

ORIGINAL RESEARCH

Substantially Elevated Atherosclerotic Risks in Japanese Severe Familial Hypercholesterolemia Defined by the International Atherosclerosis Society



Sayaka Funabashi, MD,^a Yu Kataoka, MD, PhD,^a Mika Hori, PhD,^b Masatsune Ogura, MD, PhD,^b Yuriko Nakaoku, MD, PhD,^c Kunihiro Nishimura, MD, PhD,^c Takahito Doi, MD, PhD,^a Ryo Nishikawa, MD,^d Kosuke Tsuda, MD,^e Teruo Noguchi, MD, PhD,^a Mariko Harada-Shiba, MD, PhD^b

ABSTRACT

BACKGROUND The International Atherosclerosis Society (IAS) has proposed “severe familial hypercholesterolemia” (FH) as a phenotype with the highest cardiovascular risk. However, whether this criteria could appropriately stratify a high-risk Japanese patient with FH remains unknown.

OBJECTIVES This study sought to characterize atherosclerotic cardiovascular diseases in IAS-defined Japanese subjects with severe FH.

METHODS This study analyzed 380 clinically diagnosed subjects with heterozygous FH without any history of atherosclerotic cardiovascular diseases. Severe FH was defined as untreated low-density lipoprotein cholesterol >400 mg/dL, >310 mg/dL plus 1 high-risk feature, or >190 mg/dL plus 2 high-risk features according to IAS-proposed statement. The occurrence of first and subsequent composite outcomes (cardiac [cardiac death + coronary artery disease + coronary revascularization] and noncardiac events [stroke + peripheral artery disease]) was compared between subjects with severe (n = 135) and non-severe (n = 227) FH.

RESULTS Severe FH was identified in 40.3% of study population. They had higher low-density lipoprotein cholesterol ($P < 0.001$) and lipoprotein(a) ($P = 0.03$) levels. Moreover, they more frequently received high-intensity statin ($P < 0.001$), PCSK9 inhibitor ($P < 0.001$), and lipoprotein apheresis ($P = 0.01$) than nonsevere FH subjects did, which resulted in a lower on-treatment low-density lipoprotein cholesterol level of subjects with severe FH (113 ± 47.2 vs 130 ± 53.9 mg/dL; $P = 0.007$). However, during the 7.4-year observational period, subjects with severe FH exhibited a 9.3-, 15.4-, and 5.9-fold greater risk for first composite ($P < 0.001$), cardiac ($P < 0.001$), and noncardiac outcomes ($P = 0.02$), respectively. Multivariate Cox proportional hazard model consistently revealed the 7.8- and 7.9-fold elevated risks of first ($P < 0.001$) and of subsequent ($P < 0.001$) composite outcomes in subjects with severe FH.

CONCLUSIONS Japanese subjects with severe FH present profound risks of both first and subsequent atherosclerotic cardiovascular diseases in the primary prevention settings. These findings support the clinical applicability of IAS-defined severe FH in Japanese patients, which identifies those who require further stringent antiatherosclerotic management. (JACC: Asia 2021;1:245–255) © 2021 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/>).

From the ^aDepartment of Cardiovascular Medicine, National Cerebral and Cardiovascular Centre, Suita, Osaka, Japan; ^bDepartment of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center, Research Institute, Suita, Osaka, Japan; ^cDepartment of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan; ^dDepartment of Cardiovascular, Renal and Metabolic Medicine, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan; and the ^eDepartment of Cardiology, Osaka Medical College, Takatsuki, Osaka, Japan.

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAD = coronary artery disease

FH = familial hypercholesterolemia

HDL-C = high-density lipoprotein cholesterol

HeFH = heterozygous familial hypercholesterolemia

IAS = International Atherosclerosis Society

LDL-C = low-density lipoprotein-cholesterol

PAD = peripheral artery disease

Heterozygous familial hypercholesterolemia (HeFH) is an autosomal codominant disorder that exhibits abnormal low-density lipoprotein cholesterol (LDL-C) metabolism (1). Premature atherosclerotic cardiovascular disease (ASCVD) more frequently occurs in patients with HeFH, underscoring to commence adequate lipid-lowering therapies for the primary prevention. However, cardiovascular outcome of HeFH is quite heterogeneous (2-3), which suggests the need to better stratify their ASCVD risks. The International Atherosclerosis Society (IAS) has recently proposed “severe FH” as a high-risk category of HeFH. It is defined as the presence of high LDL-C level and multiple risk factors (4).

This approach enables physicians to easily identify subjects with HeFH with substantial atherogenic risks. Given the existence of multiple atherogenic risk factors, severe FH may more extensively present atherosclerosis in systemic arteries, thereby yielding to an increased risk of cardiac and noncardiac atherosclerotic events. The Japanese Atherosclerosis Society has developed their own diagnosis criteria of HeFH in Japanese subjects (5). Whether Japanese patients with HeFH with very high cardiovascular risks are detectable by using the aforementioned IAS-proposed criteria remains to be determined yet. Therefore, the present study sought to characterize the risk of concomitant cardiac and noncardiac atherosclerotic diseases in Japanese subjects with severe FH as defined by IAS criteria.

METHODS

STUDY POPULATION. The present study retrospectively analyzed 481 patients who were clinically diagnosed with HeFH at the National Cerebral and Cardiovascular Center Hospital in Osaka, Japan, between January 1, 1978, and December 31, 2016. Genetic analysis of *LDLR* and *PCSK9* pathogenic variants was performed in all subjects at our institute from January 1, 2005, to December 31, 2016. Of these, we excluded those who had a history of ASCVD (n = 101) at the first visit to our hospital because the current analysis aimed to elucidate atherosclerotic cardiovascular event risks of severe FH in the “primary

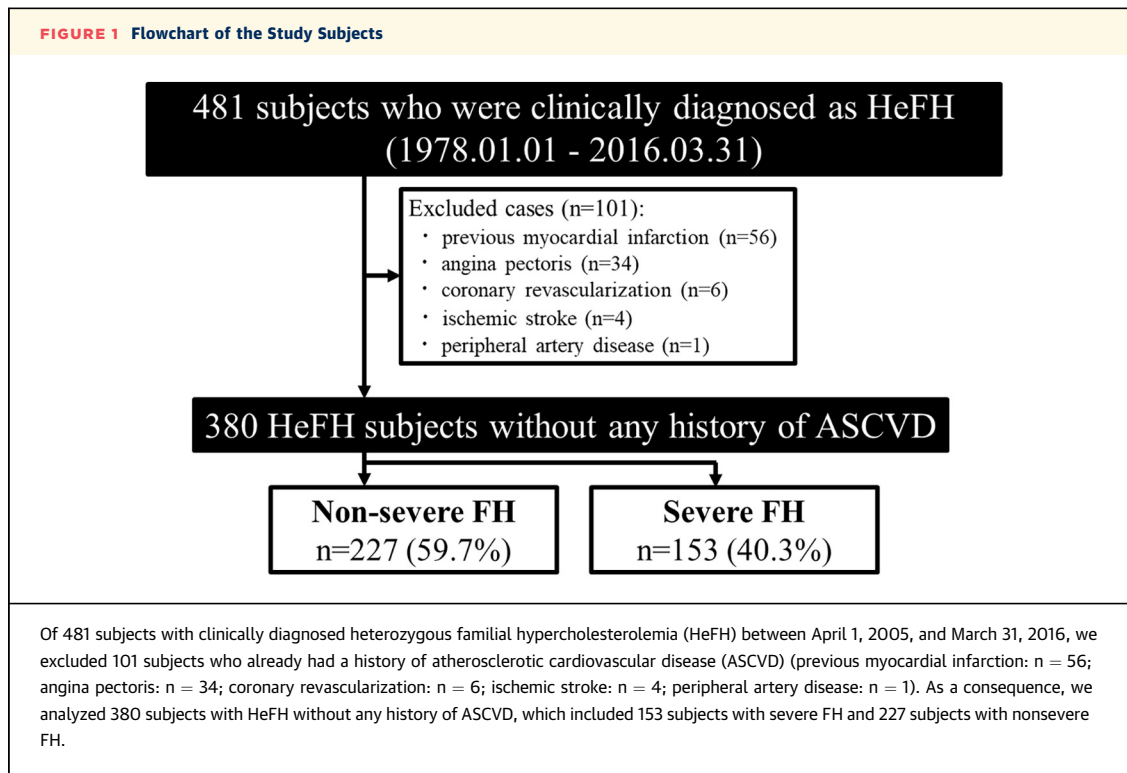
prevention settings.” The remaining 380 patients were included into the current analysis (Figure 1). HeFH was diagnosed in patients according to the Japan Atherosclerosis Society guidelines as follows: subjects who fulfilled at least 2 of clinical characteristics’ criteria including: 1) untreated LDL-C level ≥ 180 mg/dL; 2) tendon xanthoma; and 3) a history of FH or premature coronary artery disease (CAD) in second-degree relatives (5). The research protocol was approved by the ethics committee of our institution (M17-056).

DEFINITION OF SEVERE FH. According to the IAS-proposed statement, severe FH is defined if the patient has untreated LDL-C >400 mg/dL or LDL-C >310 mg/dL plus 1 high-risk feature or LDL-C >190 mg/dL plus 2 high-risk features. High-risk features are age >40 years without treatment, smoking, male sex, lipoprotein(a) >50 mg/dL, hypertension, diabetes mellitus, family history of premature ASCVD in first-degree relatives, chronic kidney disease, and body mass index >30 kg/m² (4). In addition to these clinical characteristics related to severe FH, the current study evaluated the frequency of corneal arcus, which is another important physical feature of HeFH (6).

ATHEROSCLEROTIC CARDIAC AND NONCARDIAC EVENTS. The primary outcome was the occurrence of a composite of first atherosclerotic cardiac and noncardiac events. Atherosclerotic cardiac events were defined as cardiac-cause death, CAD, or coronary revascularization. Atherosclerotic noncardiac events consisted of ischemic stroke and peripheral artery disease (PAD). CAD included acute coronary syndrome (ST-segment elevated myocardial infarction, non-ST-segment elevated myocardial infarction, and unstable angina) (7), stable angina pectoris, and silent myocardial ischemia. Coronary revascularization was counted when percutaneous coronary intervention or coronary artery bypass graft was performed. Ischemic stroke was defined as lacunar infarction, atherothrombotic brain infarction, or cardioembolic infarction. PAD was defined as the presence of intermittent claudication, an ankle/arm index <0.9 , or stenosis of peripheral arteries with percentage of diameter stenosis $>50\%$ on angiography or ultrasonography. The secondary outcome was the occurrence of: 1) each component of primary

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outcomes; and 2) subsequent atherosclerotic cardiac and noncardiac events. These outcomes were determined through medical record review and, when necessary, through a questionnaire by mail and telephone follow-up. Cardiac and noncardiac events were evaluated by 2 physicians (Y.K. and T.D.) who were blinded to clinical characteristics of HeFH.

MEASUREMENT OF LIPID PARAMETERS. Fasting serum levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and lipoprotein(a) were measured by enzymatic methods (Sekisui Medical) using an automated analyzer (Hitachi Labospect 008; Hitachi-Hitec). LDL-C levels at baseline were calculated by the Friedewald formula, except for triglycerides levels >400 mg/dL (8). High-intensity statin was defined as either atorvastatin ≥ 20 mg, rosuvastatin ≥ 10 mg, or pitavastatin ≥ 4 mg (9). In patients who had already received a statin at their first visit, as reported previously, baseline LDL-C level was estimated according to the type and dose of a statin through applying a correcting factor for LDL-C based on the reported efficacy of each drug (10).

STATISTICAL ANALYSIS. Results are presented as percentages for categorical variables and mean \pm SD

for continuous variables. When variables were not normally distributed, their results are expressed as median (interquartile range). Clinical characteristics were compared by Wilcoxon rank-sum test for continuous variables as appropriate. Categorical variables were compared using the Fisher exact test or the chi-square test as appropriate. The Kaplan-Meier method was used to estimate survival curves for cardiac and noncardiac atherosclerotic events, and the log-rank test was used to assess differences among patients with severe FH and subjects with nonsevere FH. Univariable Cox proportional hazards models were used to calculate HRs and 95% CIs for all atherosclerotic events. Multivariable Cox regression analysis was performed by using significant covariates associated with outcomes on univariate analysis. The duration from January 1, 1978, to the date of the first visit of each subject was also included into this model. Because 3 different types of unordered failure events (cardiac events, ischemic stroke, and PAD) were recorded, we adopted a model, which allowed each failure event stratum to have its own baseline hazard function, but restricting the common beta coefficients across strata enabling to estimate the common effect of predictor variables for 3 different

TABLE 1 Baseline Clinical Characteristics

	Subjects With Nonsevere FH (n = 227)	Subjects With Severe FH (n = 153)	P Value
Age, y	36.7 ± 19.0	45.7 ± 16.0	<0.001
Male	67 (29.5)	83 (54.3)	<0.001
Hypertension	17 (7.5)	53 (34.6)	<0.001
Diabetes mellitus	1 (0.4)	6 (3.9)	0.02
Smoker	27 (11.9)	68 (44.4)	<0.001
Family history of premature CAD	13 (5.7)	51 (33.3)	<0.001
Tendon xanthomas	107 (47.1)	112 (73.2)	<0.001
Skin xanthomas	13 (5.7)	24 (15.7)	0.002
Corneal arcus	41 (18.0)	55 (36.0)	<0.001
Genotype of FH			
LDLR pathogenic variants	112 (49.3)	104 (68.0)	<0.001
PCSK9 pathogenic variants	21 (9.3)	12 (7.8)	0.71
LDLR and PCSK9 pathogenic variants	10 (4.4)	6 (3.9)	1.00
Untreated lipid parameters, mg/dL			
LDL-C	212 ± 57	283 ± 64	<0.001
HDL-C	60 ± 14	53 ± 13	0.003
Triglycerides	91 (61-140)	118 (82-162)	<0.001
Lipoprotein(a)	16.7 (10.4-26.8)	22.7 (11.7-41.2)	0.03

Values are mean ± SD, n (%), or median (interquartile range).
CAD = coronary artery disease; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

failures, according to the stratified Cox model proposed by Wei, Lin, and Weissfeld (11). The Wei, Lin, and Weissfeld model allows us to consider the ordering of events as separate events (ie, strata) of

TABLE 2 Lipid-Lowering Therapies and Lipid Control

	Subjects With Nonsevere FH (n = 227)	Subjects With Severe FH (n = 153)	P Value
Lipid-lowering therapy			
Statin	166 (73.1)	143 (93.5)	<0.001
High-intensity statin	66 (29.1)	97 (63.4)	<0.001
Ezetimibe	78 (34.4)	97 (63.4)	<0.001
PCSK9 inhibitor	13 (5.7)	30 (19.6)	<0.001
Lipoprotein apheresis	0 (0)	5 (3.3)	0.01
On-treatment lipid parameters			
LDL-C, mg/dL	130 ± 53	113 ± 47	0.007
IAS-recommended realistic goal: percentage of LDL-C reduction ≥50%	68 (33.2)	108 (73.0)	<0.001
IAS-recommended ideal goal: LDL-C <100 mg/dL	63 (30.7)	56 (37.8)	0.17
Duration during IAS-recommended ideal LDL-C goal (<100 mg/dL), y	0.6 ± 1.7	0.8 ± 2.6	0.03
LDL-C <55 mg/dL	6 (2.9)	14 (9.5)	0.02
HDL-C, mg/dL	62 ± 14	54 ± 15	<0.001
Triglyceride, mg/dL	78 (58-112)	83 (61-125)	0.26
Lipoprotein(a), mg/dL	13.8 (7.5-27.2)	22.2 (10.0-44.8)	<0.001

Values are n (%), mean ± SD, or median (interquartile range).
IAS = International Atherosclerosis Society; other abbreviations as in Table 1.

interest, as well as the different types of events that may occur in the same patient (namely, cardiac events, ischemic stroke, and PAD). A subject is simultaneously included in the model for time to first event of interest, time to second event of interest, and so on, up to the maximum number of events observed for a subject in a study. In the model for time to *K*th event (*K* = 1, 2, and so on), a subject's time starts at registration in this study and ends at either: 1) the time when the subject's *K*th event has occurred; or 2) the time of death or last follow-up. Let *X_{ki}* and *C_{ki}* be the failure and censoring time of the *k*th failure type (*k* = 1, . . . , *K*) in the *i*th cluster (*i* = 1, . . . , *m*), and let *Z_{ki}* be a *P*-vector of possibly time-dependent covariates, for *i*th cluster with respect to the *k*th failure type by Lin (12). Dependencies among failure times were estimated by the covariance matrix of the estimators and adjusted to account for the additional correlation. These models can be estimated by command option of "stratum" in stcox command of STATA (StataCorp LLC) (13). With this approach, we investigated the effect of FH on the first and each subsequent event. A value of *P* < 0.05 was considered statistically significant. All statistical analyses were performed using the SAS software (version 13.0.0, SAS Institute Inc) or STATA (version 15).

RESULTS

CLINICAL CHARACTERISTICS OF SEVERE FH. In the current study, 40.3% of study subjects (n = 153 of 380) were diagnosed as having severe FH. Table 1 summarizes baseline clinical characteristics. Subjects with severe FH were more likely to be older (45.7 ± 16.0 years vs 36.7 ± 19.0 years; *P* < 0.001); male (54.3% vs 29.5%; *P* < 0.001); and have a history of hypertension (34.5% vs 7.5%; *P* < 0.001), type 2 diabetes mellitus (3.9% vs 0.4%; *P* = 0.01), and smoking habit (44.4% vs 11.9%; *P* < 0.001); and have family history of premature CAD (33.3% vs 5.7%; *P* < 0.001). Furthermore, tendon (73.2% vs 47.1%; *P* < 0.001) and skin xanthomas (15.7% vs 5.7%; *P* = 0.002) and corneal arcus (36.0% vs 18.0%; *P* < 0.001) were more frequently observed in patients with severe FH. With regard to genotypes of FH, the proportion of *LDLR* gene pathogenic variants was significantly higher in subjects with severe FH (68.0% vs 49.3%; *P* < 0.001), whereas there were no significant differences in *PCSK9* gene pathogenic variants and double heterozygous for *LDLR* and *PCSK9* gene pathogenic variants (Table 1). As expected, patients with severe FH exhibited an elevated level of LDL-C (283 ± 64 mg/dL vs 212 ± 57 mg/dL; *P* < 0.001), triglycerides (median: 118 vs

91 mg/dL; $P < 0.001$) and lipoprotein(a) (median: 22.7 vs 16.7 mg/dL; $P = 0.03$) accompanied by a lower HDL-C level (53 ± 13 mg/dL vs 60 ± 14 mg/dL; $P = 0.003$) at baseline (Table 1).

LIPID-LOWERING THERAPIES AND LIPID CONTROL.

Table 2 shows the use of lipid-lowering agents and on-treatment lipid profiles. Patients with severe FH are more likely received intensive lipid-lowering management including high-intensity statin, ezetimibe, PCSK9 inhibitor, and lipoprotein apheresis (Table 2). As a consequence, their on-treatment LDL-C level was significantly lower than that in patients with non-severe FH. Moreover, a greater proportion of patients with severe FH achieved IAS-recommended realistic goal (percentage of LDL-C reduction $\geq 50\%$: 73.0% vs 33.2%; $P < 0.001$) (Table 2). A longer duration during on-treatment LDL-C < 100 mg was observed in patients with severe FH (0.8 ± 2.6 vs 0.6 ± 1.7 ; $P = 0.03$), whereas they had lower HDL-C levels (54 ± 15 mg/dL vs 62 ± 14 mg/dL; $P < 0.001$) and higher lipoprotein(a) levels (median: 22.2 vs 13.8 mg/dL; $P < 0.001$) (Table 2).

FIRST ATHEROSCLEROTIC CARDIAC AND NONCARDIAC EVENTS IN SEVERE FH.

The frequency of first atherosclerotic cardiac and noncardiac events is summarized in Table 3. During the observational period (median: 7.4 years; interquartile range: 3.0-21.7 years; minimum and maximum follow-up periods: 0.7 and 39.5 years, respectively), 32 first cardiac (8.4%; $n = 32$ of 380) and 14 first noncardiac events (3.7%; $n = 14$ of 380) occurred in the entire study population (Table 3). On univariate Cox proportional hazards models, severe FH was associated with a 9.29-fold greater likelihood of experiencing primary composite outcomes including first atherosclerotic cardiac and noncardiac events (95% CI: 3.68-31.2; $P < 0.001$) (Figure 2 and Table 4). In addition, this univariate model showed an increased risk of cardiac events (HR: 15.4; 95% CI: 3.66-64.8; $P < 0.001$) and noncardiac events (HR: 5.86; 95% CI: 1.30-26.5; $P = 0.02$) in patients with severe FH (Figures 3A and 3B, Supplemental Table 1). Even after adjusting age, sex, on-treatment LDL-C and HDL-C, PCSK9 inhibitor use, the duration during IAS-recommended ideal LDL-C goal (< 100 mg/dL), and the period from the date at the enrollment of the first patient to the first visit of each subject, subjects with severe FH still continued to have increased risks of first atherosclerotic composite outcomes (HR: 7.76; 95% CI: 2.56-23.5; $P < 0.001$) and cardiac events (HR: 12.9; 95% CI: 2.86-58.4; $P = 0.001$) (Table 4, Supplemental Table 1A). There was a trend toward greater occurrence of noncardiac events in subjects with

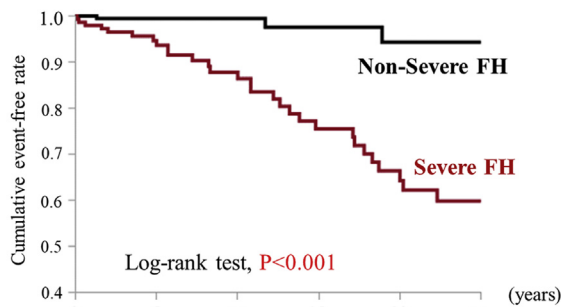
TABLE 3 Summary of First and Subsequent Atherosclerotic Events

	Overall (n = 380)	Nonsevere FH (n = 227)	Severe FH (n = 153)
First atherosclerotic events			
Composite events ^a	38 (10.0)	4 (1.8)	34 (22.2)
Cardiac events			
Cardiac-death	1 (0.3)	1 (0.4)	0 (0)
CAD	31 (8.2)	1 (0.4)	30 (19.6)
ACS	11 (2.9)	0 (0)	11 (7.2)
Stable CAD	9 (2.4)	1 (0.4)	8 (5.2)
Silent myocardial ischemia	11 (7.2)	0 (0)	11 (7.2)
Coronary revascularization	29 (7.6)	1 (0.4)	28 (18.3)
PCI	21 (5.5)	1 (0.4)	20 (13.0)
CABG	8 (2.1)	0 (0)	8 (5.2)
Noncardiac events			
Ischemic stroke	11 (2.9)	2 (0.9)	9 (5.9)
PAD	3 (0.8)	0 (0)	3 (2.0)
Subsequent atherosclerotic events			
Composite events ^a	8 (2.1)	0 (0)	8 (5.2)
Cardiac events			
Cardiac death	0 (0)	0 (0)	0 (0)
CAD	4 (1.1)	0 (0)	4 (2.6)
ACS	1 (0.3)	0 (0)	1 (0.7)
Stable CAD	0 (0)	0 (0)	0 (0)
Silent myocardial ischemia	3 (0.8)	0 (0)	3 (2.0)
Coronary revascularization	4 (1.1)	0 (0)	4 (2.6)
PCI	3 (0.8)	0 (0)	3 (2.0)
CABG	1 (0.3)	0 (0)	1 (0.7)
Noncardiac events			
Ischemic stroke	3 (0.8)	0 (0)	3 (2.0)
PAD	1 (0.3)	0 (0)	1 (0.7)

Values are n (%). ^aComposite events include cardiac and noncardiac events.
 ACS = acute coronary syndrome; CABG = coronary artery bypass graft; PAD = peripheral artery disease;
 PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

severe FH (HR: 4.45; 95% CI: 0.95-20.8), but this trend did not meet statistical significance ($P = 0.06$) (Supplemental Table 1B). Comparisons of each atherosclerotic event between subjects with severe and those with nonsevere FH were illustrated by Supplemental Figures 1 and 2.

There were 4 first atherosclerotic events in patients with nonsevere FH (Table 3). Patients with nonsevere FH with cardiovascular events were more likely to exhibit a history of hypertension (75.0% vs 6.3%; $P = 0.001$) and a greater frequency of lipoprotein(a) > 50 mg/dL (50.0% vs 4.5%; $P < 0.001$) (Supplemental Table 1). These risk factors were considered more important features of severe FH regardless of untreated LDL-C level and then included in IAS-proposed criteria (Supplemental Table 2). By using this modified criteria, we observed the occurrence of all 38 first atherosclerotic events in patients with severe FH only (Supplemental Figure 3, Supplemental Table 2).

FIGURE 2 Comparison of Primary Outcomes Between Severe and Nonsevere FH in Japanese Subjects**First Atherosclerotic Cardiac and Non-cardiac Events**

Numbers at risk	0	5	10	15	20	25
Severe FH	153	94	64	44	32	21
Non-severe FH	227	130	74	35	26	17

The Kaplan-Meier method was used to estimate survival curves for primary outcomes, and the log-rank test was used to assess differences between patients with severe familial hypercholesterolemia (FH) and those with nonsevere FH. Univariable Cox proportional hazards models were used to calculate HRs and 95% CIs for primary outcomes. During the observational period (median: 7.4 years), 32 first cardiac (8.4%; $n = 32$ of 380) and 14 first noncardiac events (3.7%; $n = 14$ of 380) occurred in the current study subjects. Severe FH was associated with a 9.29-fold greater likelihood of experiencing primary composite outcomes including first atherosclerotic cardiac and noncardiac events (95% CI: 3.68-31.20; $P < 0.001$).

SUBSEQUENT ATHEROSCLEROTIC EVENTS' RISKS IN SUBJECTS WITH SEVERE FH.

We further analyzed the risk of subsequent atherosclerotic cardiac and noncardiac events in our study population. There was a total of 8 subsequent atherosclerotic events during the follow-up period (Table 3). Of note, all of these events occurred in patients with severe FH only, and subjects with nonsevere FH did not experience any subsequent events under lipid-lowering therapies. In addition to first events, a Cox regression analysis, with stratification variables of 3 different types of unordered failure, showed severe FH substantially elevated risk of atherosclerotic events even after adjusting clinical demographics (unadjusted HR: 10.6; 95% CI: 3.96-28.5; $P < 0.001$; adjusted HR: 7.88; 95% CI: 2.97-20.9; $P < 0.001$) (Table 5).

DISCUSSION

IAS-proposed stratification of severe FH enables us to identify patients with a potential for very high-risk HeFH. The current study elucidated that Japanese subjects with severe FH defined by IAS-proposed criteria more likely exhibited a clustering of risk factors with elevated levels of LDL-C, lipoprotein(a), and triglycerides. Furthermore, despite more frequent

use of lipid-lowering therapies, severe FH was associated with a substantially elevated risk of first and subsequent atherosclerotic events at coronary and other vascular beds (Central Illustration). These observations support the clinical applicability of IAS-defined severe FH to find Japanese patients with very high-risk HeFH who require further optimized preventive therapies.

It is crucial to establish better risk stratification of HeFH because of its heterogeneity of clinical outcomes. One recent study analyzed Simon Broome Register in the United Kingdom, which included patients with FH both FH with and without a history of ASCVD. This study reported a higher mortality of CAD in subjects with severe FH (14). In addition, the current study provides additional evidence of severe FH specifically in the primary prevention settings of Japanese subjects. IAS-proposed classification stratified 40% of study population as severe FH with substantially higher risk of cardiovascular events. Considering that patients with FH have a considerable risk of ASCVD at young age, it is clinically important for physicians to predict and prevent the first event in the primary prevention setting of patients with FH. Our finding indicates the IAS-based risk stratification is a simple tool to: 1) identify specific Japanese patients with FH who are at elevated cardiovascular risk; and 2) potentially allocate adequate intensity of lipid-lowering therapies.

The current analysis characterized clinical outcome of severe FH as a frequent occurrence of not only atherosclerotic cardiac but also noncardiac events. One of the expected mechanisms behind this observation is a markedly higher level of LDL-C in patients with severe FH. As already demonstrated, LDL-C is an established atherogenic risk factor to promote disease in vascular beds including coronary, carotid, and peripheral arteries (15). Moreover, given that LDL-C normally elevates at young age in patients with FH, cumulative LDL-C burden has been considered another important contributor to their premature ASCVD (16). In our study, xanthomas were more frequently observed in patients with severe FH. Because xanthomas generally reflect lifelong exposure to an elevated LDL-C level of FH, these atherogenic features in subjects with severe FH could accelerate the formation of disease in systemic arteries, thereby causing atherosclerotic diseases in a variety of arterial beds (17).

In addition to a clustering of risk factors, lipoprotein(a) and low HDL-C in patients with severe FH could be other potential drivers for their frequent cardiovascular events. Mechanistically,

TABLE 4 Multivariable Analysis of Predictors for Composite of First Atherosclerotic Events

	Unadjusted			Adjusted		
	HR	(95% CI)	P Value	HR	(95% CI)	P Value
Age	1.04	(1.02-1.07)	<0.001	1.04	(1.01-1.07)	0.004
Male	2.55	(1.34-4.99)	0.004	2.30	(1.03-5.11)	0.04
On-treatment LDL-C	0.99	(0.98-0.99)	0.001	0.99	(0.98-1.00)	0.24
On-treatment HDL-C	0.97	(0.95-0.99)	0.002	0.99	(0.97-1.02)	0.57
Tendon xanthomas	1.44	(0.70-3.26)	0.33			
LDLR pathogenic variants	1.33	(0.69-2.74)	0.40			
High-intensity statin	1.77	(0.91-3.66)	0.09			
PCSK9 inhibitor	2.34	(1.13-4.56)	0.02	1.06	(0.45-2.54)	0.89
Duration during IAS-recommended ideal LDL-C goal (<100 mg/dL)	1.16	(1.07-1.25)	<0.001	1.11	(1.01-1.23)	0.03
Duration from January 1, 1978, to the date of the first visit	1.00	(0.96-1.04)	0.99	1.02	(0.97-1.06)	0.46
Severe FH/nonsevere FH	9.29	(3.68-31.2)	<0.001	7.76	(2.56-23.5)	<0.001

Adjusted HRs were calculated by a multivariable Cox hazard model. This model included the following variables: age, sex, on-treatment LDL-C, on-treatment HDL-C, tendon xanthomas, genotype LDL-R, lipid-lowering therapy of high-intensity statin, PCSK9 inhibitor, the duration during IAS-recommended ideal LDL-C goal (<100 mg/dL), severe FH/non-severe FH.

Abbreviations as in Tables 1 and 2.

lipoprotein(a) harbors a variety of potent properties associated with vascular inflammation and atherothrombosis (18,19). Accumulating evidence suggests the association of lipoprotein(a) with CAD, stroke, and PAD (20). Of note, ex vivo pathohistological studies reported the presence of lipoprotein(a) within coronary and carotid atheromas (21). These profound lipoprotein(a)-mediated effects may induce the formation of atheroma in peripheral arteries, yielding an elevation of stroke and PAD risks in patients with severe FH. With regard to HDL-C, its lower level of HDL-C has been shown associate with carotid atherosclerosis in patients with FH (22). HDL particles harbor atheroprotective effects such as promoting reverse cholesterol transport and mitigating

inflammation activity (23). Because function of HDL in the reverse cholesterol transport pathway is altered (24), this dysfunctional property of HDL may be a substrate causing systemic atheroma formation and progression in patients with FH who exhibit a low HDL-C level.

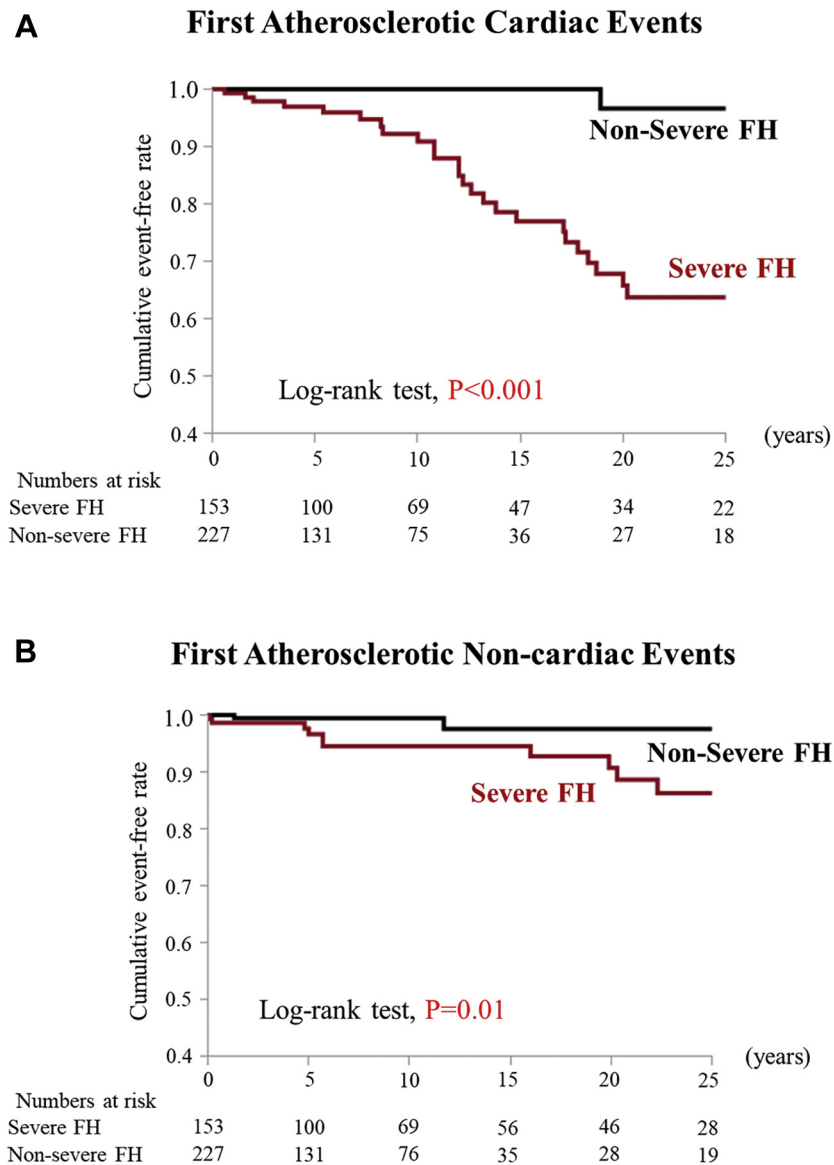
Following the occurrence of any first cardiovascular events, the risk of additional ASCVD events still continued to exist in subjects with severe FH. Of note, despite potent lipid-lowering agents being used with greater frequency in subjects with severe FH, the cardiovascular risk of these subjects was not necessarily optimized. This finding highlights the clinical needs for further refined antiatherosclerotic management. In our patients with severe FH, the

TABLE 5 Multivariable Analysis of Predictors for Composite of Subsequent Atherosclerotic Events

	Unadjusted			Adjusted		
	HR	(95% CI)	P Value	HR	(95% CI)	P Value
Age	1.05	(1.03-1.07)	<0.001	1.04	(1.02-1.07)	0.001
Male	2.24	(1.15-4.36)	0.02	1.74	(0.82-3.69)	0.15
On-treatment LDL-C	0.99	(0.98-1.00)	0.006	0.99	(0.98-1.00)	0.08
On-treatment HDL-C	0.97	(0.94-0.99)	0.002	0.99	(0.97-1.01)	0.16
High-intensity statin	1.79	(0.90-3.55)	0.10			
PCSK9 inhibitor	2.26	(1.13-4.52)	0.02	1.02	(0.44-2.32)	0.98
Duration during IAS-recommended ideal LDL-C goal (<100 mg/dL)	1.10	(1.05-1.16)	<0.001	1.04	(0.97-1.10)	0.26
Duration from January 1, 1978, to the date of the first visit	1.01	(0.97-1.04)	0.61	1.02	(0.98-1.06)	0.29
Severe FH/nonsevere FH	10.6	(3.96-28.5)	<0.001	7.88	(2.97-20.9)	<0.001

Adjusted HRs were calculated by a stratified Cox hazards model. This model included the following variables: age, sex, on-treatment LDL-C, on-treatment HDL-C, tendon xanthomas, genotype LDL-R, lipid-lowering therapy of high-intensity statin, PCSK9 inhibitor, the duration during IAS-recommended ideal LDL-C goal (<100 mg/dL), severe FH/nonsevere FH. This model considers the different baseline hazard function for each failure event, but the model assumes the common β -coefficients for prediction variables by Therneau method.

Abbreviations as in Tables 1 and 2.

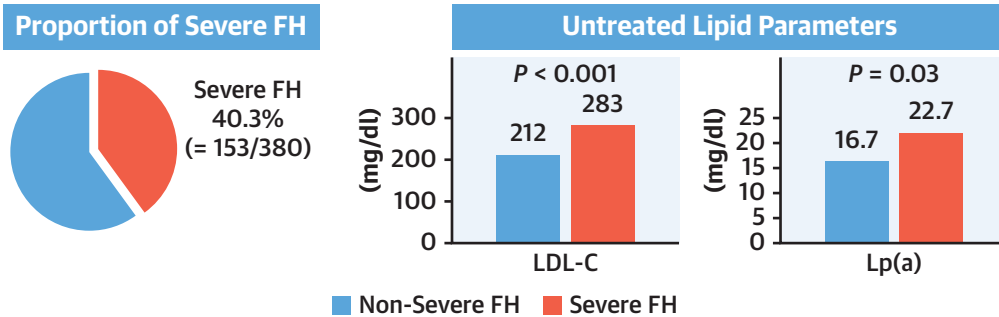
FIGURE 3 Comparison of Each Component of Primary Outcomes

The Kaplan-Meier method was used to estimate survival curves for first atherosclerotic cardiac and noncardiac events, and the log-rank test was used to assess differences between patients with severe familial hypercholesterolemia (FH) and those with nonsevere FH. Univariable Cox proportional hazards models were used to calculate HRs and 95% CIs for each component of primary outcomes. **(A)** First atherosclerotic cardiac events more frequently occurred in subjects with severe FH (HR: 15.4; 95% CI: 3.66-64.8; $P < 0.001$). **(B)** There was an increased risk of noncardiac events in patients with severe FH compared with that in patients with nonsevere FH (HR: 5.86; 95% CI: 1.3-26.5; $P = 0.02$).

frequency of their high-intensity statin use was 63.4%. In addition, only 37% of patients with severe FH achieved IAS-recommended ideal LDL-C goal, indicating the need for its more stringent control by adopting adequate intensity of a statin and additional lipid-lowering agents. In our analysis, PCSK9 inhibitor was used in 19.6% of patients with severe FH.

Greater adoption of this potent agent is required to further achieve guideline-recommended LDL-C goal. Bempedoic acid may be an additive therapeutic option for LDL-C control because this agent has demonstrated ~16% significant LDL-C lowering ability in a phase 3 clinical trial including patients with FH (25). Lipoprotein(a) and triglycerides may be other

CENTRAL ILLUSTRATION Clinical Characteristics of Severe FH in Japanese Subjects: Frequency, Lipid Parameters, and First/Subsequent Cardiovascular Event Risks



Adjusted risk for First and Subsequent Cardiovascular Events in Severe FH			
		Hazard Ratio (95% CI)	P Value
Primary outcome			
Composite of first cardiac and non-cardiac events		7.76 (2.56-23.5)	< 0.001
Secondary outcome			
Cardiac events (cardiac-cause death, CAD, coronary revascularization)		12.9 (2.86-58.4)	0.001
Non-cardiac events (ischemic stroke, PAD)		4.45 (0.95-20.8)	0.06
Subsequent cardiac and non-cardiac events		7.88 (2.97-20.9)	< 0.001

1.0 5 10 50 100

Non-Severe FH Worse Severe FH Worse

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International Atherosclerosis Society-proposed criteria identified 40.3% (n = 153 of 380) of subjects with heterozygous familial hypercholesterolemia (HeFH) as having severe FH. Subjects with severe FH were more likely to exhibit higher levels of untreated low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) [Lp(a)] than were subjects with nonsevere FH. During the 7.4-year observational period, severe FH was associated with a greater likelihood of experiencing primary outcome (first atherosclerotic cardiac and noncardiac events) (HR: 7.76; 95% CI: 2.56-23.5; $P < 0.001$). In addition, elevated risks of first cardiac events (HR: 12.9; 95% CI: 2.86-58.4; $P = 0.001$) and noncardiac events (HR: 4.45; 95% CI: 0.95-20.8; $P = 0.06$), and subsequent events (HR: 7.88; 95% CI: 2.97-20.9; $P < 0.001$) were observed in patients with severe FH. CAD = coronary artery disease; PAD = peripheral artery disease.

therapeutic targets to modulate atherosclerosis in subjects with severe FH. A recent study analyzing Japanese patients with FH reported the relationship of lipoprotein(a) with CAD (26). In addition, a sub-analysis of FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirumab) studies reported that a reduction of lipoprotein(a) level under PCSK9 inhibitors was independently associated with a lower risk of MACE even after adjusting for LDL-C level (27,28). Targeting these lipoproteins may ultimately become an additional potential approach in overcoming residual risks of severe FH.

We observed that around one-fourth of patients with nonsevere FH did not receive a statin and the

frequency of their high-intensity statin use was only 29.1%. Whereas the current analysis showed that atherosclerotic cardiovascular events less frequently occurred in patients with nonsevere FH during the 7.4-year observational period, their current lipid management could elevate a future cardiovascular event's risk for further follow-up over a longer period. Early commencement of statin with its adequate intensity should be considered even in patients with nonsevere FH.

The current study evaluated clinical applicability of IAS-proposed criteria of severe FH in Japanese subjects. Whereas patients with severe FH exhibited worse clinical outcomes, first cardiovascular events still occurred even in 1.8% of patients with nonsevere FH (n = 4 of 227). Moreover, patients with nonsevere FH with first cardiovascular events more likely exhibited a history of hypertension and a

greater frequency of lipoprotein(a) >50 mg/dL (Supplemental Table 1). Given that these risk factors have been reported to associate with the presence of CAD even in Asian patients with HeFH (26,29), it may be better to consider hypertension and lipoprotein(a) >50 mg/dL as more important high-risk features associated with worse cardiovascular outcomes in Japanese with patients FH. As shown in the Supplemental Table 2, our modified criteria of severe FH included these risks as definitive high-risk features for severe FH regardless of untreated LDL-C level. All of 38 first cardiovascular events occurred in subjects with severe FH as defined by this criteria, and there were no events in subjects with nonsevere FH (Supplemental Table 2, Supplemental Figure 3). Whether our proposed criteria would be better to find truly severe FH in Japanese subjects requires further validation study in the future.

STUDY LIMITATIONS. First, this was an observational study conducted in a single center. The number of cardiovascular events is relatively small. Second, the use and the selection of lipid-lowering therapy was conducted according to each physician's discretion. Despite these limitations, a Cox proportional hazards model consistently demonstrated a significant relationship between severe FH and cardiovascular events. Third, the current study included Japanese subjects with FH according to the Japan Atherosclerosis Society guidelines of FH diagnosis. Whether the observation can be translated to foreign patients with FH warrants further investigation. Fourth, *APOB* gene mutation was not identified in our study subjects. Because this genotype is very rare in Japan (30,31), we cannot characterize patients who have severe FH with *APOB* gene mutation. Fifth, the current study did not have any information about the occurrence of aortic aneurysm. It remains unknown whether severe FH harbors an elevated risk of aortic aneurysm. Sixth, severe FH was defined according to LDL-C levels and concomitant risk factors but not imaging data (4). Cardiovascular outcomes in patients with severe FH that are defined by imaging data remain to be determined.

CONCLUSIONS

The IAS-proposed definition identified severe FH in 40.3% of Japanese patients with HeFH in the primary prevention settings. During the observational period, subjects with severe FH harbored a heightened cardiovascular risk that involved not only the coronary artery but also other systemic arteries. In addition, the magnitude of their increased risk still continued following their first atherosclerotic events. Our findings support an IAS-proposed approach in Japanese patients with HeFH that enables us to find a high-risk phenotype of HeFH requiring the adoption of stringent lipid management.

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ADDRESS FOR CORRESPONDENCE: Dr Yu Kataoka, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1, Kishibe-shimmachi, Suita, Osaka 564-8565, Japan. E-mail: yu.kataoka@ncvc.go.jp.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: IAS-proposed approach to identify severe FH should be considered to stratify the risks of both CADs and non-CADs in the primary prevention settings of Japanese subjects with HeFH.

TRANSLATIONAL OUTLOOK: Future studies are warranted to establish optimal lipid-modifying therapies for the prevention of ASCVDs in patients with severe FH.

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KEY WORDS coronary artery, familial hypercholesterolemia, International Atherosclerosis Society, peripheral artery, stroke

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