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Distribution of High-Density Lipoprotein Subfractions and Hypertensive Status

A Cross-Sectional Study

Yan Zhang, MD, Sha Li, MD, Rui-Xia Xu, PhD, Yuan-Lin Guo, MD, Na-Qiong Wu, MD, Cheng-Gang Zhu, MD, Ying Gao, MD, Qian Dong, MS, Geng Liu, MS, Jing Sun, MS, and Jian-Jun Li, MD, PhD

Abstract: The exact mechanisms of hypertension contributing to atherosclerosis have not been fully elucidated. Although multiple studies have clarified the association with low-density lipoprotein (LDL) subfractions, uncertainty remains about its relationship with high-density lipoprotein (HDL) subfractions. Therefore, we aimed to comprehensively determine the relationship between distribution of HDL subfractions and hypertensive status.

A total of 953 consecutive subjects without previous lipid-lowering drug treatment were enrolled and were categorized based on hypertension history (with hypertension [n = 550] or without hypertension [n = 403]). Baseline clinical and laboratory data were collected. HDL separation was performed using the Lipoprint System.

Plasma large HDL-cholesterol (HDL-C) and large HDL percentage were dramatically lower whereas the small HDL-C and small HDL percentage were higher in patients with hypertension (all $P < 0.05$). The antihypertensive drug therapy was not associated with large or small HDL subfractions (on treatment vs not on treatment, $P > 0.05$; combination vs single drug therapy, $P > 0.05$). However, the blood pressure well-controlled patients have significantly lower small HDL subfraction ($P < 0.05$). Moreover, large HDL-C and percentage were inversely whereas small HDL percentage was positively associated with incident hypertension after adjusting potential confounders (all $P < 0.05$). In the multivariate model conducted in patients with and without hypertension separately, the cardio-protective value of large HDL-C was disappeared in patients with hypertension (OR 95%CI: 1.011 [0.974–1.049]).

The distribution of HDL subfractions is closely associated with hypertensive status and hypertension may potentially impact the cardio-protective value of large HDL subfraction.

Abbreviations: CAD = coronary artery disease, CI = confidence interval, DM = diabetes mellitus, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein-cholesterol, LDL = low-density lipoprotein, LDL-C = low-density lipoprotein-cholesterol, TC = total cholesterol, TG = triglyceride.

INTRODUCTION

Hypertension is a crucial independent risk factor for coronary artery disease (CAD) for all populations. According to the epidemiological reports, nearly one-fourth of the adult in the United States has hypertension based on the current definition.[1] In the Chinese population, the prevalence of hypertension is also increased sharply in recent years, reaching a prevalence of 34% in 2010.[2] Currently, hypertension has become a major public health issue in the world. However, the exact mechanisms contributing to atherosclerosis have not been fully elucidated.

Atherosclerosis, the precursor of CAD, is a very complex and multifactorial process. Besides the widely recognized inflammatory background, there is growing evidence suggesting an immunologic status,[3] especially the links between allergy and vascular or thrombotic disorders [4] as well as the mammalian target of rapamycin (mTOR) pathway, [5] also play important roles in the progression of atherosclerosis. Although these new evidences have been proposed, current perspectives still regard dyslipidemia as the leading cause of atherosclerosis. Actually, hypertension often clusters with dyslipidemia, such as higher concentrations of low-density lipoprotein (LDL)-cholesterol (LDL-C) or lower high-density lipoprotein (HDL)-cholesterol (HDL-C),[6–8] which have been supposed as major mediators of atherosclerosis. Recently, lipoprotein subfractions have been proposed to be more accurately capture the atherogenic properties than the concentrations of cholesterol contained in lipoproteins.[9,10] During the past decades, the relationship between hypertension and LDL subfractions, especially with the small dense LDL or the particle size, has been reported by multiple clinical studies.[11–13] It has, hence, suggested that hypertension may contribute to atherosclerosis with associated risk factors that influence LDL subfractions and particle size. In fact, HDL particle is more heterogeneous in its size and composition than LDL.[14] However, few studies investigated the association of hypertension with HDL subfractions till now. Although it has been reported that small HDL particles

had greater risk, whereas large HDL particles had lower risk of incident hypertension during 8 years follow-up,[15] the study was conducted in initially healthy women and could not representative of the whole population. In addition, no data is currently available regarding the relationship between HDL subfractions and hypertensive status till now.

Thus, the present study was initiated to comprehensively test the association of HDL subfractions and hypertensive status including the presence of hypertension, antihypertensive therapy, and blood pressure control and further explored the interplay between hypertension and HDL subfractions in relation to CAD susceptibility.

METHODS

Study Design and Population

The study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (FuWai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Each participant provided written, informed consent before enrollment.

A total of 4106 patients were hospitalized in our division from October 2012 to January 2015. Because the lipid-lowering medications have potential impact on HDL subfractions, confounding the association with hypertension or other clinical characteristics, we selected 982 consecutive patients who were not treated with lipid-lowering drugs. Additionally, patients with significant hematologic disorders, infectious or systemic inflammatory disease, thyroid dysfunction, severe liver and/or renal insufficiency, acute coronary syndrome (ACS), heart failure (HF) (left ventricular ejection fraction < 45%), arrhythmia, or with malignant tumors were excluded from the current analysis. Therefore, we enrolled 953 eligible patients for the present study. The flowchart of this analysis is presented in Figure 1.

The definition of traditional risk factors has been described in our previous studies.[16] Hypertension was defined as repeated blood pressure measurements ≥ 140/90 mm Hg (at least 2 times in different environments) or currently taking antihypertensive drugs. Blood pressure was measured through a mercury sphygmomanometer after checking for the device accuracy. Diabetes

mellitus (DM) was defined as a fasting serum glucose level ≥ 126 mg/dL in multiple determinations, and/or the current use of medication for diabetes. Dyslipidemia was defined by medical history or fasting total cholesterol (TC) ≥200 mg/dL or triglyceride (TG) ≥150 mg/dL and/or HDL-C < 40 mg/dL (for male) or < 50 mg/dL (for female). The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Obesity was defined as patients with BMI ≥ 30 kg/m^2. Patients with a reported smoking habit of at least 1 cigarette per day on admission were classified as current smokers.

Biochemical Examinations

After hospitalized, fasting blood samples were collected for all enrolled subjects. The automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan) was used to test the levels of lipid profiles. The levels of TC, TG, apolipoprotein AI (apo AI), and apo B levels were measured using commercially available kits. The HDL-C and LDL-C levels were analyzed by the selective solubilization method (Determiner L HDL, LDL test kit Kyowa Medex, Tokyo).

HDL Subfraction Analysis

The HDL subfractions were determined electrophoretically by the use of high-resolution 3% polyacrylamide gel tubes and the Lipoprint System (Lipoprint HDL System Quantimetrix Corporation, Redondo Beach, CA) as our previously described.[17,18] By this method, the HDL was divided into 10 subfractions. The large HDL particles included subfraction 1 to 3, the medium HDL particles comprised of subfraction 4 to 7, and the small HDL particles covered subfraction 8 to 10.

Statistical Analysis

The data were expressed as the mean ± SD for the continuous normally distributed variables and the number (percentage) for the categorical variables. The Student *t* tests were used for the comparisons between 2 groups of continuous parameters and the chi-square tests were performed for the categorical variables. Univariate and multivariate logistic regression analyses were used for determining the association of HDL subfractions with incident hypertension as well as with CAD
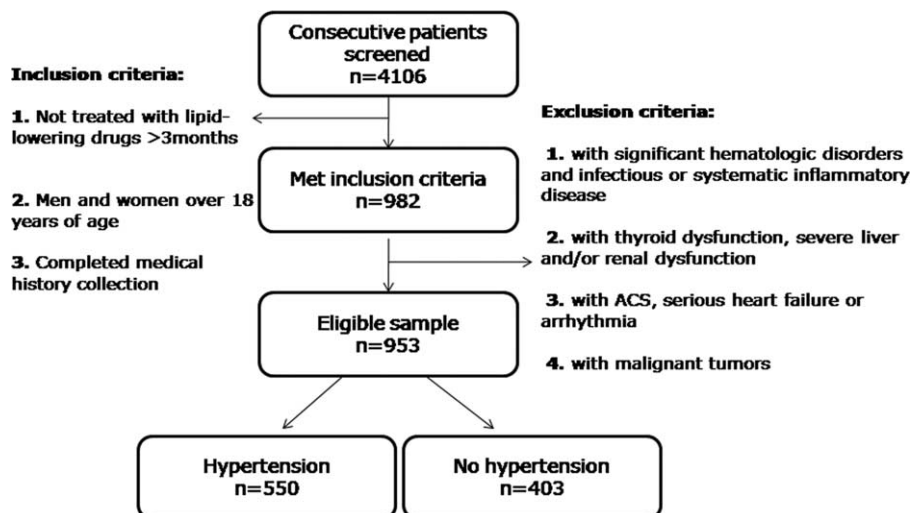

FIGURE 1. The flowchart of this study. The inclusion and exclusion criteria of population enrollment are shown.

susceptibility in patients with or without hypertension separately. A *P* value of <0.05 was considered statistically significant. Statistical studies were carried out with the SPSS program (version 19.0, SPSS, Chicago, IL).

RESULTS

Summary of Study Subjects

Selected characteristics of the study population at baseline are shown in Table 1, both overall and according to the incident hypertension. Overall, 953 patients with 606 (63.6%) men and at the mean age of 56.2 years were studied. The cholesterol levels of large, medium, and small HDL were 13.18 ± 6.80 mg/dL, 20.43 ± 5.75 mg/dL, and 8.44 ± 3.02 mg/dL, respectively.

The incident hypertension predominated among the enrolled subjects (n = 550). Patients with hypertension were more likely to be old, to have higher BMI, and to have a higher prevalence of DM, dyslipidemia, and eventually CAD, and to have higher left ventricular diastolic diameter, interventricular septal thickness, and left ventricular posterior wall thickness compared with those without hypertension. Although the mean baseline HDL-C levels were similar, the HDL subfraction

measures were significantly differed. In particular, the hypertensive populations have lower large HDL (large HDL-C: 12.51 ± 5.87 vs 14.09 ± 7.80, $P = 0.001$; large HDL percentage: 29.36 ± 7.81 vs 31.50 ± 8.47, $P < 0.001$) but higher small HDL subfractions (small HDL-C: 8.66 ± 3.12 vs 8.14 ± 2.86, $P = 0.01$; small HDL percentage: 21.35 ± 6.23 vs 19.68 ± 6.32, $P < 0.001$).

HDL Subfractions According to AntiHypertensive Drug Therapy

As indicated in Table 2, among the hypertensive patients, 319 (58.0%) applied antihypertensive treatment at least 3 months before entering the study, among which 193 (60.5%) used single drug therapy, and 126 (39.5%) patients were on drug combination therapy. In addition, 231 (42.0%) patients had life style intervention and were not on drug therapy. Obviously, the plasma HDL-C levels were markedly decreased in patients who were on drug combination therapy. Interestingly, among HDL subfractions, both the large and small HDL subfractions remained the similar level (both $P > 0.05$) except the decreased medium HDL percentage compared with the single drug therapy ($P < 0.05$). In addition, no significant difference was

TABLE 1. Baseline Characteristics

Characteristics	Total (n = 953)	Incident Hypertension (n = 550)	No Hypertension (n = 403)	*P* Value
Age (years)	56.2 ± 10.5	57.9 ± 10	54.0 ± 10.8	**<0.001**
Male sex, n (%)	606 (63.6)	356 (64.7)	250 (62.0)	0.393
Body mass index, (kg/m^2)	25.6 ± 3.4	26.23 ± 3.42	24.77 ± 3.28	**<0.001**
Current smoking status, n (%)	374 (39.2)	221 (40.2)	153 (38.0)	0.439
History of diabetes, n (%)	201 (21.1)	151 (27.5)	50 (12.4)	**<0.001**
History of dyslipidemia, n (%)	583 (61.2)	361 (65.6)	222 (55.1)	**0.001**
History of CAD, n (%)	620 (65.1)	402 (73.0)	218 (54.2)	**<0.001**
Resting heart rate (bpm)	71 ± 11	71 ± 11	71 ± 10	0.740
Systolic blood pressure (mm Hg)	128 ± 17	134 ± 17	112 ± 13	**<0.001**
Diastolic blood pressure (mm Hg)	79 ± 11	82 ± 12	75 ± 9	**<0.001**
Left ventricular diastolic diameter (mm)	47.5 ± 4.9	48 ± 5	47 ± 5	**<0.001**
Left ventricular ejection fraction (%)	65.6 ± 6.8	65.8 ± 6.4	65.4 ± 7.2	0.443
Interventricular septal thickness (mm)	0.97 ± 0.14	0.99 ± 0.13	0.94 ± 0.13	**<0.001**
Left ventricular posterior wall thickness (mm)	0.94 ± 0.12	0.96 ± 0.12	0.91 ± 0.12	**<0.001**
Traditional lipid profiles				
TC (mg/dL)	189.14 ± 41.42	187.43 ± 38.28	191.47 ± 45.30	0.136
TG (mg/dL)	172.32 ± 126.03	181.02 ± 130.70	160.44 ± 118.49	**0.013**
HDL-C (mg/dL)	41.99 ± 12.57	41.34 ± 12.06	42.88 ± 13.21	0.062
LDL-C (mg/dL)	126.37 ± 38.62	124.31 ± 34.96	129.18 ± 43.00	0.054
ApoA1 (mg/dL)	131.53 ± 29.58	132.39 ± 30.28	130.36 ± 28.60	0.296
ApoB (mg/dL)	103.41 ± 28.34	102.94 ± 26.39	104.04 ± 30.81	0.563
HDL subfractions				
Large HDL-C (mg/dL)	13.18 ± 6.80	12.51 ± 5.87	14.09 ± 7.80	**0.001**
Large HDL (%)	30.27 ± 8.16	29.36 ± 7.81	31.50 ± 8.47	**<0.001**
Medium HDL-C (mg/dL)	20.43 ± 5.75	20.27 ± 5.92	20.66 ± 5.52	0.301
Medium HDL (%)	49.02 ± 4.75	49.17 ± 4.59	48.81 ± 4.95	0.237
Small HDL-C (mg/dL)	8.44 ± 3.02	8.66 ± 3.12	8.14 ± 2.86	**0.010**
Small HDL (%)	20.64 ± 6.32	21.35 ± 6.23	19.68 ± 6.32	**<0.001**

Data are shown as mean $\pm$ SD or n (%). The bold values indicate statistical significance. Apo = apolipoprotein, CAD = coronary artery disease, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, SD = standard deviation, TC = total cholesterol, TG = triglyceride.

TABLE 2. The Impact of Antihypertensive Drug Numbers on HDL Subfractions

	On Treatment				Not On Treatment	
	Total (n = 319)	1 Drug (n = 193)	≥2 Drugs (n = 126)	P Value[*]	(n = 231)	P Value[†]
HDL-C (mg/dL)	40.95 ± 12.04	42.10 ± 13.35	39.20 ± 9.49	**0.024**	41.88 ± 12.09	0.372
HDL subfractions						
Large HDL-C (mg/dL)	12.54 ± 6.02	12.96 ± 6.41	11.90 ± 5.33	0.113	12.47 ± 5.67	0.886
Large HDL (%)	29.58 ± 7.84	29.60 ± 7.99	29.55 ± 7.63	0.963	29.06 ± 7.79	0.445
Medium HDL-C (mg/dL)	20.12 ± 6.14	20.77 ± 6.98	19.11 ± 4.40	**0.010**	20.49 ± 5.60	0.469
Medium HDL (%)	49.01 ± 4.63	21.07 ± 5.94	21.47 ± 6.08	0.902	49.41 ± 4.52	0.312
Small HDL-C (mg/dL)	8.54 ± 2.96	8.72 ± 3.18	8.25 ± 2.58	0.170	8.82 ± 3.32	0.290
Small HDL (%)	21.23 ± 5.99	21.07 ± 5.94	21.47 ± 6.08	0.558	21.52 ± 6.55	0.593

Data are expressed as mean ± SD. The bold values indicate statistical significance. HDL = high-density lipoprotein, HDL-C = high-density lipoprotein-cholesterol.

[*] P value indicated the difference between ≥2 drugs versus 1 drug.

[†] P value indicated the difference between not on treatment versus on treatment.

found in patients with or without antihypertensive drug therapy with regard to the HDL subfractions (all $P > 0.05$).

Besides that, among 319 patients on hypertensive drug therapy, 134 (42.0%) used angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, 143 (44.8%) used β-blockers, and 183 (57.4%) used calcium channel blockers. However, we did not observe statistical significance in patients who took either drug regarding plasma levels of all the HDL subfractions (all $P > 0.05$, Table 3).

Finally, a total of 271 (49.3%) patients have their blood pressure successfully controlled (systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg). Although the plasma HDL-C levels were not significantly changed compared with the uncontrolled patients, the small HDL subfractions including small HDL-C and small HDL percentage were significantly decreased in patients with well-controlled blood pressure ($8.21 ± 3.02$ vs $9.11 ± 3.16$, $P = 0.001$; $20.78 ± 6.19$ vs $21.93 ± 6.24$, $P = 0.031$, respectively, Table 4).

Association of HDL Subfractions With Incident Hypertension

After observed the interesting association of HDL subfractions with hypertension and antihypertensive therapy, logistic regression analysis was performed in the present study. In unadjusted analysis (Fig. 2A), no significant relationship was found with regard to traditional lipid profiles including HDL-C, TC, LDL-C, apoA1, and apoB except the positive association between TG and hypertension susceptibility (OR 95%CI: 1.002 [1.000−1.003]). Specifically, among different HDL subfractions, large HDL measures were inversely (large HDL-C: OR 95%CI 0.966 [0.947−0.985]; large HDL percentage: OR 95%CI 0.968 [0.953−0.984]) whereas small HDL measures were positively (small HDL-C: OR 95%CI 1.060 [1.014−1.108]; small HDL percentage: OR 95%CI 1.044 [1.022−1.066]) associated with prevalent hypertension.

Additionally, we next investigated the gender difference with regard to the presence of hypertension and the distribution of HDL subfractions. As a result, we observed that the hypertension susceptibility was similar between men and women ($P = 0.414$, supplemental Figure 1, http://links.lww.com/MD/A484). Meanwhile, the women had relatively higher HDL

subfractions especially large and medium HDL-C ($P < 0.001$, both in the whole population and hypertensive patients, supplemental Figure 2, http://links.lww.com/MD/A484). Therefore, in the following multivariate logistic regression analysis, we further adjusted for gender as well as other potential risk factors covering age, obesity, smoking, alcohol, DM, dyslipidemia, and antihypertensive drugs. Finally, we found that large HDL-C (OR 95%CI 0.957 [0.934−0.981]) and large HDL percentage (OR 95%CI 0.962 [0.942−0.983]) remained negatively whereas small HDL percentage (OR 95%CI 1.047 [1.020−1.074]) was positively related to hypertension susceptibility (Fig. 2B).

Relationship of HDL Subfractions With CAD Susceptibility According to Hypertension

To reveal whether the presence of hypertension influenced the association between HDL subfractions and the occurrence of CAD, patients were classified into 2 groups due to the incident hypertension. As presented in Table 5, for those without hypertension, large HDL-C levels were negatively associated with CAD susceptibility in univariate logistic regression analysis (OR 95%CI 0.962 [0.936−0.989]), and this association remained significant even after fully adjusting for potential risk factors, including age, gender, obesity, smoking, alcohol, DM, dyslipidemia, and antihypertensive drugs (OR 95%CI 0.962 [0.932−0.993]). In addition, the relationship between medium HDL subfraction and CAD susceptibility was unstable (medium HDL-C: OR 95%CI 0.945 [0.909−0.982]; medium HDL percentage: OR 95%CI 1.060 [1.011−1.111]) in the fully adjusted analysis. Additionally, small HDL-C was not related to CAD susceptibility after adjusting for potential confounders (OR 95%CI 0.924 [0.853−1.000]). However, for those with hypertension, all of the HDL subfractions were not associated with CAD incidence in univariate and multivariate logistic regression analysis (all $P > 0.05$).

DISCUSSION

To date, there is a paucity of studies, which are primarily aimed to determine the association of dyslipidemia including low HDL-C, hypertriglyceridemia, and even small dense LDL subfractions with hypertension.[8,18] Our study involving 953 patients who were not treated with lipid-lowering drugs is the

TABLE 3. Association Between Antihypertensive Drug Type and HDL Subfractions

	ACEI/ARB			β-Blockers			CCB		
	Yes (n = 134)	No (n = 185)	P Value	Yes (n = 143)	No (n = 176)	P Value	Yes (n = 183)	No (n = 136)	P Value
HDL-C (mg/dL)	40.75 ± 10.97	41.10 ± 12.79	0.800	40.30 ± 11.38	41.48 ± 12.57	0.386	40.06 ± 11.35	42.15 ± 12.86	0.125
HDL subfractions									
Large HDL-C (mg/dL)	12.37 ± 5.86	12.66 ± 6.16	0.670	12.38 ± 6.16	12.68 ± 5.93	0.660	12.17 ± 5.34	13.04 ± 6.82	0.216
Large HDL (%)	29.16 ± 8.03	29.88 ± 7.70	0.418	29.62 ± 7.64	29.55 ± 8.02	0.936	29.71 ± 7.61	29.41 ± 8.16	0.737
Medium HDL-C (mg/dL)	20.38 ± 5.89	19.92 ± 6.31	0.513	19.53 ± 5.19	20.59 ± 6.79	0.125	19.55 ± 5.78	20.88 ± 6.54	0.057
Medium HDL (%)	49.46 ± 4.78	48.67 ± 4.51	0.132	48.71 ± 4.23	49.24 ± 4.93	0.311	48.94 ± 4.40	49.09 ± 4.94	0.777
Small HDL-C (mg/dL)	8.52 ± 3.18	8.55 ± 2.80	0.944	8.38 ± 2.45	8.66 ± 3.32	0.411	8.45 ± 2.95	8.65 ± 2.98	0.565
Small HDL (%)	20.95 ± 6.15	21.43 ± 5.88	0.483	21.67 ± 6.17	20.86 ± 5.83	0.229	21.32 ± 5.81	21.10 ± 6.25	0.740

Data are expressed as mean ± SD. The bold values indicate statistical significance. ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein-cholesterol.

TABLE 4. Relation of HDL Subfractions to Status of Blood Pressure Control

	Uncontrolled (n = 271)	Controlled (n = 279)	P Value
HDL-C (mg/dL)	42.15 ± 11.74	40.55 ± 12.33	0.120
HDL subfractions			
Large HDL-C (mg/dL)	12.65 ± 6.04	12.38 ± 5.71	0.598
Large HDL (%)	29.00 ± 8.13	29.71 ± 7.49	0.289
Medium HDL-C (mg/dL)	20.62 ± 5.74	19.93 ± 6.07	0.173
Medium HDL (%)	48.86 ± 4.81	49.48 ± 4.34	0.119
Small HDL-C (mg/dL)	9.11 ± 3.16	8.21 ± 3.02	**0.001**
Small HDL (%)	21.93 ± 6.24	20.78 ± 6.19	**0.031**

Data are expressed as mean ± SD. The bold values indicate statistical significance. HDL = high-density lipoprotein, HDL-C = high-density lipoprotein-cholesterol

first to document the complex relationship between distribution of HDL subfractions and hypertensive status. Specifically, we found that hypertensive patients have significantly lower large HDL subfractions and higher small HDL subfractions, which were not affected by antihypertensive drugs. Patients with successfully controlled blood pressure have markedly lower small HDL subfractions. Large HDL subfractions were associated with lower risk whereas small HDL subfractions were related to higher risk of hypertension, and this relationship remained significant after adjusting for age, gender, and other potential confounders. The presence of hypertension may have potential impact on the cardio-protective value of large HDL subfractions. Our data may provide additive information to hypertension and atherosclerosis.

To date, postulated mechanisms for the relationship between hypertension and atherosclerosis have not been fully clarified. As indicated previously, although hypertension represents an independent risk factor for CAD, and evidence indicated that there were interactions with other recognized cardiovascular risk factors and could result in a multiplicative increase in risk for cardiovascular events.[19] Therefore, multiple studies investigated the relationship between hypertension and lipid profiles and found that traditional lipid measures such as lower HDL-C and higher TG were associated with increased risk.[8,20] Our study confirms these findings for TG in this group of patients who were not received lipid-lowering drug therapy, although we did not find the association between HDL-C and the prevalence of hypertension. However, the HDL particles are highly heterogeneous and the subfractions of HDL particles may be more valuable in predicting atherosclerosis. In spite of the exact role of different HDL subfractions in the pathogenesis of atherosclerosis remained in debate,[21,22] multiple studies reported that highly lipidated large HDL subfraction was inversely associated with CAD risk.[9,23,24] Hence, we thoroughly investigated HDL subfractions and hypertensive status in the present analysis.

In consistent with previous reports, we observed that large HDL subfractions were associated with lower risk of hypertension whereas small HDL subfractions were related to higher
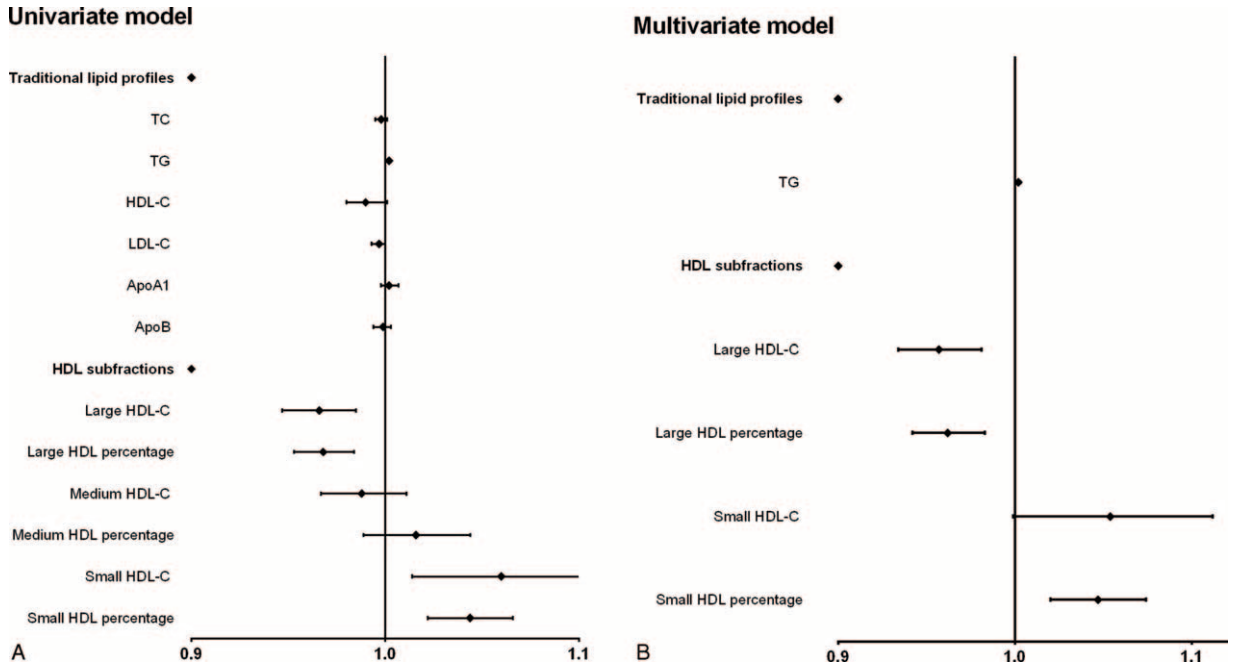
FIGURE 2. Traditional lipid profiles and HDL subfractions in relation to the incidence of hypertension. The multivariate model was adjusted for age, gender, obesity, smoking, alcohol, diabetes, dyslipidemia, and antihypertensive drugs. Apo = apolipoprotein, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, TC = total cholesterol, TG = triglyceride.

TABLE 5. The Predictive Value of Lipoprotein Subfractions to Incident CAD by Hypertension

	Univariate		Multivariate	
	OR (95%CI)	*P* Value	OR (95%CI)	*P* Value
With hypertension (n = 550)				
HDL-C (mg/dL)	1.008 (0.992–1.024)	0.351	1.011 (0.993–1.030)	0.235
HDL subfractions				
Large HDL-C (mg/dL)	1.012 (0.979–1.045)	0.490	1.011 (0.974–1.049)	0.573
Large HDL (%)	1.007 (0.983–1.032)	0.567	1.001 (0.973–1.029)	0.956
Medium HDL-C (mg/dL)	1.023 (0.988–1.059)	0.201	1.033 (0.994–1.073)	0.102
Medium HDL (%)	1.007 (0.966–1.049)	0.750	1.013 (0.969–1.059)	0.573
Small HDL-C (mg/dL)	1.003 (0.943–1.066)	0.930	1.022 (0.956–1.094)	0.520
Small HDL (%)	0.981 (0.952–1.011)	0.219	0.988 (0.956–1.021)	0.478
Without hypertension (n = 403)				
HDL-C (mg/dL)	0.972 (0.956–0.988)	**0.001**	0.973 (0.954–0.991)	**0.004**
HDL subfractions				
Large HDL-C (mg/dL)	0.962 (0.936–0.989)	**0.005**	0.962 (0.932–0.993)	**0.017**
Large HDL (%)	0.979 (0.956–1.002)	0.072	0.977 (0.950–1.005)	0.111
Medium HDL-C (mg/dL)	0.945 (0.909–0.982)	**0.004**	0.950 (0.909–0.993)	**0.022**
Medium HDL (%)	1.052 (1.010–1.096)	**0.014**	1.060 (1.011–1.111)	**0.017**
Small HDL-C (mg/dL)	0.924 (0.862–0.992)	**0.028**	0.924 (0.853–1.000)	0.050
Small HDL (%)	1.008 (0.977–1.040)	0.601	1.005 (0.968–1.042)	0.809

Logistic regression analysis was performed. Data are shown as odds ratios (OR) with 95% confidence intervals (95%CI). The bold values indicate statistical significance. The multivariate model was adjusted for age, gender, obesity, smoking, alcohol, diabetes, dyslipidemia, and antihypertensive drugs. CAD = coronary artery disease, CI = confidence interval, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein-cholesterol, OR = odds ratio.

hypertensive risk.[15] The risk of CAD in the patient with hypertension was greatly reduced with effective antihypertensive therapy. Besides the blood pressure lowering effect, whether there are any effects on HDL subfractions have not been reported yet. In the current analysis, we found that although the HDL-C levels were significantly reduced, the large and small HDL subfractions were not changed in patients with combination therapy than single therapy. However, patients with successfully controlled blood pressure have significantly lower small HDL subfractions. From this perspective, our study may provide more evidence for the benefit of blood control in hypertension management.

Based on the current guidelines, lower systolic blood pressure values may be associated with better stroke outcomes, but the evidence for CAD outcomes is equivocal.[25] Numerous data from clinical trials showed a J-shaped relationship between blood pressure and the primary cardiovascular outcomes.[26] One theoretically possible explanation was that further reduction of diastolic blood pressure could reduce coronary blood flow and translate to an upturn in the incidence of coronary events. However, this issue remains unresolved. In light of the interesting relationship of HDL subfractions with hypertensive status, we compared the protective value of large HDL subfractions on CAD susceptibility in patients with or without hypertension separately in the current analysis. As a result, we found that the large HDL-C was not related to CAD susceptibility in patients with hypertension while inversely associated with CAD in patients without hypertension. Although the small HDL subfractions were lower in patients with successfully controlled blood pressure, the cardio-protective value of large HDL subfractions were disappeared in hypertensive status in the current analysis. Therefore, our data may partly explain the undeclined CAD outcomes by intensive blood control.

There were several limitations of the present study. First, this was a single center study. The conclusions need to be testified by large-scale studies in the future. Second, the HDL subclassification was performed by the Lipoprint system, and the results should be testified by other methodologies. Finally, the cross-sectional design was another limitation. Therefore, the results should be evaluated with some degree of caution. Longitudinal follow-up and interventional studies were necessary in the following investigations.

In summary, the hypertensive patients had relatively lower large HDL subfractions whereas higher small HDL subfractions. For subjects with hypertension, successful blood pressure control is more relevant to lower small HDL subfractions irrespective what methods (lifestyle intervention, single or combination drug therapy) were applied in clinical practice; large and small HDL subfractions were independently associated with incident hypertension in a negative or positive manner respectively; hypertension may have potential impact on the cardio-protective effect of large HDL subfractions.

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