Estimated Prevalence of Heterozygous Familial Hypercholesterolemia in Patients With Acute Coronary Syndrome

Multicenter Registration Study in Japan

Hirotohi OHMURA,¹ MD, Yoshifumi FUKUSHIMA,¹ MD, Atsushi MIZUNO,² MD,
Koichiro NIWA,² MD, Yohei KOBAYASHI,³ MD, Toshiaki EBINA,⁴ MD,
Kazuo KIMURA,⁴ MD, Shun ISHIBASHI,⁵ MD, and Hiroyuki DAIDA,¹ MD,
on behalf of the Research Committee on Primary Hyperlipidemia
of the Ministry of Health and Welfare of Japan

SUMMARY

Heterozygous familial hypercholesterolemia (FH) represents a strong risk for development of premature coronary artery disease (CAD). However, the majority of patients with FH are undiagnosed and the prevalence likely represents an underestimate in most countries. In Japan, the possible contribution of FH to the development of CAD may be higher because of the low incidence of CAD among the general population. We estimated the prevalence of heterozygous FH by measuring Achilles tendon thickness (ATT) in patients with acute coronary syndrome (ACS).

A total of 359 patients suffering from ACS were enrolled in this multicenter registration study. Heterozygous FH was defined according to the diagnostic criteria proposed by the Japan Atherosclerosis Society. After excluding 63 patients because of missing ATT data or plasma triglyceride levels that were 4.5 mmol/L or more, 296 patients were eligible for inclusion in the study. The number of patients with ATT of 9 mm or more was 53 (17.9%). They were significantly younger and had significantly higher LDL cholesterol levels than patients with an ATT less than 9 mm. The prevalence of heterozygous FH was 5.7% (1/17.5) and more prominent in younger patients who were less than 60 years old (7.8%). In patients with ATT of 9 mm or more, approximately 1 in 3.5 fulfilled the criteria for heterozygous FH.

We demonstrated the usefulness of measuring ATT by radiography and the high prevalence of heterozygous FH in patients with ACS in Japan, especially in younger patients who were less than 60 years old. (Int Heart J 2017; 58: 88-94)

Key words: Premature coronary artery disease, LDL cholesterol, Achilles tendon thickness

Familial hypercholesterolemia (FH) is one of the most common inherited metabolic diseases and is characterized by severely elevated plasma low-density lipoprotein (LDL) cholesterol levels. Most common inheritance is an autosomal dominant disorder caused by a mutation of the gene for the LDL receptor (LDLR).¹⁻⁵ To date, 3 other gene mutations in the LDLR pathway have been discovered, including apolipoprotein B, proprotein convertase subtilisin kexin type 9 (PCSK9), or LDLR adaptor protein 1 (LDLRAP1).

The prevalence of the heterozygous FH has been estimated at 1/200-1/500 and of homozygous FH at 1/160,000-1/1,000,000.³⁻⁶ However, the prevalence likely represents an underestimate in most countries because of a majority of patients with FH are undiagnosed.^{4,7} The risk of premature coronary artery disease (CAD) is elevated to about 20-fold in het-

erozygous FH. Regarding the natural course of heterozygous FH patients, around 50% of men experienced adverse cardiac events by the age of 50 years and 30% of females by the age of 60 years.⁴ Nevertheless, it is necessary to perform more appropriate diagnosis and intensive cholesterol-lowering therapy to prevent the development of premature CAD,⁸ the majority of patients with FH are either underdiagnosed or undertreated.

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In Japan, the possible contribution of FH to the development of CAD may be higher because of the low incidence of CAD among the general population. Most individuals and families with FH may simply be overlooked among the huge number of patients with any CAD caused by more common risk factors.⁹ In particular, we expect the high prevalence of

From the ¹ Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, ² Department of Cardiology, St. Luke's International Hospital, Tokyo, ³ Department of Cardiology, Kokura Memorial Hospital, Fukuoka, ⁴ Department of Cardiovascular Center, Yokohama City University Medical Center, Kanagawa, and ⁵ Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Jichi Medical University, Tochigi, Japan.

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Address for correspondence: Hirotohi Ohmura, MD, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: hohmura@juntendo.ac.jp

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heterozygous FH in patients with acute coronary syndrome (ACS), but neither diagnosis nor treatment for heterozygous FH may be performed adequately.^{10,11)} A possible reason is difficulty in recognizing true LDL cholesterol levels, because most patients have been prescribed statins without the proper diagnosis of heterozygous FH, and cholesterol catabolism increases rapidly just after onset of ACS. On the other hand, tendon xanthomas were found to be strongly associated with genetic diagnosis and highly specific for FH patients.¹²⁾ Approximately 30-50% of heterozygous FH patients have tendon xanthomas.^{3,5)} Tendon xanthomas appear as Achilles tendon thickness (ATT) in many cases, which can be diagnosed easily based on inspection and palpation. Patients with ATT of 9 mm or more on radiography should be regarded as having tendon xanthomas.¹³⁾

International consensus criteria for the clinical diagnosis of FH are lacking, although 3 well-known clinical diagnostic criteria have been proposed; the US MedPed (Make Early Diagnosis To Prevent Early Death) program,¹⁴⁻¹⁶⁾ Simon Broome Register Group in the UK,^{17,18)} and Dutch Lipid Clinic Network.^{4,5,19)} The Japan Atherosclerosis Society (JAS) proposed simple but high specificity criteria for the diagnosis of heterozygous FH in 2012.²⁰⁾ In the JAS criteria for the diagnosis of heterozygous FH, a diagnosis of heterozygous FH can be made if at least 2 criteria including 1) LDL cholesterol > 4.65 mmol/L (180 mg/dL), 2) tendon xanthoma or skin nodular xanthoma, 3) family history of FH or premature CAD (men < 55 years old, women < 65 years old) are adopted.

This study aimed to estimate the prevalence of heterozygous FH in patients with ACS by measuring ATT according to the diagnostic criteria for heterozygous FH in adults proposed by JAS and to demonstrate their clinical characteristics

prospectively in a multicenter registration study.

METHODS

Study design: This study was a multicenter registration study. A total of 359 patients suffering from ACS who were admitted to 4 hospitals from January 2012 to December 2013 (Kokura Memorial Hospital, St. Luke's International Hospital, Yokohama City University Medical Center, and Juntendo University Hospital) were enrolled. After obtaining written consent from the patients, they were assessed for standard cardiovascular risk factors and medical history. Medical records were collected by using a uniform questionnaire sheet. (Figure 1)

This study was performed according to the principles expressed in the Declaration of Helsinki and the ethics policies of the institution and was approved by an internal review board. This multicenter registration research was taken responsibility for the project for overcoming from refractory disease and was supported by Scientific Research Fund from Ministry of Health, Labor and Welfare of Japan (201324014A on the work of the Research Committee on Primary Hyperlipidemia).

Definition of patient characteristics: Family history of premature CAD was defined by onset at less than 55 years old for men and at less than 65 years old for women. We categorized ACS as ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UAP) by national definition.²¹⁾ Xanthomas were considered to be present either diffusely enlarged or focal nodular tendons, or skin xanthomas. ATT was measured by radiography according to the method in conformity with the guideline and was determined as positive for Achilles tendon thickening with a

Questionnaire for ACS Patient

I. Case number: ____ (Registration date: 201 / /)

II. Patient Information: age ____ y.o., Sex: Male/Female
Height ____ cm, BW ____ Kg, WC ____ cm

III. Dx on admission: ☐ STEMI, ☐ NSTEMI, ☐ UAP
☐ first time, ☐ recurrence or progression
(first event: ____ y.o.)

IV. Past history:

a. _____, d. _____
b. _____, e. _____
c. _____, f. _____

V. Coronary risk factors:

- ☐ Family history of premature CAD (<55 for men, <65 for women)
☐ current smoker (____ cigarette/day), ☐ quit (at least 1 years before), ☐ never
☐ Diabetes (☐ under Tx, ☐ no Tx, ☐ Dx after admission)
☐ Hypertension (☐ under Tx, ☐ no Tx)
☐ Hyper LDL-C (if under Tx: ☐ statin, ☐ fibrates, ☐ ezetimibe, ☐ probucol
☐ EPA, ☐ others, ☐ no Tx)
☐ Low HDL-C

VI. Family history of Dyslipidemia* or CAD (within 2nd degree)

If someone has been already diagnosed as FH or FCH, you mention the accurate diagnosis. However, if not, you mention just the dyslipidemia.

VII. Physical findings:

- ☐ Arcus corneal
☐ skin xanthoma, ☐ tendon xanthoma
☐ Achilles tendon thickening measured by radiography (≥ 9 mm)

VIII. Blood sample (☐ within 24H onset from ACS, ☐ 24H later):

Tcho : _____ () mg/dL
LDL-C : _____ () mg/dL (☐ calculation, ☐ direct)
HDL-C : _____ () mg/dL
TG : _____ () mg/dL

* If you can get a data before admission or lipid lowering therapy, you should mention a data in blank.

Figure 1. Questionnaire sheet for patients with ACS. ACS indicates acute coronary syndrome.

maximum thickness of 9 mm or more.¹³⁾ Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Smoking status was classified into never, current, and former smoking. Current smoking was defined as positive by having a smoking habit within 1 year before admission. Hypertension was defined as the use of antihypertensive drugs or a usual blood pressure level either higher than 140 mmHg for systolic or 90 mmHg for diastolic or both. Diabetes mellitus was defined as the use of hypoglycemic agents or according to the Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013.²²⁾ A history of CAD was defined as previous myocardial infarction or any coronary revascularization for myocardial ischemia. Cerebrovascular disease (CVD) was defined as previous stroke or transient ischemic attack (TIA). A family history of CAD was defined as positive by having within 2nd degree family members.

Biochemical analysis: Plasma lipid and lipoprotein levels were measured as soon as possible when subjects were admitted irrespective of food intake. Cholesterol and triglyceride levels were measured by enzymatically using an automated analyzer in the clinical laboratories of each hospital. If possible, we obtained previous LDL cholesterol values before a prescribed statin or admission from medical records. LDL cholesterol was usually calculated using the Friedewald equation, however, we adopted LDL cholesterol values measured by the direct method if total cholesterol levels were not available.

Diagnosis of heterozygous familial hypercholesterolemia: Heterozygous FH was defined according to the diagnostic criteria for heterozygous FH in adults proposed by JAS as follows: 1) hyper-LDL cholesterol [an untreated LDL cholesterol level of $> 4.65 \text{ mmol/L}$ (180 mg/dL)], 2) tendon xanthomas (tendon xanthoma on backs of the hands, elbows, knees, or elsewhere, or Achilles tendon thickening) or xanthoma tuberosum, and 3) family history of FH or premature CAD (within a patient's 2nd degree relatives).²⁰⁾ If a patient meets two or 3 of the above-mentioned criteria, the condition should be diag-

nosed as heterozygous FH.

Statistical analysis: Continuous variables are presented as the mean $\pm$ standard deviation. Categorical data are presented as numbers and percentages. Unpaired Student's *t*-test and one-way analysis of variance (ANOVA) were used to assess differences in continuous variables between groups. Differences in categorical variables were assessed by the χ^2 -test. A *P* value < 0.05 was considered significant. All statistical analyses were performed using JMP 10 software (2012, SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient clinical characteristics with ACS: Among a total of consecutive 359 patients suffering from ACS, 63 were excluded because of missing ATT data or plasma triglyceride (TG) levels that were 4.5 mmol/L (400 mg/dL) or more. Consequently, 296 patients were eligible for inclusion in the present study. None of these patients had been diagnosed as heterozygous FH nor did they have a family history of FH in relatives. The clinical characteristics of the ACS patients who participated in this study are shown in Table I. The mean age of the subjects was 64 ± 13 years old and was significantly higher in women than in men. BMI and the prevalence of smokers and diabetes mellitus were significantly higher in men than in women. A history of CAD was present in 19 patients (6.4%) and 6 (2.0%) patients had CVD, however, there was no significant difference between men and women. Statins were being taken by only 23.3% of the subjects and the trends for men and women were similar. The plasma level of HDL cholesterol in women was significantly higher than that in men, however, there were no significant differences in the plasma levels of LDL cholesterol and TG. Concerning the clinical diagnosis of ACS, about two-thirds of the patients developed STEMI and there were no significant differences in the prevalence of clini-

Table I. Clinical Characteristics of ACS Patients in This Study

	All	Men	Women
Number	296	235	61
Age (years)	64 ± 13	63 ± 13	$72 \pm 10^{***}$
BMI (kg/m^2)	24.2 ± 3.6	24.5 ± 3.4	$23.2 \pm 3.9^*$
Smoking (%)**			
Never	80 (27.0)	45 (19.2)	35 (57.4)
Current	124 (41.9)	107 (45.5)	17 (27.9)
Former	92 (31.1)	83 (35.3)	9 (14.8)
Hypertension (%)	179 (60.5)	143 (60.9)	36 (59.0)
Diabetes mellitus (%)	102 (34.5)	84 (35.7)	18 (29.5)*
Previous CAD (%)	19 (6.4)	17 (7.2)	2 (3.3)
Previous CVD (%)	6 (2.0)	3 (1.3)	3 (4.9)
LDL-C (mmol/L)	3.13 ± 1.03	3.08 ± 1.03	3.26 ± 1.01
HDL-C (mmol/L)	1.16 ± 0.31	1.14 ± 0.28	$1.29 \pm 0.31^{**}$
TG (mmol/L)	1.40 ± 0.88	1.43 ± 0.89	1.24 ± 0.79
Statin administration (%)	69 (23.3)	55 (23.4)	14 (23.0)
ATT (mm)	7.7 ± 1.7	7.8 ± 1.6	7.4 ± 1.8
STEMI (%)*	208 (60.5)	166 (60.6)	42 (60.0)
NSTEMI (%)	57 (16.6)	51 (18.6)	6 (8.6)
UAP (%)	79 (23.0)	57 (20.8)	22 (31.4)

Data are expressed as the mean $\pm$ SD, **P* < 0.05 , ***P* < 0.005 , ****P* < 0.0001 . ACS indicates acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; ATT, Achilles tendon thickening; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; and UAP, unstable angina pectoris.

cal diagnosis of ACS between men and women.

Achilles tendon thickness (ATT): The mean ATT measured by radiography was 7.7 ± 1.7 mm and there was no significant difference between men and women. ATT demonstrated a very weak but significant positive correlation with plasma levels of LDL cholesterol ($r^2 = 0.033$, $P = 0.0016$) and a negative correlation with age ($r^2 = 0.023$, $P = 0.0092$).

Patient clinical characteristics classified by ATT: We evaluated the clinical characteristics classified by ATT (Table II). The number of patients with ATT of 9 mm or more was 53 (17.9%). They were significantly younger and had significantly higher LDL cholesterol levels and significantly lower HDL cholesterol levels than patients with an ATT less than 9 mm. The distribution of plasma LDL cholesterol in patients with ATT of 9 mm or more was varied and asymmetric, although those in patients with ATT less than 9 mm were almost normal and symmetric (Figure 2). We did not observe any significant differences in other coronary risk factors, sex, or even in the percentage of subjects taking a statin. The percentage of patients with a family history of premature CAD was almost double in patients with ATT of 9 mm or more compared with patients with ATT less than 9 mm, although there was no statistically significant difference (Table III).

Estimated prevalence of heterozygous familial hypercholesterolemia: The prevalences of hyper-LDL cholesterolemia [LDL cholesterol ≥ 4.65 mmol/L (180 mg/dL)] and definite heterozygous FH according to the diagnostic criteria of JAS were significantly higher in patients with ATT of 9 mm or more than in those patients with ATT less than 9 mm (17.0% versus 4.9%; $P < 0.005$ and 28.3% versus 0.8%; $P < 0.0001$). Approximately 1 in 3.5 subjects with ATT of 9 mm or more might be heterozygous FH among patients suffering from ACS. In all patients, the prevalence of definite heterozygous FH was 5.7% (1 in 17.5).

Clinical characteristics of heterozygous familial hypercholesterolemia: To compare the ATT or prevalence of heterozygous FH by age, we divided the subjects into two groups; those 60 years old or more and those less than 60 years old (Table IV). Both the percentage of ATT of 9 mm or more and definite heterozygous FH were more prominent in the patients less than

60 years old than in those more than 60 years old (23.5% versus 14.9%, 7.8% versus 4.6%; respectively, $P = \text{NS}$). This result suggested that 1 in 12.8 patients less than 60 years old suffering from ACS might possibly be heterozygous FH. This trend was observed in both men and women regarding the prevalence of ATT of 9 mm or more. However, we could not confirm this trend regarding the prevalence of heterozygous FH, because there were no female patients less than 60 years old with heterozygous FH.

DISCUSSION

Our study demonstrated that the prevalence of definite heterozygous FH based on the diagnostic criteria of the JAS guideline was estimated to be 5.7% (one in 17.5) among patients suffering from ACS by measuring ATT. The prevalence of heterozygous FH was more prominent in patients less than

Table II. Clinical Characteristics Classified by ATT

	ATT ≥ 9	ATT < 9
Number (%)	53 (17.9)	243 (82.1)
Age (years)	$61 \pm 13^*$	65 ± 13
Men (%)	46 (86.8)	189 (77.8)
BMI (kg/m^2)	24.6 ± 3.5	24.2 ± 3.6
Smoking (%)		
Never	12 (22.6)	68 (28.0)
Current	26 (49.1)	98 (40.3)
Former	15 (28.3)	77 (31.7)
Hypertension (%)	28 (52.8)	25 (62.1)
Diabetes mellitus (%)	20 (37.7)	82 (33.7)
Previous CAD (%)	2 (3.8)	16 (6.6)
Previous CVD (%)	0 (0.0)	7 (2.9)
LDL-C (mmol/L)	$3.49 \pm 1.29^*$	3.05 ± 0.96
HDL-C (mmol/L)	$1.09 \pm 0.23^*$	1.19 ± 0.31
TG (mmol/L)	1.59 ± 0.98	1.35 ± 0.85
Statin administration (%)	11 (20.8)	58 (23.9)

Data expressed as the mean $\pm$ SD, $^*P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0001$. BMI indicates body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; and TG, triglycerides.

Figure 2. Distribution of plasma LDL cholesterol classified by ATT. LDL indicates low-density lipoprotein; and ATT, Achilles tendon thickening.

Table III. Clinical Characteristics Classified by ATT

	All	ATT ≥ 9	ATT < 9
STEMI (%)	208 (60.5)	35 (66.0)	155 (63.8)
NSTEMI (%)	57 (16.6)	7 (13.2)	41 (16.9)
UAP (%)	79 (23.0)	11 (20.8)	47 (19.3)
Family history of premature CAD (%)	23 (7.8)	7 (13.2)	16 (6.6)
ATT (mm)	7.7 ± 1.7	10.4 ± 1.6	7.1 ± 0.9***
LDL-C ≥ 4.65 mmol/L (%)	21 (7.1)	9 (17.0)	12 (4.9)**
Definite heterozygous FH According to JAS GL (%)	17 (5.7)	15 (28.3)	2 (0.8)***

Data expressed as the mean ± SD, * $P < 0.05$, ** $P < 0.005$, *** $P < 0.0001$. STEMI indicates ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; UAP, unstable angina pectoris; CAD, coronary artery disease; ATT, Achilles tendon thickening; LDL-C, low-density lipoprotein cholesterol; FH, familial hypercholesterolemia; JAS, Japanese Atherosclerosis Society; and GL, guideline.

Table IV. Stratification by Age of 60 Years Old Among Patients With ACS

	< 60 years	≥ 60 years	All
ATT ≥ 9 mm* (%)	23.5	14.9	17.9
Men/Women (%)	23.7/20.0	16.7/10.7	19.6/11.5
Heterozygous FH (%)	7.8	4.6	5.7
Men/Women (%)	8.2/0	4.3/5.4	6.0/4.9

ACS indicates acute coronary syndrome; ATT, Achilles tendon thickening; and FH, familial hypercholesterolemia.

60 years old (one in 12.8), especially in men. Even in cases of no lipid-lowering therapy, it was reported that approximately 30% of women experienced adverse cardiac events by the age of 60.⁴⁾ Thus, it was not surprising that there were no heterozygous FH patients who were less than 60 years old in this study. The present results suggest that more careful examination should be encouraged for the adequate care of patients with ACS. The high prevalence of heterozygous FH in patients with ACS, especially in younger patients, is consistent with previous data reported by Goldstein.²³⁾ However, there is little data concerning the prevalence of potential FH among patients with established CAD. In a series of consecutive patients less than 60 years old who were admitted with an acute myocardial infarction in 1995, 36 of 292 had FH (12.3%).¹⁰⁾ Recently, EUROASPIRE IV data also demonstrated that the prevalence of potential FH in patients with acute coronary events was 8.3% (1 in 12), and more in men less than 50 years old (22%).²⁴⁾

The possible contribution of FH to CAD might be higher even in Japanese because of the low prevalence of CAD among the general Japanese population. However, it is difficult to diagnose heterozygous FH in patients with ACS because of increasing cholesterol catabolism and the fact that they take statins just after the onset of ACS. In addition, the range of plasma LDL cholesterol levels in FH overlaps with that of people with non-genetic polygenic hypercholesterolemia.^{12,25)} On the other hand, tendon xanthomas are strongly associated with a genetic diagnosis and highly specific for FH patients.¹²⁾ Achilles tendon xanthomas in particular have been used as one of the criteria for the clinical diagnosis of FH in JAS and the Simon Broome Register because of their high sensitivity and specificity.^{1,26)} A strongly positive correlation was observed between ATT and cholesterol-year scores in FH.^{27,28)} Our findings that patients with ATT of 9 mm or more had significantly higher levels of plasma LDL cholesterol and percentage of hyper-LDL cholesterol [LDL cholesterol ≥ 4.65 mmol/L (180 mg/dL)] are consistent with previous reports.²⁷⁻²⁹⁾ Approximately 1 in 3.5 patients with ATT of 9 mm or more who ful-

filled the diagnostic criteria of heterozygous FH, suggesting that ATT is a good marker for evaluating heterozygous FH. We should consider the possibility that patients with ATT of 9 mm or more suffering from ACS have heterozygous FH.

In addition, the percentage of patients with a family history of premature CAD was double in patients with ATT of 9 mm or more compared to those of less than 9 mm. As an autosomal dominant disorder, 50% of siblings and children are likely to inherit this condition. Therefore, we should make an effort to gather more details concerning their relatives in 2nd generation pedigrees in possible cases. Cascade testing is an essential part of evaluating heterozygous FH and of any cost-effective prevention program for CAD risk reduction in patients with heterozygous FH, especially among children and adolescence.^{20,32-35)} A careful family history, with regard to cholesterol levels (if known), and age of onset of CAD should be collected. The key responsibility of the cardiologist is to screen for FH through a family history, physical examination, and basic lipid profile.³⁶⁾ Once diagnosed, heterozygous FH patients can readily be treated with cholesterol-lowering medication to attenuate the development of atherosclerosis and prevent the development of CAD.³⁷⁻⁴¹⁾

Study limitations: This study had several limitations. First, the possibility of underdiagnosing heterozygous FH in patients with ACS cannot be denied because we found a considerable number of patients with ATT of 9 mm or more without diagnosing heterozygous FH. Second, the collection of blood samples varied depending on the facility and on the arrival time at the hospital. It was difficult to adopt the use of levels of LDL cholesterol as diagnosis criteria for heterozygous FH. This might be explained, in part, by differences in the prevalence of heterozygous FH between our study and previous studies. Third, we did not perform genetic molecular analysis to identify monogenic mutations associated with FH. However, the aim of our study was to estimate the prevalence of clinical FH according to the criteria of the JAS for the diagnosis of heterozygous FH.

Conclusion: We demonstrated a high prevalence of heterozygous FH in patients with ACS, especially in younger patients less than 60 years old. ATT is a good practical marker for evaluating a high risk population of heterozygous FH in patients with ACS. The measurement of ATT by radiography should be used not only as a diagnostic criteria for heterozygous FH, but also, perhaps more importantly, as a prognostic factor in high risk patients who need a more aggressive approach.

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DISCLOSURE

Conflict of interest: There are no conflicts of interest to declare.

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