



Treatment Patterns and Lipid Profile in Patients with Familial Hypercholesterolemia in Japan

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Aim: To evaluate the epidemiology and real-world treatment patterns associated with lipid-modifying therapies (LMTs) among groups of Japanese patients with familial hypercholesterolemia (FH).

Methods: A retrospective observational study was conducted using an electronic hospital-based administrative claims database and electronic medical records. Patients with existing diagnosis of FH (FH-D) and patients with suspected FH (FH-S) defined by low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL were included, and medical records of hospitals across Japan were analyzed to assess the diagnostic status, management of LDL-C levels, and treatment patterns.

Results: Among the 3,495 patients who met the inclusion criteria, 193 patients were FH-D and 3,339 patients were FH-S. Among them, 83.5% had not achieved the LDL-C of < 100 mg/dL recommended for patients with FH at the index date. Mean LDL-C levels for all patients and for FH-D and FH-S patients were 145.8 mg/dL, 119.2 mg/dL, and 147.6 mg/dL, respectively. 44.5% of the patients were not currently treated with LMTs. High-intensity statins were used only in 19.2% and 2.3% of the FH-D and FH-S patients, respectively. Furthermore, among the FH-D and FH-S statin-treated patients, 61 (69.3%) and 1,059 (89.7%) remained on monotherapy even when their LDL-C was ≥ 100 mg/dL.

Conclusions: Treatment and management of LDL-C in Japanese FH patients remain suboptimal. The results suggest that FH is underdiagnosed in real-world, routine clinical practice in Japan. There is an urgent need to improve the diagnostic rate of FH and to provide the appropriate therapy to achieve the recommended LDL-C levels of < 100 mg/dL or a more than 50% reduction for patients with FH in Japan.

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Key words: Familial hypercholesterolemia, LDL-C, Database analysis, Treatment patterns

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Introduction

Familial hypercholesterolemia (FH) is a common

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autosomal genetic disorder characterized by the triad of high low-density lipoprotein cholesterol (LDL-C), premature coronary artery disease (CAD), and tendon/cutaneous xanthoma¹⁻³). Historically, the frequency of clinical homozygous FH (HoFH) has been estimated at 1 in a million, and for heterozygous FH (HeFH), 1 in 500 throughout the world⁴). A recent report has also demonstrated a higher prevalence of HoFH and HeFH among the general population in Japan, estimated to

be 1/171,167 and 1/208, respectively⁵). It is estimated that there are more than 30 million patients with FH worldwide^{6,7}, including at least 300,000 HeFH patients in Japan¹. Patients with FH have excessive high LDL-C levels due to pathological genetic mutations and are at a significantly higher risk for cardiovascular diseases⁸⁻¹¹. The Japanese Atherosclerosis Society (JAS) guidelines have reported that patients with HeFH develop CAD typically before reaching the age of 55 in men and of 65 in women¹, and a Japanese cohort study found that 70% of HeFH patients died of CAD¹². When FH patients are left untreated, the risk for developing CAD is 20 times greater than that of FH patients treated with cholesterol-lowering medications¹³.

While early diagnosis and treatment for patients with FH are recommended to prevent CAD^{1,14}, most individuals with FH remain undiagnosed and untreated worldwide. The European Atherosclerosis Society (EAS) published a Consensus Statement in 2013 warning of the severe underdiagnosis of FH and its negative consequences¹⁵. The vast majority of the diagnosed FH is categorized as HeFH, and Nordestgaard *et al.* estimated that less than 1% of HeFH patients were diagnosed in most countries¹⁶. Among those diagnosed and treated, most were still unable to achieve the recommended LDL-C level targets, resulting in up to a 13-fold increased risk of CAD¹⁶. It is speculated that Japan is no exception in this regard¹⁶.

The 2012 and 2017 JAS guidelines and 2016 European Society of Cardiology (ESC)/EAS guidelines recommend a target of LDL-C < 100 mg/dL in patients with FH without atherosclerotic cardiovascular disease (ASCVD)^{1,2,15}. Given that this recommendation is known to be difficult for FH patients to achieve in routine clinical practice, reduction of LDL-C by more than 50% is set as the secondary management target¹. The consensus is that lifestyle modification alone is generally not sufficient to achieve normalization of the lipid profile in FH patients; therefore, drug therapy is required, with statins recommended as the first line drug therapy^{1,13}. Previous clinical trials have shown that FH can be effectively treated with lipid-modifying therapies (LMTs) such as statins by reducing LDL-C levels and the risk of cardiovascular events^{17,18}. For patients in whom target LDL-C levels cannot be achieved using conventional statin therapy, more intensive therapies using other LMTs in combination with a statin are recommended¹.

Currently, the proportion of patients diagnosed with FH and treatment patterns for FH with LMTs in real-world clinical settings in Japan are unknown. Two previous studies have reported the prevalence of FH patients, including those treated with LMTs. Teramoto *et al.* (2005) investigated patients who received LMTs

for more than 3 months in an outpatient setting in Japan and reported that 3.4% of these patients had received a diagnosis of FH¹⁹. A more recent study reported that 0.6% of the statin-treated patients who had not achieved the recommended LDL-C targets had a diagnosis of FH²⁰. With the widespread use of statins and non-statin LMTs for LDL-C lowering in recent years, diagnosis of FH has become more challenging²⁰. Given the high risk of CAD and the excessive mortality risk among undiagnosed and under-treated FH patients, there is an urgent need to better understand the management of LDL-C levels for patients with FH in Japan.

Aim

The objective of the current study was to conduct a cross-sectional analysis to evaluate the epidemiology and real-world treatment patterns associated with LMTs, and to understand the current LDL-C levels among Japanese patients with diagnosed FH (FH-D) or suspected FH (FH-S).

Methods

Database

This was a retrospective observational study. The Medical Data Vision database, an electronic hospital-based administrative claims database, was used for this study. The database consists of inpatient and outpatient medical care data from hospitals across Japan. All hospitals in the database were for acute-care, with an average bed number of 350. The database contains anonymized patient-level information on demographics, clinical diagnoses, procedures, prescriptions, and laboratory tests.

Patient Selection

Patients meeting the following inclusion criteria were selected for inclusion in the study (**Fig. 1**): at least one recorded LDL-C value (measured by direct assay) in 2013, with the most recent LDL-C measurement in 2013 defined at the index date; evidence of either a diagnosis of FH and/or LDL-C ≥ 190 mg/dL during the 2-year period prior to the index date; and ≥ 20 years of age at the index date. In order to ensure that the complete medical history was covered and to determine prior LMT use, the included patients were also required to have ≥ 2 years of continuous representation in the database prior to the index date. Patients who did not have an LDL-C level of ≥ 190 mg/dL during the 2-year pre-index period were not included in the current analysis unless they had a diagnosis of FH.

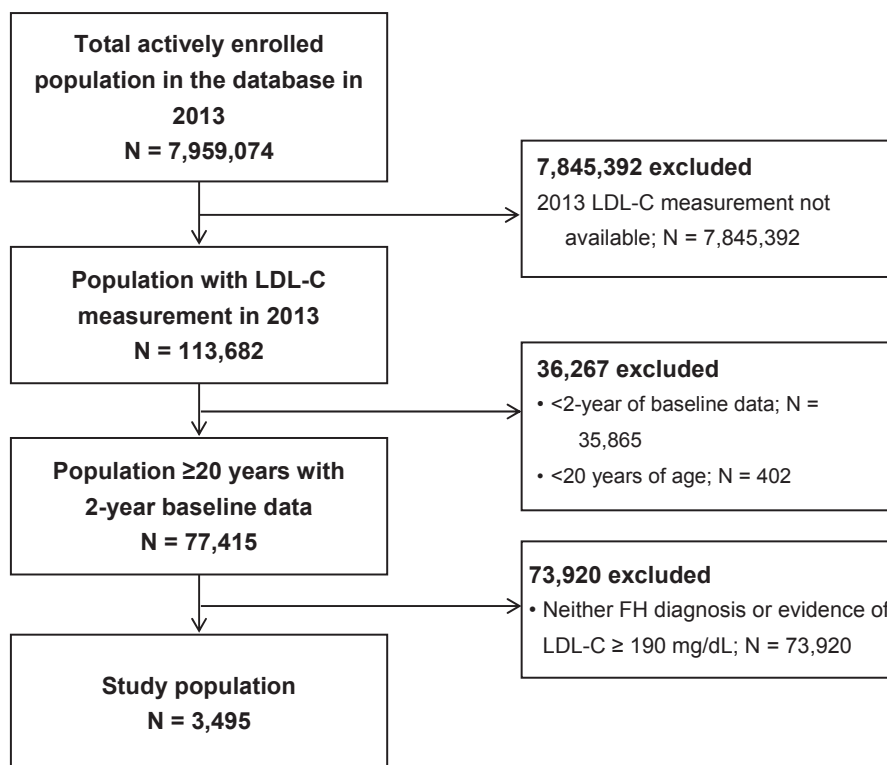


Fig. 1. Patient selection

Given that FH is likely to be underdiagnosed in Japan, our study included the following primary and secondary populations: FH-D and FH-S patients, respectively. FH-D patients were defined as patients with at least one record of FH diagnosis entered by attending physicians during the 2-year period prior to the index date, and FH-S patients were defined as patients with at least one record of LDL-C level ≥ 190 mg/dL during the 2-year period prior to the index date.

Determination of Treatment Patterns

Based on the medication utilization status at the index date, patients were classified into the following three categories: “current LMT therapy” if a recorded LMT prescription was present on the index date or within 30 days prior to it (scenario A or B in **Fig. 2**); “previous LMT therapy” if not currently treated but evidence of a prior recorded LMT during the 2-year pre-index period was present (scenario C in **Fig. 2**); and “no LMT therapy” if no recorded LMT was present during the 2-year pre-index period.

Current LMT therapy was further classified into three mutually exclusive categories: high-intensity statin therapy with or without other non-statin LMT; low-to-moderate-intensity statin with or without other non-statin LMT; and non-statin LMT only. High-intensity statin therapy was defined as atorvastatin ≥ 20 mg/day,

rosuvastatin ≥ 10 mg/day, and pitavastatin 4 mg/day. All other statins and doses were defined as low-to-moderate-intensity statins in the present study. A third category was used to categorize non-statin LMT only without statin use. This classification scheme is different from the statin classification according to the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, which consider high-intensity statins to consist of atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg²¹). Non-statin LMTs included ezetimibe, niacin (nicotinic acid), and bile acid sequestrants (cholestyramine, colestimide).

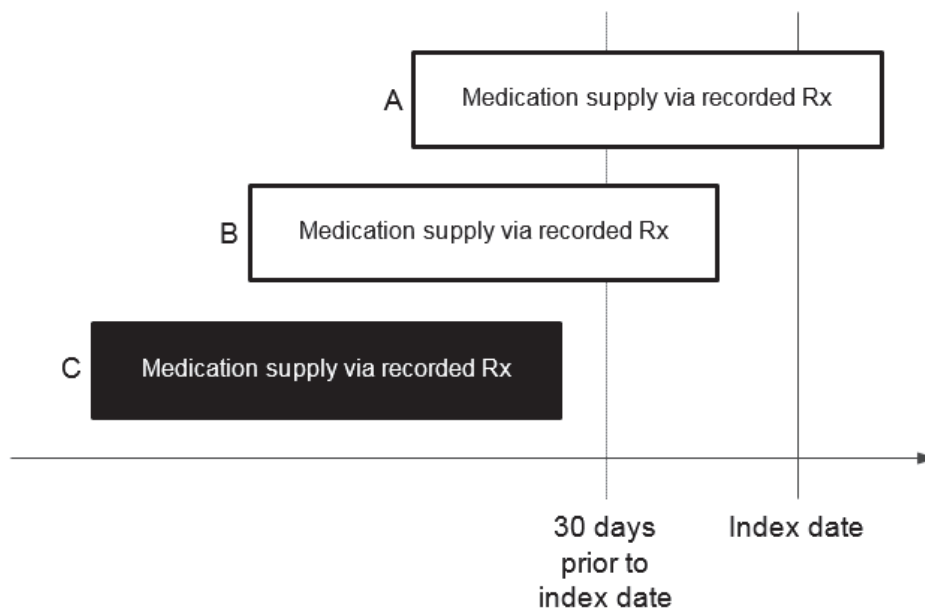
Statistical Analyses

All statistical analyses in this study were descriptive. Baseline characteristics, LMT utilization, and LDL-C levels were summarized using proportions and mean \pm standard deviation (SD) as appropriate. All analyses were conducted with SAS software version 9.4.

Results

Patient Characteristics

A total of 3,495 patients met the inclusion criteria. **Table 1** presents the baseline characteristics of all patients ($N=3,495$), FH-D patients ($N=193$), and FH-S patients ($N=3,339$, including 37 overlapping with



Both white bars representing scenarios A and B (medication supply via recorded prescription on or within 30 days prior to the index date) define the patient as being treated as of index date. The black bar representing scenario C (medication supply via recorded prescription before 30 days prior to the index date) defines the patient as not being treated as of index date.

Fig. 2. Determination of treatment status at index date

FH-D) at the index date. The average ages (SD) for all patients, FH-D patients, and FH-S patients were 63 (13.9), 67 (13.3), and 62 (13.9) years, respectively. The proportion of males for all patients, FH-D patients, and FH-S patients were 40.3%, 42.0%, and 40.1%, respectively. All diagnosed FH patients were classified as HeFH; none of the patients had HoFH.

Diagnosis of FH

Among all 3,495 patients, 5.5% ($N=193$) had a diagnosis of FH. When focused on only the 1,708 and 103 patients who were currently receiving any statins and high-intensity statin, the rate of diagnosis of FH increased to 8.3% ($N=141$) and 35.9% ($N=37$), respectively.

LDL-C Management

Fig. 3 details the LDL-C levels at the index date for all patients, FH-D patients, and FH-S patients. The mean LDL-C levels for all patients, FH-D patients, and FH-S patients were 145.8 mg/dL, 119.2 mg/dL, and 147.6 mg/dL, which indicates a 16.5%, 32.1%, and 15.6% achievement rate of the recommended LDL-C levels of < 100 mg/dL, respectively. Moreover, 42.7%

($N=35$) of the FH-D patients with CAD, 24.3% ($N=27$) of the FH-D patients without CAD, 23.9% ($N=123$) of the FH-S patients with CAD, and 14.1% ($N=397$) of the FH-S patients without CAD had achieved the LDL-C levels of < 100 mg/dL. In the FH-D and FH-S patients with CAD, 13.4% ($N=11$) and 3.7% ($N=19$) had LDL-C levels of < 70 mg/dL, respectively.

The achieved LDL-C levels were also dependent on the current treatment type. In FH-D and FH-S patients treated with statins, approximately 37.0% ($N=57$) and 24.0% ($N=447$), respectively, achieved an LDL-C of < 100 mg/dL, a greater proportion than that achieved by patients treated with non-statin LMT (21.1% for FH-D and 5.5% for FH-S) or not treated with LMT at all (5.0% for FH-D and 4.8% for FH-S).

Utilization of LMT

LMT utilization for all patients, FH-D patients, and FH-S patients is presented in **Fig. 4**. For all patients, nearly half (44.5%) were currently not treated with any LMT, of which 35.3% received no LMT therapy over the 2-year period prior to the index date, and the remaining patients (9.2%) had previous LMT therapy prior to the index date. Among patients on current

Table 1. Baseline characteristics of all patients, FH-D patients, and FH-S patients

| Characteristics | All patients (<i>N</i> =3,495) | FH-D patients (<i>N</i> =193) | FH-S patients (<i>N</i> =3,339) |
|-----------------------------|------------------------------------|-----------------------------------|-------------------------------------|
| Age | | | |
| Mean (SD), years | 62.7 (13.9) | 67.2 (13.3) | 62.4 (13.9) |
| Sex | | | |
| Male, n (%) | 1,409 (40.3) | 81 (42.0) | 1,340 (40.1) |
| Living location | | | |
| Metropolitan, n (%) | 2,843 (81.3) | 161 (83.4) | 2,710 (81.2) |
| Comorbid conditions, n (%) | | | |
| CAD | 584 (16.7) | 82 (42.5) | 515 (15.4) |
| Ischemic stroke | 42 (1.2) | 2 (1.0) | 41 (1.2) |
| PAD | 239 (6.8) | 24 (12.4) | 221 (6.6) |
| Diabetes | 1,001 (28.6) | 74 (38.3) | 937 (28.1) |
| CKD Stage IV–V ¹ | 424 (12.1) | 25 (13.0) | 402 (12.0) |
| Hypertension | 1,934 (55.3) | 133 (68.9) | 1,818 (54.4%) |

CAD: Coronary artery disease, PAD: Peripheral artery disease, CKD: Chronic kidney disease, FH: Familial hypercholesterolemia, FH-D: Diagnosed FH patients, FH-S: Suspected FH patients, SD: Standard deviation

¹CKD Stage IV–V: 30 > eGFR or dialysis

LMT therapy (55.5% of all patients), low-to-moderate-intensity statins were dominantly used (45.9%). In comparison, high-intensity statins and non-statin LMTs only were used by 2.9% and 6.6% of the patients, respectively.

For FH-D patients, 81.9% were on current LMT therapy. The majority of the FH-D patients (53.9%) were on low-to-moderate-intensity statins, and 19.2% and 8.8% of the FH-D patients were on high-intensity statins and non-statin LMTs, respectively.

For the FH-S patients, 54.1% were on current LMT therapy, with the majority (45.3%) receiving low-to-moderate-intensity statins. Among the FH-S patients, 2.3% and 6.5% were on high-intensity statins and non-statin LMTs, respectively.

A detailed breakdown of the therapies according to the LDL-C range for all patients, FH-D patients, and FH-S patients is presented in the **Supplementary Table**. Among the FH-D and FH-S patients with LDL-C \geq 100 mg/dL on any statin treatment, we found that 69.3% and 89.7% remained on monotherapy, respectively. Patients with FH-D were more likely to be treated with high-intensity statins (19.2%) compared with FH-S patients (2.3%).

Discussion

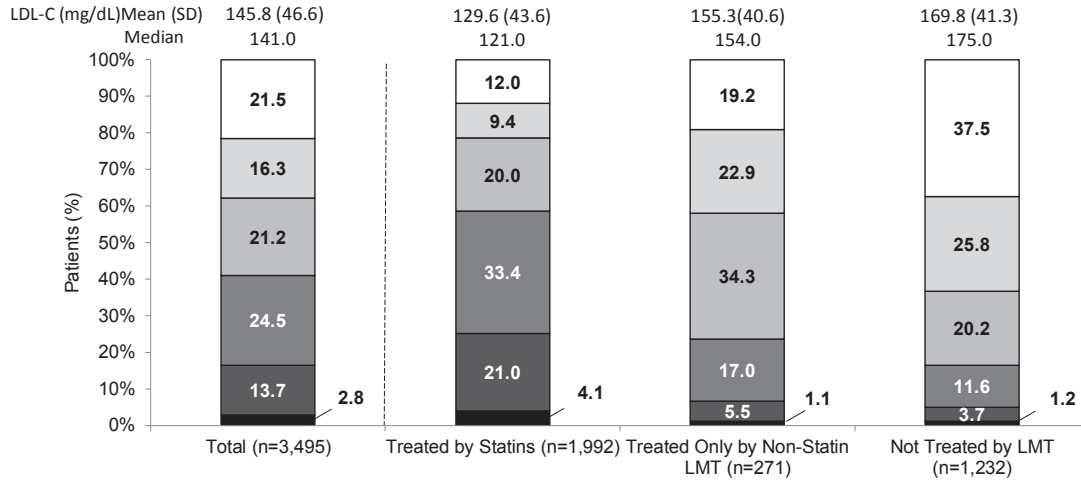
This study investigated real-world treatment patterns and clinical characteristics of LMTs among Japanese patients with FH-D or FH-S using a large hospital administrative claims database. To our knowledge, this is the first study that specifically focused on real-

world clinical practice associated with FH in Japan.

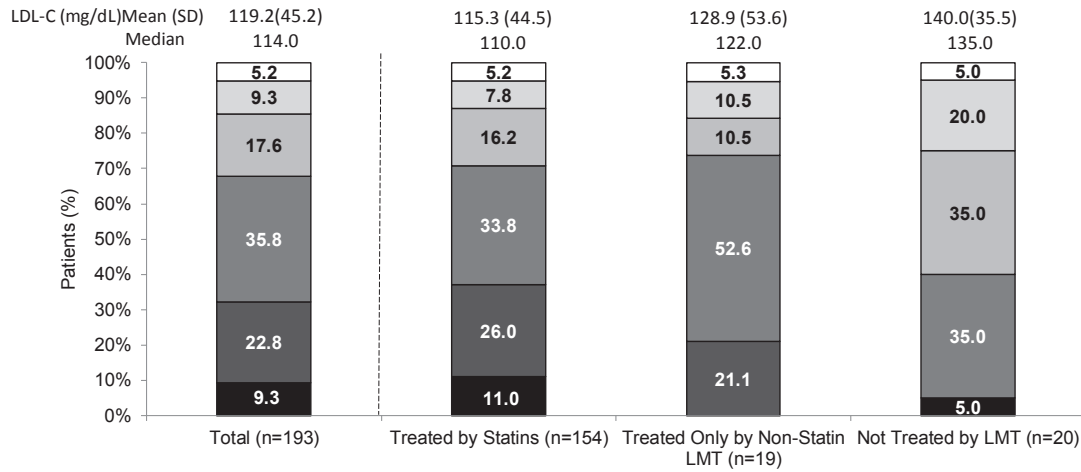
FH is a common genetic cause of premature CAD due to lifelong elevated LDL-C levels. With the right diagnosis, patients with FH can be treated with LDL-C-lowering medication to attenuate the development of atherosclerosis and to prevent CAD¹⁶. Current ESC/EAS guidelines recommend treatment to be initiated as early as possible to achieve the target LDL-C levels of <70 and <100 mg/dL in FH patients with and without ASCVD, respectively. This is also reflected in the newly revised 2017 JAS guidelines, which recommend target LDL-C levels of <70 and <100 mg/dL in FH patients with and without CAD, respectively^{1, 2, 15}.

The average LDL-C levels among FH patients in the current study (i.e., 145.8 mg/dL for all patients and 119.2 mg/dL for FH-D patients who were HeFH with or without LMT) were considerably lower than those previously reported in a study based on nationwide surveillance data from 1996–1998 (i.e., 248 mg/dL for HeFH patients without LMT)²². The widespread use of statins and other LMTs for hypercholesterolemia as well as the rising FH awareness among physicians may have improved LDL-C management over the last 20 years. However, the findings of this study suggest that LDL-C levels are still not adequately managed in the majority of the Japanese patients with either FH-D or FH-S, as 67.9% (*N*=131) and 84.4% (*N*=2,819) of the FH-D and FH-S patients, respectively, had LDL-C levels of \geq 100 mg/dL, which exceed the LDL-C target level recommended by the JAS guidelines. Although slightly higher achievements of LDL-C levels of <100 mg/dL were observed in the FH-D

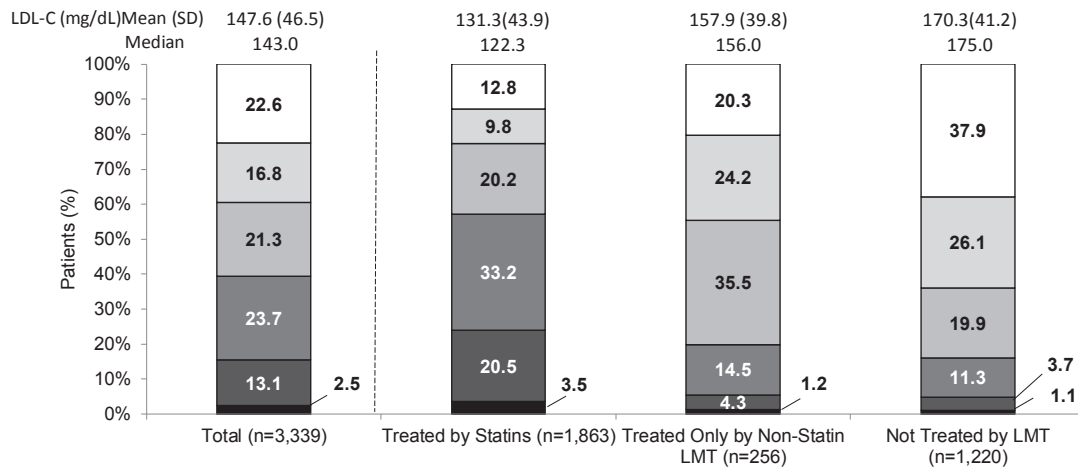
A) Total Patients



B) FH-D Patients



C) FH-S Patients



■ <70 mg/dL ■ 70 to <100 mg/dL ■ 100 to <130 mg/dL ■ 130 to <160 mg/dL ■ 160 to <190 mg/dL □ ≥190 mg/dL

Fig. 3. LDL-C levels at index date for all patients, FH-D patients, and FH-S patients

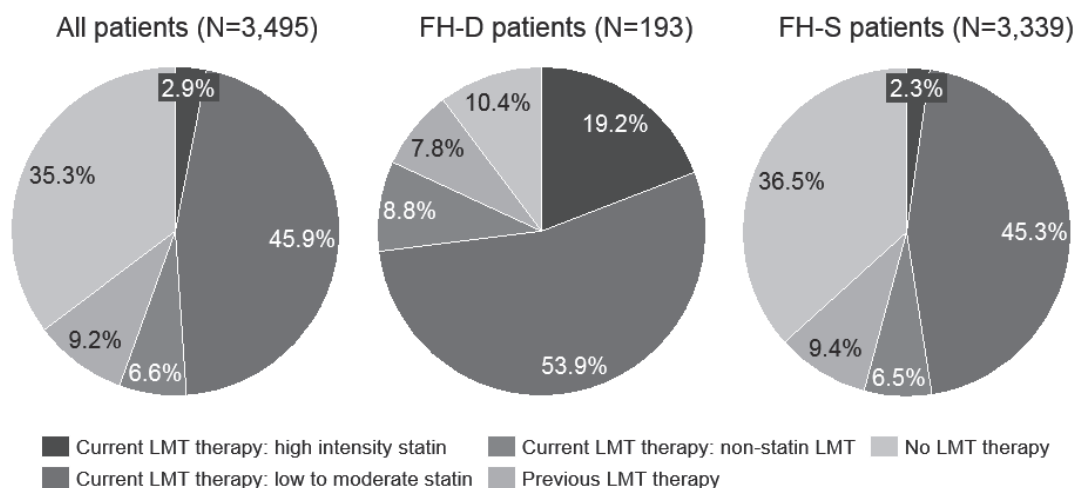


Fig. 4. LMT utilization for all patients, FH-D patients, and FH-S patients

patients, LDL-C management was inadequate regardless of the presence of CAD. In addition, few FH-D and FH-S patients with CAD achieved the LDL-C target level of < 70 mg/dL recommended by the newly revised 2017 JAS guidelines²⁾.

Inadequate treatment of FH has been reported worldwide^{16, 23)}, and the results of the present study revealed that Japan is no exception. Low-to-moderate-intensity statins were found to be the most commonly prescribed LMTs (45.9% of all patients), and 35.3% of all patients had no record of LMT prescriptions during the study period. The majority of the patients treated with statins remained on monotherapy even when their LDL-C levels were high. The JAS guidelines recommend drug therapy for patients with FH, using statins as first line followed by a combination therapy with non-statin LMT in further lines of therapy if monotherapy with statins was inadequate¹³⁾. While the JAS guidelines recommend aggressive statin therapy for FH patients, typically in the form of high doses of high-intensity statins, the majority of the patients in this study were found to receive low-to-moderate-intensity statins. Inadequate management of LDL-C levels may be partially related to lower proportions of patients receiving LMTs, especially high-intensity statins.

Low diagnostic rate of FH is another crucial factor for the lack of optimal therapy for high LDL-C levels. In this study, 5.5% of all patients had an existing diagnosis of FH. Our study also calculated the diagnosis rate among all patients currently treated with any statins and high-intensity statin to be only 8.3% and 35.9%, respectively. A report from Shiba *et al.* suggests a high likelihood of patients with LDL-C ≥ 190 mg/dL having FH²⁴⁾. We defined FH-S patients

as patients with LDL-C ≥ 190 mg/dL regardless of the status of the LDL-C-lowering therapy; therefore, we would expect our study population to have a rate of diagnosis of FH much higher than 5.5%. On the other hand, by applying a prevalence of HeFH in Japan of 1/208, as reported in a prior study⁵⁾, we could estimate that there are 372 patients with FH within our study population aged ≥ 20 years with 2-year baseline data ($N=77,415$). We can then calculate that our study population has a 51.9% diagnosis rate (193 FH-D patients out of 372). However, this value needs to be interpreted with caution due to selection bias (e.g., exclusion of patients without LDL-C ≥ 190 mg/dL and larger acute-care hospital as a data source), making the diagnostic rate of 51.9% an upper limit to an overestimation of the true diagnosis rate. Nevertheless, given the aforementioned, we could conclude that the diagnostic rate of FH in facilities associated with acute-care hospitals is significantly higher than that previously reported for the general population, which likely represents higher prevalence and higher awareness of FH in this clinical setting.

The current study has also found a tendency for increased use of high-intensity statins within FH-D patients compared to all patients (19.2% of FH-D patients vs. 2.9% of all patients). There is also a higher rate of FH-D patients as LMT therapy intensifies, highlighting the potential positive impact of an appropriate diagnosis on improving management of LDL-C levels among patients with FH. In fact, the average LDL-C levels reported in our study were considerably lower for FH-D patients (119.2 mg/dL) than for FH-S patients (147.6 mg/dL). This may reflect the trend of FH-D patients to seek treatment following a formal diagnosis and physicians to appropriately pursue more

aggressive LDL-C-lowering therapy. It is important for Japanese clinicians to be acutely suspicious and proactively aware of the following diagnostic criteria for adult FH patients (meeting at least 2 of the following 3 items): 1) hyper-LDL cholesterolemia (LDL-C levels before treatment: ≥ 180 mg/dL); 2) tendon xanthoma (tendon xanthoma on the dorsal hands, elbows, and knees, or Achilles tendon thickening of ≥ 9 mm on radiography) or nodular xanthoma on the skin; and 3) family history of FH within the second-degree relatives or premature CAD. HoFH can also be diagnosed based on clinical features: serum total cholesterol of ≥ 600 mg/dL, cutaneous xanthoma, premature CAD during childhood, and parents' family history of HeFH¹³).

There are several limitations in this study. First, the use of a hospital database may represent selection bias that limits the generalizability of the results to the overall and FH populations in Japan. The data collected were limited to reflect clinical practice at larger acute-care hospital settings and patients who returned to the same hospital or clinic for continuous care with multiple LDL-C levels measured, limiting the generalizability of the results to continuously followed patients at larger hospitals. Secondly, it was not possible to follow patients who went to a different hospital or clinic, or to identify the same patient receiving care at more than one hospital in this database. The database also does not capture health services and prescriptions outside of the hospital. Third, patient demographics and clinical characteristics were limited to the information available during the 2-year pre-index period, which may have restricted the information used for clinical decision regarding the types of LMT prescribed or the diagnosis of FH itself. On the other hand, some of the patients who would have had pre-treated LDL-C ≥ 190 mg/dL prior to the 2-year pre-index period were not included in the current analysis. Fourth, the definition of FH-D and FH-S does not perfectly represent the diagnosis of FH used in clinical practice. We used LDL-C levels only to define FH-S populations without considering other factors such as family history, xanthoma, or possible secondary cause of hyperlipidemia. Furthermore, we could not exclude patients with a recorded diagnosis of FH in order to obtain insurance approval for certain prescriptions such as atorvastatin 40 mg, which is only approved for patients with FH in Japan. Our study also used a relatively strict definition of "current therapy," defined by a recorded prescription on or within 30 days of the index date. In addition, the higher rate of females as well as younger patients included may be the reason for the lower intensity of LMT in the current analysis. Lastly, the current database did not allow an assessment of whether FH patients had lowered their LDL-C levels by more than

50% in this study. This may partly explain our findings showing that some of the treated patients remained above the LDL-C level of 100 mg/dL.

Conclusion

The results of the present study suggest that treatment and management of LDL-C levels among patients with diagnosed and suspected FH in Japan remain suboptimal. The results also revealed a low rate of FH diagnosis in real-world clinical routine practice in Japan. There is an urgent need for more proactive diagnosis of FH and aggressive treatment targeting LDL-C levels < 100 mg/dL for patients with FH in Japan.

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Conflict of Interest

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.. Dr. Teramoto received honoraria and scholarship grants from Sanofi, Daiichi-Sankyo, Bayer, Takeda Pharmaceutical, Astellas Pharma, Amgen Astellas BioPharma, Pfizer, Shionogi, Eli Lilly, Kissei Pharmaceutical, Mochida Pharmaceutical, MSD and Kowa; and was endowed courses at his affiliation by Bayer, Shionogi, Mochida Pharmaceutical, MSD, Aska Pharmaceutical and Kowa. Dr. Arai received honoraria from Sanofi, MSD, Daiichi-Sankyo, Astellas Pharma, Amgen Astellas BioPharma and Kowa. Dr. Yamashita received honoraria and scholarship grants from Sanofi, Kowa, Otsuka Pharmaceutical, Shionogi, Bayer, MSD, Takeda Pharmaceutical, Sanwa Kagaku Kenkyusho, Ono Pharmaceutical, Astellas Pharma, Daiichi-Sankyo, Astra Zeneca, Medical Review, Skylight Biotech, Kaken Pharmaceutical, Pfizer, Bristol-Meyers Squibb, Amgen Astellas BioPharma, Aegerion Pharmaceuticals, Toa Eiyo, Nippon Boehringer Ingelheim, National Institute of Biomedical Innovation, Kyowa Medex, Mochida Pharmaceutical, Hayashibara, Teijin Pharma and Kissei Pharmaceutical. Dr. Ozaki and Mr. Kai are employees of Sanofi, and Mr. Kai have some shares in Sanofi, during the conduct of this study. Mr. Crawford was an employee of IMS Japan, a healthcare consulting firm contracted for this research, during the conduct of this study.

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Supplemental Table 1. Treatment patterns according to LDL-C range for all patients

| Treatment combinations | All patients (N=3,495) | | | | | | | | | | | | | | | |
|--|------------------------|-------|-------------|--------|---------------------|--------|-------------|--------|--------------------|--------|-------------|--------|---------------------|--------|-------------|--------|
| | Total (N=3,495) | | | | <70 (N=99) | | | | 70 to <100 (N=479) | | | | 100 to <130 (N=855) | | | |
| | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % |
| Currently treated by at least one LMT | 1,940 | 55.5% | - | 73 | 73.7% | - | - | 398 | 83.1% | - | - | 634 | 74.2% | - | - | - |
| Currently on High-Intensity Statin | 103 | 2.9% | 100.0% | 7 | 7.1% | 100.0% | 100.0% | 20 | 4.2% | 100.0% | 100.0% | 23 | 2.7% | 100.0% | 100.0% | 100.0% |
| Monotherapy | 59 | 1.7% | 57.3% | 2 | 2.0% | 28.6% | 28.6% | 13 | 2.7% | 65.0% | 65.0% | 10 | 1.2% | 43.5% | 43.5% | 43.5% |
| Plus Ezetimibe | 42 | 1.2% | 40.8% | 5 | 7.1% | 71.4% | 71.4% | 7 | 1.5% | 35.0% | 35.0% | 12 | 1.4% | 52.2% | 52.2% | 52.2% |
| Plus Non-Ezetimibe | 2 | 0.1% | 1.9% | 0 | 0.0% | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 1 | 0.1% | 4.3% | 4.3% | 4.3% |
| Currently on Low- to Moderate-Intensity statin | 1,605 | 45.9% | 100.0% | 63 | 63.6% | 100.0% | 100.0% | 367 | 76.6% | 100.0% | 100.0% | 568 | 66.4% | 100.0% | 100.0% | 100.0% |
| Monotherapy | 1,442 | 41.3% | 89.8% | 48 | 76.2% | 76.2% | 76.2% | 328 | 68.5% | 89.4% | 89.4% | 527 | 61.6% | 92.8% | 92.8% | 92.8% |
| Plus Ezetimibe | 136 | 3.9% | 8.5% | 13 | 20.6% | 20.6% | 20.6% | 33 | 6.9% | 9.0% | 9.0% | 33 | 3.9% | 5.8% | 5.8% | 5.8% |
| Plus Non-Ezetimibe | 27 | 0.8% | 1.7% | 2 | 3.2% | 3.2% | 3.2% | 6 | 1.3% | 1.6% | 1.6% | 8 | 0.9% | 1.4% | 1.4% | 1.4% |
| Currently only on Non-statin LMT | 232 | 6.6% | 100.0% | 3 | 3.0% | 100.0% | 100.0% | 11 | 2.3% | 100.0% | 100.0% | 43 | 5.0% | 100.0% | 100.0% | 100.0% |
| Any Ezetimibe | 198 | 5.7% | 85.3% | 3 | 100.0% | 100.0% | 100.0% | 8 | 1.7% | 72.7% | 72.7% | 41 | 4.8% | 95.3% | 95.3% | 95.3% |
| Only non-Ezetimibe | 34 | 1.0% | 14.7% | 0 | 0.0% | 0.0% | 0.0% | 3 | 0.6% | 27.3% | 27.3% | 2 | 0.2% | 4.7% | 4.7% | 4.7% |
| No current LMT | 1,555 | 44.5% | 100.0% | 26 | 26.3% | 100.0% | 100.0% | 81 | 16.9% | 100.0% | 100.0% | 221 | 25.8% | 100.0% | 100.0% | 100.0% |
| Previously Covered by LMT | 323 | 9.2% | 20.8% | 11 | 11.1% | 42.3% | 42.3% | 36 | 7.5% | 44.4% | 44.4% | 78 | 9.1% | 35.3% | 35.3% | 35.3% |
| No Current or Prior LMT | 1,232 | 35.3% | 79.2% | 15 | 15.2% | 57.7% | 57.7% | 45 | 9.4% | 55.6% | 55.6% | 143 | 16.7% | 64.7% | 64.7% | 64.7% |
| | All patients (N=3,495) | | | | | | | | | | | | | | | |
| | 130 to <160 (N=741) | | | | 160 to <190 (N=568) | | | | ≥190 (N=753) | | | | | | | |
| | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % |
| Currently treated by at least one LMT | 435 | 58.7% | - | - | 188 | 33.1% | - | - | 212 | 28.2% | - | - | 212 | 28.2% | - | - |
| Currently on High-Intensity Statin | 21 | 2.8% | 100.0% | 100.0% | 15 | 2.6% | 100.0% | 100.0% | 17 | 2.3% | 100.0% | 100.0% | 17 | 2.3% | 100.0% | 100.0% |
| Monotherapy | 12 | 1.6% | 57.1% | 57.1% | 11 | 1.9% | 73.3% | 73.3% | 11 | 1.5% | 64.7% | 64.7% | 11 | 1.5% | 64.7% | 64.7% |
| Plus Ezetimibe | 9 | 1.2% | 42.9% | 42.9% | 4 | 0.7% | 26.7% | 26.7% | 5 | 0.7% | 29.4% | 29.4% | 5 | 0.7% | 29.4% | 29.4% |
| Plus Non-Ezetimibe | 0 | 0.0% | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 1 | 0.1% | 5.9% | 5.9% | 1 | 0.1% | 5.9% | 5.9% |
| Currently on Low- to Moderate-Intensity statin | 332 | 44.8% | 100.0% | 100.0% | 119 | 21.0% | 100.0% | 100.0% | 156 | 20.7% | 100.0% | 100.0% | 156 | 20.7% | 100.0% | 100.0% |
| Monotherapy | 295 | 39.8% | 88.9% | 88.9% | 104 | 18.3% | 87.4% | 87.4% | 140 | 18.6% | 89.7% | 89.7% | 140 | 18.6% | 89.7% | 89.7% |
| Plus Ezetimibe | 32 | 4.3% | 9.6% | 9.6% | 10 | 1.8% | 8.4% | 8.4% | 15 | 2.0% | 9.6% | 9.6% | 15 | 2.0% | 9.6% | 9.6% |
| Plus Non-Ezetimibe | 5 | 0.7% | 1.5% | 1.5% | 5 | 0.9% | 4.2% | 4.2% | 1 | 0.1% | 0.6% | 0.6% | 1 | 0.1% | 0.6% | 0.6% |
| Currently only on Non-statin LMT | 82 | 11.1% | 100.0% | 100.0% | 54 | 9.5% | 100.0% | 100.0% | 39 | 5.2% | 100.0% | 100.0% | 39 | 5.2% | 100.0% | 100.0% |
| Any Ezetimibe | 74 | 10.0% | 90.2% | 90.2% | 44 | 7.7% | 81.5% | 81.5% | 28 | 3.7% | 71.8% | 71.8% | 28 | 3.7% | 71.8% | 71.8% |
| Only non-Ezetimibe | 8 | 1.1% | 9.8% | 9.8% | 10 | 1.8% | 18.5% | 18.5% | 11 | 1.5% | 28.2% | 28.2% | 11 | 1.5% | 28.2% | 28.2% |
| No current LMT | 306 | 41.3% | 100.0% | 100.0% | 380 | 66.9% | 100.0% | 100.0% | 541 | 71.8% | 100.0% | 100.0% | 541 | 71.8% | 100.0% | 100.0% |
| Previously Covered by LMT | 57 | 7.7% | 18.6% | 18.6% | 62 | 10.9% | 16.3% | 16.3% | 79 | 10.5% | 14.6% | 14.6% | 79 | 10.5% | 14.6% | 14.6% |
| No Current or Prior LMT | 249 | 33.6% | 81.4% | 81.4% | 318 | 56.0% | 83.7% | 83.7% | 462 | 61.4% | 85.4% | 85.4% | 462 | 61.4% | 85.4% | 85.4% |

FH: Familial hypercholesterolemia; FH-D: Diagnosed FH patients; FH-S: Suspected FH patients; LDL-C: Low-density lipoprotein cholesterol; LMT: Lipid-modifying therapy

Supplemental Table 2. Treatment patterns according to LDL-C range for FH-D patients

| Treatment combinations | FH-D patients (N=193) | | | | | | | | | | | | | | | |
|--|-----------------------|-------|-------------|----|------------|--------|-------------|----|-------------------|--------|-------------|----|--------------------|--------|-------------|--------|
| | Total (N=193) | | | | <70 (N=18) | | | | 70 to <100 (N=44) | | | | 100 to <130 (N=69) | | | |
| | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % |
| Currently treated by at least one LMT | 158 | 81.9% | - | 16 | 88.9% | - | - | 41 | 93.2% | - | - | 57 | 82.6% | - | - | - |
| Currently on High-Intensity Statin | 37 | 19.2% | 100.0% | 5 | 27.8% | 100.0% | 100.0% | 7 | 15.9% | 100.0% | 100.0% | 9 | 13.0% | 100.0% | 100.0% | 100.0% |
| Monotherapy | 16 | 8.3% | 43.2% | 2 | 11.1% | 40.0% | 40.0% | 4 | 9.1% | 57.1% | 57.1% | 1 | 1.4% | 11.1% | 11.1% | 11.1% |
| Plus Ezetimibe | 21 | 10.9% | 56.8% | 3 | 16.7% | 60.0% | 60.0% | 3 | 6.8% | 42.9% | 42.9% | 8 | 11.6% | 88.9% | 88.9% | 88.9% |
| Plus Non-Ezetimibe | 0 | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 0.0% |
| Currently on Low- to Moderate-Intensity statin | 104 | 53.9% | 100.0% | 11 | 61.1% | 100.0% | 100.0% | 30 | 68.2% | 100.0% | 100.0% | 39 | 56.5% | 100.0% | 100.0% | 100.0% |
| Monotherapy | 83 | 43.0% | 79.8% | 6 | 33.3% | 54.5% | 54.5% | 26 | 59.1% | 86.7% | 86.7% | 34 | 49.3% | 87.2% | 87.2% | 87.2% |
| Plus Ezetimibe | 15 | 7.8% | 14.4% | 3 | 16.7% | 27.3% | 27.3% | 4 | 9.1% | 13.3% | 13.3% | 4 | 5.8% | 10.3% | 10.3% | 10.3% |
| Plus Non-Ezetimibe | 6 | 3.1% | 5.8% | 2 | 11.1% | 18.2% | 18.2% | 0 | 0.0% | 0.0% | 0.0% | 1 | 1.4% | 2.6% | 2.6% | 2.6% |
| Currently only on Non-statin LMT | 17 | 8.8% | 100.0% | 0 | 0.0% | - | - | 4 | 9.1% | 100.0% | 100.0% | 9 | 13.0% | 100.0% | 100.0% | 100.0% |
| Any Ezetimibe | 14 | 7.3% | 82.4% | 0 | 0.0% | 0.0% | 0.0% | 2 | 4.5% | 50.0% | 50.0% | 8 | 11.6% | 88.9% | 88.9% | 88.9% |
| Only non-Ezetimibe | 3 | 1.6% | 17.6% | 0 | 0.0% | 0.0% | 0.0% | 2 | 4.5% | 50.0% | 50.0% | 1 | 1.4% | 11.1% | 11.1% | 11.1% |
| No current LMT | 35 | 18.1% | 100.0% | 2 | 11.1% | 100.0% | 100.0% | 3 | 6.8% | 100.0% | 100.0% | 12 | 17.4% | 100.0% | 100.0% | 100.0% |
| Previously Covered by LMT | 15 | 7.8% | 42.9% | 1 | 5.6% | 50.0% | 50.0% | 3 | 6.8% | 100.0% | 100.0% | 5 | 7.2% | 41.7% | 41.7% | 41.7% |
| No Current or Prior LMT | 20 | 10.4% | 57.1% | 1 | 5.6% | 50.0% | 50.0% | 0 | 0.0% | 0.0% | 0.0% | 7 | 10.1% | 58.3% | 58.3% | 58.3% |

| Treatment combinations | FH-D patients (N=193) | | | | | | | | | | | |
|--|-----------------------|-------|-------------|----|--------------------|--------|-------------|---|-------------|--------|-------------|--------|
| | 130 to <160 (N=34) | | | | 160 to <190 (N=18) | | | | ≥190 (N=10) | | | |
| | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % |
| Currently treated by at least one LMT | 25 | 73.5% | - | 12 | 66.7% | - | - | 7 | 70.0% | - | - | - |
| Currently on High-Intensity Statin | 10 | 29.4% | 100.0% | 3 | 16.7% | 100.0% | 100.0% | 3 | 30.0% | 100.0% | 100.0% | 100.0% |
| Monotherapy | 6 | 17.6% | 60.0% | 2 | 11.1% | 66.7% | 66.7% | 1 | 10.0% | 33.3% | 33.3% | 33.3% |
| Plus Ezetimibe | 4 | 11.8% | 40.0% | 1 | 5.6% | 33.3% | 33.3% | 2 | 20.0% | 66.7% | 66.7% | 66.7% |
| Plus Non-Ezetimibe | 0 | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 0.0% |
| Currently on Low- to Moderate-Intensity statin | 13 | 38.2% | 100.0% | 7 | 38.9% | 100.0% | 100.0% | 4 | 40.0% | 100.0% | 100.0% | 100.0% |
| Monotherapy | 9 | 26.5% | 69.2% | 6 | 33.3% | 85.7% | 85.7% | 2 | 20.0% | 50.0% | 50.0% | 50.0% |
| Plus Ezetimibe | 2 | 5.9% | 15.4% | 1 | 5.6% | 14.3% | 14.3% | 1 | 10.0% | 25.0% | 25.0% | 25.0% |
| Plus Non-Ezetimibe | 2 | 5.9% | 15.4% | 0 | 0.0% | 0.0% | 0.0% | 1 | 10.0% | 25.0% | 25.0% | 25.0% |
| Currently only on Non-statin LMT | 2 | 5.9% | 100.0% | 2 | 11.1% | 100.0% | 100.0% | 0 | 0.0% | - | - | - |
| Any Ezetimibe | 2 | 5.9% | 100.0% | 2 | 11.1% | 100.0% | 100.0% | 0 | 0.0% | 0.0% | 0.0% | 0.0% |
| Only non-Ezetimibe | 0 | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 0.0% |
| No current LMT | 9 | 26.5% | 100.0% | 6 | 33.3% | 100.0% | 100.0% | 3 | 30.0% | 100.0% | 100.0% | 100.0% |
| Previously Covered by LMT | 2 | 5.9% | 22.2% | 2 | 11.1% | 33.3% | 33.3% | 2 | 20.0% | 66.7% | 66.7% | 66.7% |
| No Current or Prior LMT | 7 | 20.6% | 77.8% | 4 | 22.2% | 66.7% | 66.7% | 1 | 10.0% | 33.3% | 33.3% | 33.3% |

FH: Familial hypercholesterolemia; FH-D: Diagnosed FH patients; FH-S: Suspected FH patients; LDL-C: Low-density lipoprotein cholesterol; LMT: Lipid-modifying therapy

Supplemental Table 3. Treatment patterns according to LDL-C range for FH-S patients

| Treatment combinations | FH-S patients (N=3,339) | | | | | | | | | | | | | | | |
|--|-------------------------|-------|-------------|-------|------------|-------|-------------|-------|--------------------|-------|-------------|-------|---------------------|-------|-------------|--------|
| | Total (N=3,339) | | | | <70 (N=83) | | | | 70 to <100 (N=437) | | | | 100 to <130 (N=793) | | | |
| | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % |
| Currently treated by at least one LMT | 1,806 | 54.1% | - | 71.1% | 59 | 71.1% | - | 81.9% | 358 | 81.9% | - | 73.3% | 581 | 73.3% | - | - |
| Currently on High-Intensity Statin | 77 | 2.3% | 100.0% | 3.6% | 3 | 3.6% | 100.0% | 3.2% | 14 | 3.2% | 100.0% | 1.9% | 15 | 1.9% | 100.0% | 100.0% |
| Monotherapy | 47 | 1.4% | 61.0% | 0.0% | 0 | 0.0% | 0.0% | 2.3% | 10 | 2.3% | 71.4% | 1.1% | 9 | 1.1% | 60.0% | 60.0% |
| Plus Ezetimibe | 28 | 0.8% | 36.4% | 3.6% | 3 | 3.6% | 100.0% | 0.9% | 4 | 0.9% | 28.6% | 0.6% | 5 | 0.6% | 33.3% | 33.3% |
| Plus Non-Ezetimibe | 2 | 0.1% | 2.6% | 0.0% | 0 | 0.0% | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.1% | 1 | 0.1% | 6.7% | 6.7% |
| Currently on Low- to Moderate-Intensity statin | 1,511 | 45.3% | 100.0% | 63.9% | 53 | 63.9% | 100.0% | 77.1% | 337 | 77.1% | 100.0% | 67.0% | 531 | 67.0% | 100.0% | 100.0% |
| Monotherapy | 1,367 | 40.9% | 90.5% | 51.8% | 43 | 51.8% | 81.1% | 69.1% | 302 | 69.1% | 89.6% | 62.4% | 495 | 62.4% | 93.2% | 93.2% |
| Plus Ezetimibe | 122 | 3.7% | 8.1% | 12.0% | 10 | 12.0% | 18.9% | 6.6% | 29 | 6.6% | 8.6% | 3.7% | 29 | 3.7% | 5.5% | 5.5% |
| Plus Non-Ezetimibe | 22 | 0.7% | 1.5% | 0.0% | 0 | 0.0% | 0.0% | 1.4% | 6 | 1.4% | 1.8% | 0.9% | 7 | 0.9% | 1.3% | 1.3% |
| Currently only on Non-statin LMT | 218 | 6.5% | 100.0% | 3.6% | 3 | 3.6% | 100.0% | 1.6% | 7 | 1.6% | 100.0% | 4.4% | 35 | 4.4% | 100.0% | 100.0% |
| Any Ezetimibe | 186 | 5.6% | 85.3% | 3.6% | 3 | 3.6% | 100.0% | 1.4% | 6 | 1.4% | 85.7% | 4.2% | 33 | 4.2% | 94.3% | 94.3% |
| Only non-Ezetimibe | 32 | 1.0% | 14.7% | 0.0% | 0 | 0.0% | 0.0% | 0.2% | 1 | 0.2% | 14.3% | 0.3% | 2 | 0.3% | 5.7% | 5.7% |
| No current LMT | 1,533 | 45.9% | 100.0% | 28.9% | 24 | 28.9% | 100.0% | 18.1% | 79 | 18.1% | 100.0% | 26.7% | 212 | 26.7% | 100.0% | 100.0% |
| Previously Covered by LMT | 313 | 9.4% | 20.4% | 12.0% | 10 | 12.0% | 41.7% | 7.8% | 34 | 7.8% | 43.0% | 9.3% | 74 | 9.3% | 34.9% | 34.9% |
| No Current or Prior LMT | 1,220 | 36.5% | 79.6% | 16.9% | 14 | 16.9% | 58.3% | 10.3% | 45 | 10.3% | 57.0% | 17.4% | 138 | 17.4% | 65.1% | 65.1% |

| Treatment combinations | FH-S patients (N=3,339) | | | | | | | | | | | |
|--|-------------------------|-------|-------------|-------|---------------------|-------|-------------|-------|--------------|-------|-------------|--------|
| | 130 to <160 (N=711) | | | | 160 to <190 (N=562) | | | | ≥190 (N=753) | | | |
| | N | % | (sub-group) | % | N | % | (sub-group) | % | N | % | (sub-group) | % |
| Currently treated by at least one LMT | 413 | 58.1% | - | 32.6% | 183 | 32.6% | - | 28.2% | 212 | 28.2% | - | - |
| Currently on High-Intensity Statin | 14 | 2.0% | 100.0% | 2.5% | 14 | 2.5% | 100.0% | 2.3% | 17 | 2.3% | 100.0% | 100.0% |
| Monotherapy | 7 | 1.0% | 50.0% | 1.8% | 10 | 1.8% | 71.4% | 1.5% | 11 | 1.5% | 64.7% | 64.7% |
| Plus Ezetimibe | 7 | 1.0% | 50.0% | 0.7% | 4 | 0.7% | 28.6% | 0.7% | 5 | 0.7% | 29.4% | 29.4% |
| Plus Non-Ezetimibe | 0 | 0.0% | 0.0% | 0.0% | 0 | 0.0% | 0.0% | 0.1% | 1 | 0.1% | 5.9% | 5.9% |
| Currently on Low- to Moderate-Intensity statin | 319 | 44.9% | 100.0% | 20.5% | 115 | 20.5% | 100.0% | 20.7% | 156 | 20.7% | 100.0% | 100.0% |
| Monotherapy | 286 | 40.2% | 89.7% | 18.0% | 101 | 18.0% | 87.8% | 18.6% | 140 | 18.6% | 89.7% | 89.7% |
| Plus Ezetimibe | 30 | 4.2% | 9.4% | 1.6% | 9 | 1.6% | 7.8% | 2.0% | 15 | 2.0% | 9.6% | 9.6% |
| Plus Non-Ezetimibe | 3 | 0.4% | 0.9% | 0.9% | 5 | 0.9% | 4.3% | 0.1% | 1 | 0.1% | 0.6% | 0.6% |
| Currently only on Non-statin LMT | 80 | 11.3% | 100.0% | 9.6% | 54 | 9.6% | 100.0% | 5.2% | 39 | 5.2% | 100.0% | 100.0% |
| Any Ezetimibe | 72 | 10.1% | 90.0% | 7.8% | 44 | 7.8% | 81.5% | 3.7% | 28 | 3.7% | 71.8% | 71.8% |
| Only non-Ezetimibe | 8 | 1.1% | 10.0% | 1.8% | 10 | 1.8% | 18.5% | 1.5% | 11 | 1.5% | 28.2% | 28.2% |
| No current LMT | 298 | 41.9% | 100.0% | 67.4% | 379 | 67.4% | 100.0% | 71.8% | 541 | 71.8% | 100.0% | 100.0% |
| Previously Covered by LMT | 55 | 7.7% | 18.5% | 10.9% | 61 | 10.9% | 16.1% | 10.5% | 79 | 10.5% | 14.6% | 14.6% |
| No Current or Prior LMT | 243 | 34.2% | 81.5% | 56.6% | 318 | 56.6% | 83.9% | 61.4% | 462 | 61.4% | 85.4% | 85.4% |

FH: Familial hypercholesterolemia; FH-D: Diagnosed FH patients; FH-S: Suspected FH patients; LDL-C: Low-density lipoprotein cholesterol; LMT: Lipid-modifying therapy