



# 12-Week Effectiveness and Safety of Low-Density Lipoprotein Cholesterol-Lowering Therapy by Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition in Patients With Familial Hypercholesterolemia and Hypercholesterolemia — Data From a Real-World Observational Study of Evolocumab in Japan —

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**Background:** Evolocumab is the first monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9) approved in Japan for the treatment of patients with familial hypercholesterolemia (FH) and hypercholesterolemia (HC). This study assessed the 12-week effectiveness and safety of low-density lipoprotein cholesterol (LDL-C)-lowering therapy by PCSK9 inhibition in patients with FH (homozygous [HoFH] or heterozygous [HeFH]) and HC by analyzing evolocumab data collected in the real-world setting in Japan.

**Methods and Results:** Overall, 427 patients (mean±SD age, 61.6±13.8 years; female, 38.4%; 28 HoFH, 320 HeFH, 79 HC), enrolled from 299 clinical sites, were included in the safety analysis set. The major cardiovascular risk factors were coronary artery disease (77.3%), diabetes mellitus/impaired glucose tolerance (38.6%), and hypertension (65.1%). Median follow-up duration was 85.0 days. After 12 weeks of evolocumab treatment, the mean±SD percent change from baseline in LDL-C was −45.5%±27.0% (n=23) in HoFH (P<0.001 vs. baseline; t-test), −54.2%±29.0% (n=280) in HeFH (P<0.001), and −64.6%±22.4% (n=72) in HC (P<0.001) patients. The incidence of adverse drug reactions was 5.4% (23/427).

**Conclusions:** Results suggest that patients receiving evolocumab treatment in the real-world setting were predominantly those with FH and HC in the secondary prevention group. LDL-C-lowering effectiveness with evolocumab was observed in FH (both HoFH and HeFH) and HC patients.

**Key Words:** Evolocumab; Familial hypercholesterolemia; Heterozygous; Homozygous; PCSK9 inhibition

Several prior studies, both randomized and observational, have demonstrated that reduction in low-density lipoprotein cholesterol (LDL-C) levels in patients with hypercholesterolemia (HC), including those with familial hypercholesterolemia (FH), by statin therapy has a beneficial effect on lowering the risk of cardiovascular (CV) events and CV death.<sup>1,2</sup> Thus, LDL-C is a key modifiable risk factor in the development of CV events.<sup>3</sup>

Evolocumab is the first approved monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9) for clinical use in FH and HC in Japan.<sup>4</sup> The results of the

FOURIER trial support the efficacy of evolocumab in combination with statin therapy in significantly reducing the risk of CV events (evaluated by major composite CV events) while reducing LDL-C by 59% compared with placebo.<sup>5</sup> Recent clinical evidence-based guidelines, including those from the Japan Atherosclerosis Society (JAS) for FH and HC, recommend maintaining LDL-C values <70 mg/dL, especially in patients at high risk for CV events.<sup>6</sup>

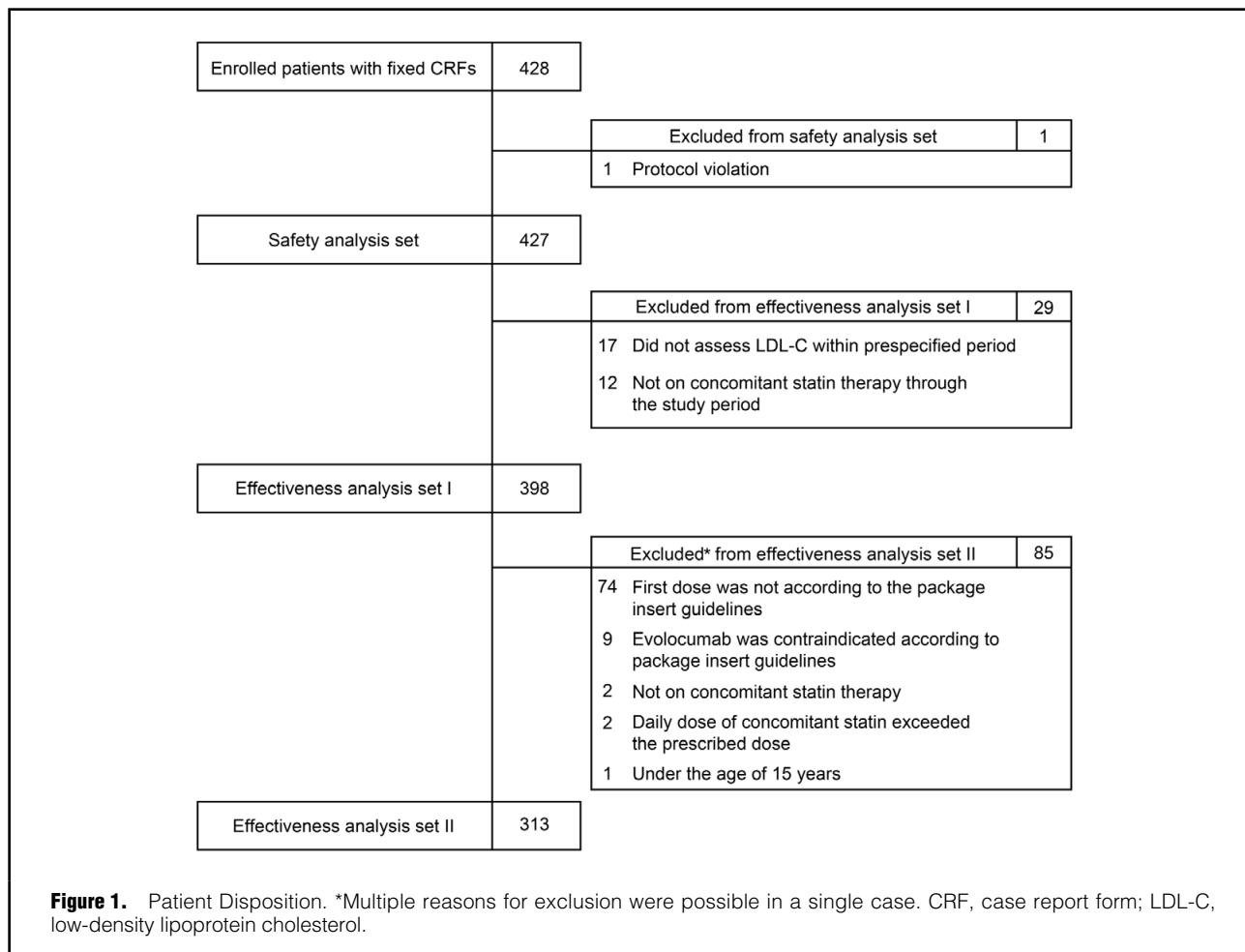
The Japanese package insert for evolocumab included randomized trials that provided efficacy and safety data for 565 Japanese subjects.<sup>4</sup> Given that patients with FH, espe-

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cially those with homozygous FH (HoFH) are limited due to the rarity of this condition, only 7 HoFH patients could be assessed in the clinical studies in Japan.<sup>7</sup> The present post-marketing observational study provides descriptive data from the real-world use of evolocumab in Japanese patients to supplement the data in the Japan-new drug application (J-NDA). We investigated (1) the effectiveness of evolocumab, when used in combination with statins or other lipid medications, in lowering LDL-C levels in patients with HC, specifically in those with FH; (2) baseline demographics and characteristics of FH patients who were receiving evolocumab treatment; and (3) the safety profile of evolocumab in the real-world setting. Here, we present the safety and effectiveness from this ongoing observational study, in order to publish the information on evolocumab in the real-world setting in Japan in a timely manner.

## Methods

### Study Design and Patients

This was an observational, post-marketing surveillance (PMS) study conducted at 299 participating centers in Japan from 24 June 2016 (first subjects in) to 17 January 2018 (inclusive). The study population consisted of patients who were evolocumab naïve and who were prescribed evolocumab according to the approved Japanese package insert (i.e., those with FH or HC who were at high CV risk

and who had inadequate response to statins).<sup>4</sup> After the first subcutaneous injection of evolocumab, patients were monitored during routine clinic visits for 12 weeks. At each visit, data for adverse events (AE) and medication use were documented following patient interview. Evolocumab was prescribed according to the dosage guidelines in the package insert. In the case of inadequate response to statins, patients with HC (including heterozygous FH [HeFH]) received evolocumab 140 mg every 2 weeks or 420 mg once monthly, and those with HoFH received evolocumab 420 mg once monthly or 420 mg every 2 weeks.

FH and HC should be diagnosed as per the criteria specified in the 2012 and 2017 JAS guidelines.<sup>6,8</sup> In the real-world clinical setting, however, physicians at the participating site could diagnose FH based on the clinical manifestations of FH, such as xanthoma tuberosum and the presence of persistently elevated LDL-C levels, without performing a genetic test. Thus, it is possible that clinically diagnosed HoFH patients in the present study were potentially HeFH patients, given that the diagnoses were not confirmed on genetic testing.

Patients eligible for safety analyses had at least 1 documented visit after the index date (date of initiation of evolocumab). Patients in whom follow-up LDL-C data were available and who received concomitant statin were included in the effectiveness analysis set I; patients who were treated with the on-label dose regimen of evolocumab

and statins were included in the effectiveness (sensitivity) analysis set II. To enable assessment of the long-term effectiveness and safety of evolocumab, this study will continue to collect data from 3,000 patients through a 2-year observation period.

The study protocol was approved by the institutional or ethics review board at each participating site or by a central ethical review board (Public Health Research Foundation, Tokyo). This study was conducted in accordance with the Pharmaceutical and Medical Devices Law, Good Post-Marketing Study Practice in Japan, and the Declaration of Helsinki. The study sponsors take responsibility for the accuracy and completeness of the data and analyses. This study is registered at ClinicalTrials.gov (identifier, NCT02808403). Written informed consent was provided by all enrolled patients.

### Background Data

All patient data were collected in a patient registration form or a case report form (CRF) using the Electronic Data Capture (EDC) system (PostMaNet, Fujitsu, Tokyo). The following data were collected at baseline: sex, age, body mass index, inpatient/outpatient setting at the time of initiation of evolocumab, diagnosis (FH [HeFH/HoFH]/HC); FH-related findings including genetic tests for FH (whether conducted or not), tendon xanthoma, xanthoma tuberosum; past medical history including that of coronary artery disease (CAD), diabetes mellitus (DM)/impaired glucose intolerance (IGT), chronic kidney disease (CKD), non-cardiogenic cerebral infarction, peripheral artery disease (PAD), hypertension, low high-density lipoprotein cholesterol (HDL-C; defined as <40 mg/dL), smoking history, family history of premature CAD, risk category (according to JAS guidelines)<sup>6</sup> using risk factor count, high-intensity statin use,<sup>9</sup> concomitant lipid-lowering medications, prior medications, and prior LDL-C apheresis

therapy. The LDL-C goal established according to the comprehensive JAS risk management goals<sup>6</sup> was <70 mg/dL in FH and <100 mg/dL in HC patients for secondary prevention; and <120 mg/dL, <140 mg/dL, and <160 mg/dL in high-risk, moderate-risk, and low-risk categories, respectively, for primary prevention. The name of the statin, its daily dose, and treatment start and end dates were collected on the CRF. High-intensity statin use was defined as atorvastatin  $\geq 10$  mg once daily (QD), rosuvastatin  $\geq 5$  mg QD, simvastatin  $\geq 20$  mg QD, fluvastatin  $\geq 80$  mg QD, pitavastatin  $\geq 2$  mg QD, pravastatin  $\geq 40$  mg QD, or any other statin in combination with ezetimibe.<sup>9</sup> Systolic and diastolic blood pressure were recorded at the baseline visit. In addition, glycated hemoglobin A1c (HbA1c) and estimated glomerular filtration rate (eGFR) at baseline were also documented.

### Outcome Measures

LDL-C concentration and other lipid concentrations, including HDL-C, total cholesterol (TC), and triglycerides, and, if feasible, apolipoprotein (Apo) A1, ApoB, ApoE, and lipoprotein(a) (Lp(a)), were measured as part of routine clinical practice at each clinical site at the baseline visit, 4 weeks (except Lp(a)), 12 weeks, or at the end of follow-up. LDL-C value was calculated using the Friedewald formula if it was not measured by direct assay.<sup>10</sup> Non-HDL-C levels were calculated by subtracting HDL-C from the TC value.

AE (including information about seriousness and causal relationship to drug) and other safety information (e.g., overdose, lack of effectiveness, pregnancy, and lactation with or without AE) were collected. Adverse drug reactions (ADR) were defined as those AE for which the causal relationship with the drug could not be excluded. AE were coded using the Medical Dictionary for Regulatory Activities Japanese version 20.1.

	HoFH	HeFH	HC	All patients
n	28	320	79	427
Sex, female	13 (46.4)	127 (39.7)	24 (30.4)	164 (38.4)
Age				
<15 years	1 (3.6)	0 (0.0)	0 (0.0)	1 (0.2)
$\geq 15$ and <65 years	21 (75.0)	168 (52.5)	30 (38.0)	219 (51.3)
$\geq 65$ years	6 (21.4)	152 (47.5)	49 (62.0)	207 (48.5)
$\geq 75$ years	2 (7.1)	57 (17.8)	22 (27.8)	81 (19.0)
Age (years)	51.9 $\pm$ 16.4	61.2 $\pm$ 13.8	66.9 $\pm$ 10.3	61.6 $\pm$ 13.8
BMI (kg/m <sup>2</sup> )	24.1 $\pm$ 5.0	25.2 $\pm$ 4.1	25.4 $\pm$ 3.9	25.2 $\pm$ 4.1
Outpatient	26 (92.9)	302 (94.4)	67 (84.8)	395 (92.5)
FH findings				
Genetic test positive	11 (39.3)	57 (17.8)	0 (0.0)	68 (15.9)
Tendon xanthoma	21 (75.0)	162 (50.6)	3 (3.8)	186 (43.6)
Xanthoma tuberosum	12 (42.9)	44 (13.8)	2 (2.5)	58 (13.6)
CAD	22 (78.6)	246 (76.9)	62 (78.5)	330 (77.3)
DM	5 (17.9)	89 (27.8)	48 (60.8)	142 (33.3)
IGT	0 (0.0)	18 (5.6)	5 (6.3)	23 (5.4)
HbA1c (%) <sup>†</sup>	8.6 $\pm$ 2.5 (5)	6.9 $\pm$ 0.9 (85)	6.9 $\pm$ 1.2 (46)	6.9 $\pm$ 1.2 (136)
CKD	4 (14.3)	32 (10.0)	22 (27.8)	58 (13.6)
Non-cardiogenic cerebral infarction	1 (3.6)	22 (6.9)	11 (13.9)	34 (8.0)

(Table 1 continued the next page.)

	HoFH	HeFH	HC	All patients
PAD	4 (14.3)	42 (13.1)	12 (15.2)	58 (13.6)
Smoking				
Absent	19 (67.9)	172 (53.8)	35 (44.3)	226 (52.9)
Current	1 (3.6)	25 (7.8)	8 (10.1)	34 (8.0)
Past	5 (17.9)	103 (32.2)	34 (43.0)	142 (33.3)
Hypertension	12 (42.9)	200 (62.5)	66 (83.5)	278 (65.1)
SBP (mmHg) <sup>‡</sup>	133.3±25.0 (11)	133.0±18.6 (172)	130.9±20.2 (62)	132.5±19.2 (245)
DBP (mmHg) <sup>‡</sup>	70.3±10.8 (11)	74.3±12.4 (172)	73.2±12.5 (62)	73.8±12.4 (245)
Low HDL-C, <40 mg/dL	15 (53.6)	78 (24.4)	14 (17.7)	107 (25.1)
Family history of premature CAD	6 (21.4)	133 (41.6)	7 (8.9)	146 (34.2)
Risk category (according to JAS guidelines)				
Secondary prevention	22 (78.6)	246 (76.9)	62 (78.5)	330 (77.3)
Primary prevention <sup>§</sup>	6 (21.4)	72 (22.5)	16 (20.3)	94 (22.0)
High risk	NA	NA	16 (20.3)	NA
Medium risk	NA	NA	0	NA
Low risk	NA	NA	0	NA
High-intensity statin medication <sup>¶</sup>				
Yes	24 (85.7)	298 (93.1)	70 (88.6)	392 (91.8)
Combination therapy with statin				
Yes	26 (92.9)	313 (97.8)	76 (96.2)	415 (97.2)
Rosuvastatin	15 (53.6)	179 (55.9)	31 (39.2)	225 (52.7)
Atorvastatin	6 (21.4)	74 (23.1)	30 (38.0)	110 (25.8)
Pravastatin	1 (3.6)	11 (3.4)	6 (7.6)	18 (4.2)
Pitavastatin	4 (14.3)	56 (17.5)	11 (13.9)	71 (16.6)
Simvastatin	0 (0.0)	1 (0.3)	1 (1.3)	2 (0.5)
Fluvastatin	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.2)
Combination therapy with other lipid medication				
Yes	21 (75.0)	210 (65.6)	27 (34.2)	258 (60.4)
Ezetimibe	20 (71.4)	188 (58.8)	13 (16.5)	221 (51.8)
Probucol	3 (10.7)	27 (8.4)	0 (0.0)	30 (7.0)
Colestimide	4 (14.3)	39 (12.2)	2 (2.5)	45 (10.5)
Bezafibrate	0 (0.0)	4 (1.3)	0 (0.0)	4 (0.9)
Prior medication				
Antihypertensive	15 (53.6)	206 (64.4)	58 (73.4)	279 (65.3)
Anti-diabetic	2 (7.1)	55 (17.2)	28 (35.4)	85 (19.9)
Antiplatelet	16 (57.1)	222 (69.4)	58 (73.4)	296 (69.3)
Anticoagulant	3 (10.7)	36 (11.3)	16 (20.3)	55 (12.9)
Anti-anginal	13 (46.4)	178 (55.6)	47 (59.5)	238 (55.7)
Prior LDL-C apheresis				
Yes	14 (50.0)	25 (7.8)	0 (0.0)	39 (9.1)
Baseline LDL-C (mg/dL)	228.8±157.9 (28)	152.6±44.3 (320)	113.9±36.1 (79)	150.4±62.8 (427)
Baseline TC (mg/dL)	294.0±176.8 (24)	228.5±52.5 (267)	188.9±49.5 (66)	225.5±71.4 (357)
Baseline HDL-C (mg/dL)	42.2±16.5 (27)	48.6±13.7 (307)	53.0±14.6 (75)	49.0±14.2 (409)
Baseline TG (mg/dL)	127.2±88.1 (27)	141.5±80.6 (312)	160.5±112.6 (76)	144.1±88.0 (415)
Baseline non-HDL-C (mg/dL)	251.4±176.9 (24)	180.0±48.8 (254)	135.0±46.7 (64)	176.6±70.8 (342)
eGFR (mL/min/1.73m <sup>2</sup> )				
≥60	20 (71.4)	189 (59.1)	40 (50.6)	249 (58.3)
≥45 and <60	5 (17.9)	50 (15.6)	20 (25.3)	75 (17.6)
≥30 and <45	1 (3.6)	19 (5.9)	10 (12.7)	30 (7.0)
≥15 and <30	0 (0.0)	4 (1.3)	3 (3.8)	7 (1.6)
<15	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.2)

Data presented as n (%) for categorical variables and mean±SD or mean±SD (n) for continuous variables. <sup>†</sup>Patients with DM or IGT. <sup>‡</sup>Patients with hypertension. <sup>§</sup>HoFH and HeFH were not subcategorized within primary prevention group. <sup>¶</sup>Japan-specific definition: intensive if atorvastatin ≥10 mg QD, rosuvastatin ≥5 mg QD, simvastatin ≥20 mg QD, fluvastatin ≥80 mg QD, pitavastatin ≥2 mg QD, pravastatin ≥40 mg QD, or any statin use in combination with ezetimibe. The name of the statin, its daily dose, and treatment start and end dates were collected on the CRF. BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CRF, case report form; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; HbA1c, glycated hemoglobin; HC, hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; IGT, impaired glucose tolerance; JAS, Japan Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; PAD, peripheral artery disease; QD, once daily; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

		HoFH	HeFH	HC
<b>Effectiveness analysis set I</b>				
Baseline LDL-C (mg/dL)	Mean±SD	204.7±88.7	152.1±44.3	112.3±34.8
%change from baseline to 12 weeks	Mean±SD	-45.5±27.0	-54.2±29.0	-64.6±22.4
	95% CI	-57.2 to -33.8	-57.6 to -50.8	-69.8 to -59.3
	P-value†	<0.001	<0.001	<0.001
	n‡	23	280	72
<b>Effectiveness analysis set II</b>				
Baseline LDL-C (mg/dL)	Mean±SD	201.7±74.0	151.1±42.8	107.5±29.8
%change from baseline to 12 weeks	Mean±SD	-49.3±16.5	-61.0±22.1	-65.5±20.9
	95% CI	-59.8 to -38.8	-64.1 to -57.9	-70.9 to -60.1
	P-value†	<0.001	<0.001	<0.001
	n‡	12	198	59

†One-sample t-test. ‡Patients with data available for %change from baseline to week 12. Abbreviations as in Table 1.

### Statistical Analysis

Summary statistics for continuous variables included the number of patients, mean, median, and SD. For categorical variables, the frequency and percentage were calculated. Missing data were not imputed. The statistical difference between lipid levels at baseline and at 12 weeks was determined using the 1-sample t-test. All reported P-values are 2-sided based on the 1-sample t-test, and 2-sided 95% CI were calculated. Multiplicity adjustments were not considered; therefore, all P-values were nominal, and no formal hypothesis testing was conducted.

The safety analysis set included all patients who had received at least 1 dose of evolocumab, had data available for safety assessment, and did not meet any prespecified criteria. The effectiveness analysis set I consisted of those patients from the safety analysis set who did not use evolocumab off label, were enrolled within the enrollment period, had evaluable efficacy data, were not lost to follow-up after the first visit, and in whom LDL-C data were adequate and calculated using the correct method. The effectiveness analysis set II included those patients from the effectiveness analysis set I in whom evolocumab dosage and use were according to the package insert, and the daily dose of concomitant statin did not exceed the prescribed dose at the time of initiation of this drug; who were >15 years; and who were co-prescribed statin at the time of evolocumab initiation.

The target sample size for the safety analysis set was determined as 3,000 patients, with an observation period of 2 years for 95% statistical power to detect at least 1 patient experiencing an AE with a 2-year incidence of 0.1%. A sample size of 6,000 enrolled patients over the 4-year enrollment period was chosen to achieve the aforementioned target for 2-year follow-up data, with an assumed discontinuation rate (lost to follow-up) of 50%, which was estimated based on PMS for Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in Japan. The additional factors that were considered while estimating the sample size included the difference in the mode of administration of evolocumab and the anticipated challenges in monitoring patients who were transferred from specialized care hospitals to general practice clinics. This report provided safety and effectiveness based on the data collected until 17 January 2018. Statistical analysis was conducted by A2 Healthcare Corporation (Tokyo) and

funded by the study sponsors. Statistical analysis was conducted using SAS, version 9.2 (SAS Institute, Cary, NC, USA).

## Results

### Patient Disposition

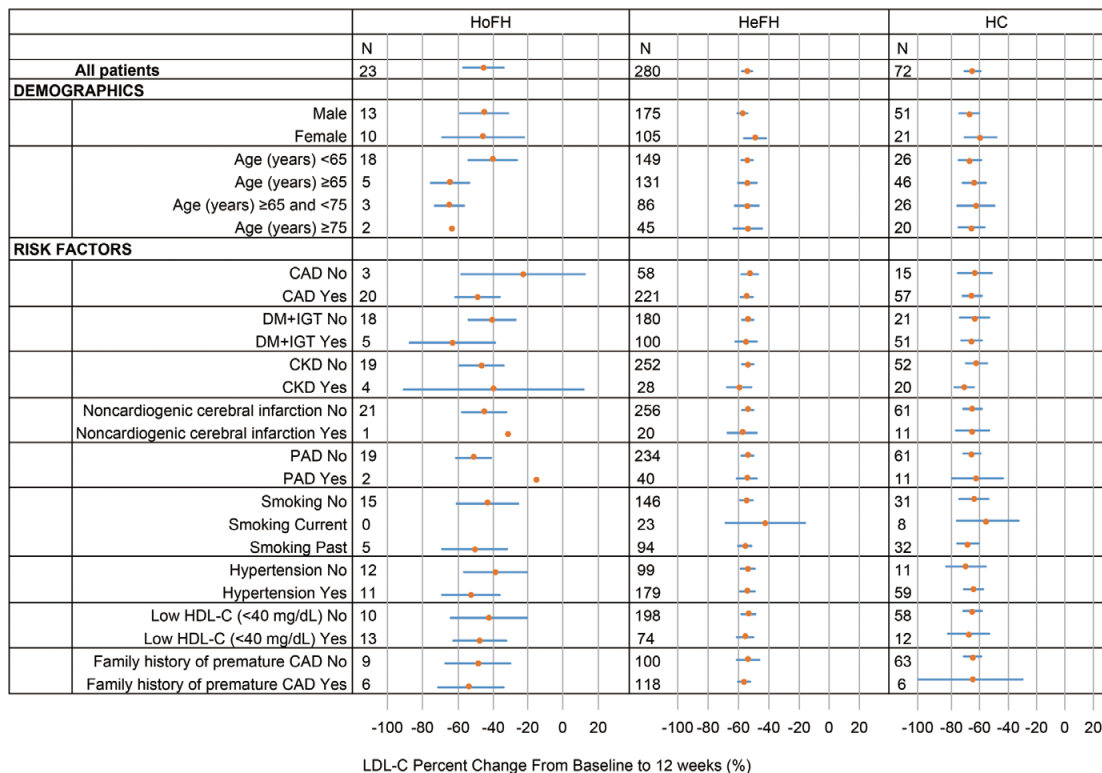
A total of 427 patients from 299 clinical sites were included in the safety analysis set after excluding 1 patient due to protocol violation. Of the patients included in the safety analysis set, 398 were eligible for inclusion in the effectiveness analysis set I, and 313 for the effectiveness analysis set II. Patient disposition, including reasons for exclusion from each analysis set, is presented in **Figure 1**.

### Patient Characteristics

The safety analysis set consisted of 28 HoFH, 320 HeFH, and 79 HC patients. Mean age was 61.6 years, and 38.4% of patients were female (**Table 1**). The median follow-up duration was 85.0 days. Of the safety analysis population, patients with major risk factors consisted of 77.3% (76.9–78.6% by diagnosis) with a medical history of CAD; 38.6% (67.1% of HC patients) with that of DM or IGT with mean HbA1c 6.9%; and 65.1% (83.5% of HC patients) with that of hypertension. Patients with a history of other risk factors consisted of 13.6% with CKD, 8.0% with non-cardiogenic cerebral infarction, 13.6% with PAD, 25.1% with low HDL-C (<40 mg/dL), 34.2% with a family history of premature CAD, and 8.0% who were habitual current smokers. Overall, 77.3% of patients were in the secondary prevention and 22.0% in the primary prevention risk category, according to JAS guidelines;<sup>6</sup> all 16 HC patients for primary prevention were categorized as having high risk. High-intensity statin was used in 91.8% of patients (85.7–93.1% by diagnosis). LDL apheresis had been conducted in 50% of HoFH and in 7.8% of HeFH patients. At baseline, mean LDL-C was 150.4 mg/dL in the overall population, and 228.8 mg/dL in the HoFH patients. Mean HDL-C at baseline was 49.0 mg/dL and the non-HDL-C was 176.6 mg/dL. Statin was co-prescribed in 97.2% of patients, and ezetimibe in 51.8%. Other frequently used medications were antihypertensives (65.3%), antiplatelets (69.3%), anti-anginals (55.7%), and anti-diabetics (19.9%).

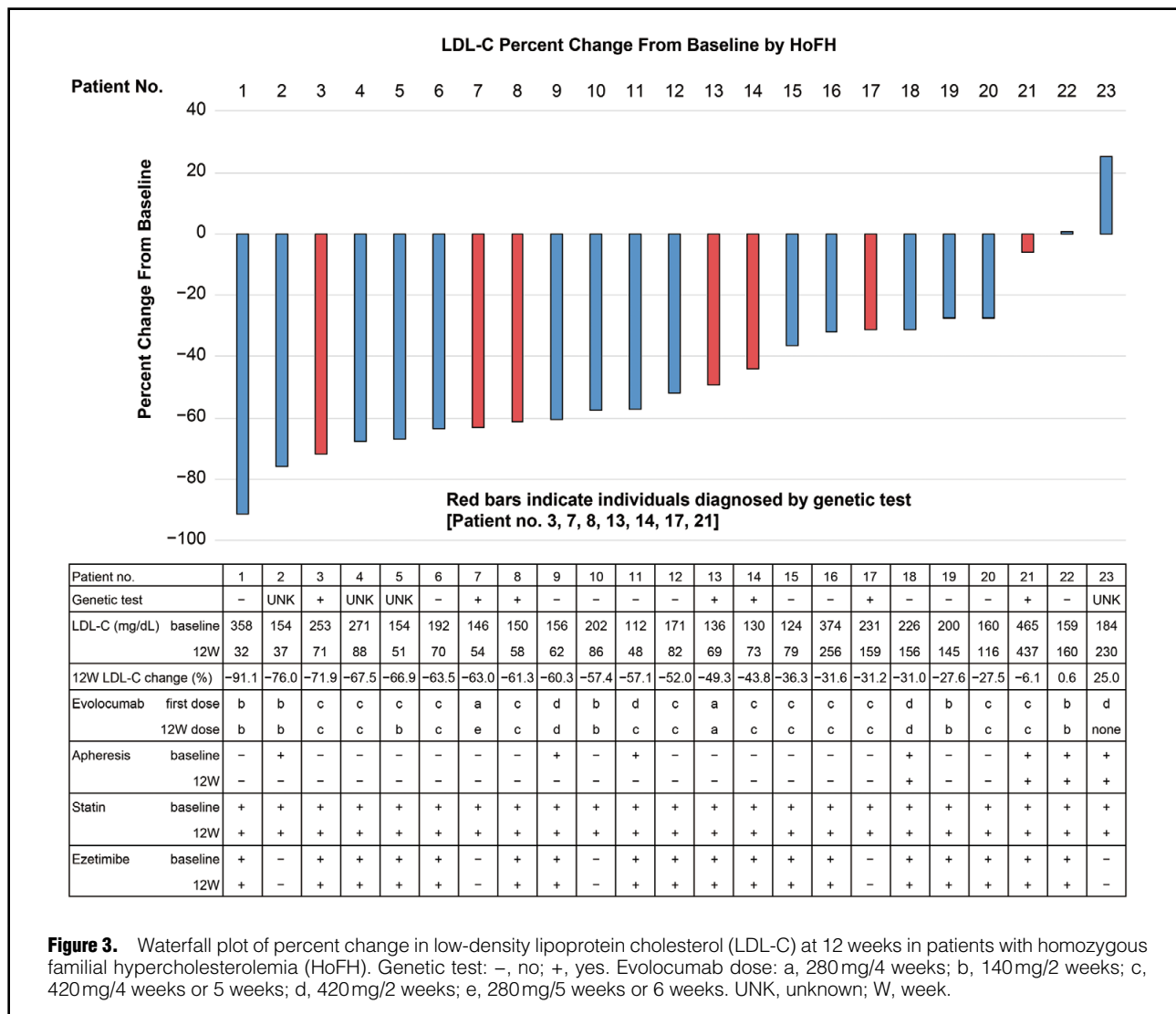
Table 3. Percent Change at 12 Weeks in Lipid Parameters (Effectiveness Analysis Set I)			
	%change from baseline to 12 weeks		
	HoFH	HeFH	HC
<b>TC</b>			
Mean ± SD	-32.2±26.1	-38.0±16.6	-40.3±15.8
95% CI	-44.8 to -19.7	-40.2 to -35.8	-44.4 to -36.2
P-value†	<0.001	<0.001	<0.001
n‡	19	222	60
<b>HDL-C</b>			
Mean ± SD	11.0±21.6	10.0±19.9	8.8±17.1
95% CI	1.7 to 20.4	7.7 to 12.4	4.6 to 13.0
P-value†	0.023	<0.001	<0.001
n‡	23	268	67
<b>TG</b>			
Mean ± SD	-2.8±63.0	-3.2±44.3	-13.8±32.8
95% CI	-30.0 to 24.5	-8.5 to 2.1	-21.7 to -5.8
P-value†	0.835	0.239	<0.001
n‡	23	271	68
<b>Non-HDL-C</b>			
Mean ± SD	-40.5±30.0	-50.1±21.2	-59.8±19.6
95% CI	-55.0 to -26.1	-53.0 to -47.2	-65.0 to -54.7
P-value†	<0.001	<0.001	<0.001
n‡	19	212	58

†One-sample t-test. ‡Patients with data available for %change from baseline to week 12 for the respective lipid parameter. Abbreviations as in Table 1.



**Figure 2.** Subgroup analysis of percent change from baseline in low-density lipoprotein cholesterol (LDL-C) at 12 weeks, according to homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH), and hypercholesterolemia (HC; effectiveness analysis set I). Orange dots, mean; blue bars, 95% CI. If the sample size is <3, 95% CI is not shown. CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; PAD, peripheral artery disease.





**Figure 3.** Waterfall plot of percent change in low-density lipoprotein cholesterol (LDL-C) at 12 weeks in patients with homozygous familial hypercholesterolemia (HoFH). Genetic test: -, no; +, yes. Evolocumab dose: a, 280 mg/4 weeks; b, 140 mg/2 weeks; c, 420 mg/4 weeks or 5 weeks; d, 420 mg/2 weeks; e, 280 mg/5 weeks or 6 weeks. UNK, unknown; W, week.

	<b>Table 4. AE by Lowest Achieved LDL-C Category (Safety Analysis Set)</b>				
	<b>All patients</b>	<b>Lowest achieved LDL-C category</b>			
	<b>n=427</b>	<b>≥40 mg/dL</b>	<b>&lt;40 mg/dL</b>	<b>≥25 and &lt;40 mg/dL</b>	<b>&lt;25 mg/dL</b>
		<b>n=236†</b>	<b>n=187†</b>	<b>n=107†</b>	<b>n=80†</b>
AE	56 (13.1)	38 (16.1)	18 (9.6)	11 (10.3)	7 (8.8)
ADR‡	23 (5.4)	16 (6.8)	7 (3.7)	5 (4.7)	2 (2.5)

Data given as n (%). †Patients with LDL-C data. ‡As reported by the site physicians. ADR, adverse drug reaction; AE, adverse event; LDL-C, low-density lipoprotein cholesterol.

**Effectiveness**

In the primary endpoint analysis of effectiveness, the percent change from baseline in mean±SD LDL-C was -45.5%±27.0% in HoFH (P<0.001 vs. baseline [the same applies hereafter]), -54.2%±29.0% in HeFH (P<0.001), and -64.6%±22.4% in HC (P<0.001) patients after 12 weeks of evolocumab treatment. All percent changes in mean LDL-C at 12 weeks were statistically significant when compared with baseline values (Table 2). In the sensitivity analyses of the effectiveness analysis set II, the percent change from baseline in mean±SD LDL-C was -49.3%±16.5% in

HoFH (P<0.001), -61.0%±22.1% in HeFH (P<0.001), and -65.5%±20.9% in HC (P<0.001) patients. As for other lipid parameters, favorable changes at 12 weeks for TC, HDL-C, and non-HDL-C were observed across diagnosis (Table 3). Changes in ApoA1, ApoB, ApoE, and Lp(a) at 12 weeks were statistically significant (Supplementary Table 1). The percentage of patients with HoFH, HeFH, and HC who achieved the LDL-C goal for comprehensive risk management was 34.8%, 65.7%, and 97.2%, respectively (Supplementary Table 2).

On subgroup analyses of sex, age, and CV risk factors

(CAD, DM and IGT, CKD, non-cardiogenic cerebral infarction, PAD, smoking, hypertension, low HDL-C [ $<40$  mg/dL], and family history of premature CAD), the 12-week LDL-C-lowering effectiveness of evolocumab did not differ between subgroups (Figure 2). A waterfall plot for individual HoFH patients showed a reduction in LDL-C value after 12 weeks of evolocumab treatment in combination with statin, ezetimibe, or apheresis as expected, although some patients had a weaker response to evolocumab treatment (Figure 3).

Overall, the incidence rate of AE was 13.1% (56/427), and that of ADR was 5.4% (23/427). AE were most frequently reported in the system organ classes (SOC) “cardiac disorders” (2.6%) and “investigations” (2.1%). Most ADR were reported in the SOC “investigations”, “general disorders and administration site conditions”, and “gastrointestinal disorders”. ADR by preferred term are presented in Supplementary Table 3. Subgroup analysis by lowest achieved LDL-C after evolocumab treatment suggested that the incidence of AE and ADR was not associated with the lowest achieved LDL-C values (Table 4).

## Discussion

There are very few reports on the effectiveness and safety of evolocumab treatment in a large number of patients with FH, especially in those with HoFH, in the real-world setting. This is the first study to present results of evolocumab from a large sample population, and the results show that LDL-C lowering by the anti-PCSK9 antibody evolocumab was beneficial in patients with FH (HoFH and HeFH) as well as HC when assessed at 12 weeks in the real-world setting.

The Japanese patients in this study were characterized by a relatively high risk in several aspects. First, FH patients with both homozygous and heterozygous genotypes represented a large majority of the enrolled population. Second, patients with HC with pre-existing CAD were predominant. In a randomized, controlled clinical trial conducted in Japan, HC patients with pre-existing CAD comprised approximately 25% of the clinical study population,<sup>9</sup> in contrast, the proportion was more than 3-fold (78.5%) in the current study.

The frequency of FH in Asian countries, including Japan, has been estimated to be 1 in 500 people.<sup>11</sup> Recently updated guidelines, however, focus on, and increase awareness about, diagnosis and management goals for FH patients,<sup>6</sup> thereby, improving diagnostic rates and management. The availability of a new LDL-C-lowering therapy in the form of a PCSK9 inhibitor could be particularly beneficial for FH patients and could be a reason for the high proportion of FH patients with CAD in this real-world study. The baseline LDL-C value, however, was relatively high in FH patients despite combination therapy with high-intensity statins. This study showed that evolocumab in combination with high-intensity statins was prescribed in the real-world setting to patients diagnosed with FH and primarily to those with HC, who were in the high CV risk group. Thus, as shown in this study so far, it is important to assess the relevant risk factors of each patient individually prior to initiating evolocumab treatment.

In the primary endpoint analysis of the effectiveness analysis set I, after 12 weeks of evolocumab treatment, mean  $\pm$  SD LDL-C percent changes were  $-45.5\% \pm 27.0\%$ ,  $-54.2\% \pm 29.0\%$ , and  $-64.6\% \pm 22.4\%$  in HoFH, HeFH, and

HC patients, respectively. This study population, however, included patients who did not follow the dosage and administration of evolocumab specified in package insert,<sup>4</sup> including that for lower doses and dose frequency. The effectiveness analysis set II that included patients who followed the package insert guidelines for dosage was used to summarize the percent change from baseline in LDL-C levels to investigate the impact of adherence to package insert guidelines on the effectiveness of evolocumab. The mean  $\pm$  SD LDL-C percent changes in the effectiveness analysis set II were  $-49.3\% \pm 16.5\%$ ,  $-61.0\% \pm 22.1\%$ , and  $-65.5\% \pm 20.9\%$  in HoFH, HeFH, and HC patients, respectively, thus suggesting that evolocumab is more effective with small variations in its efficacy in patients with HoFH, HeFH, and HC, when prescribed as per the package insert guidelines.<sup>4</sup> The change at 12 weeks in other lipid parameters and ApoA1, ApoB, and Lp(a) with evolocumab treatment showed a trend similar to that observed in the clinical trial. Compared with the response to evolocumab treatment observed for HC or HeFH patients, the waterfall plot for those with HoFH showed that not all patients responded to evolocumab treatment. Although LDL-C lowering is achievable with the anti-PCSK9 monoclonal antibody in HoFH patients, no reduction was reported in those patients who were receptor negative in a previous study.<sup>12</sup>

On subgroup effectiveness analysis, the profile of LDL-C percent change at 12 weeks was similar in each subgroup. The degree of LDL-C lowering in this study was similar to that observed in previous clinical trials in HC.<sup>9,13</sup> The waterfall plot for HoFH patients suggested that the LDL-C-lowering effectiveness of evolocumab at 12 weeks in the real-world setting was not affected by the genetic test conducted for the diagnosis of HoFH.

The incidence of ADR was 5.4%. Stratification by minimum achieved LDL-C after evolocumab treatment suggested that the incidence of reported AE and ADR was not associated with the lowest achieved LDL-C values. No association between evolocumab treatment or very low LDL-C and the emergence of AE has been reported in long-term controlled clinical trials.<sup>5</sup>

Although long-term, randomized, controlled clinical trials have been conducted or are ongoing, this observational study in the real-world setting provides useful information for clinical practice because the real-world setting allowed for inclusion of a broader range of HC patients, without the limitation of exclusion criteria as in controlled clinical trials.<sup>14,15</sup> Furthermore, a longer evolocumab exposure and observation period enabled greater insights into the LDL-C-lowering effect and safety profile of evolocumab in the real-world setting.

## Study Limitations

We recognize several potential limitations of this study. First, HoFH patients included in this study could be HeFH patients because diagnosis was not carried out according to the prescribed procedure of genetic testing; some of the patients diagnosed on genetic testing, however, had an LDL-C-lowering profile as observed in the waterfall plot. Second, because of the reduced number of FH patients (especially HoFH), there was limited power to provide meaningful results in the subgroup analyses. Finally, the effectiveness results from this study cannot be compared with that of clinical trials because of the single-arm observational design of this study. Also, unlike in a blinded,



randomized clinical study that is conducted under strictly controlled conditions, good adherence to and persistence of evolocumab in combination with statin treatment may not be possible in the real-world setting; patients in this observational study, however, may be representative of those in routine clinical practice.

## Conclusions

This real-world study demonstrated that patients on evolocumab treatment are primarily those with FH and HC in the secondary prevention group. These results add to the current pool of knowledge about LDL-C-lowering therapy with evolocumab for FH, both HoFH and HeFH, and could be useful for physicians when choosing an appropriate option for medical treatment.

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## Data Sharing

Qualified researchers may request data from Amgen clinical studies. Complete details are available at <https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/>

## Author Contributions

All authors made substantial contributions to the concept and design, or analysis and interpretation of data, and to the drafting of the manuscript, or revising it critically for important intellectual content. All authors provided final approval of the manuscript.

## Ethics Approval

The protocol of this observational study (evolocumab post-marketing survey) was approved by the Pharmaceuticals and Medical Devices Agency of Japan prior to the study. The study was conducted in accordance with the applicable Pharmaceuticals and Medical Devices law, Good Post-Marketing Study Practice of Japan and the Declaration of Helsinki.

## Informed Consent

Written informed consent was obtained from all participating patients.

## Disclosures

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## Supplementary Files

Please find supplementary file(s); <http://dx.doi.org/10.1253/circrep.CR-19-0027>