The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2023; 30: 1803-1816. http://doi.org/10.5551/jat.64081

Gaps in the Care of Subjects with Familial Hypercholesterolemia: Insights from the Thai Familial Hypercholesterolemia Registry

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Aims: Familial hypercholesterolemia (FH) is currently underdiagnosed and undertreated. The establishment of a FH registry could facilitate a deeper understanding of this disease. We described the clinical characteristics of subjects with FH from the Thai FH Registry, compared our data with the regional and global data, and identified gaps in the care of these subjects.

Methods: A multicenter, nationwide prospective FH registry was established in Thailand. Our data were compared with those of the European Atherosclerosis Society-FH Studies Collaboration. Multiple logistic regression analyses were performed for variables associated with lipid-lowering medication (LLM) use and the attainment of low-density lipoprotein-cholesterol (LDL-C) goal.

Results: The study includes 472 subjects with FH (mean age at FH diagnosis: 46±12 years, 61.4% women). A history of premature coronary artery disease was found in 12%. The percentage of LLM use in subjects with a Dutch Lipid Clinic Network score of ≥ 6 (probable or definite FH) in our registry (64%) was slightly lower than the regional data but higher than the global data. Among those who received statins, 25.2% and 6.4% achieved LDL-C levels of <100 mg/dL and <70 mg/dL, respectively. Women with FH were less likely to achieve LDL-C <70 mg/dL (adjusted odds ratio: 0.22, 95% confidence interval: 0.06–0.71, p=0.012).

Conclusions: FH in Thailand was diagnosed late, and treatment was inadequate for the majority of subjects. Women with FH were less likely to achieve LDL-C goals. Our insights could potentially help raise awareness and narrow the gap in patient care.

Clinical Trial Registration Number TCTR20181120001

Key words: **Familial hypercholesterolemia, FH registry, LDL-C goal attainment**

Introduction

Familial hypercholesterolemia (FH) is a genetic disease primarily caused by variants in genes that encode proteins involved in the regulation of low-density lipoprotein (LDL). It is characterized by an abnormally high level of circulating LDL-cholesterol (LDL-C). Complications of FH are early cardiovascular diseases (CVDs), which may lead to premature cardiovascular death[1, 2]. Subjects with FH have a 20-fold increased risk of coronary artery disease (CAD). Men are more likely to experience cardiovascular events earlier than women, as around 50% of men at the age of <50 years and 30% of women before the age of 60 years encounter cardiovascular events[3].

FH is now recognized as one of the most common heritable causes of CVDs and has become a global public health concern[2, 4, 5]. With early diagnosis, cardiovascular complications could be prevented among subjects with FH through therapeutic lifestyle changes and intensive lipid-lowering medications (LLMs). Unfortunately, it has been shown that <10% of subjects with FH worldwide have been diagnosed[4, 6]. Therefore, making the diagnosis earlier and giving proper treatment would be of utmost importance among subjects with FH.

In Thailand, like in other parts of the world, FH is almost always underdiagnosed, and there are only scarce data on subjects with FH in Thailand. Establishing a local FH registry is an important first step in collecting country-specific data and identifying gaps in the clinical care of affected subjects with FH[7]. In Thailand, the Thai FH Registry was started in 2018 as part of the global European Atherosclerosis Society-FH Studies Collaboration (EAS-FHSC). A multicenter nationwide registry was established in order to represent subjects with FH in Thailand. The Thai FH Registry has multiple objectives. First, we would like to identify FH index cases from various institutions, collect clinical data, examine the genetic basis, perform cascade screening among family members, and set up a cohort for a long-term follow-up. Second, we would like to address gaps in the knowledge and care of subjects with FH in our country. Third, we would like to raise awareness of FH among the medical community and the public in Thailand. Here, we present the first report of the Thai FH Registry in terms of its setup, the clinical characteristics of subjects with heterozygous FH in the database, a comparison of clinical information between our Thai registry and the global EAS-FHSC data, and an identification of the gaps in clinical care.

Methods

Identification of Index Cases

The Thai FH Registry was designed as a non-interventional prospective nationwide multicenter disease registry in Thailand. Thai subjects with FH at various sites around the country were recruited. Potential FH index cases were identified by key collaborators at different sites using a variety of methods, including the identification of outpatients and inpatients who already had a clinical diagnosis of FH, the identification of potential index cases in the computer database of lipid levels or ICD-10-CM (E78.0), or cases of premature CAD. After initial identification, these potential index cases of FH were verified using the Dutch Lipid Clinic Network (DLCN) criteria. Secondary causes of hypercholesterolemia, such as untreated hypothyroidism, nephrotic syndrome, and cholestasis, were excluded. If their clinical characteristics were compatible with FH, they were enrolled in the Thai FH Registry. After the opportunistic screening of the index cases, cascade screening of the family members was performed to identify more potential cases.

As of September 2022, a total of 18 tertiary care hospitals around the country were included. Twelve hospitals were in Bangkok or its vicinity, including King Chulalongkorn Memorial Hospital, Siriraj Hospital, Ramathibodi Hospital, Rajavithi Hospital, Phramongkutklao Hospital, Bhumibol Adulyadej Hospital, Vajira Hospital, Chulabhorn Hospital, Police General Hospital, Taksin Hospital,

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Received: November 24, 2022 Accepted for publication: March 29, 2023

Charoenkrung Pracharak Hospital, and Thammasat Hospital. Six tertiary care hospitals were located outside Bangkok and its vicinity: Maharaj Nakorn Chiang Mai Hospital in northern Chiang Mai, Srinagarind Hospital in northeastern Khon Kaen, Chonburi Hospital in eastern Chonburi, King Prajadhipok Memorial Hospital in eastern Chanthaburi, Songklanagarind Hospital in southern Songkhla, and Vachira Phuket Hospital in southern Phuket.

Central Institutional Review Board (IRB) approval was obtained from the Central Research Ethics Committee (CREC project code CREC009/63BRm-MED and certificate number COA-CREC005/2021), and local IRB approval was also obtained from each site. Each participant gave written informed consent.

Data collection was obtained using surveys with a questionnaire, interviews, physical examinations, and reviews of medical records. Blood samples were obtained for chemistry and stored for further genetic analysis. The human protocols were carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Thai FH Registry Database Organization

We used the Research Electronic Data Capture (REDCap), hosted at the Faculty of Medicine, Chulalongkorn University, for data entry and data retrieval[8, 9]. The format and organization of the data were according to the EAS-FHSC. To ensure data security and subject confidentiality, authorization verification was performed before data entry. The data input included:

1. Personal data, including age, gender, ethnicity, birthdate, hometown, occupation, education, smoking status, drinking status, and contact information.

2. Personal clinical data, including history of established CVDs (CAD, cerebrovascular disease, and peripheral artery disease [PAD]), history of previous coronary interventions or coronary artery bypass grafts, history of hypercholesterolemia, history of LLM use, underlying diseases, and medication use.

3. Physical examination and anthropometric data, such as cutaneous xanthoma, tendon xanthoma, and arcus cornealis (corneal arcus), and laboratory results: total cholesterol, high-density lipoprotein-cholesterol, triglyceride, LDL-C, (either calculated or direct LDL-C), fasting plasma glucose, hemoglobinA_{1c}, complete blood count, blood urea nitrogen, creatinine, electrolytes, liver function test, etc.

4. Family members' clinical data, such as the number of siblings and children, identified family members with either hypercholesterolemia, premature CVDs, xanthoma, or arcus cornealis.

After data entry, these data were verified, looking for repeated or incomplete data to ensure the accuracy of the data. Verified data from the REDCap were then uploaded anonymously without identification to the EAS-FHSC website (www.easfhsc.org) to become part of the global data for subjects with FH worldwide. Premature CAD was defined as CAD that occurs before the age of 55 years in men or 60 years in women[4]. The statin intensity was according to the American College of Cardiology/American Heart Association classification[10]. LDL-C levels for goal attainment were according to the EAS/European Society of Cardiology guidelines[11].

Data Comparison

In the Thai FH Registry, we enrolled both heterozygous and homozygous FH cases. For the current report, however, we excluded those with homozygous FH and focused only on heterozygous FH. In order to compare our data with those recently reported from the EAS-FHSC[12], we also presented data on Thai subjects with FH who had a DLCN score of ≥ 6 (probable or definite FH) for direct comparison. According to the EAS-FHSC registry, the data were analyzed overall (global) and stratified geographically by World Health Organization regions (regional). Given the low number of subjects with FH in the South-East Asia, the data from that region were combined with those from the Western Pacific region to get meaningful results. To convert cholesterol levels from mg/dL to mmol/L, the values were divided by 38.6, and to convert triglyceride levels from mg/dL to mmol/L, the values were divided by 88.6. Analysis of LDL-C goal attainment was performed only in those taking LLM.

Statistical Analysis

The data were tested for normal distribution using the Kolmogorov–Smirnov test. The continuous variables are reported as mean ± standard deviation (SD), except for the results in a certain Table, which are presented in median and interquartile range to be compared with the data reported by the EAS-FHSC. Categorical variables are presented as counts and percentages. Comparison of continuous variables was performed using Student's *t*-test, or one-way ANOVA with Bonferroni adjustment. Pearson's chi-squared test was performed for the comparison of categorical variables. For analysis of factors associated with LLM use and attainment of the LDL-C goal, a univariate logistic regression analysis was performed, and the variables with a p-value of <0.10 were then analyzed using the stepwise method in a multivariate logistic

Table 1. Clinical characteristics of FH subjects according to the DLCN score

	All FH (N = 472)	FH diagnosis category by DLCN score			
		Possible FH (N = 210)	Probable FH (N = 73)	Definite FH (N = 189)	*p*-value
DLCN score	≥ 3	3-5	6-8	>8	-
Age at FH registry entry (y)	49 ± 11	50 ± 10	50 ± 12	47 ± 12 [a]	0.028
Age at FH diagnosis (y)	46 ± 12	49 ± 10	48 ± 13	43 ± 12 [a, b]	<0.001
Women, *n* (%)	290 (61.4)	127 (60.5)	48 (65.8)	115 (60.9)	0.710
Body mass index (kg/m^2)	25.0 ± 4.2	25.2 ± 4.3	24.2 ± 4.2	25.3 ± 4.1	0.162
Smoking, *n* (%)	26 (5.7)	13 (6.7)	2 (2.7)	11 (5.8)	0.661
Hypertension, *n* (%)	92 (19.5)	42 (20.1)	16 (21.9)	34 (17.9)	0.744
Diabetes, *n* (%)	45 (9.9)	13 (6.7)	7 (9.7)	25 (13.2)	0.101
History of CAD, *n* (%)	64 (13.9)	22 (11.1)	15 (20.6)	27 (14.3)	0.131
History of premature CAD, *n* (%)	55 (11.9)	18 (9.0)	13 (17.8)	24 (12.8)	0.125
History of premature CVA or PAD, *n* (%)	11 (2.3)	5 (2.4)	2 (2.7)	4 (2.1)	0.956
History of premature CAD in a first-degree relative, *n* (%)	88 (18.7)	20 (9.6)	22 (30.1)	46 (24.3)	<0.001
History of premature CVA or PAD in a first-degree relative, *n* (%)	43 (9.2)	14 (6.7)	11 (15.3)	18 (9.6)	0.089
History of LDL-C >190 mg/dL in a first-degree relative, *n* (%)	90 (19.1)	20 (9.6)	19 (26.0)	51 (26.9)	<0.001
First-degree relative with xanthoma, *n* (%)	28 (5.9)	1 (0.5)	3 (4.2)	24 (12.7)	<0.001
First-degree relative with arcus cornealis, *n* (%)	37 (7.9)	5 (2.4)	4 (5.6)	28 (14.9)	<0.001
Presence of xanthoma, *n* (%)	154 (32.7)	0 (0)	4 (5.6)	150 (79.4)	<0.001
Presence of arcus cornealis, *n* (%)	156 (34.1)	3 (1.5)	52 (71.3)	101 (53.7)	<0.001
Highest total cholesterol (mg/dL)	325 ± 84	298 ± 32	308 ± 44	361 ± 117 [a, b]	<0.001
Highest LDL-C (mg/dL)	240 ± 75	213 ± 25	220 ± 43	279 ± 101 [a, b]	<0.001
LDL-C in subjects on LLM (mg/dL)	150 ± 75	137 ± 50	124 ± 59	169 ± 90 [a, b]	<0.001
On LLM, *n* (%) [†]	266 (56.5)	97 (46.4)	43 (58.9)	126 (66.7)	<0.001
Treatment with statin alone, *n* (%)	185 (39.6)	81 (38.8)	34 (47.9)	70 (37.4)	0.291
Treatment with combined statin + bile acid sequestrant/ezetimibe/ PCSK9 inhibitor, *n* (%)	78 (16.7)	14 (6.7)	9 (12.7)	55 (29.4)	<0.001

Data are reported in mean ± SD or count (percentage);
[a] statistically significant compared with the Possible FH group;
[b] statistically significant compared with the Probable FH group
[†] missing data = 1

regression model. The odds ratio (OR) and 95% confidence interval (CI) are presented. All data analysis was performed using the STATA 16.1 statistical program, and a two-sided *p*-value of <0.05 was regarded as statistically significant.

Results

The current report includes 472 subjects with a phenotypic diagnosis of FH in the Thai FH Registry. The baseline characteristics of our subjects are shown in **Table 1**. The mean age of those with FH diagnoses was 46 ± 12 years, and 61.4% were women. A history of premature CAD was found in 11.9% of the subjects, and only 56.5% of the subjects were on LLM. When we categorized our subjects according to the DLCN score, possible FH (score 3–5), probable FH (score 6–8), and definite FH (score >8) were found in 45%, 15%, and 40%, respectively **(Table 1)**. Those with definite FH were significantly younger and had higher levels of highest total cholesterol, highest LDL-C, and LDL-C while on LLM than those with probable FH and possible FH.

Using the results recently reported from the EAS-FHSC [12], we compared our results with those of the subjects with FH from the South-East Asia and Western Pacific regions and the global EAS-FHSC **(Table 2)**. Compared with FH subjects from the South-East Asia and Western Pacific region, we found that the median age at registry entry and the median age of FH diagnosis in our registry were relatively similar. However, the percentages of subjects with current smoking, hypertension, and premature CAD were relatively lower in our registry. In addition, the percentage of subjects with FH on LLM in our Thai registry was lower compared with that of the regional

Table 2. Clinical characteristics of subjects with FH who had a DLCN score of ≥ 6 in the Thai FH Registry compared with results from the EAS-FHSC

Clinical characteristics	Thai FH Registry (N = 262)	South-East Asia and Western Pacific Regional data (N = 2,179)	EAS-FHSC Global data (N = 42,617)
Age at registry entry (y)	49.5 (41.0–57.0)	50.0 (38.7–59.0)	46.2 (34.3–58.0)
Age at FH diagnosis (y)	47.0 (36.0–55.0)	48.2 (36.0–57.0)	44.4 (32.5–56.5)
Women, *n* (%)	163 (62.2)	1,097 (50.4)	21,999 (53.6)
Body mass index (kg/m^2)	24.3 (22.1–27.5)	25.2 (22.5–28.3)	25.1 (22.5–28.2)
Smoking, *n* (%)	16 (6.1)	318 (17.3)	8,844 (23.5)
Hypertension, *n* (%)	50 (19.1)	588 (28.0)	7,030 (19.2)
Diabetes, *n* (%)	32 (12.2)	229 (11.2)	1,843 (5.0)
History of CAD, *n* (%)	42 (16.0)	6057 (17.4)	467 (23.9)
History of premature CAD, *n* (%)	37 (14.1)	403 (20.2)	4,031 (11.3)
On LLM, *n* (%)†	168 (64.2)	1,154 (80.6)	23,175 (59.5)
Total cholesterol (mmol/L)*			
Subjects not on LLM	7.42 (6.80–8.24)	7.39 (6.50–8.43)	7.45 (6.15–8.86)
Subjects on LLM	5.49 (4.50–7.07)	6.01 (4.81–7.58)	6.15 (5.08–7.80)
LDL-C (mmol/L)*			
Subjects not on LLM	5.24 (4.68–6.08)	5.30 (4.40–6.52)	5.43 (4.32–6.72)
Subjects on LLM	3.58 (2.56–5.16)	4.35 (3.00–5.50)	4.23 (3.20–5.66)
HDL-C (mmol/L)*			
Subjects not on LLM	1.45 (1.24–1.74)	1.32 (1.10–1.60)	1.25 (1.01–1.53)
Subjects on LLM	1.46 (1.22–1.72)	1.30 (1.10–1.60)	1.23 (1.00–1.50)
Triglyceride (mmol/L)**			
Subjects not on LLM	1.42 (0.97–1.83)	1.41 (1.00–1.92)	1.28 (0.88–1.89)
Subjects on LLM	1.15 (0.81–1.56)	1.30 (0.90–1.85)	1.24 (0.85–1.82)

Data are reported in median (IQR) or count (percentage)
†missing data = 1
*To convert cholesterol from mmol/L to mg/dL, multiply by 38.6
**To convert triglyceride from mmol/L to mg/dL, multiply by 88.6

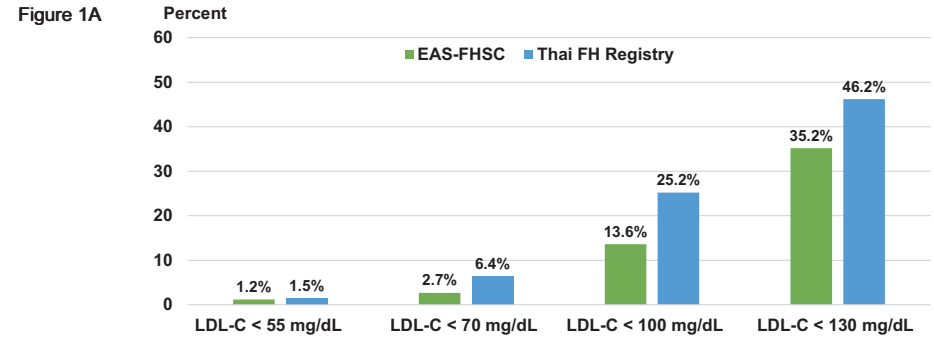
data. LDL-C levels in subjects with and without LLM were slightly lower than those of subjects with FH from the South-East Asia and Western Pacific regions.

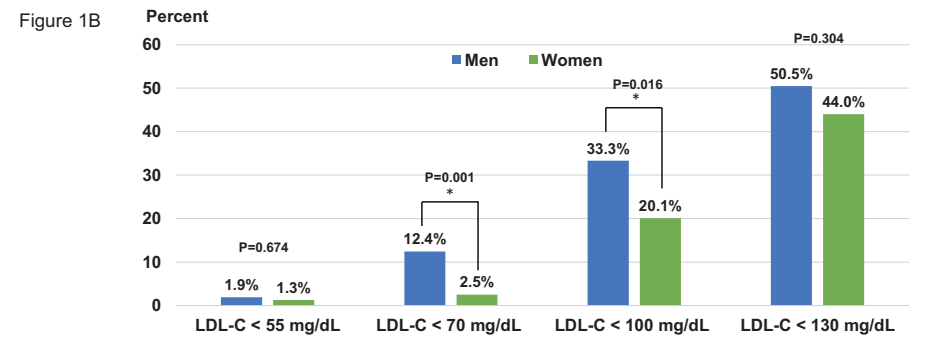
When comparing our data with the global data of 56 countries from the EAS-FHSC **(Table 2)**, we found that the median ages of our subjects with FH at registry entry and at FH diagnosis were slightly higher than those in the global data. The percentage of subjects with FH who had a current smoking status was lower, but more subjects in our registry had diabetes and premature CAD compared with those in the EAS-FHSC. The percentage of LLM use was slightly higher, and total cholesterol and LDL-C levels were also lower than those in the EAS-FHSC. The percentages of subjects who attained different levels of LDL-C goals were slightly higher in our registry **(Fig. 1A)**.

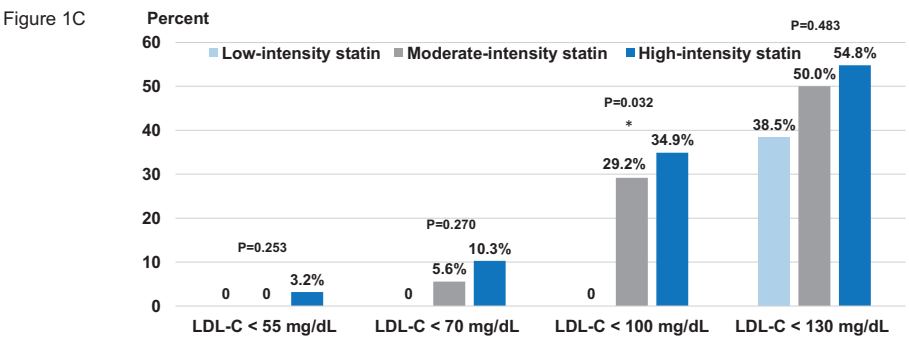
It is of note that the smoking rate in our registry is relatively lower than those in the regional and global data, mainly because Thai women have a very low smoking rate. According to the data from the 6th National Health and Nutrition Examination Survey in 2019–2020 [13], the smoking rate among Thai women was only 1.8%, whereas 30% was reported among Thai men in all age groups. In **Table 2**, all 16 current smokers with FH and a DLCN score of ≥ 6 were men, and all 163 women were non-smokers, so the percentage of smokers among men with FH was 16.2% and was 0% among women with FH.

As shown in **Table 3**, we performed subgroup analyses according to sex. We found that men with FH were more likely to have premature CAD and receive an FH diagnosis earlier than women. LDL-C levels and the proportion of subjects with FH who received LLM were not significantly different between men and women. However, the percentages of men who attained LDL-C goals of <70 mg/dL and <100 mg/dL were significantly higher than those in women, as shown in **Fig. 1B**.

In the total cohort of 472 subjects, 263 (55.7%) were on statin therapy. After excluding 51 subjects with missing data on statin intensity, we examined the proportion of subjects who reached their LDL-C treatment goal according to statin intensity. Among







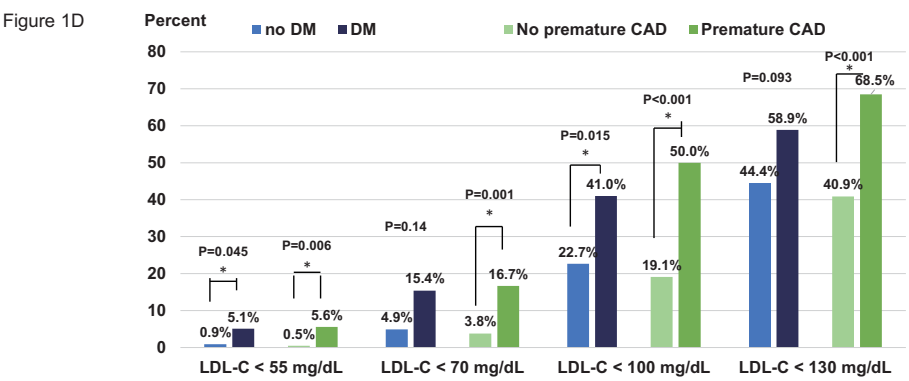


Fig. 1. The proportion of subjects with FH who received LLM and attained LDL-C goals

To convert cholesterol from mg/dL to mmol/L, divide by 38.6. *: $p < 0.05$. A: The proportion of subjects with FH and a DLCN score of ≥ 6 who received LLM and attained LDL-C goals in our registry (N = 168) compared with that of EAS-FHSC (N = 23,175). B: The proportion of subjects with FH (DLCN score ≥ 3) who received LLM and attained LDL-C goals according to sex (men = 105 and women = 159). C: The proportion of subjects with FH (DLCN score ≥ 3) who received LLM and attained LDL-C goals according to the intensity of statin. The numbers of subjects who received low-intensity, moderate-intensity, and high-intensity statins were 13, 72, and 127, respectively. D: The proportion of subjects with FH (DLCN score ≥ 3) who received LLM and attained LDL-C goals according to the presence of diabetes or a history of premature CAD. The number of subjects in the non-diabetes (no DM) group, diabetes (DM) group, no premature CAD group, and premature CAD group were 229, 38, 214, and 54, respectively.

Table 3. Clinical characteristics according to sex

	Sex		*p*-value
	Men (N=182)	Women (N=290)	
Age at FH diagnosis (y)	44±11	49±12	<0.001
History of CAD, *n* (%)	35 (19.6)	29 (10.3)	0.005
History of premature CAD, *n* (%)	31 (17.4)	24 (8.5)	0.004
Highest total cholesterol (mg/dL)	321±96	328±76	0.364
Highest LDL-C (mg/dL)	240±69	242±79	0.827
LDL-C in subjects on LLM (mg/dL)	145±78	154±73	0.368
Triglyceride (mg/dL)	141±87	123±73	0.015
HDL-cholesterol (mg/dL)	50±12	64±26	<0.001
On LLM, *n* (%)†	105 (57.7)	161 (55.7)	0.801

Data are reported in mean±SD or count (percentage)
†missing data=1

Table 4. Clinical characteristics according to the presence of diabetes and history of premature CAD

	Presence of diabetes*		*p*-value	History of premature CAD†		*p*-value
	Yes (N=45)	No (N=410)		Yes (N=55)	No (N=406)	
Highest total cholesterol (mg/dL)	333±82	325±86	0.580	331±104	324±81	0.591
Highest LDL-C (mg/dL)	253±72	241±77	0.299	252±105	239±70	0.226
LDL-C in subjects on LLM (mg/dL)	125±57	155±77	0.021	120±70	158±74	<0.001
Triglyceride (mg/dL)	134±60	130±82	0.729	123±62	130±81	0.571
HDL-C (mg/dL)	50±15	59±23	0.014	48±14	60±23	<0.001
Not on LLM, *n* (%)	6 (13.3)	179 (43.7)	<0.001	1 (1.8)	189 (46.7)	<0.001
Treatment with statin, *n* (%)	38 (84.4)	225 (54.9)	0.001	54 (98.2)	209 (51.6)	<0.001

Data are reported in mean±SD or count (percentage)
*missing data=17
†missing data=11

the remaining 212 subjects, 13 (6%), 72 (34%), and 127 (60%) were on low-intensity, moderate-intensity, and high-intensity statins, respectively. The mean±SD levels of LDL-C in subjects who received low-intensity, moderate-intensity, and high-intensity statins were 157±53, 141±65, and 144±88 mg/dL, respectively (p=0.786). It was observed that a higher percentage of subjects who were on a higher intensity of statins achieved the LDL-C goal, but statistical significance was found only for the LDL-C goal of <100 mg/dL **(Fig. 1C)**. However, it is of note that only 34.9% and 10.3% of subjects on high-intensity statins achieved LDL-C goals of <100 mg/dL and <70 mg/dL, respectively.

The presence of type 2 diabetes or CAD in subjects with FH is considered a very high cardiovascular risk[11]. In the entire cohort, 45 subjects with FH had diabetes, and 55 had premature CAD. In **Table 4**, subgroup analyses were performed according to the presence of diabetes or premature CAD. We found that subjects with FH and diabetes were more likely to receive statin therapy and achieve significantly lower LDL-C levels compared with those without diabetes. However, LDL-C levels while on LLM among the subjects with FH and diabetes were still high, and only 5.1% had LDL-C levels of <55 mg/dL **(Fig. 1D)**. Furthermore, 13.3% did not receive LLM at all.

Similarly, subjects with FH and a history of premature CAD were more likely to receive statin therapy and achieve significantly lower LDL-C levels than those without CAD **(Table 4)**. Nevertheless, LDL-C levels in subjects on LLM were still high. Only 16.7% had LDL-C levels of <70 mg/dL, and 5.6% achieved LDL-C levels of <55 mg/dL **(Fig. 1D)**.

No LLM use represents a major gap in the care of subjects with FH. We next compared subjects with FH who received and did not receive LLM, and the results are shown in **Supplementary Table 1**. Compared with those who did not receive LLM, subjects with FH who received LLM were more likely

to have a personal history of CVD, CVD risk factors (hypertension and diabetes), a family history of CVD and LDL-C >190 mg/dL, tendon xanthoma, and arcus cornealis. The highest total cholesterol and LDL-C levels were also significantly higher in those receiving LLM, but the current LDL-C levels were significantly lower. We next performed logistic regression analyses to identify factors associated with LLM use **(Supplementary Table 2)**. In univariate analysis, we found that hypertension, diabetes, the presence of xanthoma, and a family history of LDL-C >190 mg/dL or CVD were associated with LLM use. In multivariate analysis, only hypertension and a family history of LDL-C >190 mg/dL were clinical characteristics associated with significant odds of receiving LLM. We did not find significant predictors of non-LLM use.

LDL-C goal non-attainment is another major gap in the care of FH. We compared subjects who attained and did not attain LDL-C goals, and the results are shown in **Supplementary Table 3**. Diabetes and CAD were significantly more prevalent among those who attained LDL-C goals compared with those who did not. We next evaluated predictors of attaining LDL-C goals among subjects on LLM **(Supplementary Table 4)**. For the LDL-C goal of < 100 mg/dL, univariate analysis showed that diabetes, a history of premature CAD, and a family history of LDL-C >190 mg/dL were predictors of LDL-C goal attainment, whereas women, the presence of xanthoma, and LDL-C ≥ 190 mg/dL were less likely to attain the LDL-C goal. After multivariate analysis, a history of premature CAD, a family history of LDL-C >190 mg/dL, and an LDL-C level ≥ 290 mg/dL remained significant. For the LDL-C goal of <70 mg/dL, diabetes and a history of premature CAD were predictors of LDL-C goal attainment in univariate analysis. Women were also less likely to attain the LDL-C goal in both unadjusted and adjusted analyses (OR: 0.18, 95% CI: 0.05–0.57, p=0.004 and adjusted OR: 0.22, 95% CI: 0.06–0.71, p=0.012, respectively).

Discussion

In our first report of the Thai FH Registry, we described the clinical data of 472 subjects, 262 of whom had probable or definite FH based on the DLCN criteria. The median age of subjects with FH at diagnosis was comparable to that of the global EAS-FHSC registry. Only 64% of FH subjects with probable or definite FH received LLM, which was lower than the regional data but slightly higher than the global registry. Among all of those who received statin therapy, only one-quarter achieved an LDL-C level <100 mg/dL. Among very high-risk groups of subjects with FH and diabetes and/or previous CAD, only a small number reached the recommended LDL-C target.

The Thai FH Registry was established in 2018 with the purpose of increasing awareness and enhancing our understanding of the clinical, genetic, epidemiological, and socioeconomic aspects of FH in Thailand. Our ultimate goal is to improve patient care to prevent morbidity and mortality in subjects with FH. Aside from providing important information for the local community, the Thai FH Registry, as part of the global EAS-FHSC, could also provide collective data to represent the South-East Asia and Western Pacific regions.

Currently, EAS-FHSC is the largest and only global FH registry that has data on subjects with FH from >70 countries worldwide[12]. Comparing our data with the global data of 42,617 subjects from 56 countries recently reported from the EAS-FHSC[12], we found that the age of diagnosis in our registry was 3 years later than that of the global data (47 vs. 44 years, respectively). Despite being a congenital disorder, FH is still underdiagnosed worldwide. Several guidelines have addressed this important issue, and several factors have been attributed to the underdiagnosis of FH, including a lack of awareness among the medical community and the public, a lack of uniform diagnostic criteria and limited access to genetic testing to confirm a diagnosis.

Among subjects with FH who had been diagnosed, the EAS-FHSC data showed that approximately 60% of subjects with FH received LLM, whereas the number was slightly higher at 64% in our Thai subjects with FH. This treatment gap has been repeatedly identified in all parts of the world[14-17]. Unfortunately, no significant predictor of non-LLM use has been identified in our study.

Sex disparity in diagnosis and care has been shown to exist among adult patients with FH[18-20]. Specifically, women are less likely than men to receive statin therapy and achieve LDL-C goals. In the general population, it is well known that women are less likely to use statins and attain LDL-C goals than men, and a number of potential reasons have been postulated, including decreased awareness of CVD risk in women, reduced effectiveness among dyslipidemic women, a higher risk of statin intolerance in women, and non-adherence to statins[21-24]. In our study, women were diagnosed with FH 5 years later than men. The percentages of LLM use were quite similar between both genders, suggesting that there was no social difficulty for women to receive treatment. However,

the percentages of LDL-C goal attainment (LDL-C < 100 and <70 mg/dL) were significantly lower in women. In comparison to men, women had about a half (50%) lower chance to attain the LDL-C goal < 100 mg/dL and about a one-fifth (18%) lower chance to attain the LDL-C goal <70 mg/dL. The underlying reasons for this gender disparity in attaining LDL-C goals are not readily apparent from our study and merit further investigation.

Among subjects with FH on LLM, 13.6% in the EAS-FHSC registry[12] attained the LDL-C goal <100 mg/dL. Our data of 25.2% was higher than those of the global data, but still less than those reported elsewhere[25, 26]. For LDL-C <70 mg/dL, 2.7% in the EAS-FHSC registry achieved this[12] and <5% was reported from Asian and Pacific countries, such as Japan, China, Malaysia, and Vietnam[27, 28], whereas 6.4% was demonstrated in our study. Higher percentages of goal attainment, varying from 7.8% to 22.0% were observed in other reports[18, 19, 29]. Different possibilities can potentially explain the non-attainment of the LDL-C goal in our registry. First, it is possible that not all the physicians who actually cared for the subjects with FH were aware of the FH diagnosis and its very high risk of CVD. FH is well known to be underrecognized and undertreated worldwide[4, 27]. Even with the FH diagnosis, treatment inertia might still be responsible[30, 31]. Second, limited therapeutic drug options due to differences in health insurance systems are also possible. In Thailand, approximately three-quarters of Thai citizens are covered by the Universal Coverage Scheme, in which the use of simvastatin and atorvastatin is unrestricted. Although other statins, ezetimibe, and both PCSK9 inhibitors (alirocumab and evolocumab) are available in Thailand, their use in this segment of the population is restricted and generally not reimbursable by the Universal Coverage Scheme. Third, non-adherence to LLMs is also a problem in Thai subjects, partly due to misinformation about the benefits and adverse effects of statins in various social networks.

Our data, along with the global data from the EAS-FHSC and others, identify gaps in both diagnosis and treatment between guideline recommendations and current clinical practice. Our lesson reinforces the opportunity to increase the detection rate of subjects with FH and to intensify the treatment to the recommended LDL-C goal in order to help prevent cardiovascular morbidity and mortality in subjects with FH worldwide. Recently, our proposal for expanding the healthcare benefits of Thai subjects with homozygous and severe heterozygous FH in the Universal Coverage Scheme (including genetic testing and non-statin LLMs) has been preliminarily accepted for consideration by the National Health Security Office Committee.

There are certain limitations to our study. First, our registry is a collaborative effort among physicians caring for subjects with FH around the country and they were concentrated around medical school hospitals and main referral centers. Therefore, asymptomatic subjects with FH who were followed at the small community hospitals might be underrepresented. Increasing the number of smaller hospitals, which is ongoing in the next phase of our registry, would hopefully yield more generalizable results. Second, we enrolled subjects with a phenotypic diagnosis of FH using the DLCN criteria in our current report. It is still possible that certain subjects might have polygenic hypercholesterolemia and not FH. Third, only a few of the subjects with FH in our report had confirmed genetic testing, which was partly due to limited access to genetic testing. Currently, the cost of genetic testing in Thailand is still rather high and only reimbursable for certain groups. Moreover, the expertise is not yet readily available in many institutions or clinics. As a result, the limited access to genetic testing could relate to the low number of subjects diagnosed with definite FH. It is of note that the diagnostic criteria for FH in Asian and Pacific countries, for example, Japan and China, do not yet rely on genetic testing[32-34]. Nevertheless, the genetic data on Thai subjects are currently emerging as part of the government-funded Genomics Thailand Project and will soon provide instructive information on the genetics of Thai subjects with FH. Fourth, since our report is cross-sectional and observational, associations between various factors and LDL-C goal attainment do not represent causality.

Conclusion

Our first report of the nationwide multicenter Thai FH Registry showed that the diagnosis of FH in Thailand was rather late and the attainment of LDL-C goals was still far from the current guideline recommendations, suggesting that a treatment gap exists in the clinical care of patients with FH. Early diagnosis, early initiation of high-intensity statins or a combination of LLMs, evaluation and management of modifiable cardiovascular risk factors, and evaluation of the cause of non-attainment of LDL-C goals, especially in women, are key areas for improvement to close this gap.

Acknowledgements

This work was supported by fundings from the

Health Systems Research Institute (63-082 and 64-093), Ratchadapiseksompotch Funds, Chulalongkorn University (CU_GR_63_94_30_01, RA-MF-58-63 and RA-MF-18/64), the Endocrine Society of Thailand, the Medical Council of Thailand and the Royal College of Physicians of Thailand.

Conflict of Interest

All authors have no conflict of interest to declare.

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Supplementary Table 1. Comparison of clinical characteristics between subjects on and not on lipid-lowering medication (LLM)

Clinical characteristics	Subjects on LLM (N = 66)	Subjects not on LLM (N = 202)	*p*-value
Age at FH diagnosis (y)	46 ± 13	48 ± 9	0.072
Women, *n* (%)	161 (60.5)	127 (62.9)	0.606
Body mass index (kg/m^2)	24.9 ± 4.1	25.2 ± 4.4	0.543
Smoking, *n* (%)	16 (6.0)	10 (5.3)	0.753
Hypertension, *n* (%)	77 (28.9)	14 (6.9)	<0.001
Diabetes, *n* (%)	39 (14.7)	6 (3.2)	<0.001
History of CAD, *n* (%)	64 (24.1)	0 (0)	<0.001
History of premature CAD, *n* (%)	54 (20.3)	0 (0)	<0.001
History of premature CVA or PAD, *n* (%)	8 (3.0)	0 (0)	0.012
History of premature CAD in a first-degree relative, *n* (%)	63 (23.7)	24 (11.9)	0.001
History of premature CVA or PAD in a first-degree relative, *n* (%)	30 (11.3)	11 (5.5)	0.003
History of LDL-C >190 mg/dL in a first-degree relative, *n* (%)	66 (24.8)	24 (11.9)	<0.001
First-degree relative with xanthoma, *n* (%)	21 (7.9)	7 (3.5)	<0.001
First-degree relative with arcus cornealis, *n* (%)	25 (9.6)	12 (6.0)	<0.001
Presence of xanthoma, *n* (%)	98 (36.9)	55 (27.2)	0.026
Presence of arcus cornealis, *n* (%)	104 (38.8)	52 (27.4)	0.017
Family history of CVD, *n* (%)	125 (46.9)	70 (37.0)	0.008
Highest total cholesterol (mg/dL)	337 ± 101	310 ± 51	<0.001
Highest LDL-C (mg/dL)	254 ± 88	224 ± 48	0.001
Current LDL-C level (mg/dL)	150 ± 74	198 ± 51	<0.001

Data were reported as mean ± SD or count (percentage)

Supplementary Table 2. Univariate and multivariate logistic regression analyses for lipid-lowering medication (LLM) use

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)	*p*-value
Age at FH diagnosis	0.98 (0.97 - 1.00)	0.085	-	-
Women	0.90 (0.62 - 1.32)	0.610	-	-
Hypertension	4.94 (2.74 - 8.91)	<0.001	4.04 (2.01 - 8.11)	<0.001
Diabetes	5.03 (2.08 - 12.15)	<0.001	2.61 (0.96 - 7.1)	0.059
Presence of xanthoma	1.61 (1.08 - 2.39)	0.019	1.58 (0.99 - 2.51)	0.051
Family history of a first-degree relative with LDL-C >190 mg/dL	2.44 (1.82 - 3.27)	<0.001	2.06 (1.46 - 2.89)	<0.001
Family history of CVD	1.65 (1.15 - 2.37)	0.007	-	-
Highest LDL-C level				
<190 mg/dL	reference	-	-	-
190 – 289 mg/dL	0.33 (0.13 - 0.79)	0.013		
≥ 290 mg/dL	1.29 (0.45 - 3.68)	0.625		

Supplementary Table 3. Comparison of clinical characteristics among subjects with lipid-lowering medication (LLM) who attained LDL-C goal <100 mg/dL and LDL-C goal <70 mg/dL

Clinical characteristics	LDL-C goal attainment <100 mg/dL		*p*-value	LDL-C goal attainment <70 mg/dL		*p*-value
	Yes (N=67)	No (N=198)		Yes (N=17)	No (N=248)	
Age at FH diagnosis (y)	49 ± 13	45 ± 13	0.045	43 ± 13	46 ± 13	0.269
Women, *n* (%)	32 (47.8)	128 (64.7)	0.015	4 (23.5)	156 (62.9)	0.002
Body mass index (kg/m^2)	24.4 ± 3.9	25.1 ± 4.1	0.241	24.6 ± 3.3	25.0 ± 4.1	0.724
Smoking, *n* (%)	5 (7.5)	11 (5.6)	0.571	1 (5.9)	15 (6.1)	>0.999
Hypertension, *n* (%)	25 (37.3)	53 (26.3)	0.085	8 (47.1)	69 (27.8)	0.091
Diabetes, *n* (%)	16 (23.9)	23 (11.6)	0.014	6 (35.3)	33 (13.3)	0.013
History of CAD, *n* (%)	36 (53.7)	28 (14.1)	<0.001	10 (58.8)	54 (21.8)	0.001
History of premature CAD, *n* (%)	27 (40.3)	27 (13.6)	<0.001	9 (52.9)	45 (18.2)	0.001
History of premature CVA or PAD, *n* (%)	2 (2.9)	6 (3.1)	>0.999	0 (0)	8 (3.2)	>0.999
History of premature CAD in a first-degree relative, *n* (%)	13 (19.4)	49 (24.8)	0.623	3 (17.7)	59 (23.8)	0.357
History of premature CVA or PAD in a first-degree relative, *n* (%)	7 (10.5)	22 (11.2)	0.721	1 (5.9)	28 (11.3)	0.552
History of LDL-C >190 mg/dL in a first-degree relative, *n* (%)	17 (25.4)	48 (24.2)	0.072	6 (35.3)	59 (23.8)	0.153
First-degree relative with xanthoma, *n* (%)	2 (3.0)	18 (9.1)	0.054	0 (0)	20 (8.2)	0.194
First-degree relative with arcus cornealis, *n* (%)	8 (12.5)	16 (8.2)	0.588	2 (11.8)	22 (9.1)	0.370
Presence of xanthoma, *n* (%)	16 (24.2)	81 (40.9)	0.015	3 (17.7)	94 (38.1)	0.120
Presence of arcus cornealis, *n* (%)	30 (44.8)	72 (36.6)	0.371	7 (41.2)	95 (38.5)	0.915
Family history of CVD, *n* (%)	30 (44.8)	95 (47.9)	0.770	6 (35.3)	119 (47.9)	0.399
Highest total cholesterol (mg/dL)	304 ± 53	348 ± 112	0.003	312 ± 66	339 ± 104	0.292
Highest LDL-C (mg/dL)	222 ± 49	265 ± 96	0.001	233 ± 68	256 ± 90	0.312
Current LDL-C level (mg/dL)	78 ± 14	175 ± 71	<0.001	59 ± 9	157 ± 73	<0.001

Data were reported as mean ± SD or count (percentage)
There were one missing data on attaining the LDL-C goal.

Supplementary Table 4. Univariate and Multivariate logistic regression analyses for attaining LDL-C goal <100 mg/dL and LDL-C goal <70 mg/dL

Variables	LDL-C goal attainment <100 mg/dL				LDL-C goal attainment <70 mg/dL			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)	*p*-value
Age at FH diagnosis	1.02 (0.99 - 1.04)	0.050	-	-	0.97 (0.94 - 1.01)	0.262	-	-
Women	0.50 (0.28 - 0.88)	0.017	0.55 (0.29 - 1.00)	0.053	0.18 (0.05 - 0.57)	0.004	0.22 (0.06 - 0.71)	0.012
Hypertension	1.65 (0.92 - 2.98)	0.091	-	-	2.29 (0.85 - 6.18)	0.101	-	-
Diabetes	2.37 (1.16 - 4.82)	0.017	-	-	3.53 (1.22 - 10.21)	0.020	-	-
Presence of xanthoma	0.46 (0.24 - 0.87)	0.018	-	-	0.35 (0.09 - 1.25)	0.109	-	-
History of premature CAD, *n* (%)	4.25 (2.25 - 8.02)	<0.001	4.39 (2.20 – 8.77)	<0.001	5.05 (1.85 - 13.81)	0.002	4.02 (1.43 – 11.29)	0.008
Family history of a first-degree relative with LDL-C >190 mg/dL	1.46 (1.05 - 2.04)	0.023	1.47 (1.02 - 2.11)	0.037	1.67 (0.94 - 2.97)	0.079	-	-
Highest LDL-C level								
<190 mg/dL	Reference				Reference			
190 – 289 mg/dL	0.22 (0.09 - 0.57)	0.002	-	-	0.22 (0.06 - 0.80)	0.022	-	-
≥ 290 mg/dL	0.10 (0.03 - 0.33)	<0.001	0.23 (0.09 - 0.72)	0.002	0.36 (0.08 - 1.62)	0.187	-	-