ScreenPro FH – Screening Project for Familial Hypercholesterolemia in Central, Southern and Eastern Europe: Basic Epidemiology

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Summary

Introduction: Despite great recent progress, familial hypercholesterolemia (FH) is still underestimated, under-diagnosed and thus undertreated worldwide. We have very little information on exact prevalence of patients with FH in the Central, Eastern and Southern Europe (CESE) region. The aim of the study was to describe the epidemiological situation in the CESE region from data available. Methods: All local leaders of the ScreenPro FH project were asked to provide local data on (a) expert guess of FH prevalence (b) the medical facilities focused on FH already in place (c)
the diagnostic criteria used (d) the number of patients already evidenced in local database and (e) the availability of therapeutic options (especially plasma apheresis). Results: With the guess prevalence of FH around 1 : 500, we estimate the overall population of 588 363 FH heterozygotes in the CESE region. Only 14 108 persons (2.4 %) were depicted in local databases; but the depiction rate varied between 0.1 % and 31.6 %. Only four out of 17 participating countries reported the the LDL apheresis availability. Conclusion: Our data point to the large population of heterozygous FH patients in the CESE region but low diagnostic rate. However structures through the ScreenPro FH project are being created and we can hope that the results will appear soon.

**Key words:** diagnosis – epidemiology – familial hypercholesterolemia – screening

### Methods

**ScreenPro FH project**

The ScreenPro FH Project is an international network project aiming at improving complex care – from timely screening, through diagnosis to up-to-date treatment of familial hypercholesterolemia in Central, Eastern and Southern Europe including some countries of the Middle Asia.

**Data acquisition**

All local leaders were asked to provide local data on:

- expert guess of FH prevalence
- the medical facilities focused on FH already in place
- the diagnostic criteria
- the number of patient already in database
- the availability of therapeutic options (especially plasma apheresis)

**Statistics**

We used descriptive statistics only. Relative rates were used where appropriate.

### Results

The total population of the CESE regions counts 430 361 839 persons. In the majority of states the guess prevalence of FH is around 1 : 500, which translates to an overall population of 588 363 FH heterozygotes. Nevertheless only 14 108 persons (2.4 %) are evidenced in local databases, where the diagnostic rate varies considerably between countries from 0.1 % to 31.6 % (tab).

All countries used the Dutch lipid clinic network diagnostic criteria as primary diagnostic tool. Besides these MedPed criteria are being used in the Czech Republic, Latvia, Lithuania, Slovakia and the Simon Broome diagnostic criteria are being used in Lithuania, Poland, Slovakia and Ukraine.

Only four countries reported the availability of LDL apheresis (Czech Republic, Greece, Russia and Turkey).

### Discussion

The prevalence of patients with heterozygous FH was estimated mostly as 1 : 500, as the prevalence in community derived from symptomatic FH patients (from hospital patients, registries, and from models estimating also homozygous FH [13–16]). Nevertheless the epidemiological studies from unselected populations in last years, that combined also genetic analysis and cas-
cade screening, led to higher FH prevalence. In a huge unselected Danish general population the prevalence of FH was 1:223 FH was defined as Dutch lipid clinic network score higher than 5 [17]. The data derived from United States National Health and Nutrition Examination Surveys led to an estimated US prevalence of probable/definite FH 1:250. Probable and definite diagnosis was defined according to Dutch lipid clinic network score 6–8 points and more than 8 points, respectively. The probable FH prevalence was 1:267 and definite 1:4023. In China the estimated FH prevalence was 1:357 [18] and in Australia 1:353 and 1:229 [19]. In Poland, one of the countries from the CESE region, the pooled data from several studies the FH prevalence was also higher than expected: 1:248 [20]. These results correspond to the finding of Wald et al, who performed a FH screening among children during routine immunization visits. In these 1–2 years old children detected newly diagnosed FH in 4 in 1000 children, which translates to a prevalence rate of 1:250 [21]. If we assume this higher prevalence, this would lead to doubling the number of patients affected by FH in the CESE region.

In the countries of the CESE region the predominantly used diagnostic criteria are Dutch lipid clinic network diagnostic criteria. The genetic testing is not necessary for the diagnosis of FH, as in approximately 20% of patients with a clinical FH diagnosis we are unable to find a genetic mutation [3]. Nevertheless when a genetic mutation is demonstrated the diagnosis of FH is established [1]. On the other hand not all patients with a heterozygous FH mutation have LDL-cholesterol high enough to make the clinical diagnosis [1]. That is why the recommended screening criteria in the ScreenPro FH project are the Dutch lipid clinic network diagnostic criteria, which combines both possibilities: genetic and clinical diagnosis.

The number of patients already followed in databases is very low from the target FH population (2.4%) and varies from country to country. Unfortunately this is in accordance with the worldwide situation. In most countries the estimated diagnosed FH is less than 1% from the number of FH patients predicted from the prevalence of 1:500 [2]. The highest diagnosis rates are in the Netherlands and Norway, where the diagnostic process received a governmental support and in countries with dedicated physicians [1].

LDL apheresis is indicated in homozygous FH patients and severe heterozygous FH patients [1]. LDL apheresis is available only in few countries (Czech Republic, Greece, Russia, Turkey).

Conclusion
Our data points out to the large population of heterozygous FH patients in the CESE region but low diagnostic rates. However structures through the ScreenPro FH project are being created and we can hope that the results will appear soon.

Financial support
To increase our financial resources we’ve applied for the IAS independent grant: IAS/Pfizer IGLC Grant Request: Lipid Management in High-Risk Patients. The project is financially supported by Amgen and Sanofi. Local activities in different countries are also supported by local grants and sponsors.

Conflict of interest
Authors expressed these conflicts of interest:
- grants/research supports – Amgen, Sanofi
- honoraria or consultation fees – MSD, Bayer, Aegerion, Amgen, Sanofi, AstraZeneca, AOP orphan, Teva, Pfizer, Servier Laboratories, Abbott Laboratories, GlaxoSmithKline, Berlin Chemie, novo Nordisk, Boehringer Ingelheim, Mylan, Krka
- participation in a company sponsored speaker’s bureau – MSD, Bayer, Sanofi, Boehringer Ingelheim, Pfizer
- other support – advisory boards, clinical studies – MSD, Bayer, Aegerion, Amgen, Sanofi, AstraZeneca, AOP Orphan, Pfizer, Teva, Regeneron

References
## Tab. Overview of participating countries

<table>
<thead>
<tr>
<th>country</th>
<th>national coordinator</th>
<th>national center</th>
<th>other centers</th>
<th>population</th>
<th>FH prevalence</th>
<th>estimated number of FH patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosnia and Herzegovina</td>
<td>prof. Belma Pojškic, MD</td>
<td>Cantonal hospital Zenica</td>
<td>0</td>
<td>3 825 334</td>
<td>1 : 500</td>
<td>7 652</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>prof. Assen Goudev, MD, FESC</td>
<td>N/A</td>
<td>N/A</td>
<td>7 202 198</td>
<td>1 : 500</td>
<td>14 404</td>
</tr>
<tr>
<td>Croatia</td>
<td>Ivan Pecin, MD, PhD</td>
<td>University Hospital Center Zagreb</td>
<td>4 (planned)</td>
<td>4 225 316</td>
<td>1 : 500</td>
<td>8 450</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Tomas Freiberger, MD, PhD</td>
<td>General University Hospital in Prague, St. Anne’s University Hospital in Brno</td>
<td>62</td>
<td>10 538 275</td>
<td>1 : 500</td>
<td>21 077</td>
</tr>
<tr>
<td>Greece</td>
<td>prof. Alexandros D. Tselepis, MD, PhD</td>
<td>University Hospital of Ioannina</td>
<td>8</td>
<td>10 812 467</td>
<td>1 : 500</td>
<td>21 625</td>
</tr>
<tr>
<td>Hungary</td>
<td>prof. György Paragh, MD</td>
<td>Medical Center, University of Debrecen (prof. György Paragh), Semmelweis University, Budapest (prof. István Karádi)</td>
<td>20</td>
<td>9 849 000</td>
<td>1 : 500</td>
<td>19 698</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>prof. Erkin M. Mirrakhimov, MD, PhD</td>
<td>The National Centre of Cardiology and Therapy</td>
<td>2</td>
<td>5 850 687</td>
<td>1 : 500</td>
<td>11 700</td>
</tr>
<tr>
<td>Latvia</td>
<td>assoc. prof. Gustavs Latkovskis, MD</td>
<td>Latvian Institute of Cardiology and Regenerative Medicine, Riga</td>
<td>0</td>
<td>1 986 096</td>
<td>1 : 500</td>
<td>3 972</td>
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<tr>
<td>Lithuania</td>
<td>prof. Zaneta Petrušionienė, MD, PhD</td>
<td>Vilnius University Hospital Santariskiu Klinikos, Center of Cardiology and Angiology</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Poland</td>
<td>prof. Andrzej Rynkiewicz, MD, PhD, DSc</td>
<td>University of Warmia and Mazury (prof. Andrzej Rynkiewicz), Medical University of Gdańsk (prof. Marcin Gruchala)</td>
<td>7</td>
<td>38 005 614</td>
<td>1 : 500</td>
<td>76 011</td>
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<td>Romania</td>
<td>prof. Gheorghe-Andrei Dan, MD, PhD</td>
<td>Latvian Institute of Cardiology and Regenerative Medicine, Riga</td>
<td>N/A</td>
<td>19 861 408</td>
<td>1 : 500</td>
<td>39 723</td>
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<td>Russia</td>
<td>prof. Marat V. Ezhov, MD</td>
<td>Cardiology Research Center, Moscow</td>
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<td>1 461 278</td>
<td>1 : 500</td>
<td>292 535</td>
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<td>Serbia</td>
<td>prof. Nebojsa Tasic, MD, MSc</td>
<td>N/A</td>
<td>N/A</td>
<td>7 111 973</td>
<td>1 : 500</td>
<td>14 224</td>
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<tr>
<td>Slovakia</td>
<td>Branislav Vohnout MD, MD</td>
<td>Slovak Medical University, Bratislava</td>
<td>19</td>
<td>5 421 340</td>
<td>1 : 500</td>
<td>10 843</td>
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<tr>
<td>Slovenia</td>
<td>prof. Zlatko Fras, MD, PhD, FESC, FACC</td>
<td>N/A</td>
<td>N/A</td>
<td>2 062 874</td>
<td>1 : 500</td>
<td>4 126</td>
</tr>
<tr>
<td>Turkey</td>
<td>prof. Meral Kayıkcıoğlu, MD</td>
<td>Ege University, Cardiology Dept, Lipid Clinic, Izmir</td>
<td>none yet</td>
<td>84,000,000</td>
<td>1 : 200–1 : 300</td>
<td>280,000–420,000</td>
</tr>
<tr>
<td>Ukraine</td>
<td>prof. Olena Mitchenko, MD</td>
<td>National Scientific Center, Kyiv</td>
<td>4 (in development)</td>
<td>45 245 894</td>
<td>1 : 500</td>
<td>90 492</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>prof. Alexander B. Shek, MD</td>
<td>Republican Specialised Center of Cardiology (RSCC), Tashkent, Osoy</td>
<td>RSCC had 12 branches in 13 regions of Uzbekistan</td>
<td>31 025 500</td>
<td>1 : 500</td>
<td>62 051</td>
</tr>
</tbody>
</table>

FH – familial hypercholesterolemia
N/A – not available

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<table>
<thead>
<tr>
<th>FH program</th>
<th>criteria for diagnosis</th>
<th>network</th>
<th>number of patients in the database (percent of estimated number of FH patients)</th>
<th>LDL apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>identifying and screening patients with high LDL from hospital database</td>
<td>Dutch lipid clinic network diagnostic criteria</td>
<td>functional</td>
<td>900 (11.8 %)</td>
<td></td>
</tr>
<tr>
<td>collecting patients’ data in database educational activities for GPs, pediatricians, internists, ophthalmologists</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>based on the MedPed FH approach with national co-ordinating center and network of lipid clinics involved in MedPed</td>
<td>Dutch lipid clinic network diagnostic criteria</td>
<td>based on MedPed – functional</td>
<td>130 (1.5 %)</td>
<td></td>
</tr>
<tr>
<td>based on MedPed approach, functional network of centres, support of Czech Atherosclerosis Society, online nationwide database, activity of coordinator who keeps centres informed and helps them with inserting patients’ data into database, availability of DNA diagnostics</td>
<td>MedPed, Dutch lipid clinic network diagnostic criteria</td>
<td>based on MedPed – functional</td>
<td>6 652 (31.6 %)</td>
<td>available</td>
</tr>
<tr>
<td>based on national coordinating centre and network of lipid clinics involved in FH registry, Hellas FH registry (database)</td>
<td>Dutch lipid clinic network diagnostic criteria</td>
<td>expected 2 000 within one year</td>
<td>40 (0.2 %) (expected 2 000 patients within 1 year)</td>
<td>available</td>
</tr>
<tr>
<td>2 national centres are able to perform genetical examination, the examinations are sponsored from scientific grant</td>
<td>Dutch lipid clinic network diagnostic criteria</td>
<td>doesn’t exist, but it’s in development, FH registry was just developed – next step will be a pilot study and according to the experience of the study the programme will be applied in country or modified if needed</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>analysis of the FH prevalence in patients with “premature” CHD and metabolic syndrome and related management of primary and secondary prevention</td>
<td>Dutch lipid clinic network diagnostic criteria</td>
<td>at the beginning</td>
<td>13 (0.1 %)</td>
<td></td>
</tr>
<tr>
<td>FH registry – initiated in February 2015, run by the Latvian Institute of Cardiology and Regenerative Medicine, University of Latvia</td>
<td>Dutch lipid clinic network diagnostic criteria, (MedPed also calculated)</td>
<td>functional/in development</td>
<td>162 (4.1 %)</td>
<td></td>
</tr>
<tr>
<td>Polish national programme for the diagnosis and treatment of FH</td>
<td>Dutch lipid clinic network diagnostic criteria and Simon Broome diagnostic criteria</td>
<td>functional/in development</td>
<td>1 884 (2.5 %)</td>
<td></td>
</tr>
<tr>
<td>focused on detection and treatment of FH, population study, molecular biology all criteria for FH used</td>
<td>Dutch lipid clinic network diagnostic criteria</td>
<td>functional/in development</td>
<td>700 (0.2 %)</td>
<td>available in some centers (rare)</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>MedPed FH Slovakia based on the MedPed FH approach with national coordinating centre and network of lipid clinics involved in MedPed, molecular genetics is performed – covered by grants</td>
<td>Dutch lipid clinic network diagnostic criteria, Simon Broome diagnostic criteria, MedPed US</td>
<td>based on MedPed – functional</td>
<td>2 000 (18.4 %)</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>under development</td>
<td>Dutch Lipid Network</td>
<td>no but with the new registry we will establish new lipid centers connected to FH network</td>
<td>&gt; 1 000 (0.2–0.4 %)</td>
<td>18</td>
</tr>
<tr>
<td>active detection of patients with suspected FH, with the further definition of the family history, lipid profile, the identification of markers of subclinical atherosclerosis, conducting stress tests, computer tomography coronary angiography (if the diagnosis is confirmed, patients’ family is included)</td>
<td>Dutch lipid clinic network diagnostic criteria, Simon Broome diagnostic criteria</td>
<td>doesn’t exist/in development</td>
<td>81 (0.1 %)</td>
<td></td>
</tr>
<tr>
<td>in development</td>
<td>Dutch lipid clinic network diagnostic criteria</td>
<td>doesn’t exist/in development</td>
<td>46 (0.1 %)</td>
<td></td>
</tr>
</tbody>
</table>

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ScreenPro FH – Screening Project for Familial Hypercholesterolemia in Central, Southern and Eastern Europe: Rationale and Design


Summary
Familial hypercholesterolemia (FH) is a genetic disorder with well-known genetic transmission and clinical course. Despite great recent progress, FH is still underestimated, under-diagnosed and thus undertreated. Furthermore it represents a significant healthcare challenge as a common risk factor for the premature development of coronary heart disease. The ScreenPro FH Project is an international network project aiming at improving complex care – from timely screening, through diagnosis to up-to-date treatment of familial hypercholesterolemia in Central, Eastern and Southern Europe. An important task for the project is to harmonise and unify diagnostic and therapeutic
approaches in participating countries, where the situation differs from country to country. Countries with more experience should serve as a model for countries developing the FH network.

**Key words:** diagnosis – familial hypercholesterolemia – screening – treatment optimization

**Introduction**
Familial hypercholesterolemia (FH) is a genetic disorder with well-known genetic transmission and clinical course. Due to its indolent/asymptomatic clinical course, until serious clinical manifestation, FH is often underdiagnosed and thus undertreated [1–3]. The most serious clinical manifestation of FH is an acute coronary syndrome as a complication of accelerated coronary artery disease (CAD). Before the introduction of statins, the mortality rates of FH patients aged 20–40 years were 100 times higher compared to the general population [4–6]. In homozygotes, CAD occurs during the first few decades, and untreated patients die before the age of 30 years [4,7].

Nevertheless if treated, the morbidity and mortality rates approach those of the general population [8–10]. Worldwide only a minor fraction of patients is detected and even less treated to goals [8,11]. As stated in the EAS Consensus Statement [1], there exists an enormous difference in detection and treatment rates between different countries that cannot be explained only by economic conditions or the quality of the health care system. It is evident that a country with a FH research project supported by the government (e.g. in Netherlands) has an incredible advantage, resulting in the identification rates over 70 % [1,12].

The prevalence of FH in a given population can be only estimated. The estimated global prevalence of patients with FH is at least 15 million people [13]. FH is an autosomal dominant disease that occurs naturally in two forms: homozygous and heterozygous. FH homozygotes are rare and their frequency in the general population is not clearly known, but the estimates range from 1 : 1 000 000 previously to 1 : 160 000–1 : 300 000 based on current evidence of molecularly defined HeFH [7]. We have very little information on exact prevalence of patients with FH in the Central, Eastern and Southern Europe (CESE) region. With regard to the Czech population (which is similar to the American population), the more commonly cited heterozygote prevalence of 1 : 500 is still valid [14], which makes FH the most common inherited metabolic disorder. However, based on the recently published data, it is even more prevalent, 1 in 200–300 for heterozygous and 1 in 300 000 for homozygous FH [2].

**ScreenPro FH Project**
To fill the gaps in knowledge of the epidemiological situation in the CESE region and in the clinical care of patients with FH (screening, diagnosis, treatment) we have launched the ScreenPro FH Project. The ScreenPro FH Project is an international project for improvement of complex care of patients with familial hypercholesterolemia in Central, Eastern and Southern Europe, including some parts of Central Asia.

The basic aim of the project is to develop a network of centres of excellence for patients with familial hypercholesterolemia in the CESE region. The centres will optimise and unify the process of screening of patients and their families, diagnosis and effective treatment of familial hypercholesterolemia in their country. The epidemiological situation (prevalence, treatment characteristic, patient reaching the LDL goals) in different countries as well as the comparison between countries will be described.

An important part of the project lies in educating and increasing the awareness of familial hypercholesterolemia amongst the public as well as among first line physicians (GPs, internists, cardiologists, diabetologists). Also, specific centres (networks in individual countries) must be prepared for initiation and performance of modern therapies.

**Aims/Objectives of the project**
The project has the following objectives:
- the development and establishment of a functional network of lipid clinics/centres, taking care of patients with familial hypercholesterolemia and other severe hyperlipidemias and dyslipidemias (including paediatric patients)
- creation of a short user-friendly recommendation for screening, diagnosis and the complex care of familial hypercholesterolemia
- the development and establishment of a common web site along with a summary of recommendations, educational materials, and slide kits to be used in participating regions connected with the centres participating in the project
- improvement of screening in regions where centres are active/influential
- increasing the awareness of familial hypercholesterolemia in participating regions
- better risk stratification of familial hypercholesterolemia patients
- increasing the number of patients at LDL-C goal
- establishment of the databases in individual countries, with comparable data between all participating project countries
The project is coordinated by a Project leader (prof. Richard Ceska) and two Executive managers (T. Aleksicova and L. Votavova). The leadership is supported by the Board of advisers (R. Ceska, Z. Reiner, M. Banach, L. Tokgozoglu, A. V. Susekov, K. Raslova) and Administrative council (formed by all country leaders). The country leaders are responsible for the local coordination of the project and for the communication with Regional centers and Cooperating physicians (general practitioners, internists, diabetologists, cardiologists and other physicians who could encounter patients with FH).

Diagnostic criteria
There are several FH scoring systems (see Appendix [15]. The Simon Broome system used in the UK, and the MedPed criteria used in the USA, are both very well known. Nevertheless Dutch Lipid Clinic Network criteria, which, in our opinion, are the most sophisticated and suited for our region will be preferred for the purpose of ScreenPro FH project. (See Appendix diagnostica, p. 49).

Website
ScreenPro FH project website (www.screenprofh.com) was developed as a crucial information sharing platform for the project and for participating countries.

Epidemiological data from CESE countries are under development. The accuracy and amount of data differ from country to country (very good in Czech and Slovak Republics and good in Poland, Hungary, Greece, while some countries are at the beginning of the development – Uzbekistan, Kazakhstan…). The preliminary results have been published on the website and are to be regularly updated.

The Educational section focuses basically on FH but also on other dyslipidaemias and cardiovascular prevention in general. A short summary on diagnostic and therapeutic procedures in patient with FH is provided. A picture gallery of patients xanthomas and other FH manifestations is shown as well (all pictures are provided by the Centre of Preventive Cardiology in Prague). Because statin intolerance represents a significant issue of FH treatment (and also in treatment of high risk patients) we decided to add “statin intolerance paper” into educational section of the project website.

The development of practical tools for unified and harmonised care of FH patients is under development, and beside the educational content, it will become the most important part of the website. Practical instruments like card for patients with FH, formalised informed consent, information for patient or information for family members from FH families are prepared and will be available in English for all participating centres and are already available in some countries in local mutations. The translation to local language is the responsibility of the country leadership.

The website already serves also as an information source about the project as project structure, contacts, meetings etc.

The “Familial Hypercholesterolemia” book
Due to the lack of expert monograph dedicated to FH on the market, Richard Ceska at all published a FH book in Czech which has been subsequently translated into English language. This made it the first one [14]. The FH book was translated into English language, which made it available for all ScreenPro FH Project country leaders and other interested physicians in the CESE region. Due to language barriers in the some CESE regions, the English version of the book would not be easily readable by many physicians. These physicians (general practitioners, some internists, cardiologists, diabetologists) are very important for screening, diagnosis and basic treatment of FH patients. Therefore the English version of the book was offered to all country leaders to be published in their local languages to increase the awareness of FH in all ScreenPro FH Project countries. Each country leader was asked to describe the situation in his/her country, to add a “country specific chapter” and become a co-author of the book in his/her country. Nowadays, the book is available in 6 languages (English, Czech, Russian, Serbian-Croatian, Lithuanian, Kyrgyz), the Russian one with big impact in many countries is translated and will be published by the end of 2016.

Data collection
A local database is built in participating countries. Because of financial reasons in some countries we rely on local “paper work” or local electronic records to enter the local data. We plan to collect pooled data from all participating countries. The definite form of the dataset is being discussed. The dataset will be divided into mandatory and optional data, which allow us to compare results from different countries and with other FH projects. The project cooperates with EAS-FH Studies Collaboration (FHSC) [1]. FHSC aims at building a worldwide database of FH patients. However it is the decision of each participating country which data and to which extent it will share.

Data ownership
ScreenPro FH Project has no ambition to own any local country data. Data from the country are owned by the national participating authorities. This is only national leadership decision whether and how data will be provided for any central registry.

Future/planned activities
After a several ScreenPro FH Project Member meetings we are now focusing on practical part of the project. Educational materials for practitioners and patients (Informed consent, Information for patients, questionnaires, etc.) are under development. FH patient card, similar to the diabetic patient’s card, is being translated. The advantage is that doctors could see patients’ previous treatments, find information about the cholesterol levels and it can also raise awareness among patients of their health conditions.
To support the first line physicians educational and some basic materials for everyday practice materials will be available on the website (Informed consent, Letter for relatives, Information for patients, Questionnaire, Questionnaire for GPs, FH patient card, etc.) for voluntary usage. A guideline how to establish a lipid clinic/center – what is necessary for a good care of patients with FH, is on the way.

The introduction of electronic audit tool, such as flagging of abnormal values, can increase the identification of index cases of patients with FH [16]. Thus for screening reasons the cooperation with laboratory (flagging of abnormal values) is suitable. The ScreenPro FH accepted a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine concerning lipid profile determination. The paper will be available at web page of the project. All country leaders are advised to start negotiations with clinical chemistry and laboratory medicine specialist in their countries.

Patient organisations represent a very important part of the complex care about FH. The ScreenPro FH Project is mapping the situation in CESE countries. One of the aims of the project is the support of patients’ organisations that already exist and the constitution and development of such organisations in countries where this kind of activity does not yet exist. In some cases it will be possible to join “general patient organisation” and bring the FH topic into them.

Possible new countries
The ScreenPro FH Project is a project open to the cooperation with other countries. Some new countries already expressed their wish to participate in the ScreenPro FH project. Representatives from Lebanon and Oman participated at the ScreenPro FH meeting in St Petersburg 2016, some other countries Israel, Emirates, Saudi Arabia have started preliminary talks with the ScreenPro FH leadership. We will discuss their participation in cooperation with the International Atherosclerosis Society (IAS) (as all countries are IAS members).

Partners
ScreenPro FH Project is endorsed by International Atherosclerosis Society and cooperates with the FH Australasia Network collaborative research project – 10 Countries Study [17] and with the EAS-FH Studies Collaboration (FHSC) [1].

We started our cooperation 10 Countries Study initiative in 2015. The dataset of the ScreenPro FH will include, but will not be limited to all variables used in the 10 Countries Study [17]. This questionnaire is widely used in Australia and Asia and is also available at our website for the ScreenPro FH Project countries. In the near future (2017) we would aim to compare the results with Ten Countries Study outcomes.

We have also started our cooperation with the EAS-FH Studies Collaboration (FHSC). ScreenPro FH Project members participated at the FHSC meetings in Gothenburg, Sweden, in December 2015. We will participate at meeting supported by European Atherosclerosis society (as active participants, as well as participants) in Warsaw on 25 and 26 November 2016.

Discussion
The screening programs represent a big advantage for FH patients. As seen in the Netherlands 5 years after screening program initiation, more than 2 000 people have been newly diagnosed as having FH. At the moment of diagnosis only 39 % received any form of lipid lowering therapy, but only 1 year later this number increased to 93 %. The patients diagnosed due to the cascade screening of relatives were younger which gives them the opportunity to stop the deleterious effect of high LDL-cholesterol on vessel wall earlier [12]. Timely initiated lipid lowering therapy decreases the lifelong LDL-cholesterol burden, which leads not only to the decrease of cardiovascular mortality to the level of general population as seen in primary prevention [18], but also to the decrease in cancer related mortality. In an analysis of a British registry the use of statins in the population of patients with FH led to a significant 37 % lower risk of fatal cancer [10]. Moreover cascade screening appears to be cost-effective. The cost effectiveness is dependent on FH prevalence. Although the prevalence of 1 : 500 is still being used, some data point to much higher prevalence especially in selected populations (in populations with founder effect [19], in the setting of coronary care unit [20]), but also in general population of selected nations e.g. 1 : 137 in Danish population [2]. In countries with established registries the estimated prevalence of heterozygous FH ranges between 1 : 211 to 1 : 359 [21].

Since new therapy of familial hypercholesterolemia is becoming available, it is necessary to identify groups of patients, who would get the biggest profit from such a treatment. Centres have to be well educated in providing the recent, modern therapy. The ScreenPro FH network will be locally responsible for reasonable treatment and modern therapy usage, including modalities such as PCSK9-inhibitors [22] or LDL apheresis [23].

Our project is in line with the other ongoing projects [21]. Regional activity, very similar to our project is “Ten Countries FH Study”. The International Atherosclerosis Society has begun a study in Asia and the Pacific Rim to provide the first comprehensive investigation of familial hypercholesterolaemia, the world’s commonest genetic disorder, in the region. The mission of this project is to improve the care of patients and families with familial hypercholesterolaemia in cooperating countries. The aim of the project is to investigate diagnostic, epidemiological and service aspects, as well as primary care physician (PCP) awareness and patient perceptions, of FH in order to inform best practice in the care of the condition.

The other international project, endorsed and developed by the European Atherosclerosis Society is the
Familial Hypercholesterolemia Studies Collaboration (FHSC). The final target of this very ambitious, worldwide project is to develop the global database of FH patients. These international projects are witnessing the fact, that the only way, how to improve care about FH patient from global point of view is, besides local and national activities, the international, regional as well as global collaboration.

Conclusion
The basic structure of the project exists, 18 countries from CESE region are actively involved in the Screen- Pro FH Project and the network of lipid centres in all countries is under development. The local national databases are arising. The functional website is now available for project members as well as for interested medical specialists. We hope that based on the ScreenPro FH Project activities, such as educational content of website, FH book availability and regular country leaders meetings, the awareness of FH in the CESE region will increase.

Financial support
To increase our financial resources we’ve applied for the IAS independent grant: IAS/Pfizer IGLC Grant Request: Lipid Management in High-Risk Patients. The project is financially supported by Amgen and Sanofi. Local activities in different countries are also supported by local grants and sponsors.

Conflict of interest
- Authors expressed these conflicts of interest:
  - grants/research supports – Amgen, Sanofi
  - honoraria or consultation fees – MSD, Bayer, Aegerion, Amgen, Sanofi, AstraZeneca, AOP Orphan, Teva, Pfizer, Servier Laboratories, Abbott Laboratories, GlaxoSmithKline, Berlin Chemie, Novo Nordisk, Boehringer Ingelheim, Mylan, Kowa, Krka
  - participation in a company sponsored speaker’s bureau – MSD, Bayer, Sanofi, Boehringer Ingelheim, Pfizer
  - other support – advisory boards, clinical studies – MSD, Bayer, Aegerion, Amgen, Sanofi, AstraZeneca, AOP Orphan, Pfizer, Teva, Regeneron

References


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**Appendix diagnostica – Familial hypercholesterolemia diagnostic criteria**

**Simon Broome system**

Definite familial hypercholesterolemia (FH) is defined as follows:

a) cholesterol levels > 6.7 in children under 16 years of age and > 7.5 in adults; or LDL-C levels > 4.9 in adults and

b) tendinous xanthomas in a patient or a first-/second-degree relative.

Possible familial hypercholesterolemia is defined as follows:

a) cholesterol levels > 6.7 in children under 16 years of age and > 7.5 in adults; or LDL-C levels > 4.9 in adults and one of the following criteria:

b) family history of myocardial infarction prior to 50 years of age in second-degree relatives, or prior to 60 years in first-degree relatives

c) family history of elevated cholesterol > 7.5 in first-/second-degree relatives.

**MedPed criteria used in the United States**

<table>
<thead>
<tr>
<th>age (years)</th>
<th>first degree relative with FH</th>
<th>second degree relative with FH</th>
<th>third degree relative with FH</th>
<th>general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>5.7</td>
<td>5.9</td>
<td>6.2</td>
<td>7.0</td>
</tr>
<tr>
<td>20–29</td>
<td>6.2</td>
<td>6.5</td>
<td>6.7</td>
<td>7.5</td>
</tr>
<tr>
<td>30–39</td>
<td>7.0</td>
<td>7.2</td>
<td>7.5</td>
<td>8.8</td>
</tr>
<tr>
<td>≥ 40</td>
<td>7.5</td>
<td>7.8</td>
<td>8.0</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Diagnosis: FH is diagnosed if total cholesterol levels exceed the Cut Point.

**Dutch Lipid Clinic Network criteria for FH**

<table>
<thead>
<tr>
<th>criteria</th>
<th>points</th>
</tr>
</thead>
<tbody>
<tr>
<td>family history</td>
<td></td>
</tr>
<tr>
<td>i. first-degree relative with CAD, M ≤ 55 years, F ≤ 60 years</td>
<td>1</td>
</tr>
<tr>
<td>ii. first-degree relative with LDL-C above 95th percentile for a given country</td>
<td>1</td>
</tr>
<tr>
<td>iii. first-degree relative with tendinous xanthoma and/or arcus lipoides</td>
<td>2</td>
</tr>
<tr>
<td>iv. children under 18 years with LDL-C above 95th percentile for a given country</td>
<td>2</td>
</tr>
<tr>
<td>personal clinical history</td>
<td></td>
</tr>
<tr>
<td>i. premature CAD, M ≤ 55 years, F ≤ 60 years</td>
<td>2</td>
</tr>
<tr>
<td>ii. premature peripheral or cerebral atherosclerosis, M ≤ 55, F ≤ 60 years</td>
<td>1</td>
</tr>
<tr>
<td>physical exam</td>
<td></td>
</tr>
<tr>
<td>i. tendinous xanthoma</td>
<td>6</td>
</tr>
<tr>
<td>ii. arcus lipoides in patients under 45 years</td>
<td>4</td>
</tr>
<tr>
<td>biochemical exam (LDL-C (mmol/L))</td>
<td></td>
</tr>
<tr>
<td>&gt; 8.5</td>
<td>8</td>
</tr>
<tr>
<td>6.5–8.4</td>
<td>5</td>
</tr>
<tr>
<td>5.0–6.4</td>
<td>3</td>
</tr>
<tr>
<td>4.0–4.9</td>
<td>1</td>
</tr>
<tr>
<td>molecular biology – diagnostic mutation testing</td>
<td></td>
</tr>
<tr>
<td>i. mutations in the genes encoding LDL-R, ApoB or PCSK9</td>
<td>8</td>
</tr>
</tbody>
</table>

CAD – coronary artery disease M – male F – female LDL-C – low density cholesterol

The Dutch criteria are then interpreted as follows: For a definite diagnosis of FH, the subject must have more than 8 points; a probable diagnosis of FH requires 6–8 points; and a possible diagnosis of FH is indicated by 3–5 points. Patients who score 0–2 points most likely do not have FH.