Atherosclerosis 277 (2018) 341–346

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

What have we learned from Turkish familial hypercholesterolemia registries (A-HIT1 and A-HIT2)?

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https://doi.org/10.1016/j.atherosclerosis.2018.08.012

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HIGHLIGHTS

- Early diagnosis and effective LDL lowering are essential in the treatment of FH.
- FH is still undertreated even in specialized centers in Turkey.
- LDL targets are not reached even in FH patients receiving intense doses of statins.
- Awareness on FH is extremely low among both patients and physicians.

ARTICLE INFO

Keywords:
Familial hypercholesterolemia
Turkey
Registry

ABSTRACT

Background and aims: Familial hypercholesterolemia (FH) is a common genetic disease of high-level cholesterol leading to premature atherosclerosis. One of the key aspects to overcome FH burden is the generation of large-scale reliable data in terms of registries. This manuscript underlines the important results of nation-wide Turkish FH registries (A-HIT1 and A-HIT2).

Methods: A-HIT1 is a survey of homozygous FH patients undergoing low density lipoprotein (LDL) apheresis (LA). A-HIT2 is a registry of adult FH patients (homozygous and heterozygous) admitted to outpatient clinics. Both registries used clinical diagnosis of FH.

Results: A-HIT1 evaluated 88 patients (27 ± 11 years, 41 women) in 19 centers. All patients were receiving regular LA. There was a 7.37 ± 7.1-year delay between diagnosis and initiation of LA. LDL-cholesterol levels reached the target only in 5 cases. Mean frequency of apheresis sessions was 19 ± 13 days. None of the centers had a standardized approach for LA. Mean frequency of apheresis sessions was every 19 ± 13 (7–90) days. Only 2 centers were aware of the target LDL levels.

A–HIT2 enrolled 1071 FH patients (53 ± 8 years, 606 women) from 31 outpatients clinics specialized in cardiology (27), internal medicine (1), and endocrinology (3); 96.4% were heterozygous. 459 patients were on statin treatment. LDL targets were attained in 23 patients (2.1% of the whole population, 5% receiving statin) on treatment. However, 66% of statin-receiving patients were on intense doses of statins. Awareness of FH was 9.5% in the whole patient population.

Conclusions: The first nationwide FH registries revealed that FH is still undertreated even in specialized centers in Turkey. Additional effective treatment regiments are urgently needed.

1. Introduction

Familial hypercholesterolemia (FH) is one of the most common inherited diseases leading to significant cardiovascular (CV) mortality and morbidity. It is characterized by premature coronary artery disease (CAD) and widespread cholesterol depositions as a consequence of lifelong excessively high levels of cholesterol [1,2]. Untreated cholesterol levels typically range between 250 and 300 mg/dL in heterozygous individuals (HeFH), and CV events develop in men by 30–50 years of age, and in women by 40–60 years of age [1–5]. In homozygous individuals (HoFH), serum cholesterol levels are much higher (500–1000 mg/dl), and severe atherosclerotic events begin from early childhood. If left untreated, homozygous patients generally die before the age of 30 years due to accelerated severe atherosclerotic CV events [6].

As FH patients are exposed to high cholesterol levels since birth, early diagnosis and effective lipid-lowering treatment (LLT) are crucial for the management of these patients [1,6]. However, FH is a globally underdiagnosed and undertreated disease. The European Atherosclerosis Society (EAS) has launched a global initiative to overcome the existing gaps in care and reduce the preventable global burden of FH [7]. EAS states one of the key aspects to overcome the FH burden is generation of large-scale reliable data on how FH is detected and managed in terms of registries. In line with this action call, a series of FH registries (A-HIT 1, 2, and 3) is planned and conducted as part of the Turkish FH Initiative endorsed by the Turkish Society of Cardiology (TSC) [8]. The acronym A-HIT stands for **A** registry of familial **H**ypercholeterolem**I**a managemen**T** in Turkey. The first registry, A-HIT1, is a nation-wide survey of adult HoFH patients undergoing low density lipoprotein (LDL) apheresis (LA) in Turkey. A-HIT2 is the registry of adult FH patients admitted to outpatient clinics in Turkey. And finally, A-HIT3 is planned as a registry of FH patients admitted to coronary care units with a diagnosis of premature myocardial infarction in Turkey. This article provides results and important insights obtained from these first 2 registries (A-HIT1 and 2) on patients with FH in Turkey.

2. Methods and data collection in A-HIT registries

The rationale and design of both A-HIT 1 and A-HIT 2 studies have been described previously [8].

A-HIT 1 study was conducted to provide insight into the clinical status of HoFH patients undergoing LDL-apheresis in Turkey (Table 1). Primary objective was to identify how HoFH patients on LDL-apheresis treatment are managed [9]. Secondary objectives included: identification of the patients and physicians awareness of the disease (HoFH) at each participating apheresis center and understanding of the frequency and major drawbacks of the LA treatment. Inclusion criteria were: age ≥12 years, with a HoFH diagnosis and undergoing regular LA. Patients undergoing LA for isolated hypertriglyceridemia or high lipoprotein (a) levels were excluded. Patients aged < 18 years were enrolled only with the consent of a parent or legal guardian. The diagnosis of HoFH was clinically confirmed according to EAS Diagnostic Criteria based on total cholesterol exceeding 500 mg/dL at the time of diagnosis, the presence

Table 1
Overall characteristics of Turkish FH Registries.

Registry	A-HIT 1	A-HIT 2
Number of patients	88	1000 (planned) 1071 recruited
Type of study	Multicenter	Multicenter
Ethics committee approval (date, no)	25.05.2015 15–3.2/52	23.01.2017 16–3.2/55
Data collection interval	July 31, 2015 June 20, 2016	February 26, 2017 February 26, 2018
Patient population	HoFH undergoing lipid apheresis	HeFH & HoFH
Diagnosis criteria	EAS, HoFH criteria	Dutch Lipid Clinic Network Criteria
Data collected	Q1: clinical data of the pts completed by the physcians Q2: LA centers attitude for LDL-apheresis by the physicians Q3: information on the psychosocial status of the patients including quality of life, (SF-36), SCL-90, and Hospital Anxiety-Depression Scale (HADS) completed by patients > 18 years of age	Q1: An electronic case report completed by the physicians for each patient Q2: Short survey assessing the level of disease awareness, also patients perceptions and knowledge on cholesterol, its adverse effects, and lipid lowering treatment

FH: familial hypercholesterolemia, HoFH: homozygous FH, HeFH; heterozygous FH, EAS; European Atherosclerosis Society, Q: questionnaire, pts: patients.

Table 2
Overall characteristics of Turkish FH Registries.

Registry	A-HIT 1	A-HIT 2
Number of patients	88	1071 recruited
Clinical characteristics		
Current age, years	27 ± 11	54 ± 13
Female, n (%)	41 (46.6)	606 (56.6%)
Cardiovascular risk factors, n (%)		
Diabetes mellitus, n (%)	2 (2.3)	240 (22.4)
Hypertension, n (%)	12 (13.6)	458(43.5) Data available for 1053 pts
Current smoking, n (%)	11 (12.5)	280 (26.1)
Coronary artery disease, n (%)	44 (51.8)	432 (44.8) Data available for 965 pts
Age at first coronary event, (years) (min-max)	21 ± 10 (7–51) Data available for 41 pts	50 ± 10 (27–76)
Carotid artery disease, n (%)	21(30.4) Data available for 69 pts	41(5.2) Data available for 790 pts
Serum LDL-cholesterol (mg/dL) (min-max) on treatment	338 ± 82 (168–561)*	215 ± 72 (54–914)
LDL goal attainment, n(%) on treatment	5 (5.7%) all were on treatment	23 (2.1) 459 pts were on treatment
Known family history		
Coronary artery disease, n (%)	57 (67.9) Data available for 84 pts	719 (71.1) Data available for 1012 pts
Age at first coronary event in the family, years (min-max)	42 ± 13 (17–75) Data available for 44 pts	49 ± 11 (12–87)
Consanguineous marriage, n (%)	49 (59) Data available for 83 pts	163 (15.2)

FH: familial hypercholesterolemia, Pts: patients, LDL: low density lipoprotein.
*Interval mean LDL calculated with Kroon formula.

of xanthomas at an early age, and the presence of primary hypercholesterolemia in the proband's parents or other first-degree relatives. The baseline evaluation included 3 different data sets. A questionnaire was completed for each patient by the attending physician responsible for patient care. The obtained data included demographics, CV risk factors, clinical characteristics and phenotypic data, age of symptom onset and age of diagnosis, detailed family history including consanguinity, pre and post session LDL-cholesterol levels of the last four LA sessions, LA procedures and frequency, CV involvement, and complications. Time-averaged LDL-cholesterol levels were calculated with the formula described by Kroon et al. [10]. A second form was filled in by the principal physicians of each LA center on the center's attitude for LDL-apheresis. A third questionnaire providing information on the psychosocial status of the patients was completed by patients > 18 years of age. Patient and physician questionnaires are available as Supplemental Materials.

A-HIT2 is also designed as a National FH registry and at least 1000 FH (both HeFH and HoFH) patients were planned to be enrolled from 30 outpatient clinics representing the 12 Nuts statistical Regions in Turkey, proportional to the 2015 Turkey's census [11]. The primary objective of the baseline evaluation was to detect the clinical status and management of the patients diagnosed with FH in Turkey. The secondary objectives were to identify the pattern of clinical presentation, the medication use, the clinical response to LLT, the attainment of LDL-cholesterol goals and the rates of resistance and/or intolerance to LLT. The inclusion criteria were age > 18 years and being diagnosed as possible FH according to the Dutch Lipid Clinic Network (DLCN) criteria [12]. Patients with triglyceride levels > 400 mg/dl or secondary hyperlipidemia (ie, untreated hypothyroidism, nephrotic syndrome, cholestasis, etc.) were excluded. Two different data sets were collected for A-HIT2 (Table 1). An electronic case report form was completed by the physicians for each patient and the patients filled in a short survey assessing the level of disease awareness, perceptions and knowledge on cholesterol, its adverse effects, and LLT.

Both A-HIT1 and 2 registries were not hypothesis-driven, therefore, no specific medical therapies or interventions were given to patients. Moreover, for both registries, clinical evaluation was regarded as

sufficient for the diagnosis of FH, i.e. genetic analysis was not generated, only if already available, previous genetic results were recorded.

Both registry protocols have been reviewed and approved by the Ege University Institutional Review Board (Table 1). Written informed consent was obtained from all participants.

All statistical analyses were conducted using SPSS Version 22.0 (SPSS Inc., Chicago, IL). Data are presented as mean SD for continuous variables (or as medians and interquartile ranges for variables with skewed distributions), and as frequencies or percentages for categorical variables.

3. Results

The general results of A-HIT1 and 2 are presented in Table 2.

3.1. General results of A-HIT1

Cross-sectional baseline evaluation of A-HIT1 included 88 patients (mean age: 27 ± 11 years, 41 women) undergoing regular therapeutic LA, with clinical diagnosis of HoFH in 19 specialized centers. A-HIT1 consisted of a population of HoFH patients with 2.3% diabetes, 13.6% hypertension, and 12.5% current smokers. Family history of early-onset CV disease was present in 67.9% of patients with a mean age of first coronary event in first-degree relatives of 42 ± 13 (17–75). Parental consanguineous marriage was present in 59% of the study population.

Overall, 67.5% of the patients were suffering from CV involvement including aortic stenosis (AS). Early onset CAD was documented in 57.8% of the cases. The mean age at the time of the first coronary event was 21 ± 10 (range 7–51) years. Carotid artery disease was reported in 30.4% of cases. Both CAD and extra-coronary artery involvement were reported in 27 cases. The aortic valve was affected in 41.7% of the cases (32.1% had severe AS, 42.9% moderate and 25% slight AS). Ten patients had undergone aortic valve replacement.

All patients were on maximal doses of statins (either atorvastatin 80 mg/day or rosuvastatin 40 mg/day) combined with ezetimibe. Patients had started LA late in the course of the disease; mean age at first LA was 21 ± 12 years. There was a delay of 2.6 ± 4 (range 0–16) years between first symptoms of HoFH and confirmation of diagnosis. Moreover, there was an additional 7.37 ± 7.1 (range 0.6–31) year delay between diagnosis and initiation of therapeutic apheresis treatment.

None of the apheresis centers had a standardized approach for LA in HoFH. Only one center (the only lipid clinic in country) governed the frequency of LA sessions according to the LDL-cholesterol levels. Mean frequency of apheresis sessions was every 19 ± 13 (range 7–90) days. Only 11 (12.5%) patients were undergoing LA weekly. Meanwhile, there were patients even undergoing LA every 60 or 90 days (Fig. 1). Assessment of the last four LA sessions revealed that LDL-cholesterol levels reached the target only in five cases. Only 2 centers were aware of the target LDL-cholesterol levels for individual patients. The calculated interval mean LDL-cholesterol level between the latest apheresis sessions was 338 ± 82 (168–561) mg/dL.

Patient survey revealed that most of the patients were suffering not only from HoFH but also from drawbacks of the LA treatment. For most of the patients, LA was a difficult to bare treatment; the major complaint was related to pain and needles in 34.8%, time spent for apheresis in 27.5%, and both in 17.4%. Most of the patients were travelling a long distance to reach the apheresis centers (mean time spent travelingl 102 ± 154 min (5–720 min). Moreover, the average time spent in the apheresis center was 234 ± 73 min (110–480 min). Only 11.6% were considering increasing their visits for LA treatment.

3.2. General results of A-HIT2

A total of 1071 patients (mean age: 53 ± 8 years, 606 women) were recruited from 31 outpatient clinics specialized in cardiology (n:27), internal medicine (n:1), and endocrinology (n:3). None of the centers were specialized as lipid clinics. Only 3.6% (n:36) of the population has the clinical diagnosis of HoFH. Evaluation of the CV risk factors revealed that 22.4% had diabetes, 43.5% had hypertension, and 26.1% were current smokers. Family history of CAD was present in 71.1% and the mean age of first coronary event in first-degree relatives was 49 ± 11 (range 12–87) years. Parental consanguineous marriage was present in 15.2% of patients. Overall, 48.1% of the cases had documented CV disease. The mean age at the time of the first coronary event was 50 ± 10 (range 27–76) years. Carotid artery disease was reported to be present in 5.2%.

Nearly 1/5th of A-HIT2 population consisted of patients with definite FH (score > 8) (18.6%), 29.2% with probable FH (score 6–8) and 52.2% with possible FH (score 3–5).

Less than half of the study population (n: 459, 43%) was on statin treatment. Most of the statin-receiving patients (n = 304) were on intense doses of statins (of 125 were receiving either rosuvastatin 40 mg or atorvastatin 80 mg daily). The number of patients with an add-on treatment of ezetimibe was 32. On treatment LDL-cholesterol levels were far away from the LDL targets (Table 2); treatment targets were attained only in 23 patients (2.1%). Moreover, when only HeFH patients were evaluated, only 4.3% of the patients receiving intense doses of statins reached the LDL-goals. Only 9.5% of the patient population was aware of a disease named FH.

4. Discussion

In Turkey, the prevalence of FH is unknown, however, extrapolating from different nation's data and higher prevalence of consanguinity in Turkey (23%), HeFH prevalence is estimated to be 1 in 200 people. This suggests that at least 429,000 people are suffering from FH in Turkey. Both A-HIT 1 and A-HIT 2 registries did not help in the calculation of FH prevalence in the country. These first nation-wide registries provided some important evidence on the real-life management of Turkish FH patients. In particular, results of A-HIT 2 reflect the common attitude of physicians (cardiologists, endocrinologist, and internists) to FH patients in routine daily practice as none of the study centers were specialized as lipid clinics.

A-HIT 1 revealed that there is a long delay between diagnosis and initiation of LA in HoFH patients in real clinical practice. Although LA is a lifesaving therapy for patients with HoFH, according to A-HIT 1, most patients experience ineffective LA and fail to reach LDL targets, even in a country where LA is reimbursed and widely available. In addition, A-HIT 1 showed that none of the centers had a standardized approach to LA. Most of the centers were unaware of the individuals patient's target LDL-cholesterol levels, delineating the awareness of physicians on FH. The lack of awareness among physicians specialized on apheresis or FH is probably the major reason of the failure of LA treatment in attaining LDL targets.

The average price of a LA session is 800–1000 US dollars, and it is

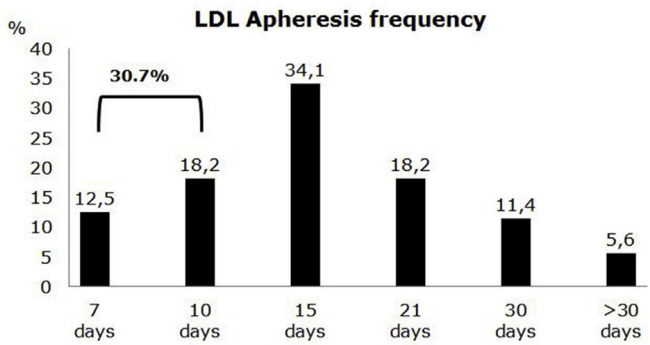

Fig. 1. Lipoprotein apheresis frequency.

fully reimbursed and widely available in Turkey. All LA methods could be used depending on the centers of choice, and there is no age restriction for LA in Turkey. In addition, any criteria available in Europe are valid to determine the indications of LA. However, medical staff are not willing to perform LA as the required procedures need too much paperwork for such an expensive and elaborate treatment. Moreover, regulations only allow LA to be performed in hematology centers where many other apheresis modalities occupy most of the daily work. All these factors may drive to suboptimal frequency of therapeutic LA. Moreover, A-HIT 1 results also showed that for most of the patients, LA treatment was painful, tiring, and time-consuming. Therefore, although LDL levels were far away from the targets, most of the patients were not willing to increase the frequency of apheresis sessions.

Overall, results of A-HIT 2 were compatible with other country registries. However, A-HIT 2 represents an outpatient clinic population and, therefore, patients had more frequency of diabetes and hypertension. Moreover, the inclusion criteria according to DLNC with a score ≥ 3 might also explain the higher rates of diabetes and hypertension in the study population. In line with A-HIT 1 results, A-HIT 2 showed that diagnosis was delayed even in patients with severe early family history of CV disease. More than half of the patients were not receiving statins and treatment targets were attained only in 23 patients (2.1%) on statin treatment. All these results uncover the lack of awareness among physicians besides the lack of awareness of patients.

The major limitation of both registries is probably the lack of genetic testing for the diagnosis of FH. Genetic testing increases the diagnostic accuracy and patients with positive genetic testing have a higher CV risk. However, we preferred to use clinical criteria for the diagnosis of FH as the cost of genetic analysis is high. Moreover, if genetic variant is not detected, FH cannot be excluded, particularly if the clinical phenotype is strongly suggestive of FH. Possible and definite FH patients have been reported to have mutation in 20–30% and 60–80% of cases [13]. Moreover, Khera et al. have reported that among the survivors of an acute coronary syndrome with a LDL-cholesterol level of ≥ 190 mg/dl, gene sequencing only identifies an FH mutation in $< 2\%$ [14].

Another limitation might be accepted as the enrollment of possible FH patients. Almost half of the A-HIT 2 population consisted of possible FH patients according to the DLNC (score 3–5 points). This possible FH group would be expected to include more hypercholesterolemic subjects unlikely to have FH compared to probable FH patients (score 6–8 points).

During the enrollment period of both registries, PCSK9 inhibitors, an important treatment alternative both in HoFH and HeFH, were not available. Currently, both alirocumab and evalocumab are pending reimbursement. As the evaluation of the HeFH population of A-HIT 2 revealed that LDL goals were attained only in less than 5% of the patients receiving intense statin treatment, PCSK9 inhibitors will probably be more readily accepted by both Turkish patients and physicians when they become reimbursed.

Both Turkish FH registries reflect the clinical characteristics and management of FH patients in a country with high consanguinity. To the best of our knowledge, A-HIT 1 is the largest real-world cross-sectional HoFH population on LA. The Malaysian registry included only 15 HoFH patients on LA treatment [15]. The Norwegian registry also enrolled just seven cases with HoFH undergoing LA [16]. Bruckert et al. have reported more than 20 years of experience with 40 HoFH cases undergoing LA every two weeks from of a single lipid center in France [17]. There are also several retrospective surveys of HoFH patients such as the evaluation of a single center with 50 years of experience with 44 patients of whom only 60% of the patients have received apheresis (or plasmapheresis) treatment [18]. The report from the US by Kolansky et al. included 39 HoFH patients (of whom, only 43% were on apheresis treatment) [19], and that from South Africa by Raal et al. [20] included the retrospective analysis of 149 HoFH patients between 1972 and 2009. The whole population of The South African HoFH cohort was not on LA treatment. These reports provided important information on the outcomes of HoFH patients. The presented data included only baseline descriptions of the A-HIT 1 population, and the prospective follow-up is underway (A-HIT 1 extended). Different from these, all registries A-HIT 1 data included a survey filled in by the attending physicians from each LA centers. A similar survey was conducted online by Stefanutti et al. [21], in 24 centers from Europe, however, 65% of these centers performed the LA treatment. All these registries and surveys have served the generation of the position statements of HoFH [22]. A-HIT 2 has a small sized population compared to other countries with completed registries, including Netherlands, Spain, and Norway [23–25]. Nevertheless, it gives important insights into the management of FH in Turkey.

In conclusion, both A-HIT 1 and A-HIT 2, as the first nationwide FH registries in Turkey, revealed that the management of FH is ineffective even in specialized centers. Both in HoFH and HeFH patients, LDL targets are not reached even in patients receiving intense doses of statins. These results will contribute to a better understanding of FH in Turkish patients and should be used as guide in establishing a national policy for the diagnosis and treatment of FH.

Conflicts of interest

Meral Kayikcioglu has received honoraria (for lectures and consultancy) from Abbott, Abdi İbrahim, Aegerion, Amgen, Bayer Schering, Merck, Mylan, Sanofi, Pfizer, and research funding from Aegerion, Amgen, Pfizer, and Sanofi, and has participated in clinical trials with Amgen, Bayer Schering, Merck, Sanofi-Genzyme and Pfizer.

Leylagul Kaynar has received honoraria (for lectures) from Amgen, Pfizer, MSD, BMS, Novartis, Astellas, and has participated in clinical trials with PPD Global, Celgene, Johnson&Johnson.

For the last 2 years, Melih Aktan has participitated in clinical trials with Roche, Pharmacyclics, Glaxo Smith Kline, Jahnssen, Milleneum Pharmaceuticals, Acerta-Pharma and Pharma Olam.

Harika Okutan: None.

Ozen Oz Gul has received honoraria (for lectures) from Sanofi, Novo Nordisk, Novartis, Boehringer Ingelheim, Ipsen and has participated in clinical trials with Merck, Sanofi and Novo Nordisk.

Mustafa Yenercag: None.

Melis Demir Kose: None.

Zafer Pekkolay: None.

Sinan Demircioglu: None.

Levent Hurkan Can: None.

Fahri Bayram has participated in clinical trials with Sanofi,Abbott,Sanovel,Novonordisk,Lilly,Novartis and Regeneron.

Ahmet Temizhan has received honoraria (for lectures and consultancy) from Abdi İbrahim, Sanofi, MSD, Meranini, Deva, Novartis, Sanovel, Astra Zeneca, Daichii and Boehrinfer İngelheim.

Selim Topcu: None.

Ayse Hazdalıc: None.

Saim Sag has received honoraria (for lectures and consultancy) from Sanofi-Genzyme.

Tevfik Sabuncu has received honoraria (for lectures and consultancy) from Novo Nordisk, Sanofi, Astra Zeneca and Boehringer Ingelheim.

Osman Ilhan has received honoraria (for lectures and consultancy) from Roche, Novartis, Abdi Ibrahim, Amgen, Kocak, Alexion, Astra Zeneca, Janssen, and has participated in clinical trials with Roche, Astra Zeneca, GSK and Pharmacyclics.

Ibrahim Etem Dural None.

Ersel Onrat has received honoraria (for lectures and consultancy) from Recordati, Abdi Ibrahim, Pfizer, Novartis, Daichi Sankio, Sandoz and research funding Amgen, Dalcor Pharma, Pfizer and has participated in clinical trials with Amgen, Dalcor pharma.

Mirac Vural Keskinler, has received honoraria from Novartis, Astra Zeneca, Boehrinfer İngelheim involved in clinical trials sponsored

Sanofi, Astra Zeneca, Bayer, Nova Nordik and Amgen.

Lale Tokgozoglu has received honoraria/consultancy fees from Merck, Amgen, Astra, Novartis, Abbott, Daichi Sankyo, NovaNor disk, Pfizer, Actelion, Servier, Sanofi, Boehringer Ingelheim, Menarini, Kowa, Aegerion, and Abbott.

Ahmet CELİK has received honoraria (for lectures and consultancy) from Servier, Astra Zeneca, Pfizer, Novartis, Daichi Sankio, Sandoz and research funding Amgen, Bayer and has participated in clinical trials with Amgen, Pfizer and Regenerone.

Özen Öz Gül has received honoraria (for lectures) from Sanofi, Novartis, Boehringer Ingelheim, Ipsen and has participated in clinical trials with Sanofi and Novo Nordisk.

Oner Ozdogan has received honoraria (for lectures and consultancy) from Amgen, Boehringher Ingelheim, Phizer, Daiichi Sankyo, Ibrahim Ethem Menarini, Servier, Astra Zeneca, Bayer and has participated in clinical trials with Bayer and Pfizer.

Zafer Salcioglu has received honoraria (for lectures and consultancy) from Pfizer, Novo nordisk and Baxalta.

Acknowledgements

A-HIT1 and 2 registries are sponsored by the Turkish Society of Cardiology that receives funding from a variety of sources (including unrestricted research grants from Aegerion, Amyrit, Amgen, Pfizer, and Sanofi).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.08.012.

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