyceride levels also modify their response to a lifestyle intervention in the setting of obesity and type-2 diabetes mellitus?: The action for health in diabetes (look ahead) study. *Circ Cardiovasc Genet* 2013; 6: 391–399.
32 Sarbakhsh P, Mehrabi Y, Daneshpour MS, *et al.* Logic regression analysis of association of gene polymorphisms with low hdl: Tehran lipid and glucose study. *Gene* 2013; 513: 278–281.