Association between high-density lipoprotein cholesterol levels and major adverse cardiovascular events in patients who underwent coronary computed tomography angiography: FU-CCTA Registry

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Short title: Coronary artery disease and intensive lowering of blood pressure

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Abstract

Background: It is unclear whether higher levels of serum high-density lipoprotein cholesterol (HDL-C) prevent major adverse cardiovascular events (MACE).

Methods: We prospectively evaluated 501 patients who had undergone coronary computed tomography angiography at Fukuoka University Hospital (FU-CCTA registry) and either were clinically suspected of having coronary artery disease (CAD) or had at least one cardiovascular risk factor with a follow-up of up to 5 years. The primary endpoint was MACE (cardiovascular death, ischemic stroke, acute myocardial infarction and coronary revascularization). The patients were divide into tertiles according to the HDL-C level: 47 mg/dl ≥ HDL-C level [n=167, lower HDL-C level (L-HDL)], 58 mg/dl ≥ HDL-C level ≥ 48 mg/dl [n=167, middle HDL-C level (M-HDL)] and HDL-C level ≥ 59 mg/dl [n=167, higher HDL-C level (H-HDL)] groups.

Results: There were significant differences in %CAD among the L-HDL (62 %), M-HDL (55 %) and H-HDL (47 %) groups. Unexpectedly, there was no difference in %MACE between M-HDL (2 %) and H-HDL (8 %), although %MACE in M-HDL was significantly lower than that in L-HDL (9 %) ($p<0.05$). By a multivariate logistic regression analysis, MACE in H-HDL-C was independently associated with diabetes mellitus (DM) ($p=0.03$). A Kaplan-Meier curve according to the HDL subgroup indicated that M-HDL, not H-HDL, enjoyed the greatest freedom from MACE among the 3 groups (log-rank test: $p=0.047$). Finally, the results of a Cox regression model indicated that L-HDL [hazard ratios (HR): 3.19; 95%confidence interval (CI): 1.02-10.0 ($p<0.047$)] and H-HDL [HR: 4.45; 95% CI: 1.39-14.2 ($p<0.011$)] had significantly higher risk of MACE than M-HDL.

Conclusions: Patients with middle HDL-C levels, not higher HDL-C levels, showed the greatest freedom from MACE. Patients with higher HDL-C levels need to be strictly managed for DM to prevent MACE.

Key Words: high-density lipoprotein cholesterol; major adverse cardiovascular events; coronary

computed tomography angiography; coronary artery disease; gender; diabetes mellitus; chronic kidney disease.

Introduction

Statin treatment prevents the onset and progression of atherosclerotic cardiovascular disease (ASCVD) in one-third of cases, but not in the remaining two-thirds [1]. The relative residual risk of ASCVD is still a major problem after statin treatment. One of the major problems regarding the residual risk of ASCVD is low serum levels of high-density lipoprotein cholesterol (HDL-C) [2, 3]. Although serum HDL-C levels should be maintained ≥ 40 mg/dL for primary and secondary prevention, according to the Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017 [4], there are no guidelines regarding whether higher levels of HDL-C would be better.

While cholesteryl ester transfer protein (CETP) inhibitors significantly increased HDL-C levels in blood, CETP inhibition provides little cardiovascular benefit [5, 6]. HDL mainly enhances reverse cholesterol transport, in which HDL takes up peripheral cholesterol and transfers it to the liver for excretion in the bile and feces. Recent prospective studies have revealed that cholesterol efflux capacity independent of HDL-C levels was inversely associated with the incidence of CV events, restenosis rates after coronary stent implantation and graft failure in renal transplant recipients [7-9]. Thus, HDL functionality, in addition to HDL-C levels, is important for preventing events. In addition, extremely high levels of HDL-C (≥90 mg/dL) were significantly associated with an increased risk of ASCVD mortality and an increased risk for coronary heart disease and ischemic stroke in a pooled analysis of Japanese cohorts [10]. However, the prognostic value of higher HDL-C levels is still controversial.

Coronary computed tomography angiography (CCTA) has become more widely available in many general hospitals and has emerged as a potential non-invasive method worldwide, and particularly in Japan. Over the past decade, many researchers have investigated the prognostic value of CCTA [11-16]. We have been studying the value of performing CCTA in the Fukuoka University CCTA (FU-CCTA) Registry [17-27], and these studies included patients who were

clinically suspected to have coronary artery disease (CAD) and who underwent CCTA. We previously reported that serum levels of HDL-C in patients with CAD were significantly lower than those in patients without CAD [20]. Since that report was cross-sectional, we did not determine their prognosis.

We hypothesized that higher HDL-C levels at the time of CCTA are associated with a lower rate of MACE. Thus, we investigated the associations between higher, middle and lower HDL-C levels and major adverse cardiovascular events (MACE).

Methods

Subjects

We prospectively evaluated 501 patients who had undergone CCTA and either were clinically suspected of having CAD or had at least one cardiovascular risk factor with a follow-up of up to 5 years. The patients were divided into tertiles according to the serum HDL-C level: 47 mg/dl ≥ HDL-C level [n=167, lower HDL-C level (L-HDL)], 58 mg/dl ≥ HDL-C level ≥ 48 mg/dl [n=167, middle HDL-C level (M-HDL)] and HDL-C level ≥ 59 mg/dl [n=167, higher HDL-C level (H-HDL)] groups. Patients with creatinine >2.0 mg/dl or contrast-induced allergy did not undergo MDCT. The protocol in this study was approved by the ethics committee of Fukuoka University Hospital, and all subjects gave their written informed consent to participate.

Evaluation of coronary stenosis using CCTA

We evaluated coronary stenosis using CCTA as previously described [17, 26]. Briefly, the region of interest was placed within the ascending aorta, and the scan was started when the CT density reached 100 Hounsfield Units higher than the baseline CT density. The scan was performed between the tracheal bifurcation and diaphragm. Overall, 15 coronary artery segments were assessed in all patients. Narrowing of the normal contrast-enhanced lumen to ≥ 50 % that could

be identified in multiplanar reconstructions or cross-sectional images was defined as significantly stenosed coronary vessels. In addition, in all patients, the atherosclerotic severity of coronary artery disease was assessed by the number of significantly stenosed coronary vessels (VD) and the Gensini score [28]. Coronary artery calcification (CAC) was defined on CT images as the presence of more than two contiguous pixels with greater than 130 Hounsfield Units. The CAC score in each lesion was then computed by the Agatston method [29].

Evaluation of various hemodynamic and biochemical parameters

Data regarding body mass index (BMI), systolic blood pressure (SBP), diastolic BP (DBP), pulse rate (PR), the areas of visceral fat (VFA), serum levels of triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), uric acid (UA), family history (FH) [myocardial infarction, angina pectoris or sudden death], history of HTN, DL, DM and smoking (past and current smokers), chronic kidney disease (CKD) and medication use were obtained from medical records.

BP was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer after at least 5 minutes of rest. To measure the VFA, a CT scan was performed. The value was measured from CT cross-sectional scans at the level of the umbilicus with a Ziostation (Ziosoft Inc., Tokyo. Japan). All of the blood samples were drawn in the morning after the patients had fasted overnight. Patients who had a current SBP/DBP ≥ 140/90mmHg or who were receiving antihypertensive therapy were considered to have HTN [30]. Patients with LDL-C ≥ 140 mg/dl, TG ≥ 150 mg/dl, and/or HDL-C < 40 mg/dl or who were receiving lipid-lowering therapy were considered to have DL [4]. DM was defined using the American Diabetes Association criteria [31] or the administration of a glucose-lowering drug. CKD was defined as an eGFR of < 60 mL/min/1.73m^2 and/or

proteinuria.

Medications

Medication use was determined from medical records. Medications included angiotensin II receptor blocker and/or angiotensin-converting-enzyme inhibitor (ARB/ACEI), calcium channel blocker (CCB), β-blocker, diuretic (DU), statin, eicosapentaenoic acid (EPA), sulfonylurea (SU), biguanide, dipeptidyl peptidase-4 inhibitor (DPP4I) and insulin.

Evaluation of MACE

We determined MACE (cardiovascular death, ischemic stroke, acute myocardial infarction and coronary revascularization) as a primary endpoint in patients with a follow-up of up to 5 years (average: 3.5±0.6 years). When the patients had significant coronary stenosis as assessed by CCTA and received coronary intervention immediately after CCTA, the intervention was not included in MACE as coronary vascularization.

Statistical analysis

All of the data analyses were performed using the SAS (Statistical Analysis System) Software Package (Ver. 9.4, SAS Institute Inc., Cary, NC, USA) and Excel 2016 (SSRI, Tokyo, Japan) at Fukuoka University (Fukuoka, Japan). Continuous variables are shown as the mean ± standard deviation. Categorical and continuous variables were compared between the groups by a chi-square analysis and t-test, respectively. When multiple groups were compared, data were analyzed by an analysis of variance with a Bonferroni post hoc test. A Kaplan-Meier analysis (log-rank test) was applied to verify the time-dependent occurrence of MACE in HDL subgroups stratified according to whether they were or were not smokers (smoking and non-smoking groups). A multivariate analysis was performed by logistic regression for independent variables

that were related to the presence or absence of CAD in all patients and the L-HDL, M-HDM and H-HDL groups. Multivariate Cox proportional hazard models were constructed to assess the relationships between tertiles according to the HDL-C level and MACE. Adjustment was carried out using conventional risk factors [age, male, VFA, HTN, DL, DM, family history, CKD and smoking). We used VFA instead of BMI as a risk factor because VFA is better marker of central obesity than BMI. A value of $p<0.05$ was considered significant.

Results

Patient characteristics, biochemical parameters and medications at baseline in the L-HDL, M-HDL and H-HDL groups.

Table 1 shows the characteristics, biochemical parameters and medications in the L-HDL, M-HDL and H-HDL groups. There were several significant differences in patient characteristics among the L-HDL, M-HDL and H-HDL groups. The patients in the H-HDL group had significantly lower %male, %smoking, BMI, VFA, %DL, and TG, and higher HDL-C than those in the L-HDL group. In addition, the H-HDL group showed significantly lower %male, BMI, VFA, %DL, and TG, and higher HDL-C compared to M-HDL group.

%CAD, number of VD, CAC score and Gensini score at baseline in the L-HDL, M-HDL and H-HDL groups.

%CAD, number of VD, CAC score and Gensini score are shown in Figure 1. While %CAD, number of VD and Gensini score significantly decreased as the HDL-C level increased, there were no differences in CAC score among the 3 groups.

%MACE in the L-HDL, M-HDL and H-HDL groups.

%MACE values in the L-HDL, M-HDL and H-HDL groups were 9 %, 2 %, and 7 %,

respectively (Figure 2). Unexpectedly, there was no significant difference in %MACE between the M-HDL and H-HDL groups, although %MACE in the M-HDL group was significantly lower than that in the L-HDL group ($p<0.05$),

Predictors of MACE in the L-HDL, M-HDL and H-HDL groups.

Table 2 shows predictors of MACE in the L-HDL, M-HDL and H-HDL groups using independent variables by a logistic regression analysis. We considered conventional coronary risk factors (age, gender, VFA, smoking, FH, HTN, DL, DM and CKD). The predictors of MACE in the L-HDL and M-HDL groups were none (Table 2ABC). MACE in the H-HDL group was significantly associated with DM ($p=0.03$) (Table 2D).

Kaplan-Meier curves for freedom from MACE in the L-HDL, M-HDL and H-HDL groups.

Kaplan-Meier curves in Figure 3 show the freedom from MACE in the L-HDL, M-HDL and H-HDL groups. The M-HDL group, not the H-HDL group, showed the greatest freedom from MACE among the 3 groups (log-rank test: $p=0.047$).

Cox regression model results for HDL-C levels and MACE.

Table 3 shows the results of a Cox regression model for HDL-C levels and MACE. Unadjusted and adjusted HDL-C levels, when stratified by tertiles, correlated with MACE. L-HDL [hazard ratios (HR): 3.19; 95%confidence interval (CI): 1.02-10.0 ($p<0.047$)] and H-HDL [HR: 4.45; 95% CI: 1.39-14.2 ($p<0.011$)] had significantly higher risk of MACE than M-HDL.

Discussion

In the present study, we hypothesized that higher HDL-C levels are associated with a lower rate

of MACE at the time of CCTA as screening for CAD. The most important finding was that patients in the middle tertile of HDL-C levels, not the highest tertile enjoyed the greatest freedom from MACE. Patients with higher HDL levels had significantly higher risk of MACE than patients with middle HDL-C levels. Patients with higher HDL-C levels need to be strictly managed for DM to prevent MACE.

%MACE in H-HDL was not significantly lower than those in L-HDL and M-HDL. This does not simply mean that patients with higher HDL-C levels did not receive some benefit regarding the occurrence of MACE. Hirata *et al*. estimated the adjusted hazard ratio in each HDL-C category for all-cause death and cause-specific deaths compared with HDL-C (40-59 mg/dL) using a cohort-stratified Cox proportional hazards model [10]. Subjects with extremely high levels of HDL-C (HDL-C levels ≥ 90 mg/dL) were significantly associated with an increased risk of atherosclerotic CVD mortality. The HDL-C (40-59 mg/dL) levels in the reference group were similar to those in the M-HDL group (58 mg/dl ≥ HDL-C level ≥ 48 mg/dL) in the present study. Our study did not analyze patients with extremely high levels of HDL-C because there were only 14 of these patients. The results indicated that patients in the middle HDL-C group had the lowest risk, and higher levels of HDL-C might be associated with a worse prognosis. However, we could not conclude that higher levels of HDL-C were associated with a worse prognosis because MACE in H-HDL was independently associated with DM according to a multivariate analysis. Since CAD patients generally have several risk factors, one risk factor alone may not cause MACE. Therefore, when patients show a higher level of HDL-C at the time of CCTA as screening for CAD, they need more rigorous management of other risk factors.

There was another issue regarding HDL functionality in the H-HDL group. HDL functionality is associated with cholesterol efflux capacity, as well as anti-oxidation, anti-inflammation, anti-proliferation and anti-thrombosis effects [32, 33]. Dysfunctional HDL has been defined as HDL that is associated with lower cholesterol efflux capacity and greater oxidation, inflammation,

proliferation and thrombosis. Even though patients showed higher serum HDL-C levels, some of them might have mainly dysfunctional HDL, rather than functional HDL. Rohatgi *et al*. reported that there was a 67 % reduction in cardiovascular risk in the highest quartile of cholesterol efflux capacity versus the lowest quartile in a fully adjusted model that included traditional risk factors, HDL-C levels, and HDL particle concentration [7]. We also reported that the percentage of cholesterol efflux capacity using a fixed amount of isolated HDL was not associated with CAD [34]. On the other hand, the calculated total cholesterol efflux capacity that was dependent on the HDL-C level was significantly associated with the presence of CAD. Thus, cholesterol efflux capacity is a cardiovascular risk that is both independent of and dependent on HDL-C levels. Further detailed studies will be needed to resolve these issues.

We found that the H-HDL group showed a lower %CAD and less severe CAD than the L-HDL and M-HDL groups at baseline, whereas the H-HDL group did not show the lowest %MACE. At the time of screening by CCTA, patients with H-HDL did not have higher % CAD or more severe coronary atherosclerosis. MACE in the H-HDL group was independently associated with DM. These patients need to be strictly managed for DM to prevent MACE, even though they show higher levels of HDL-C.

This study has several important limitations. First, the data were obtained from a single center. Second, MDCT is not a gold standard for the evaluation of CAD, although recent studies have shown that its sensitivity and specificity are both approximately 95 % of those for invasive coronary angiography for the identification of significant coronary stenosis [35]. Third, the history of medication use was not considered in the analysis. A large-scale prospective multi-center study will be needed to address these issues.

In conclusion, patients with middle HDL-C levels, not higher HDL-C levels, showed the greatest freedom from MACE. Patients with higher HDL-C need to be strictly managed for other risk factors, such as DM and CKD, to prevent MACE.

Conflict(s) of Interest

We have no conflicts of interest.

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Figure legends

Figure 1.

%coronary artery disease (CAD) (A), number of significantly stenosed coronary vessels (VD) (B), coronary artery calcification (CAC) score (C) and Gensini score (D) in the L-HDL, M-HDL and H-HDL groups. AU, arbitrary unit.

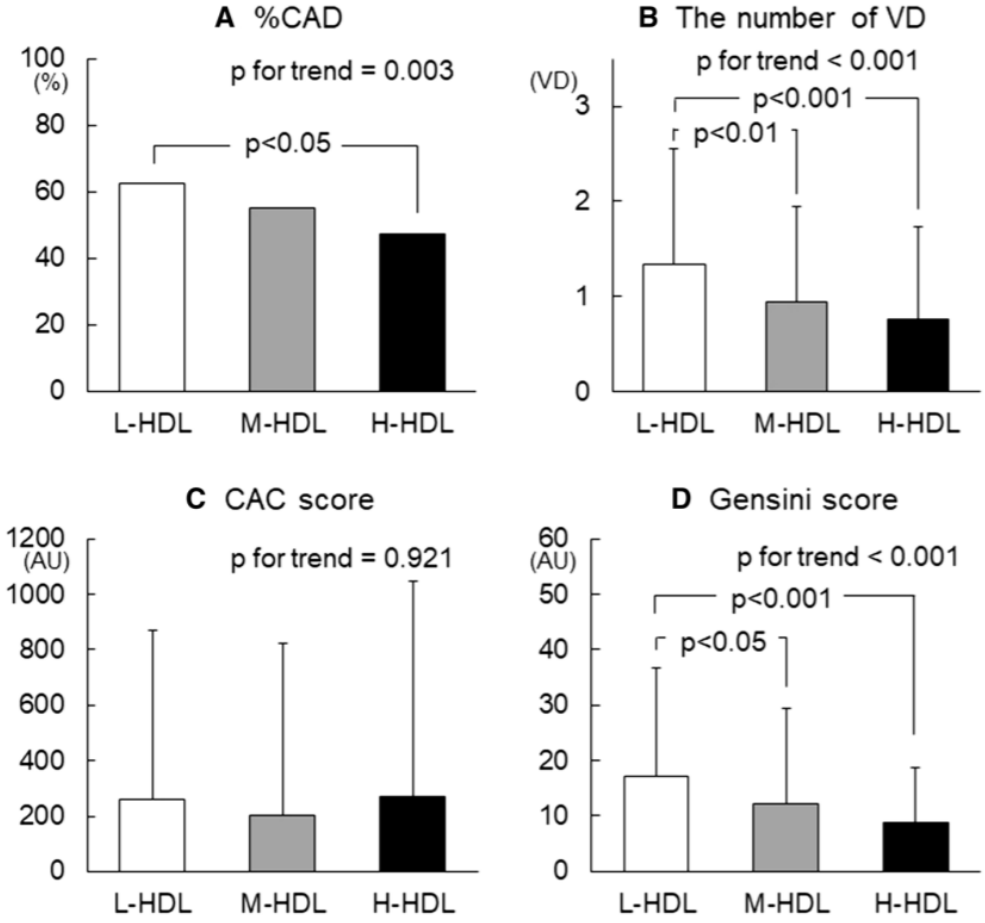

Figure 2.

%MACE in the L-HDL, M-HDL and H-HDL groups.

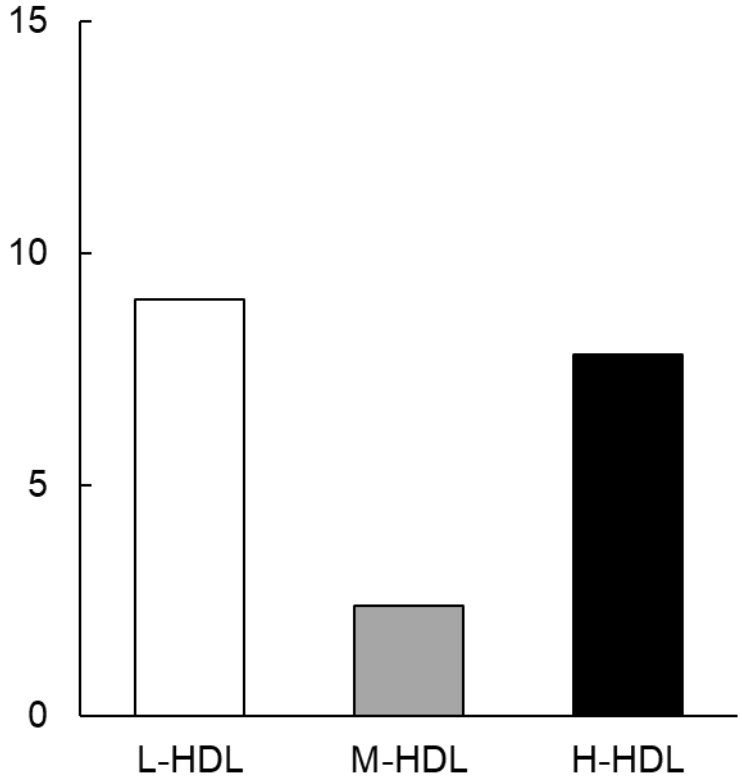

Figure 3.

Kaplan-Meier curves showing freedom from MACE in the L-HDL, M-HDL and H-HDL groups.

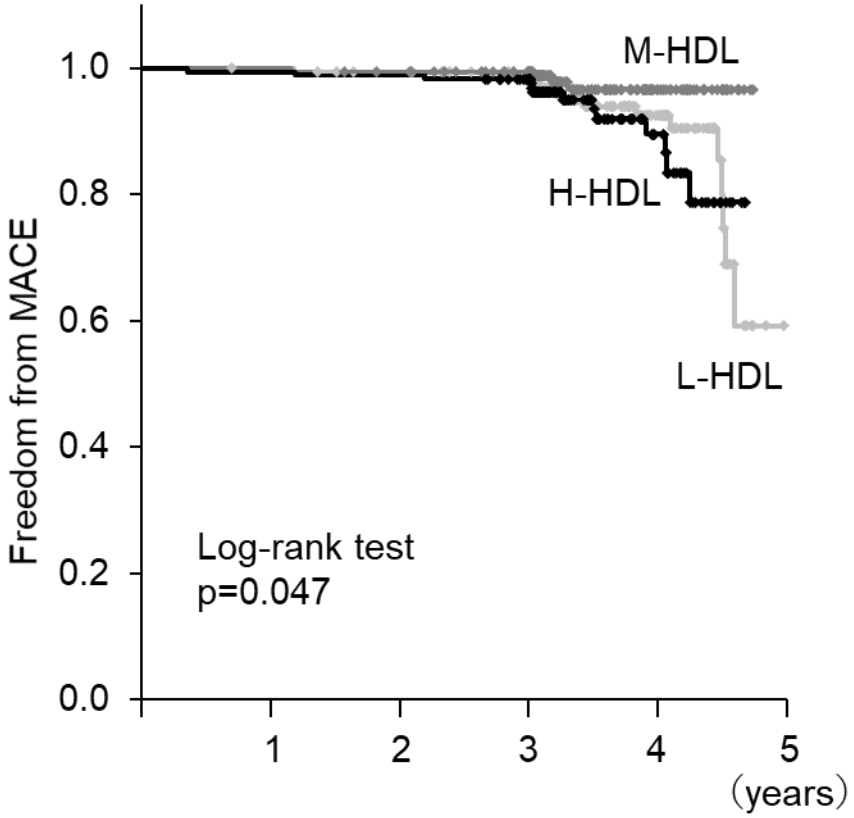

Table1 Patient characteristics, biochemical parameters and medications at baseline in the L-HDL, M-HDL and H-HDL groups.

	L-HDL	M-HDL	H-HDL	p value		
	(n=167)	(n=167)	(n=167)	Low vs Middle	Low vs High	Middle vs High
Age, yrs	65±11	66±11	67±10	1.0	0.725	1.0
Gender (male), %	65	50	35	0.015	<0.001	0.015
Family history, %	26	26	22	1.0	0.931	1.0
Smoking, %	49	32	26	0.004	<0.001	0.734
BMI, kg/m^2	24.8±3.6	24.2±3.2	22.9±3.6	0.48	<0.001	0.002
VFA, cm^2	135±55	116±50	96±57	0.005	<0.001	0.003
HTN, %	69	73	67	1.0	1.0	0.577
SBP, mmHg	135±17	137±21	136±19	1.0	1.0	1.0
DBP, mmHg	77±12	77±13	78±12	1.0	1.0	1.0
DL, %	71	65	55	0.625	0.006	0.203
TG, mg/dl	170±96	134±87	99±51	<0.001	<0.001	<0.001
HDL-C, mg/dl	40±5	52±3	72±12	<0.001	<0.001	<0.001
LDL-C, mg/dl	112±31	114±31	112±30	1.0	1.0	1.0
DM, %	25	27	16	1.000	0.150	0.056
HbA1c, %	6.0±1.2	5.9±1.1	5.9±1.1	0.926	0.964	1.0
FBG, mg/dl	112±33	108±35	108±33	1.0	0.917	1.0
Gensini score	17±20	12±17	9±10	0.019	<0.001	0.228
Medications						
ARB/ACE-I, %	42	43	34	1.0	0.440	0.282
CCB, %	37	37	42	1.0	0.939	1.0
β-blocker, %	11	10	8	1.0	0.811	1.0
DU, %	10	12	12	1.0	1.0	1.0
Statin, %	35	38	36	1.0	1.0	1.0
Fibrate, %	1	1	1	1.0	1.0	1.0
Ezetimib, %	1	2	2	1.0	1.0	1.0
EPA, %	4	4	3	1.0	1.0	1.0
SU, %	11	12	7	1.00	0.704	0.523
α-GI, %	6	4	1	1.0	0.024	0.231
Biguanide, %	10	7	5	0.887	0.180	1.0
Thiazolidine, %	2	2	2	1.0	1.0	1.0
DPP-4I, %	13	13	8	1.0	0.686	0.507
Insulin, %	4	4	3	1.0	1.0	1.0

Continuous variables are expressed as mean ± SD. L-HDL, lower HDL-C level; M-HDL, middle HDL-C level; H-HDL, higher HDL-C level; BMI, body mass index; VFA, visceral fat area; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; DL, dyslipidemia; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DM, diabetes mellitus; HbA1c, hemoglobin A1c; FBG, fasting blood glucose; ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; DU, diuretic; EPA, eicosapentaenoic acid; SU, sulfonylurea; α-GI, α-glucosidase inhibitor; DPP-4I, dipeptidyl peptidase-4 inhibitor.

Table2 Predictors of MACE in the L-HDL, M-HDL and H-HDL groups.

A. L-HDL Variables	Odds ratio	(95%CI)	p value
Age	0.959	(0.911-1.010)	0.111
Male	2.632	(0.565-12.27)	0.218
VFA	0.988	(0.976-1.000)	0.059
HTN	2.473	(0.52-11.753)	0.255
DL	1.200	(0.314-4.586)	0.790
DM	1.686	(0.481-5.906)	0.414
FH	0.434	(0.082-2.308)	0.328
CKD	1.520	(0.264-8.755)	0.639
Smoking	0.657	(0.182-2.372)	0.521
B. M-HDL Variables	Odds ratio	(95%CI)	p value
Age	1.075	(0.905-1.277)	0.412
Male	0.056	(0.02-1.524)	0.087
VFA	1.014	(0.986-1.042)	0.347
HTN	0.410	(0.026-6.48)	0.526
DL	0.735	(0.034-15.93)	0.845
DM	1.143	(0.07-18.59)	0.925
FH	4.998	(0.43-58.11)	0.199
CKD	1.083	(0.034-34.11)	0.964
Smoking	14.822	(0.622-353.1)	0.096
C. H-HDL Variables	Odds ratio	(95%CI)	p value
Age	1.030	(0.953-1.114)	0.456
Male	5.047	(0.904-28.17)	0.065
VFA	1.003	(0.992-1.014)	0.598
HTN	2.005	(0.346-11.62)	0.438
DL	0.710	(0.153-3.28)	0.661
DM	4.536	(1.157-17.80)	0.030
FH	0.814	(0.125-5.290)	0.829
CKD	4.544	(0.726-28.43)	0.106
Smoking	1.862	(0.430-8.066)	0.406

MACE, major adverse cardiovascular events; L-HDL, lower HDL-C level; M-HDL, middle HDL-C level; H-HDL, higher HDL-C level; VFA, visceral fat area; HTN, hypertension; DL, dyslipidemia; DM, diabetes mellitus; FH, family history; CKD, Chronic kidney disease.

Table3 Cox regression model results for HDL-C levels and MACE.

Factor		Unadjusted		* Adjusted	
		HR (95% CI)	p value	HR (95% CI)	p value
HDL-C	L-HDL	3.17 (1.05-9.57)	0.041	3.19 (1.02-10.0)	0.047
	M-HDL	** Ref.		** Ref.	
	H-HDL	3.69 (1.20-11.35)	0.023	4.45 (1.39-14.2)	0.011

HDL-C, high-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; L-HDL, lower HDL-C level; M-HDL, middle HDL-C level; H-HDL, higher HDL-C level; HR, hazard ratio; CI, confidence interval. * Adjusted, adjusted for age, males, visceral fat area, hypertension, dyslipidemia, diabetes mellitus, family history, chronic kidney disease and smoking. ** Ref, reference value (1.00).