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Burden of cardiovascular disease in a large contemporary cohort of patients with heterozygous familial hypercholesterolemia

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ABSTRACT

Background and aims: Heterozygous familial hypercholesterolemia (HeFH) is increasingly better diagnosed and treatments can improve the cardiovascular prognosis. We evaluated the long-term cardiovascular risk of HeFH using the French REgistry of Familial hypERCHOLesterolemia (REFERCHOL).
Methods: We studied HeFH patients diagnosed genetically and clinically by the Dutch Lipid Clinic Network (DLCN) criteria in all lipid clinics across the country and their 5-year risk of cardiovascular events (all fatal and non-fatal acute coronary, cerebral and peripheral arterial disease events, aortic valve replacement surgery) using the French national health data system.
Results: The database comprised 3202 individuals, 2010 (62.8%) with genetically verified HeFH and 1192 (37.2%) a DLCN score ≥6. Of these individuals, 2485 (77.6%) were in primary prevention and 717 (22.4%) in secondary prevention. The incidence of cardiovascular events was 24.58 per 1000 person-years for the overall sample, 19.15 in primary prevention and 43.40 in secondary prevention. The incidence of myocardial infarction, cerebral infarction and death was 16.32 per 1000 person-years for the overall sample, 12.93 in primary prevention and 28.08 in secondary prevention. The incidence of aortic valve replacement was 1.78 per 1000 person-years. In the overall sample, at inclusion, 41% were not treated for LDL cholesterol, 48% of these in primary prevention and 20% in secondary prevention and high-dose statins were used by only 24% of individuals, 15% of these in primary prevention and 45% in secondary prevention.
Conclusions: The incidence of cardiovascular events in HeFH is high and lipid-lowering treatment is far from optimal. The cardiovascular risk of HeFH is underestimated and patients are inadequately treated.

1. Introduction

Heterozygous familial hypercholesterolemia (HeFH) is a common genetic disease, but one which is still little known [1]. Its pathophysiology and genetic characteristics have long been

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particularly well described [2]. However, knowledge of the disease at the population level is entirely relative as this is a silent and lifelong atherosclerosis [3]. It is often only diagnosed when the patient is admitted to hospital for an acute coronary syndrome [4,5].

For several years, many teams worldwide have been attempting to record all cases of HeFH in their respective countries. The Netherlands and Norway were forerunners [6,7] in the field and France also started a registry a few years ago [8].

Nevertheless, there are few data on the long-term course of patients with HeFH on a nation-wide or region-wide scale. Data are also sparse on management of the disease at the population level [9].

The aim of this work was to describe at a population level the incidence and recurrence of cardiovascular events in HeFH and individual management of the disease on a nationwide scale.

2. Materials and methods

2.1. Study design and population

The New French Society of Atherosclerosis has established a national registry, the French REgistry of Familial hypERCHOLesterolemia (REFERCHOL), to identify patients with HeFH in France with the objective of assessing screening practices, treatments, and clinical outcomes [10–12]. Patients eligible for our study were those who visited a participating lipid clinic and were diagnosed with HeFH, either clinically (Dutch Lipid Clinic Network score (DLCN) $\geq$6) or genetically.

Twenty-three lipid clinics contributed data. The registry was declared to the French National Agency for the Safety of Medicines and Health Products (ANSM) under the number 2014-A01549-38. The study protocol was evaluated by two committees: the French advisory committee on data processing for medical research (CCTIRS) and the French data protection authority (*Commission Nationale Informatique et Libertés*, CNIL) in May and November 2015, respectively. These 3 authorizations guarantee the scientific and ethical validity of the study and include the informed consent of the patients.

Clinical and laboratory data from the patients' medical records were obtained during routine clinic visits and were entered into the registry database by trained research staff. Patient data (age, height, weight, blood pressure, smoking status, previous personal and family cardiovascular history, a full lipid profile, use of lipid-lowering drugs) were collected. Premature cardiovascular disease was defined as the occurrence of a first event before 55 years in men and before 65 years in women. Cardiovascular history and associated risk factors were obtained from the REFERCHOL registry at the start of the study and cardiovascular events including coronary heart disease, aortic valve surgery, stroke or transient ischemic attack, peripheral artery disease and death were obtained from the French national health data system (*Système National des Données de Santé*, SNDS) for follow-up.

2.2. Exposure and outcomes

This cohort study used data from the SNDS [13]. The SNDS includes claims data for $\geq$65 million beneficiaries and is highly representative of the French population, covering 99% of the total population. The datasets used in the analysis included the *Système National d'Information Inter-Régime de l'Assurance Maladie* (SNIIRAM, the national information system for the health insurance dataset), which contains demographic and administrative patient data, date of death, healthcare visits and procedures reimbursed. Data from hospitals and other healthcare facilities were extracted from the *Programme de Médicalisation des Systèmes d'Information* (PMSI, the French national hospital informatics database), which includes inpatient data such as medical information, related diagnoses (based on International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] codes), and medical procedures. SNDS data are linked through a unique patient ID (social security number) to various databases, providing a lifelong patient history of prescriptions and cardiovascular events.

Lipid-lowering treatment (LLT) was identified at baseline and during follow-up using reimbursement data available from the pharmacy claims data (part of the SNIIRAM database). LLT intensity categories were based on LDL-C reduction observed in clinical trials and were classified as low intensity (LDL-C reduction <30%), moderate intensity (30%–50%) and high intensity ($\geq$50%). High-intensity statins include atorvastatin 40–80 mg and rosuvastatin 20–40 mg. Moderate-intensity statins include atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, and fluvastatin 80 mg. Low-intensity statins include simvastatin 10 mg, pravastatin 10–20 mg, fluvastatin 20–40 mg. Ezetimibe monotherapy was considered as low intensity, whereas any combination of ezetimibe with a statin (whatever the dose) was considered as high intensity. Adherence was measured annually by the proportion of days covered (PDC) using prescription data and correcting for overlapping prescriptions (13). Patients were considered adherent if PDC >80%.

The primary endpoint, total cardiovascular events, was defined as all fatal and non-fatal acute coronary, cerebral and peripheral arterial disease events and aortic valve replacement surgery. The secondary endpoint was defined as all-cause mortality, acute coronary and cerebral events.

2.3. Statistical analysis

Continuous data were expressed as mean ± standard deviation when following a normal distribution and as median (interquartile range) when not. Categorical data were displayed as counts and percentages. Groups were compared using Student's t-test or analysis of variance for continuous variables and χ^2 or Fisher exact tests for categorical variables. Incidence rates for total cardiovascular events or all-cause mortality, acute coronary and cerebral events during follow-up were computed. Outcome incidence rates during follow-up were expressed per 1000 person-years (PY). Survival analyses were conducted using the Kaplan-Meier method. A p-value of 0.05 was considered significant for all tests. All analyses were performed with SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 4022 patients with familial hypercholesterolemia identified in the REFERCHOL registry were sought in the national health database. These patients were matched with the HeFH data collected by the registry and also with the data on follow-up and prognosis collected in the national SNDS database (Fig. 1).

After exclusion of patients with homozygous familial hypercholesterolemia and those who did not have probable or definite HeFH (DLCN <6), 3202 patients with a verified diagnosis of HeFH and complete follow-up were studied. The observation period extended from January 1, 2013 to December 31, 2018: a 1-year period for risk factors identification and 5 years of follow-up (Supplementary Fig. 1). During follow-up, 234 cardiovascular events were recorded in 2485 patients who were in primary prevention at the beginning of the study and 153 cardiovascular events in 717 patients who were in secondary prevention at the beginning of the study.

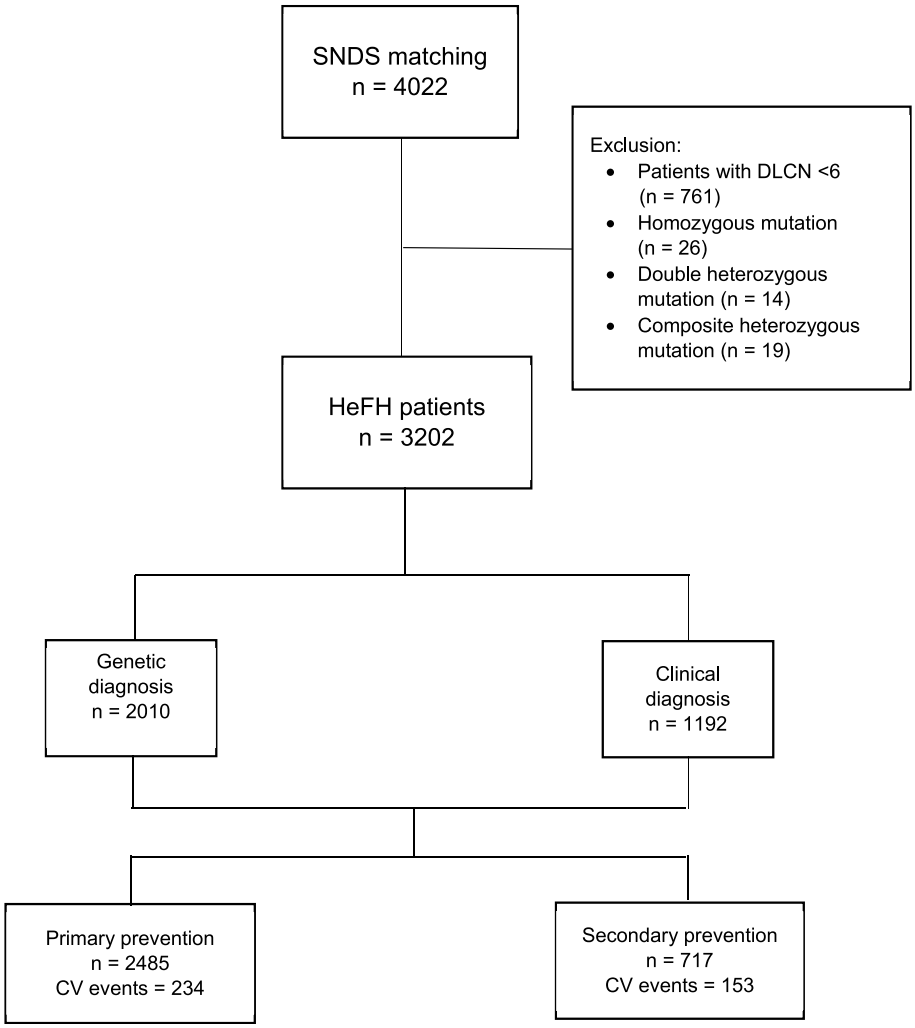

Fig. 1. REFERCHOL cohort flowchart.
SNDS, French national health data system; HeFH, heterozygous familial hypercholesterolemia; DLCN, Dutch Lipid Clinic Network; CV, cardiovascular.

The cardiovascular events recorded during the follow-up period are presented in Table 1. The majority were coronary events. However, around 11–12% were events related to cerebral or peripheral atherosclerosis. The cardiovascular events according to gender are presented in Supplementary Table 1. The cardiovascular events according to the type of diagnosis (genetic or clinical) are presented in Supplementary Table 2.

The incidence of all cardiovascular events was 24.58 per 1000 PY in the total sample, 19.15 per 1000 PY in primary prevention and 43.40 per 1000 PY in secondary prevention.

When only total mortality and acute coronary and cerebral episodes (3-point major adverse cardiovascular events) were taken into account, the incidence of events was 16.32 per 1000 PY in the total sample, 12.93 per 1000 PY in primary prevention and 28.08 per 1000 PY in secondary prevention. The incidence of aortic valve replacement was 1.78 per 1000 PY in the total sample.

In primary prevention, HeFH men have a cardiovascular risk twice as high as HeFH women. In secondary prevention, the cardiovascular risk is 30% higher in HeFH men compared to HeFH women.

The incidence of cardiovascular events in the 3 clinical contexts (total sample, primary prevention and secondary prevention) is shown in Fig. 2.

The clinical parameters are presented in Table 2. Our national sample consisted of young individuals aged around 49 years and the majority (52%) were men. In primary prevention, age was around 46 years and the majority were women, while in secondary prevention age was around 59 years and 28% were women. The clinical parameters according to the type of diagnosis (genetic or clinical) are presented in Supplementary Table 3. HeFH patients in primary prevention with a genetic diagnosis are younger, more often female patients and have a more favorable cardiovascular risk profile with less smoking, less diabetes, and less high blood pressure.

With regard to cardiovascular events occurring during follow-up, 53% of patients in primary prevention and 63% in secondary prevention had genetically verified HeFH. With regard to risk factors, body mass index was 25 (±5) kg/m^2, 28% of patients were regular smokers, 7% had diabetes, 20% had arterial hypertension and 28% had a family history of premature cardiovascular disease in first-degree relatives (before the age of 55 years in men and before the age of 65 years in women).

The laboratory results of the HeFH patients recorded in the registry at the baseline visit are presented in Supplementary Table 4. Mean maximum LDL cholesterol values (across life span) were around 300 mg/dL. In primary prevention, LDL cholesterol in untreated HeFH patients was 249 mg/dL and in secondary prevention it was 231 mg/dL. The laboratory results of the HeFH patients according to the type of diagnosis (genetic or clinical) are presented in Supplementary Table 5. The maximum LDL cholesterol

Table 1
Cardiovascular events according to previous CVD history.

Type of event	Primary prevention n = 2485 n (%)	Incidence per 1000 person-years	Secondary prevention n = 717 n (%)	Recurrence per 1000 person-years	Total (n = 3202) n (%)	Rates per 1000 person-years
Follow-up, months (median) [Q1-Q3]	**59** [59; 59]		**59** [59; 59]		**59** [59; 59]	
Total CVD events	**234 (9.4%)**	**19.15**	**153 (21.3%)**	**43.40**	**387 (9.0%)**	**24.58**
3-point MACE *(all-cause mortality, AMI, stroke)*	**158 (6.3%)**	**12.93**	**99 (13.8%)**	**28.08**	**257 (8.0%)**	**16.32**
All-cause mortality	**37 (1.5%)**	**3.03**	**41 (5.7%)**	**11.63**	**78 (2.4%)**	**4.95**
Distribution of cardiovascular events						
Coronary events	**183 (78%)**	**14.98**	**113 (74%)**	**32.05**	**296 (76%)**	**18.80**
Acute myocardial infarction (AMI)	108 (46%)	8.84	47 (31%)	13.33	155 (40%)	9.85
Aortic valve replacement	18 (8%)	1.47	10 (7%)	2.84	28 (7%)	1.78
Unstable angina	53 (23%)	4.34	49 (32%)	13.90	102 (26%)	6.48
Other acute heart disease	4 (2%)	0.33	7 (5%)	1.99	11 (3%)	0.70
Cerebral events	**29 (12%)**	**2.37**	**15 (10%)**	**4.26**	**44 (11%)**	**2.79**
Stroke	13 (6%)	1.06	11 (7%)	3.12	24 (6%)	1.52
Transient ischemic attack	16 (7%)	1.31	4 (3%)	1.13	20 (5%)	1.27
Peripheral arterial disease	**22 (9%)**	**1.80**	**25 (16%)**	**7.09**	**47 (12%)**	**2.99**
Arterial embolism and thrombosis	14 (6%)	1.15	18 (12%)	5.11	32 (8%)	2.03
Occlusion and stenosis	8 (3%)	0.65	7 (5%)	1.99	15 (4%)	0.95

CVD, cardiovascular disease; MACE, major adverse cardiovascular events.

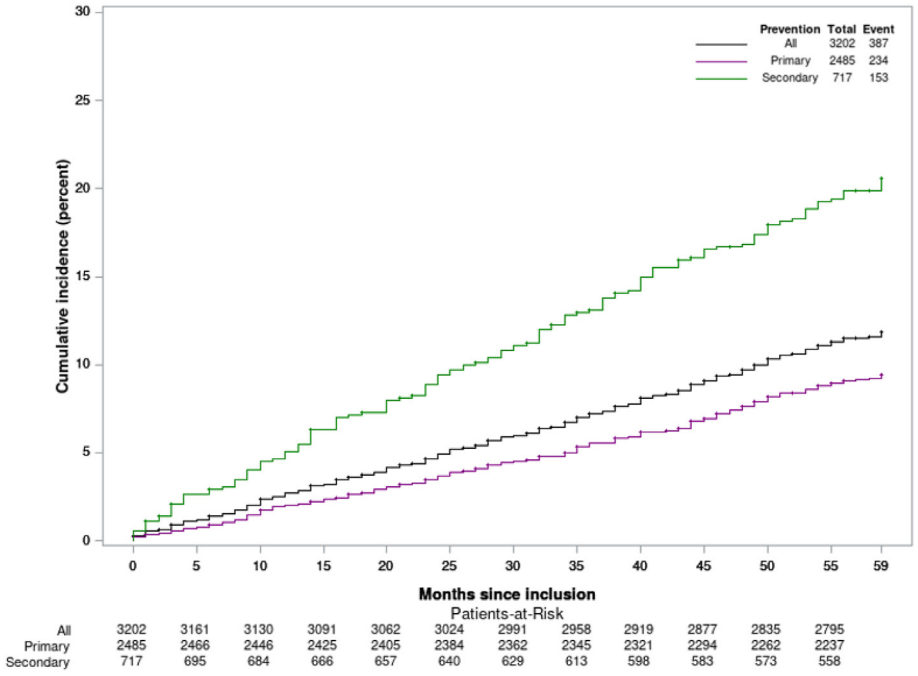

Fig. 2. Cumulative rates of all cardiovascular events according to previous cardiovascular history.

is higher in HeFH patients with a genetic diagnosis compared to HeFH patients with a clinical diagnosis both in primary prevention and in secondary prevention.

Lipid-lowering treatments at the start of the study and compliance with treatment during follow-up were obtained from the SNDS (Table 3).

In primary prevention, 48% of patients were not receiving lipid-lowering medication while in secondary prevention this proportion was 20%.

In both primary and secondary prevention, the majority of patients were not prescribed high-dose statins: only 15% in primary prevention and 45% in secondary prevention were receiving this treatment. Compliance with lipid-lowering treatments (PDC >80%) during the follow-up period was only 51% in primary prevention (51% in patients without events during follow-up and 52% in patients with events during follow-up, non-significant difference), while compliance was 58% in secondary prevention (57% in patients without events during follow-up and 61% in patients with events during follow-up, non-significant difference).

4. Discussion

4.1. Incidence of cardiovascular events in HeFH

Combined analysis of the data of the national HeFH registry and the exhaustive data on hospital admissions, consultations and

Table 2
Baseline characteristics of REFERCHOL patients.

Characteristics		Primary prevention				Secondary prevention			
		Without event n = 2251 n (%)	With CV event n = 234 n (%)	Total n = 2485 n (%)	p-value	Without event n = 564 n (%)	With CV event n = 153 n (%)	Total n = 717 n (%)	p-value
Sex	Male	985 (44)	148 (63)	1133 (46)	<0.0001	400 (71)	118 (77)	518 (72)	0.13
Age (years)	Mean (SD)	46 (16)	51 (13)	46 (16)	<0.0001	59 (11)	59 (12)	59 (11)	0.72
Age group (years)	[14–18 [	99 (4)	0	99 (4)	<0.0001	–	–	–	0.34
	[18–30 [	317 (14)	12 (5)	329 (13)		2 (0)	2 (1)	4 (1)	
	[30–50 [	840 (37)	101 (43)	941 (38)		119 (21)	31 (20)	150 (21)	
	[50+	995 (44)	121 (52)	1116 (45)		443 (79)	120 (78)	563 (79)	
Type of diagnosis	Clinical	684 (30)	110 (47)	794 (32)	<0.0001	214 (38)	56 (37)	270 (38)	0.76
	Genetic	1567 (70)	124 (53)	1691 (68)		350 (62)	97 (63)	447 (62)	
Duration of disease (years)[a]	Mean (SD)	13.81 (14.42)	10.65 (14.67)	13.52 (14.47)	0.001	14.62 (15.69)	13.15 (15.91)	14.31 (15.74)	0.31
Body mass index	Mean (SD)	25 (5)	26 (7)	25 (5)	<0.0001	27 (5)	27 (4)	27 (5)	0.43
Smoking		544 (26)	99 (44)	643 (27)	<0.0001	153 (29)	44 (32)	197 (30)	0.56
Type 2 diabetes		88 (4)	15 (7)	103 (4)	0.054	68 (13)	29 (20)	97 (14)	0.03
Hypertension		303 (14)	64 (30)	367 (16)	<0.0001	185 (35)	67 (48)	252 (38)	0.01
Premature CV event		–	–	–	–	442 (78)	128 (84)	570 (79)	0.15
Premature CV event in 1st degree relative		621 (28)	72 (31)	693 (28)	0.30	178 (32)	40 (26)	218 (30)	0.20

CV, cardiovascular. Values are numbers (%) unless otherwise indicated.
[a] Period of time from diagnosis of hypercholesterolemia to inclusion in the registry.

Table 3
Lipid-lowering treatment (LLT) obtained from the SNDS database.

Treatment		Primary prevention				Secondary prevention			
		Without event n = 2251 n (%)	With CV event n = 234 n (%)	Total n = 2485 n (%)	p-value	Without event n = 564 n (%)	With CV event n = 153 n (%)	Total n = 717 n (%)	p-value
Any LLT		1210 (54)	89 (38)	1299 (52)	<0.0001	453 (80)	123 (80)	576 (80)	0.98
LLT[a]	None	1041 (46)	145 (62)	1186 (48)	0.0002	111 (20)	30 (20)	141 (20)	0.74
	Statins + Ezetimibe	512 (23)	36 (15)	548 (22)		307 (54)	80 (52)	387 (54)	
	Ezetimibe alone	62 (3)	5 (2)	67 (3)		23 (4)	11 (7)	34 (5)	
	Statins alone	581 (26)	42 (18)	623 (25)		106 (19)	27 (18)	133 (19)	
	Other[b]	55 (2)	6 (3)	61 (2)		17 (3)	5 (3)	22 (3)	
Statin regimen [c]	Low	236 (21)	17 (22)	253 (21)	0.10	46 (11)	13 (12)	59 (11)	0.30
	Moderate	716 (64)	43 (55)	759 (64)		180 (43)	55 (50)	235 (44)	
	High	160 (14)	18 (23)	178 (15)		195 (46)	42 (38)	237 (45)	
Global compliance[d] at baseline (2013)	<0.3	66 (6)	9 (12)	75 (6)	0.09	21 (5)	5 (5)	26 (5)	0.13
	[0.3; 0.5]	113 (10)	5 (7)	118 (10)		22 (5)	10 (9)	32 (6)	
	]0.5; 0.8]	310 (28)	24 (33)	334 (28)		75 (18)	28 (26)	103 (20)	
	>0.8	616 (56)	35 (48)	651 (55)		288 (71)	66 (61)	354 (69)	
Global compliance[d] LOCF	<0.3	49 (4)	6 (9)	55 (4)	0.22	17 (4)	3 (3)	20 (4)	0.70
	[0.3; 0.5]	173 (15)	9 (14)	182 (15)		45 (11)	13 (13)	58 (12)	
	]0.5; 0.8]	360 (30)	16 (25)	376 (30)		112 (28)	23 (23)	135 (27)	
	>0.8	607 (51)	34 (52)	641 (51)		230 (57)	61 (61)	291 (58)	

SNDS: French national health data system.
[a] At least 3 deliveries.
[b] Statins + fibrates, statins + colestyramine, fibrates, colestyramine.
[c] High-intensity statins include atorvastatin 40–80 mg and rosuvastatin 20–40 mg. Moderate-intensity statins include atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, and fluvastatin 80 mg. Low-intensity statins include simvastatin 10 mg, pravastatin 10–20 mg, fluvastatin 20–40 mg.
[d] Average compliance between statins and ezetimibe at baseline and at Last Observation Carried Forward (LOCF). Compliance is defined as the proportion of days covered with delivered treatment within a 1-year period, based on the theoretical regimen reported in the REFERCHOL registry.

mortality of the French national health insurance database revealed a particularly high incidence of cardiovascular events in our sample of patients with HeFH. We also confirmed that there are considerable sex differences in the development of cardiovascular events even in HeFH [14].

Using a health insurance database in Catalonia, Masana et al. [15] analyzed the incidence of cardiovascular disease in potential HeFH patients in the general population. This database covers about 85% of the Catalan population. These authors found an incidence of 14.9 events per 1000 PY in primary prevention and 89.8 per 1000 PY in secondary prevention. This incidence is coherent with our data. However, HeFH was defined as high untreated LDL cholesterol levels in this Spanish study.

In another Spanish study [16], carried out in a working population and thus in individuals without overt cardiovascular disease, the incidence of cardiovascular disease was 5.11 events per 1000 PY,

markedly lower than the incidence that we observed. On the other hand, it is consistent with the incidence of 5.6 per 1000 PY observed in the SAFEHEART study [17], which is also an HeFH registry-based study. As far as we are aware, the French REFERCHOL registry is one of the largest in the world, as it currently includes around 9004 patients with HeFH [1].

The second major finding of our work is the serious nature of relapses in HeFH patients who had already experienced cardiovascular events. In this particular context, the recurrence was 43.40 per 1000 PY. Genetic familial hypercholesterolemia therefore carries an extremely high cardiovascular risk [18,19].

Lastly, the incidence of aortic valve replacement was particularly high in patients with HeFH at 1.78 per 1000 PY. In the province of Ontario, Canada, aortic valve replacement was 0.20 per 1000 PY [20], markedly lower than in our study. In Norway, a cohort of 3161 patients with genetically verified HeFH were followed for 11.1 years [21]. The incidence of aortic stenosis was 2.9 per 1000 PY and the incidence of aortic valve replacement was 1.3 per 1000 PY. The risk of undergoing surgery for aortic valve replacement was 7.7 times higher than in the general Norwegian population [21]. In consequence, patients with HeFH should be monitored clinically for the classic symptoms of aortic valve stenosis and by regular echocardiography as part of systematic examinations.

4.2. Level of risk factors in familial hypercholesterolemia

It is very surprising to observe in our French registry a prevalence of tobacco smoking of around 28%. Smoking and familial hypercholesterolemia are the two principal risk factors for coronary atherosclerosis and premature coronary events. It is therefore urgent to target tobacco smoking as well as LDL cholesterol among families in the hope of reducing the incidence of cardiovascular events [8]. The prevalence of diabetes (7% in REFERCHOL) is similar to that in the general French population at 6.5% [9].

4.3. Management of HeFH and treatment adherence

It is particularly disturbing to observe that 48% of patients in primary prevention are not using lipid-lowering treatment (according to reimbursement data) and that even in secondary prevention 20% of patients are untreated. The guidelines of the European Cardiology Society published in 2021 [22] have confirmed those of 2019 [23] on the management of dyslipidemia. In particular, these guidelines stress the value of treating children from the age of 8 or 10 years with a statin in order to achieve an LDL cholesterol level below 135 mg/dL.

Moreover, according to the most recent European guidelines, in patients with HeFH and cardiovascular disease the aim should be to reach a level below 55 mg/dL [22,23]. In our work, we observed an LDL cholesterol level of 153 mg/dL in secondary prevention, which is very far from the therapeutic aim in Europe. Patients with HeFH in primary prevention and who had a cardiovascular event during follow-up had an initial LDL cholesterol level of 175 mg/dL, also very far removed from the optimal target.

These findings all indicate that HeFH is not seen as a threat to cardiovascular prognosis, unlike diabetes whose management has markedly improved in recent years. Yet, lipid-lowering treatment is henceforward based on 3 major agents: statins, ezetimibe and PCSK9 monoclonal antibodies (which were not available in France at the time of this study). If these 3 treatments were used appropriately, it is highly probable that the therapeutic objective would be achieved in the majority of cases in our registry [24,25].

Our study also raises the problem of the dose of statins used, which in all cases was suboptimal and inadequate. In HeFH patients with and without coronary disease, reticence toward high-dose statins no doubt arises from an unfavorable opinion of statins in French and European society and from the presence of muscle symptoms that are not necessarily attributable to taking statins [26].

Adherence to long-term statin treatment is also far from optimal: we observed 51% adherence in primary prevention and 58% in secondary prevention. In France, concerning myocardial infarction with a 6-month follow-up and using the same national health database, adherence of prescribed statins was 76% [13]. The presence of genetic familial hypercholesterolemia thus does not appear to be an argument for intensifying lipid-lowering treatment in this context. It is noteworthy that HeFH is a silent disease that does not cause suffering and there is no doubt that as patients do not have their laboratory test results constantly before them, this may contribute to suboptimal management. The availability of tools for regular monitoring of LDL cholesterol could be an aid to better observance in these patients [27].

4.4. Strengths and limitations of our study

Although nearly all lipid clinics in France participate in the REFERCHOL registry, it is far from certain that all patients with HeFH are recorded in this database. It is also possible that the database preferentially records patients at high risk of cardiovascular events, which would lead to overestimation of the incidence of cardiovascular disease in these patients. Nevertheless, the fact that 1 in 5 individuals are not treated in secondary prevention and that 1 in 2 are not treated in primary prevention suggest that REFERCHOL is a nationwide registry, since all these patients had been seen by a physician specialized in lipid disorders and had been referred to the centers in order to improve their management. It is therefore probable that the incidence of cardiovascular disease in patients with HeFH in France may in reality be higher.

The strength of our work is that it links the clinical data of the REFERCHOL registry with the exhaustive follow-up data of the French national health insurance database that records all prescriptions and clinical events, since all prescriptions and hospital admissions are free of charge in France. It is therefore highly probable that we have a complete record of cardiovascular events during follow-up.

In another respect, we assessed adherence to treatment on the basis of prescription drugs delivered by pharmacists, which does not mean that these drugs were taken regularly by the patient. Lastly, these patients had genetically verified HeFH and it would be useful to explain in a further study the difference of incidence of cardiovascular disease in patients with a pathogenic mutation with the incidence in patients in whom genetic diagnosis was not possible or was negative. The data presented in the appendices seem to show differences according to the genetic profiles of the HeFH patients, with also clinical and biological differences. The fact that these patients in primary prevention are younger, more often women and with a more favorable risk factor profile probably explains the fact that the incidence of cardiovascular events is lower. An article is being written to explain how clinical and biological differences can predict different cardiovascular disease risk in HeFH patients.

5. Conclusions

The French national HeFH registry highlights two main messages. The incidence of cardiovascular events during follow-up was far from negligible in both primary and secondary prevention. In spite of this high incidence, lipid-lowering treatment with statins and ezetimibe was far from optimal, since 1 in 5 patients in secondary prevention and 1 in 2 patients in primary prevention were

not receiving lipid-lowering treatment at the start of the study. This finding demonstrates a clinical discrepancy between the high cardiovascular risk of HeFH and the difficulty of pursuing appropriate drug treatment in the long term.

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None.

CRediT authorship contribution statement

Jean Ferrières: Conceptualization, Formal analysis, Investigation, Supervision, Validation, Visualization, Writing - original draft. Michel Farnier: Visualization, Writing - review & editing. Eric Bruckert: Funding acquisition, Conceptualization, Investigation, Supervision, Validation, Visualization, Writing - review & editing. Alexandre Vimont: Data curation, Formal analysis, Methodology, Software. Vincent Durlach: Writing - review & editing. Emile Ferrari: Writing - review & editing. Antonio Gallo: Writing - review & editing. Franck Boccara: Writing - review & editing. Dorota Ferrières: Writing - review & editing. Sophie Béliard: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of competing interest

JF reports personal fees from Amgen, Sanofi and Servier. MF reports having received grants, consulting fees and/or honoraria and delivering lectures for Abbott, Amarin, Amgen, AstraZeneca, Austell, Kowa, Merck and Co, Organon, Pfizer, Recordati, Sanofi/Regeneron, Servier, SMB and Viatris. EB reports grants from Sanofi and Amgen, and personal fees from Aegerion, Danone, Genfit, MSD, Sanofi/Regeneron Pharmaceuticals, Inc., AstraZeneca, Servier, AMGEN, AKCEA, Mylan. AV has no conflict of interest to declare. VD reports fees payed to him or his institution for membership of advisory boards, speaker and clinical trials from Amgen, Sanofi, Lilly, Servier, Novo and Bioprojet. EF has no conflict of interest to declare. AG has received honoraria for public speaking or consultancy support from Akcea Therapeutics, AMGEN, Mylan, Novartis, Organon, Sanofi and Regeneron, Unilever and MSD. FB reports research grants from Amgen, lecture fees from Gilead, ViiV Healthcare, Amgen, Sanofi, MSD, Novo Nordisk and Servier outside the submitted work. DF has no conflict of interest to declare. SB has received honoraria for board, conferences, clinical trial or congress from Aegerion, Akcea, Amgen, Elivie, Sanofi, Novartis, Regeneron.

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Appendix A. Supplementary data

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