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Cholesterol Metabolism as a Prognostic Marker in Patients with Mildly Symptomatic Nonischemic Dilated Cardiomyopathy

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ABSTRACT

Background Little is known about whether the alteration of cholesterol metabolism reflects abdominal organ impairments due to HF. Therefore, we investigated the prognostic value of cholesterol metabolism by evaluating serum campesterol and lathosterol levels in patients with early-stage nonischemic dilated cardiomyopathy (NIDCM).

Methods We enrolled 64 patients with NIDCM (median age 57.5 years, 31% female) with New York Heart Association functional class I/II. Serum campesterol and lathosterol levels were measured in all patients. The patients were then divided into four subsets based on the median non-cholesterol sterol levels (campesterol 3.6 μg/mL, lathosterol 1.4 μg/mL): reference (R-subset), high-campesterol/high-lathosterol; absorption-reduced (A-subset), low-campesterol/high-lathosterol; synthesis-reduced (S-subset), high-campesterol/low-lathosterol; double-reduced (D-subset), low-campesterol/low-lathosterol. Endpoint was a composite of cardiac events, including cardiac-related death, hospitalization for worsening heart failure, and lethal arrhythmia.

Results Median brain natriuretic peptide (BNP) level was 114 pg/mL. Mean left ventricular ejection fraction was 31.4%. D-subset had the lowest total cholesterol level and cardiac index and the highest BNP level and pulmonary capillary wedge pressure. D-subset also had the highest cardiac event rate during the mean 3.8 years of follow-up (log-rank $p = 0.001$). Multivariate regression analysis showed that D-subset was an independent determinant of cardiac events. The receiver operating characteristic curve

analysis revealed that total cholesterol <153 mg/dL was a best cutoff value for discrimination of the D-subset.

Conclusions The combined reduction of campesterol and lathosterol that indicated intestinal cholesterol absorption and liver synthesis predicts future cardiac events in patients with mildly symptomatic NIDCM.

Introduction

Heart failure (HF) is a systemic clinical syndrome characterized by multiple impaired organs. Recently, the importance of congestion and low perfusion in abdominal organs, leading to malnutrition and cardiac cachexia, has been reported [1-3]. Numerous patients with advanced HF complain of gastrointestinal symptoms (e.g., nausea, abdominal fullness, anorexia). Because these symptoms are rare in patients with early-stage HF [4], it is difficult for cardiologists to recognize abdominal organ impairment as a sign of HF progression, particularly in asymptomatic or mildly symptomatic patients. Thus, a reliable marker for early detection of subclinical impairment is needed for physicians.

Nonischemic dilated cardiomyopathy (NIDCM) is a progressive disease of myocardium accompanied by HF and is clinically manifested at a wide range of ages [5-6]. Although a high total cholesterol (TC) level is known as an established risk factor for ischemic heart disease, a low plasma TC level predicts a poor prognosis in patients with HF [7-9]. Rauchhaus et al. proposed that low-density lipoproteins contribute to impaired survival because of their ability to neutralize endotoxins, thereby preventing systemic inflammation caused by various endotoxin-induced cytokines [10]. However, the underlying mechanisms have not been established.

We hypothesized that low TC would be a potential marker for abdominal organ impairment caused by fluid congestion or low tissue perfusion in patients with HF because the plasma TC level is mainly regulated by intestinal absorption and liver

synthesis. According to previous studies, non-cholesterol sterols, such as the plant sterol campesterol and the cholesterol precursor lathosterol, serve as markers for cholesterol absorption and synthesis, respectively [11]. We hypothesized that a low-absorption/low-synthesis pattern would be associated with worse outcomes in patients with HF.

Therefore we investigated the prognostic value of reduction of campesterol and lathosterol in patients with asymptomatic or mildly symptomatic NIDCM. Additionally, we also investigated the availability of cholesterol metabolism for early diagnosis of intestinal and liver impairment due to HF.

Methods

Patients

We performed analyses of prospectively collected database. We enrolled 103 consecutive patients with NIDCM at our institute between January 2008 and December 2014. All patients had undergone echocardiography, cardiac catheterization, and laboratory measurements including campesterol and lathosterol assays within a 1-week period. Those examinations were performed under the each individual stable condition of HF. NIDCM was defined as previously reported [12, 13]. Briefly, it diagnosed by the presence of a left ventricular ejection fraction of <50% and a dilated left ventricular cavity on echocardiography in the absence of coronary heart disease, valvular heart disease, or secondary cardiac muscle disease caused by any known systemic condition

as determined by endomyocardial biopsy. We excluded patients with (i) advanced HF, which was defined as New York Heart Association (NYHA) functional class III/IV or prior hospitalization for HF within 6 months (n=14), (ii) any lipid-lowering therapy (n=15), and (iii) any other disorders that influence cholesterol metabolism [e.g., viral hepatitis (n=5), endocrine disorders (n=3), malignant co-morbidities (n=2)]. Finally, 64 patients with stable NIDCM were analyzed. The local institutional review board approved the study protocol, and written informed consent was obtained from all participants.

Non-cholesterol Sterol Measurements

We collected fasting blood samples at rest in the spine position, and measured campesterol and lathosterol levels (analyzed by SRL Co., Ltd., Tokyo, Japan.). All of the patients were hospitalized 5 days before the sample collection and were fed the fixed hospital diet whose component balance was approximately 60% carbohydrates, 25% fats, and 15% proteins in 30 kcal/kg. The amount of dietary cholesterol was approximately 400 mg per day. We handled the cases with lathosterol ≤1.0 μg/mL as those with lathosterol =1.0 μg/mL because of the limit of quantification.

Hemodynamic Examinations

All patients underwent echocardiography using a Vivid 7 system (GE Healthcare, Milwaukee, WI, USA) equipped with a 2.5- to 3.5-MHz transducer. Standard M-mode and two-dimensional echocardiography imaging were performed in agreement with the American Society of Echocardiography guidelines [14].

All patients also underwent routine diagnostic right heart catheterization to evaluate cardiac hemodynamics. Pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and cardiac index (CI) were measured with a Swan–Ganz catheter. Selective coronary angiography and endomyocardial biopsy were performed to exclude ischemic heart disease or secondary cardiomyopathy.

Patient Classification

To clarify the significance of the non-cholesterol sterols as markers for impaired cholesterol homeostasis, we divided the 64 patients into four subsets based on the median campesterol and lathosterol levels, as follows: reference (R-subset), campesterol ≥3.6 μg/mL and lathosterol ≥1.4 μg/mL; absorption-reduced (A-subset), campesterol <3.6 μg/mL and lathosterol ≥1.4 μg/mL; synthesis-reduced (S-subset), campesterol ≥3.6 μg/mL and lathosterol <1.4 μg/mL; double-reduced (D-subset), campesterol <3.6 μg/mL and lathosterol <1.4 μg/mL (Figure 1).

Follow-up and Endpoint

All patients were followed by expert cardiologists with optimal medical therapy according to the current guidelines for treatment of HF [4, 15]. The endpoint of this study was defined as a cardiac event including cardiac-related death, unplanned hospitalization because of worsening HF and lethal arrhythmias required implantable cardiac defibrillator. The follow-up data were researched up to 5 years.

Statistical Analysis

Continuous variables are presented as means ± standard deviation if they were of normal distribution and median and interquartile range if of non-normal distribution. Comparison of continuous variables among four subsets was performed by one-way analysis of variance. If any variables showed skewed distribution, parametric analyses of those variables were performed after natural logarithm transformation. Categorical variables were expressed as the number and percentage and compared by χ^2 analysis. Dunnett's *t*-test was used to compare A-, S-, and D-subsets with the R-subset. Cumulative event-free survival rates were calculated using the Kaplan−Meier method, with differences among the survival curves being assessed by the log-rank test. Cox proportional hazard analyses were performed to calculate the hazard ratio and 95% confidence interval for cardiac events. In bivariate and multivariate analyses, the variables with $p<0.05$ in univariate analyses were included in bivariate analyses, and those with $p<0.005$ were in multivariate analyses. The differences in survival time between the model with or without the covariates were provided by joint chi-square

value, which was defined as twice the positive difference of logarithmic likelihood. Receiver operating characteristic (ROC) analysis was performed to assess the clinical utility of plasma TC for discriminating the D-subset. All statistical analyses were performed with JMP 10.0 software (SAS Institute, Cary, NC, USA). A value of $p<0.05$ was considered to indicate statistical significance.

Results

Patient Characteristics

None of the patients had gastrointestinal symptoms. The comparisons of baseline characteristics and laboratory measurements among the four subsets are shown in **Table 1** and **Table 2**, respectively. D-subset had the highest PCWP, the highest brain natriuretic peptide (BNP) level and the lowest CI. The serum creatinine levels were similar. The usage rate of warfarin in D-subset was significantly higher than the other subsets, although the percentages of atrial fibrillation were same among 4 subsets. There were 6 patients with LVEF <20%: 3 in D-subset, 2 in S-subset, and 1 in A-subset. Regarding the inter-subsets analyses compared with the R-subset as a reference, the TC level of the D-subset was significantly lower, whereas those of the A-subset and S-subset showed no difference (**Figure 2A**). In addition, the BNP level and PCWP of the D-subset were significantly higher, and the CIs were lower than those of the R-subset (**Figure 2B–D**), although there were no significant differences in CVP between the D- and R-subsets (**Figure 2E**).

Survival Analyses

The Kaplan–Meier survival analyses of the four subsets are shown in **Figure 3**. The follow-up ratios of enrolled patients were 100% at 1 year, 89% at 2 years, 72% at 3 years, 58% at 4 years, and 39% at 5 years. During the mean of 3.8 years follow up periods, 15 cardiac events (2 cardiac-related deaths, 10 worsening HF, and 3 lethal arrhythmias) were documented. The event-free survival rate for the D-subset was 79% at 1 year, 50% at 3 years, and 36% at 5 years. Univariate determinants of cardiac events are shown in **Table 3**. The D-subset had a 6.5 times higher risk of cardiac events than the other subsets. Exploring the predictive power of D-subset independent of other prognostic indicators, the bivariate analyses demonstrated that the D-subset predicted increased cardiac events risk-independent of NYHA functional class, BNP, total bilirubin (T-Bil), γ-glutamyl transpeptidase (GGT), PCWP, CVP, and CI. In multivariate analyses, the D-subset was an independent predictor of cardiac events.

Cutoff Value of Plasma TC

We performed ROC analyses to assess the clinical utility of the TC level to discriminate the D-subset. We found that the best cutoff value was 153 mg/dL, with 57% sensitivity and 92% specificity (area under the curve 0.76, 95% confidence interval 0.56–0.88, p = 0.0011) (**Figure 4A**). In addition, the patients with TC <153 mg/dL had a significantly higher cardiac event rate than those with TC ≥153 mg/dL (**Figure 4B**).

Determinants of Plasma TC

Univariate and multivariate regression analysis for plasma TC was performed to detect its determinant. The univariate analyses revealed that 26% of the plasma TC level was explained by lathosterol and only 6% by campesterol. However, those two non-cholesterol sterols were independent determinants of the plasma TC level in the multivariate analysis (**Table 4**).

Discussion

The main findings of the present study were the following: (1) Double reduction of cholesterol absorption and synthesis predicted a poor outcome. (2) Double reduction was associated with low plasma TC levels. (3) Plasma TC <153 mg/dL was a reliable marker of double reduction, with risk stratification, even when NIDCM patients had no gastrointestinal symptoms. Although the previous studies reported that a low level of plasma TC predicts the poor prognosis in patients with HF [7, 8], the mechanisms which contribute to lowing plasma TC has not been clarified. To the best of our knowledge, this is the first report which investigate the significance of cholesterol metabolism in patients with NIDCM.

Prognosis and Cholesterol Metabolism

We hypothesized that low TC would be results of abdominal organ impairment in patients with HF, and as expected, double reduction of campesterol and lathosterol (D-subset) had a prognostic value with impaired hemodynamic findings. Actually, we demonstrated that the hemodynamic status of D-subset was more impaired than the others and might successfully discriminate the patients with more advanced HF who had higher BNP and PCWP, lower cardiac index, relatively lower LVEF. This result indicates that the cholesterol metabolism is important for the risk stratification even in patients without gastrointestinal symptoms.

Low tissue perfusion due to left-side HF and tissue congestion due to right-side HF are the two mechanisms suggested to contribute to intestinal and liver impairment in patients with HF [1]. We found that the D-subset had higher PCWP and lower CI than those of the R-subset. Those results indicated that left-side HF could play an important role in intestinal and liver impairment. In contrast, we found no significant differences in CVP among the four subsets, and in 78% of all patients the CVP was not elevated (<8 mmHg). Therefore left-side HF or low tissue perfusion might have a larger impact on abdominal organ impairment than right-side HF or tissue congestion in our population. However, these results are not intended to deny the contribution of tissue congestion to impaired cholesterol metabolism. Previous studies reported that the gastrointestinal tract and liver work as fluid reservoirs, which could buffer 40% and 20% of infused excess blood volume, respectively, without any systemic hemodynamic effects [16, 17]. Latent tissue congestion might exist, even when patients have no

gastrointestinal symptoms or elevated CVP. We speculated that the altered TC metabolism might reflect somewhat these latent congestions in the intestine and liver.

Accordingly, it is assumed that double reduction of campesterol and lathosterol could be a reliable marker for early diagnosis of abdominal organ impairment chiefly due to left-side HF, which could lead to a poor outcome.

Impact of Double Reduction on Cholesterol Metabolism

We demonstrated that the TC level of the D-subset was significantly lower than those in the other three subsets, which were similar to each other (**Figure 2**). Our results indicate that double (but not single) reduction of intestinal absorption and liver synthesis is clinically important for NIDCM patients because it contributes to the TC being at a low level, which reflects decompensated cholesterol homeostasis.

Cholesterol is an essential substance for cellular membrane structure and hormone production. Therefore, cholesterol synthesis is regulated by the cholesterol intake [18]. Increased liver synthesis usually compensates for decreased intestinal cholesterol absorption. Also, intestinal absorption of cholesterol is activated when patients are prescribed a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor [19-21]. In fact, an inverse correlation between cholesterol absorption and synthesis was reported [22]. However, we found no correlation between campesterol and lathosterol ($r=0.0213$, $p=0.86$) in the present study. These results might indicate that

decompensation of cholesterol homeostasis could occur even in patients at NYHA functional class I/II.

Timing of Intestinal and Liver Impairment

We demonstrated that liver synthesis made a larger contribution to altering the plasma TC level than intestinal absorption (lathosterol: R^2=0.26, p<0.0001; campesterol: R^2=0.06, p=0.049), and they were independent of the high-sensitivity C-reactive protein (hs-CRP) level (**Table 4**). In addition, the S-subset had a significantly higher BNP level than the R-subset (p=0.04) and tended to have a lower CI (**Figure 2B, D**). The S-subset was characterized by impaired liver synthesis that was compensated for by intestinal absorption.

Conversely, we think that the single absorption reduction seen in the A-subset might not mean the intestinal impairment. A previous study indicated that a sufficient cholesterol pool, which indicated good nutritional status, suppressed cholesterol absorption and simultaneously activated cholesterol synthesis [23]. In addition, the hemodynamic findings of the A-subset were not significantly different with those of the R-subset. Therefore, we assumed that single absoption reduction might reflect active suppression of cholesterol absorption. Our results suggested that impaired liver synthesis might occur earlier than intestinal absorption, which would be clinically significant when the two are combined.

Involvement of Inflammation

Previous study reported that patients with chronic HF present with intestinal barrier dysfunction and increased paracellular permeability [24]. This situation could contribute to an increase in plasma endotoxins, thereby inducing the appearance of inflammatory cytokines [25]. Because the plasma lipoproteins have been reported to be able to remove endotoxins, a low TC level could be associated with worse outcomes [10]. Although we did not measure endotoxins or any specific inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor α) in this study, the median hs-CRP level for all patients was 0.088 mg/dL, and there were no significant differences among the four subsets. Additionally, although a previous study reported that hs-CRP had prognostic value in patients with HF [26, 27], it had no impact on outcomes in our population (**Table 3**). This result suggests that double impairment of the intestine and liver occurs earlier than systemic chronic inflammation. Consequently, it could be a useful marker for early detection of abdominal organ impairment.

Detection of Double Impairment Using the Plasma TC Level

The measurement of campesterol and lathosterol is not common in clinical settings. Therefore, we identified the best cutoff value of plasma TC to detect double reduction of the intestinal absorption and liver synthesis of cholesterol (D-subset). We showed that 92% of NIDCM patients with TC <153 mg/dL were classified into the

D-subset. Importantly, these patients had a significantly higher cardiac event rate (**Figure 4B**). Therefore, we suggest that more attention be paid to TC levels <153 mg/dL (without lipid-lowering therapy) as a marker of abdominal organ impairment even when the patient has no gastrointestinal symptoms.

Limitations

The present study has several limitations. First, we enrolled patients with homogeneous status and etiology. Therefore, the results of this study cannot be extrapolated to patients with advanced HF, taking lipid-lowering therapy, or having an ischemic etiology. Second, there were no standard values for campesterol or lathosterol and the sterol levels under several conditions were previously reported with wide variations [11, 20]. Additionally, those sterols levels in NIDCM patients have not been clarified, although we subclassified our patients according to the median of these two entities as having impaired cholesterol absorption and synthesis below the median. Therefore, our results did not consider the individual differences. Third, we could not investigate the influence of the enterohepatic circulation or in vivo cholesterol pool, which are known as main components of cholesterol metabolism. In addition, the present study had rather insufficient power to conclude the causal relationship between low non-cholesterol sterol level and cardiac events. Further investigations with larger numbers of patients such as propensity score adjustment are needed to establish the

importance of cholesterol metabolism in patients with HF.

In conclusion, the combined reduction of campesterol and lathosterol is associated with a higher cardiac event rate in NIDCM patients at NYHA functional class I/II. A low level of TC indicated double impairment of intestinal absorption and liver synthesis and plasma TC level <153 mg/dL would be a reliable marker for early detection of abdominal organ impairment and poor prognosis, even when patients had no gastrointestinal symptoms.

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Disclosures: The authors declare that there is no conflict of interest.

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Figure Legends

Figure 1. Classification of the four subsets and scatter plot of sterols

We defined below the median of campesterol, those of lathosterol, and a combination of the two as absorption reduced (A-subset), synthesis reduced (S-subset), and double-reduced (D-subset), respectively. The others were defined as reference (R-subset). The cases with lathosterol ≤1.0 μg/mL are plotted as 1.0 μg/mL because of the limit of quantification.

Figure 2. Comparison of the four subsets

R-subset was deemed the reference for Dunnett's test. TC: total cholesterol. BNP: brain natriuretic peptide. PCWP: pulmonary capillary wedge pressure. CVP: central venous pressure.

Figure 3. Kaplan–Meier event-free survival rate

Cumulative event-free survival by four non-cholesterol subsets. Composite of cardiac events were defined as cardiac-related death, unexpected hospitalization due to decompensated heart failure, and lethal arrhythmia. TC: total cholesterol.

Figure 4. Cutoff value of low total cholesterol

The best total cholesterol cutoff value for discriminating the D-subset was 153 mg/dL **(A)**. In Kaplan-Meier survival analysis, this cutoff value discriminated the patients with poor outcome **(B)**. TC: total cholesterol. AUC: area under the curve

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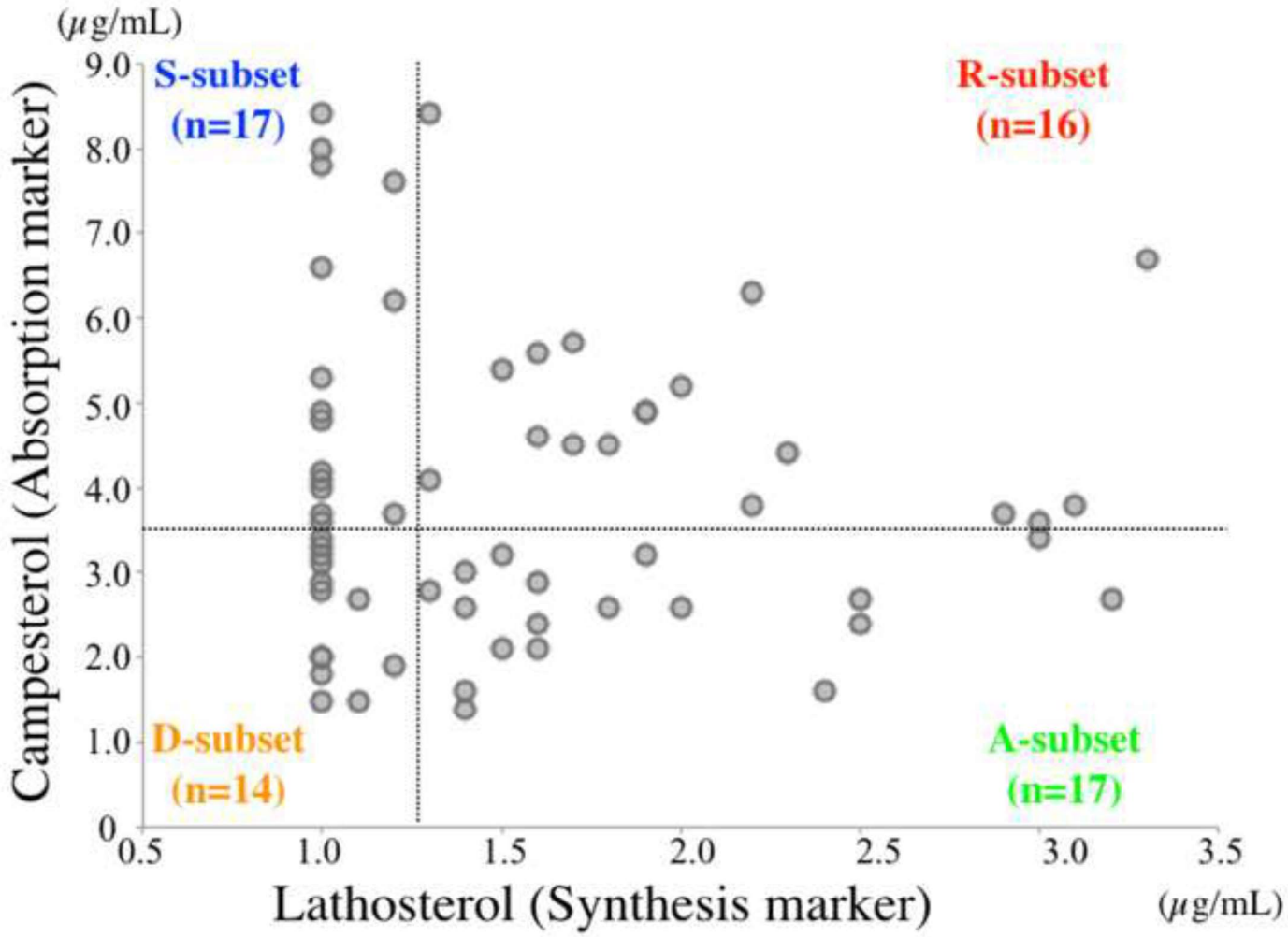

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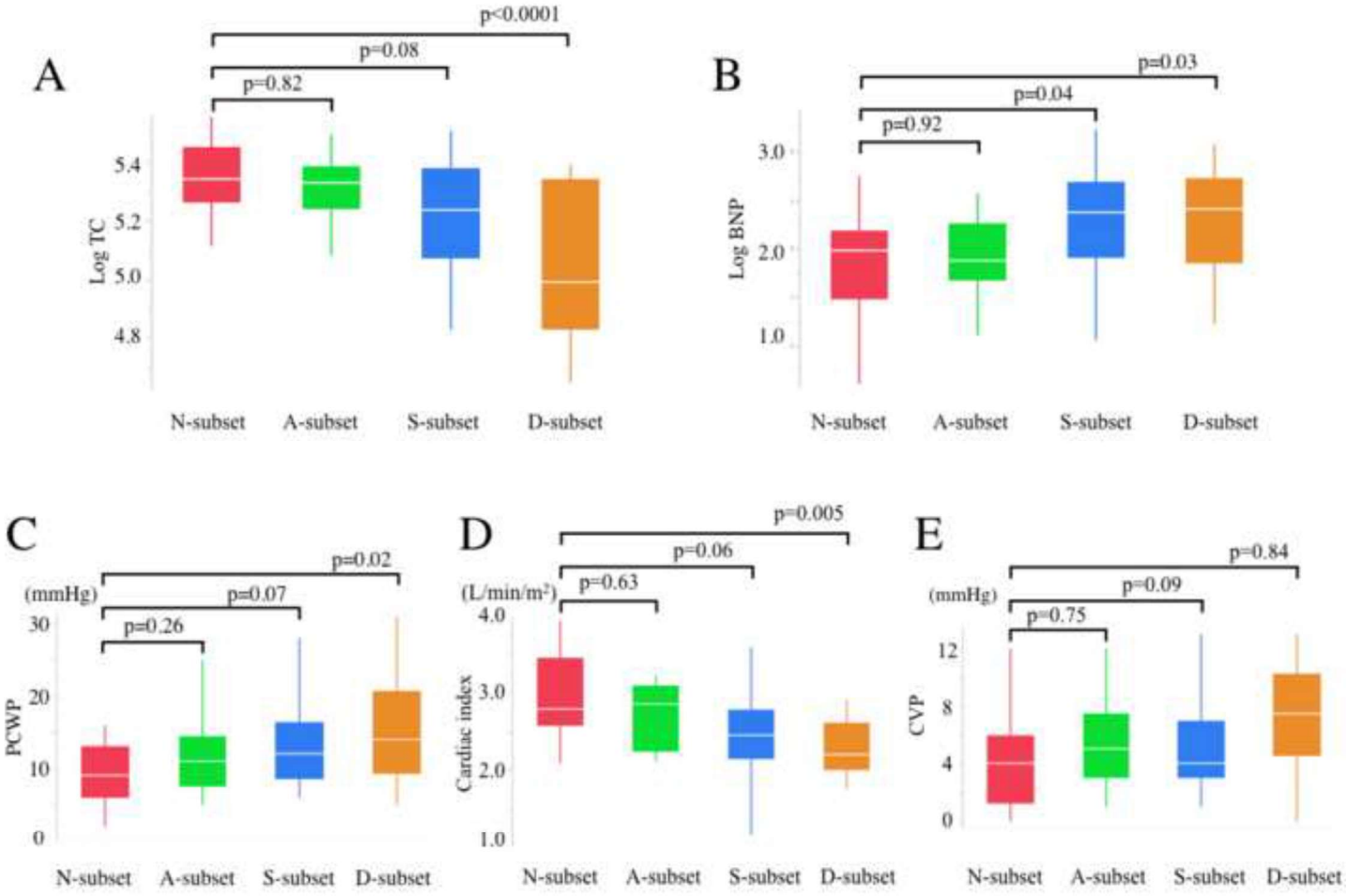

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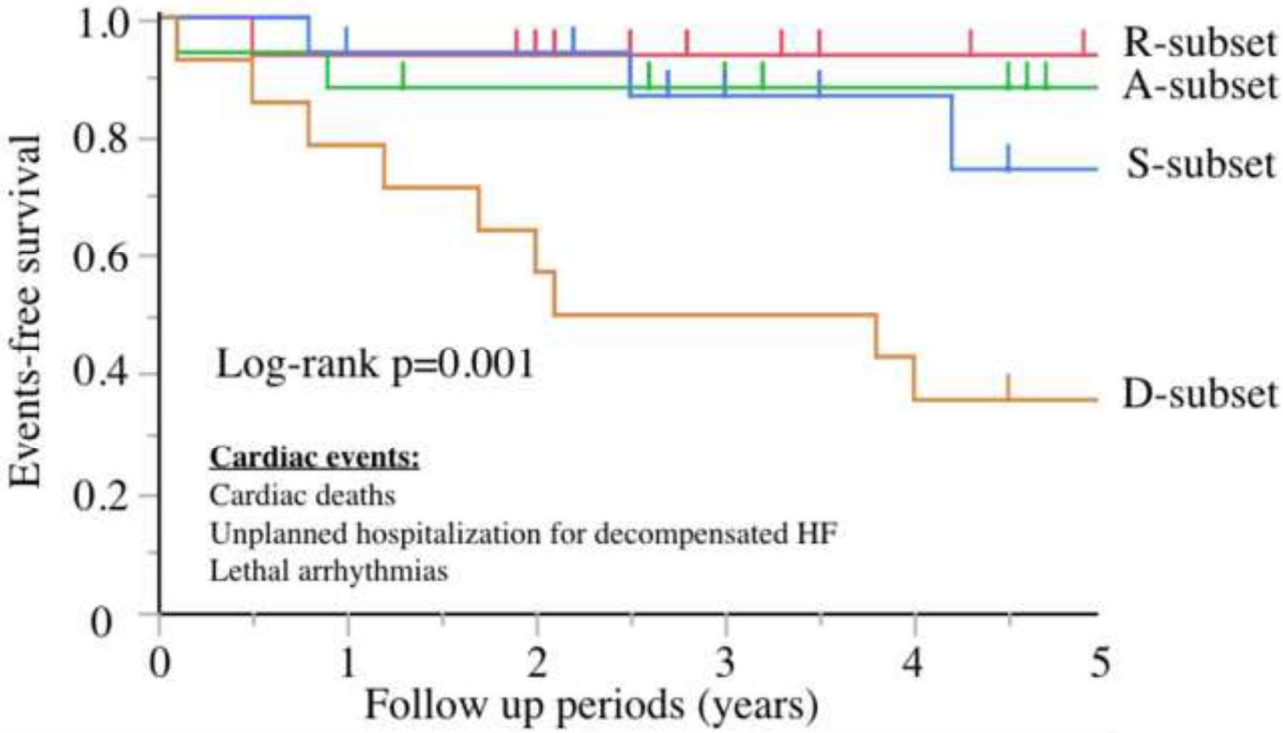

Number at risks						
R-subset	16	15	13	7	5	3
A-subset	17	15	14	13	11	7
S-subset	17	16	15	11	7	5
D-subset	14	11	9	7	6	4

Figure 4(revised ver)
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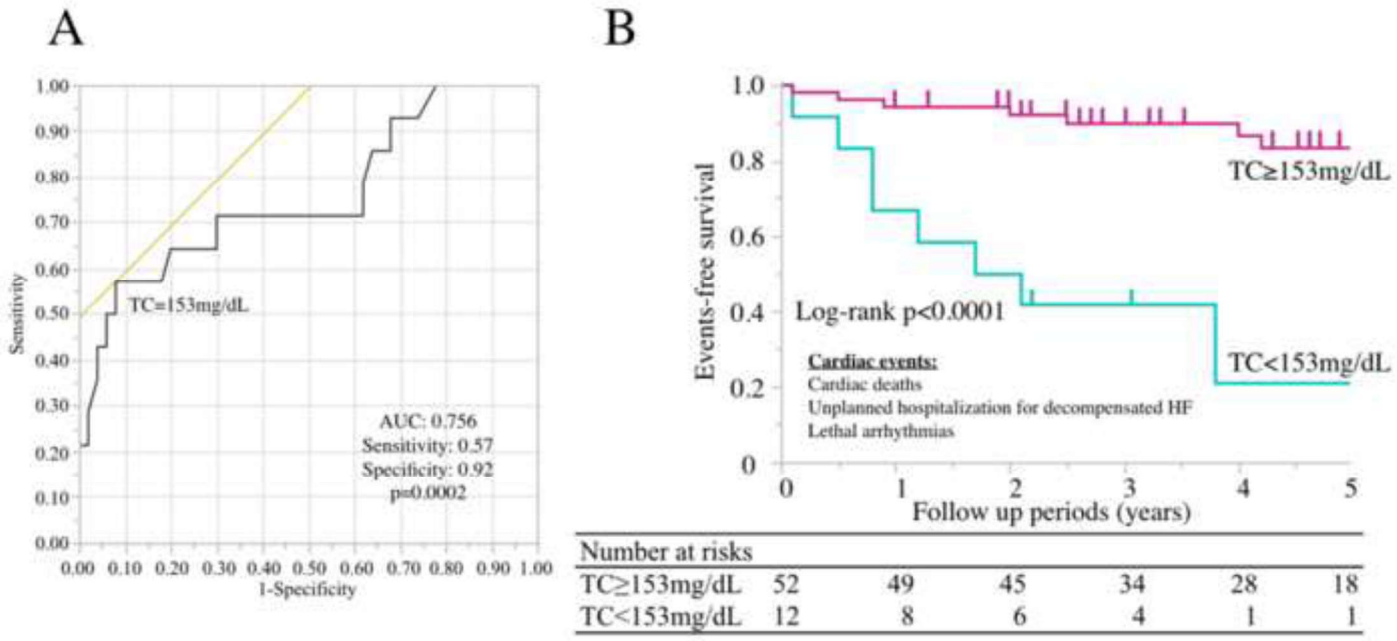

Number at risks						
TC≥153mg/dL	52	49	45	34	28	18
TC<153mg/dL	12	8	6	4	1	1

Table 1

TABLE 1 Baseline characteristics

Characteristic	R-subset n=16	A-subset n=17	S-subset n=17	D-subset n=14	p
Age, years	53 ± 11	52 ± 9	57 ± 14	51 ± 18	0.68
Female, n (%)	7 (44)	4 (24)	4 (24)	5 (36)	0.52
BMI, kg/m^2	23 ± 2	24 ± 4	20 ± 2	22 ± 2	0.003
SBP, mmHg	124 ± 23	123 ± 19	127 ± 24	110 ± 22	0.19
DBP, mmHg	75 ± 14	79 ± 15	76 ± 14	69 ± 11	0.28
Hear rate, bpm	82 ± 12	93 ± 16	85 ± 18	79 ± 17	0.12
NYHA II, n (%)	5 (31)	8 (47)	8 (47)	10 (71)	0.18
Previous history, n (%)					
Prior hospitalization for HF	3 (18)	8 (47)	8 (47)	7 (50)	0.23
HT	5 (31)	5 (29)	5 (29)	3 (21)	0.94
DM	1 (6)	1 (6)	4 (24)	4 (29)	0.18
DL	5 (31)	2 (12)	2 (12)	4 (29)	0.35
AF	2 (13)	3 (18)	1 (6)	2 (14)	0.77

Smoking	4	(25)	4	(24)	2	(12)	3	(21)	0.78
Medication, n (%)									
Diuretics	6	(38)	9	(53)	11	(65)	9	(64)	0.37
ACEI/ARBs	12	(75)	15	(88)	16	(94)	12	(86)	0.46
BBs	12	(75)	15	(88)	15	(88)	14	(100)	0.23
MRAs	3	(19)	8	(47)	7	(41)	6	(43)	0.34
Warfarin	1	(6)	4	(24)	7	(41)	8	(57)	0.02
Echocardiography									
LVEF, %	35	± 9	31	± 8	33	± 13	30	± 12	0.59
LVDD, mm	61	± 8	61	± 7	62	± 7	65	± 9	0.53
LVDS, mm	50	± 9	52	± 8	51	± 9	55	± 12	0.51
IVSTD, mm	8.8	± 1.8	9.0	± 2.3	8.8	± 2.0	9.2	± 3.1	0.95
PWTD, mm	8.8	± 2.3	9.2	± 3.7	8.8	± 1.5	9.0	± 2.1	0.96
Cardiac catheterization									
PCWP, mmHg	8.6	± 5.1	12.3	± 6.3	13.8	± 7.0	15.1	± 7.5	0.04
CVP, mmHg	4.4	± 8.5	5.3	± 2.8	5.1	± 3.4	7.0	± 3.8	0.20

CI, L/min/m^2	2.91	±	0.54	2.73	±	0.40	2.49	±	0.70	2.29	±	0.38	0.01

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HT = hypertension; DM = diabetes mellitus; DL = dyslipidemia; AF = atrial fibrillation; ACEI/ARBs = angiotensin-converting enzyme inhibitor/aldosterone receptor blockers; BBs = beta-blockers; MRAs = mineralocorticoid receptor antagonists; LVEF = left ventricular ejection fraction; LVDD = end-diastolic left ventricular dimension; LVDS = end-systolic left ventricular dimension; IVSTD = end-diastolic intraventricular septum dimension; PWTD = end-diastolic posterior wall dimension; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CI = cardiac index.

Table 2

TABLE 2 Laboratory measurements

Variable	R-subset n=16	A-subset n=17	S-subset n=17	D-subset n=14	p
Campesterol, µg/mL	4.8 (4.0–5.6)	2.6 (2.1–3.0)	4.9 (4.1–7.7)	2.8 (1.9–3.1)	-
Lathosterol, µg/mL	2.0 (1.7–2.8)	1.6 (1.5–2.5)	1.0 (1.0–1.2)	1.0 (1.0–1.1)	-
TC, mg/dL	209 (193–233)	207 (189–219)	188 (160–218)	147 (125–210)	0.0002
Triglycerides, mg/dL	117 (83–155)	157 (117–272)	82 (65–100)	73 (63–135)	0.007
HDL-C, mg/dL	56 (49–70)	50 (41–64)	46 (39–64)	44 (30–50)	0.11
LDL-C, mg/dL	134 (108–152)	124 (103–139)	119 (102–137)	89 (68–117)	0.01
Hemoglobin, g/dL	13.8 ± 1.1	14.7 ± 1.4	13.5 ± 1.5	14.6 ± 1.8	0.051
BNP, pg/mL	96 (30–156)	75 (48–185)	235 (81–543)	261 (71–556)	0.02
SCr, mg/dL	0.8 ± 0.1	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.2	0.27
Sodium, mEq/L	140 ± 2	138 ± 3	140 ± 4	139 ± 4	0.40
Potassium, mEq/L	4.1 ± 0.4	4.3 ± 0.3	4.1 ± 0.5	4.0 ± 0.4	0.13
AST, U/L	18 (15–25)	20 (17–25)	25 (22–33)	24 (21–29)	0.03
ALT, U/L	17 (14–21)	19 (13.5–28.5)	18 (14.5–22)	20 (17–31.5)	0.35

ALP, U/L	186	(172–202)	265	(176–307)	229	(180–407)	223	(170–277)	0.054
GGT, U/L	21	(12–57)	45	(24–53)	47	(23–98)	47	(31–91)	0.07
T-Bil, mg/dL	0.8	(0.6–1.0)	0.6	(0.5–0.8)	0.7	(0.6–1.4)	0.9	(0.6–1.9)	0.20
Albumin, g/dL	4.1	± 0.3	4.0	± 0.3	3.8	± 0.3	3.9	± 0.3	0.13
hs-CRP, mg/dL	0.03	(0.02–0.07)	0.07	(0.02–0.52)	0.20	(0.03–0.72)	0.09	(0.05–0.28)	0.17

TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; BNP = brain natriuretic peptide; SCr = serum creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = γ-glutamyl transpeptidase; T-Bil = total bilirubin; hs-CRP = high-sensitivity C-reactive protein.

Table 3

TABLE 3. Cox proportional hazard analyses of determinants of cardiac events

Factor	HR	95%CI		χ^2 value	p	Joint χ^2
Univariate analysis						
BMI	1.108	0.936	1.278	1.533	0.22	
NYHA II	5.326	1.688	23.403	8.627	0.003	
BNP	1.002	1.001	1.002	8.413	0.004	
Serum creatinine	0.669	0.048	8.076	0.095	0.76	
Albumin	0.523	0.123	2.388	0.730	0.39	
ALP	1.001	0.996	1.006	0.292	0.59	
GGT	1.013	1.006	1.020	12.438	0.0004	
T-Bil	3.232	1.313	7.322	6.233	0.01	
hs-CRP	1.117	0.228	3.375	0.027	0.869	
Campesterol	0.605	0.381	0.879	7.596	0.01	
Lathosterol	0.252	0.044	0.824	5.574	0.02	
D-subset	6.463	2.326	19.318	12.317	0.0004	
PCWP	1.095	1.021	1.170	6.233	0.001	

CVP	1.225	1.059	1.425	7.415	0.004	
Cardiac index	0.453	0.184	1.107	3.011	0.08	
Bivariate analysis						
D-subset	4.827	1.700	14.755	8.608	0.003	17.2356
NYHA II	3.772	0.059	14.755	4.918	0.03	
D-subset	6.485	2.301	19.792	12.105	0.001	20.5175
BNP	1.002	1.001	1.003	8.200	0.004	
D-subset	5.452	1.879	16.742	9.468	0.002	15.7013
T-Bil	7.594	0.946	4.969	3.384	0.07	
D-subset	5.832	2.045	17.693	10.490	0.001	22.9276
GGT	1.013	1.005	1.021	10.610	0.001	
D-subset	6.235	2.228	18.758	11.746	0.001	17.9793

PCWP	1.097	1.017	1.181	5.662	0.02	
D-subset	5.026	1.737	15.531	8.728	0.003	16.1428
CVP	1.158	1.000	1.354	3.825	0.051	
Multivariate analysis						
NYHA II	1.947	0.073	28.814	0.839	0.360	24.9248
BNP	2.312	0.725	28.814	0.298	0.585	
GGT	49.855	0.725	5204	3.289	0.070	
D-subset	4.388	1.470	13.988	6.965	0.008	
PCWP	1.014	0.904	1.129	0.059	0.808	
CVP	1.054	0.875	1.285	0.295	0.587	

HR = hazard ratio; 95%CI = 95% confidence interval. Other abbreviations are the same as in Tables 1 and 2.

Table 4

TABLE 4. Univariate and multivariate analyses for plasma total cholesterol level

Factor	Adjusted R^2	β	95%CI		p
Univariate analysis					
Age	0.037	0.229	−0.0003	0.008	0.07
Female	−0.015		−0.101	0.137	0.76
BMI	0.012	0.165	−0.006	0.028	0.19
Log hs-CRP	0.102	0.274	0.014	0.247	0.006
Log lathosterol	0.264	0.525	0.171	0.411	<0.0001
Log campesterol	0.060	0.274	−0.062	0.028	0.03
Multivariate analysis					
Log hs-CRP	0.347	−0.017	−0.040	0.035	0.89
Log lathosterol		0.482	0.136	0.420	0.0003
Log campesterol		0.325	0.044	0.304	0.01

Abbreviations are the same as in Tables 1, 2, and 3.