ORIGINAL ARTICLE

The rationale and design of the national familial hypercholesterolemia registries in Turkey: A-HIT1 and A-HIT2 studies

Türkiye'deki ulusal ailevi hiperkolesterolemi kayıt çalışmalarının temel ve tasarımı: A-HIT1 ve A-HIT2 çalışmaları

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ABSTRACT

Objective: Familial hypercholesterolemia (FH) is a genetic disease characterized by extremely high levels of cholesterol, leading to premature atherosclerosis. Although many countries have already addressed the burden of FH by means of national registries, Turkey has no national FH registry or national screening program to detect FH. Creation of a series of FH registries is planned as part of Turkish FH Initiative endorsed by the Turkish Society of Cardiology to meet this need. This article provides detailed information on the rationale and design of the first 2 FH registries (A-HIT1 and A-HIT2).

Methods: A-HIT1 is a nationwide survey of adult homozygous FH (HoFH) patients undergoing low-density lipoprotein (LDL) apheresis (LA) in Turkey. A-HIT1 will provide insight into the clinical status of HoFH patients undergoing LA. Primary objective of this cross-sectional study is to identify how HoFH patients on LA are managed. Inclusion criteria are age >12 years, diagnosis of HoFH, and regular LA treatment. All available apheresis centers were electronically invited to participate in the study. The principal physicians of each center will respond to a questionnaire regarding their attitude toward LA. For each patient, another questionnaire will be used to collect data on clinical status, medication use, and disease data. In addition, patients will be asked to complete self-report questionnaires that provide information on quality of life, disease-related anxiety, and depression. A-HIT2 is a registry of adult FH patients presenting at outpatient clinics. At least 1000 FH patients will be recruited from 30 outpatient clinics representing the 12 statistical regions in Turkey based on the EU NUTS classification. Sites specializing in cardiology, internal medicine, and endocrinology were invited to participate. The primary objective of this cross-sectional study is to determine clinical status and management of patients in Turkey diagnosed with FH. Eligibility for screening was defined as having LDL-cholesterol level >160 mg/dL. Inclusion criteria are age >18 years and diagnosis as possible FH (total score of >2 according to Dutch Lipid Clinic Network criteria). In addition to measuring clinical status of patients, a short survey to assess patient level of disease awareness will also be administered.

Conclusion: A-HIT1 and A-HIT2 are the first nationwide FH registries in Turkey and will provide important information on the management of Turkish FH patients. In addition, it is planned that they will guide establishment of a national policy for the diagnosis and treatment of FH in Turkey.

ÖZET

Amaç: Ailevi hiperkolesterolemi (AH), erken ateroskleroza yol açan aşırı yüksek kolesterol düzeyleri ile karakterize genetik bir hastalıktır. Birçok ülke ulusal kayıt çalışmaları vasıtasıyla AH yükünü belirlemiş olmalarına rağmen, Türkiye'de Ulusal AH kayıt çalışması veya AH saptanması için ulusal bir tarama programı bulunmamaktadır. Bu eksiği gidermek için Türk Kardiyoloji Derneği tarafından desteklenen Türk AH projesi kapsamında bir dizi AH kayıt çalışması planlanmıştır. Bu yazı, AH kayıt çalışmalarının ilk ikisinin (A-HIT 1 ve A-HIT2) temeli ve tasarımı hakkında ayrıntılı bilgi vermek üzere hazırlandı.

Yöntemler: A-HIT1, Türkiye'de LDL-aferezi (LA) tedavisi altındaki yetişkin Homozigot AH (HoAH) hastalarının ülke çapında kayıt çalışmasıdır. A-HIT1, LA altındaki HoAH hastalarının klinik durumuyla ilgili bilgi sağlayacaktır. Bu kesitsel çalışmanın birincil amacı, LA tedavisi alan HoAH hastalarının nasıl yönetildiğini saptamaktır. Çalışmanın içleme kriterleri, 12 yaşından büyük olmak, HoAH tanısı konmuş ve düzenli LA tedavisi altında olmaktır. Tüm mevcut aferez merkezleri, elektronik ortamda çalışmaya davet edilmiştir. Her merkezden bir sorumlu hekim, merkezin LA'ya karşı tutumuyla ilgili bir anket dolduracaktır. Her hasta için de klinik durumu, tedavisi ve hastalığı ile ilgili bir anket tamamlanacaktır. Buna ek olarak hastaların yaşam kaliteleri, hastalıkla ilgili endişe ve depresyonları hakkında bilgi sağlayan 3 anket hastalar tarafından dolduracaklardır. A-HIT2, polikliniklere başvuran yetişkin AH hastalarının kayıt çalışmasıdır. Türkiye'nin 12 "Nuts" İstatistiki Bölgesini temsil eden 30 poliklinikten en az 1000 AH hastası alınacaktır. Kardiyoloji, iç hastalıkları ve endokrinoloji üzerine uzmanlaşmış merkezler çalışmaya davet edilmişlerdir. Kesitsel yapıdaki bu çalışmanın birincil amacı, Türkiye'de AH tanısı almış hastaların klinik durumlarını ve tedavilerini saptamaktır. Tarama için uygunluk LDL-kolesterol düzeylerinin >160 mg/dL olması olarak tanımlanmıştır. Çalışmaya dahil edilme kriterleri >18 yaş ve olası AH tanı almak olarak belirlenmiştir (Hollanda Lipid klinikleri ağı kriterlerine göre toplam >2 puan). Hastaların klinik durumunu belirleyen bilgilere ek olarak, hastalığın farkındalık düzeyini değerlendirmek için kısa bir anket uygulanacaktır.

Sonuç: A-HIT1 ve A-HIT2, Türkiye'deki ilk ülke çapındaki AH kayıt çalışmalarıdır ve Türk AH hastalarına yaklaşımın durumu hakkında önemli bilgiler sağlayacaklardır. Aynı zamanda, AH'nin tanı ve tedavisi için ulusal bir politika oluşturmaya rehberlik etmek üzere planlanmışlardır.

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Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disorder characterized by elevated serum low-density lipoprotein (LDL)-cholesterol level and premature coronary artery disease.[1–4] Untreated cholesterol levels typically range between 250–300 mg/dL in heterozygous individuals with FH (HeFH); cardiovascular (CV) events develop in men by 30 to 50 years of age, and in women by 40 to 60 years of age.[1,3,4] In homozygous individuals with FH (HoFH), severe atherosclerotic events begin in early childhood.[1,2] Untreated HoFH patients generally die before the age of 30 years due to atherosclerotic CV events.[1,2]

Prevalence of HoFH has been estimated as 1 in 1 million people,[5] whereas prevalence of HeFH in general population has been accepted as 1/500. In certain populations with founder effect, such as the Afrikaners in South Africa, French Canadians, or Christian Lebanese, prevalence of FH has been reported to be much higher.[1,6,7] Moreover, recent data revealed that prevalence of FH might be as high as 1 in 200 for HeFH, and 1 in 160,000 for HoFH in unselected general populations.[8] In Turkey, prevalence of FH is unknown; however, extrapolating data from different nations and given relatively high prevalence of consanguinity in Turkey (23%), HeFH prevalence is estimated to be 1 in 200 people, which suggests that at least 429,000 people are suffering from FH in Turkey.

As FH patients are exposed to high cholesterol levels since their birth, early diagnosis and effective lipid-lowering treatment (LLT) are critical for management of these patients.[1,8] However, FH is globally underdiagnosed and undertreated. To overcome the existing gaps in care and to reduce preventable global burden of FH, European Atherosclerosis Society (EAS) launched a global initiative in 2013.[9] According to an EAS statement ("Familial hypercholesterolaemia: A global call to arms"), one of the key aspects to be addressed to face the FH burden is the generation of large-scale reliable data on how FH is detected and managed, and the clinical implications thereof.[9,10]

Abbreviations:

CV	*Cardiovascular*
DLCN	*Dutch Lipid Clinic Network*
EAS	*European Atherosclerosis Society*
FH	*Familial hypercholesterolemia*
HeFH	*Heterozygous FH*
HoFH	*Homozygous FH*
LA	*LDL apheresis*
LDL	*Low-density lipoprotein*
LLT	*Lipid-lowering treatment*

Although many countries have already addressed the burden of FH with national registries, Turkey has no national FH registry or national screening program for the detection of FH. To overcome this gap, a series of FH registries (A-HIT1, A-HIT2, and A-HIT3) is planned as part of the Turkish FH Initiative endorsed by the Turkish Society of Cardiology. The first registry, A-HIT1, is a nationwide survey of adult HoFH patients undergoing LDL apheresis (LA) in Turkey. A-HIT2 is a registry of adult FH patients presenting at outpatient clinics in the country. Finally, A-HIT 3 will be a registry of FH patients admitted to coronary care units with diagnosis of premature myocardial infarction in Turkey. This article provides detailed information on the rationale and design of the first 2 registries (A-HIT-1 and A-HIT2) for patients with FH in Turkey.

METHODS

Overall characteristics of the first 2 FH registries are summarized in Tables 1 and 2.

A-HIT1 study will be conducted to provide insight into the clinical status of HoFH patients undergoing LA in Turkey. Primary objective is to identify how HoFH patients in LA treatment are managed.

Table 1. Overall characteristics of Turkish FH registries

Registry	A-HIT1	A-HIT2
Number of patients	88	1000 (planned)
Type of the study	Multicenter cross-sectional	Multicenter cross-sectional
Ethics committee approval	May 25, 2015	January 23, 2017
Patient population	HoFH undergoing lipid apheresis	HeFH & HoFH
Diagnosis criteria	EAS, HoFH criteria	Dutch Lipid Clinic Network criteria

EAS: European Atherosclerosis Society; FH: Familial hypercholesterolemia; HeFH: Heterozygous FH; HoFH: Homozygous FH.

Table 2. Data to be collected in A-HIT1 and A-HIT2 registries

	Demographic information	Medical history	Family history	Current Status (including lab and treatment data, etc.)	Other
A-HIT1	• Date of visit • Date of birth • Gender	• Patient history (CV comorbidities, cardiac operations/procedures) • Concomitant diseases • CV risk factors	• Diseases • CV risk factors • FH in family • Consanguinity • Screening status	• Age at FH diagnosis • Age at first FH symptoms • Specialty of the first attending physician • Date earliest cholesterol test was performed • FH signs and symptoms • Lipid apheresis information (initiation age, frequency, duration, psychological support etc) • LDL-C levels (at diagnosis, highest pretreatment, pre and post apheresis sessions)	• Education • Occupation • Marital Status • FH understanding • Psychosocial questionnaires for patients: • -SF-36 quality of life • -HAD score • -SCL-90 depression • Awareness questionnaire for physicians
A-HIT2	• Date of visit • Date of informed consent • Date of birth • Gender	• Patient history (CV comorbidities, cardiac operations/procedures) • Concomitant diseases • CV risk factors • Detailed history for premature atherosclerosis	• Diseases • CV risk factors • FH in family • CV disease in family • Consanguinity	• LDL-C (value within the last 3 months) • Waist circumference • Height / weight • Blood pressure • Secondary causes of hyperlipidemia • Lab values • (Total cholesterol • Triglycerides • HDL, LDL, TSH, FBG, HbA1c, liver enzymes, uric acid, hs-CRP) • Genetic tests (if already available) • Anti-lipid treatment • Lipid apheresis information (frequency, duration)	• FH understanding • Awareness questionnaire for patients

CV: Cardiovascular; FBG: Fasting blood glucose; FH: Familial hypercholesterolemia; LDL: Low-density lipoprotein; HbA1c: Glycated hemoglobin; HADS: Hospital Anxiety and Depression Scale; HDL: High-density lipoprotein; hs-CRP: High-sensitivity C-reactive protein; SCL-90: Symptom Checklist-90; SF-36: 36-Item Short Form Health Survey; TSH: thyroid stimulating hormone.

Secondary objectives include identifying awareness about the disease (HoFH) in the patients and attending physicians of each participating apheresis center and understanding the frequency and major drawbacks of apheresis treatment in HoFH patients. Inclusion criteria are age ≥12 years, diagnosis of HoFH, and undergoing regular LA treatment. Patients undergoing apheresis for isolated hypertriglyceridemia will be excluded. Patients aged <18 years will be enrolled only with the consent of a parent or legal representative. Diagnosis of HoFH will be confirmed according to EAS diagnostic criteria for HoFH[7] (Table 3). All available apheresis centers were invited to participate in the study by electronic letter. An invitation was also presented on the website of the Turkish Society of Cardiology. During this cross-sectional study, 3 sets of data

Table 3. EAS Consensus Panel diagnostic criteria for homozygous familial hypercholesterolemia

Genetic confirmation of 2 mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus or
Cutaneous or tendon xanthoma before age 10 years or
Untreated elevated LDL-cholesterol level consistent with heterozygous FH in both parents
(These LDL-cholesterol levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude homozygous FH)

Apo B: Apolipoprotein B; EAS: European Atherosclerosis Society; FH: Familial hypercholesterolemia; LDL: Low-density lipoprotein; LDLR: Low-density lipoprotein receptor; PCSK9: Proprotein convertase subtilisin/kexin type 9.

are to be collected. From each center, the principal physicians will complete a questionnaire about attitude toward LA. A second questionnaire will be completed for each patient. Data related to demographic details, CV risk factors, clinical characteristics, age at symptom onset and diagnosis, detailed family history, lipid levels of at least last 4 apheresis sessions (pre and post session values), treatment, LA, CV events, complications, etc. will be collected (Table 2). The third effort will be to obtain self-report questionnaires from patients to record psychosocial status, including quality of life assessment (36-Item Short Form Health Survey),[11] Symptom Checklist-90,[12] and Hospital Anxiety and Depression Scale.[13] Self-reported questionnaires providing information on disease-related anxiety and depression will only be administered to patients >18 years of age.

A-HIT2, the second national FH registry, will recruit at least 1000 FH patients from 30 outpatient clinics representing the 12 statistical regions in Turkey based on the EU NUTS classification and proportional to the 2015 population distribution of Turkey.[14] Both HeFH and HoFH patients are eligible for enrollment. Sites specializing in cardiology, internal medicine, and endocrinology were invited to participate by the Turkish Society of Cardiology. The primary objective of this cross-sectional study is to determine clinical status and management of patients diagnosed with FH in Turkey. The secondary objectives are to detect pattern of clinical presentation, to learn medication use, to define clinical response to LLT, to evaluate attainment of LDL-cholesterol goals, and to identify resistance and/or intolerance to LLT. Defining CV risk factors and approach to these factors taken by physicians, and comparing attitudes of different specialty groups (cardiology, endocrinology, and internal medicine) are also among the secondary objectives of the registry. Eligibility for screening was defined as having LDL-cholesterol level >160 mg/dL, either as in-treatment or untreated value. Centers may enroll both incident and prevalent patients. Inclusion criteria are age >18 years and diagnosis of possible FH. Possible FH was defined as total score of >2 according to Dutch Lipid Clinic Network (DLCN) criteria (Table 4).[15] Patients with triglyceride levels ≥400 mg/dL or secondary hyperlipidemia (i.e., untreated hypothyroidism, nephrotic syndrome, cholestasis, etc.) will be excluded from the study. Two different data sets will be collected for A-HIT2. Physicians will complete electronic case report forms for each patient (Table 2). Patients will also complete a short survey to assess level of disease awareness. This survey is also designed to provide information about patient perceptions and knowledge of cholesterol, its harm, and LLT. All data will be collected in a single visit. Data verification will be based on source document control of 5% sample randomly selected per center.

As both A-HIT1 and A-HIT2 registries are not hypothesis-driven, no specific medical therapies or interventions will be introduced to patients. Also, genetic analyses will not be generated for diagnosis of FH. If available, previous genetic results will be recorded, so clinical evaluation will be sufficient to diagnose FH.

Standard statistical methods commonly used in observational analyses will be applied. A-HIT registries are sponsored by the Turkish Society of Cardiology, which receives funding from a variety of sources (including unrestricted research grants from Aegerion, Amgen, Pfizer, and Sanofi). Both registry protocols have been reviewed and approved by the Ege University Institutional Review Board and A-HIT2 is registered on www.clinicaltrials.gov. Written informed consent will be obtained from all participants.

Table 4. Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia

Criteria	Points
Family history	
First-degree relative with known premature* coronary and vascular disease, OR	1
First-degree relative with known LDL-C level above the 95th percentile	
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR	2
Children aged less than 18 years with LDL-C level above the 95th percentile	
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels mg/dL mg/dL (mmol/L)	
LDL-C >= 330 mg/dL (≥8.5)	8
LDL-C 250 – 329 mg/dL (6.5–8.4)	5
LDL-C 190 – 249 mg/dL (5.0–6.4)	3
LDL-C 155 – 189 mg/dL (4.0–4.9)	1
DNA analysis	
Functional mutation in the LDLR, apo B or PCSK9 gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite familial hypercholesterolemia	>8
Probable familial hypercholesterolemia	6–8
Possible familial hypercholesterolemia	3–5
Unlikely familial hypercholesterolemia	<3

*Premature = <55 years in men; <60 years in women.
Apo B: Apolipoprotein B; FH: Familial hypercholesterolemia; LDL-C: Low-density lipoprotein cholesterol; LDLR: Low-density lipoprotein receptor; PCSK9: Proprotein convertase subtilisin/kexin type 9.

DISCUSSION

A-HIT1 and A-HIT2, to our knowledge, will be the first nationwide FH registries in Turkey, and will provide important evidence on the management of Turkish FH patients.

It is well known that registries are helpful in rapid and efficient collection of data. Many researchers prefer registries, as they allow analysis of a disease in real-life conditions. Data obtained from registries provide perspective of a problem in a community and also allow for comparison of results with larger reference populations, which may stimulate improvements in quality and consistency of practice.[16] Moreover, they help by establishing a database that could guide illumination of the nature of a specific disease or condition. Therefore, EAS and many other FH initiatives recommend creation of national and international FH registries.[7] The A-HIT registries will add to the literature regarding the burden of FH in Turkey as a developing country with high consanguinity rate. A-HIT1 will uncover major drawbacks of LA and help to generate a standard model of care in apheresis centers in Turkey. The results of A-HIT2 will enable comparison of the attitudes held in different disciplines, including cardiology, internal medicine, and endocrinology. Moreover, both registries will help to eliminate the existing gap in knowledge and will enable Turkish physicians and researchers to develop enhanced detection and prevention strategies.

For both registries, accurate calculation of FH prevalence will be difficult, as we will only obtain data from apheresis centers for A-HIT1, and from hospital

outpatient clinics for A-HIT2. Therefore, to alleviate the difficulty in extrapolation to the general population, we invited centers representing the 12 statistical regions of Turkey to participate in A-HIT2. With this distribution of centers, we may overcome the major limitation of the A-HIT1 and generate a better idea of FH prevalence in Turkey.

Lack of genetic testing analyses might be accepted as a limitation of the A-HIT registries. Genetic testing increases diagnostic accuracy, and patients with positive genetic testing have higher CV risk. However, if genetic variant is not detected, FH cannot be excluded, particularly if clinical phenotype is strongly suggestive of FH. Possible and definite FH patients are reported to have mutations in 20% to 30% and 60% to 80% of cases.[17] Moreover, Khera et al.[18] reported that among acute coronary syndrome survivors with LDL-cholesterol level of >190 mg/dL, gene sequencing identified FH mutation in only <2%. Furthermore, although molecular diagnostic techniques have advanced and genotyping has become an integral part of clinical practice for FH, the cost is still high for developing countries. Therefore, we preferred to use only clinical criteria for diagnosis of FH.

There are several diagnostic criteria used for HeFH: Make Early Diagnosis to Prevent Early Deaths criteria,[19] Simon Broome criteria,[20] Japanese criteria,[21] and DLCN criteria. We preferred to use the DLCN criteria, as it is more comprehensive and recommended by EAS. More than 1 set of criteria might have been used; however, this would lengthen duration of completing case report form questionnaires.

In conclusion, A-HIT1 and A-HIT2, will be the first nationwide FH registries in Turkey. Their results will contribute to a better understanding of FH in Turkish patients. These registries will help to estimate prevalence of FH, and in addition, will guide in establishing a national policy for the diagnosis and treatment of FH in our country.

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