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ORIGINAL ARTICLE
Ischemic Heart Disease

Prevalence and Prognosis of Familial Hypercholesterolemia in Patients With Acute Coronary Syndrome in Mie Prefecture, Japan

— Report From Mie ACS Registry —

Akihiro Takasaki, MD; Tairo Kurita, MD, PhD; Jun Masuda, MD, PhD; Kozo Hoshino, MD, PhD; Tetsuya Seko, MD, PhD; Takashi Tanigawa, MD, PhD; Tetsuya Kitamura, MD, PhD; Takehiko Ichikawa, MD, PhD; Masaaki Ito, MD, PhD; Kaoru Dohi, MD, PhD

Background: Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by elevated low-density lipoprotein cholesterol concentration and premature acute coronary syndrome (ACS). However, hereditary diseases may have regional characteristics, and few data are available regarding the prevalence of FH throughout particular regions in Japan. This study investigated the prevalence and prognosis of FH in patients with ACS in Mie Prefecture, Japan.

Methods and Results: This study investigated 738 ACS patients from the Mie ACS Registry in Mie Prefecture, and 706 (95.7%) with sufficient data to diagnose FH were enrolled for analysis. Eighteen patients (2.5%) were diagnosed with FH, which was similar to findings of another multidistrict registry conducted in Japan. Patients with FH were significantly younger and had a higher prevalence of premature onset of ACS than patients with non-FH (P<0.01). Incidence of major adverse cardiac and cerebrovascular events (MACCE) was not statistically different between patients with FH and non-FH in this study population, even in the propensity score-matched analysis.

Conclusions: Prevalence of FH in ACS patients from the Mie Prefecture was similar to that found in another Japanese multidistrict registry. Among ACS patients, short-term incidence of MACCE was not statistically different between patients with FH and non-FH in this study population.

Key Words: Acute coronary syndrome; Familial hypercholesterolemia; Prognosis

Familial hypercholesterolemia (FH) is an autosomal dominant disorder caused by a mutation of the gene for the low-density lipoprotein receptor (LDL-R) or genes for related molecules, and it is characterized by an elevated low-density lipoprotein cholesterol (LDL-C) concentration and premature coronary artery disease (CAD).[1–3] Patients with untreated heterozygous FH are reportedly ~13-fold more likely to develop CAD such as acute coronary syndrome (ACS) and angina pectoris than those with treated heterozygous FH.[1] Additionally, untreated men with FH reportedly develop CAD during their 30–50s, and untreated women develop CAD during their 50–70s.[2,3]

Although an estimated 300,000 people are affected by FH, the diagnosis rate is only <1% of the estimated number of patients with FH in Japan.[1,2,4] Unfortunately, many patients with FH are diagnosed after their first coronary event, which is usually in the form of ACS.[1,5] One survey showed that only 47% of Japanese primary care physicians are aware of the FH guideline. This rate is significantly lower than that in the United Kingdom (61%), and this difference might explain the underdiagnosis of FH in Japan.[6]

According to previous reports, the estimated prevalence of heterozygous FH ranges from 1/200 to 1/500, and that of homozygous FH ranges from 1/160,000 to

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Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu (A.T., T. Kurita, M.I., K.D.); Department of Cardiology, Mie Prefectural General Medical Center, Yokkaichi (J.M.); Department of Cardiology, Nagai Hospital, Tsu (K.H.); Department of Cardiology, Japanese Red Cross Ise Hospital, Ise (T.S.); Department of Cardiology, Matsusaka Chuo General Hospital, Matsusaka (T.T.); Department of Cardiology, Suzuka Chuo General Hospital, Suzuka (T. Kitamura); and Department of Cardiology, Kuwana City Medical Center, Kuwana (T.I.), Japan

Mailing address: Tairo Kurita, MD, PhD, Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu 514-8507, Japan. E-mail: k_siho_yuu@hotmail.com

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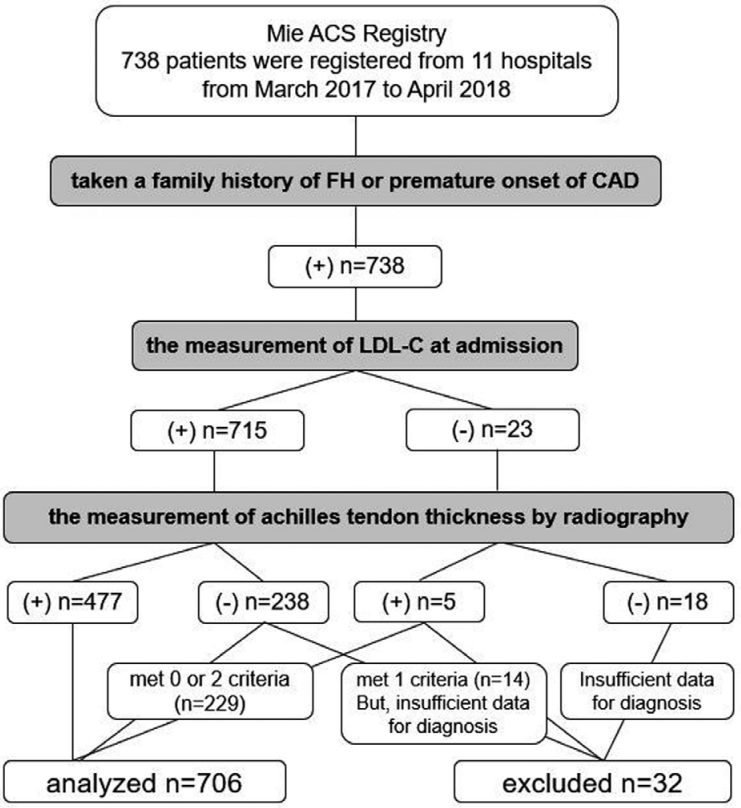

Figure 1. Flow chart of patient enrollment. ACS, acute coronary syndrome; FH, familial hypercholesterolemia; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol.

1/1,000,000.[1,7–11] Hereditary diseases may have regional characteristics, and previous studies have suggested that heterozygous FH occurs more frequently in certain populations of the world (Christian Lebanese in Lebanon, French Canadians in Quebec, Afrikaners in South Africa, and Ashkenazi Jews).[2,12] In addition, the frequency of some LDL-R mutations might differ among regions in Japan.[9,13,14] Multidistrict registries showed that the prevalence of FH in patients with ACS ranges from 2.7% to 5.7% in Japan.[15,16]

A multicenter prospective cohort study of patients with ACS in Switzerland (SPUM-ACS study) showed that FH was associated with poorer prognosis among patients with ACS.[17] Recent studies have proven the effectiveness of intervention with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for patients with early-stage FH and those with concurrent ACS and FH; thus, early diagnosis of FH will be of great benefit to patients.[18–20] However, no reports have addressed the prevalence of FH in patients with ACS throughout a particular region or the prognostic importance of FH in patients with ACS in Japan.

The present study was conducted to estimate the prevalence of heterozygous FH in patients with ACS in Mie Prefecture, Japan, and to compare the prognosis between FH and non-FH.

Methods

Study Population

The Mie ACS Registry is a prospective multicenter registry that started in 2013 in Mie Prefecture,[21,22] and we focused on evaluating the prevalence of FH and prognosis of 738 consecutive patients with ACS enrolled from 11 hospitals participating in the Mie ACS Registry between March 2017 and April 2018. Of the 738 patients, 32 (4.3%) were excluded because of insufficient data. Of these 32 patients, 18 had insufficient data for both plasma LDL-C concentration at admission and Achilles tendon thickness, and 14 patients were excluded because they met 1 of the 3 criteria of the 2017 Japan Atherosclerosis Society (JAS) guidelines for the diagnosis of FH and could not be diagnosed because of missing data for at least 1 criterion. Finally, we analyzed 706 (95.7%) patients with ACS to determine the prevalence and prognosis of FH (**Figure 1**). We also investigated the rate of successful diagnosis of FH by attending physicians at each institution, and compared the treatment effects, including changes in LDL-C concentration, during follow up between FH patients who were successfully diagnosed and those who were misdiagnosed by their attending physicians.

This registry was approved by the Institutional Review Board of Mie University Graduate School of Medicine and each participating institutional ethics committee (Reference number 2881). The UMIN Clinical Trial Registry number is UMIN 000036020.

Definition of FH

FH was diagnosed according to the 2017 JAS guidelines for the diagnosis of FH in adults.[2] Adults (aged ≥15 years) meeting 2 or more of the following criteria were diagnosed with FH: hyper-LDL cholesterolemia (untreated LDL-C

Table 1. Baseline Patient Characteristics

	All patients (n=706)	FH patients (n=18)	Non-FH patients (n=688)	P value
Age, years	70.0 (61.0–79.0)	55.5 (49.0–65.5)	70.0 (62.0–79.0)	<0.01
Male gender, n (%)	547 (77.5)	14 (77.8)	533 (77.5)	1.00
Premature onset, n (%)	112 (15.9)	10 (55.6)	102 (14.8)	<0.01
BMI, kg/m^2	23.1 (21.0–25.2)[a]	24.0 (22.7–25.2)[b]	23.1 (21.0–25.2)[c]	0.04
Cardiovascular risk factors				
Hypertension, n (%)	439 (62.2)	7 (38.9)	432 (62.8)	0.05
Diabetes mellitus, n (%)	232 (32.9)	2 (11.1)	230 (33.4)	0.07
Dyslipidemia, n (%)	330 (46.7)	15 (83.3)	315 (45.8)	<0.01
Hyperuricemia, n (%)	46 (6.5)	3 (16.7)	43 (6.3)	0.11
Current smoking, n (%)	202 (28.6)	8 (44.4)	194 (28.2)	0.18
Family history of CAD, n (%)	61 (8.6)	8 (44.4)	53 (7.7)	<0.01
Prior myocardial infarction, n (%)	47 (6.7)	1 (5.6)	46 (6.7)	1.00
Prior PCI, n (%)	30 (4.2)	0 (0.0)	30 (4.4)	1.00
Prior CABG, n (%)	4 (0.6)	0 (0.0)	4 (0.6)	1.00
Prior cerebral infarction, n (%)	30 (4.2)	0 (0.0)	30 (4.4)	1.00
Diagnosis rate of FH before ACS, n (%)		0 (0.0)		
Diagnosis of FH				
LDL-C, mg/dL				
Direct method at admission	124.6 (37.3)[d]	181.3 (44.4)[e]	116.3 (35.8)[f]	<0.01
Calculated method at admission	118.4 (38.2)[g]	193.7 (46.4)	122.4 (34.8)[h]	<0.01
Achilles tendon thickness ≥9 mm, n (%)	79 (16.4)[i]	13 (72.2)	66 (14.2)[j]	<0.01
Achilles tendon thickness, mm	7.4 (6.7, 8.5)[i]	9.3 (8.9, 10.5)	7.3 (6.6, 8.3)[j]	<0.01
Family history of FH or premature CAD, n (%)	15 (2.1)	10 (55.6)	5 (0.7)	<0.01

Data are presented as mean (standard deviation), median (interquartile range) or number (percentage). ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; FH, familial hypercholesterolemia; LDL-C, low density lipoprotein-cholesterol; PCI, percutaneous coronary intervention. [a]n=667. [b]n=18. [c]n=649. [d]n=549. [e]n=17. [f]n=532. [g]n=622. [h]n=604. [i]n=482. [j]n=464.

concentration of 180 mg/dL); tendon xanthomas (including Achilles tendon hypertrophy of ≥9 mm) or xanthoma tuberosum; and a family history of FH or premature CAD in a first- or second-degree relative. Premature CAD was defined as the occurrence of CAD in men aged <55 years and women aged <65 years.[2] A family history of premature CAD was based on patient reports of a coronary event in one or more of the patient's first- or second-degree relatives. Achilles tendon thickness was evaluated by means of radiography; it was measured at each site by highly trained cardiologists according to the method that conformed with the guideline.

Lipid Profile

The lipid profile was measured from the first blood draw at the emergency department at each institute. The total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were enzymatically measured using an automated analyzer in the clinical laboratories of each institution. The LDL-C concentration was calculated with the Friedewald method, unless the triglyceride concentration was >400 mg/dL.[23] We adopted the LDL-C concentration measured by the direct method if adaptation of the Friedewald method was inappropriate. For patients in whom lipid-lowering drugs had been prescribed before admission, we obtained their baseline LDL-C concentrations prior to starting lipid-lowering therapy.

Definitions of Covariables

The diagnosis of acute myocardial infarction (MI) was based on the third universal definition of MI.[24] Cardiovascular (CV) death was defined using the classification established by the Academic Research Consortium. Briefly, all deaths caused by heart conditions (e.g., MI, heart failure, or fatal arrhythmia), deaths without witnesses, deaths for which other causes could not be identified, deaths related to procedures, and deaths caused by conditions affecting blood vessels other than the coronary arteries (e.g., CV disease, pulmonary embolism, rupture of an aortic aneurysm, or aortic dissection) were considered CV deaths.

Outcomes

Outcome data were collected by performing patient interviews at the outpatient clinic, hospital chart reviews, or telephone interviews with the patient or close relatives, and the clinical events were recorded in a Web-based system by a well-trained cardiologist. Patients who were lost to follow up were censored using data from the last contact. Major adverse cardiac and cerebrovascular events (MACCE) were defined as CV death, non-fatal MI, unstable angina pectoris requiring admission, heart failure requiring admission, and stroke requiring admission during follow up.

Statistical Analysis

Continuous variables with a normal distribution are expressed as the mean±standard deviation, and those without a normal distribution are expressed as median and interquartile range. Categorical variables are expressed as number and percentage. The chi-squared test or Mann-

Table 2. Laboratory Data and Medication Use Prior to Admission and After Discharge

	All patients (n=706)	FH patients (n=18)	Non-FH patients (n=688)	P value
Laboratory data				
Total cholesterol, mg/dL	195.1 (41.5)[a]	271.3 (52.8)	192.9 (39.2)[b]	<0.01
Triglyceride, mg/dL	108.0 (77.0–162.8)[c]	139.0 (85.0–139.0)[d]	107 (76.0–162.0)[e]	0.34
HDL-C, mg/dL	49.0 (41.0–58.0)[f]	49.0 (45.1–61.8)	49.0 (41.0–58.0)[g]	0.47
LDL-C, mg/dL				
Direct method at admission	124.6 (37.3)[h]	181.3 (44.4)[i]	116.3 (35.8)[j]	<0.01
Calculated method at admission	118.4 (38.2)[k]	193.7 (46.4)	122.4 (34.8)[l]	<0.01
Creatinine, mg/dL	0.86 (0.71–1.05)	0.78 (0.69–0.84)	0.86 (0.71–1.05)	0.07
Hemoglobin, g/dL	14.1 (12.8–15.2)	14.5 (13.9–15.3)	14.1 (12.7–15.2)	0.11
Glucose, mg/dL	153 (124–201)[m]	127 (102–140)	155 (125–202)[n]	<0.01
HbA1c, %	6.0 (5.7–6.9)[o]	5.8 (5.5–6.2)[p]	6.0 (5.7–6.9)[q]	0.15
Peak CPK, IU/L	1,655 (627–3,082)[r]	2,207 (1,195–3,335)[s]	1,648 (615–3,069)[t]	0.29
Medication prior to admission				
Statin, n (%)	138 (19.5)	2 (11.1)	136 (19.8)	0.55
Ezetimibe, n (%)	9 (1.3)	1 (5.6)	8 (1.2)	0.21
Fibrates, n (%)	4 (0.6)	4 (22.2)	0 (0)	1.00
EPA/DHA, n (%)	8 (1.1)	8 (44.4)	0 (0)	1.00
Medication at discharge				
ACE-I or ARB, n (%)	593 (84.0)	16 (88.9)	577 (83.9)	0.75
β-blocker, n (%)	385 (54.5)	11 (61.1)	374 (54.4)	0.64
Calcium channel blocker, n (%)	137 (19.4)	3 (16.7)	134 (19.5)	1.00
Statin, n (%)	639 (90.5)	17 (94.4)	622 (90.4)	1.00
Ezetimibe, n (%)	61 (8.6)	7 (38.9)	54 (7.8)	<0.01
Fibrate, n (%)	0 (0)	0 (0)	0 (0)	NA
EPA/DHA, n (%)	23 (3.3)	0 (0.0)	23 (3.3)	1.00
Insulin, n (%)	47 (6.7)	1 (5.6)	46 (6.7)	1.00
Oral antidiabetic, n (%)	162 (22.9)	1 (5.6)	161 (23.4)	0.09

Data are presented as mean (standard deviation), median (interquartile range) or number (percentage). ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CPK, creatinine phosphokinase; EPA/DHA, eicosapentaenoic acid/docosahexaenoic acid; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NA, not available. [a]n=669. [b]n=651. [c]n=674. [d]n=17. [e]n=657. [f]n=674. [g]n=656. [h]n=549. [i]n=17. [j]n=532. [k]n=622. [l]n=604. [m]n=703. [n]n=685. [o]n=609. [p]n=16. [q]n=593. [r]n=638. [s]n=15. [t]n=623.

Whitney U-test was used to compare categorical variables according to a nominal or ordinal scale. The Student's t-test or the Wilcoxon rank sum test was used for continuous variables, as appropriate. Event analyses are displayed using Kaplan-Meier survival curves and were compared with the log-rank test. A Cox regression model was used to investigate the independent predictors of MACCE. The propensity score was estimated using a multivariable logistic regression model that included the following variables: age, hypertension, family history of premature CAD, and LDL-C concentration. Statistical significance was defined as $P<0.05$. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and R software packages V.4.0.0 for Windows (R Development Core Team).

Results

Baseline Characteristics of the Entire Study Population

In total, 706 patients (95.7%) with sufficient data for diagnosis were enrolled for analysis (**Figure 1**). We took a family history of FH or premature onset of CAD from all enrolled patients. There was no patient who had detected xanthoma by physical examination, even for the patients not receiving X-ray examination. The patients' median age was 70.0 years, and 77.5% were men (**Table 1**). The median body mass index was 23.1 kg/m^2. The prevalence of CV risk factors such as hypertension, diabetes mellitus, dyslipidemia, and current smoking was 62.2%, 32.9%, 46.7% and 28.6%, respectively. A history of prior MI was present in 6.7% of patients. Regarding the clinical diagnosis of ACS, approximately two-thirds of the patients developed ST-elevation MI, and approximately 80% of the patients were classified as having Killip class 1 MI. The prevalence of premature ACS was 15.9%. Although statins and ezetimibe were prescribed for 19.5% and 1.3% of patients before hospitalization due to ACS, respectively, the rate of prescription increased to 90.5% and 8.6% at discharge, respectively (**Table 2**).

The overall rate of missing data from analyzed patients was 1.9%, and only 6 parameters had a missing rate of >5% (BMI: 5.7%, final TIMI 3 flow grade: 7.6%, peak CPK: 9.4%, LDL-C concentration on admission: 9.7%, HbA1c: 13.8% and Achilles tendon thickness: 32.6%). The missing data rate of peak CPK among patients with acute MI (AMI: n=641) was only 0.3%. Although the data missing rate for Achilles tendon thickness was relatively high (n=224, 32.6%), all 224 patients were successfully diagnosed with non-FH regardless of the result of Achilles tendon thickness. In addition, all these patients had no

Table 3. Angiographic Data and PCI Procedure

	All patients (n=706)	FH patients (n=18)	Non-FH patients (n=688)	P value
Diagnosis				
STEMI, n (%)	478 (67.7)	10 (55.6)	468 (68.0)	0.31
NSTEMI, n (%)	163 (23.1)	5 (27.8)	158 (23.0)	0.58
UAP, n (%)	65 (9.2)	3 (16.7)	62 (9.0)	0.23
Killip 1, n (%)	564 (79.9)	16 (88.9)	548 (79.7)	1.00
2/3, n (%)	84 (11.9)	1 (5.6)	83 (12.1)	
4, n (%)	58 (8.2)	1 (5.6)	57 (8.3)	
LVEF, %	57.5 (11.7)	57.0 (12.6)	57.5 (11.6)	0.86
Angiographic data				
Culprit artery				
LMT, n (%)	15 (2.1)	0 (0.0)	15 (2.2)	1.00
LAD, n (%)	320 (45.3)	10 (55.6)	310 (45.1)	0.47
RCA, n (%)	255 (36.1)	5 (27.8)	250 (36.3)	0.62
LCX, n (%)	108 (15.3)	3 (16.7)	105 (15.3)	0.75
Multi vessel disease, n (%)	215 (30.5)	5 (27.8)	210 (30.5)	1.00
Strategy of ACS				
PCI, n (%)	676 (95.8)	17 (94.4)	659 (95.8)	0.55
Final non-TIMI 3 flow grade, n (%)	40 (6.1)[a]	1 (6.7)[b]	39 (6.1)[c]	1.00
CABG, n (%)	13 (1.8)	1 (5.6)	12 (1.7)	0.29

Data are presented as mean (standard deviation). ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction trial; UAP, unstable angina pectoris. [a]n=651. [b]n=15. [c]n=636.

Table 4. Lipid-Lowering Therapy and LDL-C Control for FH Patients

	Admission data		Follow-up data									
	Patient number	LDL-C (mg/dL)	LDL-C (mg/dL)	Reduction of LDL-C (mg/dL)	LDL-C <100 mg/dL	LDL-C <70 mg/dL	Statin	Statin (Intensive)	Ezetimibe	PCSK9 inhibitor	Follow-up duration	Follow-up rate
All	18	187.4 (50.4)	74.4 (34.5)	116.9 (68.9)	80% (12/15)	33.3% (5/15)	100% (15/15)	46.7% (7/15)	80% (12/15)	20% (3/15)	550 (402–626)	83.3% (15/18)
Diagnosis of FH by a physician	6	193.8 (75.2)	60.5 (43.3)	133.3 (99.6)	83.3% (5/6)	50% (3/6)	100% (6/6)	100% (6/6)	100% (6/6)	50% (3/6)	466 (391–527)	100% (6/6)
Diagnosis of FH by study analysis	12	184.3 (36.3)	83.6 (25.9)	105.9 (41.9)	77.8% (7/9)	22.2% (2/9)	100% (9/9)	11.1% (1/9)	66.7% (6/9)	0% (0/9)	563 (539–641)	75% (9/12)
P value		0.72	0.22	0.47	0.80	0.28	0.43	<0.01	0.12	0.02	0.20	0.19

Data are presented as mean (standard deviation), median (interquartile range) or number (percentage). P value for comparison between "Diagnosed during follow up" and "Undiagnosed during follow up". LDL-C, low-density lipoprotein-cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9. Intensive statin: atorvastatin ≥20 mg, rosuvastatin ≥10 mg and pitavastatin ≥4 mg.

Achilles tendon xanthoma, as determined by physical examination.

Prevalence and Clinical Characteristics of FH

The characteristics of patients with FH and non-FH are shown in **Table 1**. Of the 706 patients, 18 (2.5%) were diagnosed with FH. Patients with FH were significantly younger than those with non-FH (55.5 vs. 70.0 years, respectively; P<0.01). Of 112 patients with premature onset of ACS, 10 (8.9%) had FH. The prevalence of premature onset of ACS was significantly higher in patients with FH than non-FH (55.6% vs. 14.8%, respectively; P<0.01). A history of hypertension and diabetes mellitus was more prevalent in patients with non-FH than FH. No patients had been diagnosed with FH before hospitalization for ACS. The Achilles tendon was significantly thicker in patients with FH than non-FH (9.3 vs. 7.3 mm, respectively; P<0.01; **Table 1**). Of all 706 patients, 156 patients (22.1%) were prescribed lipid-lowering drugs before admission. We obtained baseline LDL-C concentrations prior to starting lipid-lowering therapy for 115 out of 156 patients. The total cholesterol and LDL-C concentrations were higher in patients with FH than non-FH, without significant differences in triglycerides and high-density lipoprotein cholesterol. Although the prescription rate of statins at discharge was not significantly different between patients

Table 5. Outcome Data

	All patients (n=706)	FH patients (n=18)	Non-FH patients (n=688)	P value
Follow-up period, days (median)	385.6 (365.0–468.0)	394.0 (365.0–512.7)	385.5 (365.0–467.5)	0.23
MACCE, n (%)	70 (9.9)	1 (5.6)	69 (10.0)	1.00
Cardiovascular death, n (%)	29 (4.1)	0 (0.0)	29 (4.2)	1.00
Non-fatal myocardial infarction, n (%)	13 (1.8)	0 (0.0)	13 (1.9)	1.00
Unstable angina pectoris requiring revascularization, n (%)	5 (0.7)	0 (0.0)	5 (0.7)	1.00
Heart failure requiring hospitalization, n (%)	16 (2.3)	0 (0.0)	16 (2.3)	1.00
Stroke requiring hospitalization, n (%)	15 (2.1)	1 (5.6)	14 (2.0)	0.32

Data are presented as median (interquartile range) or number (percentage). FH, familial hypercholesterolemia; MACCE, major adverse cardiac or cerebrovascular events.

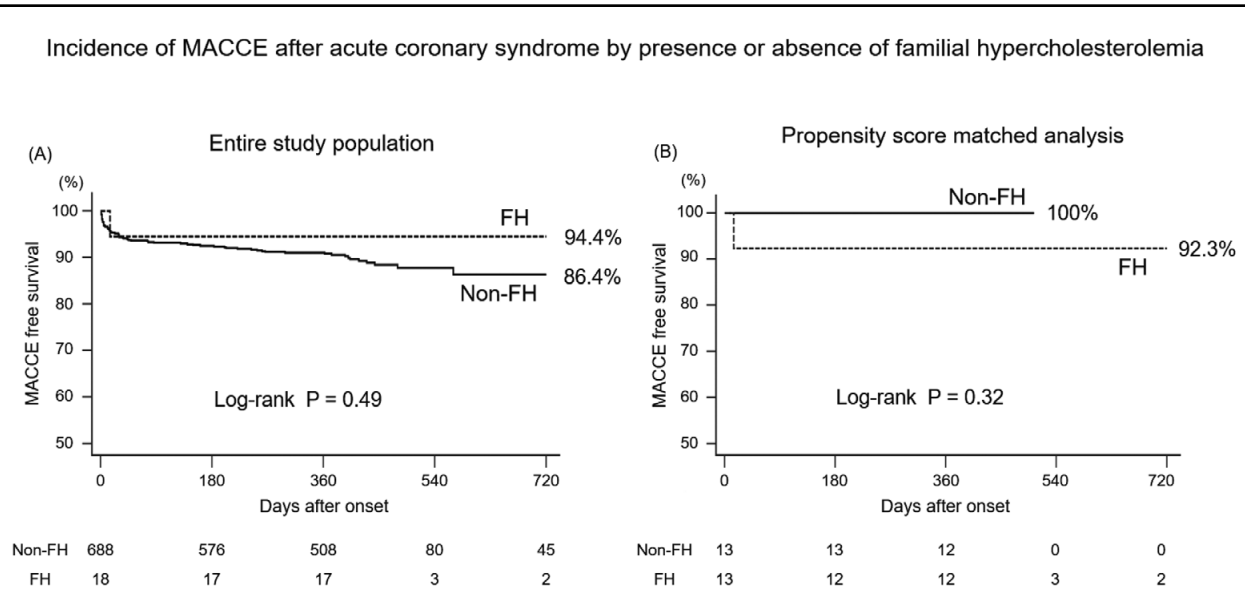

Figure 2. Incidence of MACCE after acute coronary syndrome in patients with FH and non-FH. (**A**) Kaplan-Meier survival curve for the entire study population. (**B**) Kaplan-Meier survival curve for the propensity score-matched patients. MACCE, major adverse cardiac and cerebrovascular events; FH, familial hypercholesterolemia.

with FH and non-FH (94.4% vs. 90.4%, respectively; P=1.00), ezetimibe was prescribed significantly more often at discharge in patients with FH than non-FH (38.9% vs. 7.8%, respectively; P<0.01; **Table 1** and **Table 2**).

No significant differences were found in angiographic data or percutaneous coronary intervention procedures between patients with FH and non-FH (**Table 3**).

Changes in Lipid Profiles in Patients With FH

Changes in the lipid profiles and management regimens after ACS among patients with FH are reported in **Table 4**. Of 18 patients with FH, only 2 (11.1%) had been prescribed statins before hospitalization for ACS under the diagnosis of dyslipidemia. Furthermore, only 6 (33.3%) patients were successfully diagnosed by their attending physicians at each institution during follow up. The remaining 12 (66.7%) patients were retrospectively diagnosed as having FH after the data analysis of the present registry. In addition, 50.0% (3 of 6) of FH patients who were diagnosed during hospitalization and 22.2% (2 of 9) of those who were misdiagnosed during hospitalization achieved an LDL-C concentration <70 mg/dL during follow up. The rate of intensive statin administration was 100% for the former but remained at 11.1% for the latter. Furthermore, the rate of PCSK9 inhibitor administration was 50% for the former but remained at 0% for the latter. All patients with FH who had an LDL-C concentration <70 mg/dL were treated with a PCSK9 inhibitor (**Table 4**).

Prognosis of FH in Patients With ACS

During the median follow-up period of 386 days (range, 365–468 days), 70 (9.9%) patients developed MACCE. A total of 29 (4.1%) patients died due to cardiovascular cause; 13 (1.8%) had non-fatal MI, and 15 (2.1%) had a stroke requiring hospitalization. Only 1 (5.6%) patient with FH developed MACCE (a stroke requiring hospitalization). Thus, the incidence of MACCE was not statistical different between patients with FH and non-FH in this study population (5.6% vs. 10.0%, respectively; P=0.50; **Table 5**). In addition, the Kaplan-Meier survival curves demonstrated

a MACCE rate without statistical difference between patients with FH and non-FH (94.4% vs. 86.4%, respectively; P=0.49) (**Figure 2A**). Incidence of MACCE was evaluated after propensity score matching for age, hypertension, family history of CAD, and the LDL-C concentration on admission, and 13 patients from each group were well matched when a 1:1 matching algorithm was used. MACCE was documented in only 1 patient with FH, and no MACCE occurred in patients with non-FH. There was no significant difference in the MACCE rate between patients with FH and non-FH (92.3% vs. 100%, respectively; P=0.32; **Figure 2B**).

Discussion

This is the first study in Japan to investigate the prevalence and prognosis of FH in patients with ACS throughout a particular region (Mie Prefecture). The prevalence of FH in patients with ACS was similar between the present study and the EXPLORE-J study. However, it was significantly lower in patients with ACS in the present study and in the EXPLORE-J study than that reported by Ohmura et al. Additionally, the rate of short-term MACCE between ACS patients with FH and non-FH was not statistical different in this study population.[15,16]

Prevalence of FH in Patients With ACS

It is considered difficult to estimate the actual prevalence of heterozygous FH in Japan because of underdiagnosis in daily clinical practice. Underdiagnosis is problematic because of the low penetration of the FH diagnostic guideline. In one study, however, the prevalence of heterozygous FH, estimated from the prevalence of homozygous FH using the Hardy–Weinberg equilibrium equation, was 1 in 208 people in the Hokuriku District of Japan.[9] In the DNA analysis of that study, LDL-R mutants and PCSK9 mutants were found, and the frequency of K790X LDL-R mutation was different from that in another district in Japan.[9] Therefore, it is important to consider regional characteristics in epidemiological studies of hereditary diseases.

The prevalence of FH was 2.5% in all patients with ACS and 8.9% in those with premature onset in the Mie prefecture. According to these results, the prevalence of FH in ACS patients is at least 5- to 12-fold higher than the estimated prevalence of FH in the general population (0.2–0.5% based on the 1/200–1/500 prevalence).[25] These results are consistent with previous findings in the EXPLORE-J study, which involved 69 Japanese institutes from various districts in Japan.[15] Based on these results, it may be reasonable to assume that the prevalence of FH in patients with ACS in the Mie Prefecture is almost identical to that in other areas of Japan, and that there is no regionality. In contrast, Ohmura et al found a significantly higher prevalence of FH in ACS patients than that in the present study population, presumably because of a lower number of patients and a greater rate of missing data for the diagnosis of FH among enrolled patients.[16]

A previous study reported that Achilles tendon thickness is known to have a significant correlation with age.[26] In addition, statin therapy for ACS patients before onset might affect the measurement of Achilles tendon thickness, which might affect the diagnosis of FH. Non-FH patients in the Mie-ACS Registry showed a higher Achilles tendon xanthoma rate compared to the EXPLORE-J study, presumably because patients in the present study were older and there was a lower prevalence of statin therapy before ACS onset compared to that for patients in the EXPLORE-J study. In addition, this might be one of the differences that the EXPLORE-J study had compared with the present study, whereby the central reading when measuring the Achilles tendon thickness to obtain a more accurate measurement was used.[15]

Underdiagnosis of FH and Underutilization of Lipid-Lowering Therapies

Of 18 patients with FH, only 6 (33.3%) were successfully diagnosed by their attending physicians during follow up after ACS onset in this study. This finding indicates the low diagnosis rate of FH in Japan, which is consistent with previous studies.[1] There are several possible reasons for this low diagnosis rate. First, the use of statins is widespread, and the true LDL-C concentration is not known in many patients because statins were already prescribed before ACS admission without a proper diagnosis of FH. We obtained the previous LDL-C concentration before starting statin for 115 out of 156 patients (73.7%). In this study, these findings may have helped to minimize underestimation of FH prevalence in ACS patients. Second, the LDL-C concentration may be low because of cholesterol catabolism after hospitalization for ACS, masking the true LDL-C concentration (one of the criteria for FH).[27] Several previous reports revealed that the LDL-C level in the acute phase of AMI decreases, and the degree of decrease depends on the myocardial damages and presence or absence of reperfusion therapy.[27–30] These findings make it difficult to identify the native LDL-C of AMI patients in the acute phase, which leads to a more difficult diagnosis for FH. In the present study, the number of ACS patients for which a blood sample was collected after 24h exceeded that obtained at onset, which was 10.9% (77/706 analyzed patients). In these patients, LDL-C, prior to admission, was revealed in 9 patients, and 1 patient was diagnosed with FH, using 2 other diagnostic criteria. Of the remaining 67, 8 had Achilles tendon thickening. If all those patients were assumed to have FH, the probability of FH could increase from an initial 2.5% to 3.7%. These findings demonstrated that there is a limitation to diagnosing FH properly in ACS patients in the statin era. For these ACS patients, genetic molecular analysis might be needed for long-term management. Third, premature onset of ACS is no longer unusual because of Westernization of the Japanese lifestyle. Fourth, low penetration of the diagnostic guideline for FH has led to insufficient examination of tendon xanthomas and insufficient interviews of patients regarding their family history of FH and premature CAD. Although all patients with FH were prescribed statins during follow up in this study, the rate of intensive statin use was only 46.7%. In addition, only 33.3% of patients with FH had a LDL-C concentration controlled at <70 mg/dL, which is the recommended LDL-C target value in the guideline.[31–33] Likewise, Singh et al reported that only two-thirds of patients with FH were discharged on high-intensity statin therapy, and the vast majority had an elevated LDL-C concentration at 1 year.[34] Moreover, despite the rate of prescription for ezetimibe increasing from 38.9% to 80.0% during follow up, the rate of PCSK9 inhibitor administration remained at only 20.0% in patients with FH and concurrent ACS. A recent study demonstrated that the addition of a PCSK9 inhibitor (alirocumab) to intensive

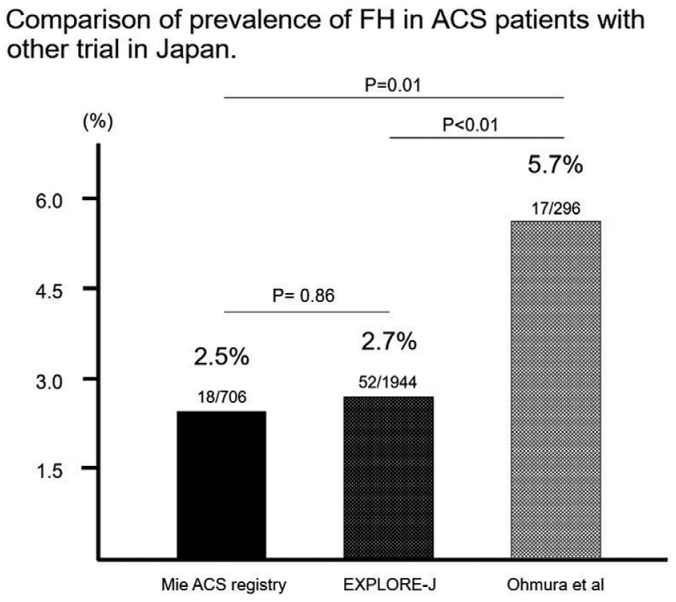

Figure 3. Comparison of prevalence of FH in ACS patients with other trials in Japan. FH, familial hypercholesterolemia; ACS, acute coronary syndrome. P=0.01.

statin therapy has the potential to reduce the risk of death after ACS.[20] Because underdiagnosis leads to underutilization of adequate medication, an effort to ensure the timely diagnosis of FH followed by an aggressive treatment regimen is of utmost importance for patients with FH in Japan.

Prognosis of FH in Patients With ACS

The SPUM-ACS study in Switzerland showed that ACS patients with FH did not have a higher rate of recurrent CV events than those with non-FH during 1-year follow up.[17] However, when the analysis was limited to young patients with ACS, all-cause mortality and CV mortality risk were higher in FH than non-FH patients, with an adjusted hazard ratio of 2.46 using the American Heart Association (AHA) definition.[17] Even after adjustment using propensity score matching for age, hypertension, family history of premature CAD, and LDL-C concentration, our study did not demonstrate a significant difference in MACCE during follow up between patients with FH and non-FH. There are some reasons why this study did not show the difference in prognosis between FH and non-FH patients, which is unlike the SPUM-ACS study in Switzerland. First, there is a difference in LDL-C target achievement rate. In FH patients who were in the Mie ACS registry, the achievement rate of LDL ≤70 mg/dL and ≤100 mg/dL was 33.3% and 80%, respectively, whereas in FH patients (diagnosed using the AHA criteria) within the SPUM-ACS study, the levels are 8.8% and 49.1%, respectively. In addition, FH patient in the SPUM-ACS study did not receive PCSK9 inhibitors because SPUM-ACS study data were collected before the PCSK9 inhibitor was available on the market. In contrast, 20% of FH patients in the Mie ACS registry received PCSK9 inhibitors. As described above, FH patients in the Mie ACS registry showed a better LDL-C target achievement rate, which might lead to improved FH patient prognosis. Second, FH patients in the Mie ACS registry showed lower prevalence of preexisting CV disease compared to FH patients (diagnosed using AHA criteria) in the SPUM ACS study (5.6% vs. 14.9%). From these findings, FH patients who were in the ACS registry might have shown favorable prognosis compared to those in the SPUM ACS study, which might lead to similar prognosis between FH and non-FH patients in the Mie ACS registry even after propensity score matching. In addition, it was the one of the reasons that the relatively low number of FH patients with ACS in this study limits the statistical power to provide the statistical difference in prognosis.

Comparison of FH Prevalence in Patients With ACS Among Other Trials in Japan

The prevalence of FH in patients with ACS was similar between the present study and the EXPLORE-J study (2.5% vs. 2.7%, respectively; P=0.86). However, it was significantly higher in patients with ACS in the study by Ohmura et al (5.7%) than that observed in the present study and in the EXPLORE-J study (P<0.01). The rate of analysis in the report by Ohmura et al was significantly lower than that in the present study and the EXPLORE-J study (82.4% vs. 95.7% and 96.4%, respectively; P<0.001) (**Figure 3**).[15,16]

Comparison of Patient Characteristics Among Clinical Studies Concerning ACS Patients With FH in Japan

There are several differences in patient background characteristics among clinical studies in Japan, as shown in the **Supplementary Table**. Compared to the EXPLORE-J study, the previous statin prescription rate (19.5% vs. 27.3%, P<0.01) and the prevalence of dyslipidemia (46.7% vs. 77.8%, P<0.01) were significantly lower in Mie ACS Registry. However, the previous statin prescription rate in the Mie ACS Registry was similar to that found by Ohmura et al (19.5% vs. 23.3%, P=0.19). In addition, Achilles tendon thickness (≥9 mm) rate of non-FH patients in the Mie ACS Registry showed a similar rate to that found by Ohmura et al (14.2% vs. 13.6%, P=0.82); it showed a significantly higher rate compared to that found in the EXPLORE-J

study (14.2% vs. 4.7%, P<0.01; **Supplementary Table**).[15,16,35]

Study Limitations

This study has several limitations. First, we did not perform genetic testing for the diagnosis of FH. According to the JAS guideline, genetic testing is recommended for patients strongly suspected of having FH. However, it is sometimes difficult to perform genetic testing in daily clinical practice because of the lack of patient and family consensus. Second, the relatively low number of ACS patients limits the statistical power and the strength of the conclusion regarding geographic factors of the genetics. Although the present study is one of the largest studies evaluating the prevalence of FH in Japanese ACS patients, and is the first report evaluating the prognostic differences between FH and non-FH patients with ACS in Japan, a larger scale prospective trial is needed to confirm our findings. Third, we did not have the historical immigration records of our patients. We assume that some patients with ACS and their ancestors had moved to Mie from outside the prefecture. Fourth, there were a few missing data for some parameters. However, overall rate of missing data from analyzed patients was 1.9%, and only 6 parameters had a missing rate of >5%. Although the missing data rate of Achilles tendon thickness was relatively high (n=224, 32.6%), all 224 patients were successfully diagnosed with non-FH regardless of the result of Achilles tendon thickness.

Clinical Implication

This study demonstrated the frequency of FH in patients with ACS and showed that there is insufficient recognition and treatment of FH in the Mie Prefecture. Improvements in these aspects of clinical practice will help to improve patients' prognosis.

Conclusions

There was no significant difference in the prevalence of FH in patients with ACS between the Mie Prefecture and other Japanese districts. In addition, the rate of short-term MACCE in patients with ACS was not significantly different between patients with FH and non-FH in this study.

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IRB Information

This study was approved by the Mie University Hospital Institutional Review Board (Reference number 2881).

Data Availability

(1) Individual deidentified participant data (including data dictionaries) will be shared.
(2) Excel data used for analysis will be shared. The data of each table and figure will be shared upon request. The study protocol will be also available.
(3) The data will be available during the review process and 1 year after acceptance.
(4) The data will be available to reviewers and anyone else who is interested in this article after acceptance if they contact to the corresponding author.
(5) The data will be available in an Excel sheet, and the data will be applicable only to verify our research results.

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Supplementary Files

Please find supplementary file(s);
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