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Low-density lipoprotein cholesterol goal achievement in patients with familial hypercholesterolemia in countries outside Western Europe: The International ChoLesterol management Practice Study

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BACKGROUND: The cross-sectional observational International ChoLesterol management Practice Study study assessed achievement of European Society of Cardiology/European Atherosclerosis Society low-density lipoprotein cholesterol (LDL-C) targets in patients outside Western Europe.

OBJECTIVE: The aim of the study was to assess LDL-C goal achievement in International ChoLesterol management Practice Study participants with familial hypercholesterolemia (FH).

METHODS: A total of 334 patients (aged ≥18 years) with definite or probable FH (Dutch Lipid Clinic Network score ≥6; 43.1% genetically confirmed) who had been receiving stable lipid-modifying therapy (LMT) for ≥3 months were enrolled.

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Data sharing: Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

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RESULTS: The mean ± standard deviation age of the patients was 58.5 ± 13.1 years, 49.1% were male, and 48.2% had coronary artery disease. Most were receiving statin (~99%). Of these, 57.6% were on high-intensity statin therapy, 49.1% on the highest dose available, and 13.0% used a statin together with a cholesterol absorption inhibitor (CAI). Mean ± standard deviation LDL-C level was 5.6 ± 3.0 mmol/L before LMT and 3.3 ± 2.0 mmol/L at enrollment. Overall, 32.0% of patients achieved their LDL-C target. Target achievement rates were 36.6% for patients with coronary artery disease, and 27.5% for those without, and 27.9%, 28.0%, and 37.5% for patients treated with a statin plus CAI, highest-dose statin (no CAI), and lower-dose statin (no CAI), respectively.

CONCLUSIONS: LDL-C target achievement rates were low in patients with FH, even in those receiving intensive LMT. Factors that are likely to have contributed to the low LDL-C target achievement rates include high baseline LDL-C, inadequate statin dosages, and low use of CAI. Many patients would have been eligible for proprotein convertase subtilisin/kexin type 9 inhibitor therapy.

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder that results in markedly elevated levels of low-density lipoprotein cholesterol (LDL-C) and, which is associated with a high risk of premature atherosclerotic cardiovascular disease (ASCVD). FH is common, affecting 1 person in every 200 to 500[1–4]; therefore, it represents a substantial contribution to the global prevalence of ASCVD. Early diagnosis and effective treatment of FH with lipid-modifying therapies (LMTs) can reduce the risk of adverse cardiovascular outcomes.[5,6] However, FH is still underdiagnosed and undertreated.[3,4,7–9]

There is no universally agreed diagnostic strategy for FH. Diagnosis is usually based on the presence of LDL hypercholesterolemia together with a combination of clinical signs, family history, or genetic testing. The Dutch Lipid Clinic Network (DLCN) criteria, which provide a score based on several clinical and laboratory indicators,[4] are used in many countries, but genetic testing is uncommon in many countries because of the associated cost.[3]

The International ChoLesterol management Practice Study (ICLPS) was a multinational, cross-sectional, observational study to investigate the achievement of European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guideline LDL-C targets[10] and their determinants in real-world clinical practice in countries outside Western Europe.[11] In this article, we present data from a subgroup of ICLPS participants with definite or probable FH according to DLCN criteria. Although it is likely that not all the patients included had FH, this group represents a population of patients with severe hypercholesterolemia who are at high risk of ASCVD.

Methods

ICLPS was conducted in 452 centers in 18 countries in Africa, Asia, Eastern Europe, Latin America, and the Middle East between August 2015 and August 2016. A full list of participating physician investigators (physicians) is provided in Supplementary Table 1. The methods are described in detail elsewhere.[11]

The study was conducted according to the Declaration of Helsinki principles, as well as guidelines for good epidemiology practice and local regulations. Local or regional institutional review boards and/or ethics committee approval was obtained, where required. Participants provided written informed consent.

Patients

Patients (aged ≥18 years) who had been receiving a stable dose and type of LMT for ≥3 months before enrollment and who had had their LDL-C value measured on stable LMT in the previous 12 months were eligible. Patients who had received a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in the previous 6 months were excluded.

Data collection and management

During a single visit, investigators collected the following data: demographics, physical examination, medical history, FH confirmation by genetic testing, lipid values (on current treatment and untreated, if available), current LMTs and cardiovascular risk categorization.

Identification of patients with FH

The primary definition of FH for this analysis was a retrospectively calculated DLCN score ≥6, indicating definite or probable FH (Supplementary Table 2). LDL-C measured in the untreated state was used for the score computation. We included patients with genetically confirmed FH even if untreated LDL-C was not available.

Additional analyses were performed in patients with FH according to the following secondary definitions of FH: definite, probable, or possible FH (DLCN ≥ 3), and definite or probable FH determined by DLCN score estimating untreated LDL-C in patients with missing untreated LDL-C values. The method for estimation of untreated LDL-C is described in the Supplementary Appendix (Supplementary Table 3).

Statistical analysis

The primary outcome was the proportion of patients who failed to achieve their appropriate LDL-C target at enrollment, as defined by the 2011 ESC/EAS guidelines,[10] that is, <1.8 mmol/L or 50% LDL-C reduction (for those patients for whom baseline untreated LDL-C was available) when target levels could not be reached for very high-risk patients, <2.5 mmol/L or 50% LDL-C reduction for high-risk patients, and <3.0 mmol/L for moderate-risk patients.

The proportion of patients with definite or probable FH on intensive LMT who were potentially eligible for treatment with PCSK9 inhibitors was estimated based on criteria specified in the 2017 update of the ESC/EAS guidelines for the use of PCSK9 inhibitors[12] (see Supplementary Appendix).

Results

DLCN score based on measured untreated LDL-C could be calculated in 3334 (36.8%) of the 9049 ICLPS participants (Supplementary Fig. 1). A total of 334 patients (10.0%) had definite or probable FH and comprised the primary analysis population (range 0%–30% across participating countries; Supplementary Table 4). Of these, 144 (43.1%) were reported to have genetic confirmation of FH. Physicians assessed patients as presenting with primary hypercholesterolemia/FH in 83.8%, 51.7%, 16.5%, and 10.4% of patients in the definite, probable, possible, and unlikely FH categories, respectively.

Demographics, medical history, and presenting characteristics

Demographic data, medical history, and presenting characteristics are presented in Supplementary Tables 5 and 6.

The mean ± standard deviation (SD) age of patients with definite or probable FH was 58.5 ± 13.1 years, and half were male. Additional cardiovascular risk factors and comorbidities such as hypertension (62.6%), diabetes (37.4%), smoking (15.3%), and being overweight (body mass index 25 to <30 kg/m^2; 42.8%) or obese (body mass index ≥30 kg/m^2, 37.7%) were common.

Approximately half the patients (48.2%) with definite or probable FH had coronary artery disease (CAD; Supplementary Table 5). Cardiovascular risk factors and comorbidities were more common in the subgroup with CAD compared with patients without CAD.

Lipid profile and LMT

Lipid values at diagnosis and enrollment and LMTs at enrollment are shown for patients with definite or probable FH, possible FH, and unlikely FH in Table 1 and Supplementary Table 7.

The untreated LDL-C level was available in 249 patients (74.6%) with definite or probable FH. Mean ± SD untreated LDL-C and LDL-C at enrollment was 5.6 ± 3.0 and 3.3 ± 2.0 mmol/L, respectively. Median (interquartile range) change in LDL-C from diagnosis was −37.4% (−54.8% to −8.8%), and LDL-C was <1.8 mmol/L in 12.9% and ≥3.4 mmol/L in 31.2% of these patients at enrollment (Supplementary Fig. 2).

Most patients were taking a statin (~99%; Table 1). Of these, 57.6% with definite or probable FH were taking a high-intensity statin (49.1% on the highest dose available). The primary reason given for not prescribing statin at the highest dose (Supplementary Tables 8 and 9) was that the physician was satisfied with the patient's LDL-C level at the current dose (67.3%). Of patients with definite or probable FH, 74.3% were treated with statin monotherapy. Statin plus cholesterol absorption inhibitor (CAI) combination therapy was used by 12.9% of these patients, which equates to 13.0% of statin-treated patients.

The mean ± SD LDL-C level at enrollment was 2.9 ± 1.6 mmol/L in patients with CAD compared with 3.6 ± 2.3 mmol/L in patients without CAD (Supplementary Table 7). The LDL-C level at enrollment was <1.8 mmol/L in 18.6% of patients with CAD and 7.2% of patients without CAD. Of statin-treated patients with CAD, 65.6% were taking high-intensity statin and 55.6% were on the highest dose available, compared with 50.6% and 42.7%, respectively, in patients without CAD.

In patients with genetically confirmed FH (n = 144), mean ± SD LDL-C was 4.6 ± 2.2 mmol/L before LMT and 2.9 ± 1.3 mmol/L at enrollment compared with 5.9 ± 3.2 mmol/L and 3.6 ± 2.4 mmol/L, respectively, for patients without genetic confirmation (Supplementary Table 7). In patients with and without tendon xanthomata, untreated mean ± SD LDL-C was 4.5 ± 2.1 mmol/L and 6.3 ± 3.3 mmol/L, respectively, and 3.0 ± 1.4 mmol/L and 3.4 ± 2.3 mmol/L, respectively, at enrollment (Supplementary Table 7).

At diagnosis, mean ± SD LDL-C was 6.3 ± 2.2 mmol/L, 5.8 ± 3.4 mmol/L, and 4.9 ± 2.4 mmol/L in patients who were treated with a statin-CAI combination, with statin at the highest dose available or statin at a lower dose, respectively (Table 2). Mean ± SD LDL-C at enrollment in these treatment groups was 3.8 ± 1.9 mmol/L, 3.5 ± 2.2 mmol/L, and 2.8 ± 1.6 mmol/L, respectively, corresponding to a median (interquartile range) change in LDL-C from diagnosis of −47.7% (−65.1% to −5.0%), −36.1% (−56.6% to −7.6%), and −39.4% (−52.2% to −13.3%), respectively.

Achievement of ESC/EAS LDL-C targets

Overall, 32.0% of patients with definite or probable FH achieved their target LDL-C (Fig. 1A). LDL-C goal attainment rates were similar in patients with (31.3%) and without (32.6%) genetic confirmation of FH. Target achievement rates were 36.6% in the subgroup of patients with CAD and 27.5% in those without CAD. LDL-C target

Table 1 Lipid levels at diagnosis and enrollment, and LMTs at enrollment, in patients with definite or probable FH,* possible FH,* and unlikely FH*

	FH category		
	Definite or probable (n = 334)	Possible (n = 535)	Unlikely (n = 2465)
Lipid values at diagnosis†			
LDL-C, mmol/L, mean ± SD	n = 249 5.6 ± 3.0	n = 535 4.8 ± 1.1	n = 2465 3.5 ± 0.9
Total cholesterol, mmol/L, mean ± SD	n = 231 7.1 ± 2.3	n = 492 6.9 ± 1.4	n = 2340 5.6 ± 1.2
HDL-C, mmol/L, mean ± SD	n = 218 1.3 ± 0.6	n = 486 1.2 ± 0.6	n = 2316 1.2 ± 0.4
Triglycerides, mmol/L, median (IQR)	n = 230 1.8 (1.3:2.6)	n = 492 2.0 (1.4:2.7)	n = 2336 1.8 (1.3:2.6)
Lipid values at enrollment			
LDL-C, mmol/L, mean ± SD	n = 334 3.3 ± 2.0	n = 535 2.9 ± 1.1	n = 2465 2.5 ± 0.9
Total cholesterol, mmol/L, mean ± SD	n = 322 5.0 ± 1.5	n = 510 4.9 ± 1.3	n = 2399 4.3 ± 1.1
HDL-C, mmol/L, mean ± SD	n = 315 1.3 ± 0.4	n = 512 1.2 ± 0.3	n = 2393 1.2 ± 0.4
Triglycerides, mmol/L, median (IQR)	n = 321 1.5 (1.2:2.1)	n = 516 1.6 (1.2:2.2)	n = 2416 1.5 (1.1:2.0)
LMT			
Any statin, n (%)	330 (98.8)	529 (98.9)	2402 (97.4)
High-intensity statin (in statin-treated patients),‡ n/N (%)	190/330 (57.6)	204/529 (38.6)	564/2402 (23.5)
On highest-dose (in statin-treated patients),§ n/N (%)	162/330 (49.1)	171/529 (32.3)	538/2401 (22.4)
Statin monotherapy, n (%)	248 (74.3)	452 (84.5)	2081 (84.4)
Statin + fibrate ± other LMT, n (%)	23 (6.9)	38 (7.1)	167 (6.8)
Statin + CAI ± other LMT, n (%)	43 (12.9)	27 (5.0)	96 (3.9)
Highest-dose statin§ + CAI ± other LMT, n (%)	19 (5.7)	8 (1.5)	26 (1.1)

CAI, cholesterol absorption inhibitor; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; N, sample size; SD, standard deviation.

*According to the Dutch Lipid Clinical Network Criteria.

†Before LMT.

‡Atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg.

§Marketed in the country at the time of the study.

was achieved in 27.9%, 28.0%, and 37.5% of patients treated with statin-CAI combination, highest-dose statin and lower-dose statin, respectively (Fig. 1B).

Potential eligibility for PCSK9 inhibitors

A total of 162 patients with definite or probable FH were treated with maximally tolerated statin therapy (89 with ASCVD and 73 without ASCVD) and were included in the assessment of eligibility for PCSK9 inhibitors. According to eligibility criteria specified by the 2017 updated ESC/EAS recommendations,[12] 55.7% of patients on intensive LMT were potentially eligible for treatment with a PCSK9 inhibitor. When LMT therapy was considered as maximum statin dose with or without ezetimibe for all patients, the corresponding value was 44.4% (Supplementary Fig. 3). For the subgroup of patients on the highest possible dose of statin plus ezetimibe, the proportion of patients eligible for PCSK9 inhibitor therapy was 91.7% in patients with ASCVD, and 42.9% in those without ASCVD.

Secondary definitions of FH

Results of analyses performed in patients with definite, probable, or possible FH are presented in Supplementary Figure 4 and Tables 10–13. These results were generally consistent with those of the primary analysis population.

Results of analyses of patients with definite or probable FH, with untreated LDL-C estimated if the value at diagnosis was missing, are presented in Supplementary Figures 5–7 and Tables 14–17.

Table 2 Lipid levels at diagnosis and enrollment for patients with definite or probable FH* by type of LMT at enrollment

	LMT		
	Statin + CAI (n = 43)	Statins at highest dose† (no CAI) (n = 143)	Statin at < highest dose† (no CAI) (n = 144)
Lipid values at diagnosis‡			
LDL-C, mmol/L, mean ± SD	n = 34 6.3 ± 2.2	n = 112 5.8 ± 3.4	n = 99 4.9 ± 2.4
Total cholesterol, mmol/L, mean ± SD	n = 33 8.5 ± 2.6	n = 102 7.2 ± 2.4	n = 92 6.7 ± 1.9
HDL-C, mmol/L, mean ± SD	n = 31 1.2 ± 0.4	n = 96 1.3 ± 0.7	n = 88 1.3 ± 0.4
Triglycerides, mmol/L, median (IQR)	n = 32 1.5 (1.2:2.3)	n = 102 1.9 (1.4:2.7)	n = 92 1.8 (1.3:2.4)
Lipid values at enrollment			
LDL-C, mmol/L, mean ± SD	n = 43 3.8 ± 1.9	n = 143 3.5 ± 2.2	n = 144 2.8 ± 1.6
Total cholesterol, mmol/L, mean ± SD	n = 40 5.6 ± 2.0	n = 137 5.2 ± 1.5	n = 141 4.7 ± 1.2
HDL-C, mmol/L, mean ± SD	n = 41 1.3 ± 0.4	n = 134 1.2 ± 0.5	n = 137 1.3 ± 0.4
Triglycerides, mmol/L, median (IQR)	n = 43 1.2 (1.0:1.5)	n = 136 1.6 (1.2:2.1)	n = 139 1.6 (1.1:2.1)

CAI, cholesterol absorption inhibitor; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; SD, standard deviation.

*According to the Dutch Lipid Clinic Network criteria.

†Marketed in the country at the time of the study.

‡Before LMT.

Discussion

This study examined ESC/EAS LDL-C target achievement in ICLPS participants with definite or probable FH, defined according to DLCN criteria, of whom 43.1% were reported to have genetically confirmed FH. Overall, LDL-C target achievement rate was 32.0%. On-treatment LDL-C was <1.8 mmol/L in 12.9% of patients and <2.6 mmol/L in 39.8% of patients.

Previous registry studies have reported similar findings. The Spanish SAFEHEART study in patients with genetically diagnosed FH (n = 4132) reported that 11.2% of participants had LDL-C <2.6 mmol/L despite 71.8% taking maximal LMT.[8] In the same study, only 4.7% of FH patients with ASCVD achieved LDL-C <1.8 mmol/L, compared with 18.6% of patients with FH and CAD in our study. Another study in Dutch patients with genetically or clinically diagnosed heterozygous FH (n = 1249; 96% on statins) observed that 21% of patients reached a goal of <2.6 mmol/L, and 46% of those with LDL-C >2.6 mmol/L achieved a >50% reduction in LDL-C.[7] Recently, a study of 222 patients from Poland with definite or probable FH (according to DLCN criteria) reported that 25.2% of patients achieved an LDL-C goal of <1.8 mmol/L or <2.6 mmol/L, for those at very high or high CV risk, respectively, and 55.9% of patients achieved an LDL-C reduction of at least 50%.[13]

Only 43.1% of patients with definite or probable FH had genetically confirmed FH. It was not possible to distinguish whether patients without genetic confirmation were not tested, or were tested but no mutation was identified. Given that genetic testing is not common,[3] it is likely that most of these patients were not tested.

A greater proportion of patients with definite or probable FH received high-intensity statin therapy and combination LMT compared with patients with possible or unlikely FH. In addition, LDL-C at diagnosis was positively related to the intensity of statin therapy at enrollment. However, less than half of patients with definite or probable FH were taking the highest dose of statin available, and few patients (12.9%) were receiving statin-CAI combination therapy. The primary reason given for not prescribing statin at the highest dose was that the physician was satisfied with the patient's LDL-C level at the current dose. Such acceptance by the physician of a higher target LDL-C level than recommended has been identified previously.[7] Our data suggest that this "clinical inertia" is a key reason for patients with FH failing to achieve their LDL-C goal.

Although the use of statin-CAI combination in patients with definite or probable FH was more than double that in patients with possible or unlikely FH, at 12.9%, it was still far below what would be needed to control lipid levels in these patients. Even with intensive therapy, patients with

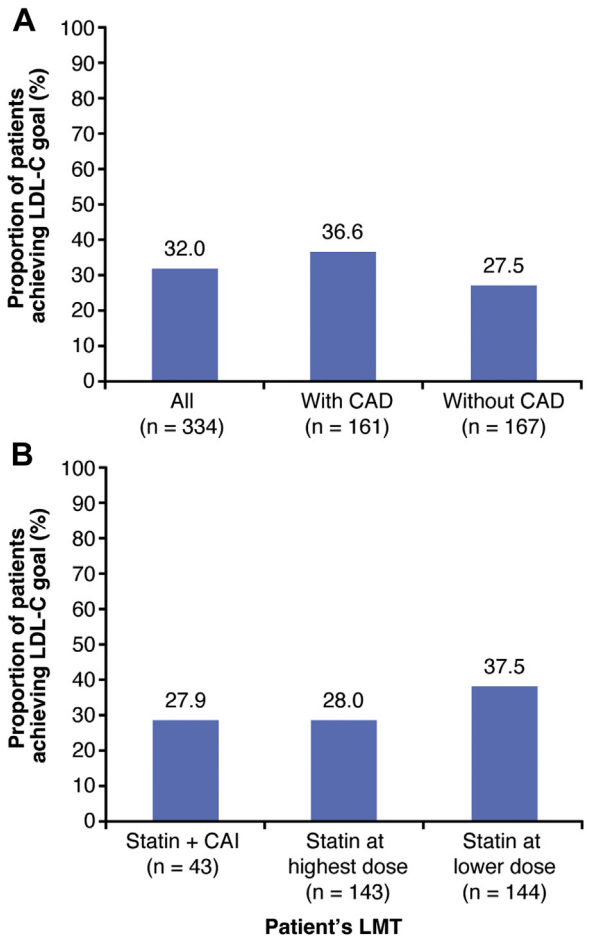

Figure 1 Patients with definite or probable FH* who achieved their 2011 ESC/EAS LDL-C goal[10] at enrollment (A) overall, and with and without CAD separately, and (B) by LMT. CAD, coronary artery disease; CAI, cholesterol absorption inhibitor; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy. *According to the Dutch Lipid Clinic Network criteria.

FH are unlikely to achieve LDL-C targets with commonly used LMT regimens.[8] This is supported by the findings that target achievement rate was low even in those patients receiving the highest dose of statin available (28.0%), and in those treated with statin-CAI combination therapy (27.9%). The low LDL-C target achievement rate in patients taking a statin-CAI combination likely reflects the use of ezetimibe in patients that are difficult to treat because of either higher baseline LDL-C levels or poor response to LMT resulting from either intrinsic factors or poor adherence to medication.

The reductions in LDL-C between diagnosis and enrollment, which were used to determine the conversion factors for estimating untreated LDL-C in patients with missing values at diagnosis, provide further evidence of the limited effectiveness of current LMTs in this study. The observed LDL-C reductions (36.0% with lower than high-intensity statin plus CAI; <30% for other treatment groups) were lower than values previously specified for the anticipated therapeutic response to statin therapy (50% with high-intensity statin; 30 to <50% with lower-dose statin).[14] Incomplete adherence to long-term statin therapy likely limits the observed effectiveness of statins in patients with FH in the real-world setting.

We estimated that 55.7% of patients with definite or probable FH on intensive LMT were eligible for PCSK9 inhibitor therapy according to guideline recommendations,[12] reduced to 44.4% when patients on maximum statin but without ezetimibe were included.

Almost half (48.2%) of patients with definite or probable FH had CAD compared with 36.7% in the ICLPS population overall.[11] LDL-C goal achievement was 36.6% in patients with CAD compared with 27.5% of those without, whereas LDL-C levels were lower both at diagnosis and enrollment in patients with than without CAD. Greater recognition of high or very high ASCVD risk by physicians in patients with CAD and the greater intensity of LMT in this group may explain the lower LDL-C in patients with CAD at enrollment. A potential selection bias toward primary prevention patients with more severe dyslipidemia and potential inaccuracy in reporting of LDL-C at diagnosis (see Limitations) may have contributed to the higher untreated LDL-C in the patients without CAD.

Study limitations

The ICLPS study was subject to several limitations, as outlined previously.[11] In addition, the nature of ICLPS, which enrolled patients primarily from cardiology and other specialist outpatient clinics, may have introduced a patient selection bias such that primary prevention patients with FH may have had severe hypercholesterolemia or a strong family history of FH, and non-FH patients may have high prevalence of comorbidities such as diabetes. Another limitation is that LDL-C at diagnosis was reported by patients or retrieved from medical records where available rather than measured, which may have reduced the reliability of this variable. In addition, less than half of the patients with definite or probable FH had a genetic diagnosis of FH, and ICPLS did not collect detailed information on the genetic confirmation of FH; therefore, we are unable to verify physician-reported genetic confirmation. As our diagnosis of FH was based on a scoring system rather than genetic testing, some patients, for example those with severe dyslipidemia but not FH, may have been incorrectly labeled as having FH.

Population characteristics, including ethnic mix, mutation spectrum, dietary factors, and lifestyle, may influence the diagnosis of FH, and it is unclear whether DLCN criteria apply equally to different populations.[3] Additional limitations include the potential lack of accurate diagnosis of xanthomata, and lack of available data on other effective LMTs such as apheresis and on the dose of statin prescribed. The number of patients eligible for PCSK9

inhibitor therapy is an estimate only because data on additional risk factors were incomplete.

Conclusions

This observational study demonstrated that achievement of ESC/EAS 2011 LDL-C targets was low in patients with definite or probable FH, even among those treated with intensive LMT. Underdiagnosis of FH, undertreatment, and the limited effectiveness of the LMTs assessed in the study are likely to have contributed to this low LDL-C target achievement rate. Greater use of intensive LMTs is needed to improve LDL-C management and lower cardiovascular risk in patients with FH, and this may be facilitated by the increased availability of more effective LMT regimens.

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Disclosures

D.J.B. has received honoraria for lectures and/or consultancy from Aegerion, Akcea, Amgen, AstraZeneca, Gemphire, MSD, and Sanofi. V.D. is an employee of Sanofi. M.K. has received honoraria (for lectures and consultancy) from Abbott, Aegerion, Amgen, Sanofi, and Pfizer; research funding from Aegerion, Amgen, Pfizer, and Sanofi; and has participated in clinical trials with Amgen, Esperion, and Regeneron Pharmaceuticals, Inc. A.J.R. has received honoraria for lecturing and/or participation in advisory boards from Sanofi, Amgen, Pfizer, Valentech, and Merck. R.D.S. has received honoraria related to consulting and/or speaker activities and research from Akcea, Amgen, AstraZeneca, Biolab, Esperion, Kowa, Novo-Nordisk, Merck, and Sanofi/Regeneron Pharmaceuticals, Inc. F.M. is the CEO of a contract research organization performing data management and statistical analyses for various companies. W.A., K.A-R., J.A., and F.M. have no conflicting interests to disclose.

Supplementary data

Supplementary data related to this article can be found online at https://dx.doi.org/10.1016/j.jacl.2019.05.004.

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