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Application of the Japanese Guidelines for the Diagnosis of Familial Hypercholesterolemia in General Practice:

It is to be Validated in International Harmonization

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The Japan Atherosclerosis Society has proposed guidelines for the diagnosis of familial hypercholesterolemia (FH) (JASG) in 2012[1)] and has published the renewed version in 2018[2)]. According to the guidelines, FH is identified by two of three major symptoms of high amounts of low-density lipoprotein (LDL)-cholesterol (≥ 180 mg/dL), family history of FH/premature coronary artery diseases (CAD), and tendon/skin xanthomas as Achilles tendon thickness (ATT) ≥ 9 mm[1)]. It is designed to encourage the identification of FH patients in the general practice[2)]. On the other hand, the Dutch Lipid Clinic Algorism (DLCA)[3)] is widely used for FH diagnosis in the European Union countries and else being based on a scoring system by family and clinical history, physical examination, and LDL cholesterol for the levels of certainty in diagnosis.

FH is a hereditary disorder in the receptor-mediated cellular uptake of LDL resulting in a marked elevation of plasma LDL and a high risk of CAD[2)]. Causative mutations are predominantly in the LDL receptor gene but also in other related genes, such as apoB, PCSK9, or ARH[2)]. Altogether, the prevalence of the FH allele is estimated to be 0.2–0.5% in the general population regardless of the ethnic background. Since more than one-half of the untreated FH is likely to develop premature CAD, a substantial portion of the CAD patients are from the FH population. A lower incidence of CAD in Japan than the West may make this contribution higher. It is therefore important to compare the FH contribution to CAD between Japan and the West to estimate the impact of FH management in our public health. The guidelines help in the survey of FH that is generally underdiagnosed in routine practice.

We investigated the prevalence of FH by using JASG and DLCA in consecutive 141 acute coronary syndrome (ACS) patients who visited Ichinomiya Nishi Hospital from May 2010 to December 2017. Informed consent was obtained from all the patients. The hospital with 464 beds and visited daily by some 1000 outpatients covers suburban-rural community of Ichinomiya city with a population of 390,000 as one of the 3 major hospitals of similar capacity. Plasma cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride levels were measured at the institutional clinical laboratory, and LDL cholesterol was determined using a homogeneous assay method standardized for the Friedewald procedure. ATT was measured on X-ray films as previously described[4)]. The study protocol was approved by the institutional ethics committee in accordance with Ethical Guidelines for Epidemiological Research, and Ethical Guidelines for Medical and Health Research Involving Human Subjects by Ministry of Health, Labor and Welfare of Japan.

Patients backgrounds are shown in the supplementary tables. The prevalence of FH by JASG and DLCA in this ACS population is described in **Table 1**. Tendinous xanthoma is one of the major symptoms in these guidelines but not quantitatively defined in DLCA. Arbitrary definitions were therefore introduced as ATT ≥ 9 mm following JASG and as ATT ≥ 12 mm to match its apparent palpable sign in physical

Key words: **Familial hypercholesterolemia, Acute coronary syndrome, Xanthoma, Japan Atherosclerosis Society guideline, Dutch Lipid Clinic Algorism**

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Table 1. Prevalence of FH in the ACS patients (N, %) based on diagnosis by JASG and by DLCA using ATT ≥ 9 mm and ATT ≥ 12 mm as categories Definite and Definite/Probable, in all ages and in Age groups under 60 year-old and the group of 60 or above

Age group	All	<60	60 ≤	*p*
N	141	26	115	
JASG	6 (4.3)	4 (15.4)	2 (1.7)	<0.002
DLCA, ATT ≥ 9mm				
Definite	4 (2.8)	3 (11.5)	1 (0.9)	0.003
Definite/Probable	21 (14.9)	6 (23.1)	15 (13.0)	0.194
DLCA, ATT ≥ 12mm				
Definite	2 (1.4)	1 (3.8)	1 (0.9)	0.246
Definite/Probable	6 (4.3)	3 (11.5)	3 (2.6)	0.042

Categorical variables were compared using the chi-square test or Fisher's exact test. A value of $P<0.05$ is considered statistically significant between the age groups

examination. According to JASG, 7 patients met the criteria of family history, 21 patients met the ATT criteria, and 13 met by LDL cholesterol criteria (**Supplementary Table 3**). Accordingly, 6 patients were identified as FH patients (4.3%). The prevalence of FH was much higher in the group aged <60 years (15.4%) than the other age group aged ≥ 60 years (1.7%; $p=0.002$). DLCA by using ATT ≥ 9 mm showed a definite FH of 2.8% overall with 11.5% under 60 years of age and 0.9% at over 60 years ($p=0.003$). Definite/probable FH was 14.8% overall, with 23.1% under 60 years of age and 13.0 at/over 60 years ($p=0.194$). With ATT ≥ 12 mm, the overall definite FH was 1.4%, with 3.8% under 60 years of age and 0.9% at/over 60 years ($p=0.246$). Consequently, under this definition, the definite/probable FH was 4.3% overall, with 11.5% in those <60 years of age and 2.6% in the older group ($p=0.042$).

Fig. 1 compares JASG and DLCA in finding FH in this cohort groups by showing the prevalence of FH in each 4-age group of under 60 years, 60 to 69 years, 70 to 79 years, and 80 years and higher. To make comparison easier, the results by DLCA were represented by "definite" with ATT ≥ 9 mm and "probable/definite" with ATT ≥ 12 mm. JASG and "definite" by DLCA with ATT ≥ 9 mm demonstrated more FH in the younger age group, but the other did not show significant difference.

A Switzerland study by DLCA identified 1.6% and 4.8% of probable/definite FH among ACS in all ages and those under 60 years of age, respectively[5]. A Danish study found a probable/definite FH of 2.0% and 7.0% in those with the first myocardial infarction of all ages and under 60 years of age, respectively[6, 7]. In contrast, EUROASPIRE covering 7044 coronary patients from 24 European countries found a more definite/probable FH of 8.3% in all ages and 15.4%

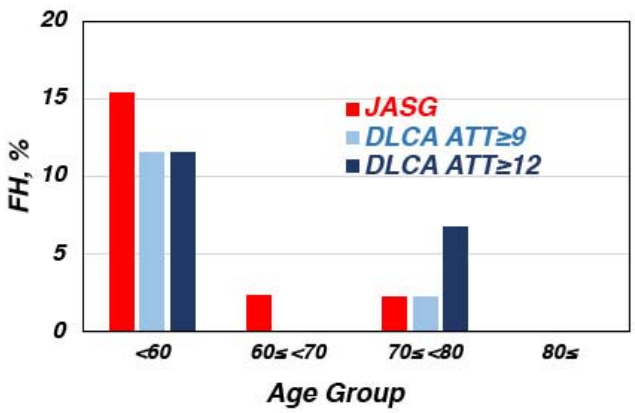

Fig. 1. Prevalence of familial hypercholesterolemia patients in each age groups of those with acute coronary syndrome

A total of 141 ACS patients are divided into those aged <60 years ($n=26$), 60 ≤ those <70 ($n=42$), 70 ≤ those <80 ($n=45$) and 80 ≤ those ($n=28$). Each age group is characterized in Supplementary Table 3. JASG indicates FH diagnosed by JASG, ATT ≥ 9 shows FH identified as definite by DLCA by using ATT ≥ 9 mm for tendon xanthoma criteria, and DLCA ATT ≥ 12 mm shows FH as definite/probable by DLCA with ATT ≥ 12 mm for tendon xanthoma. Data were analyzed using the 2-tailed Student *t* test for two groups, as ** indicates $p<0.01$ and * indicates $p<0.05$ against the age group of under 60 years.

and 5.1% for under and above 60 years, respectively[8]. Similar reports from China demonstrated a contribution of FH to CAD by adopting the DLCA definite/probable criteria, with 3.9% for all ages and 7.1% for under 60 years[9]. The higher prevalence of FH in ACS patients in the younger age group is consistent throughout these reports, while inconsistency may exist in the rate of FH contribution.

Ohmura, *et al.* reported that FH was 5.7% and 7.8% in all ages and under 60, respectively, using

JASG among 359 Japanese ACS patients from 5 major urban hospitals[10], which was higher than those of Swiss and Danish studies using DLCA. Our data using JASG among 141 ACS patients in a single community hospital in Japan demonstrated an FH of 4.3% in all and 15.4% in under 60 years of age, largely consistent with the previous report[10]. However, the application of DLCA to the same cohort yielded diverse data. The critical problem in DLCA appears to be the high score given to tendon xanthoma without clear definition. We may need more effort for harmonization and standardization among the guidelines for a reliable international comparison of FH contribution to public health. The most recent publication by Harada-Shiba, *et al*. found FH as 2.7 % among overall 1944 Japanese ACS patients[11]. It is of interest to analyze their data in a comparable manner to ours including grouping by age and application of DLCA.

The diagnosis of FH in general practice is not straightforward even with currently proposed guidelines. Genetic analysis does not cover all aspects, and its clinical features are diverse. Family history information is very important but inevitably overlooked in general practice. The common use of statin also causes difficulty and confuses masking the LDL cholesterol level of FH patients. Twenty-six percent of the patients in this study indeed took statins before the first visit. This may be beneficial for the patients but sometimes underdosed for FH. We always consider the possibility of underestimation of FH in such studies.

Footnotes

Nobukiyo Tanaka at nobukiyo282000@yahoo.co.jp is responsible for collecting and primary analysis of the data.

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Disclosures

None.

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Supplementary Table 1. Patients Characteristics

	N = 141
Age (y)	69.5 ± 11.9
Female (*n*, %)	36 (25.5%)
Diabetes Mellitus (n,%)	58 (41.1%)
Dyslipidemia (*n*, %)	95 (67.4%)
Hypertension (*n*, %)	98 (70.0%)
Smoking (*n*, %)	92 (65.2%)
Acute Coronary Syndrome (ACS)	3 (2.1%)
Age of initial ACS (y)	69.2 ± 12.4
Effort Angina	2 (1.4%)
Cerebral Infarction	14 (9.9%)
Cerebral Hemorrhage	1 (0.7%)
Family history within second degree relatives (*n*, %)	38 (27.1%)
Male relative with CAD under 50 yrs old (*n*, %)	5 (4.0%)
Female relative with CAD under 60 yrs old (*n*, %)	2 (1.5%)
Relative with Familial Hypercholesterolemia (*n*, %)	1 (0.7%)
Height (m)	1.60 ± 0.10
Body weight (kg)	61.6 ± 15.0
Body mass index (kg/m^2)	23.8 ± 4.2
Systolic blood pressure (mmHg)	139 ± 32
Diastolic blood pressure(mmHg)	81 ± 18
Heart Rate (bpm)	77 ± 23
Achilles' Tendon Thickness (mm)	7.6 ± 2.2
Total cholesterol (mmol/L)	5.02 ± 1.42
LDL cholesterol (mmol/L)	3.25 ± 1.24
HDL cholesterol (mmol/L)	1.14 ± 0.34
Triglyceride (mmol/L)	1.56 ± 1.49
Hemoglobin a1c (%)	6.4 ± 1.2
eGFR (mL/min/1.73 m^2)	64.4 ± 21.9

eGFR was estimated as $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ for men, and eGFR of men × 0.739 for women according to the estimate equation proposed by the Japanese Society of Nephrology.

Supplementary Table 2. Oral Medications (*N*, %)

	N=141
Aspirin	22 (15.6%)
Thienopyridine	12 (8.5%)
Anticoaglant	3 (2.1%)
Nicorandil	4 (2.8%)
Statin	36 (25.5%)
Fibrate	5 (3.5%)
EPA	3 (2.1%)
Ezetimibe	0 (0.0%)
Nicotinate	1 (0.7%)
ACE inhibitor	7 (5.0%)
ARB	43 (30.5%)
βblocker	7 (5.0%)
Calcium blocker	56 (39.7%)
Diuretics	11 (7.8%)
αglucosidase inhibitor	12 (8.5%)
Biganide	11 (7.8%)
Thiazolidine	9 (6.4%)
SGLT2 inhibitor	2 (1.4%)
DPP4 inhibitor	14 (9.9%)
Incletin	1 (0.7%)
Sulfonylureas and glinides	10 (7.1%)
Insulin	5 (3.5%)

Supplementary Table 3. Patients Characteristics by Age groups (*n*, %, unless otherwise defined)

Age group, *N*	< 60, *N* = 26	60 ≤ < 70, *N* = 42	70 ≤ < 80, *N* = 45	≤ 80, *N* = 28
Age, Ave ± SE (y)	50.3 ± 6.0	65.5 ± 2.8	74.7 ± 2.8	85.0 ± 3.0
Female	2 (7.7%)	9 (21.4%)	16 (35.6%)	9 (32.1%)
Diabetes Mellitus	8 (30.1%)	20 (47.6%)	22 (48.9%)	8 (28.6%)
Dyslipidemia	22 (84.6%)	33 (78.6%)	28 (62.2%)	12 (42.9%)
Hypertension	16 (61.5%)	26 (61.9%)	35 (77.8%)	21 (75.0%)
Smoking	24 (92.3%)	31 (73.8%)	23 (51.1%)	14 (50.0%)
Acute Coronary Syndrome (ACS)	0 (0.0%)	2 (4.8%)	0 (0.0%)	1 (3.6%)
Effort Angina	1 (3.8%)	1 (2.4%)	0 (0.0%)	0 (0.0%)
Cerebral Infarction	0 (0.0%)	4 (9.5%)	4 (8.9%)	6 (21.4%)
Cerebral Hemorrhage	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)
Family history in 2nd deg. relatives	9 (34.6%)	11 (26.3%)	13 (28.9%)	5 (17.9%)
Male relative with CAD under 50 yo	2 (7.7%)	1 (2.4%)	1 (2.2%)	1 (3.6%)
Female relative with CAD under 60 yo	1 (3.8%)	1 (2.4%)	0 (0.0%)	0 (0.0%)
Relative with FH	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)
Height (m)	1.69 ± 0.09	1.63 ± 0.10	1.57 ± 0.08	1.53 ± 0.09
Body weight (kg)	79.0 ± 15.9	62.6 ± 12.3	56.3 ± 9.5	52.6 ± 11.2
Body mass index (kg/m^2)	27.6 ± 5.1	23.6 ± 3.8	22.8 ± 2.7	22.3 ± 3.8
Systolic blood pressure (mmHg)	143 ± 27	140 ± 26	141 ± 34	130 ± 39
Diastolic blood pressure (mmHg)	91 ± 17	83 ± 17	79 ± 14	72 ± 21
Heart Rate (bpm)	76 ± 17	74 ± 18	79 ± 23	77 ± 33
Achilles' Tendon Thickness (mm)	8.1 ± 2.7	7.0 ± 1.2	7.9 ± 2.9	7.4 ± 1.5
Total cholesterol (mmol/L)	5.37 ± 1.42	4.94 ± 1.18	5.24 ± 1.77	4.44 ± 0.92
LDL cholesterol (mmol/L)	3.68 ± 1.32	3.40 ± 1.05	3.24 ± 1.45	2.63 ± 0.80
HDL cholesterol (mmol/L)	1.14 ± 0.35	1.08 ± 0.31	1.16 ± 0.36	1.21 ± 0.36
Triglyceride (mmol/L)	2.13 ± 2.23	1.47 ± 1.10	1.60 ± 1.49	1.11 ± 0.96
Hba1c	5.9 ± 0.7	6.5 ± 1.5	6.3 ± 1.1	6.2 ± 0.9
eGFR (mL/min/1.73 m^2)	76.9 ± 17.4	68.0 ± 21.2	61.6 ± 20.4	52.1 ± 22.4
LDL-C (mg/dL) > 180 mg/dl	6 (23.1%)	5 (11.9%)	2 (4.4%)	0 (0.0%)
Family History	3 (11.5%)	2 (4.8%)	1 (2.2%)	1 (3.6%)
ATT(mm) > 9.0 mm	6 (23.1%)	3 (7.1%)	7 (15.6%)	5 (17.9%)
Familial Hypercholesterolemia by JASG	4 (15.4%)	1 (2.3%)	1 (2.2%)	0 (0.0%)

Data are expressed as mean ± SD for continuous variables and as numbers (%) for categorical variables