FAMILIAL HYPERCHOLESTEROLAEMIA: A GLOBAL CALL TO ARMS

Supplementary Material

Supplementary Material 1

Familial Hypercholesterolaemia situation, policies and initiatives in different regions around the world

- **ARGENTINA**

The FH situation in Argentina has been improved during the last three years. The Ibero-American FH network was launched in 2013. This new independent network brings together different national and international initiatives and connects stakeholders to work in synergy.

Since February 2015 the first regional pilot program for a registry of FH in Argentina have been started; the main objective of this project is to detect FH patients and calculate the prevalence of FH in Argentina. This collaborative work joins the effort of two different Universities (Buenos Aires University and FASTA University of Mar del Plata), the local government of Mar del Plata city and unrestricted private support. The main aims focus on screening, diagnosis and management of FH for two years. The second part of this programme consists of establishing a continuous programme to detect and follow-up the patients with FH, an effort requiring the collaboration of different stakeholders (academics, clinicians, FH patients, government). Likewise, a registry is needed to provide more in depth insights on the current burden of this disease, screening and management of patients with FH. Important efforts are being done in these areas. Within the programme we also encourage collaborative working strategies as we are aware of the need to learn from experiences and expertise from other countries with much more experience; this otherwise may take a long time to resolve.

- **ASIA**

There are currently no true estimates of the incidence or prevalence of FH in Asia. A limited number of studies from diverse regions in Asia have studied mutations in LDLR, APO-B and PCSK-9, and reported some novel variants in these populations. The high prevalence of cardiovascular disease in Asians has been attributed mainly to lifestyle factors, and the contribution of FH is largely unknown. Systematic screening for FH is available only rarely in many parts of Asia.

1- Livy a, Lye sh. Familial Hypercholesterolemia in Asia: A Review. OMICS Res 2011;1(1):22-31.

- **AUSTRALIA**

It is estimated 1 in 300 people have FH in Australia[1] i.e. 77,000 people of which approximately 80% have not yet been diagnosed. National guidelines have been published to improve the care of FH[2]; lipid clinic services have been established in almost every state. However, active cascade screening and genetic services are mostly concentrated in two state capitals, Sydney and Perth. A cost-effective cascade screening program has been implemented in Western Australia[3]. A National Registry for FH, coordinated by the FH Australasia Network (FHAN; http://www.athero.org.au/fh-home) aims to collate data to facilitate clinical service planning, research and clinical trials, and to inform best clinical practice and the development of models of care for FH. Efforts are being made to increase FH screening via general practices[4], laboratories[5] and coronary care units[6].

Statins and lipoprotein apheresis are subsidised by state and federal health; newer treatments are only at present available through special access schemes or clinical trials. There are gene founder effects among the Dutch Afrikaans and Christian Lebanese groups. An FH Family Support Group (http://www.fhfamilysupportgroup.websyte.com.au/), affiliated to the national FH Network, has been established and conducts group meetings and publishes newsletters, and is closely involved in awareness raising and advocacy.

1- Watts GF, Shaw JE, Pang J, et al.Prevalence and treatment of familial hypercholesterolaemia in Australian communities. Int J Cardiol 2015;185:69-71.
2- Watts GF, Sullivan DR, Poplawski N, et alFamilial hypercholesterolaemia: a model of care for Australasia. AtherosclerSuppl 2011;12:221-263.
3- Bell DA, Pang J, Burrows S, et al. Effectiveness of genetic cascade screening for familial hypercholesterolaemia using a centrally co-ordinated clinical service: an Australian experience. Atherosclerosis 2015;239:93-100.
4- Vickery AW, Bell D, Garton-Smith J, et al. Optimising the detection and management of familial hypercholesterolaemia: central role of primary care and its integration with specialist services. Heart Lung Circ 2014;23:1158-1164.
5- Bell DA, Edwards G, Hooper AJ, et al.The potential role of an expert computer system to augment the opportunistic detection of individuals with familial hypercholesterolaemia from a community laboratory.ClinChimActa 2015;448:18-21.
6- Pang, J et al. J ClinLipidol 2015 (in press).

▪ AUSTRIA

Similar to the situation in other European countries, there exist no reliable data on the overall frequency of FH in Austria. Extrapolating the internationally accepted current figures for allele frequencies also for Austria, up to 40,000 heterozygous and 40 homozygous FH patients are living in Austria; more than 80% of them most likely to be undiagnosed, therefore untreated and unaware of their life-threatening disorder. This situation is particularly astonishing for homozygous FH patients because only very few of them have been actually diagnosed. There have been several ambitious projects performed in the past (including the international MED-PED programme[1]) to overcome this unsatisfactory situation; however, all these initiatives did not result in a nation-wide screening programme for detection and efficient treatment of FH in Austria. The Austrian Atherosclerosis Society (AAS) (www.aas.at) has therefore initiated a project aiming at establishing a nation-wide registry for FH following a successful country-wide screening programme. This initiative will be performed in close collaboration with related scientific societies (including cardiologists, diabetologists, human geneticists, epidemiologists, etc.) and the Austrian FH patient organisation FHchol-Austria (www.fhchol.at) and seeks financial support from industry and public funding. At the final stage, the nation-wide FH registry will serve patients and doctors to cope with this still under-diagnosed and under-treated disease.

1- Widhalm K, Dirisamer A, Lindemayr A, et al. Diagnosis of families with familial hypercholesterolaemia and/or Apo B-100 defect by means of DNA analysis of LDL-receptor gene mutations. J Inherit Metab Dis 2007;30:239-47.

▪ BELGIUM

Most likely 22,000 to 38,000 people have Familial Hypercholesterolaemia (FH) in Belgium based on the theoretical reported frequency for FH (1/300 – 1/500). Only a few of them (estimated in around 2,000) have been genetically diagnosed. We do not have a clear view of how the vast majority of FH patients are taken care and by whom (presumably by general physicians, cardiologists and endocrinologists, like most hypercholesterolaemic patients). Of note, based on the statistics of the national insurance, around 16,000 patients are fulfilling the special criteria for statin reimbursement close to the definition of the FH conditions (total cholesterol >300 mg/dL and one first degree relative with premature cardiovascular disease), though we suspect that most of these patients are not true FH patients. Moreover, a lot of FH patients, especially the

young ones, do not fulfil such criteria. In 2011, the Belgian Society of Atherosclerosis in collaboration with others specialists (paediatrics, cardiology, diabetology, and general practice) published a guideline to improve the care of FH patients, especially in children[1]. Active cascade screening and genetic services have only been initiated locally in some cities since 1995[2,3] and a national registry for FH is still absent. However, the FHSC initiative is currently used to encourage such a registry and to increase awareness for FH screening via general practices, endocrinologists and cardiologists, especially in the centres for cardiac revalidation. Lipoprotein apheresis and newer medications for homozygous FH are not yet reimbursed in Belgium. A patient association (www.belchol.be) has just been created in September 2015 and will be involved in awareness raising.

1- Descamps OS, Tenoutasse S, Stephenne X, et al. Management of familial hypercholesterolemia in children and young adults: consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization. Atherosclerosis. 2011;218(2):272-80.
2- Descamps O, Hondekijn JC, Van Acker P, et al. High prevalence of a novel mutation in exon 4 in the LDL receptor gene in Belgium. Clin Genet 1997;51:301-308.
3- Descamps OS. Familial hypercholesterolemia in a Belgian community. Acta Cardiologica 2000;55(6):327-333.

- **BRAZIL**

It is estimated that Brazil has between 400,000 to 1,000,000 FH patients, however FH is severely underdiagnosed and undertreated. Overall there is a small number of lipid clinics in Brazil and most of these are concentrated in the city of Sao Paulo which is the largest city in the country. HipercolBrasil (www.hipercolesterolemia.com.br) from the Heart Institute (InCor) University of Sao Paulo Medical School Hospital is the only genetic FH cascade-screening program active in Brazil. Since 2012, 995 index cases and 1482 relatives of 225 families were and are being screened. On the first phase of the program FH causing mutations were found in approximately 50% and 60% of index cases and relatives respectively[1]. FH patients are admitted to InCor's lipid clinic. HipercolBrasil performs molecular diagnosis for satellite sites in the cities of Rio de Janeiro and Fortaleza (Northeast of Brazil). Funding for molecular diagnosis comes from tax exemption programs mainly from the Samaritano Hospital in Sao Paulo. The HipercolBrasil program is trying to expand for the whole State of Sao Paulo (44 million inhabitants) in partnership with other clinics funded by the State and Federal governments. No founder effect is yet described in Brazil. Statins are available for free from the government but lipoprotein apheresis and newer medications for homozygous FH are not obtainable. In order to increase awareness of FH in Brazil, the Department of Atherosclerosis of the Brazilian Society of Cardiology published its FH guidelines[2] in 2012. The FH patients association (AHF) was founded in 2014 (http://www.ahfcolesterol.org).

1- Jannes CE, Santos RD, de Souza Silva PR, et al. Familial hypercholesterolemia in Brazil: cascade screening program, clinical and genetic aspects. Atherosclerosis 2015;238:101-7.
2- Santos RD, Gagliardi AC, Xavier HT, et al; Sociedade Brasileira de Cardiologia. First Brazilian Guidelines for Familial Hypercholesterolemia. Arq Bras Cardiol 2012;99(2 Suppl 2):1-28

- **CANADA**

FHCanada (The Canadian FH registry) estimates that there are at least 84,000 Canadians with FH –using conservative estimates. The majority remain undiagnosed. Due to founder effects, the prevalence is higher in the province of Quebec, with an estimated prevalence of 1/270 vs. 1/500 for the rest of the Country.

The MISSION of the Canadian FH Registry is to bring together a multi-disciplinary group of physicians, basic and clinical researchers to improve the delivery of care to patients with severe lipoprotein disorders, especially FH, and to foster collaborative research. The VISION is to create a Canada-wide network of academic clinics,

integrating lipid specialists, endocrinologists and cardiologists to treat patients with the highest standard of care and to create a collaborative research environment. Using a "hub and spoke" model, the registry will be extended in various communities to link primary care physicians with provincial academic centers. The GOALS are to improve care to patients with FH and to reduce cardiovascular disease in this population at high risk.

Further information can be found at www.FHCanada.net.

- **CHINA**

The prevalence of Familial Hypercholesterolemia (FH) in general population in China is not clear. In 2014, Zumin Shi et al[1] reported the prevalence of FH in Jiangsu province of China. According to adjusted diagnostic criteria based on LDL-cholesterol (LDL-C) levels, the age standardized prevalence rate of FH was 0.31%, with the prevalence rate being 0.65% in people over 50 years old. Of 10 patients with FH and elevated cholesterol, 7 took lipid lowering drugs, but 100% of patients were not up to recommended LDL-C goals. However, the prevalence rate of FH was only 0.022% or 0.043% if the Japanese diagnostic criteria[2] or the Simon Broome diagnostic criteria[3] were adopted, respectively. In short, the rates of diagnosis and treatment for patients with FH are very low in China. It is an urgent task to develop a research strategy, use a diagnostic criteria suitable for Chinese population, identify FH patients by using the method of cascade screening and offer appropriate treatment.

1- Shi Z, Yuan B, Zhao D, et al. Familial hypercholesterolemia in China: Prevalence and evidence of underdetection and undertreatment in a community population. Int J Cardiol 2014;174(3):834-6.
2- Harada-Shiba M, Arai H, Oikawa S, et al. Guidelines for the management of familial hypercholesterolemia. J Atheroscler Thromb 2012;19:1043–60.
3- Watts GF, Sullivan DR, Poplawski N, et al. Familial hypercholesterolaemia: a model of care for Australasia. Atheroscler Suppl 2011;12:221–63.

- **CZECH REPUBLIC**

The Czech MedPed project (Make early diagnoses to Prevent early deaths), aimed to prevent premature deaths in FH patients, started in 1998 under the organizational as well as financial support of the Czech Atherosclerosis Society. Since then it has grown into a network of 63 centres covering all regions of the country. Roughly each of the formal regions of the country is served by one regional centre for adults being coupled by a paediatric centre in most cases. All of the project´s sites are responsible for examination, diagnosis and treatment of FH patients, as well as DNA collection for genetic analyses. They also perform cascade screening in the identified pedigrees and serve as educational centres for their respective regions. All the identified FH subjects enter a nationwide FH database that is being run and supervised by national centres. Currently the database comprises data of more than 6,100 FH individuals, including 4,560 index cases (which corresponds to approximately 18.5% out of 33,000 people expected to suffer from FH in the Czech Republic, considering a prevalence of 1:300). FH causing mutation has been detected in more than 2,100 patients so far. The medical part of the project has been recently complemented by foundation of an FH patients´ organization. The webpage of the organization (www.diagnozafh.cz) provides patients, their relatives as well as the general public reliable and up-to-date information regarding the disease, its treatment options and FH care centres.

- **DENMARK**

It is estimated that 1 in 200 people have heterozygous Familial Hypercholesterolaemia (FH) in Denmark[1-3]. Thus, it would be expected that 1 in 160,000 individuals have homozygous FH (that is, if most of those have not already died). Indeed, theoretically, there should be 35 individuals with homozygous FH, but only 2 are well identified. Heterozygous FH is not registered in any nationwide registry and there is no official diagnostic WHO code for FH. As a result, of the expected 27,500 individuals with heterozygous FH in Denmark (based on the 1 in 200 figure and a population size of 5.5 million) maybe only 1000 or a few more receive appropriate treatment in a lipid clinic. There is also no systematic approach to find family members with FH in Denmark. Nevertheless, the Danish Society for Cardiology has produced two publications informing physicians about FH[4-5] and the Danish Heart Foundation offers some information to patients about FH[6]. Lipid clinics are found at many major hospital throughout the country (possibly at 10 or more hospitals) and genetic testing is offered in at least 3 university hospitals in different parts of the country. Also, the use of statins is prevalent in Denmark where roughly 15 individuals of those above the age of 40 receive a statin. In summary, therefore, Denmark has a public healthcare system with all the necessary requirements for finding and treating individuals and families with FH – however, it just needs nationwide policies, organisation and funding to find FH families in order to diagnose and treat this deadly, common and hereditary disorder at a standard equivalent to that offered in most other programs in the Danish healthcare system.

1- Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease and Cholesterol-lowering medication. J Clin Endocrin Metab 2012;97:3956-64.
2- Corrigendum to: Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease and Cholesterol-lowering medication. J Clin Endocrinol Metab 2014;99:4758–59.
3- Nordestgaard BG, Chapman MJ, Humphries SE, et al, for the European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus statement for the European Atherosclerosis Society. Eur Heart J 2013;34:3478-90.
4- The Danish Society of Cardiology about familial hypercholesterolemia: Bang LI et al. Holdningspapir fra Dansk Cardiologisk Selskab om Familiær hyperkolesterolæmi (http://www.cardio.dk/docman/cat_view/48-rapporter/61-holdningspapirer?start=10) (accessed 30-08-2015).
5- The Danish Society of Cardiology about hereditary heart disease including familial hypercholesterolemia: Christensen AH et al. Vejledning fra Dansk Cardiologisk Selskab om Arvelige Hjertesygdomme (http://www.cardio.dk/docman/cat_view/48-rapporter/49-kliniske-rapporter) (accessed 30-08-2015).
6- The Danish Heart Foundation about familial hypercholesterolemia: (http://www.hjertelunge.dk/forebyggelse/risikofaktorer/kolesterol/arvelig_forhoejet_kolesterol/) (accessed 30-08-2015).

▪ FINLAND

While there are national guidelines for the treatment of Familial Hypercholesterolaemia (FH) and hyperlipidemia in Finland, there isn't a national FH-registry or a national screening program for the detection of FH. Thus, the overall prevalence of FH in Finland remains unknown. Previous studies of Finnish FH-patients show that the spectrum of disease-causing mutations in the LDL-receptor gene is characterized by an enrichment of a limited number of founder mutations[1,2]. The estimated overall prevalence of heterozygotic carriers of these founder mutations approaches 1/500. However, it is unknown to what extent these founder mutation carriers actually have been diagnosed and adequately treated. Moreover, since the prevalence of FH likely is considerably higher than previously appreciated[3], a substantial proportion of Finnish FH may also still be molecularly undefined.

Promoted by the activities of the Finnish Atherosclerosis Society, the awareness of FH and the need for more efficient screening and treatment strategies is now raised in Finland. A positive outcome is that the first outpatient clinic specifically focusing on screening and treatment of FH will be established at the Helsinki University Central Hospital this upcoming fall.

1- Vuorio AF, Aalto-Setala K, Koivisto UM, et al. Familial hypercholesterolaemia in Finland: common, rare and mild mutations of the LDL receptor and their clinical consequences. Finnish FH-group. Ann Med 2001;33:410-421.

2- Lahtinen AM, Havulinna AS, Jula A, et al. Prevalence and clinical correlates of familial hypercholesterolemia founder mutations in the general population. Atherosclerosis 2015;238:64-69.
3- Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-3490a.

▪ FRANCE

The French Research Network for autosomal dominant hypercholesterolemia (Réseau National de Recherche sur les Hypercholestérolémies Familiales) has recruited families with familial hypercholesterolemia from several regions of France. Through this network molecular data from 1358 French ADH probands were analysed to provide the spectrum of mutations responsible for ADH in this country[1]. This network also led to the identification of the third cause of ADH i.e. gain of function mutation in the PCSK9 gene[2]. Under the auspices of the new Society of Atherosclerosis specific recommendations were launched for the treatment of patient with ADH both in the adult and pediatric populations[3,4]. More recently the French registry has provided data which emphasizes undertreatment even in patients being followed in specialized centers[5]. Together with the patient organization (Association Nationale des patients touchés par l'hypercholestérolémie familiale) several actions have launched to increase awareness of the disease (www.anhet.fr).

1- Marduel M, Carrié A, Sassolas A, et al. Molecular spectrum of autosomal dominant hypercholesterolemia in France. Hum Mutat 2010;31(11):E1811-24.
2- Abifadel M, Varret M, Rabès J-P, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154-6.
3- Farnier M, Bruckert E, Boileau C, et al; Nouvelle société française d'athérosclérose. Diagnostic and treatment of familial hypercholesterolemia (FH) in adult: guidelines from the New French Society of Atherosclerosis (NSFA). Presse Med 2013;42(6 Pt 1):930-50.
4- Luc G, Girardet JP, Bruckert É, et al; Nouvelle Société Française d'Athérosclérose; Société Française de Pédiatrie. Recommendations for hypercholesterolemic children. Presse Med 2011;40(2):138-50.
5- Béliard S, Carreau V, Carrié A, et al. Improvement in LDL-cholesterol levels of patients with familial hypercholesterolemia: can we do better? Analysis of results obtained during the past two decades in 1669 French subjects. Atherosclerosis 2014 May;234(1):136-41.

▪ GERMANY

The precise prevalence of FH in Germany is unknown and awareness of FH needs to be increased[1,2]. There are a number of active lipid clinics throughout the country, however there is no national FH registry. Regional[3] but no national screening programs exist. Clinical scores such as the Dutch Lipid Clinic Network or the score of the Simon Broome Register Group are hardly ever used in Germany outside of university hospitals or lipid clinics. Their categories of "possible" or "probable" are perceived as confusing and hamper communication. Genetic testing is available. The high cost (approximately 2000 €) is reimbursed by most of the mandatory heath insurances but access requires significant effort ("paperwork") of the physician. Genetic research is needed to improve the positive and negative prediction of current genetic analysis[4] and simplified clinical algorithms may help to communicate the detection of FH[5].

The concept of LDL targets and LDL as causal agent for atherosclerotic cardiovascular disease (ASCVD) is communicated by the medical societies[6,7] but has not been accepted by regulatory bodies (such as the Gemeinsamer Bundesausschuß, GBA[8]). Oral lipid lowering medications such as statins, fibrates and cholesterol absorption inhibitors are easily available and fully reimbursed. Compared with other European countries, lipid apheresis is widely available for patients with homozygous FH, patients with LDL- or Lp(a)-hyperlipidemia and progressive ASCVD despite optimal oral therapy. PCSK9 inhibitors will be available in Germany in September 2015, however their reimbursement after one year (Sept. 2016) is open to be determined by the authorities (AMNOG).

1- Klose G, Laufs U, März W, Windler E. Familial hypercholesterolemia: developments in diagnosis and treatment. Dtsch Arztebl Int 2014;111:523–529.
2- www.cholco.de
3- http://www.dach-praevention.eu/familiaere-hypercholesterinaemie/kaskadenscreening-rhein-neckar-region/
4- Brænne I, Kleinecke M, Reiz B, et al. Systematic analysis of variants related to familial hypercholesterolemia in families with premature myocardial infarction. Eur J Hum Genet 2015 Jun 3. doi: 10.1038/ejhg.2015.100.
5- Laufs U, Parhofer K. Simplified algorithm to facilitate communication of familial hypercholesterolaemia. Eur Heart J 2015 Sept; in press.
6- http://leitlinien.dgk.org/leitlinien/
7- http://www.dach-praevention.eu/leitlinienstellungnahmen/
8- https://www.g-ba.de/

- **GREECE**

It is estimated that 1 in 250 people have FH in Greece i.e. approximately 40,000 patients. The vast majority of these patients (~90%) remain undiagnosed. National guidelines have emphasised the need to improve knowledge, diagnosis and management of FH[1]. Lipid clinic services remain limited and there is no active cascade screening and genetic service. A National Registry for FH, the HELLAS FH Registry, has been recently established. This registry is coordinated by the Hellenic Atherosclerosis Society (HAS; http://www.atherosclerosis.gr). Adults with LDL-C >190 mg/dL (4.9 mmol/L) (>160 mg/dL or 4.1 mmol/L for children) will be evaluated for the presence of FH by means of the Dutch Lipid criteria. If the diagnosis of FH is possible, probable or definite, the patient will be registered under the HELLAS FH Registry and cascade family screening will be offered. Because electronic prescription covers almost 100% of the population and actual LDL-C levels are required for hyperlipidaemic treatment to be prescribed, the aim is to detect patients with very high LDL-C values at this stage in collaboration with the national health care provider (EOPYY). A practical FH score application for the implementation of the Dutch Lipid Criteria has been launched and is available for free in App Store (https://appsto.re/gr/wF4Q7.i), Google Store (https://play.google.com/store/apps/details?id=com.ajjumax.helleniccalculat) and for desktop download (http://web.alphabit.gr/FHCalculator/index.html).

1- Elisaf M, Pitsavos C, Liberopoulos E, et al. Updated guidelines of the Hellenic Atherosclerosis Society for the management and treatment of dyslipidemia-2014. Hellenic J Atheroscler 2014;5:151-163.

- **ISRAEL**

Israel is the residing place of many populations with distinct founder effect. Such are the Ashkenazi Jews, Iraqi Jews, Druze, and muslin Arabs. For each of these populations distinct novel FH mutations were found[1]. Consanguineous marriages are very common in Israel. Therefore, Homozygote FH is common. Currently, 22 people are diagnosed with homozygote FH, giving an estimated prevalence of 1:350,000 based on the current population size. Screening efforts for FH detection in relatives of patients are being made locally in several medical centers. The largest registry holds records of 421 families. An effort is being made in collaboration between the largest Health Medical Organization in the country that issuers 50% of the Israeli population and the Israeli Atherosclerosis society, to establish cascade screening mechanism for FH. We hope that once this program begins FH detection rates will significantly improve.

1- Reshef A, Nissen H, Triger L, et al. Molecular genetics of familial hypercholesterolemia in Israel. Hum Genet 1996;98(5):581-6.

- **ITALY**

The LIPIGEN project has been launched last year via a network of lipid clinics (more than 40) that cover the whole nation. The LIPIGEN has also started a registry for FH with retrospective and prospective activities. The estimated number of diagnosed patients is roughly 8000. For further information please refer to the website:

http://www.sisa.it/index.php?class=Comp&className=Content&op=Show&param=cid,617,preview,0

- **LATVIA**

The national Latvian Registry of Familial Hypercholesterolemia is established in early 2015 and this initiative is funded by a research grant from the state within the frames of the State Research Programme Biomedicine for Public Health. The Registry is run as a collaboration of the Latvian Research Institute of Cardiology at the University of Latvia and the Latvian Center of Cardiology at the Paul Stradins Clinical University Hospital.

The exact prevalence of heterozygous FH in Latvia is unknown. If the frequency is assumed 1:200 to 1:300, the total number of FH patients is estimated at approximately 7 000 to 10 000. Less than 1% of them are diagnosed. The educational and informative activities targeted at health care providers, general public and patients are in process. This includes an active involvement of a patient organization called Parsirdi.lv (http://www.parsirdi.lv).

Most cases are diagnosed according to phenotype, and genetic testing is not performed routinely. There is little data on genetic spectrum of FH in Latvia. Due to historic reasons the population is rather heterogeneous, and the founder effect of any genetic disease is rather unlikely. Although a genetic test on eight common mutations characteristic to other European countries is available, it is not feasible in clinical practice and use of it is discouraged[1]. The use of next generation sequencing is limited to a minority of cases due to high cost.

1- Radovica I, Berzins R, Latkovskis G, et al. Evaluation of massive parallel sequencing as the diagnostic tool for Familial Hypercholesterolemia. Proceedings of the Latvian Academy of Sciences. Section B. Vol. 69 (2015), No. 1/2 (694/695): 1-7.

- **LEBANON**

The incidence of Familial Hypercholesterolemia (FH) is particularly high in the Lebanese population and is underdiagnosed and undertreated. It was through studies of the Lebanese population that Khachadurian[1,2] first clearly delineated the existence of homozygous FH and the inheritance of the disease. The frequency of the homozygous condition in Lebanon is high and attributable to a high prevalence of heterozygosity of FH among Lebanese, coupled with a high incidence of consanguinity[2,3].

The p.Cys681X mutation in the LDL receptor gene, suspected to have a founder effect and so-called "Lebanese allele"[3], accounts for approximately 81.5 % of the FH Lebanese probands in a study recently performed[4]. The high prevalence of a same mutation and the other mutations reported facilitate: 1) rapid and early screening strategy for FH genetic diagnosis in Lebanon and in FH families of Lebanese origin around the world, 2) an appropriate genetic counselling to reduce the risk of occurrence of new homozygote FH cases in a country with social traditions of inbreeding, 3) phenotype-genotype correlations studies and identification of factors modifying the phenotype[4].

A National LDL-apheresis Centre has been established in a Governmental Hospital in Lebanon. Nevertheless, despite the high prevalence of FH in Lebanon, (estimated to be at least ten-fold higher for homozygotes) compared to other populations[2,3] there is no national FH registry, no exact statistics, no cascade screening program, no FH patient organization, probably because of economic and political reasons. Awareness campaigns and national strategies are highly needed to prevent, diagnose and treat FH in Lebanon.

1- Khachadurian AK. The inheritance of essential familial hypercholesterolemia. Am J Med 1964;37:402-407.
2- Khachadurian AK, Uthman SM. Experiences with the homozygous cases of familial hypercholesterolemia. A report of 52 patients. Nutr Metab 1973;15:132-40.
3- Lehrman MA, Schneider WJ, Brown MS, et al. The Lebanese allele at the low density lipoprotein receptor locus. Nonsense mutation produces truncated receptor that is retained in endoplasmic reticulum. J Biol Chem 1987;262:401-10.
4- Abifadel M, Rabès JP, Jambart S, et al. The molecular basis of familial hypercholesterolemia in Lebanon: spectrum of LDLR mutations and role of PCSK9 as a modifier gene. Hum Mutat 2009;30(7):E682-91.

▪ MEXICO

The prevalence of dyslipidemia has been described in Mexico in three nation-wide population-based surveys. The lipid profile "LDL cholesterol > 190 mg/dl and triglycerides < 150 mg/dl" was present in 0.29% of the adult population[1]. However, this information is not enough to establish the FH prevalence since the surveys did not include the search of tendinous xanthomata or a specific FH definition. A national lipid guideline[2] and position documents[3] are available, but their impact is very limited, especially amongst primary care physicians. FH is unrecognized and undertreated. Series of FH cases are limited to lipid clinics located in Mexico City and Guadalajara. A national registry is being developed. The identification of the causal mutations in Mexican populations has been informed in two reports[4,5]. A greater than expected proportion of cases without LDL receptor mutation was found in both studies. Few lipid clinics have standardized protocols for cascade and genetic testing. Statins are available in all health systems, but it accessibility is insufficient. LDL-apheresis is not available. There is no FH government program or a patient organization as well.

1- Aguilar-Salinas CA, Olaiz G, Valles V, et al. High prevalence of low HDL cholesterol concentrations and mixed hyperlipidemia in a Mexican nation wide survey. J Lipid Research 2001;42:1298-307.
2- Norma Oficial Mexicana sobre Dislipidemias. Available at: http://www.dof.gob.mx/nota_detalle.php?codigo=5259329&fecha=13/07/2012
3- Aguilar Salinas CA, Gomez Perez FJ, Lerman I, et al. Diagnóstico y tratamiento de las Dislipidemias; Postura de la Sociedad Mexicana de Nutrición y Endocrinología. Revista de Endocrinología y Nutricion. 2004;12:7-41.
4- Robles L, Huerta A, Ordoñez ML, et al. Mutational and genetic linkage analyses of autosomal dominant hypercholesterolemia in Mexico: Evidence for further genetic heterogeneity. Arch Med Res 2006;37:102-108.
5- Vaca G, Vazquez A, Magaña MT, et al. Mutational analysis of the LDL receptor and APOB genes in Mexican individuals with autosomal dominant hypercholesterolemia. Atherosclerosis 2011;218(2):391-6.

▪ MIDDLE EAST

Data on the prevalence of heterozygous FH (HeFH) and homozygous (HoFH) in the Middle East region are lacking. Only 57 mutations were reported in 17 Middle East and North Africa (MENA) countries[1]. This can be attributed to the lack of national FH registries and cascade screening programmes in the region. Furthermore, the Middle East region has an epidemic of diabetes and metabolic syndrome that can complicate treatment and mask the diagnosis of FH. Consanguineous marriages are also common.

There are few lipid clinics and lipoprotein apheresis centres in the region. The Gulf FH foundation was founded in February 2015. It will provide a supporting role to identify undiagnosed FH and initiate treatment as well as family screening. This foundation will also update physicians and improve patient support and education as well as political and media awareness about FH in the region.

A regional guidance document on HoFH management in the Middle Eastern population was formulated by regional panel of experts (Bahrain, Iran, Oman, Saudi Arabia and the United Arab Emirates together with experts from outside the region). It provides guidelines tailored for the region[2].

The International Atherosclerosis Society (IAS) and Oman Society of Lipid and Atherosclerosis (OSLA) organized a residential course - "Lipid Metabolism and Cardiovascular Risk" in Muscat, Oman, 8-10 February 2015 - that aimed to increase the knowledge and experience of early-to mid-career practicing clinicians from the MENA region interested in the management of lipid disorders. Such activities will support the development of a lipid clinic network. http://www.athero.org/meetingHighlights.asp.

1- Bamimore MA, Zaid A, Banerjee Y, et al. Familial hypercholesterolemia mutations in the Middle Eastern and North African region: a need for a national registry. J Clin Lipidol 2015;9(2):187-94.
2- Abdullah Al-Ashwal, Fahad Alnouri, Hani Sabbour, et al. Identification and treatment of patients with homozygous familial hypercholesterolaemia: information and recommendations from a Middle East advisory panel. Curr Vasc Pharmacol 2015; in press.

- **NETHERLANDS**

In the Netherlands there has been a major focus on the identification of patients with FH, ever since 1994. The Foundation for Identification of Persons with Inherited Hypercholesterolemia (in Dutch: StOEH) was a government subsidized organisation responsible for the conduct of a nationwide cascade screening program. Under the assumption that the prevalence of FH was 1:500, a total of 33,000 patients was anticipated to be present in the Netherlands, and a total of 20 years was considered to be sufficient to identify all patients with FH. The nationwide coverage was ensured by a network of specialists in cardiology, vascular medicine and endocrinology. The screening program exploited a genetic cascade testing approach and patients that were suspected to have FH were referred to the StOEH and analyzed for the presence of an LDL-Receptor or APOB mutation, and, if indicated, for PCSK9 mutations. Furthermore, a questionnaire was used to collect information on medical history and a blood sample was drawn to determine lipid profiles. At the moment the program was stopped in 2014, over 26,000 individuals were diagnosed with FH and a total of 37,000 individuals were found to be unaffected individuals. In recent years, the prevalence has been shown to be 1:250[1] and, as a consequence, not even half of all FH patients have been identified. By means of a new organization (LEEFH) continuing attempts are made to pursue the cascade screening.

1- Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. Eur Heart J 2015;36(9):560-5.

- **NORWAY**

Estimated prevalence of FH in Norway is 1/300 based on data obtained from a study in the Eastern part of Norway, corresponding to a total of approximately 17 000 FH patients in Norway. More than 6500 patients (personal communication Trond P. Leren), including 12 homozygous FH patients, have been diagnosed genetically due to great combined effort of Lipid Clinic in Oslo (founded by Leiv Ose and treating FH patients from 1984) and the Unit for Cardiac and Cardiovascular Genetics (UCCG, founded in 1991 and still run by Trond P. Leren). A new National Advisory Unit on Familial Hypercholesterolemia was established September 1st 2014 to help further increase in the awareness of FH and estabilishing a nationwide FH treatment registry (with more prospective patient- and treatment data compared to the existing genetic registry at UCCG).

1- Heiberg A, Berg K. The inheritance of hyperlipoproteinaemia with xanthomatosis. A study of 132 kindreds. Clin Genet 1976;9:203-33.

- **POLAND**

The first steps associated with the familial hypercholesterolemia (FH) issues in Poland started in June 2005 when the first national registry of FH patients was founded within Polish Ministry of Health National Program of Cardiovascular Diseases Prevention and Therapy (2003-2005)[1,2]. The registry was next continued as a National Centre for Familial Hypercholesterolemia Diagnosis and Treatment (2010-2014), which was financed within European Union grant[2]. Based on the abovementioned activities the authors of the registry (Prof. Andrzej Rynkiewicz and colleagues) were able to include a group of over 1500 subjects (mainly from the northern part of Poland), in which the disease was confirmed in 42% of FH patients with genetic testing[2]. The registry also allowed estimating a prevalence of heterozygous FH (HeFH) of 1:200-1:250, what means that in Poland we might expect to have even 200,000 heterozygous FH patients[1,3].

FH in Poland is severely underdiagnosed and undertreated[1,3]. Therefore one of the priorities of Polish Lipid Association (PoLA; founded by Prof. Maciej Banach in 2011)[4] is to create a National FH Registry led by the trained physicians in (outpatient) lipid clinics (which have not still existed in Poland). To realize this aim, in December 2013, the experts of PoLA started the series of 4 workshops on lipid disorders for the group of over 60 physicians of different specializations (from family doctors to neurologists, cardiologists and geriatrics) from different parts of Poland. The aim was to create the network of certified lipidologists working in the lipid clinics in order to enable them to take care of the most complicated dyslipidemic patients, including those with FH. In December 2014 they finished their dyslipidemia course and passed the exam, receiving PoLA certificate of "Expert in Lipidology". In the meantime the PoLA experts included within the Polish Lipid Expert Forum published the first recommendations how to manage with familial hypercholesterolemia both in children and adolescents as well as in adult patients[1,3].

In 2015 the applications for different financing institutions will be submitted in order, based on this group of experts, create the All-Polish FH Registry, which is planned to effectively continue the efforts of the authors of the first registry started 10 years ago.

1- Rynkiewicz A, Cybulska B, Banach M, et al. Management of familial heterozygous hypercholesterolemia: Position Paper of the Polish Lipid Expert Forum. J Clin Lipidol 2013;7(3):217-21.
2- Rynkiewicz A. How to increase the familial hypercholesterolemia diagnosis in Poland. Is it a time for the FH registry in Poland. Presentation at the IV Annual Congress of Polish Lipid Association, 7-8 November 2014, Warsaw, Poland.
3- Myśliwiec M, Walczak M, Małecka-Tendera E, et al. Management of familial hypercholesterolemia in children and adolescents. Position paper of the Polish Lipid Expert Forum. J Clin Lipidol 2014;8(2):173-80.
4- Banach M, Davidson M, Toth PP. Polish Lipid Association--a strong response to the problem of lipid disorders in Poland and Central and Eastern Europe. J Clin Lipidol 2012;6(2):105-7.

- **PORTUGAL**

The current prevalence of Familial Hypercholesterolaemia (FH) in Portugal is not well known due to the change in population demographics resulting from migration over the last 40 years. Based on the historical global prevalence figure of 1:500 affected individuals there could be as many as 20,000 individuals with heterozygous FH in Portugal.

FH has been diagnosed in clinical daily practice using both the Simon Broom Register criteria[1-3] and more recently the Dutch Lipid Clinic Network criteria. The number of clinically diagnosed patients is about 2,300. Unlike other European countries, a milder phenotype has been observed, especially in older women without CVD and in young adults with LDL-receptor mutation[2]. Tendon xanthomas are seen in <1%. Most homozygous FH patients receive combination therapy with statins and ezetemibe, but only a small percentage are treated using LDL apheresis[3].

The first specialized clinical services (including LDL apheresis) started in the nineties. Since then a number of different initiatives have been undertaken. For instance, the Portuguese FH Study started in 1999 at the

National Institute of Health supported by the Portuguese Cardiology Society (http://www.spc.pt/hgs/), with the aim to create awareness and establish the genetic diagnosis of FH. To date approximately 700 patients have been identified with a putative causative mutation (corresponding to 3.4% of the estimated patients) within more than 2,000 index cases and relatives studied[3]. These numbers support the view that FH remains underdiagnosed in Portugal. More recently, the Portuguese Atherosclerosis Society (http://spaterosclerose.org/) has established a nationwide clinical data network and started a national registry involving all hospitals and medical societies. Finally, the Portuguese FH Patient Association (http://fhportugal.pt) was founded in 2012 and has been actively involved in raising awareness for this condition, providing educational information and promoting screening programs. FH is currently included in some medical curriculum and specialist training programs for healthcare professionals. The Portuguese Atherosclerosis and Cardiology Societies and the National Institute of Health promote awareness among physicians by organizing lectures about FH.

1- Medeiros AM, Alves AC, Francisco V, et al. Update of the Portuguese Familial Hypercholesterolaemia Study. Atherosclerosis. 2010 Oct; 212(2):553-8.
2- Alves AC, Medeiros AM, Francisco V, et al. Molecular diagnosis of familial hypercholesterolemia: an important tool for cardiovascular risk stratification. Rev Port Cardiol. 2010 Jun; 29(6):907-21.
3- Medeiros AM, Alves AC, Bourbon M. Mutational analysis of a cohort with clinical diagnosis of familial hypercholesterolemia: considerations for genetic diagnosis improvement. Genet Med 2015 May 28.

- **SOUTH AFRICA**

In South Africa probably due to a founder effect, the prevalence of heterozygous FH (HeFH) in the Afrikaner, Jewish and Indian sub-populations is as high as 1:80[1,2] and that of homozygous FH (HoFH) is as high as 1:30 000[3] However the prevalence of FH amongst the Black population, not only in South Africa, but in the whole of the African continent remains unknown. Over 80% of subjects with clinical heterozygous FH in South Africa will have one of 5 founder mutations[2]. Evaluating genotype-phenotype interactions within founder populations with only a small number of mutations like South Africa may be of benefit in identifying risk factors for premature atherosclerosis and assessing the benefits of lipid-lowering therapy[5]. However, despite the high prevalence of FH in South Africa, there is no FH registry, no cascade screening programme, no FH patient organisation, and, probably because of other priorities such as the pandemic of HIV infection and tuberculosis, little support or involvement from Government sources. As a result FH remains undiagnosed and untreated in the vast majority.

1- Steyn K, Goldberg YP, Kotze MJ, et al. Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. Hum Genet 1996;98:479-84.
2- Rubinsztein DC, van der Westhuyzen DR, Coetzee GA. Monogenic primary hypercholesterolaemia in South Africa. S Afr Med J 1994;84:339-344.
3- Seftel HC, Baker SG, Sandler MP, et al. A host of hypercholesterolaemic homozygotes in South Africa. Br Med J 1980;281:633-6.
4- Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation 2011;124:2202-7.

- **SPAIN**

It is estimated that over 100,000 people have FH in Spain. Since chronic lipid lowering treatment became available at no cost to patients in 2004, awareness of the condition has increased and diagnosis has received an impetus. More than 20,000 individuals are diagnosed with FH, accounting for approximately 20% of the estimated population. Of these, more than 60% were diagnosed with clinical criteria[1]. In recent years, some autonomous regions have implemented different strategies for detection of FH, including genetic diagnosis. This has led to genetic identification of more than 7000 people with FH. However, there is no homogeneous

program and cascade screening is very limited. Castile and Leon is the only region in which the screening strategy involves general practices (GP). This region, in collaboration with the FH Foundation (FHF), a Family Support Group founded in 1997 (http://www.colesterolfamiliar.org), implemented the FH Screening Program, which includes training for physicians. To date, almost 1000 patients have been diagnosed by genetic study[1]. An FH Detection Program in Spain involving GPs and specialists is due for approval at the end of 2015.

From 2004, the FHF runs the Spanish Familial Hypercholesterolemia Cohort (SAFEHEART). This prospective registry provides a way to raise awareness, improve patient outcomes and set up a model for cascade screening[2-4]. To date, 4151 cases from 761 families have been recruited. Around 3000 individuals in this study have a positive genetic test. National guidelines have been published[5] to improve the detection and treatment of FH.

1- Mata P, Alonso R, Perez-Jimenez F. Screening for Familial Hypercholesterolemia: a Model for Preventive Medicine. Rev Esp Cardiol 2014;67:685-8.
2- Mata N, Alonso R, Badimón L, et al. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). Lipids Health Dis 2011;10(94).
3- Alonso R, Mata N, Badimon L, Perez-Jimenez F, Mata P. Prognostic factors of cardiovascular disease mortality and morbidity in a cohort of families with genetic diagnosis of familial hypercholesterolemia. Nature Rev Cardiol 2009;6:23-7.
4- http://safeheart.colesterolfamiliar.org/
5- Mata P, Alonso R, Ruiz A, et al. Diagnosis and treatment of Familial Hipercholesterolemia in Spain: consensus document. Aten Primaria 2015;47:56-65.

▪ SWEDEN

The prevalence of heterozygous FH in Sweden has not been firmly established, but is estimated to be approximately the same as in the neighbour country of Denmark, i.e. 1/200[1]. For many years, case finding and cascade screening programmes have been very limited and confined to a few university hospitals of the larger cities. In 2008, the patient organization FH-Sweden (http://www.fhsverige.se) was founded and together with a network of FH doctors a strategy programme was drawn up on how to improve diagnosis and treatment of FH on a national level. A national quality registry for FH was founded in 2013 (http://www.kardiogenetik.se) and is now part of the SWEDEHEART registries. In 2015, national guidelines for cardiac care included FH for the first time[2]. The guidelines strongly recommend health care organisations to identify children and adults with severe hypercholesterolemia and to provide proper FH diagnostics (including genetic analysis), followed by cascade screening once a case of FH has been identified. The number of hospitals offering FH care is slowly but steadily increasing. Despite these efforts and signs of progress, to date only some 4 per cent or 1800 individuals have been formally diagnosed with FH in Sweden.

1- Benn M, Watts GF, Tybjaerg-Hansen A, et al. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012;97(11):3956-64.
2- National Board of Health and Welfare. National guidelines for cardiac care 2015. http://www.socialstyrelsen.se/riktlinjer/nationellariktlinjer/nationella-riktlinjer-hjartsjukvard

▪ TAIWAN

The nation-wide Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia in 2002 revealed that phenotypic familial hypercholesterolemia (FH), defined as cholesterol level at or above 290 mg/dL and low-density lipoprotein cholesterol level at or above 190 mg/dL, accounted for 0.82% (male: 0.88%, and female: 0.76%) of 6,596 ≥15 years-old age population in Taiwan[1]. Genetic diagnosis of FH was only available among a limited number of patients participating in clinical studies. The high prevalence of phenotypic FH, even higher than in previous reports, indicates the urgent need of public health action and the development of strategies for prevention and management of hypercholesterolemia-related cardiovascular diseases (CVDs).

The critical challenges facing current status in Taiwan include the lack of government support and of any foundation or organization for FH patients and their families. In addition, the National Health Insurance Administration set up unreasonable criteria to limit the use of lipid-lowering therapy, thus many patients being unable to receive adequate treatment, particularly those with high-risk CVDs and FH[2].

1- Su TC. Familial hypercholesterolemia in Taiwan. FH Patient Advocacy Group Representatives Meeting, 21-22 March 2015, Glasgow, UK. Satellite Symposium of the 83th European Atherosclerosis Society Congress.
2- Treatment guideline for hyperlipidemia, August 1, 2013, modified by National Health Insurance Administration, Department of Health and Welfare, Taiwan. http://www.nhi.gov.tw/resource/bulletin/4616

▪ TURKEY

Turkey is a developing Eurasian country located in the Eastern-Mediterranean region with 84 million inhabitants. Turkey is among the countries with the highest cardiovascular mortality in Europe[1]. Due to founder effect and high prevalence of consanguinity (23%), prevalence of inherited diseases is extremely high. The prevalence of Familial hypercholesterolemia (FH) is estimated to be 1:200-300[2,3]. EUROASPIRE-IV suggested 8.9% prevalence of potential FH in coronary patients in Turkey[4]. Lipid lowering drugs and apheresis are reimbursed by social insurance of the government. The main problem is the lack of awareness of FH[5]. Therefore, there is no FH registry, no family screening programme, and no FH patient organisation in Turkey. There is only one Lipid Clinic[5] with a constructed FH programme including genetics, family screening, and family support.

Turkish National FH program is in development under the leadership of Turkish Society of Cardiology (TSC). The primary objectives of this initiative are to raise the awareness, address the burden of FH and implement a uniform standard of care. Web-based educational materials are prepared for public and physicians. Educational meetings are also planned with health authorities and policy makers. A National Registry for FH, coordinated by the TSC is getting started. Centres admitting this registry will be educated to become Lipid clinics. A registry for homozygous FH (A-HIT) has also been started in 28 apheresis centres and estimated to reach approximately 150 patients with homozygous FH undergoing regular apheresis. An FH patient organisation is also underway. We hope that in the next 5 years, the increasing awareness will promote early diagnosis and effective treatment of FH and decrease the premature cardiovascular deaths in Turkey.

1- http://www.escardio.org/The-ESC/Communities/European-Association-for-Cardiovascular-Prevention-&-Rehabilitation-(EACPR)/Prevention-in-your-country/Country-of-the-Month-Turkey
2- Kayikcioglu M. Homozygous familial hypercholesterolemia. Turk Kardiyol Dern Ars 2014;42 Suppl 2:47-55.
3- Kayikçioğlu M. Familial hypercholesterolemia. Turk Kardiyol Dern Ars 2014;42 Suppl 2:vii.
4- De Backer G, Besseling J, Chapman J, et al; EUROASPIRE Investigators. Prevalence and management of familial hypercholesterolaemia in coronary patients: An analysis of EUROASPIRE IV, a study of the European Society of Cardiology. Atherosclerosis 2015;241:169-75.
5- Kayıkçıoğlu M, Kısmalı E, Can L, Payzin S. Long-term follow-up in patients with homozygous familial hypercholesterolemia; 13-year experience of a university hospital lipid clinic. Turk Kardiyol Dern Ars 2014;42:599-611.

▪ UNITED KINGDOM

The estimated frequency of heterozygoous familial hypercholesterolaemia (HeFH) in the UK is 1 in 500[1], suggesting some 120,000 of its population are affected. The Simon Broome register was established in 1980 from a charitable endowment provided by the widow of a man with hyperlipidaemia who had died due to lack of medical knowledge. Patients with HeFH were recruited to the Register from UK clinicians attuned to its recognition. It has been maintained in Oxford initially by Professor Jim Mann and subsequently by Professor Andrew Neil, 3653 with HeFH and 340 with severe hypertriglyceridaemia are registered to date and the group

published many papers contributing significantly to our understanding of the natural history of HeFH and the value of therapeutic intervention. For example, the committee reported a reduction in all-cause, cancer, and coronary mortality in statin-treated patients with HeFH in 2008[3]. Simon Broom's diagnostic criteria for HeFH was adopted by the National Institute Care and Health Excellence (NICE) (NICE clinical guideline 71, published 2008)[4].

Grant support for the register has come from the British Heart Foundation and in recent years it has come under the aegis of the Hyperlipidaemia Education and Research Trust UK (HEART UK) as the Simon Broome Register subcommittee. HEART UK represents both patients and healthcare professionals with hyperlipidaemia. To support the implementation of the NICE FH guidelines to ensure that people at risk and all of their family members are identified and appropriately treated HEART UK formed the FH implementation team producing documents, toolkits and advice (http://heartuk.org.uk/).

FH care in UK remains unsatisfactory with no UK national diagnostic register yet with only some 15-20 per cent having been formally diagnosed[5]. This is despite Simon Broome committee's and HEART UK's efforts, NICE clinical guideline 71[4], British Heart Foundations (BHF) support and grants and also the fact that it is now more than 14 years work from Manchester first showed a strong case for organising a genetic register approach and family cascade testing linking lipid clinics nationally[6]. Adoption of NICE guideline 71 varies between different parts of the UK. Wales, Scotland and Northern Ireland have launched a genetic diagnostic service for FH combined with family cascade testing. However, issues associated with the local commissioning structure have hampered the development of a nationally coordinated and integrated FH services and access to genetic testing in England generally, despite some regional successes.

1- Durrington P. Hyperlipidaemia Diagnosis and Management. 3rd ed. London: Hodder Arnold; 2007.
2- Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolaemia: a HuGE Prevalence Review. Am J Epidemiol 2004;160:407-420.
3- Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008;29:2625-2633.
4- National Institute for Health and Clinical Excellence. Clinical guidelines and evidence review for familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia. 2008. (Clinical guidelines 71) www.nice.org.uk/CG71.
5- http://heartuk.org.uk/files/uploads/documents/HUK_SavingLivesSavingFamilies_FHreport_Feb2012.pdf
6- Bhatnagar D, Morgan J, Siddiq S, et al. Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia. BMJ 2000; 321: 1497–1500.

▪ URUGUAY

GENYCO (from "Genes y Colesterol" in Spanish) is the National Programme for Early Detection and Treatment of Familial Hypercholesterolemia (FH) in Uruguay. The programme was supported and developed by the Uruguayan Commission for Cardiovascular Health (www.cardiosalud.org) and is intended to reverse the situation of insufficient diagnosis and inadequate treatment of FH patients in Uruguay. The programme was created in November 22, 2012 (**Law 18,996, item 12, art. 207**) followed by a **Regulatory Decree (357/013)** approved by the Ministry of Health in November 2013. It is a centralized national registry providing access to genetic testing, cascade screening and coordination of the caring process for patients with FH and their affected relatives. Based on an estimated prevalence for heterozygous FH of 1/400 to 1/500 affected individuals, there could be 6,000 to 8,000 carriers within a population of 3.3 million individuals; the programme represents an opportunity to identify 80% of FH patients in the next 8 years.

All medical institutions (public and private, primary prevention and specialties) are intended to be gradually included in the programme during the first five years, in order to progressively expand its benefits to the whole country. Each institution is responsible for the identification of FH patients by using the MEDPED criteria (facilitated through distribution of a specific software). The clinical information and a saliva sample are sent to

the GENYCO Coordinating Unit for cascade screening and molecular diagnosis when indicated. The programme has identified more than 146 index cases so far. Molecular tests were already performed in 55 family groups, and a total of 113 heterozygous carriers of LDLR mutations, 3 homozygous for a promoter mutation and 4 carries of ApoB 3527 have been identified, including 26 different mutations in the LDLR.

The Spanish FH strategy and guidelines were incorporated to conduct the diagnosis and treatment of FH patients and have inspired the development of the Uruguayan programme. In 2013 the programme organized the first meeting of the Ibero-American FH Network at Montevideo, Uruguay, with the participation of Prof. P. Mata from Spain and delegates from Argentina, Brazil, Chile, Mexico and Uruguay.

1- Stoll Mario et al. Previniendo el infarto en el adulto joven: GENYCO, un registro nacional de hipercolesterolemia familiar. Rev Urug Cardiol 2011;26:16-26.

2- Esperón P, Raggio V, Stoll M. Una nueva mutación en el promotor del gen del receptor de las lipoproteínas de baja densidad asociada a hipercolesterolemia familiar en homocigosis y heterocigosis. Clínica e Investigación en Arteriosclerosis 2009;21:51-55.

3- Stoll M, et al. Mutación en el gen de apolipoproteína B responsable de hipercolesterolemia familiar: primeros dos casos clínicos reportados en Uruguay. Rev Urug Cardiol 2013;28: 182-188.

Supplementary Material 2

The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)

http://www.eas-society.org/?page=fhsc

TheEuropean Atherosclerosis Society (EAS) Familial Hypercholesterolaemia Studies Collaboration (FHSC) is a global initiative that aims to empower the medical and global community to seek changes in their respective countries or organizations regarding FH detection and management and to promote early diagnosis and effective treatment. Through international collaboration of stakeholders the FHSC aims to generate large-scale robust data on how FH is detected and managed, their clinical implications, and to disseminate this information to sensitising about the contemporary burden of FH, encouraging discussion on its management, promoting a uniform, evidence-based standard of care, encouraging physicians to contribute to research and promoting interaction with patient's organizations. The objective of the FHSC is to establish an international registry of observational studies on Familial Hypercholesterolaemia(FH) with a view to better quantifying more reliably than hitherto possible:

- The contemporary burden of both homozygous FH and heterozygous FH globally.
- How patients with FH are being managed.
- What treatments FH patients are being offered/advised and how their efficacy is being monitored including what proportion of FH patients meet targets.
- The impediments in attaining LDL-cholesterol targets (including patient, physician, healthcare, and societal factors, acting either singly or in consort).
- The cross-sectional burden and long-term risk of cardiovascular disease (CVD) in FH, and whether survival has changed over time with evolving treatments (including, where possible, estimates of the years of life lost due to FH).
- The impact of patient-specific factors (e.g. family history of CVD, diet, lifestyle, ethnicity, comorbid medical conditions like hypertension or diabetes, etc.), socio-economic factors, and

treatment-related factors (especially awareness of LDL-C targets by treating physicians, knowledge-attitudes- and-practices [KAPs] with regard to using lifelong medical therapy for an otherwise asymptomatic condition, side-effects to medication and treatment compliance) on LDL-C goal attainment and/or CVD risk.

- The role played by societal factors (such as access to healthcare and availability of specialist advice) in enabling treatment to target LDL-C goal.
- The influence of gene-drug interactions in attaining LDL-C targets.
- Whether current screening strategies for FH are adequate and, if not, what could be done differently (especially local solutions to a global problem) to maximise coverage.
- To develop a global infrastructure through which collaborative research on FH can be conducted.
- To develop a secure web-based portal for prospective data collation and sharing for use by patients and the medical community.
- To create of a set of indicators of performance and effectiveness of the quality of care of FH.

A consortium of major FH registries worldwide is being established and a number of national leaders in the field have already agreed to contribute to this project (suppl. material 3). The FHSC collaboration joins efforts from different regions around the world to establish a solid FH network that allows to more efficiently face the FH burden and further support national and regional initiatives and patients and professionals organizations. Once the registry is established and results available, a more reliable understanding of the FH situation around the world and the real needs will be accessible. Consequently, it is foreseeable that this will help support further educational activities and awareness, promote FH programmes, implement uniform standard of cares, drive research projects and funding application (e.g. EU Horizon 2020), and establish new actions such as e-Health tools development for FH (web platforms, mobile and web app's, artificial networks…), among other opportunities. The global scope of the FHSC initiative might ultimately allow to work in partnership with WHO to develop common strategic actions on FH.

Supplementary Material 3

Regions/countries and respective National Lead Investigators currently involved in the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) initiative (at the time of the present article submission)

Region	National Lead Investigator
▪ Argentina	Dr. P. Corral
▪ Australia	Prof. G.F. Watts
▪ Austria	Prof. H. Dieplinger
▪ Belgium	Prof. O. Descamps
▪ Brazil	Prof. R.D. Santos
▪ Canada	Prof. J. Genest
▪ Czech Republic	Dr. T. Freiberger
▪ Chile	Dr. R. Alonso
▪ China	Dr. L. Jiang
▪ Denmark	Prof. B.G. Nordestgaard
▪ Finland	Dr. E. Widén
▪ France	Prof. E. Bruckert
▪ Germany	Prof. U. Laufs, Prof. H. Schunkert
▪ Greece	Dr. E. Liberopoulos
▪ Iran	Dr. A. Sahebkar
▪ Israel	Dr. R. Durst
▪ Italy	Prof. A. Catapano
▪ Japan	Prof. M. Harada-Shiba
▪ Latvia	Assoc. Prof. G. Latkovskis
▪ Lebanon	Prof. M. AbiFadel
▪ Mexico	Dr. C.A. Aguilar-Salinas
▪ Netherlands	Prof. G.K. Hovingh
▪ Norway	Dr. M.P. Bogsrud
▪ Oman	Prof. K. Al Rasadi
▪ Poland	Prof. M. Banach
▪ Portugal	Prof. M. Bourbon, Dr. I. Mendes Gaspar
▪ Russia	Prof. A. Susekov
▪ Saudi Arabia	Dr. F. Alnouri
▪ Singapore	Prof. C. Lam
▪ South Africa	Prof. F.J. Raal
▪ Spain	Prof. P. Mata
▪ Sweden	Prof. L. Nilsson
▪ Taiwan	Dr. T.C. Su
▪ Turkey	Prof. M. Kayikcioglu
▪ United Arab Emirates	Prof. A. Shehab
▪ United Kingdom	Dr. H. Soran
▪ Uruguay	Dr. M. Stoll
▪ Partnership with “The 10 Countries Study”, lead: Prof. G.F. Watts. Australia (G. Watts), Brazil (R.D. Santos), China-Beijing (J. Lin), China-Hong Kong (B. Tomlinson), Japan (S. Yamashita), Malaysia (H.M. Nawawi), New Zealand (P. George), Philippines (L. Santos), South Africa (D. Marais), South Korea (J.E. Park), Taiwan (P. Ding), Vietnam (T.H. Truong)	
▪ Partnership with "ScreenPro FH Project", lead: Prof. R. Ceska. Bosnia and Herzegovina (B. Pojskic), Bulgaria (A. Goudev), Croatia (Z. Reiner), Czech Republic (T. Freiberger), Greece (A. Tselepis), Hungary (G. Paragh), Kyrgyzstan (T. M. Murataliev, E. M. Mirrakhimov), Latvia (G. Latkovskis), Lithuania (Z. Petrulioniene), Poland (A. Rynkiewicz), Romania (D. Gaita, A. Dan), Russia (A. V. Susekov, M. V. Ezhov), Serbia (D. Djuric, N. Tasic), Slovakia (K. Raslova, B. Vohnout), Slovenia (Z. Fras), Turkey (L. Tokgozoglu, M. Kayikcioglu), Ukraine (E. Mitchenko)	

Supplementary Material 4

Summary of the Familial Hypercholesterolaemia Patient Advocacy Group Meeting

March 2015, Glasgow, UK

The first of an intended series of "FH Patient Advocacy Group" Meetings was organized by the Familial Hypercholesterolaemia Studies Collaboration (FHSC) in conjunction with the European Atherosclerosis Society (EAS) in March 2015 in the context of the 83rd EAS Congress held in Glasgow, UK. About 60 participants from 32 countries from Europe, South and North America, Asia, Pacific region and Africa attended the meeting, including clinicians and patients' organizations representatives, with the common aim of looking to learn from each other and ultimately discuss how to face the burden of FH by partnership. After some initial presentations to learn about the situation of FH and organizations in some countries around the world (presentations are available at http://www.eas-society.org/?page=fhsc_events) an extended discussion was carried out among all participants covering different topics such as successes and failures in eliciting changes around FH, sharing experiences and knowledge among organizations and countries, impediments to optimum management of FH, raising public and clinician (primary care in particular) awareness of the contemporary burden of FH and the consequences of its underdiagnosis and undertreatment, or how to promote a uniform evidence-based standard of care.

Whilst concerns about FH as an underdiagnosed and undertreated disease were widely acknowledged, the patient organizations were seen as effective tools to increase FH awareness, support patients, promote education and potentially influence public health policies. The contacts and sharing experiences among organizations from different regions and countries may support each other in driving their common objectives and help new starting organizations to consolidate and expand. However, the lack of funding and institutional and professional support, among others, are problems that the patients' organizations still have to face.

Increasing awareness among general population, patients, healthcare providers and policy makers was highlighted as a key action to be encouraged. The lack of awareness ultimately may lead to a lack of funding, early diagnosis and effective treatment. Different actions, such as social campaigns, production of fact sheets, newsletters, dissemination through social media, websites, patients' forums, etc. could be useful to make people aware of the burden of FH; the messages sent must be clear and simple, may emphasize the impact on outcomes and might target certain specific groups in first instance. Similarly, education was considered to play a major role to favour the correct identification and appropriate management of FH. Some actions, such as the inclusion of FH in the medical curriculum and specialization programs or activities from professional bodies for their members, were suggested. A special attention for both, raising awareness and education, should be paid in primary care providers. The inclusion of a note with the laboratory results when LDL-C is high above certain limits suggesting the consideration of FH could facilitate the identification of FH patients and referral for specialist care; in the same way, specialists should support general physicians in the management of FH patients.

Other aspects that were raised during the discussion included the general lack of FH strategies, regulations, timeframe and budgets from governments and policy makers; concerns about the availability and accessibility to treatments, especially new therapies; lack of financial support for patients to take these chronic medications (e.g. reduced prices); inequalities of treatment among different countries; the need for a real and effective contact and collaboration among patients, nurses and clinicians and therefore an integrated model of patient care. As an inherited disease, genetic testing may increase awareness and patients' compliance with therapy and allow family counselling; however, as a mutation is not always found or its causality might not be clear, where this case happens it must be well explained to the patient and relatives.

The development of networks among different regions including patients and professional organizations, allowing sharing of information and joint strategies may help to face the current burden of FH and promote prevention.