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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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ABSTRACT

Background and aims: Familial hypercholesterolaemia (FH) is an autosomal dominant lipoprotein disorder characterized by significant elevation of low-density lipoprotein cholesterol (LDL-C) and markedly increased risk of premature cardiovascular disease (CVD). Because of the very high coronary artery disease risk associated with this condition, the prevalence of FH among patients admitted for CVD outmatches many times the prevalence in the general population. Awareness of this disease is crucial for recognizing FH in the aftermath of a hospitalization of a patient with CVD, and also represents a unique opportunity to identify relatives of the index patient, who are unaware they have FH. This article aims to describe a feasible strategy to facilitate the detection and management of FH among patients hospitalized for CVD.

Methods: A multidisciplinary national panel of lipidologists, cardiologists, endocrinologists and cardiogeneticists developed a three-step diagnostic algorithm, each step including three key aspects of diagnosis, treatment and family care.

Results: A sequence of tasks was generated, starting with the process of suspecting FH amongst affected patients admitted for CVD, treating them to LDL-C target, finally culminating in extensive cascade-screening for FH in their family. Conceptually, the pathway is broken down into 3 phases to provide the treating physicians with a time-efficient chain of priorities.

Conclusions: We emphasize the need for optimal collaboration between the various actors, 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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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 suspects potential FH patients, then the expertise of an "FH specialist" and later on, the involvement of the patient him/herself as an "FH ambassador".

Since FH is a very specific and time-consuming condition to manage, a cardiologist, endocrinologist or general internist with a dedicated interest and time for FH (the "FH specialist") should be identified in each hospital, ideally assisted by a trained nurse (to educate and contact relatives for family screening) and a geneticist (to demonstrate causality of ambiguous genetic variants). Like a "diabetes clinic", a "FH clinic" should be organized to provide state-of-the-art care for FH patients and their family. The general practitioner also has a role in encouraging patients' adherence to lipid-lowering drugs (LLD), and helping to perform cascade screening as extensively as possible (See Fig. 1).

The collaboration of the patient is central to approaching and motivating his/her family members and facilitating cascade screening. He/she should therefore be fully informed on the hereditary nature of his/her hypercholesterolaemia (especially when FH is confirmed) and be taught how to raise awareness in the family about the necessity to perform a cholesterol test. This may be facilitated by providing informational material on FH or referring to the website of the national patient's association for FH (www.belchol.be in Belgium).

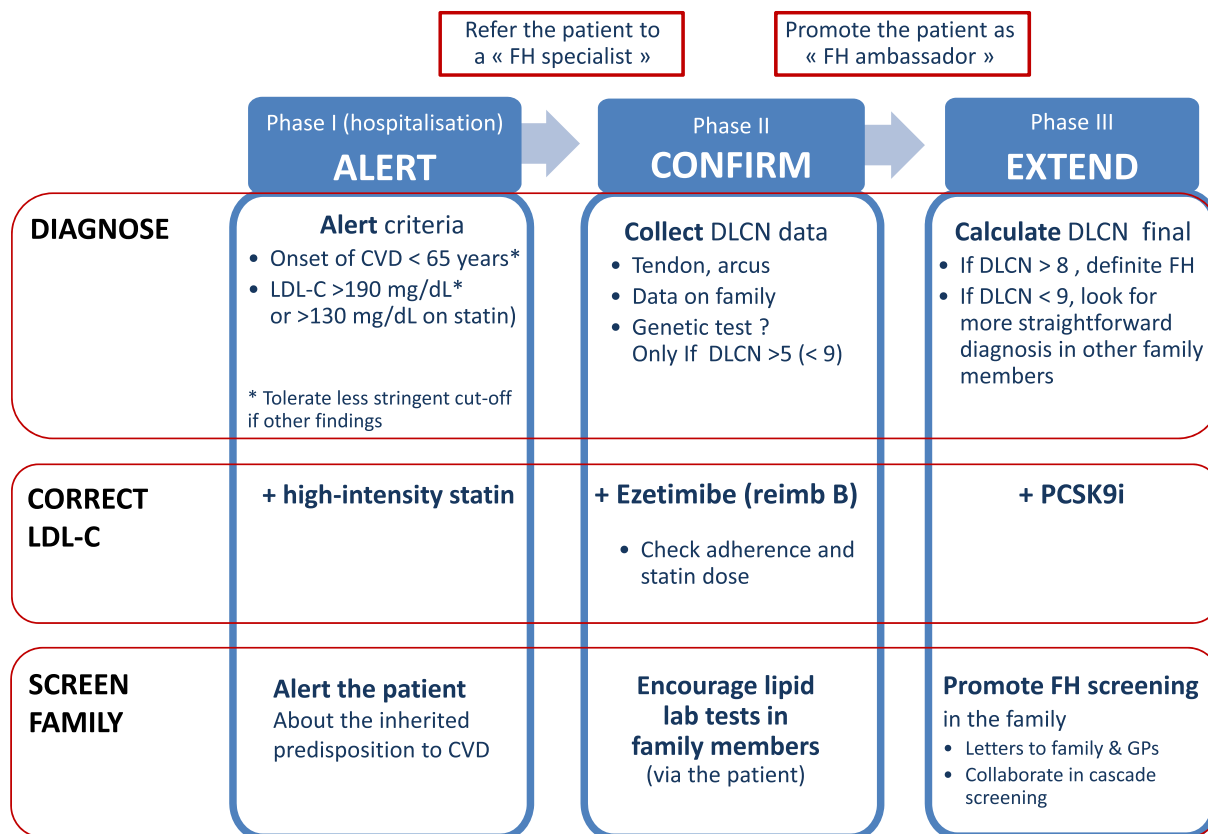


Fig. 1. Algorithm of diagnosis (“DIAGNOSE”), therapeutic management (“CORRECT LDL 70”) and family screening promotion (“FAMILY SCREEN”) of familial hypercholesterolaemia.

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 (taking into account the most commonly-used statins, simvastatin 20 or atorvastatin 10 mg, which lower 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.

These criteria, given as indication, must be nuanced using common clinical sense. For example, the age cut-off may be increased in the presence of conditions decreasing the likelihood of an earlier CV event: absence of any other CV risk factors, healthy lifestyle, longer history of LLD use. The LDL-C cut-offs may also be lowered (>155 mg/dL without previous LLD, and >120 mg/dL with LLD) in the presence of strong pathognomonic signs suggesting FH: very early (<50 years) personal CVD disease, history of premature CVD and/or hypercholesterolaemia in numerous relatives, tendon xanthomas or corneal arcus before 45 years.

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 or 130 mg/dL with LLD) whereas 6% met the “broader” criteria (age cut off at 65 plus LDL-C > 155 or 115 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 discovered before the age of 45 years. However, the finding of an extensive or complete corneal arcus even at 50 years of age, is indicative of an earlier-onset. Xanthelasma (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 hypercholesterolaemia 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 (adoption; parents deceased at a younger age from non-CV causes, no contact with the family), presence of corneal arcus in a patient older than 45 years or previous history of local disease on the tendon.

We developed a table with criteria selected for helping clinicians to decide whether or not to prescribe genetic tests (Table 1). Supplementary Tables 1 and 2 summarize some of the ethical issues, benefits, indications and cautions regarding genetic testing. 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 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 LLD 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-

Table 1
Probabilities that a genetic test will be positive in various situations where DLCN is ≤ 9.

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

*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.

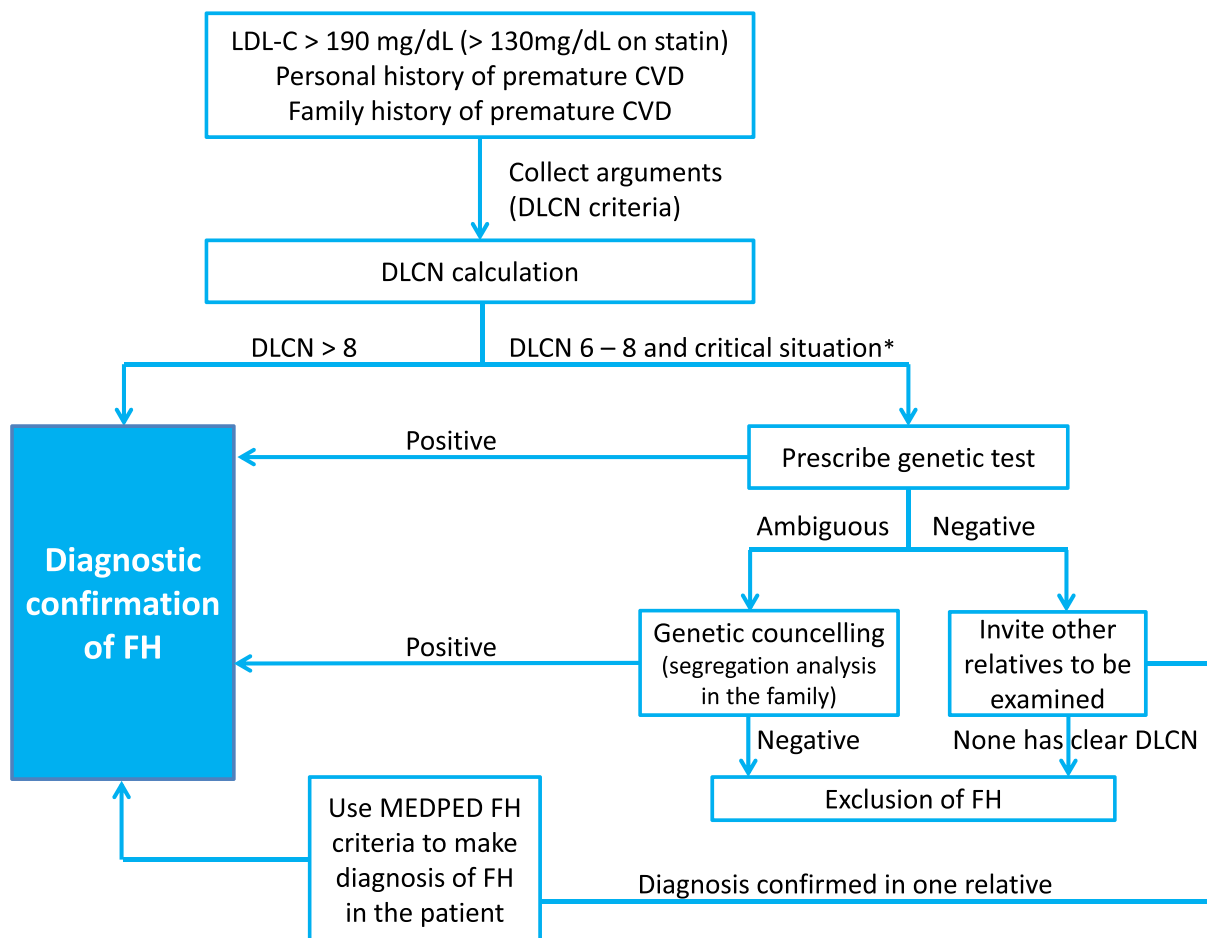


Fig. 2. Algorithm of progression in the diagnostic confirmation (or exclusion) of FH.

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-

Familial Hypercholesterolaemia

Recommendations for screening in adults

Atherosclerotic disease < 65 years
AND
LDL-C > 190 mg/dL without statin²
OR LDL-C > 130 mg/dL with high or moderate statin dose¹
AND
Family history of premature* cardiovascular events

*premature: men < 55 year, women < 60 year

Probable Familial Hypercholesterolaemia

Refer the patient to Doctor ... to confirm the clinical diagnosis using **DLCN score^{3,4}**, to achieve LDL-C target (< 70 mg/dL) and initiate **cascade screening** of the family members³

Categories	Points	
1. Family history : First-degree relative with		Add up the score for each category (e.g. family history, clinical history, LDL-C level etc.) to determine the diagnosis
a. known premature* coronary heart disease (CHD)	1	
b. (In adult) LDL-C ≥190 mg/dl	1	
c. (in children) LDL-C ≥135 mg/dl	2	
c. with corneal arcus before age 45 and/or tendon xanthoma	2	
2. Premature * personal history of		
a. Coronary disease	2	
b. cerebral or peripheral vascular disease	1	
3. Physical examination		
Tendon xanthoma	6	
Corneal arcus in a person <45 years	4	
4. Baseline LDL-C level (before treatment)**		Total score >8 : Definite FH 6–8 : Probable FH 3–5 : Possible FH 0–2 : Unlikely FH
LDL-C ≥ 330mg/dl	8	
LDL-C between 250 et 329mg/dl	5	
LDL-C between 190 et 249mg/dl	3	
LDL-C between 150 et 189mg/dL	1	
5. Molecular genetic testing (DNA analysis)		* Premature : men < 55 year, women < 60 year
Causative mutation shown in the LDLR, APOB or PCSK9 genes	8	

**** How to extrapolate baseline LDL-C: multiply the correction factor specific to treatment with the current LDL-C**

Correction factors specific to treatment	
Type and dose of statin	Without ezetimibe / With ezetimibe
None	- / 1,2
Pravastatin	10 / 1,2
	20 / 1,3
	40 / 1,5
Simvastatin	10 / 1,4
	20 / 1,6
	40 / 1,7
Atorvastatin	10 / 1,6
	20 / 1,8
	40 / 2,2
Rosuvastatin	5 / 1,8
	10 / 1,9
	20 / 2,1
	40 / 2,4

Treated LDL	Correction Factor																																
	1,1	1,2	1,3	1,4	1,5	1,6	1,7	1,8	1,9	2	2,1	2,2	2,3	2,4	2,5	2,6	2,7	3	3,3														
70	77	84	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	231															
80	88	96	104	112	120	128	136	144	152	160	168	176	184	192	200	208	216	264															
90	99	108	117	126	135	144	153	162	171	180	189	198	207	216	225	234	243	297															
100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	330															
110	121	132	143	154	165	176	187	198	209	220	231	242	253	264	275	286	297	363															
120	132	144	156	168	180	192	204	216	228	240	252	264	276	288	300	312	324	396															
130	143	156	169	182	195	208	221	234	247	260	273	286	299	312	325	338	351	429															
140	154	168	182	196	210	224	238	252	266	280	294	308	322	336	350	364	378	462															
150	165	180	195	210	225	240	255	270	285	300	315	330	345	360	375	390	405	495															
160	176	192	208	224	240	256	272	288	304	320	336	352	368	384	400	416	432	528															
170	187	204	221	238	255	272	289	306	323	340	357	374	391	408	425	442	459	561															
180	198	216	234	252	270	288	306	324	342	360	378	396	414	432	450	468	486	594															
190	209	228	247	266	285	304	322	342	361	380	399	418	437	456	475	494	513	627															
200	220	240	260	280	300	320	340	360	380	400	420	440	460	480	500	520	540																
210	231	252	273	294	315	336	357	378	399	420	441	462	483	504	525																		
220	242	264	286	308	330	352	374	396	418	440	462	484	506	528																			
230	253	276	299	322	345	368	391	414	437	460	483	506	529																				
240	264	288	312	336	360	384	408	432	456	480	504	528																					
250	275	300	325	350	375	400	425	450	475	500	525	550																					
260	286	312	338	364	390	416	442	468	494	520																							
270	297	324	351	378	405	432	459	486	513	540																							
280	308	336	364	392	420	448	476	504	532																								
290	319	348	377	406	435	464	493	522	551																								
300	330	360	390	420	450	480	510	540	570																								
310	341	372	403	434	465	496	527	558	589																								
320	352	384	416	448	480	512	544	576	608																								

1. Schiele F et al. EHJ Acute Cardiovasc Care, p8,online 17 nov 2016; 2.EHJ Adv. Access publ. Apr 26, p12,2016;3. EHJ Adv. Access publ. Aug 27, p37,2016; 4.Pijlman QH et al. Atherosclerosis 2010; 209(1):189-194

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"

Promoting hypercholesterolemia screening in the family must be done whatever the final diagnosis. However, if an FH diagnosis is well established, it must be pursued with all the more stamina, especially in children. Such family screening must be promoted through the patient ("FH ambassador"), through the patient's GP, and GPs (when identified) of relatives, and ideally with a dedicated nurse.

As first step for FH screening, the panel recommends assessment of routine lipids only, without genetic testing. Based on LDL-C, it is indeed possible to diagnose FH in adult relatives using the MEDPED criteria [24,25] or in children using specific diagnostic criteria [26]. The MEDPED criteria published by Roger William in 1993 (25) can readily be used in Belgium as the distribution of LDL-C level in general Belgian population (131 ± 34 mg/dl) [27] is almost identical to that of the general US population (130 ± 31.4 mg/dl). The diagnosis may be confirmed subsequently using genetic testing. Having non-elevated LDL-C does not necessarily rule out the transmission of pathogenic variants to the next generation, as incomplete penetrance of gene variants may (rarely) occur in FH [28]. In all cases, the FH specialist must be ready to respond to queries and requests for advice of screened relatives or to transfer relevant information to other colleagues if they live in a remote area.

4. Discussion

The aim of this consensus statement is to achieve a consistent management strategy for the identification of FH in patients undergoing acute CV events, for the provision of treatment and the organization of cascade screening in relatives of patients hospitalized for CVD in Belgian hospitals. Focusing on ACS, and given that each year about 10,000 ACS occur in Belgium and given that in the EUROASPIRE IV study it was estimated that 8% of adults hospitalized for ACS have clinical criteria compatible with potential undiagnosed FH [17], there is the hope that each year, there may be up to 800 new FH patients diagnosed in Belgium. More importantly, this will result in additional FH patients being diagnosed earlier assuming that cascade screening is adequately performed.

Currently, this strategy is being implemented in most coronary care units in Belgium. To achieve the successful implementation, a poster summarizing the strategy was created and distributed to all the coronary care units in Belgium at the end of 2017 (Fig. 3). Prior to this, face-to-face meetings with the cardiologists responsible for the CCU and their colleagues were organized to explain the rationale of the consensus strategy and the different procedures associated with it. We discussed with them the need to designate a well identified FH specialist, to whom all suspected patients can be referred for the validation study, we proposed to those specific centers better equipped with research coordinators to prospectively enter the data of all suspected patients as well as all other patients in order to collect more precise data on the prevalence of FH in the CCU and their clinical characteristics.

Conflicts of interest

Consensus Panel members (their department, their institution or personally) have received lecture honoraria, consultancy fees and/or research funding from Abbott (O.D.S., A.V., E.H.P., A.M., C.D.B., M.H.P.), Aegerion (O.D.S., A.M.), Akcea/Ionis (O.D.S., A.M.),

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Appendix A. Supplementary data

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

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