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ORIGINAL RESEARCH

IMAGING

Coronary Artery and Carotid Artery Plaques in Patients With Heterozygous Familial Hypercholesterolemia

Hayato Tada, MD,[a] Atsushi Nohara, MD,[b] Soichiro Usui, MD,[a] Kenji Sakata, MD,[a] Kenshi Hayashi, MD,[a] Noboru Fujino, MD,[a] Masa-aki Kawashiri, MD,[c] Masayuki Takamura, MD[a]

ABSTRACT

BACKGROUND Little is known regarding the formation of coronary and carotid plaques and their impact on cardiovascular disease in patients with familial hypercholesterolemia (FH).

OBJECTIVES This study aimed to determine: 1) if the development of coronary and carotid plaques is correlated; and 2) if these plaques are associated with major adverse cardiac events (MACEs) defined as cardiovascular-related death, unstable angina, myocardial infarction, or staged revascularization.

METHODS This was a retrospective review of 622 patients with heterozygous FH (HeFH) at Kanazawa University Hospital, assessed coronary and carotid plaque scores using coronary computed tomography and carotid ultrasound within 1 year. Spearman correlation coefficients were assessed among variables. Risk factors for MACEs were determined using the Cox proportional hazard model.

RESULTS Coronary and carotid plaque scores were significantly correlated in patients with HeFH in both sexes (Spearman's r = 0.82; $P < 0.001$ in males and Spearman's r = 0.87; $P < 0.001$ in females). We observed 132 MACEs during the median follow-up of 13.2 years. These scores were significantly associated with the occurrence of MACE (HR: 3.33; 95% CI: 1.88-4.78; $P < 0.001$, HR: 2.24; 95% CI: 1.28-3.20; $P < 0.001$, respectively).

CONCLUSIONS Coronary and carotid plaque scores were significantly correlated, and both were independently associated with MACEs. The assessments for coronary and/or carotid plaque are useful for further risk stratifications in patients with HeFH. (JACC Adv 2023;2:100594) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Patients with familial hypercholesterolemia (FH) caused by pathogenic mutations in the low-density lipoprotein receptor (*LDLR*) or its associated genes, including apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), and *LDLR* adaptor protein 1 (*LDLRAP1*), have an extremely high risk of developing coronary artery disease and carotid atherosclerosis caused by

From the [a]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan; [b]Department of Clinical Genetics, Ishikawa Prefectural Central Hospital, Kanazawa, Japan; and the [c]Department of Internal Medicine, Kaga Medical Center, Kaga, Japan.

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ABBREVIATIONS AND ACRONYMS

APOB = apolipoprotein B

CT = computed tomography

FH = familial hypercholesterolemia

HeFH = heterozygous familial hypercholesterolemia

LDLR = LDL receptor

LDLRAP1 = LDL receptor adaptor protein 1

MACEs = major adverse cardiac events

PCSK9 = proprotein convertase subtilisin/kexin type 9

chronic exposure to high LDL cholesterol.[1-3] Clinical guidelines across the world suggest assessing for systemic atherosclerosis in patients with heterozygous FH (HeFH).[4-6] However, it is unclear when we should assess their atherosclerosis because of lack of data regarding the natural history of coronary and carotid artery plaque progression in such patients. Previously, in a limited sample size, we have shown that coronary artery plaques may start to progress at around 23 and 34 years old in males and females, respectively, as seen on coronary computed tomography (CT).[7] On the other hand, carotid artery plaques develop at around 17 and 26 years old in males and females, respectively, based on carotid ultrasound.[8] So far, several studies with small to moderate sample size have investigated the associations between coronary and carotid plaques and cardiovascular disease among patients with HeFH.[9,10] However, it remains unclear: 1) if coronary and carotid artery plaque are correlated with each other; and 2) if these plaques are associated with cardiovascular events among patients with HeFH. Accordingly, the objectives of this study were to determine: 1) if the development of coronary and carotid plaques is correlated; and 2) if these plaques are associated with cardiovascular events among one of the largest cohorts of patients with HeFH who underwent coronary CT and carotid ultrasound.

METHODS

STUDY POPULATION. We analyzed data from 932 patients diagnosed with HeFH using the Japan Atherosclerosis Society 2017 criteria.[4] These patients were admitted to Kanazawa University Hospital between 2000 and 2020 and were diagnosed with coronary and carotid plaque within 1 year. In our institute, carotid ultrasound is routinely performed for any patients with HeFH at the initial assessment, and then coronary CT is strongly recommended for patients with any carotid plaque. Coronary CT is also recommended for patients with any chest discomfort in cases with HeFH. We excluded 121 patients due to history of coronary revascularization, 96 because of missing data, and 93 who were lost to follow-up. Finally, 622 patients were included in this study (Supplemental Figure 1).

CLINICAL DATA ASSESSMENT. Hypertension was defined as having a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use. For diabetes, we adopted the definition set by the Japan Diabetes Society.[11] The current smoking status of the patients was considered. Using automated instrumentation, we enzymatically measured the serum concentrations of triglycerides, high-density lipoprotein cholesterol, and total cholesterol. The LDL cholesterol level was enzymatically determined when the triglyceride level was ≥400 mg/dL and using the Friedewald formula otherwise. Major adverse cardiac event (MACE) was defined as cardiovascular-related death, unstable angina, myocardial infarction, or staged revascularization. All clinical data were obtained from reviewing electrical health records of the patients.

ASSESSMENT OF CORONARY PLAQUE SCORE. Coronary CT was performed using a dual-source 64-slice system (Somatom Definition Flash, Siemens Medical System), as described in a previous study.[7] Two experienced radiologists, blinded to clinical status, evaluated all scans separately. The segments that were uninterpretable were scored as the same as most proximal interpretable segment. Discrepancies in evaluation were resolved during a consensus reading. Angiographic analysis by coronary CT was performed according to the 15-segment American Heart Association classification.[12] We assigned a score (0-5) to each of the 15 coronary artery segments according to the Society of Cardiovascular Computed Tomography guidelines (0 normal: absence of plaque and no luminal stenosis; 1 minimal: plaque with <25% stenosis; 2 mild: 25%-49% stenosis; 3 moderate: 50%-69% stenosis; 4 severe: 70%-99% stenosis; and 5 occluded).[13] We defined a coronary plaque score as the sum of scores of all the segments of coronary arteries.

ASSESSMENT OF CAROTID PLAQUE SCORE. The parameters for carotid ultrasonography were measured using the Aplio carotid ultrasonography machine (Toshiba Medical Systems) with a 7.5-MHz transducer by trained sonographers blinded to the clinical data. Carotid plaque score was computed by summing the maximal thickness of carotid plaques, defined as focal intima-media thickening ≥1.1 mm, in each segment on both sides (a + b + c + thickness of the contralateral plaques in each segment on both sides), as described previously.[14]

GENETIC ANALYSIS. A next-generation sequencer was used to evaluate genotypes. The coding regions of *APOB*, *LDLR*, *LDLRAP1*, and *PCSK9* were sequenced, as described previously.[15] Copy number variations at the *LDLR* were also assessed, as described previously, using the eXome Hidden Markov Model.[16] We used the standard American College of Medical Genetics and Genomics criteria

("pathogenic" or "likely pathogenic") to determine whether the genetic variants were pathogenic.[17]

ETHICAL CONSIDERATIONS. The Ethics Committee of Kanazawa University approved this study. All procedures conformed to the ethical standards of the Human Research Committee (institutional and national) and the Declaration of Helsinki (1975, revised in 2008). All study participants gave informed consent for genetic analysis.

STATISTICAL ANALYSIS. Normally distributed continuous variables are presented as mean ± SD. Meanwhile, continuous variables that did not follow a normal distribution are presented as median (IQR). All comparisons between categorical variables were performed using Fisher's exact test or the chi-square test, and the results are reported as numbers and percentages. For independent variables, Student's *t*-test was used to compare the means of continuous variables, and the nonparametric Wilcoxon-Mann-Whitney rank-sum test was used to compare the median values. The chi-square test or Fisher's post hoc test was performed for categorical variables as indicated. Spearman correlation coefficients were assessed among variables, including coronary and carotid plaque scores and age. Regression equations between coronary and carotid plaques were assessed. We calculated MACEs per 1,000 person-years. Cox proportional hazard model was used to identify risk factors associated with MACEs adjusting age, sex, hypertension, diabetes, smoking, LDL cholesterol, and pathogenic variants. Beginning at baseline, cumulative Kaplan-Meier survival curves were generated to compare the time to the first MACE. The R Project for Statistical Computing was used for all statistical analyses. *P* values <0.05 were used to denote statistical significance.

RESULTS

CLINICAL CHARACTERISTICS. The study participants' clinical characteristics are presented in **Table 1**. The mean age was 54 years, with an approximately equal sex distribution. At baseline, the median LDL cholesterol level was 229 mg/dL. Overall, 425 patients (68.3%) had a pathogenic variant of FH. After grouping patients based on the occurrence of MACEs, we observed several differences in age, sex, diabetes, hypertension, smoking, total cholesterol, high-density lipoprotein cholesterol, baseline LDL cholesterol, the prevalence of FH pathogenic variants, coronary plaque score, and carotid score between the groups. The distributions of coronary and carotid plaque score were skewed to the right (**Figure 1**). A summary of the follow-up medical treatments administered is presented in Supplemental Table 1. Most patients received statin therapy, followed by ezetimibe and colestimide.

TABLE 1 Baseline Characteristics

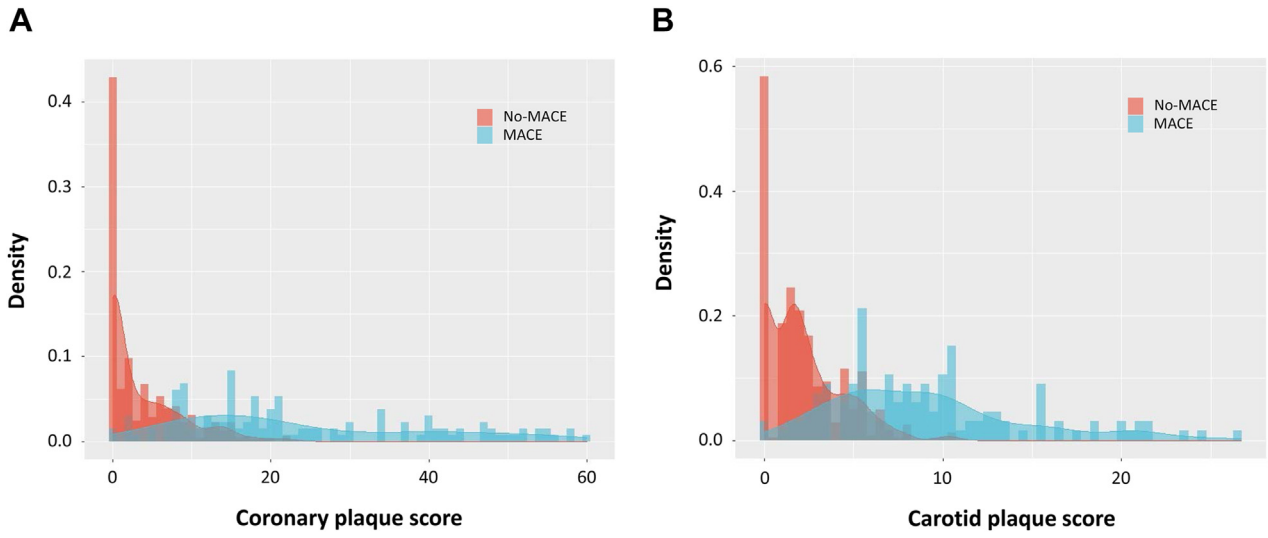
	All (N = 622)	MACE (n = 132)	NO MACE (n = 490)	*P* Value
Age (y)	54 ± 13	61 ± 13	52 ± 13	<0.001
Male	306 (49.2%)	82 (62.1%)	224 (45.7%)	0.009
Hypertension	200 (32.1%)	89 (67.4%)	111 (22.7%)	<0.001
Diabetes	64 (10.3%)	30 (22.7%)	34 (6.9%)	<0.001
Smoking	217 (34.9%)	74 (56.1%)	143 (29.2%)	<0.001
Total cholesterol (mg/dL)	318 (286-360)	321 (287-389)	316 (286-352)	0.040
Triglyceride (mg/dL)	130 (91-176)	133 (95-178)	129 (89-173)	0.17
High-density lipoprotein cholesterol (mg/dL)	46 (39-56)	42 (34-51)	48 (40-59)	<0.001
LDL cholesterol (at baseline, mg/dL)	229 (205-275)	258 (216-310)	225 (202-265)	<0.001
LDL cholesterol (at follow-up mg/dL)	108 (90-127)	108 (89-129)	107 (90-125)	0.53
FH pathogenic variants	425 (68.3%)	115 (87.1%)	310 (63.3%)	<0.001
Coronary plaque score	4 (0-10)	18 (11-35)	2 (0-6)	<0.001
Carotid plaque score	2.3 (1.2-5.4)	8.1 (5.4-11.3)	1.6 (0.0-3.3)	<0.001

Values are mean ± SD, n (%), or median (IQR). FH = familial hypercholesterolemia; LDL = low-density lipoprotein; MACE = major adverse cardiac event.

CORRELATION BETWEEN THE CORONARY PLAQUE SCORE AND CAROTID PLAQUE SCORE. We assessed the correlation between coronary and carotid plaque scores. These scores were significantly correlated in patients with HeFH in both sexes (Spearman's r = 0.82; $P < 0.001$ in males and Spearman's r = 0.87; $P < 0.001$ in females) (**Central Illustration**).

FACTORS ASSOCIATED WITH MACEs. Overall, 132 patients had MACEs (cardiovascular-associated death, unstable angina, myocardial infarction, and staged revascularization) over a median follow-up period of 13.2 years (IQR: 9.8-18.4 years) (Supplemental Table 2). Using the Cox proportional hazard model, we found that the following risk factors were significantly associated with MACEs: age (HR: 1.07; 95% CI: 1.03-1.11; $P < 0.001$), male sex (HR: = 1.80; 95% CI: 1.22-2.38; $P < 0.001$), hypertension (HR: 2.60; 95% CI: 1.80-3.40; $P < 0.001$), diabetes (HR: 1.88; 95% CI: 1.18-2.58; $P < 0.001$), smoking (HR: 3.12; 95% CI: 1.90-4.34; $P < 0.001$), LDL cholesterol (HR: 1.01; 95% CI: 1.00-1.02; $P = 0.039$, per 10 mg/dL), and the presence of pathogenic variants (HR: 2.54; 95% CI: 1.34-3.74; $P < 0.001$) (**Table 2**). In addition to these classical risk factors, both coronary plaque score (natural-log [coronary plaque score + 1]) and carotid plaque score (natural-log [carotid plaque score + 1]) were also associated with MACEs (HR: 3.33; 95% CI: 1.88-4.78; $P < 0.001$ and HR: 2.24; 95% CI: 1.28-3.20; $P < 0.001$, respectively).

FIGURE 1 Histogram of Coronary and Carotid Plaque Score



Blue = patients with MACE. Red = patients without MACE. (A) Histogram of coronary plaque score. (B) Histogram of carotid plaque score. MACE = major adverse cardiac event.

PROGNOSIS ACCORDING TO CORONARY AND CAROTID PLAQUE SCORE. We found trends that patients with higher plaque scores had higher event rates (MACEs per 1,000 person-years) (Supplemental Figure 2). After dividing patients into 3 groups based on coronary and carotid plaque score, we found that patients with both coronary and carotid plaque scores ≥ median exhibited the worst prognosis, followed by those with 1 score ≥ median, then by those with both scores < median (**Central Illustration**).

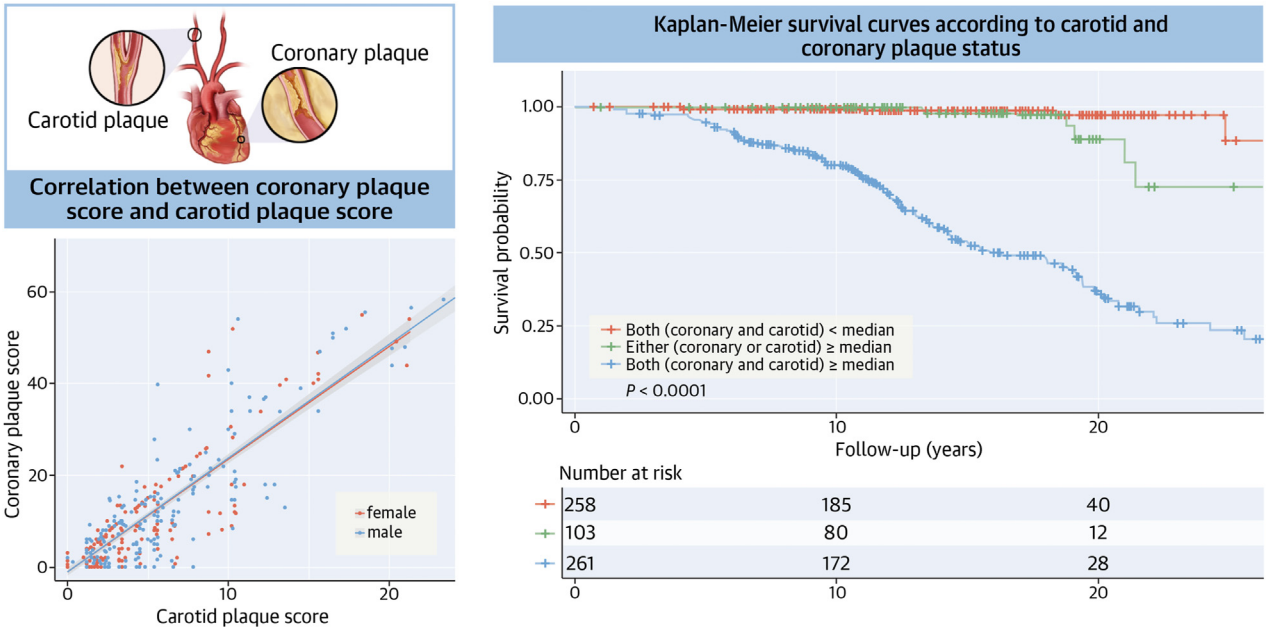
CLINICAL IMPACT OF CORONARY AND CAROTID PLAQUE SCORES OF ZERO. We identified 210 patients with coronary plaque score = 0 and 145 patients with carotid plaque score = 0. We calculated the event rates (MACEs per 1,000 person-years) of them and found that the event rate (MACEs per 1,000 person-years) of the patients without coronary plaque (coronary plaque score = 0) was significantly lower than that of patients with any coronary plaque (coronary plaque score >0) (0.68 vs 24.13 per 1,000 person-years, $P < 0.001$). Similarly, we found that the event rate (MACEs per 1,000 person-years) of the patients without carotid plaque (carotid plaque score = 0) was significantly lower than that of patients with any carotid plaque (carotid plaque score >0) (1.01 vs 20.53 per 1,000 person-years, $P < 0.001$).

DISCUSSION

In this study, we aimed to determine: 1) if the development of coronary and carotid plaques is correlated; and 2) if these plaques are associated with cardiovascular events among patients with HeFH both in primary prevention settings and in secondary prevention settings. We found that: 1) coronary and carotid plaque scores were significantly correlated; and 2) coronary and carotid plaque scores were significantly associated with MACEs.

Recent studies on FH have repeatedly shown the great advantages of the early diagnosis and treatment of this disease.[18,19] In fact, patients with HeFH who have been treated since childhood exhibited much better prognosis compared to those diagnosed and treated in adulthood.[20] Ideally, we need to diagnose patients with HeFH via universal screening and/or cascade screening in order to identify pediatric patients with FH without any manifestations other than elevated LDL cholesterol.[21] In reality, however, the diagnostic rate of HeFH is still quite low worldwide.[22] Moreover, the attainment of LDL cholesterol target among patients with HeFH has been inadequate.[23] Currently, clinical guidelines for FH recommend assessing systemic atherosclerosis via carotid ultrasound and/or coronary CT, although there is no clear indication regarding when and how they should be

CENTRAL ILLUSTRATION **Coronary Artery and Carotid Artery Plaques in Patients With Heterozygous Familial Hypercholesterolemia**



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(Right) Correlation between coronary plaque score and carotid plaque score. Each dot represents patients with HeFH. Blue = males. Red = female. (Left) Kaplan-Meier survival curves according to carotid and coronary plaque status. Red = patients whose coronary and carotid plaque score < median. Green: patients whose coronary or carotid plaque score ≥ median. Blue = patients whose coronary and carotid plaque score ≥ media.

used due to lack of clinical data. Carotid ultrasound should be the first-line diagnostic, since it allows for the noninvasive assessment of an important surrogate marker for HeFH. On the other hand, coronary CT can assess their coronary atherosclerosis more directly, but some patients avoid this because of radiation exposure and use of contrast agent. This study clearly demonstrated that coronary and carotid plaque development was significantly correlated with HeFH. Accordingly, we propose that carotid plaques should be initially assessed, then coronary CT should be considered among patients with any carotid plaques. Based on the strong correlation between carotid plaque and coronary plaque, we can estimate the progression of coronary plaque via carotid plaque that can be assessed noninvasively and routinely, and thus we can decide to assess coronary plaque invasively (**Central Illustration**). Moreover, it is interesting to note that patients without any plaque either in coronary or carotid artery rarely experienced MACEs despite their high-risk state for cardiovascular disease as HeFH.

Additionally, our results provide another useful insight into the timing of the initiation of LDL-lowering therapies in patients with HeFH. Current guidelines in Japan and other countries stipulate that LDL-lowering therapies should start at 8 to 10 years old, despite a lack of evidence from randomized controlled trials.[4-6] Based on our findings that carotid and coronary plaque start to progress at approximately 20 to 30 years, as well as results from observational studies showing that cardiovascular events start to occur at around 20 years old,[24,25]

TABLE 2 **Factors Associated With Major Adverse Cardiac Events**

	HR	95% CI	*P* Value
Age (per year)	1.07	1.03-1.11	<0.001
Male (yes vs no)	1.80	1.22-2.38	<0.001
Hypertension (yes vs no)	2.60	1.80-3.40	<0.001
Diabetes (yes vs no)	1.88	1.18-2.58	<0.001
Smoking (yes vs no)	3.12	1.90-4.34	<0.001
LDL cholesterol (per 10 mg/dl)	1.01	1.00-1.02	0.039
Pathogenic variants (vs without variants)	2.54	1.34-3.74	<0.001
Natural log (coronary plaque score + 1)	3.33	1.88-4.78	<0.001
Natural log (carotid plaque score + 1)	2.24	1.28-3.20	<0.001

LDL = low-density lipoprotein; MACE = major adverse cardiac event.

LDL-lowering therapies should be considered before these occur. Thus, starting LDL-lowering therapies at 8 to 10 years may be sufficient to prevent the development of atherosclerosis.

This study has several limitations. First, this was a single-center retrospective study, and thus, our study findings may not be generalizable to the broader population with FH. However, our institution has one of Japan's largest databases and a long history of treating patients with HeFH. Furthermore, we have validated the results of other studies involving patients with different ethnicities. Second, we were unable to account for treatment discontinuations or alterations during follow-up. Third, some patients were excluded from the analysis due to missing data or because they were lost to follow-up. Especially, the exclusion of patients with prior revascularization may significantly bias the results of age at atherosclerosis. Moreover, the age of onset is limited by the time of the HeFH diagnosis, leading to attenuate the results. Further studies comprehensively evaluating these conditions will be useful in estimating their overall risk assessment.

CONCLUSIONS

Coronary and carotid plaque scores were significantly correlated, and both were independently associated with MACEs. The assessments for coronary and/or carotid plaque are useful for further risk stratifications in patients with HeFH.

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ADDRESS FOR CORRESPONDENCE: Dr Hayato Tada, Department of Cardiovascular Medicine, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa 920-8641, Japan. E-mail: ht240z@sa3.so-net.ne.jp.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with heterozygous familial hypercholesterolemia: 1) coronary and carotid plaque scores were significantly correlated; and 2) coronary and carotid plaque scores were significantly associated with MACEs. These findings may help us understand when and how we should assess systemic atherosclerosis for patients with heterozygous FH.

TRANSLATIONAL OUTLOOK: Further research is warranted to reveal when the coronary and carotid plaque start to develop among patients with heterozygous familial hypercholesterolemia.

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KEY WORDS carotid plaque, coronary CT, familial hypercholesterolemia, genetics, LDL cholesterol

APPENDIX For supplemental tables and figures, please see the online version of this paper.