



Prevalence of potential familial hypercholesteremia (FH) in 54,811 statin-treated patients in clinical practice



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ABSTRACT

Background and aims: Familial hypercholesterolemia (FH) is a life-threatening disease, characterized by elevated LDL-C levels and a premature, increased risk of coronary heart disease (CHD) that is globally underdiagnosed. The percentage of patients with possible or probable FH in various countries was examined in the Dyslipidemia International Study (DYSIS).

Methods: DYSIS is a multinational, cross-sectional observational study of 54,811 adult outpatients treated with statin therapy. The percentages of patients with high levels of LDL-C, and with possible or probable FH, were assessed using the Dutch scoring method for FH across 29 countries, in age subgroups for the analysis population and among diabetes patients.

Results: Despite statin therapy, 16.1% (range 4.4–27.6%) of patients had LDL-C >3.6 mmol/L (140 mg/dL) across countries and the prevalence of possible FH was 15.0% (range 5.5–27.8%) and 1.1% (range 0.0–5.4%) for probable FH. The highest percentages of probable FH occurred in Egypt (5.4%), the Baltic states (4.2%), Russia (3.2%), and Slovenia (3.1%), with the lowest rates in Israel (0.0%), Canada (0.2%), and Sweden (0.3%). Rates of FH were the highest in younger patients (45–54 years) for secondary prevention, regardless of the presence/absence of diabetes.

Conclusions: Despite statin therapy, high LDL-C levels and rates of possible and probable FH were observed in some countries. The prevalence of FH was the highest in younger age patients, and >60% of patients with probable FH displayed CHD. Earlier diagnosis and treatment of patients with FH are needed to reduce CHD risk in these patients.

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1. Introduction

Familial hypercholesterolemia (FH) is a serious, life-threatening

disease [1–4], and is widely underdiagnosed [3,4]. It is clear that only rigorous screening in the population can identify affected patients and could reduce the high risk of cardiovascular disease (CVD) in these patients. FH is caused by a group of inherited genetic disorders in low-density lipoprotein (LDL) catabolism, attributed to defects in the LDL-receptor, apolipoprotein B, proprotein convertase subtilisin/kexin type 9 (PCSK9), and LDL receptor adaptor protein 1 (also known as autosomal dominant hypercholesterolemia), that result in elevated LDL-cholesterol (C) levels, as well as a

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premature and increased, life-threatening risk of coronary heart disease (CHD) [1–4]. In most populations worldwide [1], heterozygous (He) forms are more common than previously thought (1 in 250) and, as a consequence, the homozygous (Ho) form of FH affects approximately 1 in 160–300,000 in most populations worldwide [1]. In most European countries, a minority of patients (<1%) have been identified with FH, while in other countries the incidence is much higher [2].

Premature cardiovascular disease is common in HoFH and HeFH patients, with an increased risk of CVD, including stroke and myocardial infarction, occurring at young ages. Given the increased lifetime CHD risk associated with FH, lifestyle intervention and appropriate lipid-lowering therapy are recommended that can greatly reduce this risk [5]. Treatment recommendations include long-term cholesterol-lowering therapy for all adult HeFH and HoFH patients to reduce LDL-C by $\geq 50\%$, and more intensive lipid-lowering therapy to achieve levels of LDL-C <1.8 mmol/L (70 mg/dL) and <2.6 mmol/L (100 mg/dL) and non-HDL-C <3.4 mmol/L (130 mg/dL) when needed [1–3,5–8].

Diagnosis of FH is based on genotyping and/or evaluation in clinical practice that takes into account LDL-C levels, the presence of premature CHD in patients or in first-degree relatives, as well as a clinical examination for tendon xanthomata and arcus cornealis (at a young age) [2]. While only a genetic evaluation can confirm a diagnosis of FH, estimation based on scoring systems is widely accepted as well. The Dutch Lipid Network scoring method [9] is recommended in recent guidelines for FH diagnosis [10]. Other combined methods, such as the Simon Broome register group estimation [11], are similar to the Dutch scoring approach. Results from global registries, surveys, observational studies or other analyses reporting on the prevalence of FH are limited [12]. Hence, we sought to evaluate the percentage of patients with high LDL-C levels and possible or probable FH in various countries using the Dutch scoring method in the population of $>50,000$ adult outpatients treated with statins in the previously reported multinational, cross-sectional Dyslipidemia International Study (DYSIS) [13,14].

2. Materials and methods

2.1. DYSIS patient enrollment

This is an analysis of the population previously reported in DYSIS, an epidemiological, cross-sectional, multicenter study [13,14]. The study was conducted in Europe, China, Canada, Russia, South and northern Africa, as well as the Middle East (Austria, Belgium, Baltic states, Canada, China, Germany, Denmark, Egypt, France, Greece, United Arab Emirates, Israel, Ireland, Italy, Lebanon/Jordan, Netherlands, Norway, Portugal, Russia, Saudi, Slovakia, Slovenia, South Africa, Spain, Sweden, United Kingdom). The first patient was enrolled in 2008 and the last in 2013. A total of 6–10 statin-treated outpatients were enrolled consecutively per center ($n = 60,768$). Patients on combination therapy, such as statin plus ezetimibe, niacin, fibrates and bile-acid sequestrants, were also included. Informed consent was obtained from all patients, and the local ethical review committees approved the study protocol. On-site visits were performed to ensure the correctness of collected data. Source documentation and data accuracy was verified by site visits in randomly selected sites. Participants were enrolled based on the following criteria: ≥ 45 years old, treated with statins within 6–12 months, and had at least one fasting blood lipid profile available while on statins for ≥ 3 months within that 6–12 month time period. LDL-C was assessed per standard procedure in each country. Details are described elsewhere [13]. At the single examination visit, the full lipid profile, anthropometric parameters, and

the patients' clinical history including premature cardiovascular disease in first-degree relatives were assessed.

2.2. Data collection

Patient data were documented using local language case report forms and entered into one central database housed and managed at the Institut für Herzinfarktforschung, Ludwigshafen, Germany. Serum lipid levels were determined based on the patients' most recent blood tests (within 6–12 months, but at least three months on statin therapy). The lipid-lowering regimen used by each patient at the time of lipid measurement was also recorded. In particular, information was collected pertaining to statin type, dose level, and other lipid-modifying therapies utilized in combination with statins.

2.3. Diagnosis of FH and methods

To evaluate the rate of patients with possible FH per country, we based our analysis on the *Advanced method for the identification of patients with inherited hypercholesterolemia* as recommended by the recent European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidaemias [10]. A stepwise approach was subsequently applied. First, patients with high LDL-C despite statin treatment were identified. While baseline values of LDL cholesterol before treatment were not available, we estimated an approximate reduction of LDL-C by 30% (corresponding to the correction applied in this analysis). Therefore in treated patients who had an LDL-C >3.6 mmol/L (140 mg/dL), baseline values were correspondingly estimated to be > 5.2 mmol/L (200 mg/dL). A blood cholesterol of >5.2 mmol/L (200 mg/dL) is defined as a diagnostic criterion for FH by the authors of the European guidelines [10]. As a second step, we applied the Dutch scoring methods to all patients included in DYSIS, when completed information on the following criteria was available including age, gender, premature coronary artery disease (CAD) (male before 55, women before 60 years of age), first-degree relative known with premature CAD, and LDL-C values (Table 1). The sample represents 90.2% ($n = 54,811$) of the entire patients included in DYSIS, while in 9.8% one or more of the above parameters was missing. Parameters assessed were LDL-C, first-degree relative premature CAD, premature CAD and extra-coronary vascular disease in the patients themselves. Data on first-degree relative LDL-C and physical examinations for tendon xanthomata and arcus cornealis were not collected in DYSIS.

2.4. Statistical analysis

Descriptive analysis was performed using standard statistical methods. Values are displayed as medians and inter-quartile range (IQR) or percentages (%). Statistical testing for comparison was performed with the Kruskal-Wallis or Chi-square tests. The prevalence of potential FH was categorized by age using the Cochran-Armitage-test for trend. LDL-C as a continuous variable was transformed into a categorical one, for the identification of patients possibly suffering from FH. Additionally, age was further assessed per ten-year intervals. Statin equivalence was assessed using the equation on the relative LDL-C-lowering efficacy published by the FDA (<http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm#Relative>) [15]. In brief, an atorvastatin equivalent of 20 mg was considered to be equivalent to pravastatin 80 mg, rosuvastatin 5 mg, and simvastatin 40 mg, while atorvastatin 10 mg was equivalent to pravastatin 40 mg, and simvastatin 20 mg. A p -value <0.05 was considered statistically significant. SAS version 9.3 was used for all calculations. Analyses were performed at the Institut

Table 1
Diagnostic criteria for the clinical diagnosis of HeFH [10].

Criteria	Score
Family history	1
First-degree relative known with premature CAD &/or first degree relative with LDL-C >95th centile	2
Clinical history	2
Patient has premature CAD	1
Patient has premature cerebral/peripheral vascular disease	6
Physical examination	4
Tendon xanthomas (TX)	8
Arcus cornealis below the age of 45 years	5
LDL-C	3
>8.5 mmol/L (~330 mg/dL)	1
6.5–8.5 mmol/L (~250–329 mg/dL)	Score >8
4.9–6.5 mmol/L (~190–249 mg/dL)	Score 6–8
4.0–4.9 mmol/L (~155–189 mg/dL)	Score 3–5
Clinical diagnosis	
Definite FH	
Probable FH	
Possible FH	

CAD, coronary artery disease; LDL-C, low density lipoprotein cholesterol; TX, tendon xanthomas; FH, familial hypercholesterolemia. To convert SI units to conventional units divide by 0.0259 for cholesterol.

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3. Results

A total of 54,811 patients from 29 countries were included in the analysis. Of these, 83.8% of patients were categorized with a clinical diagnosis as 0–2 points for FH, 15% as 3–5 points for possible FH, and 1.2% as >6 points for probable FH (Table 2). The mean age of all patients across categories was 65 years, 45.4% of the subjects were females, and the mean baseline levels of LDL-C, HDL-C and total cholesterol were 3.3 mmol/L (129 mg/dL), 1.3 mmol/L (50 mg/dL) and 4.6 mmol/L (178 mg/dL), respectively. Higher levels of BMI, LDL-C, total cholesterol and triglycerides were present in the probable FH (>6 point) group compared with the FH 0–3 and 3–5 points groups ($p < 0.0001$ for all). Baseline comorbidities for all patients and those with possible and probable FH are provided by country in Supplementary Tables 1, 2 and 3, respectively.

Ischemic cardiovascular diseases occurred at a statistically significantly and clinically-relevant higher level in the group of patients with probable FH compared with the total population (Table 2). Ischemic heart disease was most pronounced with 60.1% vs. 38.8% in the total population ($p < 0.0001$), and similar

differences were observed for peripheral artery disease (PAD) (12.8% vs. 6.0%) and cerebrovascular disease (17.3% vs. 13.6%, $p < 0.001$). Strikingly, we also detected a difference in the prevalence of congestive heart failure (14.9% vs. 7.8%, $p < 0.0001$). In contrast, there were no relevant differences detected for those with hypertension and diabetes, regardless of the potential FH status.

The most widely used statin doses were atorvastatin equivalents of 10 mg per day in 41.2% and 20 mg in 37.7% (11.1% 5 mg, 8.3% 40 mg, and 1.8% 80 mg) of patients (Table 3). There were also a small proportion of patients (11.9%) treated with combination therapy (6.6% with ezetimibe, 4.3% with a fibrate, 0.7% with niacin, and 0.3% with a bile acid sequestrant). There were no differences in the use of concomitant medications between the FH groups (Table 3).

Despite statin therapy, evaluating the percentage of patients suffering from high LDL-C levels, 16.1% ($n = 8832$) of the patients displayed LDL-C levels >3.6 mmol/L (140 mg/dL), 8.2% ($n = 4500$) had LDL-C >4.1 mmol/L (160 mg/dL), 2.5% ($n = 1366$) had LDL-C >4.9 mmol/L (190 mg/dL) and 0.8% ($n = 427$) had LDL-C >5.7 mmol/L (220 mg/dL). The range was 4.7–27.6% among the different countries. The highest prevalence of >25% with high LDL-C on statin treatment was found in the Baltic states (Estonia, Latvia,

Table 2
Characteristics and comorbidities of patients depending on estimated probability of FH.

Median (range)	Total n = 54,811	0–2 points n = 45,936	3–5 points n = 8219	>6 points n = 656	<i>p</i> -value ^a
Age, years	65 (57–72)	65 (58–73)	60 (53–68)	56 (52–62)	<0.0001
Female %	45.4	44.0	52.0	54.7	<0.0001
BMI, kg/m ²	27 (24–30)	26 (24–30)	27 (24–30)	28 (25–32)	<0.0001
Total cholesterol, mmol/dL	4.6 (3.9–5.4)	4.4 (3.7–5.1)	6.2 (5.5–6.7)	7.4 (6.6–8.2)	<0.0001
LDL-C, mmol/dL	3.3 (2.6–4.2)	3.1 (2.5–3.8)	5.4 (5.0–5.9)	6.9 (6.3–7.9)	<0.0001
Triglycerides, mmol/dL	1.5 (1.1–2.1)	1.5 (1.0–2.1)	1.7 (1.3–2.4)	2.1 (1.5–2.8)	<0.0001
FPG, mmol/dl ^b	5.8 (5.1–7.0)	5.8 (5.1–7.0)	5.7 (5.1–7.0)	5.7 (5.0–6.9)	ns (0.12)
SBP, mmHg	130 (120–140)	130 (120–140)	132 (120–142)	140 (130–150)	<0.0001
DBP, mmHg	80 (70–85)	80 (70–84)	80 (75–88)	80 (79–90)	<0.0001
Hypertension, % ^c	78.2	78.7	74.8	84.0	0.0001
Ischemic heart disease, %	38.8	38.7	38.0	60.1	<0.001
Cerebrovascular disease, %	13.6	13.7	12.6	17.3	<0.0001
Peripheral artery disease, %	6.0	5.8	6.3	12.8	<0.0001
Congestive heart failure, % ^d	7.8	7.7	7.8	14.9	<0.0001
Diabetes mellitus, %	40.2	41.3	34.5	33.8	<0.0001

BMI, body mass index; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; ns, non-significant; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are reported as median and interquartile range or percentages.

To convert SI units to conventional units divide by: 0.0259 for cholesterol, 0.0113 for triglycerides, and 0.0555 for fasting glucose.

^a Chi-Square or Kruskal Wallis test; *p*-values are 3-way comparisons between FH groups (0–2, 3–5, 6+ points).

^b FPG availability: 70.8% (36.76/51.93).

^c BP $\geq 140/90$ mmHg or use of antihypertensive medication.

^d Congestive heart failure includes patients with chronic heart failure (NYHA graded 2–3), as diagnosed by the treating physician.

Table 3
Cardiovascular medications of patients depending on estimated probability of FH.

%	Total n = 54,811	0–2 points n = 45,936	3–5 points n = 8219	>6 points n = 656
Beta-blockers	31.4	31.9	28.1	38.9
Calcium channel blockers	30.6	31.3	26.9	29.9
Diuretics	22.2	22.6	19.8	26.7
Angiotensin converting enzyme inhibitors	27.5	27.6	26.6	36.4
Angiotensin receptor blockers	26.1	26.9	22.0	23.7
Aspirin	55.7	57.1	47.8	58.4
Clopidogrel	14.0	14.3	12.2	19.7
Statin dose ^a mg/day (SD)	16.2 (12.4)	15.9 (12.1)	17.0 (13.6)	23.1 (18.2)

^a Calculated in atorvastatin equivalent mmol/L (mg/dL).

Lithuania; 27.6%), Portugal (26.0%), and Spain (28.0%), the lowest prevalence of <10% in Belgium (8.7%), Canada (4.7%), Denmark 6.3%, United Arab Emirates (5.2%), Israel (6.3%), Ireland (9.0%), Netherlands (8.8%), Saudi (5.8%), Sweden (6.6%), and UK (5.1%). Of note, 5 countries/regions displayed a high percentage ($\geq 4.0\%$) of high LDL-C levels (>4.9 mmol/dL [190 mg/dL]) including the Baltic states 9.0%, Egypt (5.2%), Greece (4.5%), Russia (4.3%), and Spain (4.0%). These results were derived before correcting for LDL-C.

According to the Dutch scoring method, FH was considered possible in individuals with 3–5 score points and probable in individuals with 6–8 score points [7]. After correcting for the statin treatment effect (estimated naïve LDL-C), 15.0% (range 5.5–27.8%) of patients could possibly and 1.1% (range 0.0–5.4%) could probably suffer from FH (Figs. 1 and 2). The highest levels of probable FH were found in Egypt (5.9%), the Baltic states (4.9%), Russia (3.2%), and Slovenia (3.4%), lowest in Israel (0.0%), Canada (0.2%), and Sweden (0.3%) (Fig. 2).

An age-directed analysis was performed at 10-year intervals. The prevalence of possible or probable FH was highest in the youngest age group of 45–54 years (27.5% and 2.9%, respectively; $n = 9488$) and declined thereafter to 15.5% and 1.2% in the 55–64 years ($n = 18,058$) group, 10.8% and 0.5% in 65–74 years ($n = 17,796$) and 9.3% and 0.4% in patients ≥ 75 years of age ($n = 9469$). This distribution was highly significant (p for trend

<0.0001). The percentage of patients suffering from possible or probable FH, further stratified as primary and secondary prevention, confirmed the observation of the highest prevalence rate of FH in younger patients, but more specifically in those who already suffered from an ischemic heart or cerebrovascular disease event (Fig. 3 and Supplementary Table 4). However, within this study, only statin-treated patients and not the general population were included, which could create a selection bias.

An age-related analysis among the diabetes patients was also performed. Similarly, the prevalences of possibly or probably FH in diabetics were also more pronounced in the younger age group (Fig. 4). However, there was little difference between patients with and without diabetes (Supplementary Table 5).

4. Discussion

In this multinational study of 54,811 patients enrolled between 2008 and 2013, we found a large proportion of patients with high LDL-C levels of >4.9 mmol/L (190 mg/dL) that ranged from 0.4 to 9.0% per country, despite statin therapy with atorvastatin equivalents of 10 and 20 mg in $\sim 40\%$ of the patients for ≥ 3 months. Screening for FH according to criteria set by the EAS/ESC guidelines revealed that 15.1% of individuals could possibly, and 1.1% may probably suffer from a genetic disposition to elevated blood

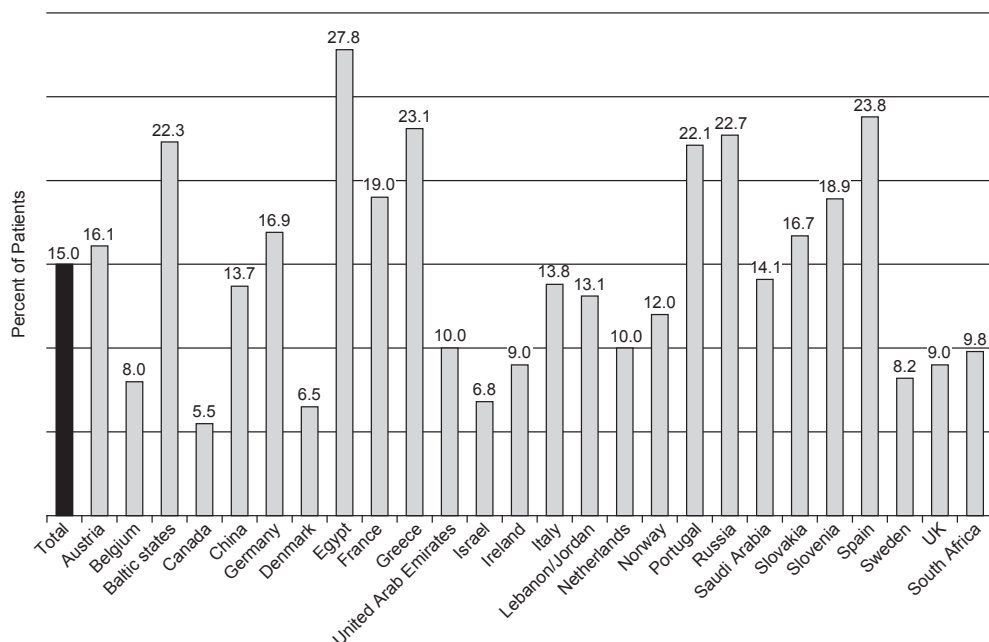


Fig. 1. Percentage of statin-treated patients potentially suffering from FH per country. Possible FH (3–5 score points) category. Baltic states: Estonia, Latvia, Lithuania.

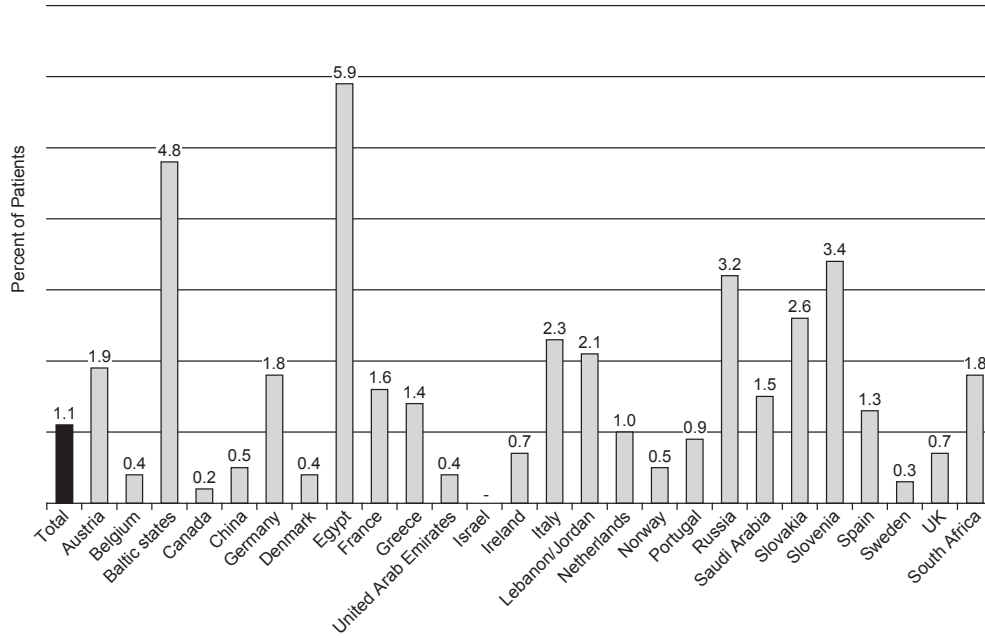


Fig. 2. Percentage of statin-treated patients probably suffering from FH per country. Probable FH (6–8 score points) category. Baltic states: Estonia, Latvia, Lithuania.

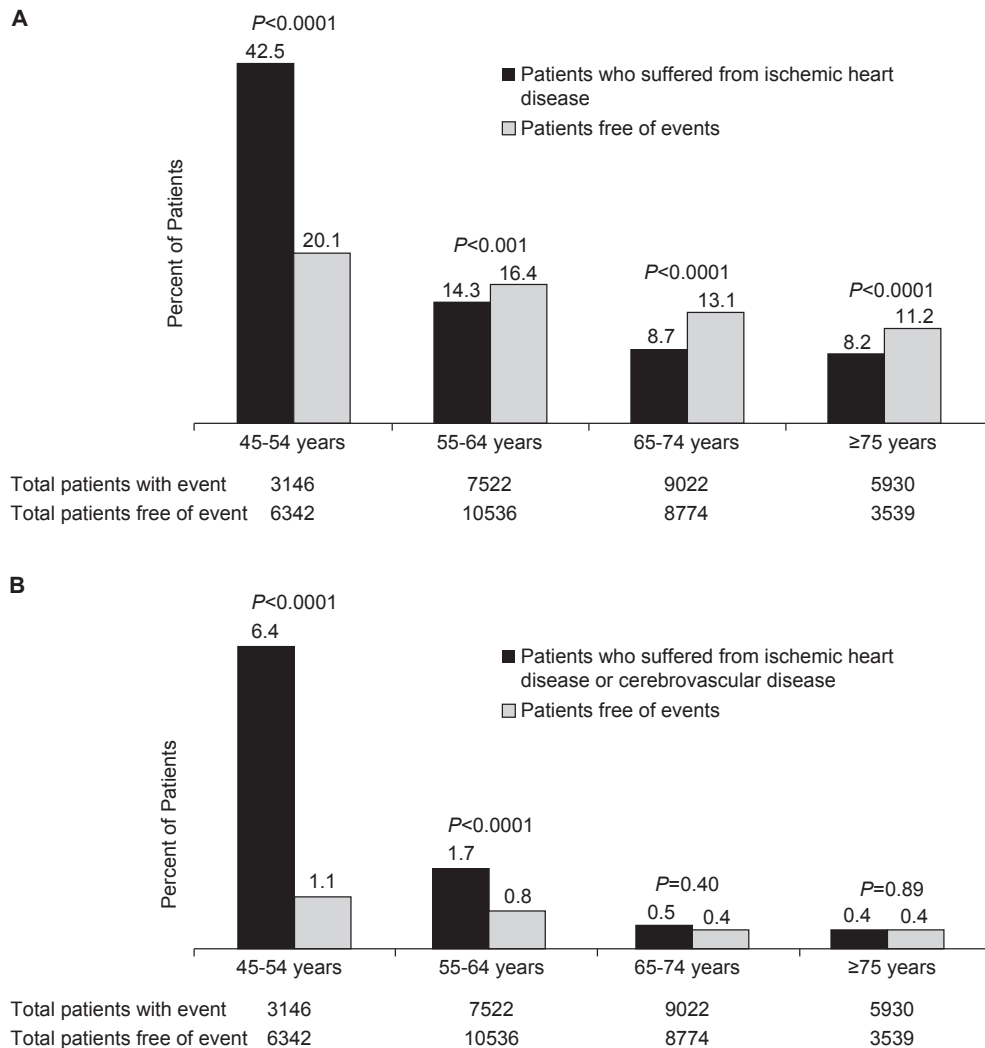


Fig. 3. Distribution of patients potentially suffering from FH for age groups 45–54, 55–64, 65–74, and ≥75 years, and stratified for primary and secondary prevention. (A) Possible FH defined as 3–5 score points; (B) probable FH defined as 6–8 score points.

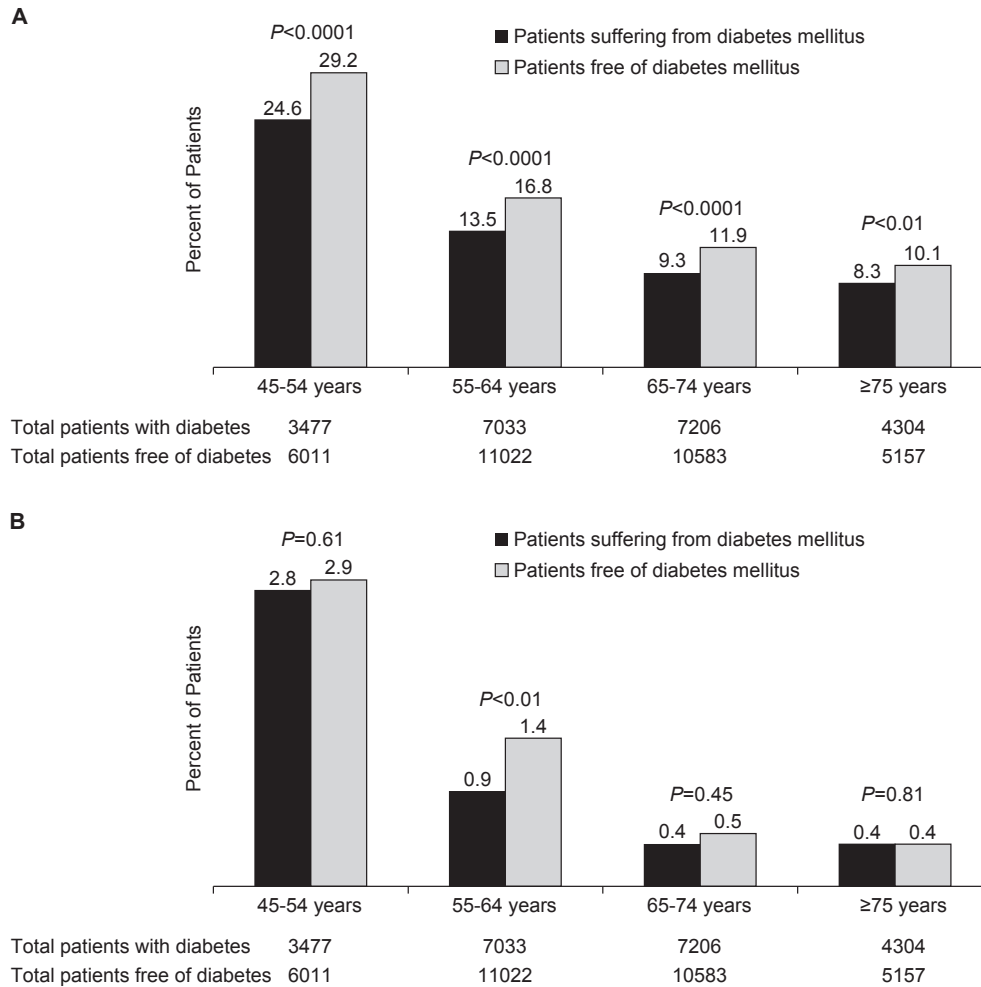


Fig. 4. Distribution of patients potentially suffering from FH for age groups 45–54, 55–65, 65–74, and ≥75 years, and stratified for diabetes mellitus. (A) Possible FH defined as 3–5 score points; (B) probable FH defined as 6–8 score points.

cholesterol levels. Prevalence for possible and probable FH is reported for the first time, especially for China ($n = 23,973$), Egypt ($n = 1322$), and Austria ($n = 753$) among several other countries.

High LDL-C values can be related to genetic, environmental, and secondary causes. These include (1) loss-of-function polymorphisms in the LDL-receptor, adaptor protein, and ApoB, and gain of function polymorphisms in PCSK9 [2]; (2) environmental factors such as a high-density calorie-rich diet of saturated fat or trans-fatty acids [16,17]; (3) chronic use of cholesterol-increasing medication (e.g., corticosteroids) [18]; and (4) endocrine diseases, with hypothyroidism being the most prevalent [19]. While dietary factors may account for high LDL-C levels, this is more limited to certain age groups; whereas genetically-related, high blood cholesterol levels occur at birth and are life-long [20].

Consequences of hyperlipidemia include the early development of atherosclerotic disease leading to myocardial infarction [2], with subsequent remodeling of the left ventricle that can result in congestive heart failure [21,22]. This widely under-appreciated fact is supported by findings from a follow-up analysis of the WOSCOPS trial [23]. In the original 5-year period of the trial, pravastatin lowered LDL-C by 26% and the risk of fatal or nonfatal coronary events by approximately 30% compared with placebo; whereas in a 10-year follow up of the study in which patients in the original statin and placebo groups were treated equivalently with statins to similar LDL-C levels, there was a significantly greater reduction in

major cardiovascular events and heart failure in those in the original pravastatin group who received treatment during the full 10-year period compared with those in the less-treated, original placebo group. The data presented in our study indicate a similar trend with an approximate 2-fold increase in not only ischemic diseases, but also in CHF in the group with the highest probability of FH (Table 2). In patients with FH, the elevation in serum levels of LDL-C occurs from the moment of conception and greatly increases the likelihood of developing atherosclerotic disease at a young age [2].

Both the effect of developing and reducing CVD risk is related to the absolute amount of blood cholesterol over time. The clinical implications of this can be extreme since homozygous FH patients can suffer from major vascular events early in childhood and, if untreated, can result in mortality by the age of 30 [1]. Mendelian randomization studies have confirmed that long-term exposure to even small elevations in blood cholesterol levels can substantially increase CHD risk over time [20] and is consistent with the observations in our epidemiologic study indicating a significantly higher burden of CVD in patients probably suffering from FH.

The EAS called for nationwide screening of FH in a recent position paper [2]. Similarly, the expert panel of the US National Lipid Association documented an under diagnosis of FH and a need for better screening [7]. The data presented herein indicate large regional differences in percentages of probable FH ranging from 0.0% in Israel to 5.4% in Egypt, 4.2% in the Baltic states, and 3.2% in

Russia. To our knowledge, this very high rate observed for Egypt is a novel finding. These differences may be attributed to the founder effect or consanguinity, and/or selection of patients by high LDL-C and treatment. Our study extends the results of a previously reported analysis of data in coronary patients from 24 European countries (EUROASPIRE IV) [24] which documented high age-standardized rates (>10%) of potential FH in Bosnia, Ireland, Latvia, Lithuania, Poland, Russia and Serbia, as well as regional variation. Although the data in our analysis were not determined in study patients who had been hospitalized for a coronary event as in the EUROASPIRE survey, similar rates of FH were observed in the 2 studies. EUROASPIRE IV reported a 7.2% rate for probable FH and a 31.6% rate for possible FH in coronary post-PCI patients, whereas our analysis of DYSIS revealed a 6.4% rate for probable FH and a 42.5% rate for possible FH in patients 45–54 years of age who did suffer from a prior cardiovascular event. Moreover, both studies showed that the greatest prevalence of FH occurred in younger patients (<50 years of age) and highlight the need for early detection given the life-long elevated LDL-C and premature CHD in these high risk patients. The results of these studies indicate a need for further analyses of FH worldwide and, importantly, better screening and therapeutic action in these patients. In this context, it is striking that patients with >6 score points in our analysis manifested evidence of atherosclerotic disease with a high prevalence, but were not treated in a manner different from that of the general analysis population, similar to observations in EUROASPIRE IV [24].

The continuum of CV disease burden can be substantially reversed by effective lipid-lowering therapy, as proven for statin therapy in numerous trials [25], and for ezetimibe in the recently reported IMPROVE-IT outcomes trial [26] [27], while the effect of PCSK9 inhibitors on cardiovascular outcomes is being evaluated in ongoing clinical trials [28,29]. Optimal treatment of FH patients has been addressed in respective guidelines and consensus statements [1,4,7,10] and follows an approach of treatment goals [1,2] or a $\geq 50\%$ reduction of LDL-cholesterol and if additional LDL-C lowering is needed, combination therapy can be considered [7,30]. After correcting for treatment effect on the basis of LDL-C lowering efficacy, 16% of the patients included in our study had LDL-C levels >3.6 mmol/L (140 mg/dL), and <2% were treated with a high-dose statin equivalent and ~12% with a statin/non-statin combination. Based on the variability of LDL-C lowering response demonstrated for high-dose statin therapy in achieving optimal LDL-C lowering [31], combination therapy may be needed in high-risk patients in order to achieve treatment goals. The authors of the EAS consensus statement [2] highlight the need for intensified lipid-lowering therapy (statins in the highest tolerated dose, followed by ezetimibe and bile acid sequestrants) in an age-dependent manner to reduce risk levels to those of primary prevention in the general population. We could not identify differences in statin-treatment among FH risk groups, nor in the utilization of antihypertensive or antithrombotic medications which were used at a strikingly low level given the manifestation of ischemic heart disease in nearly two thirds of the patients probably suffering from FH (39% beta blockers, 20% clopidogrel). This is further in line with data from EUROASPIRE IV that showed no significant difference in the use of drugs for cardiovascular disease between FH risk groups [24].

There are several limitations to our study. In DYSIS, physical examination of the patients was not performed (e.g., xanthomas, arcus cornealis). Thus, we were not able to include this information in the score points and the assessment of FH may be somewhat incomplete. However, this reflects a more conservative approach in our analysis, that may even under-report the actual genetic rate of FH patients, but nonetheless provides a better understanding regarding the prevalence of this widely under-diagnosed and under-treated disease. Further, we did not have baseline LDL-C

levels, but only treated LDL-C levels for ≥ 3 months and performed a correction for this treatment effect. The correction of baseline LDL-C values, estimated based on an approximate LDL-C reduction of 30%, may also be a limitation particularly in countries with poor adherence to therapy. In DYSIS, cholesterol was not assessed in a centralized lab, but was analyzed individually in the countries as per daily practice routine, and thus may introduce some variability in regional comparisons. We were also unable to perform genetic screening in these respective countries and thus could not confirm our data by that means. Additionally, differences in the various cholesterol guidelines used in the countries, traditions and lifestyles, as well as referral criteria from the many different medical centers and physicians across the countries, may have contributed to selection bias. It should also be considered that the age-related analysis in this prospective registry study may be somewhat over-estimated attributed to the selection criteria for identification of the young subjects who were already being treated with lipid-lowering therapy and may have had premature CHD; however, these results are in line with prior reports of higher prevalences for FH in younger patients. Our analysis was designed to survey FH data for each country in general terms; thus, we did not ascertain additional ethnic, religious and socioeconomic information which may vary among countries and is furthermore, restricted from documentation in many European countries.

In conclusion, in this multinational study of 54,811 patients including 23,973 individuals in China, we found unexpectedly high rates of possible and probable FH, as well as very high cholesterol levels in some countries, despite statin therapy. The highest rates of FH were found in Egypt, the Baltic states, Russia, and Slovenia. The prevalence of FH was more common in younger age groups, while >60% of patients probably suffering from a genetic form of hypercholesterolemia displayed CVD. Furthermore, treatment of these potential FH patients with therapy equivalent to the LDL-C lowering efficacy of a mean atorvastatin dose of ≤ 20 mg in the majority of patients (~38% on statins, ~12% on combination therapy) was insufficient to adequately control LDL-C levels. This suggests that intensification of therapy with higher statin doses and/or a greater use of combination therapy is needed to further reduce the burden of CVD (e.g., CHD or PAD) in these patients. Additionally, these data are novel, providing first-time reports of FH prevalence in many of the countries, indicating the need for widespread screening and treatment of FH patients with high blood cholesterol levels, in order to reduce CVD risk. The scoring method used herein and proposed by the EAS/ESC guidelines provides a tool for routine use in daily clinical practice that could help to further reduce the burden of this disease through earlier diagnosis and treatment of patients.

Conflict of interest

A. L. Catapano has received research grants from Merck, Schering-Plough and AstraZeneca, and received honoraria from Amgen, AstraZeneca, Eli Lilly, Genzyme, Kowa, Merck, Novartis, Pfizer, Recordati, Roche and Sanofi-Regeneron. L. Tokgözoğlu has received honoraria/consultancy fees from Merck, Amgen, Astra, Novartis, Abbott, Daiichi Sankyo, Pfizer, Actelion, Servier, Sanofi, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Menarini, Kowa, Aegerion and Synageva. A. Gitt received honoraria from Merck & Co., Inc. for contribution to the DYSIS study. M. Horack, reports that his institution received funding for recruitment and biostatistics for the DYSIS registry. J. Ferrieres received consulting fees from AstraZeneca, Amgen, Merck and Sanofi. M. Farnier reports having received grants, consulting fees and/or honoraria and delivered lectures for Abbott, Amgen, AstraZeneca, Eli Lilly, Genzyme, Kowa, Merck, Novartis, Pfizer, Recordati, Roche and Sanofi-Regeneron. P.P. Toth has served on speaker's bureaus for Amarin, AstraZeneca, GSK,

Merck, Kowa, and is a consultant to Amgen, AstraZeneca, Kowa, Merck, and Novartis. B. Ambegaonkar, P. Brudi, D. Lautsch and J. Tomassini are employees of Merck, Sharp & Dohme, a subsidiary of Merck & Co. Inc., Kenilworth, NJ, USA.

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Author contributions

All authors critically reviewed and provided substantial input on all manuscript outlines and drafts. All authors approved the final version of this manuscript for submission.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2016.07.007>.

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