

EAS FHSC NEWSLETTER

Issue 03, August 2017

Issue 03

In this Issue:

From the
Coordinating Centre

EAS FHSC Steering
Committee Meeting

From EAS FHSC
Investigators

- Italy
- Saudi Arabia
- Egypt
- China

FHSC at EAS Congress
2017 in Prague

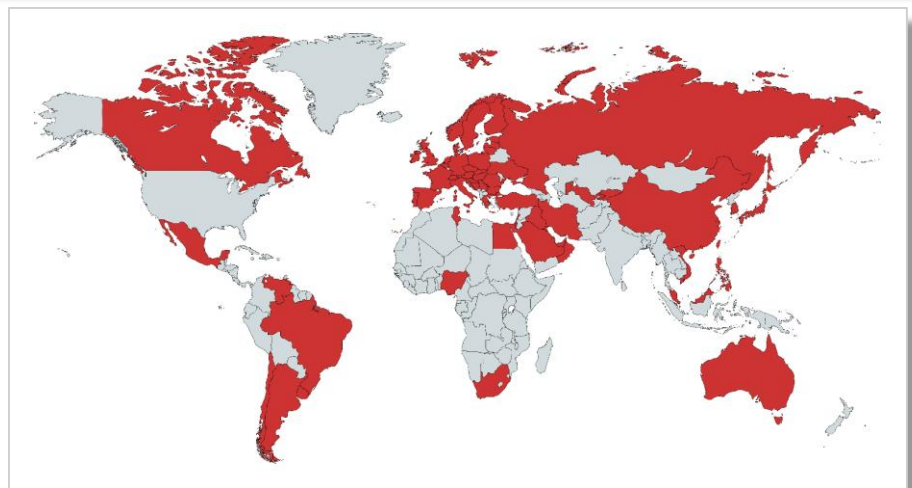
- From the
Advanced Clinical
Seminar on FH –
Practice
Essentials
- FHSC booth at
EAS Congress

Next Events

- FH-awareness
week Sept. 2017

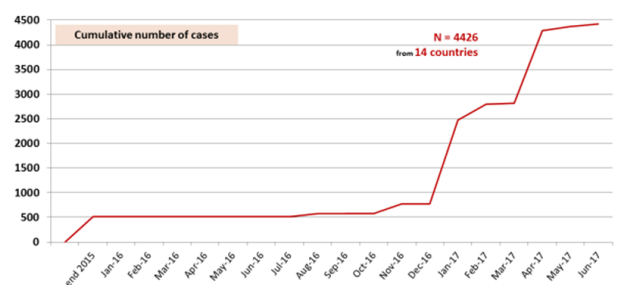
Publications

From the FHSC Coordinating Centre



The EAS FHSC collaboration keeps growing and we are currently 77 lead investigators from 66 countries. We have received data sets from 14 countries so far, including a total of over 4400 cases. A data dictionary with an update of the variables of interest will be released soon, once it has been reviewed by the FHSC Executive Committee.

FHSC Registry – Data



We keep developing the FHSC platform for the registry. The FHSC web is ready and will be made available soon. The School of Public Health at Imperial College London has recently created a new securer environment and we have been asked to move the system there, what has delayed the release of the web.

EAS FHSC Meeting April 2017 (Prague)

EAS FH Studies Collaboration National Lead Investigators meeting

Wednesday, April 26, 2017

Corinthia Towers Hotel – Bellevue Room, 24th floor

Last EAS FHSC Steering Committee meeting took place after the EAS Congress in Prague, Czech Republic, on April 26th, 2017. The meeting brought together over 70 lead investigators involved in the EAS FHSC collaboration. It served as a forum on the matters of the FHSC project and on initiatives carried out by different investigators around Familial Hypercholesterolaemia (FH) in their respective countries/regions. It also represented a good chance for networking with peers similarly interested in FH. The meeting was very successful and we have received positive feedback.

We would like to thank all the investigators who attended the meeting for their involvement and participation, comments and discussions, what definitely led to the meeting success. We would also like to thank the EAS and all those involved in the organisation of this event for their effort for the successful development of the meeting.

Next FHSC meeting is expected to be held just after the next EAS Congress in May 2018 (Tuesday the 8th, from noon) in Lisbon, Portugal. We would welcome any comments and suggestions for the next FHSC meeting.



Italy

CHARACTERIZATION OF ITALIAN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA: THE LIPIGEN STUDY

By M. Casula, on behalf of the LIPIGEN Group. Familial hypercholesterolemia (FH) is a genetic disorder that implies exposure to high levels of LDL-cholesterol (LDL-C) from birth, with accelerated atherosclerosis and premature coronary events. Although tools are available for clinical and genetic diagnosis, and the use of lipid-lowering drugs have demonstrated a beneficial effect in FH patients, especially for early therapy, evidence from literature showed that FH is underdiagnosed and undertreated. LIPIGEN (Lipid TransPort Disorders Italian GEnetic Network) study aimed to create a national database of FH patients, to deeply investigate the phenotypic and genetic characteristics of affected patients, and to help raise awareness about FH, both among health professionals and among patients.

LIPIGEN study collects anamnestic, biochemical, and genetic data of a population of FH subjects followed by a lipid clinic network throughout Italy (figure). The centres of the network work in concert, following shared protocols according to the recommendations of major scientific societies, such as the European Atherosclerosis Society. The approach to the patient includes a personal and family medical history of hypercholesterolemia and cardiovascular and cerebrovascular events, a clinic visit for the detections of pathognomonic signs (including xanthomas and arcus cornealis), and the measurement of lipid levels. These data allow the application of the Dutch score Lipid Clinic Network (DCLN) for the clinical diagnosis of FH. If DCLN score is ≥ 6 (probable or definite diagnosis) the genetic analysis is recommended.

An analysis of patients with information for clinical diagnosis according to the Dutch score and results from the genetic analyses (searching for mutations in the candidate genes coding for Low Density Lipoprotein receptor [LDLR], apolipoprotein b [APOB], Proprotein Convertase Subtilisin/Kexin Type 9 [PSCK9], and Low Density Lipoprotein Receptor Adaptor Protein 1 [LDLRAP1]), showed that 25.3% of FH patients were diagnosed within 18 years (mean \pm SD 33.8 \pm 19.1 years at diagnosis). The mean LDL-C levels without lipid-lowering treatment were 257.9 \pm 96.3 mg/dL (median 261.0 mg/dL). Overall, 70.7% of FH patients had DCLN score ≥ 6 . Genetic analysis was performed in almost the entire sample (97.8%). In subjects with score ≥ 6 , mutations were detected in 84% of FH subjects. More than 98% of subjects with genetic diagnosis showed mutations of LDL receptor (LDLR) gene; among them, 49 (1.7%) were homozygotes, 46 (1.6%) compound heterozygotes and 28 (1.0%) double heterozygotes. The average LDL-C levels in these groups were 623.7 \pm 231.0, 499.0 \pm 254.4 and 298.9 \pm 98.1 mg/dL respectively, while mean levels in heterozygotes (N 2720; 95.7%) were 274.5 \pm 70.9 mg/dL.



If you are interested in contributing to the next issues of the EAS FHSC Newsletters with any text, publications, events, etc. please contact us on:

info@eas-fhsc.org

coordinator@eas-fhsc.org

Saudi Arabia

By Dr. F. Alnouri. FH is the commonest autosomal co-dominantly inherited condition affecting man. It is underdiagnosed and undertreated in the general population [Nordestgaard BG et al, *Eur Heart J* 2013]. It is a common genetic cause of premature coronary heart disease (i.e. ischaemic heart disease), namely myocardial infarction and angina pectoris, due to lifelong elevated plasma LDL cholesterol levels [Goldstein JK et al, 2001 *New York McGraw-Hill*; Austin MA et al, *Am J Epidemiol* 2004].

Cardiovascular disease is the most common cause of death in the Kingdom of Saudi Arabia, accounting for up to 46% of total deaths [WHO *Non-communicable Disease country Profile, 2014*]. The prevalence of FH in the Arabian Gulf Countries (Bahrain, Kuwait, Oman, Saudi Arabia, Qatar and the United Arab Emirates) is unknown due to lack of national registries and genetic screening for FH [Bamimore MA, et al *J Clin Lipidol* 2015; Al-Ashwal A, et al *Curr Vasc Pharmacol* 2015; Vallejo-Vaz AJ et al, *Atherosclerosis* 2015], but is expected to be higher than that of the rest of the world due to high consanguinity, which for example is estimated to be 57.7% in Saudi Arabia [El-Hazmi MA et al, *J Med Gent* 1995].

A FH registry was started in the Arabian Gulf countries in 2016. I have established the Cardiovascular Prevention and Rehabilitation Unit in Prince Sultan Cardiac Centre in Riyadh in 2010. One of this unit's responsibilities is to diagnose and treat patients with Monogenic FH. We have, so far, diagnosed 34 families using Next Generation Sequencing test (NGS). Of those families, 10 patients were found to be Homozygous and 78 are Heterozygous. Three Homozygous patients are treated with Plasma Exchange method twice per month.

We recently purchased an LDL apheresis machine, which will replace the plasma exchange. This machine will help us to expand our service to the rest of the homozygous patients. The Heterozygous patients are treated with Statin and Ezetimibe and those who are not reaching the desired lipids targets are started on PCSK9 drug. We also provide counselling for patients affected by this disease and their families and I published a booklet in Arabic to help in this matter.



Egypt

By Prof. Ashraf Reda, President of the Egyptian Association of vascular biology and Atherosclerosis (EAVA). The problem of FH is underestimated in Egypt as well as in many other countries around the world. We have recently joined the FHSC of the European Atherosclerosis Society.

EAVA has recently announced the foundation of FHRF in Egypt (FH research forum). The main objective of the forum, in addition to CME activities and public awareness program, is to run a cross sectional observational registry and on-line data base system (www.cardio-risk.org) recruiting cases from more than 35 investigators across the country. Inclusion criteria include cases with definite and probable FH and patients with premature atherosclerosis. Data recruitment and case submission is going on and results will be shared with FHSC of EAS. The recently published phase II results of the Egyptian Cardiorisk project showed that premature atherosclerosis represents 42% of Egyptian patients with ACS highlighting the need to address the prevalence of FH among this group.



China

By Prof. Jie Lin, MD, PhD. Beijing Institute of Heart, Lung & Blood Vessel Diseases; Beijing Anzhen Hospital, Capital Medical University.

FH patients group management: We have been practicing index patient diagnosis and cascade screening in clinic. We worked collaboratively with imaging department to follow up on progress of atherosclerosis. The longest follow-up has been over 15 years. Patients management (both HoFH and HeFH) before and after CV events is our major task. We set up suspected cases database as well. The data collected includes physical examination, personal and family medical history, lipid levels, treatment, cardiovascular outcomes and genetic diagnosis if applicable.

FH Survey for doctors and patients: As a member of the "Ten Countries Study", we offered formal questionnaires about knowledge and practices for Chinese doctors of different professional background, including cardiologist, endocrinologist, etc. During the survey, we found the shortfall in awareness and knowledge of doctors. We also offered questionnaires for FH patients and the preliminary results showed poor understanding of the disease. Then we did patient education in clinic to emphasize the importance of lifestyle intervention and long-term therapy, and enhance their confidence and coherence to treatment.

Phase IV clinical trial of combination therapy for FH patients: 17 hospitals from 14 provinces of China participated in a Phase 4 clinical trial of combination therapy for severe hypercholesterolemia patients including about 200 FH. The start meeting began in 2013 and the trial will be finished in March, 2017. During the trial we set up a FH patient database and built a study cohort.

Asian-Pacific Society of Atherosclerosis and Vascular Disease (APSAVD) FH Exchange Program and co-authored publication: A research fellow had a short-term exchange from Jan 2017-July 2017 in Perth, Australia. This program enhanced the collaboration of FH management in China and Australia, such as FH registry, genetic testing and novel therapy. Two co-authored abstracts were poster presentation in 85th EAS Congress (2017), titled "Reverse Cascade Screening for FH in Very High Risk Families in China" and "Cascade Screening, Clinical Features and Genetic Aspects – FH Study in China". Two co-authored abstracts will be poster presentation in 65th Annual Scientific Meeting (2017) of the Cardiac Society of Australia & New Zealand (CSANZ), titled "Homozygous FH in children and adolescents from China: clinical features and disease progression" and "Knowledge and practice gaps in the care of FH in Australia compared with China".

Guidelines of Adult Dyslipidemia in China mentioned FH patients intervention: In 2016, Chinese National Guidelines on the Prevention and Treatment of Adult Dyslipidemia particularly published the management of FH patients due to the recently results. Firstly, patients need strict lifestyle intervention and to prevent other risk factors such as hypertension and diabetes. Secondly, long-term statin treatment for FH patients should start at their teenagers to reduce the risk of ASCVD. The goal of lipid lowering treatment is LDL-C <2.6 mmol/L. To achieve the goal, combination therapy and LDL apheresis may be considered.

Epidemiological study of FH: In a community population in 2015 showed the prevalence of probable/definite FH was 0.28% in China by using modified DLCN definition, including the results of our group. The high prevalence suggested that FH is relatively common and remains under-detected in China.

Publications: Under the international collaboration with G.F. Watts(Australia), there has been a publication "Translational research for improving the care of FH: The "Ten Countries Study" and beyond". Furthermore, by joining the study of EAS FHSC, there has been a publication " Pooling and expanding registries of FH to assess gaps in care and improve disease management and outcomes: Rationale and design of the global EAS FHSC".

In conclusion, FH in China is an underdiagnosed and undertreated disease. To practise index cases finding and cascade screening, education for both doctors and patients were urgent needs. We will set up a patient group to deliver more FH education in the future and will participate in more international collaboration.

From the Advanced Clinical Seminar on FH – Practice Essentials

In this session, Professor Kausik Ray (Imperial College, UK), lead of the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) provided an update on the status of this important initiative. Publication of the Call to Action paper in 2015 highlighted the need for urgent global action to improve FH care. The FHSC has now published the rationale and methods of this collaboration, which is available free to download <https://www.ncbi.nlm.nih.gov/pubmed/27939304>. 74 lead investigators from 62 different regions, covering every continent, had agreed to take part in this initiative, with data received so far from more than 4000 patients from 10 countries. The ultimate aim of the EAS FHSC is to drive policy change to improve FH care.

As part of the EAS FH Studies Collaboration, the Homozygous FH (HoFH) International Clinical Collaboration (HICC) registry has been launched to collect data specific to this very rare condition. The key aims are to investigate the prevalence, clinical consequences and treatment of HoFH. One of the lead Co-ordinators, Dr G. Kees Hovingh (Academic Medical Center, Amsterdam, The Netherlands) provided an update on the status of the HICC registry at EAS Congress Prague. Currently, HICC has received data from nearly 200 of the planned 500-600 HoFH patients, and it is anticipated that data from the first 300 patients will be presented next year. During the discussion session, questions were raised whether the data was sufficiently detailed to investigate key regional issues. For example, the frequency of HoFH may be higher where there is both a higher prevalence of heterozygous FH, and consanguinity is common as in some countries in the Middle East.

Professor Steve Humphries (Institute of Cardiovascular Science, University College London, UK) presented the results of a recently published UK modelling analysis which confirmed that cascade testing for FH was highly cost effective in the NHS setting in England and Wales. The estimated incremental cost effectiveness ratio (ICER) was £5,806 (substantially below the threshold of £20,000 used in the UK). More than 80% of lifetime costs were diagnosis-related and incurred in the first year. Based on estimates of an average reduction of 44% in coronary heart disease mortality, and 60% reduction in MI, for every 1,000 relatives tested, over 30 years, 64 MIs, 57 cases of angina, 15 strokes and 23 deaths would be averted, at a cost saving of £2.8 million. The analysis also highlighted the importance of diagnosing at a young age because of the greater impact on events and associated complications avoided. However, Prof. Humphries did note that there was a low rate of relatives tested per mutation-positive index case (1.33). Given that this is a key driver of the cost of testing, if this rate was increased to 3.2 (as predicted based on the UK National Institute for Health and Care Excellence in 2008), the ICER would reduce to £2280.

Finally, there were data from the Slovenia universal hypercholesterolaemia paediatric screening programme, including 155 children with FH and 117 with multifactorial FH, presented by Dr Urh Groselj (University Children's Hospital, UMC Ljubljana, Ljubljana, Slovenia). FH was confirmed in over half of patients referred through this screening programme. Consistent with data reported for adults, cholesterol levels were higher in children with FH compared with those for whom hypercholesterolaemia was considered to be polygenic or multifactorial.

FHSC booth at the EAS Congress

The FHSC booth at the EAS Congress in Prague was very successful. Many attendees to the Congress dropped by to get information and showed their interest in initiative. It also served as a point for meeting for FHSC investigators, and sessions on the development and working of the FHSC registry were attended by a number of FHSC investigators.

We would like to thank the EAS for giving the FHSC the chance to have the booth at the ESC Congress.



FH-awareness week September 18-24, 2017

Take the opportunity to promote local FH events taking place in your country/region on the FHSC website and through the EAS regular newsletters (ca. 8500 contacts).

Like last year - EAS and the EAS FH Studies Collaboration are planning an email campaign during the FH-awareness week (18-24 September) with a series of daily newsletters going out via EAS regular newsletters (ca. 8500 contacts) and social media channels.

This is an opportunity to promote and share information about FH related activities and events going on in your country and we would encourage you to send in some short facts about your activities going on during 2017/2018.

We would need to know:

- Type of FH related activity (public awareness, health care, political, educational initiatives etc.)
- Who is the organiser (institute, organisation, cooperation)
- Date and duration of activity
- Venue of the activity (if public and not by invitation only)
- Link to any event information online and/or contact details to get further information

Send the information to info@eas-fhsc.org.

Publications

- FH infographic: [“What is Familial Hypercholesterolaemia?”](#) From the Hellenic Atherosclerosis Society.
- Santos RD, et al; Ibero-American Familial Hypercholesterolemia Network. [Clinical and molecular aspects of familial hypercholesterolemia in Ibero-American countries](#). J Clin Lipidol 2017;11(1):160-66.
- Kerr M, et al. [Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK](#). Eur Heart J 2017. doi: 10.1093/eurheartj/ehx111.
- Pérez de Isla L, et al. [Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry \(Spanish Familial Hypercholesterolemia Cohort Study\)](#). Circulation 2017;135:2133-44.
- Lázaro P, et al. [Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia](#). J Clin Lipidol 2017;11:260-271.
- Kwok S, et al. [An online questionnaire survey of UK general practitioners' knowledge and management of familial hypercholesterolaemia](#). BMJ Open 2016;6(11):e012691.
- Schofield J, et al. [Knowledge gaps in the management of familial hypercholesterolaemia. A UK based survey](#). Atherosclerosis 2016;252:161-5.
- Watts GF, et al; for the members of the "Ten countries Study". [Translational Research for Improving the Care of Familial Hypercholesterolemia: The "Ten Countries Study" and Beyond](#). J Atheroscler Thromb 2016;23(8):891-900.
- Corral P, et al. [Xanthomas and dyslipidaemia, an association that should not go unnoticed](#). Rev Fed Arg Cardiol 2016;45:110-3.

