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

Jean Ferrières[1], Eric Bruckert[2], Alexandre Vimont[3], Sophie Béliard[4]

1, Department of Cardiology, Toulouse Rangueil University Hospital, Toulouse, France; 2 Department of Endocrinology and Cardiovascular Disease Prevention, La Pitié-Salpêtrière Hospital, AP-HP, Paris, France; 3 Public Health Expertise, Paris, France; 4 APHM, Department of Nutrition, Metabolic Diseases, Endocrinology, La Conception Hospital, Marseille, France

BACKGROUND

Heterozygous familial hypercholesterolemia (HeFH) is a common genetic disease, and its pathophysiology and genetic characteristics have been particularly well described [1].

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

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.

BACKGROUND

Population

Patients eligible were diagnosed with HeFH, either clinically (Dutch Lipid Clinic Network score (DLCN) >6) or genetically identified in the French REgistry of Familial hypercholesterolemia (REFERCHOL).

Database

This cohort study used data from the French National claims database (SNDS) which were matched to included patients to gather medical procedures and treatments to provide 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.

Study design

Patients matched to the SNDS database were follow-up for 5 years (at-risk period), from 2014 (baseline) to 2018 (end-of-study).

Outcomes

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.

Figure 1. Design of the study

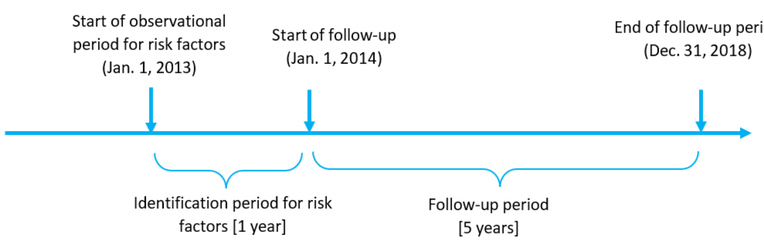
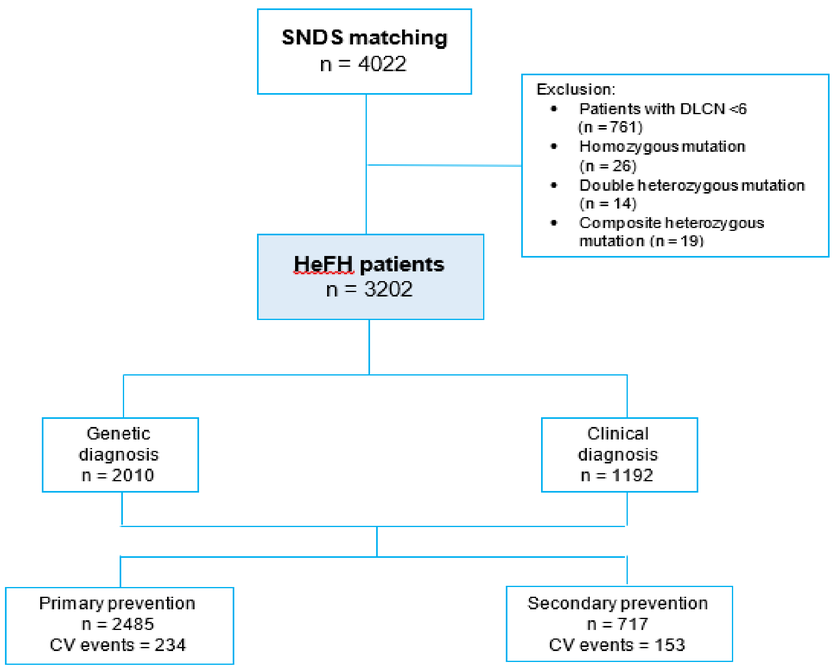


Figure 2. Flowchart of included patients and matched to SNDS database



CONCLUSION

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.

Reference

1. J. Ferrières, J. Lambert, S. Lussier-Cacan, J. Davignon, Coronary artery disease in heterozygous familial hypercholesterolemia patients with the same LDL receptor gene mutation, Circulation 92 (3) (1995) 290-295
2. J. Ferrières, Hypercholesterolaemia and coronary artery disease: A silent killer with several faces, Arch. Cardiovasc. Dis. 112 (2) (2019) 75-78
3. . Ferrières, V. Banks, D. Pillas, F. Giorgianni, L. Gantzer, et al., Screening and treatment of familial hypercholesterolemia in a French sample of ambulatory care patients: A retrospective longitudinal cohort study, PLoS One 16 (8) (2021) e0255345

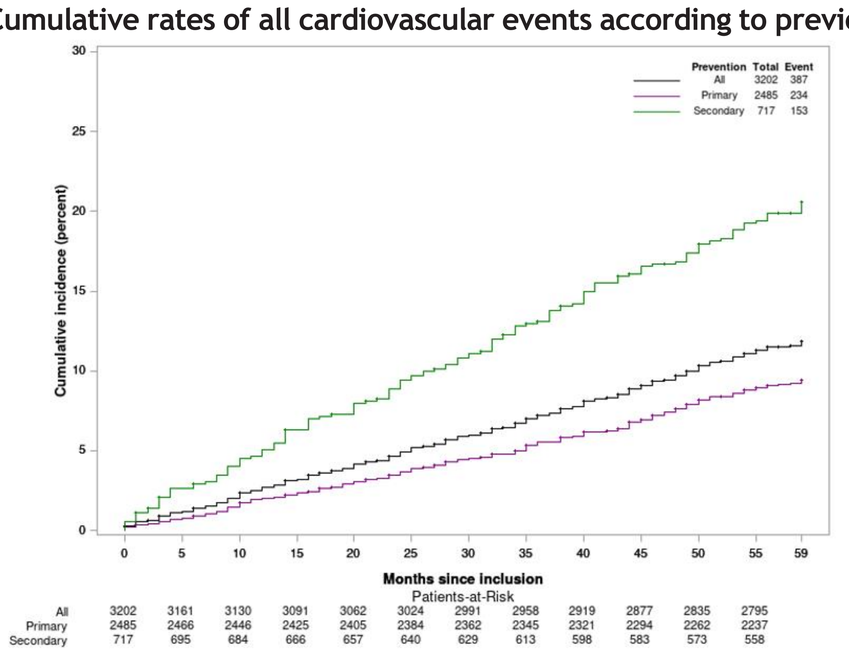
RESULTS

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.

Table 1. Incidence of cardiovascular events according to previous CVD history.

Type of event	Primary prevention n = 2485	Incidence 1000 pts-yrs	Secondary prevention n = 717	Recurrence 1000 pts-yrs
Follow-up, months (median)	**59**		**59**	
[Q1-Q3]	[59 ; 59]		[59 ; 59]	
Total CVD events	**234 (9.4%)**	**19.15**	**153 (21.3 %)**	**43.40**
3-point MACE *(mortality, AMI, stroke)*	**158 (6.3%)**	**12.93**	**99 (13.8%)**	**28.08**
All-cause mortality	**37 (1.5%)**	**3.03**	**41 (5.7%)**	**11.63**
Repartition of cardiovascular events				
Coronary events	**183 (78%)**	**14.98**	**113 (74%)**	**32.05**
Acute myocardial infarction (AMI)	108 (46%)	8.84	47 (31%)	13.33
Aortic valve replacement	18 (8%)	1.47	10 (7%)	2.84
Unstable angina	53 (23%)	4.34	49 (32%)	13.90
Other acute heart disease	4 (2%)	0.33	7 (5%)	1.99
Cerebral events	**29 (12%)**	**2.37**	**15 (10%)**	**4.26**
Stroke	13 (6%)	1.06	11 (7%)	3.12
Transient ischemic attack	16 (7%)	1.31	4 (3%)	1.13
Peripheral arterial disease	**22 (9%)**	**1.80**	**25 (16%)**	**7.09**
Arterial embolism and thrombosis	14 (6%)	1.15	18 (12%)	5.11
Occlusion and stenosis	8 (3%)	0.65	7 (5%)	1.99

Figure 3. Cumulative rates of all cardiovascular events according to previous CVD history



Overall, 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.

Table 2. Lipid-lowering treatment (LLT) compliance estimated from the SNDS database (n, %)

Treatment		Primary prevention Without event n = 2251	Primary prevention With CV event n = 234	Secondary prevention Without event n = 564	Secondary prevention With CV event n = 153
Any LLT		1210 (54)	89 (38)	453 (80)	123 (80)
LLT*	None	1041 (46)	145 (62)	111 (20)	30 (20)
	Statins + Eze	512 (23)	36 (15)	307 (54)	80 (52)
	Ezetimibe alone	62 (3)	5 (2)	23 (4)	11 (7)
	Statins alone	581 (26)	42 (18)	106 (19)	27 (18)
	Other	55 (2)	6 (3)	17 (3)	5 (3)
Statin regimen	Low	236 (21)	17 (22)	46 (11)	13 (12)
	Moderate	716 (64)	43 (55)	180 (43)	55 (50)
	High	160 (14)	18 (23)	195 (46)	42 (38)
Global compliance* at baseline (2013)	<0.3	66 (6)	9 (12)	21 (5)	5 (5)
	[0.3;0.5]	113 (10)	5 (7)	22 (5)	10 (9)
	]0.5;0.8]	310 (28)	24 (33)	75 (18)	28 (26)
	>0.8	616 (56)	35 (48)	288 (71)	66 (61)
Global compliance* LOCF	<0.3	49 (4)	6 (9)	17 (4)	3 (3)
	[0.3;0.5]	173 (15)	9 (14)	45 (11)	13 (13)
	]0.5;0.8]	360 (30)	16 (25)	112 (28)	23 (23)
	>0.8	607 (51)	34 (52)	230 (57)	61 (61)

• Proportion of days covered (PDC) using prescription data and correcting for overlapping prescriptions
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

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