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Prevalence and management of familial hypercholesterolaemia in coronary patients: An analysis of EUROASPIRE IV, a study of the European Society of Cardiology

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ABSTRACT

Background: Familial hypercholesterolaemia (FH) is a hereditary disorder predisposing to premature coronary heart disease (CHD) and is until now mainly diagnosed clinically on the basis of a classical phenotype. Its prevalence varies and is estimated around 1 in 200–500; in patients with established CHD the prevalence is less well documented.

Methods and results: In EUROASPIRE IV data were collected in coronary patients from 24 European countries by means of a standardized interview, bioclinical examination and venous blood sampling. Potential FH was estimated using an adapted version of the Dutch Lipid Clinic Network Criteria.

Among the 7044 patients eligible for analysis, the prevalence of potential FH was 8.3%; 7.5% in men and 11.1% in women. The prevalence was inversely related to age with a putative prevalence of 1:5 in those with CHD <50 yrs of age in both sexes. Even among women aged 70 the prevalence was 1:10. Irrespective of age and gender, prevalence differed substantially between European regions; potential FH patients were more likely to smoke, had higher triglycerides levels and their blood pressure was less well controlled. The use of cardioprotective drugs and the prevalences of diabetes, obesity and central obesity were similar.

Conclusions: The prevalence of potential FH in coronary patients is high; the results underscore the need to promote identification of FH in CHD patients and to improve their risk factor profile.

1. Introduction

Dyslipidaemias represent a heterogeneous group of disorders that are related to genetic and environmental factors. Familial forms can arise from mutations in one or different genes. Already more than 40 years ago J.L Goldstein et al. [1] had observed that three of these disorders – familial hypercholesterolaemia (FH), familial hypertriglyceridaemia and familial combined hyperlipidaemia – occurred in about 20% of survivors of a myocardial infarction below 60 yrs of age and in 7% of the older survivors. In this report attention is given to the prevalence and management of potential FH in a large group of coronary patients.

FH is an autosomal co-dominant inherited disorder of lipoprotein metabolism characterized by high low density lipoprotein cholesterol (LDL-C) plasma levels from birth and an increased risk of premature coronary heart disease (CHD). Mutations in the gene encoding the LDL receptor (*LDLR*) are the most commonly identified in these patients although mutations in *APOB* and *PCSK9* have also been shown to result in FH. Historically, FH has been diagnosed clinically and the classical phenotype of heterozygous FH was a

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patient with premature CHD, severely elevated LDL-C, a family history of premature CHD and tendon xanthomas. Genomic analysis to identify mutations in the *LDLR, APOB* or *PCSK9* is readily available, but the application of genetic screening varies considerable across countries. Homozygous FH is rare requiring therapeutic interventions in the first decade of life and while the prevalence was believed to be ~1 in 1million current estimates suggest that the figure could be as high as ~1 in 250 000 [2–4].

Heterozygous FH (HeFH) is more common; historically its prevalence was estimated at 1 in 500 people; however, results from more recent studies suggest a higher prevalence up to 1 in 200–250 [5]. The phenotype of HeFH comprises particularly high levels of LDL-C in the range of 5–10 mmol/L (200–400 mg/dL) in adulthood. The identification of patients with HeFH is still very incomplete in Europe and different criteria have been proposed (the Simon Broome Register Diagnostic Criteria [6], the MedPed/WHO Criteria [7] and the Dutch Lipid Clinic Network (DLCN) Diagnostic Criteria [8]) to aid diagnosis. These algorithms are mainly based on the measured LDL-C level, a positive family history of CHD, personal CHD history and physical signs. Patients with established CHD and HeFH are at particularly elevated risk of recurrent events and current management of these patients focuses on the use of potent statins and ezetimibe in order to reach at least a 50% reduction and/or an LDL-C level of <1.8 mmol/L (70 mg/dL). In patients where these targets cannot be reached by statins alone or in case of statin intolerance, other drug treatments or combinations have been suggested in clinical guidelines [9].

Recognizing potential FH patients is of importance for two reasons: firstly, the absolute lifetime cardiovascular risk is sharply increased in HeFH patients and the need for intensive preventive strategies to mitigate this risk are deemed crucial; secondly, by means of cascade screening unidentified affected relatives can be detected. A major challenge therefore in clinical practice is to raise awareness of potential HeFH and identify potential patient groups where HeFH is particularly over-represented which would in turn assist cascade screening.

In order to address some of these uncertainties we aim to estimate the prevalence of clinical HeFH in a large group of patients with CHD who participated in the EUROASPIRE IV survey. Moreover, we compared these potential HeFH patients with the other patients with respect to different clinical characteristics and their management.

2. Study population and methods

2.1. The EUROASPIRE IV survey

The design and methodology of the EUROASPIRE IV study have been described in detail [10] The survey was performed in 24 European countries; patients aged ≥ 18 and <80 years who had been hospitalized for a coronary event (defined as an acute myocardial infarction, acute myocardial ischaemia or procedure [CABG, PCI]) between 6 months and 3 years before the interview, were eligible. They were invited to participate in an interview during which trained technicians collected information through standardized methods.

Height and weight were measured in light indoor clothes without shoes (SECA scales 701 and measuring stick model 220). Obesity was defined as a body mass index ≥30 kg/m^2.

Waist circumference was measured using a metal tape applied horizontally at the point midway in the mid-axillary line between the lowest rim of the rib cage and the tip of the hip bone (superior iliac crest) with the patient standing. Central obesity was defined as a waist circumference ≥88 cm for women and ≥102 cm for men.

Blood pressure was measured twice on the right upper arm in a sitting position using an automatic digital sphygmomanometers (Omron M6) and the mean was used for all analyses.

Breath carbon monoxide was measured in ppm using a smokelyser(Bedfont Scientific, Model Micro +). Smoking at the time of interview was defined as self-reported smoking, and/or a breath carbon monoxide exceeding 10 ppm. Persistent smoking was defined as smoking at interview among patients reporting to be smokers in the month prior to the index event. Habitual physical activity was assessed by means of the International Physical Activity Questionnaire (IPAQ). High physical activity was defined as proposed in http://www.ipaq.ki.se/scoring.pdf.

All patients were asked to come fasting for 10–12 h and the fasting time was recorded at interview. The analyses with LDL-C and triglycerides were limited to those patients fasting for at least 6 h. Venous blood samples were taken with the patients in a sitting position with light stasis into a tube containing clot activator (Venosafe, Terumo Europe, Leuven, Belgium) for lipid assays and into a potassium EDTA tube (Venosafe) for HbA1c assay. Serum was separated by centrifuging at 2000 g for 10 min at room temperature. After that serum was aliquoted into two bar-code-labelled tubes and stored together with whole EDTA blood tubes locally at a minimum of −70 °C and then transported frozen to the central laboratory where all measurements were performed on a clinical chemistry analyzer (Architect c8000; Abbott Laboratories, Abbott Park, Illinois, USA).

Total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides were analysed in serum, and HbA1c in whole blood with the following methods: enzymatic method for total cholesterol, a homogenous method for direct measurement of HDL-C, an enzymatic glycerol phosphate oxidase method for triglycerides, and an immunoturbidimetric method for HbA1c. LDL-C was calculated according to Friedewald's formula; if the triglycerides level was >4 mmol/L patients were excluded from this analysis.

The central laboratory was the Disease Risk Unit, National Institute for Health and Welfare, Helsinki, Finland, and is accredited by the Finnish Accreditation Service and fulfils the requirements of the standard SFS-EN ISO/IEC 17025:2005.

The laboratory takes part in Lipid Standardization Program organized by CDC, Atlanta, Georgia, USA and External Quality Assessment Schemes organized by Labquality, Helsinki, Finland. During the course of the study, comprising two months in 2013, the coefficient of variation (mean ± SD) and systematic error (bias) (mean ± SD) were 1.3% ± 0.2 and 1.7% ± 1.1 for total cholesterol, 1.6% ± 0.5 and −1.5% ± 1.6 for HDL-C, 2.3% ± 0.1 and −1.2% ± 2.6 for triglycerides, and 1.9% ± 0.1 and 1.4% ± 0.2 for HbA1c, respectively.

2.2. Diagnostic criteria for potential FH

The prevalence of FH was estimated using a modified version of criteria used in the MedPed/WHO algorithm [7] and by the DLCN [8]; 2 points were given if the age at the index event was <55/60 years for men/women OR if self-reported age of first diagnosis of CHD was <55/60 years for men/women; 1 point was given for a positive family history of premature (<55/65 years for men/women) CVD. The presence of arcus cornealis or tendon xanthomata was not recorded in the EUROASPIRE IV survey. A large majority of the patients (85.7%) was on statin therapy at the moment of blood sampling. To estimate the “untreated” LDL-C plasma level in these patients, information on the current intake of statins was collected. Participants were asked to bring all the drugs that they were taking on a daily basis to the interview and the interviewer collected the data regarding the dose; in case the interview was done at the home of the patients, detailed information was also collected as to the type of statin and the dosage. At the interview there was one question on compliance: “In the past month how often did you take your medication?” Possible answers were: “all the time (100%); nearly all of the time (90%); most of the time

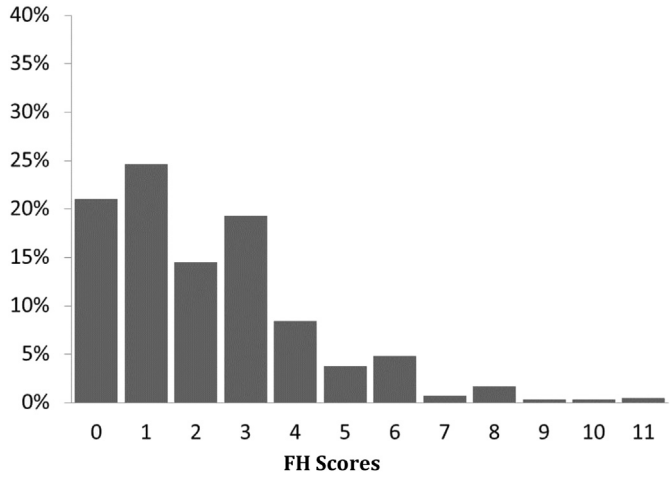

Fig. 1. Distribution (in %) of FH scores in 7044 EAIV patients.

(75%); about half of the time (50%); and less than half of the time (<50%)".

In the patients on statin therapy "untreated" LDL-C level was estimated by multiplying their LDL-C level on treatment with correction factors published by J. Besseling et al. [11] taking into consideration the kind of statin and the dosage; if 'uncommon dosages' were reported or for the combination of ezetimibe with statins other than simvastatin, correction factors were calculated by extrapolation. All these correction factors were further modified by taking the answers to the question on drug compliance into consideration: in those taking their drugs all the time the correction factors were used unaltered; in those taking their drugs nearly all of the time the weight of the correction factors were reduced by 10%, in those taking their medication most of the time by 25%, in those taking their drugs about half of the time by 50%, and in those taking their drugs less than half of the time by 75%.

"Untreated LDL-C" was then entered in the algorithm by giving 1 point to a corrected LDL-C of 4.0–4.9 mmol/L, 3 points to an LDL-C of 5.0–6.4 mmol/L, 5 points to a LDL-C of 6.5–8.4 mmol/L and 8 points to a LDL-C of 8.5 mmol/L or more.

The result of this algorithm was interpreted as follows:

'unlikely FH' ← Total score 0–2
'possible FH' ← Total score 3–5
'probable FH' ← Total score 6–8
'definite FH' ← Total score >8

The categories ' definite' and 'probable FH' were combined into 'potential FH'.

3. Statistical methods

Prevalences were given as percentages. Gender- and center-specific prevalences of potential FH were age-standardized according to the direct method using the total sample as reference. Groups of patients with and without potential FH were statistically compared according to multilevel logistic modelling. These hierarchical models accounted for the clustering of patients within centres. In addition, P-values were adjusted for potential confounding due to differences in distributions of gender and age at interview. A level of <0.05 was a priori chosen to indicate statistical significance. All analyses were performed by means of SAS statistical software release 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

4. Ethical procedures

National coordinators were responsible for obtaining Local Research Ethics Committees approvals. Written informed consent was obtained from each participant by the investigator by a signed declaration. The research assistants signed in the Case Record Form to confirm that informed consent was obtained and stored the original signed declaration consent in the patient file.

5. Results

From the original cohort of 7998 participants, 746 were excluded because of missing LDL-C level at interview, 93 because of missing information on the use of statins, and 115 using lipid lowering drugs other than statins or ezetimibe. The distribution of the total FH score in the remaining 7044 patients (5335 men; 1709 women) is presented in Fig. 1: 587 patients (8.3%) had a score of 6 or more and 77 (1.1%) of more than 8.

In Table 1 the prevalence is given for the different categories of FH for all patients, by gender and by age groups. The prevalence of potential FH was higher in women than in men and among those aged <60 yrs compared to the 60+. The mean age at interview of the group with potential FH was 58.2 years (SD 10.0) compared with 64.8 years (SD 9.3) in the other patients.

The association between potential FH versus age and gender is further demonstrated in Fig. 2. The prevalence of potential FH was significantly higher in men than in women ($p < 0.0001$) and was 8 times greater in the patients aged <50 years compared to those aged 70+. Among women, even those aged between 60 and 69 years, the prevalence was about 1 in 10. The effect of age is likely due to the definition of potential FH where additional weight is given to younger patients who developed CHD prematurely. CHD had occurred prematurely in 78% and 73% of respectively male and female patients with potential FH as compared to 33% and 37% in the other male and female patients.

In Table 2 age-standardized prevalences of potential FH are given by gender and centre. The difference by gender, standardized for age, is somewhat larger; the differences between centres are very large: the prevalence of potential FH varies from 3.4% in the Finish centres to 20.8% in the centres from Bosnia-Herzegovina.

In Table 3 the prevalences of CHD risk factors are presented in

Table 1
Prevalence of unlikely, possible, probable, definite and potential FH.

	N	FH classification				
		Unlikely	Possible	Probable	Definite	Potential
All	7044	60.1% (4234)	31.6% (2223)	7.2% (510)	1.1% (77)	8.3% (587)
Men	5335	62.4% (3330)	30.1% (1607)	6.7% (357)	0.8% (41)	7.5% (398)
Women	1709	52.9% (904)	36.0% (616)	9.0% (153)	2.1% (36)	11.1% (189)
Age <60 years	2212	32.5% (719)	52.1% (1152)	13.7% (304)	1.7% (37)	15.4% (341)
Age ≥60 years	4832	72.7% (3515)	22.2% (1071)	4.3% (206)	0.8% (40)	5.1% (246)

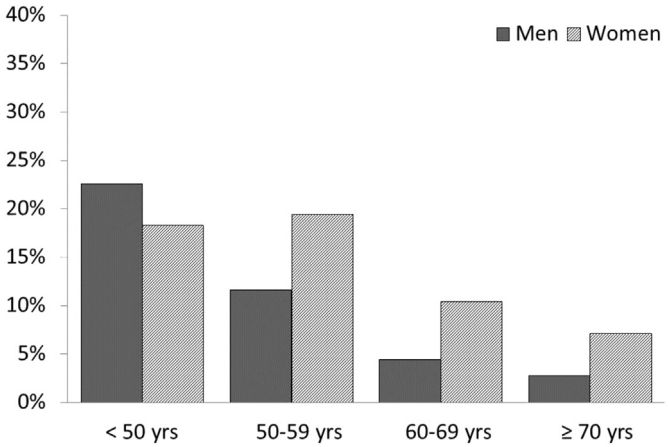

Fig. 2. Prevalence of potential FH (in %) by age at interview and gender.

the group with potential FH (probable/definite) compared to the other (unlikely/possible). Smoking was more prevalent among the patients with potential FH (P = 0.012); there were no differences in prevalence of obesity, central obesity, and self-reported diabetes. The proportion of patients with a low HDL-C was smaller in those with potential FH compared to the other patients. On the contrary the proportion with elevated triglyceride levels was greater among patients with potential FH.

In Table 4 control of CHD risk factors is presented between the groups. Patients with potential FH had their blood pressure less well controlled; among those who were smokers before the index event almost half had stopped smoking at the time of the interview in both groups; those with potential FH tended to be less physically active (P = 0.06); control of diabetes was comparable.

In Table 5 the use of cardioprotective drugs is compared between the groups; there were no significant differences in the use of aspirin or other anti-platelet drugs, beta-blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB's).

Among all the patients with potential FH 55% were on a high-intensity statin (atorvastatin 40 or 80 mg/d, rosuvastatin 20 or 40 mg/d, simvastatin 80 mg/d) compared to 31% in the other patients.

Table 2
Age-standardized prevalence of potential FH by gender and centre.

	N	Age-standardized[a] prevalence of potential FH (95% CI)
Men	5335	7.1% (6.4%–7.8%)
Women	1709	12.1% (10.6%–13.7%)
Belgium	329	5.0% (2.6%–7.3%)
Bosnia Herzegovina	119	20.8% (13.5%–28.1%)
Bulgaria	112	9.0% (3.7%–14.2%)
Croatia	403	9.1% (6.3%–11.9%)
Cyprus	68	7.9% (1.5%–14.3%)
Czech Republic	458	7.1% (4.8%–9.5%)
Finland	438	3.4% (1.7%–5.1%)
France	332	4.4% (2.2%–6.6%)
Germany	493	3.5% (1.8%–5.1%)
Greece	44	3.8% (0.0%–9.5%)
Ireland	192	10.3% (6.0%–14.6%)
Latvia	278	9.9% (6.4%–13.4%)
Lithuania	433	11.8% (8.8%–14.9%)
Netherlands	393	6.1% (3.7%–8.5%)
Poland	357	11.4% (8.1%–14.7%)
Romania	482	8.8% (6.2%–11.3%)
Russian Federation	384	13.8% (10.3%–17.2%)
Serbia	373	12.2% (8.9%–15.5%)
Slovenia	231	4.8% (2.1%–7.6%)
Spain	163	4.1% (1.1%–7.2%)
Sweden	330	4.9% (2.6%–7.2%)
Turkey	207	8.9% (5.0%–12.7%)
Ukraine	231	12.7% (8.4%–17.0%)
United Kingdom	194	6.0% (2.6%–9.3%)

[a] Using age distribution of total sample as reference.

Table 3
Prevalence of CHD risk factors in patients with potential FH.

	FH classification		Significance[f]
	Unlikely/Possible	Probable/Definite	
Current smoking[a]	14.8% (958/6457)	25.0% (147/587)	P = 0.012
Self-reported diabetes	26.6% (1710/6425)	21.1% (123/584)	P = 0.10
Obesity[b]	36.6% (2358/6440)	39.1% (228/583)	P = 0.80
Central obesity[c]	57.4% (3647/6349)	59.8% (345/577)	P = 0.64
Low HDL[d]	36.8% (2374/6457)	34.6% (203/587)	P = 0.011
High TG[e]	30.0% (1823/6087)	46.2% (259/560)	P < 0.0001

[a] Self-reported smoking or CO in breath >10 ppm.
[b] Body Mass Index ≥30 kg/m^2.
[c] Waist circumference ≥102 cm for men or ≥88 cm for women.
[d] HDL cholesterol <1 mmol/L for men and <1.2 mmol/L for women.
[e] Fasting triglycerides ≥1.7 mmol/L.
[f] Adjusted for age and gender.

6. Discussion

Among the coronary patients of the EUROASPIRE IV survey the prevalence of potential FH was calculated at 8.3% or 1 in 12. The prevalence of FH in selected series in the literature varies from 1 in 200 to 1 in 2000 [12–14]. In the Danish general population it was 1 in 200 according to the DLCN criteria [15]. In the US population the prevalence of potential FH according to an adapted version of the DLCN criteria in the NHANES 1999–2012 data was 0.23% or 1 in 427 [16]. In a Chinese community, aged 20 yrs and above the prevalence of probable and definite FH according to modified DLCN criteria was 0.28% or 1 in 357 [17]. Among patients with established CHD however, the prevalence of potential FH is not clear. In a series of consecutive patients aged <60 years admitted with an acute myocardial infarction to hospitals in the Yorkshire region in 1995 and in whom cholesterol had been measured (n = 292), 36 cases of FH (12.3%) were identified [18]. This prevalence is slightly higher compared to the prevalence we found, which might be explained by a younger study population in the previous study.

In our study the prevalence of potential FH was inversely related to age, and more so in men than in women; in men aged <50 years the prevalence was 22%. This association with age may largely be explained by the weight given to younger age of CHD in the DLCN Criteria; it could also be that patients with FH die earlier resulting in a decline of the prevalence of potential FH by age. However, the Copenhagen General Population Study did not show a relationship between age and FH [15].The difference in the prevalence of potential FH by gender may partially be artificial due to the difference in defining premature CHD in men and women. But it could also be related to differences by gender in the interaction between different CHD risk factors.

The higher prevalence of potential FH in women compared to men may reflect the later onset of CHD in women in general but also in those with FH [19]. In the Copenhagen General Population Study the prevalence of potential FH was also higher in the female population aged >60 years [15].

Large regional differences were observed in the prevalence of potential FH, independent of age. This might be explained by differences between the centers participating in this survey. Specifically, if only high-standard tertiary centers in a specific country were involved, recruiting more severely affected patients, the

Table 4
Control of CHD risk factors in patients with potential FH.

	FH classification		Significance[d]
	Unlikely/Possible	Probable/Definite	
SBP/DBP<140/90 mmHg	62.8% (4050/6447)	58.5% (343/587)	P < 0.0001
Quit smoking[a]	51.9% (965/1859)	46.5% (120/258)	P = 0.18
High physical activity[b]	42.4% (2110/4982)	40.7% (175/430)	P = 0.06
HbA1c <7% in diabetes[c]	53.8% (916/1702)	57.7% (71/123)	P = 0.21

[a] Stopped smoking since recruiting event.
[b] According to the IPAQ Short Form questionnaire.
[c] HbA1c < 7% among patients with diabetes.
[d] Adjusted for age and gender.

chance of diagnosing potential FH in this center would be higher. Differences in participating rates between regions may also have influenced the differences in prevalence of potential FH.

In the US National Heart, Lung and Blood Institute's exome sequencing project (ESP) exome sequencing was used as a tool to identify genes contributing to early-onset myocardial infarction (MI) risk. The range of possible *LDLR* mutations with dysfunctional consequences went from 2.4 to 6.6% [20]. These figures were comparable with estimates of the prevalence of FH in coronary patients based on an analysis of total cholesterol levels in 1973(1).

Assuming that FH has been diagnosed in CHD patients, one would expect that an intensive treatment strategy was initiated to prevent recurrent CHD events. However, only 55% of them where on a high-intensity statin; this proportion may even be an overestimation due to the method for estimating 'untreated' LDL-C levels where higher correction factors are given to those on a high-intensity statin. This results in a higher likelihood to belong to the potential FH group. It was further hypothesized that among patients with potential FH the control of other CHD risk factors would have been better. Paradoxically, this was also not the case; smoking was more prevalent among potential FH patients, hypertension was less well controlled, and they were physically less active. No differences were found in prevalence of obesity, central obesity, diabetes and the control of diabetes. In contrast, lower levels of HDL-C were less frequently observed in potential FH patients, whereas high triglyceride levels occurred more often in them. Overall the CHD risk profile seemed to be worse in patients with potential FH.

FH is well recognized as an important risk factor for developing accelerated atherosclerosis and its clinical consequences. For diagnosing FH in adults it is still recommended to use phenotypic assessment based on tools that have been developed; one of these are the DLCN Criteria. A numerical score is calculated based on the personal and family history of premature CHD, the blood level of LDL-C and the presence of arcus cornealis or tendon xanthomata. The relation of molecular genetic to the phenotypic identification of FH with the DLCN Criteria was subject of a Danish study [21]; from these results it was concluded that possible FH should also be included as potential FH if one wants to identify most single gene mutation carriers. The statement "treat the phenotype but counsel the genotype" [22] is according to these observations still very relevant.

Table 5
Use of cardioprotective drugs in patients with potential FH.

	FH classification		Significance[a]
	Unlikely/Possible	Probable/Definite	
ASA	94.2% (6081/6457)	96.4% (566/587)	P = 0.35
Beta-blockers	83.2% (5374/6457)	85.7% (503/587)	P = 0.48
ACE inhibitor or ARB	75.4% (4866/6457)	76.3% (448/587)	P = 0.35

ASA: aspirin; ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blockers.
[a] Adjusted for age and gender.

The high prevalence of potential FH in CHD patients, especially in those aged <50 years, opens the opportunity to increase the detection rate among family members. When a suspicious case is detected family screening protocols are warranted. All those identified with potential FH should receive high-intensity statins; even then a large proportion will probably not reach the LDL-C goal of <1.8 mmol/L (70 mg/dL) and combination therapies should be considered in these patients. High intensity lipid-lowering therapy for these patients is recommended in both, the European ESC/EAS [9] as well as in the US ACC/AHA [23] guidelines, since it can markedly improve their life expectancy [24]. Screening for the phenotype of FH in patients with premature CHD should also be complemented by a search for other dyslipidaemias that may cause premature CHD. Clinicians should be suspicious of increased levels of Lp(a) or triglycerides in patients with premature CHD. It has been shown that Lp(a) is frequently elevated in FH patients [25].

There are some methodological considerations in our study. It has the advantage of large numbers with more than 7000 patients participated; CHD was well documented and by protocol consecutive series were identified and invited in each center; drug intake was carefully enquired by trained technicians not only regarding the kind of statin but also the dose. Furthermore, all lipid measurements were performed in one central laboratory, which allowed us to estimate the 'untreated LDL-C' level more carefully than in studies where a correction factor was applied in patients on statins independent of the kind and the dose [15]. Nonetheless, using these more specific correction factors may still be insufficient and could introduce inaccurate estimations of the 'true untreated LDL-C' at the level of the individual; indeed, the coefficients that have been proposed [11] are based on observations by MR Law [26] where a fixed level of LDL-C of 4.8 mmol/L has been used as the baseline value; therefore these coefficients may be correct for estimating the untreated LDL-C of a group of patients but not for individuals with varying baseline levels. The coefficients that are used to estimate 'untreated LDL-C levels' in patients using statins have not been validated, which is a limitation of our analyses. The individual variability in treatment response, which is considerable, is not taken into account in this approach as well. Its origins are incompletely understood and do not only depend on compliance; differences in lipid-lowering response to statins have also been ascribed to genetic factors. There are also other reasons which all might influence the individual response to statin treatment [27].

This study has some other limitations such as the post hoc design of this analysis; given the cross-sectional design of the study it is not possible to interpret the proportion of patients at goal. A fully compliant patient at goal (with an LDL-C level of <1.8 mmol/L according to the guidelines) could never enter the 'potential FH' group even on the highest dose of a high intensity statin: i.e. on

atorvastatin 80 mg/d he ends up with an untreated LDL-C of 1.7 × 2.12 = 3.77 resulting in 0 points according to the DNLC Criteria; even with a positive family history and premature personal history he ends up with only 3 points. The prevalence of FH may have been overestimated in the absence of analyses of gene variants; some of the patients could have polygenic hypercholesterolaemia and not FH.

Last, the time of the interview after the index CHD event varied between 6 months and 3 years. During this timeframe, some patients might have experienced a second, fatal event which prevented them from participation in the EUROASPIRE IV survey. Since potential FH is a risk factor for CHD, it can be anticipated that these patients are more represented in the deceased patients. Theoretically, the prevalence of potential FH we found might be an underestimation.

7. Conclusion

Potential FH is highly prevalent among patients that have experienced a CHD event and control of other CHD risk factors seemed to be less optimal than in other patients. Our results should increase the awareness of this serious condition with high CHD risk among treating physicians, and should encourage them to treat all risk factors aggressively, as well as to actively search for related potential FH patients among family members.

Disclosures

GDB was a consultant on an advisory panel of MSD and consulted with Amgen. GKH is holder of a Veni grant (91612122) from the Dutch Science Organisation (NWO), and his department has received research grant/lecture/adboard fees on his behalf from Amgen, AstraZeneca, Sanofi, Pfizer and Roche. JJPK acted as a consultant and received honoraria from the following companies: Aegerion, Amgen, AstraZeneca, Atheronova, Boehringer Ingelheim, Catabasis, Cerenis, CSL Behring, Dezima Pharmaceuticals, Eli Lilly, Esperion, Genzyme, Isis, Merck, Novartis, Omthera, Pronova, Regeneron, Sanofi, The Medicines Company, UniQure, Vascular Biogenics and Vivus.

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JC, JB and DDB have no interests to declare.

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