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Isfahan familial hypercholesterolemia cohort (IFHC) study: Methods, insights and early results

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Abstract

BACKGROUND: Familial hypercholesterolemia (FH) is the most common monogenic disorder in humans. There is a lack of data on the clinical characteristics and natural history of FH patients in Iran, which necessitates performing a longitudinal study.

METHODS: In this five-year prospective longitudinal cohort study, we enrolled patients with high LDL cholesterol who were registered in the Iranian Registry of Hypercholesterolemia (IFHR), diagnosed as definite and probable FH cases based on the Dutch Lipid Clinic Network Score (DLCN ≥6). General characteristics, lipid profiles, and cardiovascular disease assessments were evaluated in the baseline phase, and whole blood samples were stored for future genetic and epigenetic studies. This study will evaluate the incidence and recurrence rates of cardiovascular disease (CVD) and mortality as the main outcomes during five years of follow-up.

RESULTS: During the initial year, we successfully identified and enrolled patients with FH. We are reporting the whole methodology and the results of the first 50 who were followed up. At the study's outset, the patients exhibited a mean age of 50.27±12.06 years, with 64% being men and 36% women. The mean LDL level recorded was 312.8 ±106.3 mg/dL, with the highest LDL concentration observed at 623.5 mg/dL. A total of 62.0% of patients were on lipid-lowering treatment mostly of the PCAD group.

CONCLUSION: In this paper, we present the design and methodology of the Isfahan Familial Hypercholesterolemia Cohort (IFHC) study in detail with the aim of helping future research generate evidence from comprehensive IFHC data sources.

Keywords: Hypercholesterolemia; LDL-Cholesterol; Cardiovascular Diseases; Lipid-lowering therapy

Introduction

Familial hypercholesterolemia (FH) is a condition that is inherited in an autosomal dominant manner and is characterized by an increase in low-density lipoprotein cholesterol levels. This elevation primarily arises from mutations occurring in genes governing LDL-C metabolism, notably the LDL-C receptor (LDLR) and apolipoprotein B (APOB), alongside an augmentation in proprotein convertase subtilisin kexin type 9 (PCSK9) functionality[1]. FH substantially increases the lifetime risk of coronary heart disease (CHD)[1]. Although FH is primarily attributed to mutations in LDLR, APOB, and PCSK9, approximately 20% of cases exhibit a polygenic effect, and some individuals may not manifest molecular defects, termed FH phenocopies[2,3].

Numerous studies have consistently demonstrated that individuals with FH are more likely to develop atherosclerotic cardiovascular disease (ASCVD) compared to normolipidemic individuals, albeit lower than those with monogenic disorders[4–6]. Atherosclerotic plaques may develop in coronary, cerebral, and pulmonary vessels due to prolonged exposure to elevated LDL-C levels[7]. Despite the genetic origin of FH, clinical manifestations often do not emerge until the occurrence of an acute cardiovascular event. Furthermore, FH patients, particularly younger individuals, face a greater risk of CVD compared to non-FH individuals or those with polygenic hypercholesterolemia[8,9].

Identifying FH patients can be achieved through various means, including clinical presentation, incidental LDL-C measurements, or screening programs such as cascade screening targeting first-degree relatives or population-based screening[10]. Implementing early and aggressive management, including lipid-lowering therapies, has proven effective in preventing cardiovascular events in individuals with FH. As FH represents a modifiable risk factor for CHD, current guidelines emphasize intensive lifestyle modifications and pharmacological interventions[11,12].

Although the risk of cardiovascular diseases in FH can be highly variable, the risk of incident ASCVD may be estimated in patients with FH using simple clinical predictors. This finding may improve risk stratification and could be used to guide therapy in these patients. It can also help to develop tools and models to predict those who are at the highest risk[13]. The SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study) is a long-term prospective cohort study of the FH population in Spain. This study showed that the risk of incident ASCVD may be estimated in patients with FH using simple clinical predictors. A robust risk prediction equation has been developed in this cohort study[14]. Another significant registry, such as CASCADE-FH in the United States and the HELLAS registry, highlights the importance of evaluating first-degree family members of patients. The HELLAS registry revealed that the majority of patients had a family history of high cholesterol and cardiovascular disease. Additionally, nearly half of the included patients had a first-degree relative with cardiovascular disease (CVD), often beginning at a young age. These findings regarding family history of premature coronary heart disease (CHD) align with those of the CASCADE-FH registry in the United States (45%)[15,16]. Similarly, the initial findings of our study (Table 1) yielded comparable results. This study, along with others, emphasizes the critical role of registry and cohort studies in this regard. Cohort studies can offer a reliable dataset for evaluating the incidence of coronary heart disease (CHD) events in FH individuals and their first- and second-degree family members, factors affecting patients' adherence to treatment, and they also allow calculation of frequency rates, relative risks, and confidence intervals[17].

In Iran, there is a lack of comprehensive longitudinal data on CVD incidence and LDL-C level changes in FH patients and their relatives who received treatment. Therefore, we decided to perform the Isfahan Familial Hypercholesterolemia Cohort (IFHC) longitudinal study, aiming to provide valuable insights into the natural history, mortality, and morbidity among FH patients with or without CVD. IFHC

Table 1. Baseline characteristics and laboratory parameters of the FH patients (Heterozygote and Homozygote at enrollment)

Demographics	Value
Sex	
Male **	32 (64.0%)
Female **	18 (36%)
Age (years) *	50.27±12.06
Body mass index (kg/m^2) *	26.3±4.4
FH History	
Family history of premature CVD[a]**	45 (90.0%)
History of CVD**	19(38.0%)
CVD Risk Factor	
Smoking**	
Never	39 (78.0%)
Current	8 (16.0%)
Previous	3 (6.0%)
Hypertension **	23(46.6%)
Diabetes mellitus **	7(14.0%)
Biochemical measures	
Total cholesterol (mg/dL) *	329.8±97.6
LDL without treatment [b] (mg/dL) *	312.8±106.3
LDL with treatment (mg/dL) *	250.1±80.6
HDL-cholesterol [c] (mg/dL) *	59.0±10.0
Non-HDL cholesterol (mg/dL)	271.0±92.5
Triglycerides (mg/dL) *	150.0±74.0
FBS (mg/dL) [d] *	97.1±20.8
WBC * 10^3/µl	5.90±1.13
RBC * 10^6 /µl	5.01±0.51
Hb * (g/dL)	15.9±1.7
HCT ** (%)	43.0±3.9
History of medication use	
Lipid-lowering drugs**	31 (62.0%)

[a]CVD: Cardiovascular disease. [b]LDL-cholesterol: Low-density Lipoprotein cholesterol.
[c]HDL -cholesterol: High-density lipoprotein cholesterol. [d]FBS: Fasting blood sugar.
*Data are shown as the mean± SD. ** Data are shown as frequencies (%).

aims to address this gap through a structured cohort design and help with future strategies for facilitating early detection, treatment, and preventive strategies.

Material and Methods

Design and Patients

This study is an ongoing five-year prospective longitudinal cohort study. FH cases were recruited from the Iranian Familial Hypercholesterolemia Registry (IFHR), which was initiated in Isfahan in 2017 and is still ongoing. The IFHR-registered individuals were referred from laboratories and health centers due to LDL-C ≥190 mg/dL or LDL-C ≥150 mg/dL under pharmacological treatment. Participants were screened using the Dutch Lipid Clinic Network Score (DLCN). The complete methodological population approach for the baseline registry has been explained elsewhere[18–20]. In this cohort study, individuals aged 18 years or older with a DLCN score indicating probable FH (6–8 points) or definite FH (more than 8 points) were included (Fig. 1). Inclusion criteria encompassed patients

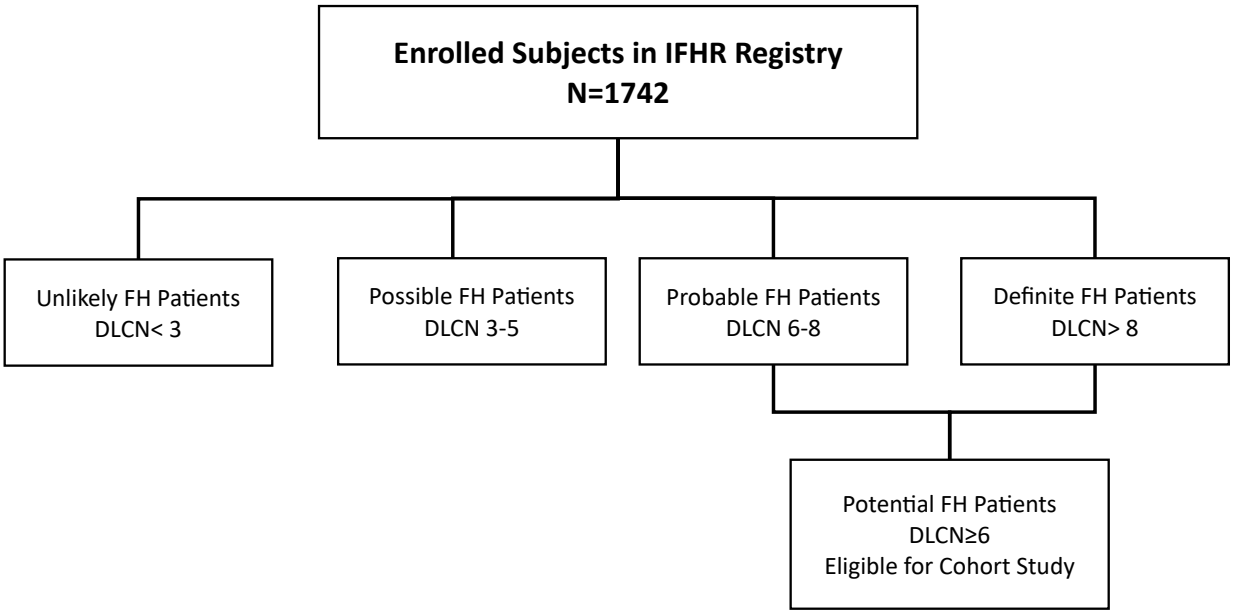

Figure 1. Flowchart of case recruitment in the Isfahan Hypercholesterolemia Cohort Study (IFHC)

with FH detected via DLCN (DLCN ≥6), as well as their relatives with FH who were identified through CASCADE screening[19]. Exclusion criteria included DLCN <6, secondary hyperlipidemia diagnosis, triglyceride levels >400 mg/dL, hypothyroidism, obstructive liver disease, and nephrotic syndrome. Premature CVD was defined as the occurrence of the first CVD event before 55 years of age in men and before 60 years of age in women. A five-year follow-up was planned for all enrolled patients, during which patients were monitored for clinical outcomes, treatment adherence, and any adverse events. Written informed consent was obtained from all subjects for this study, and the study protocol was approved by the Local Ethics Committee of Isfahan University of Medical Sciences. To date, 50 patients diagnosed with familial hypercholesterolemia (FH) have been recruited into this cohort. Recruitment is ongoing and aims to reach a minimum of 300 participants, as determined by the calculated sample size[21].

Data Collection

Demographic characteristics were collected at baseline. Lifestyle habits, including smoking status, dietary habits, and physical activity, were assessed using validated questionnaires comprising the International Physical Activity Questionnaire (IPAQ) for physical activity[22], a semi-quantitative Food Frequency Questionnaire (FFQ) to assess dietary habits[23], the Hospital Anxiety and Depression Scale (HADS) for evaluating depression and anxiety conditions, and the Smoking Assessment Questionnaire (SAQ) for smoking status[24].

The height and weight of participants were measured using a wall-fixed stadiometer while participants were barefoot and minimally clothed, ensuring a sensitivity of 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated by dividing weight in kilograms by height squared in meters. Waist circumference (WC) was measured using a tape measure between the lowest rib and iliac crest to the nearest 0.1 cm[25]. Blood pressure was measured twice using a digital sphygmomanometer (BC 08, Beurer, Germany) after the participants had been seated for at least 5 minutes, and the average value was documented[26].

A complete physical examination was performed, focusing on signs of hypercholesterolemia, such as tendon xanthomas and corneal arcus. An electrocardiogram (EKG) test

was performed for all patients at the baseline visit and during the follow-ups. Additional cardiologist visits and echocardiography tests were conducted at baseline and during the follow-up period.

Biochemical measurements

A 12-hour fasting blood sample was taken to measure fasting blood sugar (FBS), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and LDL-C. Serum lipids and glucose were measured using the enzymatic method, based on calorimetry, utilizing commercial kits (Pars Azmoun, Iran) with an automatic device (Selecta E, Vita Lab, Netherlands) in the central laboratory of the Isfahan Cardiovascular Research Institute (a WHO Collaborating Centre). The serum LDL-C concentration was measured directly using a related kit. Liver enzymes, including ALT and AST, were measured at baseline. An extra blood sample was obtained and plasma and whole blood samples were frozen at −70°C for future genetic studies.

Follow-up

All recruited patients were followed for five years after the baseline visit; follow-up visits were carried out every six months. However, if patients faced any problems, they were asked to refer to our lipid clinic to visit a general practitioner and, if needed, a cardiologist to assess any CVD outcomes. During their follow-up visits, some biochemical measurements, including blood glucose, lipid profile, and liver enzymes, were performed. Clinical examinations, including EKG or echocardiography, were conducted by cardiologists during follow-up visits if necessary (Fig. 2). Furthermore, participants were administered a brief checklist regarding any newly emerging clinical symptoms and signs, as well as documentation of any pharmacological treatments received, particularly anti-lipid medications. All patients received recommendations on how to follow a healthy lifestyle and adhere to prescribed medication for their high LDL-C according to the latest guidelines[27].

Following a six-month follow-up, if LDL-C levels were successfully controlled, subsequent visits were scheduled in accordance with the established six-month follow-up protocol. If LDL-C levels remained high or any side effects occurred, then their hypolipidemic drugs might be changed[28]. This process continued until the target LDL-C level was achieved. In the event of any occurrence or hospitalization within the intervals between these six-month periods, participants were instructed to attend the lipid clinic and submit their documents to be reviewed by a cardiologist.

In each follow-up, structured interviews were performed based on a questionnaire with three main parts: presence of CVD symptoms, hospitalization (with a specific focus on cardiovascular and cerebrovascular events), and vital status (living or deceased). In case of death, hospitalization, or CVD symptoms, the interview entailed obtaining the date of events, diagnosis, and hospital name. The reported events were checked with the MI and stroke registry database of the Surveillance Department of the Isfahan Cardiovascular Research Institute. A panel of specialists consisting of cardiologists and neurologists reviewed all relevant documents of every patient (primary questionnaires, medical records, secondary interviews, registry records, verbal autopsies, or death certificates) and made the final decision on all main events (fatal and non-fatal MI, fatal and non-fatal stroke, sudden cardiac death, and unstable angina)[14].

All clinical and laboratory data were systematically entered into a secure electronic database following initial collection. These data represent the total number of FH patients, including both homozygotes and heterozygotes.

Outcomes

The incidence rate of any CVD events (including MI, angina pectoris, percutaneous coronary interventions or other invasive coronary procedures, coronary artery bypass grafting, ischemic stroke, and peripheral artery diseases), CVD recurrence, all-cause mortality, and CVD-specific mortality were considered primary

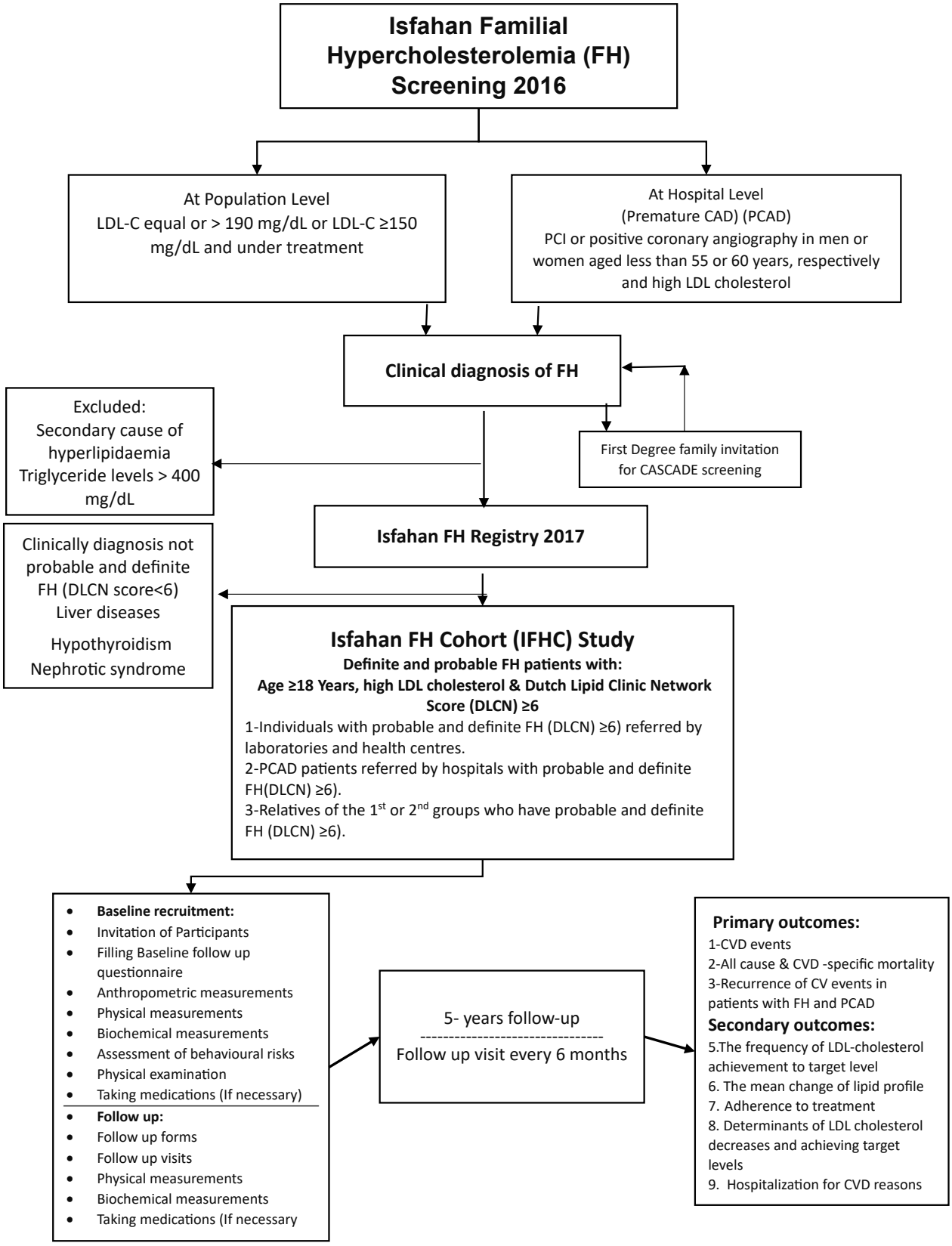

Figure 2. Methodological Framework of Isfahan Familial Hypercholesterolemia Cohort Study (IFHC) Study

outcomes. Secondary outcomes included the frequency of achieving target LDL-C levels, mean changes in LDL-C, TG, and HDL-C levels, factors influencing LDL-C reduction and attainment of target levels, as well as adherence to treatment protocols.

Definition of incident CVD

Incident CVD during follow-up was defined as the occurrence of one of the following events: fatal or non-fatal MI, fatal or non-fatal ischemic stroke, coronary revascularization, peripheral artery revascularization, cardiovascular death, or any death related to cardiovascular diseases[14].

Statistical analysis

Data were represented by frequency (%) for categorical variables and mean ±SD for continuous variables. Statistical analysis was performed using IBM Corp. (2020). IBM SPSS Statistics for Windows (Version 25.0).

Results

Fifty registered patients diagnosed with probable and definite FH were included in this cohort study. Patient recruitment continued until the target sample of 300 participants. The baseline characteristics of subjects with definite and probable familial hypercholesterolemia are shown in Table 1. The patients included 18 (36.0%) women and 32 (64.0%) men. The mean age was 50.27±12.06 years. A total of 90.0% of patients had a family history of premature CVD, 46.6% had hypertension, 14.0% had diabetes mellitus, and 38.0% had a history of CVD. The mean LDL-C level was 312.8±106.3 mg/dL. The mean TC and TG concentrations were 329.8±97.6 and 150.0±74.0 mg/dL, respectively. A total of 62.0% of patients were receiving lipid-lowering treatment.

Discussion

IFHC is the first prospective longitudinal study in Iran with a 5-year follow-up of individuals diagnosed with probable and definite FH. The incidence of CVD and mortality are the main outcomes, while achieving LDL-C targets and adherence to treatment are secondary outcomes. All participants were visited every six months. In this article, we report the complete methodology of the IFHC study and the results of 50 enrolled patients. FH is recognized as a key risk factor for the development of CVD, particularly premature coronary artery disease, which is notably frequent in Iran. This justifies the need for further studies into underlying risk factors and determinants, such as hyperlipidemia. Patients with PCAD represent one of the most important categories that should be thoroughly examined for the potential risk of developing hyperlipidemia and hypercholesterolemia. The IFHC study fills a critical gap in this area by focusing on the Iranian population, which is underrepresented in global FH research[29,30].

There are a number of existing FH registries worldwide that include patients based on either clinical or genetic diagnosis, or both[31]. The Netherlands FH registry is considered the largest, with more than 30,000 FH patients identified[31]. The goals of these registries are to evaluate the prevalence, genetic characteristics, clinical management, and cardiovascular disease (CVD) outcomes of FH in adult patients. These studies show that FH has a prevalence rate of 1 out of 200 to 250 in some countries[32,33]. Some newer studies have shown a higher prevalence; for example, based on an assessment of 98,098 individuals in the Copenhagen General Population Study, FH-causing mutations were estimated to occur at a frequency of 1:217[34]. In the region, the results of the Gulf Familial Hypercholesterolemia Registry (Gulf FH) showed that the prevalence of FH in the adult population of the region is high[35].

Assuming a prevalence of 1 in 250 for FH in Iran, with Isfahan's population of approximately 2 million, our registry identified between 3% to 12% of individuals with FH (Dutch Lipid Clinic Network Score (DLCN) higher than 3)[18]. Unfortunately, as confirmed by the IFHR registry and other screening programs, many FH cases are not detected by national health systems worldwide[36]. Additionally, even after diagnosis, when considering all available therapies to

decrease LDL-C, most FH patients do not achieve the suggested LDL-C level[37]. This group of patients is still at risk of cardiovascular diseases[38]. For example, in a recent study involving participants exhibiting LDL cholesterol levels of 190 mg/dL or higher, gene sequencing unveiled an FH mutation in less than 2% of the cohort. This finding underscores the imperative for enhanced patient treatment strategies[39]. Hence, the diagnosis and reduction of serum LDL-C levels contribute to increased life expectancy and mitigation of the risk of premature cardiovascular disease development in FH patients[40].

A study conducted in the Persian Gulf region found that among citizens admitted with ACS (acute coronary syndrome), the prevalence of "probable/definite" familial hypercholesterolemia (FH) was seven times higher than the estimated prevalence in the general population. This rate was also more than double that of a comparable Swiss ACS cohort using the same DLCN criteria. Additionally, the study reported that the incidence of atherosclerotic cardiovascular disease (ASCVD) outcomes was higher in patients diagnosed with probable/definite FH after a 1-year follow-up[35].

Consequently, both the identified FH patient and their relatives warrant thorough evaluation, and both lifestyle modification and pharmacological treatment are needed for these patients[11,36].

Consequently, both the identified FH patient and their relatives warrant thorough evaluation, and both lifestyle modification and pharmacological treatment are needed for these patients[11,36]. Studies in the field of the impact of lipid-lowering medications on coronary artery diseases have demonstrated that early diagnosis and initiation of treatment in patients with FH are associated with a lower incidence of premature CVD. Lipid-lowering medications, especially statins, ezetimibe, and PCSK9 inhibitors, not only reduce cholesterol levels but also directly influence the structure and stability of coronary artery plaques, which is critical in preventing heart attacks and other cardiovascular events[40].

Furthermore, the findings indicate a relatively late age at diagnosis of FH, which is consistent with the results of other studies[41]. As a result, early identification of FH, especially in children, can aid in the initiation of lipid-lowering therapy at a young age to prevent CVD. Therefore, FH screening is suggested from childhood[42]. In our study, initial results presented markedly elevated LDL-C levels, despite limited prior exposure to lipid-lowering therapies. A positive family history of premature cardiovascular disease was observed in many of these patients, further highlighting the inherited nature of FH within this population.

Due to the role of LDL cholesterol in cardiovascular diseases, and as there is no data or organized follow-up to determine the incidence of CVD or track the change of LDL cholesterol levels in FH individuals and their first relatives who are under treatment in Iran, we decided to perform this prospective longitudinal study. This study can provide a dataset to evaluate the incidence of CVD events in such individuals and their first- and second-degree family members, which can be useful in identifying, treating, and preventing cardiovascular events in these patients.

To our knowledge, this is the first study in Iran to screen patients with FH and follow them for clinical management. The results of our Family Heart Database in IFHR and IFHC studies provide further evidence that there is a profound and necessary need for education and aggressive follow-up of patients with FH. One of the most striking findings of our studies was the significantly higher levels of untreated LDL-C observed in patients enrolled in our registry, which is consistent with the results obtained from other studies[18].

Strengths and Limitations

The IFHC study is the first FH study to adopt a comprehensive approach and evaluate all the characteristics of FH patients in Iran. Our results confirm and extend those reported in other cohorts worldwide and highlight the need to refocus on current recommendations

for screening, diagnosis, and treatment of FH with follow-ups. The findings of this study have the potential to enhance healthcare provider awareness regarding the significance of not only treating patients with FH or severe hypercholesterolemia but also ensuring the continuation of treatment and diligent patient monitoring until the LDL-C target is achieved. In addition, the results can assist in developing national guidelines for dyslipidemia diagnosis, treatment, and control in Iran. This study will provide valuable information about the management of these patients in the country.

Despite the operation being initiated in Isfahan, a scale-up pilot study will start at the national level. This study may improve the quality and consistency of clinical practice and lead to the establishment of a national policy for the diagnosis and treatment of patients with FH. These data can be utilized as a resource for both local and international research. We emphasize advocacy, including screening programs and conducting cohort studies to identify FH early, initiate treatment, and prevent its global burden.

We did not perform genetic testing and solely used clinical scores to enroll patients. Additionally, in this study, patients with familial hypercholesterolemia were analyzed without distinguishing between homozygous and heterozygous mutations.

Conclusions

In this paper, we present the design and methodology of the Isfahan Familial Hypercholesterolemia Cohort (IFHC) study in detail. This study, as an ongoing prospective cohort, can offer a reliable dataset for evaluating the incidence of CAD events in individuals and their first- and second-degree family members. Additionally, it can provide determinants of LDL-C reduction and response to treatment, as well as factors affecting patients' adherence to therapy. It also allows the calculation of frequency rates, relative risks, and confidence intervals. This study can define and evaluate key risk factors for predicting incidents of CHD in FH patients.

This study has led to another important scientific and practical output. The "Diagnosis, Management and Treatment of Dyslipidemia Guidelines" were developed at the request of the Ministry of Health and Medical Education (MOH). After approval by MOH, they were issued to all universities for implementation in health systems.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: SN, VG, MN
Data Acquisition: ZS, DM, NJ, SM, HSh
Data Analysis or Interpretation: DM
Manuscript Drafting: SN, VG
Critical Manuscript Revision: ZS, VG, MN, NJ, SM, HSh, HK
All authors have approved the final manuscript and are responsible for all aspects of the work.

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