A Belgian consensus strategy to identify familial hypercholesterolaemia in the coronary care unit and its subsequent cascade screening and treatment: BEL-FaHST (The BELgium Familial Hypercholesterolaemia STrategy)

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1. Introduction

FH remains under-diagnosed and under-treated worldwide [1]. Up to 2013 in Belgium, only a fraction of HeFH carriers have been genetically characterized [2–8]. Many FH patients continue to suffer from early-onset cardiac complications before being diagnosed [9]. Because of the very high coronary risk associated with this disease, the prevalence of FH in patients admitted in coronary care units (CCU) outmatches more than 10 times the frequency observed in the general population (1/300) [10]. In the EUROASPIRE IV study [9], up to 8% of adults hospitalized for acute coronary syndrome (ACS) had clinical criteria compatible with potential FH. The probability of having FH was even greater in women (11%) and in younger patients (15% in those <60 years). Even if this is an unfortunate reality, the hospitalization of such patients for CVD is a unique opportunity to initiate the first step of FH screening. The present paper summarizes the recommendations based on current evidence and guidelines [2,11,12] from a consensus panel composed of Belgian cardiologists, endocrinologists, lipidologists and cardiogeneticists to better organize the practice of identifying and managing FH patients following acute admission to CCU.

2. Materials and methods

OD and ER prepared a series of questions intended to achieve a consensus about a number of basic principles and to examine the feasibility and practicality of various actions to take in order to facilitate the suspicion of FH, the confirmation of the diagnosis of FH, the prescription of an appropriate treatment, and the initiation of family screening. A panel of national experts composed of lipidologists, cardiologists, endocrinologists and cardiogeneticists examined the current evidence and guidelines and discussed the possible organization of FH management in their local clinics. Afterwards, OD and ER provided a first draft which was then distributed (2 cycle of reviewing) amongst the other co-authors to receive their comments, suggestions and the final agreement on the paper content.

3. Results

3.1. Basic principles

Briefly, the management of FH implies the ability to suspect FH amongst admitted patients, to adequately control their LDL-C level and, in case of confirmed FH, to propose cascade screening for FH in the patient's family. To reach such objectives, we developed an algorithm that splits each of the processes of diagnosis (“DIAGNOSE”), therapeutic management (“TREAT”) and family screening (“FAMILY CARE”) of FH into three phases named “ALERT”, “CONFIRM” and “EXTEND” (Fig. 1). The idea of breaking down these processes into 3 phases is to provide doctors with a blueprint of what needs to be prioritized during each stage for the 3 processes.

It involves the efforts of several stakeholders, starting with a “vigilant doctor” who actively develops the capability or framework to recognize potential FH patients, continuing with an “FH specialist”, and finally involving the patient himself as “FH ambassador” to approach his/her family and facilitate cascade screening and subsequent treatment of relatives.

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3.2. Diagnose

3.2.1. Phase 1. “ALERT”
In a CCU, the first and major step of identifying a potential FH carrier must be integrated amongst other priorities, during a short stay and into the flow of all admitted patients. In such an acute and busy setting, it may not be appropriate to promote the use of an additional score specific to non-urgent FH diagnosis. Therefore, the panel recommends raising suspicion based on 2 simple warning signs for FH which should be checked in all patients admitted for incident CVD.

1. LDL cholesterol level (LDL-C) above 190 mg/dl without treatment, or above 130 mg/dL on LLD(s) in a blood sampling performed as soon as possible after admission (not necessarily in the fasting state); and
2. Age of onset of the acute coronary syndrome (ACS) or any other atherosclerotic disease before 65 years.

LDL-C level is little affected by the postprandial state [13] or by ACS-induced systemic inflammation, an habitual LDL-C lowering effect (10–15%) being maximal after 4 days [14,15]. The cut-off of 190 mg/dL is the limit proposed by guidelines for suspecting FH (1). In patients currently treated with LLD, the inferior limit is expected to be around 130 mg/dL. The cut-off of LDL-C by an average 35%, but in case of more intensive LLD, baseline LDL-C may be calculated using the correction factor specific of the ongoing LLD [16]. The panel considers a unique age cut-off for both sexes to facilitate awareness and set at an older age than usual to be more sensitive. The definition of premature family history in the DLCN is indeed far too restrictive for screening at this stage in such an environment.

In a preliminary observation of 144 admissions for ACS in one CCU (O.V.C., personal observation), it was observed that only 2% of patients met the two criteria (age cut off at 65 years plus LDL-C > 190 mg/dL) whereas 6% met the “broader” criteria (age cut off at 65 plus LDL-C > 155 mg/dL with LLD). Therefore, although these criteria may not seem very specific, they already enable efficient initial selection.

In the presence of these two criteria, the patient must be referred for a visit to an FH specialist.

3.2.2. Phase 2. “CONFIRM”
The first and the subsequent visits to the “FH specialist/clinic” aim at confirming an FH diagnosis using DLCN score and/or deciding whether or not to prescribe confirmatory genetic test. This may often require more than one visit. We try here to answer some questions that are often encountered in clinical practice.

Previous history of abnormally high cholesterol levels or LLD(s). The lifelong persistence of elevated LDL-C (especially if > 190 mg/dL in adults or > 130 mg/dL before 18 years) or early
initiation of LLD during the course of life are indicative of FH. In contrast, existence of previously “normal” LDL-C (around average population level) or elevated triglycerides >200 mg/dL may lower the likelihood of monogenic FH, and rather suggest a polygenic form of FH (eg, familial combined hyperlipidaemia).

3.2.2.1. Corneal arcus and tendon xanthomas. Detecting these requires some skills when examining the eyes and tendons. Tendon xanthomas are most often visible in Achilles tendons and more rarely in extensor tendons of the hands, elbows, heels and knees. Frequently, they are more palpable (feeling a nodule, or abnormal thickening) rather than visible. In case of doubt, an increase in antero-posterior thickness of Achilles tendon (>5.8 mm) demonstrated by echography is suggestive of xanthomas and may reinforce the probability of FH [17]. Unless the thickening is very high (>0.9 mm as suggested by Harada-Shiba M et al. [18]), this cannot replace the criterium ‘tendon xanthomas’ in the DLCN score. History of tendinitis is also indicative, as it occurs more frequently in FH patients. In interpreting these findings, it is important to exclude a previous history of tendon surgery, trauma, hyperuricemia or other conditions for tendinitis or tendon swelling.

Corneal arcus is more difficult to see on a clear (blue or green) iris, is often incomplete and/or hidden behind eyelids (it is thus important to raise eyelids, and instruct patients to look down). It is only pathognomonic of FH if observed before the age of 45 years. However, the finding of a extensive or complete corneal arcus even at 50 years of age, is indicative of an earlier-onset. Xanthelasmas (sharply demarcated yellowish collections of cholesterol underneath the skin, usually on or around eyelids) are not specific of FH.

3.2.2.2. Family data. History of hypercholesterolemia in other members of the family (including children above 4 years) is often difficult to ascertain. The information that a relative was given a statin at a younger age may be of great interest. These points should ideally be further clarified during the forthcoming visit by asking the patient to collect more data on his/her relatives.

3.2.2.3. First DLCN assessment and genetic test prescription. On the basis of the evidence already gathered, the FH specialist can compute the DLCN score. If >8, it follows that the patient has FH with a high level of confidence. In this case, a genetic test is not necessary but could confirm the diagnosis as well as identify the molecular defect underlying the dyslipidemia, and may be of help in subsequent cascade screening (especially to facilitate identification of relatives with borderline cholesterol levels, especially in children). The borderline situation of DLCN between 6 and 8 often occurs in the absence of tendon xanthomas, corneal arcus <45 years, or LDL-C >330 mg/dL. Efforts should primarily be made to gain additional data (lipid levels in children or tendon echography, ...) that may raise the DLCN score > 8. Otherwise, it is worth in such situation to ask for a genetic test. For a DLCN score between 3 and 5, when there are strong suggestive elements to suspect FH, ordering a genetic analysis may also be justified. There are also situations where calculation of DLCN score is somewhat compromised and in which genetic testing may be useful: no known or living relatives where calculation of DLCN score is somewhat compromised and in a genetic analysis may also be justiﬁed.

When there are strong suggestive elements to suspect FH, ordering genetic analysis has a signiﬁcant cost, is potentially time-consuming (obtaining results may take 2–5 months), requires informed consent of patients on the various ethical issues, and may identify genetic variations of uncertain signiﬁcance requiring additional investigations to conﬁrm/refute causality in hypercholesterolemia. A negative genetic test does not automatically exclude FH if the DLCN score is high. In previous studies, when patients were classiﬁed on the basis of the DLCN score, 70% of “deﬁnite” FH patients were found to carry a pathogenic variant, only 29% of “probable” FH and 11% of “possible” FH patients were variant positive [19].

3.2.3. Phase 3. “EXTEND”

At this stage, a diagnosis of FH can be ﬁnalized using all conﬁrmation data collected (including genetic test if performed). If the DLCN score remains <8 and the genetic test is negative (Supplementary Tables 1 and 2), the clinician should not necessarily abandon the search. Sometimes, a conﬁrmatory diagnosis may prove easier to obtain from one relative and the clinician should make every possible effort to invite some adult relatives to be examined in search of FH-speciﬁc signs (such as corneal arcus in those <45 years or tendon xanthomas) or children with LDL-C >190 mg/dL (Fig. 2). Such conﬁrmation in other family member(s) is a good argument to reinforce clinical diagnosis in the index patient.

3.3. TREAT

3.3.1. Phase 1. “ALERT”

For patients with established CHD, as considered in the present paper, initiation of LDL does not really depend upon conﬁrmation of FH and must be implemented as early and as intensively as possible in order to achieve target LDL-C level (<70 mg/dL, which in FH patients with very elevated baseline LDL-C means a LDL-C reduction of >50%) as per current European guidelines for patients in secondary prevention [12]. This requires prescription of high-intensity statins at the highest-tolerated dose (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) as soon as possible, preferably on first admission day for ACS. If the patient is already on low- or moderate-intensity statin, a shift to a high-intensity statin must be considered. If the patient is already on high-intensity statin, the combination of statin with ezetimibe should be considered.

3.3.2. Phase 2. “CONFIRM”

Successive visits to the “FH specialist” also have as objective ensuring drug compliance and adherence, titrating statins and/or adding other LLD in order to achieve LDL-C <70 mg/dL. Often, early combination with ezetimibe is required to achieve an extra 20–25% LDL-C reduction, far greater than the 6% additional reduction obtained by doubling statin dosage.

3.3.3. Phase 3. “EXTEND”

Even with high-intensity statins combined with ezetimibe, many FH patients still have elevated LDL-C. Therefore, at this stage, one may consider the addition of anti-PCSK9 monoclonal antibodies. Alirocumab in the ODYSSEY HIGH FH trial [20,21] and evolocumab in the RUTHERFORD trial [22] have induced drastic reductions of LDL-C (~40 to ~60%) in FH patients on maximally-tolerated statin (>other LLD), allowing to achieve LDL-C target (<70 mg/dL or <100 mg/dL) in the majority of these patients [23].

3.4. Family care

The process of “FAMILY CARE” includes different objectives: raising awareness of familial predisposition to CVD risk, collecting data on cholesterol values to calculate DLCN scores and cascade-
screening for FH. The patient’s collaboration is absolutely necessary at all stages and they need to be thoroughly motivated.

3.4.1. Phase 1: “ALERT”

When a patient suffers from CVD at an early age (<55 years in men and <60 years in women), it is usually recommended that family members be screened for lipid- and non-lipid-related CV risk factors. In this case, it is vital to notify the patient, as soon as possible, on the existence of a familial predisposition to CVD, so they may alert relatives on possible CV risk. Conversely, relatives may provide patient with additional information regarding their personal histories of hypercholesterolaemia, LLDs, and CVDs, which may help refining family data. It is however premature, at this stage, to work more actively on risk identification within the family.

3.4.2. Phase 2: “CONFIRM”

At this phase, still considered exploratory, the “FH specialist” will essentially try to “confirm” as much as possible the data regarding family history. At this stage, the patient may be provided with requests for laboratory testing (total cholesterol, LDL-C, HDL-

Table 1

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Other findings</th>
<th>Probability that genetic test will be positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥330</td>
<td>None (no family data)</td>
<td>Very high</td>
</tr>
<tr>
<td>250–329</td>
<td>Family (±personal) history but no tendon xanthomas * or corneal arcus before age 45 years **</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>No family data***, with or without personal history and no other findings</td>
<td>High</td>
</tr>
<tr>
<td>190–249</td>
<td>Family (±personal) history but no tendon xanthomas * or corneal arcus before age 45 years **</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>No family data***, with or without personal history and no other findings</td>
<td>Moderate</td>
</tr>
<tr>
<td>150–189</td>
<td>Family (±personal) history but no tendon xanthomas * or corneal arcus before age 45 years **</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>No family data***, with or without personal history and no other findings</td>
<td>Low</td>
</tr>
</tbody>
</table>

*No tendon xanthomas or presence of tendon swelling but possibly due to other causes than FH.
**Patients is younger than 45 but has no corneal arcus or patients has corneal arcus but is older than 45 years at the moment of the examination.
***No family data may occur for example in the absence of know parents (orphan), if parents and grand-parents died early of other causes, when contact was lost with the family or in case of small family.

Fig. 2. Algorithm of progression in the diagnostic confirmation (or exclusion) of FH.
Fig. 3. Poster proposed to be displayed in coronary care unit for reminding the alert signs, the name of the “FH specialist” to whom the patient should be referred and eventually a mean to calculate the baseline LDL-C if the patient is under lipid-lowering therapy (without the need of a calculator).
C, and triglycerides) for relatives (including children) with whom the patient feels close enough to share his/her health issues. For results monitoring, the laboratory may be asked to send a copy of lab results to the relative and his/her GP.

3.4.3. Phase 3. "EXTEND"


Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.05.037.

References


Conflicts of interest

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