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RESEARCH ARTICLE

The Gulf Familial Hypercholesterolemia Registry (Gulf FH): Design, Rationale and Preliminary Results

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Abstract: ***Aim*:** To determine the prevalence, genetic characteristics, current management and outcomes of familial hypercholesterolaemia (FH) in the Gulf region.

***Methods*:** Adult (18-70 years) FH patients were recruited from 9 hospitals and centres across 5 Arabian Gulf countries. The study was divided into 4 phases and included patients from 3 different categories. In phase 1, suspected FH patients (category 1) were collected according to the lipid profile and clinical data obtained through hospital record systems. In phase 2, patients from category 2 (patients with a previous clinical diagnosis of FH) and category 1 were stratified into definitive, probable and possible FH according to the Dutch Lipid Clinic Network criteria. In phase 3, 500 patients with definitive and probable FH from categories 1 and 2 will undergo genetic testing for 4 common FH genes. In phase 4, these 500 patients with another 100 patients from category 3 (patients with previous genetic diagnosis of FH) will be followed for 1 year to evaluate clinical management and cardiovascular outcomes. The Gulf FH cohort was screened from a total of 34,366 patients attending out-patient clinics.

***Results*:** The final Gulf FH cohort consisted of 3,317 patients (mean age: 47±12 years, 54% females). The number of patients with definitive FH is 203. In this initial phase of the study, the prevalence of (probable and definite) FH is 1/232.

***Conclusion*:** The prevalence of FH in the adult population of the Arabian Gulf region is high. The Gulf FH registry, a first-of-a-kind multi-national study in the Middle East region, will help in improving underdiagnosis and undertreatment of FH in the region.

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1. INTRODUCTION

Familial hypercholesterolaemia (FH) is a common genetic cause of premature coronary heart disease (CHD), due to lifelong elevated plasma low-density lipoprotein cholesterol (LDL-C) levels [1, 2]. The most common definitions used to diagnose FH are the Simon Broome Register criteria [2] and the Dutch Lipid Clinic Network (DLCN) criteria [3].

Both criteria are based on the presence of personal and first-degree family members of high cholesterol levels, premature CHD and tendon xanthomas. Another method to

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identify FH is by DNA analysis of the 4 common FH genes: low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*ApoB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*) and low-density lipoprotein receptor adaptor protein (*LDLRAP1*) [4].

There are two forms of FH. For heterozygous FH (HeFH) the total cholesterol (TC) levels are around 8-15 mmol/L, patients typically develop CHD before 55 years of age and the prevalence in the general population varies between 1/200-500 [2]. This prevalence can be higher in subpopulations with founder effects [2]. For homozygous FH (HoFH), the TC levels are around 12-30 mmol/L, patients typically develop CHD very early in life and the prevalence can vary between 1/160,000-300,000 [2]. HeFH remains largely underdiagnosed with <5% of individuals being identified in most regions around the world [5]. Despite the high risk of CHD in patients with FH, many patients with FH remain untreated as shown by several studies [5-7]. There are a few reports on the clinical, molecular characteristics and management of FH in the Arabian Gulf region [8-13]. The exact prevalence of FH in the Arabian Gulf countries is unknown due to the lack of national FH registries [14].

The goals of this Gulf FH registry are to evaluate the prevalence, genetic characteristics, clinical management and cardiovascular disease (CVD) outcomes of FH in adult patients living in the Arabian Gulf region followed-up for 12 months. This manuscript describes the design and rationale of this multinational registry as well as presenting preliminary descriptive findings of phases I and II.

2. METHODS

2.1. Study Design and Population

Details of the study methodology are shown in Fig. (**1**). The registry is a mixture of both cross-sectional (phases 1, 2 and 3) and prospective (phase 4), multicentre, multi-national studies with a longitudinal clinical follow-up (phase 4). FH patients were recruited from out-patient (primary care, cardiology, endocrinology and lipid) clinics in 9 centres across 5 Arabian Gulf countries (Saudi Arabia, Oman, United Arab Emirates, Kuwait and Bahrain). The 4 phases of the registry are as follows:

2.2. Phase 1: Screening

Suspected FH patients from category 1 (new patients with no previous diagnosis of FH before the inclusion to this study) and category 2 (patients with previous clinical diagnosis of FH but with no genetic diagnosis before inclusion to this study) were recruited according to the lipid profile results and clinical data obtained through the hospital information systems over the previous 2-5 years and after satisfying the listed inclusion and exclusion criteria in the protocol. Patients who were on lipid-lowering treatments (LLTs), were included if the corrected LDL-C was ≥4.9 mmol/L (≥190 mg/dL) using an accepted correction formula [15, 16].

The final data was entered into the electronic case report form (eCRF), https://apex.oracle.com/pls/apex/f?p=111053:LOGIN_DESKTOP:113154011744149 and included patients from categories 1, 2 and 3 [patients with previous confirmed genetic diagnosis of FH before the inclusion to this study regardless of whether they have a baseline LDL-C above or below 4.9 mmol/L (190 mg/dL)]. Site investigators were encouraged to bring the patients to the clinics for full medical history and physical examination.

2.3. Phase 2: Stratification According to the DLCN Criteria

Patients from category 1 and 2 were stratified into possible FH (PoFH), probable FH (PrFH) and definitive FH (DFH) using the DLCN criteria [3].

2.4. Phase 3: Enrolment

Around 500 selected patients (300 from Saudi Arabia and 200 from other Arabian Gulf countries) with DFH and PrFH from categories 1 and 2 will undergo genetic testing for the 4 FH genes (*LDLR, APOB, PCSK9* and *LDLRAP*1). The 500 patients will be mainly selected from the list of patients with definitive and probable FH based on the DLCN criteria. In case more patients are required, then those with possible FH and >4 points can be added.

Table 1. Sample size calculation.

Country	National Population	Expected HeFH (1:500)	Sample Size as 10% of the Regionl Sample
Bahrain	630,990	1,262	126
Kuwait	1,281,712	2,563	256
Oman	2,323,954	4,648	465
Saudi Arabia	20,708,462	41,417	4,142
United Arab Emirates	950,368	1,901	190
Total	25,895,486	51,791	5,179

Abbreviations: HeFH, heterozygous familial hypercholesterolemia.

2.5. Phase 4: Follow-up

The previous 500 patients from phase 3 with another 100 patients from category 3 (patients with previous genetic diagnosis of FH) will be followed for 1 year to evaluate their clinical management and CVD outcomes (including unstable angina, myocardial infarction, coronary revascularization, stroke and CVD morbidity defined as hospitalisation for myocardial infarction, coronary revascularization, stroke, heart failure and arrhythmia). The data was entered into the 12 months follow-up eCRF. https://apex.oracle.com/pls/apex/f?p=111053:LOGIN_DESKTOP:113154011744149.

2.6. Inclusion and Exclusion Criteria

The inclusion criteria were age 18-70 years, Gulf nationals, LDL-C ≥4.9 mmol/L (≥190 mg/dL) and/or total cholesterol (TC) ≥7.5 mmol/L (≥290 mg/dL) not on LLTs or cor-

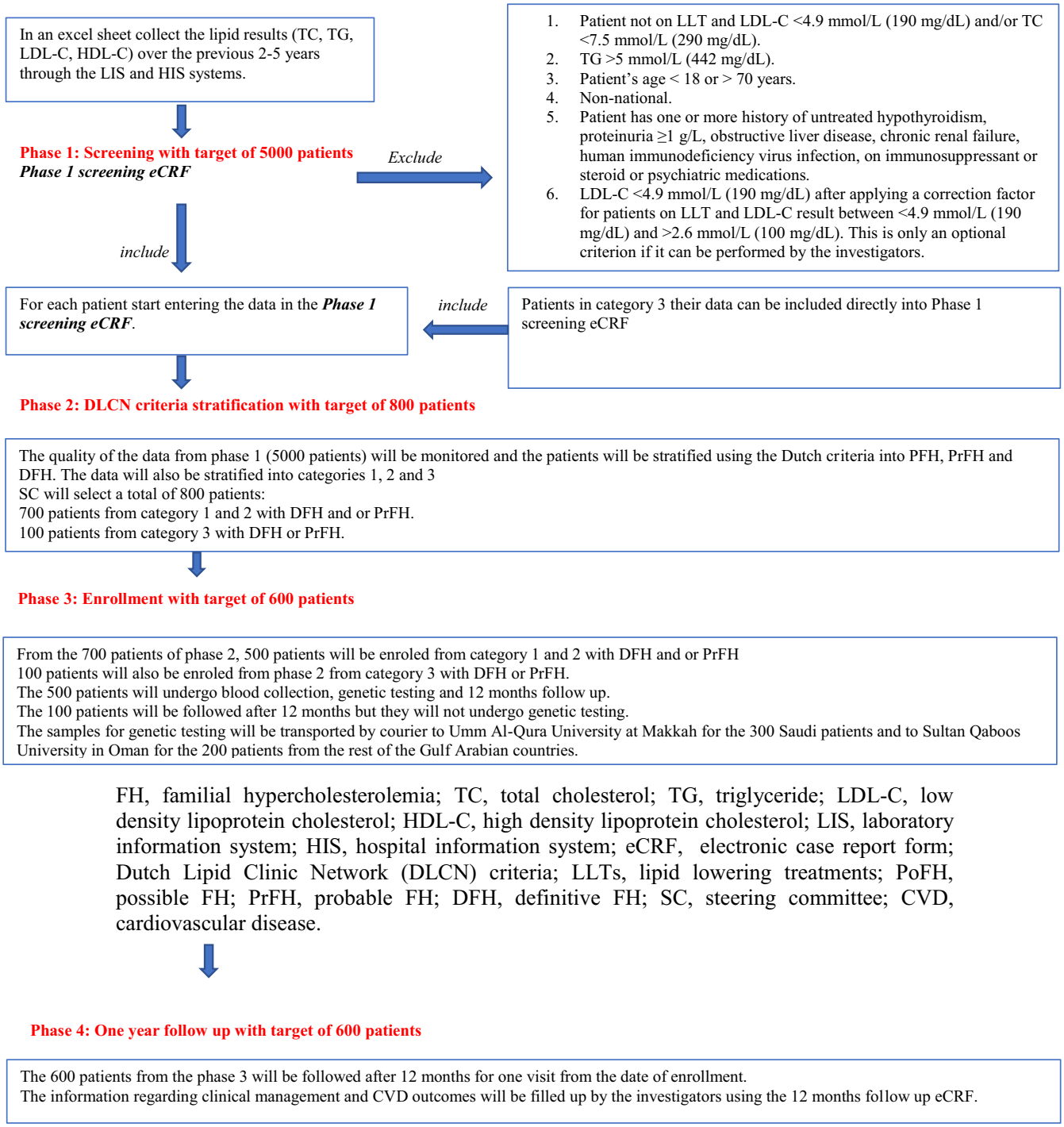

Fig. (1). Work flow for the Gulf FH Study. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

rected LDL-C ≥4.9 mmol/L (≥190 mg/dL) and category 3. The lipid results in this study are collected retrospectively, therefore, we cannot assure the fasting status although currently many laboratories in the region require collection of blood samples in the fasting status. The exclusion criteria were: triglyceride levels >5 mmol/L (442 mg/dL), history of untreated hypothyroidism, proteinuria ≥ 1 g/L, obstructive liver disease, chronic renal failure, human immunodeficiency virus infection (HIV) and use of immunosuppressants, steroids or psychiatric medications.

2.7. Sample Size

The sample size was derived from a 10% proportional sample of expected HeFH in each of the 5 Arabian participating countries as outlined in Table **1** based on a prevalence of expected HeFH of 1/500 [2].

2.8. Blood Samples and Genetic Testing Protocol

Two EDTA tubes will be collected from the selected 500 patients in phase 3 through the participating centres. The EDTA tubes will be shipped to Core Genetic laboratory centres in Saudi Arabia (Umm Al-Qura University, Makkah) and Oman (College of Medicine & Health Sciences, Sultan Qaboos University, Muscat). The EDTA tubes will be processed for DNA extraction and analysis of the 4 known genes *LDLR, APOB, PCSK9* and *LDLRAP1* using Ion PGM NGS platform in Saudi Arabia and Ion torrent NGS platform (Thermo Fisher Scientific, USA) in Oman. Target will cover all the exons (including the exon-intron boundaries), and 5′and 3′ untranslated regions of the four FH-related genes (*LDLR, APOB, PCSK9* and *LDLRAP1*). Ion AmpliSeq™ Designer tool will be used to custom design the assay primers. The human (Hg19) reference genome will be used to generate 200-bp amplicons.

The raw data acquired will be aligned to the human reference genome (Hg19) using the Torrent suite and recent version of the variant caller will be used. Standard stringency setting will be used for variant calling. Integrative Genomics Viewer (IGV) software [17] will be used to check for errors in variant calling. Variant annotation will be conducted using ANNOVAR tool [18] and filtering will cover exonic, splice sites and promoter regions. Synonym and intronic SNPS will be excluded. Allele frequency will be set to <10% using the Exact database and Greater Middle East Variome. The remaining variants will be analysed by comparing them with the Leiden Open Variation Database, the Familial Hypercholesterolemia Variants Database and scientific publications, for annotation purposes. Annotation *in-silico* will also be performed using tools that predict the functional effects of human SNPs: PolyPhen-2, SIFT and Mutation Taster. The genetic variants will be confirmed using direct sequencing. If no variants in the 4 major FH genes are found, then the DNA will be tested using Multiple Ligation-dependent Probe Amplification (MLPA) to detect large deletion or whole genome sequencing to detect new possible genes. For quality assurance and results verification, some samples will be exchanged between the 2 core laboratories with previously identified FH genetic mutations.

2.9. Statistical Analysis

Descriptive statistics (of phases 1, 3 and 4 findings) will be used to describe the data. For categorical variables, frequencies and percentages will be reported. Differences between groups will be analysed using Pearson's χ^2 tests (or Fisher's exact tests for cells <5). For continuous variables, mean and standard deviation will be used to present the data while analysis will be performed using Student's t-tests. For non normally distributed continuous variables, median and interquartile range (IQR) will be used to summarize the data and the analysis will be performed by using Wilcoxon and Mann-Whitney tests. An a *priori* two-tailed level of significance will be set at 0.05. Statistical analyses will be conducted using STATA version 13.1 (STATA Corporation, College Station, TX, USA).

2.10. Confidentiality

Patients' confidentiality will be maintained with no mention of their names or their national identification numbers. Each patient will be recognized in the registry by using an assigned unique registry number.

2.11. Ethical Considerations

The Gulf FH registry was approved by the local institutional ethics committees of each of the participating centres. Participants were also required to sign consent forms including an agreement for clinical and laboratory data sharing, blood collection for molecular testing and 1 year follow up for the collection of clinical and laboratory data.

3. RESULTS

Out of the total screened (n=34,366), 4,198 patients, forming the initial Gulf FH cohort, were entered into the eCRF (Phase 1) which also included patients from category 3 (n=184). The raw data from the eCRF was extracted into an Excel sheet and was filtered further based on the inclusion/exclusion criteria and the missing essential data for the DLCN criteria (Fig. **2**). The final data consisted of 3,317 patients that were further classified according to the DLCN criteria (Phase 2) as shown in Table **3**. The total number of patients with DFH, PrFH and PoFH were 203, 129 and 2,753, respectively (Table **2**). A total of 232 patients were classified as unlikely FH. For Phase 3 and in only patients with no previous FH genetic diagnosis, around 500 patients will be selected from those shown in Table **3** (300 patients from Saudi Arabia and 200 patients from the rest of the 4 Arabian Gulf countries) to undergo FH genetic analysis, according to the genetic testing protocol highlighted above.

Considering the total number of patients screened, the prevalence of FH (based on both PrFH and DFH) was 0.43%, *i.e.* 1/232 (148/34,366).

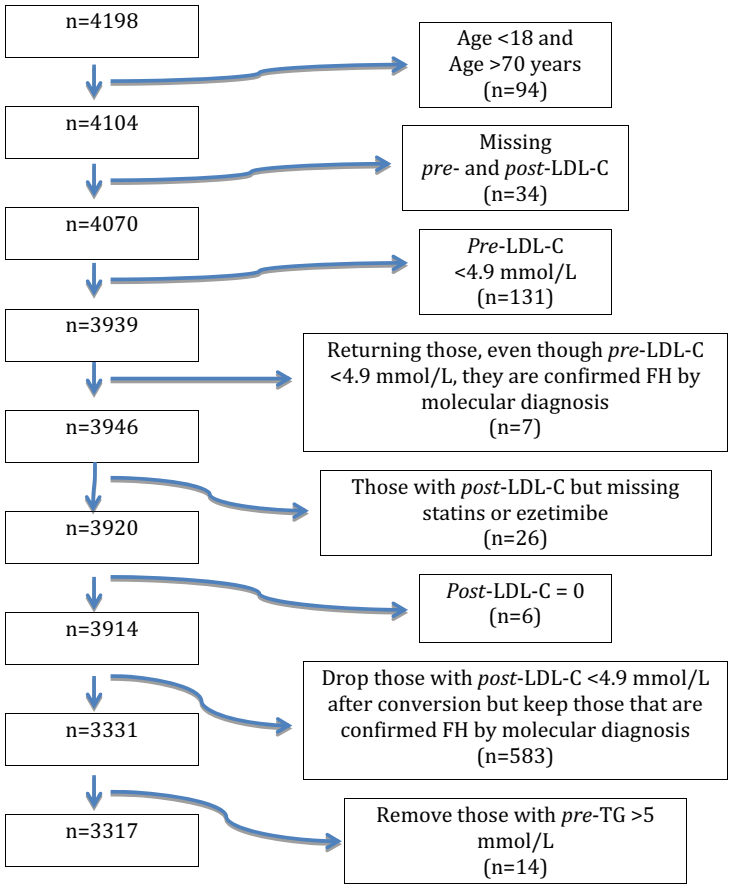

Fig. (2). Schematic diagram of patient flow of Gulf FH study.
FH, familial hypercholesterolemia; TG, triglyceride; LDL-C, low density lipoprotein cholesterol. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Number of patients of FH per country stratified according to the DLCN criteria and including previous identified positive genetic mutation for FH.

FH Type	KSA	Oman	UAE	Kuwait	Bahrain	Total
Unlikely FH	191	4	9	13	15	232
PoFH	2119	280	105	164	85	2753
PrFH	71	44	4	8	2	129
DFH	104	87	9	2	1	203
Total	2485	415	127	187	103	3317

Abbreviations: FH, familial hypercholesterolemia; Dutch Lipid Clinic Network (DLCN) criteria; PoFH, possible FH; PrFH, probable FH; DFH, definitive FH.

Table 3. Number of patients of FH per country stratified according to DLCN criteria and excluding previous identified positive genetic mutation.

FH Type	KSA	Oman	UAE	Kuwait	Bahrain	Total
Unlikely FH	191	4	9	13	15	232
PoFH	2119	280	105	164	85	2753
PrFH	55	44	4	8	2	113
DFH	10	19	4	1	1	35
Total	2375	347	122	186	103	3133

Abbreviations: FH, familial hypercholesterolemia; Dutch Lipid Clinic Network (DLCN) criteria; PoFH, possible FH; PrFH, probable FH; DFH, definitive FH.

4. DISCUSSION

The Gulf FH registry is the first multi-national study of its kind in the Middle East region to determine the prevalence, genetic characteristics, clinical management and 12-month CVD outcomes of FH. The prevalence of FH in this study was 0.43% (1/232). However, this could be an overestimate as it only considered screened patients. Nevertheless, we believe this could also be a realistic estimate due to the high rate of consanguinity in the Gulf region [19]. In Norway, the prevalence of FH [20] is estimated to be around 1/300 and in the Copenhagen General Population Study [21] the prevalence of patients with PrFH or DFH combined using DLCN criteria is around 1/200.

Worldwide there are a number of existing FH registries that include patients based on either clinical or genetic diagnosis or both [22]. The Netherlands FH registry is considered the largest and >30,000 FH patients has been identified [22] but despite that, many FH patients are still underdiagnosed in many countries [5]. The situation in the Arabian Gulf countries is not different and FH remains underdiagnosed [14]. In the current study 203 and 129 are identified as DFH and PrFH, respectively. This could be due to the lack of local and regional registries, presence of only a few centres to perform genetic analysis, few lipid clinics in the region as well small number of educational programs on FH which could affect physician awareness about FH. A study conducted in Saudi Arabia to assess physician awareness, practice, and knowledge of FH in 4 tertiary hospitals showed that around 93% of the participants had poor knowledge of FH and only 7% had acceptable knowledge. Physicians' knowledge of FH in this study was assessed by 11 questions. A correct answer for each question was scored as 1 point, while an incorrect answer was given a score of 0. A mean knowledge score was computed by summing the correct answers to all 11 questions; possible total mean scores ranged from 0 to 11. The knowledge of FH was considered acceptable if the total score was >50%) [23]. In addition, data from the Gulf RACE (1 and 2) and Gulf COAST registries [24-26] showed that patients in the Arabian Gulf region who present with an acute coronary syndrome (ACS) were 10 to 12 years younger than those in Western countries. In the sub-analysis from the Gulf COAST, in citizens from the Gulf region who were admitted with an ACS, the prevalence of "probable/definite" FH was 7 times higher than the estimated prevalence of FH in the general population, more than twice the one from a similar Swiss ACS cohort using the same DLCN criteria [13]. Moreover, in the same study, the incidence of atherosclerotic CVD (ASCVD) outcomes was higher in patients with probable/definite FH diagnosis after a 1-year follow-up [13].

Different methods can be used to screen for FH using clinical and/or genetic methods. Examples include universal screening of the general population or a more selective process, like screening patients from hospital information systems, patients admitted to acute coronary units with premature myocardial infarction or family cascade screening of patients with FH [27-33]. In the current study, we identified suspected FH cases through hospital laboratory and clinical data. The majority of patients were identified as possible FH according to the DLCN criteria and this could be due to missing important clinical information such as the presence of tendon xanthomas, family history of hypercholesterolaemia or premature CHD leading to mis-diagnosis and misclassification of patients with FH in this study. Nonetheless, this is considered as an initial initiative that will help to support subsequent national programs for FH screening in the Arabian Gulf region using other universal or selective screening methods including family cascade screening of patients with known FH.

Patients with FH are at high risk of developing ASCVD if not treated early and adequately [21]. Despite the presence of consensus clinical recommendations for the management of FH in the region [34-36] and the wide availability of statins and other LLTs, >50% of patients with FH in the Arabian Gulf region did not achieve their therapeutic LDL-C targets [13, 37]. Statins can reduce LDL-C up to 50% in HeFH and up to 25% in homozygous FH (HoFH) patients [38]. The combination of ezetimibe with a statin can decrease LDL-C by 60-70% in FH patients [39]. There are few lipoprotein apheresis centres for the treatment of HoFH and severe HeFH in the region. Lipoprotein apheresis can reduce the LDL-C levels by 50-70% [40]. Furthermore, there are few patients with HoFH on lomitapide which can reduce LDL-C up to 46% [40]. Recently, both alirocumab and evolocumab has become available in the region and are becoming widely used in combination with a statin and ezetimibe for the treatment of FH and severe ASCVD patients. Alirocumab can lower LDL-C levels by 60-68% [41] and evolocumab by 61-66% [42].

We believe that data analysis and future publications from this registry will enrich the existing literature and provide local health care authorities with an insight and recommendations regarding the challenges and quality improvement programs and policies for FH screening, diagnosis and management. One such policy implication is the development of premarital screening program and newborn screening for FH. Moreover, the detection of new FH patients in this registry will support the initiation of cascade genetic screening of family members, thus narrowing the gap of underdiagnosis and undertreatment of FH in the region.

Our study has some limitations which can be expected in any retrospective data mining. There are some missing data regarding the presence of tendon xanthomas, corneal arcus either in the patient or the first-degree family members. Also, there are missing data regarding first-degree family members with high LDL-C and premature CVD, which could affect the true estimation of FH prevalence in this population.

CONCLUSION

The prevalence of FH in the adult population of the Arabian Gulf region is high. The Gulf FH registry aims to improve underdiagnosis and undertreatment of FH in the region.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by Gulf Registry of Prince Sultan Cardiac Centre Riyadh, Saudi Arabia with approval number: E16014.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. All reported experiments on humans were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the *Helsinki Declaration* of 1975, as revised in 2008.

CONSENT FOR PUBLICATION

Written and informed consent has been obtained from all the patients.

FUNDING

The study was financially sponsored by Sanofi. The sponsor had no role in study design, data collection, analysis and interpretation; in the writing of the report and in the decision to submit the paper for publication.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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