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CLINICAL RESEARCH

Dutch Lipid Clinic Network low-density lipoprotein cholesterol criteria are associated with long-term mortality in the general population

Les niveaux de cholestérol des lipoprotéines de basse densité du Dutch Lipid Clinic Network sont associés à la mortalité à long terme en population générale

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KEYWORDS
Heterozygous familial hypercholesterolaemia;
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Mortality;
LDL-cholesterol

Summary
Background. — Heterozygous familial hypercholesterolaemia (HeFH) is a severe autosomal dominant disease that is underdiagnosed, inadequately treated and has a severe long-term cardiovascular risk. Few studies have evaluated the long-term risk of high low-density lipoprotein cholesterol (LDL-C) concentrations.
Aim. — To evaluate long-term mortality in a large cohort of healthy subjects, according to LDL-C concentrations.

Abbreviations: CHD, Coronary heart disease; CI, Confidence interval; DLCN, Dutch Lipid Clinic Network; HDL-C, High-density lipoprotein cholesterol; HeFH, Heterozygous familial hypercholesterolaemia; HR, Hazard ratio; LDL, Low-density lipoprotein; LDL-C, Low-density lipoprotein cholesterol.

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Methods. — Based on a sample of 6956 subjects visiting a preventive cardiology department, we selected adult subjects without a personal history of cardiovascular disease. From 1995 to 2011, 4930 healthy subjects were examined and followed up until 31 December 2011. All-cause deaths were collected exhaustively. A Cox-based multivariable analysis evaluated long-term total mortality risk according to Dutch Lipid Clinic Network (DLCN) LDL-C concentrations.

Results. — After a mean follow-up of 8.6 years, 123 all-cause deaths were recorded (cumulative mortality rate, 2.5%). In the final multivariable model, major risk factors such as age, sex, tobacco use and diabetes were significantly associated with mortality. After adjustment for age, sex, tobacco use, hypertension, diabetes and statin therapy, and in comparison with subjects with LDL-C < 4 mmol/L (< 155 mg/dL), subjects with LDL-C between 4 and < 5 mmol/L (155 to < 190 mg/dL) had a hazard ratio (HR) of 1.99 (95% confidence interval [CI] 1.31—3.02; $P = 0.001$), subjects with LDL-C between 5 and < 6.5 mmol/L (190 to < 250 mg/dL) had an HR of 1.81 (95% CI, 1.06—3.02; $P = 0.030$), subjects with LDL-C between 6.5 and < 8.5 mmol/L (250 to < 330 mg/dL) had an HR of 2.69 (95% CI, 1.06—6.88; $P = 0.038$) and subjects with LDL-C ≥ 8.5 mmol/L (≥ 330 mg/dL) had an HR of 6.27 (95% CI, 0.84—46.57; $P = 0.073$). After excluding patients on statins at baseline, subjects with LDL-C ≥ 8.5 mmol/L (≥ 330 mg/dL) had an HR of 8.17 (95% CI, 1.08—62.73; $P = 0.042$).

Conclusions. — The severity of LDL-C elevation is associated with a higher risk of death in healthy subjects. DLCN LDL-C concentrations may be used in daily practice to identify patients with HeFH who warrant aggressive treatment.

MOTS CLÉS
Hypercholestérolémie familiale hétérozygote ;
Cohorte ;
Mortalité ;
Cholestérol LDL

Résumé

Contexte. — L'hypercholestérolémie familiale hétérozygote (HeFH) est une maladie autosomique dominante sévère. L'HeFH est une maladie qui est sous-diagnostiquée et insuffisamment traitée. Le risque cardiovasculaire à long terme de l'HeFH est sévère. Peu d'études ont évalué le risque à long terme des valeurs élevées de LDL-cholestérol (LDL-C).

Objectif. — Le but de ce travail a été d'évaluer la mortalité à long terme d'une large cohorte de sujets sains en fonction des niveaux de LDL-C.

Méthodes. — À partir d'un échantillon de 6956 patients examinés dans un service de cardiologie préventive, nous avons isolé les sujets majeurs sans antécédents personnels de maladie cardiovasculaire. De 1995 à 2011, 4930 sujets sains ont été examinés et suivis jusqu'au 31 décembre 2011. L'ensemble des décès toutes causes a été collecté. Une analyse multivariée par méthode de Cox a permis d'évaluer le risque de mortalité totale à long terme en fonction des niveaux de LDL-C du Dutch Lipid Clinic Network (DLCN).

Résultats. — Après un suivi moyen de 8,6 ans, 123 décès toutes causes ont été enregistrés (mortalité cumulative de 2,5 %). Dans le modèle multivarié final, les facteurs de risque majeurs tels que l'âge, le sexe, le tabagisme et le diabète sont associés significativement à la mortalité. Après ajustement pour l'âge, le sexe, le tabac, l'hypertension artérielle, le diabète et un traitement par statines et en comparaison avec les sujets dont le LDL-C est < 4 mmol/L (< 155 mg/dL), les sujets présentant un LDL-C entre 4 et < 5 mmol/L (155 à < 190 mg/dL) ont un *hazard ratio* (HR) de 1,99 (intervalle de confiance [IC] à 95 %, 1,31—3,02 ; $p = 0,001$], les sujets présentant un LDL-C entre 5 et < 6,5 mmol/L (190 à < 250 mg/dL) ont un HR de 1,81 (IC à 95 %, 1,06—3,02 ; $p = 0,030$), les sujets présentant un LDL-C entre 6,5 et < 8,5 mmol/L (250 à < 330 mg/dL) ont un HR de 2,69 (IC à 95 %, 1,06—6,88 ; $p = 0,038$) et les sujets dont le LDL-C est ≥ 8,5 mmol/L (≥ 330 mg/dL) ont un HR à 6,27 (IC à 95 %, 0,84—46,57 ; $p = 0,073$). Après exclusion des patients sous statines à l'entrée, les sujets dont le LDL-C est ≥ 8,5 mmol/L (≥ 330 mg/dL) ont un HR à 8,17 (IC à 95 %, 1,08—62,73 ; $p = 0,042$).

Conclusions. — La sévérité de l'élévation du LDL-C est liée à une augmentation de la mortalité totale chez les sujets sains. Les niveaux de LDL-C de la DLCN peuvent être utilisés en pratique quotidienne pour sélectionner les patients porteurs d'une HeFH et ainsi engager une thérapeutique agressive.

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Background

Heterozygous familial hypercholesterolaemia (HeFH) is an autosomal dominant disorder with a severe cardiovascular prognosis. A definite diagnosis of HeFH requires genetic testing for mutations primarily located on the low-density lipoprotein (LDL) receptor, apolipoprotein B and proprotein convertase subtilisin/kexin type 9 (PCSK9). Patients with HeFH are perceived as being at high risk, according to the European Society of Cardiology [1]. The European Society of Atherosclerosis recommends extensive screening for HeFH in the general population [2]. Screening of a given subject allows the whole family to be assessed and leads to management of all those exposed to hypercholesterolaemia [3].

HeFH is a severe disease because of its well-documented cardiovascular and survival prognosis [4,5]. As a definite diagnosis is based on testing for mutations [6], this genetic diagnostic test is appropriate for the majority of subjects with elevated LDL-cholesterol (LDL-C) concentrations. Nevertheless, most developed countries are not equipped with sufficient genetic centres to conduct extensive diagnostic tests in subjects for whom this diagnosis has been suggested. Hence, scientific societies mostly propose the use of scores, such as the USA MEDPED (Make Early Diagnosis to Prevent Early Death) score, the UK Simon Broome score and the Dutch Lipid Clinic Network (DLCN) score [2]. With the exception of the USA score, the other scores are based on a collection of clinical and laboratory data, which are not necessarily found in the medical records.

The DLCN score [2] is based on a combination of five dimensions. The first group corresponds to a first-degree relative with known premature (< 55 years, men; < 60 years, women) coronary heart disease (CHD) (1 point), or a first-degree relative with known LDL-C > 95th percentile by age and sex for country (1 point), or a first-degree relative with tendon xanthoma and/or corneal arcus (2 points), or a child/children aged < 18 years with LDL-C > 95th percentile by age and sex for country (2 points). The second group corresponds to premature (< 55 years, men; < 60 years, women) CHD (2 points) or premature (< 55 years, men; < 60 years, women) cerebral or peripheral vascular disease (1 point). The third group corresponds to the presence of tendon xanthoma (6 points) or corneal arcus in a person aged < 45 years (4 points). The fourth group corresponds to LDL-C concentrations: $\geq$ 8.5 mmol/L ($\geq$ 330 mg/dL) (8 points); $\geq$ 6.5 to < 8.5 mmol/L ($\geq$ 250 to < 330 mg/dL) (5 points); $\geq$ 5.0 to < 6.5 mmol/L ($\geq$ 190 to < 250 mg/dL) (3 points); $\geq$ 4.0 to < 5.0 mmol/L ($\geq$ 155 to < 190 mg/dL) (1 point). The fifth group corresponds to deoxyribonucleic acid (DNA) analysis and the finding of a causative mutation (8 points). A ''definite HeFH'' diagnosis can be made if the subject scores > 8 points. A ''probable HeFH'' diagnosis can be made if the subject scores 6 to 8 points. A ''possible HeFH'' diagnosis can be made if the subject scores 3 to 5 points. An ''unlikely HeFH'' diagnosis can be made if the subject scores 0 to 2 points. However, this long list of variables is not usually found in current clinical charts. So, we sought to propose a simpler tool for screening for HeFH in general practice.

The aim of this research was to determine whether DLCN LDL-C concentrations affect the survival prognosis in healthy subjects, and may thus be used in the general population.

Methods

Study population

We conducted a prospective cohort study, which included 6956 apparently healthy asymptomatic subjects. Participants were included between November 1995 and December 2011 at the Department of Preventive Cardiology in our teaching institution (Toulouse University Hospital, Toulouse, France). These subjects were either self-referred or referred by their primary-care physician or their cardiologist for cardiovascular risk assessment, management of cardiovascular risk factors or routine ambulatory screening for cardiovascular diseases (CVDs) [7—10]. Patients with a personal history of coronary heart disease (International Classification of Disease, 9th revision, codes 410.0 to 414.9), a personal history of stroke (codes 433.0 to 438.9 except 437.3 to 437.7), a personal history of atherosclerosis (codes 440.0 to 440.9) or a personal history of aneurysms (codes 441.0 to 442.9) were excluded. Vital status on 31 December 2011 was obtained for each participant through the national database that records all deaths occurring in the French population each year (RNIPP) [11]. Authorisation to use these data was obtained in accordance with French law (Commission nationale de l'informatique et des libertés [CNIL]).

Questionnaires and measurement of clinical variables

At baseline, extensive questionnaires were filled in by trained medical staff during a personal interview with the participant. Information on exposures was collected at baseline only. Data concerning socioeconomic level, personal medical history, cardiovascular risk factors, lifestyle habits and drug intake were recorded. Participants were asked to bring their latest drug prescription to the inclusion visit. All drugs taken during the 2 weeks preceding the visit were recorded. Family history of premature CVD (before 55 years in father/65 years in mother) was recorded. People who currently smoked or who had stopped for < 3 years were considered as current smokers. Height, weight and arterial blood pressure (mean of two measurements performed with a standard sphygmomanometer in a seated position after $\geq$ 5 minutes rest) were measured according to standardised protocols by the medical staff. Body mass index was calculated as weight divided by height squared (kg/m2). Hypertension was assessed for people with blood pressure $\geq$ 140/90 mmHg or on treatment. Diabetes was assessed for subjects receiving hypoglycaemic drugs or with fasting blood glucose $\geq$ 7 mmol/L.

Laboratory methods

Blood samples were taken after $\geq$ 10 hours of overnight fasting. Serum total cholesterol and triglycerides were measured by enzymatic assays (Boehringer, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-C) was measured after sodium phosphotungstate-magnesium chloride precipitation of apolipoprotein B-containing lipoproteins. LDL-C was determined by the Friedewald formula when triglycerides were < 4.6 mmol/L (< 400 mg/dL) [12]. Glucose concentrations were measured using a

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conventional enzymatic method based on hexokinase-glucose-6-phosphate dehydrogenase.

Statistical analysis

Statistical analysis was performed using STATA statistical software, release 11.2 (STATA Corporation, College Station, TX, USA). Subjects with a history of CVD were excluded from the analysis.

We first described the baseline characteristics of participants and compared baseline characteristics by outcome occurrence, comparing subjects who did not die (i.e. those alive on 31 December 2011) with subjects who had a fatal event during follow-up. Qualitative variables were compared between groups using the χ^2 test (or Fisher's exact test when necessary). Student's *t*-test was used to compare the distribution of quantitative data (or the Mann—Whitney test when distribution departed from normality or when homoscedasticity was rejected).

Survival was then analysed. Events were cases of death, and exposure was defined by LDL-C concentration at inclusion. Hazard ratios (HRs) for mortality and 95% confidence intervals (CIs) were assessed using a Cox model. The independent variables initially introduced into the survival model were LDL-C concentrations at inclusion and all variables associated with mortality in the univariate analysis (P-value < 0.20). A backward analysis was then applied until only variables significantly and independently associated with mortality (P-value < 0.05) remained. Hypertension was included in the final model because it is a classical risk factor. The proportional-hazard assumption was tested for each covariate by the ''log-log'' plot method curves (−ln{−ln[survival]}), for each category of nominal covariate, versus (ln[analysis time]). None of the assumptions could be rejected.

Results

A total of 6956 subjects visited the Department of Preventive Cardiology from November 1995 to December 2011. After excluding minors and patients with CVD at inclusion, together with patients who returned to the same department on several occasions, we reached a total of 4930 subjects who could be followed up until 31 December 2011 (Table 1).

After a mean follow-up period of 8.6 years, 123 deaths were recorded (cumulative mortality rate of 2.5%). Among the 4930 healthy subjects at baseline, LDL-C could not be calculated in 106 patients (including two deaths) because of excessively high triglyceride concentrations.

The clinical and laboratory characteristics of the study population are shown in Table 2. The mean age of subjects was 52 years, 59.4% were men, 25.3% were regular smokers and 5.2% were diabetic. At inclusion, 26.8% of patients were receiving statin therapy and the mean LDL-C value was 4 mmol/L (155 mg/dL) in the overall sample.

When the sample was stratified according to DLCN LDL-C concentrations, 54.6% had LDL-C < 4 mmol/L (< 155 mg/dL), 28.3% had LDL-C between 4 and < 5 mmol/L (155 to < 190 mg/dL), 14.2% had LDL-C between 5 and < 6.5 mmol/L (190 to < 250 mg/dL), 2.5% had LDL-C between 6.5 and < 8.5 mmol/L (250 to < 330 mg/dL) and 0.4% had LDL-C ≥ 8.5 mmol/L (≥ 330 mg/dL).

Table 1 Subjects taking part in the cohort study.

	Number of patients
Total examined up to 31 December 2011	6956
Examined for the first time	5182
Minors (< 18 years)	10
History of ischaemic heart disease	131
History of stroke	66
History of documented atherosclerosis	34
History of vascular aneurysm	3
Undocumented blood pressure	4
Lipid profile not performed	4
Followed up	4930
Cumulative number of deaths among those followed up	123

All of the conventional risk factors were more severe among those who died during follow-up; this was particularly true for LDL-C concentration. Table 3 presents the multivariable analysis, adjusted for age and sex, which shows the influence of the main risk factors on survival prognosis, together with the risk level related to LDL-C concentrations.

In the multivariable analysis, LDL-C concentrations were statistically associated with overall mortality (Table 4). After adjustment for age, sex, tobacco use, hypertension, diabetes and statin therapy, and in comparison with subjects with LDL-C < 4 mmol/L (155 mg/dL), subjects with LDL-C between 4 and < 5 mmol/L (155 to < 190 mg/dL) had an HR of 1.99 (95% CI, 1.31—3.02; $P = 0.001$), subjects with LDL-C between 5 and < 6.5 mmol/L (190 to < 250 mg/dL) had an HR of 1.81 (95% CI, 1.06—3.02; $P = 0.030$), subjects with LDL-C between 6.5 and < 8.5 mmol/L (250 to < 330 mg/dL) had an HR of 2.69 (95% CI, 1.06—6.88; $P = 0.038$) and subjects with LDL-C ≥ 8.5 mmol/L (330 mg/dL) had an HR of 6.27 (95% CI, 0.84—46.57; $P = 0.073$). After excluding patients on statins at baseline, subjects with LDL-C ≥ 8.5 mmol/L (≥ 330 mg/dL) had an HR of 8.17 (95% CI, 1.08—62.73; $P = 0.042$) (Table 5). After excluding patients treated with statins at inclusion, all DLCN LDL-C concentrations (with the exception of the LDL-C class between 5 and < 6.5 mmol/L [190 to < 250 mg/dL]) were statistically associated with an impaired survival prognosis. When these thresholds were modified (Appendix A), LDL-C between 4 and < 6.5 mmol/L (155 to < 250 mg/dL) was associated with an HR of 2.07 (95% CI, 1.33—3.23; $P = 0.001$) and LDL-C ≥ 6.5 mmol/L (≥ 250 mg/dL) was associated with an HR of 3.82 (95% CI, 1.46—10.07; $P = 0.006$) in healthy subjects not treated with a statin at inclusion.

Discussion

In a large sample of healthy subjects undergoing long-term follow-up, LDL-C > 4 mmol/L (155 mg/dL) was significantly associated with higher overall mortality. When LDL-C reached high values, such as 6.5 mmol/L (250 mg/dL) or

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Table 2 Clinical and laboratory characteristics.

	All	Alive	Deceased	*P*
	(*n* = 4930)	(*n* = 4807)	(*n* = 123)	
Age (years)	52 ± 10	52 ± 10	55 ± 11	< 0.01
Men	2927 (59.4)	2821 (58.7)	106 (86.2)	< 0.01
Current smoker	1248 (25.3)	1198 (24.9)	50 (40.7)	< 0.01
Body mass index (kg/m^2)	26 ± 9	26 ± 9	25 ± 5	0.3
Diabetes	255 (5.2)	237 (4.9)	18 (14.6)	< 0.01
Family history of premature CVD	723 (14.7)	708 (14.7)	15 (12.2)	0.62
Systolic blood pressure (mmHg)	136 ± 18	136 ± 17	146 ± 20	< 0.01
Diastolic blood pressure (mmHg)	83 ± 9	82 ± 9	86 ± 10	< 0.01
Pulse pressure (mmHg)	54 ± 13	53 ± 13	60 ± 16	< 0.01
Estimated GFR (mL/min/1.73 m^2)	80 ± 17	80 ± 17	79 ± 18	0.5
Antihypertensive drug treatment	981 (19.9)	952 (19.8)	29 (23.6)	0.3
Statins	1323 (26.8)	1298 (27.0)	25 (20.3)	0.09
Total cholesterol (mmol/L)	6.17 ± 1.30	6.16 ± 1.30	6.46 ± 1.45	0.01
LDL-C (mmol/L)[a]	4.00 ± 1.19	3.99 ± 1.19	4.37 ± 1.21	< 0.01
HDL-C (mmol/L)	1.41 ± 0.42	1.41 ± 0.42	1.30 ± 0.38	< 0.01
Triglycerides (mmol/L)	1.75 ± 1.72	1.75 ± 1.73	1.79 ± 1.21	0.79
LDL-C < 4 mmol/L (< 155 mg/dL)[a]	2632 (54.6)	2587 (55.0)	45 (37.2)	< 0.01
4 ≤ LDL-C < 5 mmol/L (155 to < 190 mg/dL)[a]	1367 (28.3)	1318 (28.0)	49 (40.5)	< 0.01
5 ≤ LDL-C < 6.5 mmol/L (190 to < 250 mg/dL)[a]	684 (14.2)	663 (14.1)	21 (17.4)	0.31
6.5 ≤ LDL-C < 8.5 mmol/L (250 to < 330 mg/dL)[a]	123 (2.5)	118 (2.5)	5 (4.1)	0.26
LDL-C ≥ 8.5 mmol/L (≥ 330 mg/dL)[a]	18 (0.4)	17 (0.4)	1 (0.8)	0.41

Data are expressed as mean ± standard deviation or number (%). CVD: cardiovascular disease; GFR: glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.
[a] LDL-C could not be calculated in 106 of 4930 patients (including two deaths) because of excessively high triglyceride concentrations.

Table 3 Survival, as per the multivariable analysis (adjusted for age and sex).

	HR	95% CI	*P*
Current smoking	2.2	[1.50—3.22]	< 0.01
Body mass index (kg/m^2)	1.01	[0.99—1.02]	0.39
Diabetes	2.62	[1.57—4.36]	< 0.01
Family history of premature CVD	0.85	[0.49—1.46]	0.56
Systolic blood pressure (mmHg)	1.01	[1.01—1.02]	0.02
Diastolic blood pressure (mmHg)	1.01	[0.99—1.03]	0.48
Pulse pressure (mmHg)	1.02	[1.01—1.03]	0.01
Estimated GFR (mL/min/1.73 m^2)	1	[0.99—1.01]	0.86
Hypertension	1.21	[0.83—1.78]	0.32
Statins	0.7	[0.45—1.09]	0.11
Total cholesterol (mmol/L)	1.21	[1.06—1.38]	< 0.01
LDL-C (mmol/L)	1.25	[1.09—1.44]	< 0.01
HDL-C (mmol/L)	0.97	[0.59—1.61]	0.91
Triglycerides (mmol/L)	0.99	[0.87—1.12]	0.84
LDL-C < 4 mmol/L (< 155 mg/dL)	1		
4 ≤ LDL-C < 5 mmol/L (155 to < 190 mg/dL)	1.84	[1.23—2.77]	< 0.01
5 ≤ LDL-C < 6.5 mmol/L (190 to < 250 mg/dL)	1.64	[0.97—2.76]	0.06
6.5 ≤ LDL-C < 8.5 mmol/L (250 to < 330 mg/dL)	2.47	[0.97—6.28]	0.06
LDL-C ≥ 8.5 mmol/L (≥ 330 mg/dL)	5.57	[0.75—41.07]	0.09

CI: confidence interval; CVD: cardiovascular disease; GFR: glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol.

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Table 4 Association between overall mortality and Dutch Lipid Clinic Network low-density lipoprotein cholesterol concentrations, as per the multivariable analysis (adjustment for age, sex, tobacco use, hypertension, diabetes and statin therapy).

	HR	(95% CI)	*P*
LDL-C < 4 mmol/L (< 155 mg/dL)	1		
4 ≤ LDL-C < 5 mmol/L (155 to < 190 mg/dL)	1.99	(1.31—3.02)	0.001
5 ≤ LDL-C < 6 .5 mmol/L (190 to < 250 mg/dL)	1.81	(1.06—3.02)	0.03
6.5 ≤ LDL-C < 8.5 mmol/L (250 to < 330 mg/dL)	2.69	(1.06—6.88)	0.038
LDL-C ≥ 8.5 mmol/L (≥ 330 mg/dL)	6.27	(0.84—46.57)	0.073

CI: confidence interval; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol.

Table 5 Association between overall mortality and Dutch Lipid Clinic Network low-density lipoprotein cholesterol concentrations, as per the multivariable analysis (adjustment for age, sex, tobacco use, hypertension and diabetes), with exclusion of all patients on statins.

	HR	(95% CI)	*P*
LDL-C < 4 mmol/L (< 155 mg/dL)	1		
4 ≤ LDL-C < 5 mmol/L (155 to < 190 mg/dL)	2.19	(1.37—3.50)	0.001
5 ≤ LDL-C < 6.5 mmol/L (190 to < 250 mg/dL)	1.81	(0.98—3.35)	0.059
6.5 ≤ LDL-C < 8.5 mmol/L (250 to < 330 mg/dL)	3.38	(1.17—9.97)	0.024
LDL-C ≥ 8.5 mmol/L (≥ 330 mg/dL)	8.17	(1.08—62.73)	0.042

CI: confidence interval; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol.

8.5 mmol/L (330 mg/dL), the risk was very high, with a relative risk of 3 or 8 for overall mortality. These high LDL-C values strongly suggest a diagnosis of HeFH and warrant aggressive management.

HeFH is a severe disease, which is straightforward to diagnose if the patient presents tendon xanthomas, corneal arcus, family history of early-onset CVD or high cholesterol in the family [2,3]. The presence of other risk factors increases the cardiovascular risk in HeFH [5]. A definite diagnosis of HeFH is obtained when a genetic diagnostic test is used; a network of centres offering this genetic testing exists in France [6].

HeFH is a common autosomal dominant disease, the prevalence of which is estimated at 1 in 500 subjects. Nevertheless, because of time constraints general practitioners or cardiologists rarely diagnose it. However, this diagnosis can be readily suggested when faced with elevated LDL-C concentrations associated with a higher cardiovascular risk [4].

In the general population, initiation of statin therapy for primary prevention is associated with an improvement in cardiovascular mortality and overall mortality [13,14]. Similarly, in the general population, LDL-C is associated with higher overall mortality. In NHANES III [15], LDL-C concentrations ≥ 3.35 mmol/L (≥ 130 mg/dL) were associated with a relative risk of overall mortality of 2.0 (95% CI, 1.70—2.33) after a 14-year follow-up.

Initiation of aggressive treatment for HeFH is equally able to correct the cardiovascular prognosis and improve the survival prognosis. Hence, in two recent studies, when HeFH was treated as part of primary prevention, life expectancy was identical to that of the general population [16,17].

In a recent study [16] based on the follow-up of 1688 patients with HeFH confirmed by a genetic diagnosis, the authors recorded 113 deaths over a mean follow-up period of 8 years (cumulative mortality rate of 2.4%). Our sample in the general population presents the same overall mortality as this sample of subjects with genetically-diagnosed HeFH. This appears to favour the inclusion, in our sample, of patients genuinely presenting HeFH, who had not been clinically or genetically diagnosed. Furthermore, in the MEDPED study conducted in 1993 [18], LDL-C values of 6.5 mmol/L (250 mg/dL) in the general population were associated with a 68.4% probability of having HeFH, LDL-C values of 6.8 mmol/L (264 mg/dL) were associated with an 88.2% probability of having HeFH, while LDL-C values in the region of 8.5 mmol/L (330 mg/dL) were linked with a 100% probability of having HeFH. Hence, the values observed in our sample suggest a high probability of undiagnosed HeFH.

Our study has a number of limitations. Cardiovascular mortality was not recorded because it is known to be considerably underestimated based on death certificates in France. We recorded family history of CVD in a conventional manner; however, we are not convinced that this was a fully comprehensive approach, as most patients cannot remember the date of onset of the disease in family members. Furthermore, observations did not include reporting of tendon xanthomas or corneal arcus. Lastly, routine

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genetic diagnostic tests have only become available at the centre very recently, so we were unable to make use of genetic diagnostic results obtained in recent years. However, according to the literature, in 10% to 40% of all cases, no causative mutations are found, despite a typical clinical presentation [2].

Our sample population can be assumed to be at greater risk than the general population. In a recent study (Bérard E., personal communication), we showed that the life expectancy of our sample was similar to that of the general population in the same region. Consequently, DLCN LDL-C concentrations may be used in the general population to screen for potential HeFH patients. In these patients with high LDL-C concentrations, extending the patient interview to include specific investigation of a family history of hypercholesterolaemia or early-onset CVD and the clinical examination to include investigation of corneal arcus and tendon xanthomas may be proposed.

Conclusions

DLCN LDL-C concentrations are associated with overall mortality in France. Total mortality increases as LDL-C concentrations increase. These findings should prompt the French medical community to screen for HeFH as extensively as possible, and to adopt an aggressive management approach for those patients with the highest LDL-C concentrations. Lastly, elevated LDL-C concentrations in a given patient should prompt us to screen all family members for HeFH.

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Disclosure of interest

Jean Ferrières: educational grants from the companies AMGEN, AstraZeneca, MSD Chibret, Sanofi, Novartis and Servier.

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Vanina Bongard, Emilie Bérard, Dorota Taraszkiewicz and Jean-Bernard Ruidavets declare that they have no conflicts of interest concerning this article.

Appendix A.

Table 1 Association between overall mortality and Dutch Lipid Clinic Network low-density lipoprotein cholesterol concentrations, as per the multivariable analysis (adjustment for age, sex, tobacco use, hypertension, diabetes and statin therapy).

	HR	(95% CI)	*P*
LDL-C < 4 mmol/L (< 155 mg/dL)	1		
4 ≤ LDL-C < 6.5 mmol/L (155 to < 250 mg/dL)	1.93	(1.31—2.85)	0.001
LDL-C ≥ 6.5 mmol/L (≥ 250 mg/dL)	2.98	(1.25—7.08)	0.014

CI: confidence interval; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol.

Table 2 Association between overall mortality and Dutch Lipid Clinic Network low-density lipoprotein cholesterol concentrations, as per the multivariable analysis (adjustment for age, sex, tobacco use, hypertension and diabetes), with exclusion of all patients on statins.

	HR	(95% CI)	*P*
LDL-C < 4 mmol/L (< 155 mg/dL)	1		
4 ≤ LDL-C < 6.5 mmol/L (155 to < 250 mg/dL)	2.07	(1.33—3.23)	0.001
LDL-C ≥ 6.5 mmol/L (≥ 250 mg/dL)	3.82	(1.46—10.07)	0.006

CI: confidence interval; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol.

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