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Review article

The development of the Mexican Familial Hypercholesterolemia (FH) National Registry

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ABSTRACT

Background and aims: In Mexico, familial hypercholesterolemia (FH) is, as in other parts of the world, largely underdiagnosed and undertreated, and represents a significant burden to the healthcare system. However, there is not enough information to design public policies against the disease. Genetic studies have shown that *LDLR* mutations are the most common cause, but in a large percentage of the cases, no mutation has been identified in the FH genes.
Methods: In accordance with the procedures of the European Atherosclerosis Society (EAS) FH registries network, the Mexican FH registry (www.fhmexico.org.mx) was launched in December 2017 to address the gaps in knowledge regarding this disease. Reference centres and the main nationwide public health providers have been invited to participate.
Results: To date, 142 cases have been registered. The mean age at diagnosis of probands is 36.42 ± 19.9 years (adults and children). Tendon xanthomas or premature corneal arcus were present in 40% and 17.6%, respectively. Molecular analysis was present in 70%, with over 95% of alterations located on the LDL receptor gene. The median untreated LDL-C is 6.5 (5.6–8.4) mmol/l and the median on treatment LDL-C level is 4.3 ± 1.7 mmol/l.
Conclusions: The Mexican FH registry aims to obtain real world information regarding the management of patients in this country. By participating in this global call to action, we hope to improve both short and long term outcomes for all FH patients in Mexico.

1. Introduction

Familial hypercholesterolemia (FH) is an inherited disorder characterised by defective clearance of low density lipoproteins (LDL-C), resulting in patients with a lifelong exposure to high LDL-C levels and increased cardiovascular risk [1]. The overall prevalence estimates suggest a figure of 1 in 200 adults, signifying a global number of cases of between 13 and 34 million persons [3]. Autosomal dominant FH is attributed to mutations in 3 different genes: low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*). Mutations in the *LDLR* account for the majority of cases. However, around 10–50% of patients may be mutation negative, especially in populations without "founder" effects and with significant non-Caucasian ancestry [1]. FH diagnosis is based on clinical phenotype ± mutational analysis, utilizing instruments such as the Dutch Lipid Clinics Network (DLCN), Simon Broome Registry, and US MEDPED (Make Early Diagnosis To Prevent Early Death) criteria [4–6]. Once an FH proband is identified, systematic cascade screening of first-degree relatives should be performed to permit opportune diagnosis and treatment of other affected individuals: this is a cost effective method to identify new FH cases. Despite

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remarkable advances in its treatment, cardiovascular mortality is still significantly higher in FH patients as compared with the general population [2]. Lifelong high intensity statin therapy, with or without ezetimibe is required. In homozygous cases, lipid apheresis is needed. Because early diagnosis and treatment increase life expectancy in this population, awareness campaigns and quality of care programs are needed in every nation [7–9].

2. Rationale for FH registries

A health care registry can be considered as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical, or policy purpose(s)" [10]. Hence, a patient registry can be a powerful instrument to observe the natural history of a disease; to record treatment and outcomes; to examine factors that influence prognosis and quality of life; to describe care patterns, including appropriateness of care and disparities in the delivery of care; to assess effectiveness of management in preventing outcomes; to monitor safety; and to measure quality of care and aid in quality improvement [11]. Registries are needed for conditions with a prevalence below 6% of the target population; regional or nation-wide studies did not have the power to identify a number of cases large enough. Institutional or regional FH registries have existed for decades, but their ability to provide evidence for the creation of public policies is inadequate due to their limited external validity. In 2015, the European Atherosclerosis Society published a "call to action" to integrate efforts across the world to tackle the health burden and gaps in the care of FH [7–9]. One of the key actions was the acquisition of large scale reliable data through the creation FH national registries. Several national FH registries have been successfully implemented, particularly in the United Kingdom, Norway, the Netherlands, the United States, Canada, Spain and the Middle East and North Africa [13–21]. Recent additions to this list include Greece, Turkey, Saudi Arabia and France [22–25]. A recent review affirms that "familial hypercholesterolemia registries are tools for clinical research and improving healthcare planning and patient care" [12].

3. What have we have learnt so far from such initiatives?

Registries have provided evidence to fill out several gaps in knowledge regarding FH management. For example, the UK Paediatric Registry has shown that the use of lipid lowering therapies is not limited by adverse events (i.e. decreased growth rate or elevations in liver enzymes or creatinine phosphokinase) [26]. The Norwegian FH registry has shown that in 1093 women with heterozygous FH, the rates of preterm delivery (<37 weeks of gestation), low birth weight (<2500 g), and congenital malformations were similar to those in the general population [27]. Mortality and morbidity data have also been collected by several registries [28]. The Norwegian registry reported that the most common cause of death was cardiovascular disease, mean age being 64.5 years. For those aged 20–39 years, the risk of cardiovascular death occurring out of hospital was increased 12-fold [29]. They also mentioned that the majority of death certificates did not record FH as a contributing factor, despite the fact that patients had a known FH mutation. The diagnosis of FH is often late and treatment targets are not universally obtained despite lipid lowering medication. In the CASCADE-FH registry, the median age of diagnosis was 47 years and the median age for initiating lipid lowering medication was 39 years [30]. Only 25% of patients had an LDL-C <100 mg/dL and 41% had a 50% reduction in their LDL-C. The prevalence of coronary artery disease in this population was 36%. More than half the population (61%) had at least 1 additional cardiovascular risk factor. Both diabetes mellitus and arterial hypertension were significantly associated with cardiovascular disease. Gender differences were also explored: the authors reported that women were less likely to receive statin therapy and achieve treatment targets compared to men [31]. Likewise, ethnic differences were found, with Asians and Blacks less likely to achieve LDL-C goals (LDL-C <100 mg/dL or a 50% reduction), suggesting under-treatment in these groups. The authors speculate that this finding can be explained by variable access to specialty lipid clinics, differences in socioeconomic status, perceptions regarding LDL-C lowering goals, ethnic variations in tolerability of statins or differences in patients' comorbidities.

The drawbacks of current diagnostic criteria have also been explored using registry data. The diagnosis of FH has been based on variables such as cholesterol levels, physical examination (i.e., tendon xanthomas, corneal arcus), personal/family history of premature atherosclerotic disease, and mutational analysis if available. It is now recognized that the classical presentation of FH is often not present due to changes in secular trends and improvements in therapy [32]. In the SAFEHEART study, in genetically confirmed patients, only 13.7% had tendon xanthomas [19,33]. As a consequence, the 2015 American Heart Association scientific statement on FH as well as the Canadian guidelines have removed this criteria from their heterozygous FH screening definition [34,35]. Another problem faced by the current diagnostic criteria is the reliance on family history of atherosclerotic disease. Kindt et al. point out that statins have been available for more than 30 years, increasing the likelihood that parents of probands have been exposed to lipid lowering treatment, and therefore may not have had any events [32]. In addition, family history is often unreliable or unavailable. The final observation is that population LDL-C levels have decreased due to diets containing less saturated fat intake and the universal use of statins.

In addition, registry data has highlighted the importance of understanding the relationship between the genetics and the clinical presentation of FH. Khera et al. found that in patients with an LDL-C $\geq$190 mg/dL, those who had no FH mutation had a six-fold increase in atherosclerotic disease risk compared to the control group with LDL $\leq$130 mg/dL. In contrast, those with an FH mutation (only <2% of patients with an LDL-C $\geq$190 mg/dL) had a 22-fold increase in risk compared to the same control group [36]. This suggests that the simple diagnostic criteria that we use now may not adequately distinguish FH from polygenic hypercholesterolemia. These authors also confirmed that the clinical severity of FH differs based on the type of mutation (i.e., loss of function *vs.* missense mutation) and affected gene. Mutations on the ApoB and PCSK9 genes generally present with a less severe clinical phenotype. In the future, Kindt et al. speculate that if genetic information is coupled with registry data, we will be able to more fully understand the genotype-phenotype relationship in FH [32].

Finally, FH registries provide us with a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness [11]. The main disadvantage is common to all observational studies, namely the possibility of bias and confounding factors. Wong et al. mention that although registries are a convenient source for assessing cardiovascular risk, one must acknowledge the potential for patient selection and ascertainment bias [29]. Quality control measures, with respect to data collection and input, should also be implemented. Such limitations are even greater in developing countries. For example, the percentage of undiagnosed cases cannot be estimated in these nations, as can be done in countries with a consolidated primary care system and universal coverage. In addition, heterogeneity of the population and quality of care is remarkably greater, increasing the possibility of biased conclusions if only reference centres participate in the survey. Despite the

above, a national registry could be a learning tool to standardize clinical assessment and follow up for unexperienced physicians.

4. Characteristics of FH in Mexico: the Mexican FH registry

In Mexico as in other parts of the world, FH is largely underdiagnosed and undertreated [7]. It is estimated that there are more than 200,000 affected FH individuals; the majority do not know they are affected [38]. There is a general unawareness of FH in the medical community maintaining the identification of this condition infrequent. The absence of national FH guidelines, means that there is no routine identification and management of cases. The disease is often diagnosed late; early diagnosis is only carried out in specialized centres. Patients regularly present with premature coronary events, but in a large proportion of cases the diagnosis is not considered. As a consequence, population prevalence estimates are unavailable and the provision of medical care for these patients is often inadequate. Hypercholesterolemia, irrespective of the cause, tends to be treated with low/moderate intensity statin therapy; the actual proportion of FH patients receiving statins is unknown. Furthermore, since medication is an out of pocket expense, even in diagnosed individuals, treatment goals are often not reached. The main public health providers do not include high intensity statin therapy among their services. PCSK9-based therapies are not available in public institutions and are rarely covered by private insurance companies. The unavailability of LDL apheresis hampers the adequate treatment of severe forms of the disease.

Molecular testing is uncommon in Mexico. No founder effect has been reported and the most frequently reported mutations are located on the *LDLR* (95%), with only one case found to have a mutation on the apolipoprotein B gene [7]. To date, the 5 most common alterations have been c.1055G.A, c.1090 T.C, c.682G.A, c.2271delT, and c.338insG; the latter 2 reported only in Mexicans [38]. A significant proportion of cases have no identifiable mutation. We can speculate, from the limited molecular information available, that there is little overlap with European populations. This is not surprising since the ethno-racial composition of Mexico combines indigenous American populations, with an influence from Iberian colonizers. We can anticipate that more ethnic specific variants may be encountered in the future. Homozygous cases are usually found in remote isolated communities in southern or western Mexico.

The healthcare system in Mexico is fragmented with no centralized co-ordination. Diagnosed FH cases are treated mainly in reference centres; some of them have lipid clinics, usually coordinated by endocrinologists. Similar to other Ibero-American countries, there is no organized national cascade screening protocol or genetic screening program [38]. Government funding for such initiatives is lacking. An ineffective provision of healthcare and inconsistency in the quality of care are often a problem in this region. The poorer sections of society are generally less aware of disease risk (in particular chronic non-transmissible diseases, which are often asymptomatic) and cultural barriers are also present (language barriers for indigenous populations). There is a FH patient organization focused in education and awareness.

Finally, in Mexico, the establishment of a model of care for FH, focused on empowering patients, is essential to allow the adequate multidisciplinary management of this disease [7]. Models of care involve the development of systems, supported by scientific evidence (clinical experience, expert opinion, published evidence and consultations), for the provision of quality healthcare services to a defined population. Effective co-operation with various stakeholders is necessary in order to achieve this. These include patient support groups, public, foundations, universities and academic centres, non-government organizations, health economists, policy makers/politicians and government ministers. Once a model of care is established, regular auditing and economic evaluation will be necessary to maintain the standard of care.

FH manifests a significant burden in terms of direct and indirect costs, to the healthcare system, but it remains to be quantified. The creation of a national registry will aid in addressing these issues.

The role and aims of the Mexican FH registry are outlined below [32]:

1. Identify the gaps (unmet needs) in the diagnosis and treatment of this disease
2. Obtain data on the frequency of the disease in Mexico
3. Provide information on the natural history of the disease
4. To describe how patients with FH are being managed (diagnosis and treatment options utilized). This includes evaluating the effectiveness of treatment (proportion of patients at target LDL levels) and the presence of responders vs. non responders.
5. Presence of additional modifiable cardiovascular risk factors
6. Identify the mutations associated with the disease in the Mexican population
7. Improve cascade screening for the identification of new cases of FH
8. Long term safety data with respect to lipid lowering agents
9. Evaluation of the performance of current diagnostic criteria and FH guidelines
10. Identify the treatment barriers for attaining LDL-cholesterol targets (including patient, physician, healthcare, and societal factors, acting either singly or in consort). Sources of information include predefined questionnaires for health providers and patients
11. Improve the education of the patient and doctor on specific aspects of the disease (side effects of statins and other lipid lowering medication, diet, management of the patient in pregnancy, etc.)
12. Assess the burden of the disease (years of life lost due to the disease) and long-term cardiovascular risk. Evaluate cardiovascular morbidity and mortality. This data would generate information to evaluate the cost-effectiveness of the treatment and permit future healthcare planning.

5. Methodology

The aim was to create a secure web-based registry to capture information about persons with heterozygous/homozygous familial hypercholesterolemia (FH). The variables included are in accordance with the European Atherosclerosis Society (EAS) FH recommendations (Table 1). This will permit harmonization of the data items, allowing collaboration with other investigators and registries worldwide. This registry has been available on-line since December 2017 (www.fhmexico.org.mx).

5.1. Data collection and management

Investigators from reference centres around the country have been invited to register information regarding the FH patients at their sites (www.fhmexico.org.mx). Each investigator has their own access code so that they can identify and review inputs from their site.

The Mexican Healthcare System is composed of both public and private sectors; investigators from both may participate in this initiative [37] (Fig. 1):

Table 1
Data collected in the FH registry.

Data collected in Mexican FH Registry			
General and demographic information	Medical history	Treatment, laboratory and examination	Additional
Name	**Patient history**	**FH treatment**	**Burden of FH**
Age	Cardiovascular comorbidities	Diet/exercise	Deaths
Gender	Imaging and diagnostic tests	Medications (type, dose, frequency)	Years of life lost
Date of birth	Cardiac operations/	Side effects	Years living with disability
Ethnic	procedures	**Examination/laboratory**	Prevalence
Education level	Smoking history	Blood pressure	Life expectancy
Occupation	Age at FH diagnosis	Anthropometric measurements	Healthy life expectancy
	FH genetic testing and results	Lipid values	
	FH signs and symptoms	Imaging results (echocardiograms, calcium scores, carotid ultrasounds)	
	Family history		
	Diagnosis status		
	Screening status		
	Cardiovascular events		
	Signs and symptoms		
	Genetics		
	Mutation if known		

- Public sector consists of institutions that provide healthcare for their workers (IMSS, ISSSTE, PEMEX, SEDENA, and SEMAR). The remaining public institutions provide coverage to those segments of society who do not have access to healthcare (SPS, SSA, SESA and IMSS-Prospera).
- Private sector provides care to persons who have health insurance or the economic capacity to consultations.

Investigators are encouraged to utilize the Dutch Lipid Clinic Network criteria for establishing the diagnosis in their patients. In the registry, each patient is assigned a unique code in order to preserve anonymity. Follow data on each patient will also be collected once a year.

The principle variables in the registry can be divided into the following groups (Table 1): general and socio-demographic information, family/personal history of cardiovascular disease, results of lipid profile, FH diagnostic criteria, lipid-lowering medication with doses and presence of side effects, LDL-apheresis (if relevant), follow-up data and clinical outcomes. If mutational analysis results are available, this information is captured in the core data. Information regarding factors such as statin intolerance, incidental diabetes, imaging results, aortic valve/supra-valvular disease or cancer are included. Finally, epidemiological data relevant for evaluating the burden of the disease to Mexican society is also captured. This data is in accordance with the European atherosclerosis society initiative to establish global FH registries. Where possible, standardized field definitions have been used and free entry text avoided. The main long-term outcomes of interest include all-cause and cardiovascular mortality, and fatal/non-fatal cardiovascular events.

Systematic cascade screening is recommended to all investigators in order to identify further FH cases. This consists of testing the first degree relatives of each proband; this strategy will permit the identification of all affected relatives and permit appropriate treatment and follow-up.

5.2. FH Mexico website and registry

The maintenance of the FH Mexico website (which contains the FH registry) is carried out with the help of an informatics engineer. The data architecture and platform supports the secure incorporation of data. The data collected is checked for consistency and accuracy by at least 2 independent investigators from the central coordinating centre (scientific coordinator, and data manager), and any discrepancies are resolved by raising queries with the individual investigators. Regular monitoring of various stages of data

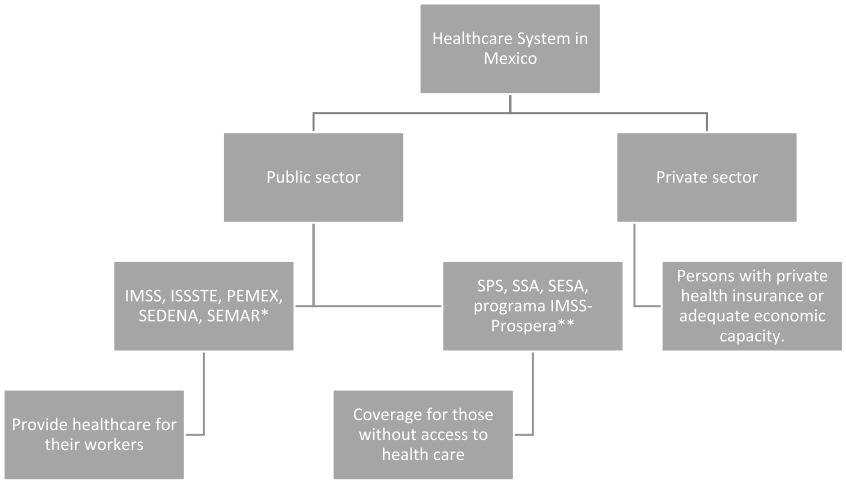

Fig. 1. Healthcare System in Mexico.
* Instituto Mexicano del Seguro Social (IMSS), Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), Petróleos Mexicanos (PEMEX), Secretaría de la Defensa Nacional (SEDENA), Secretaría de Marina (SEMAR). **Seguro Popular de Salud (SPS), Servicios Estatales de Salud (SESA), Secretaría de Salud (SSA).

flow will ensure that appropriate quality standards are maintained. The central coordinating centre supervises these processes, and is responsible for collaboration among individual sites, and liaises with relevant associations and patient organizations. The impact of any registry is enhanced through strong networking between research centres, clinical services, other registries and health data systems. The webpage includes educational materials for health professionals, patients and the public. A decision support tool (CardioRisk) for the FH diagnosis is also available (access kindly provided by Drs Jacques Genest, G. B. John Mancini and Arnold Ryomoto from FH Canada). The Mexican FH registry has been endorsed by the Sociedad Mexicana de Nutrición y Endocrinologia (www.endocrinologia.org.mx).

5.3. Subjects

Initially, an estimated 3000 FH cases can potentially be included in the registry (considering the number of reference centres that have agreed to participate in this project). This sample size will probably grow over subsequent 5 years, as cascade screening identifies new cases.

5.4. Inclusion criteria

All patients with baseline LDL-C levels >190 mg/dL (adults) or >160 mg/dL (children) are evaluated in accordance with the Dutch Lipid Clinic Network criteria. Only those cases that have a definite or probable diagnosis are included. Willingness to participate in the study and informed consent form (ICF) are obtained from each subject. Approval by the corresponding Ethics Committees is requested.

5.5. Exclusion criteria

Patients with other primary hyperlipidemias (familial combined hyperlipidemia, polygenic hypercholesterolemia etc.) and secondary causes of severe hypercholesterolemia (hypothyroidism, cholestasis, nephrotic syndrome, medication (other than lipid lowering drugs) known to affect cholesterol levels) are excluded. In addition, another exclusion factor is any clinically significant disorder which, at the discretion of the investigator, would limit the assessment of endpoints (e.g. major systemic diseases, patients with short life expectancy).

5.6. Statistical methods

The registry is established through a secure web based portal. The variables and outcomes are registered in accordance with the European Atherosclerosis Society methodology. Annual visits will be requested during the first five years of the study. After ensuring consistency and compatibility of the information, data from various providers will be merged and analyzed at an individual level as a composite dataset. Standard validated statistical procedures and models for observational studies and weighted meta-analyses will be applied. Various exposure-outcome associations will be quantified (unadjusted and adjusted) and epidemiological interactions using standard regression models. Risk prediction models using measures of discrimination (concordance index [Cindex], discrimination measure [D-measure]) and reclassification (net reclassification index [NRI]) will be performed. Cox proportional hazards regression models stratified by certain variables of interest (e.g. by gender) and Kaplan-Meier estimates of survival will be generated where time-to-event data is available.

6. Current progress

To date, 142 cases have been registered. The main socio-demographic characteristics are shown in Table 2. The mean age at diagnosis of probands is 36.42 ± 19.9 years (adults and children). This highlights the delay in identification of cases that is prevalent in this condition. In the CASCADE- FH registry, the median age at initiation of lipid-lowering therapy was 39 years, and the median age at FH diagnosis was 47 years [30]. Approximately 90% of the population mentioned a first degree relative with FH. About half reported a family history of coronary artery disease; a personal history of coronary artery disease or coronary catheterization was registered 6.3% and 2.1% respectively. In Latin America, Santos et al. describe a cardiovascular disease prevalence of between 10 and 42% depending on the country [38]. It is interesting to note that about 15% register a family history of consanguinity. Tendon xanthomas or premature corneal arcus were present in 40% and 17.6% respectively. Molecular analysis was present in 70%, with over 95% of alterations located on the LDL receptor gene. The median untreated LDL-C is 6.5 (5.6–8.4) mmol/l and the median on treatment LDL-C level is 4.3 ± 1.7 mmol/l. It is evident that although the majority of patients are on statin therapy (88.7%) they are not at goal.

Finally, we must acknowledge certain limitations regarding the data captured in this registry. Firstly, genetic confirmation may not be available at all sites; molecular analysis is not systematically carried out, reliance on only clinical data is often necessary. Family cascade screening is generally carried out in specialized/tertiary care centres; this will also limit the registration of affected individuals. We hope as awareness of this disease increases we can overcome these barriers.

Table 2
Characteristics of patients registered to date in the Mexican FH registry.

Parameter	N = 142
Female	91 (64.1)
Male	51 (35.9)
Age at diagnosis (years)	36.42 ± 19.9
Current age (years)	44.9 ± 20.2
Consanguinity	21 (14.8)
Familial history of coronary artery disease	73 (51.4)
Familial history of FH	126 (88.7)
Coronary artery disease	9 (6.3)
Coronary catheterization	3 (2.1)
Cerebrovascular disease	1 (0.7)
Diabetes mellitus	
Type 1	1 (0.7)
Type 2	9 (6.3)
Arterial hypertension	17 (12.0)
Genetic study available	104 (73.2)
Mutation/gene	
LDL receptor	100 (70.42)
ApoB	4 (2.8)
Xanthoma	57 (40.1)
Corneal arcus	25 (17.6)
Xanthelasma	11 (7.7)
Statin therapy	126 (88.7)
Ezetimibe	25 (17.6)
Body mass index (Kg/m^2)	26.07 ± 6.53
Diagnostic total cholesterol (mmol/l)	8.5 (7.7–9.6)
Diagnostic HDL-C (mmol/l)	1.13 (0.94–1.3)
Diagnostic LDL-C (mmol/l)	6.5 (5.6–8.4)
Diagnostic triglycerides (mmol/l)	1.5 (1–2.1)
Current total cholesterol (mmol/l)	6.3 ± 2
Current HDL-C (mg/dL)	48 (36–55)
Current LDL-C (mg/dL)	163.9 ± 64.9
Current non-HDL-C (mg/dL)	183.51 ± 66.5
Current triglycerides (mg/dL)	123 (98.5–168.5)

7. Conclusions

The Mexican FH registry aims to obtain real world information regarding the management of patients in this country. We hope to complete the aims of this registry and armed with this information address the gaps in both diagnosis and treatment. The data collected is in accordance with the European Atherosclerosis Society initiative: this will permit comparisons between populations and allow collaboration among investigators. Participating in this global call to action, we hope to improve both short and long term outcomes for all FH patients in Mexico.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Study conception and design: Mehta, Martagon AJ, Vazquez-Cardenas, Aguilar-Salinas.

Acquisition of data: Mehta, Martagon AJ, Galan Ramirez, Gonzalez Retana, Martinez-Beltran, Vargas Vazquez, Vazquez-Cardenas, Aguilar-Salinas.

Analysis and interpretation of data: Mehta, Martagon AJ, Galan Ramirez, Gonzalez Retana, Martinez-Beltran, Vargas Vazquez, Vazquez-Cardenas, Aguilar-Salinas.

Drafting of manuscript: Mehta, Martagon AJ, Galan Ramirez, Gonzalez Retana, Martinez-Beltran, Vargas Vazquez, Vazquez-Cardenas, Aguilar-Salinas.

Critical revision: Mehta, Martagon AJ, Vazquez-Cardenas, Aguilar-Salinas.

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