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# Prevalence and management of hypercholesterolemia in France, the Esteban observational study

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## Abstract

Hypercholesterolemia is a major risk factor for cardiovascular diseases. However, its management in everyday clinical practice is often suboptimal. The aims of the Esteban study were to estimate the prevalence of hypercholesterolemia and to describe its management in France in 2015.

Esteban is a cross-sectional, publicly funded survey, representative of the French population. Data were collected using questionnaires and biological and clinical examinations in 3021 adults aged 18-74.

The lipid-lowering treatments were obtained by matching the individual data of the subjects included in the Esteban survey with data from the *Système national de données de santé*. Hypercholesterolemia was defined as either a low density lipoprotein cholesterol value higher than the goal set in the European Society of Cardiology/European Atherosclerosis Society guidelines as a function of individual cardiovascular risk level, or at least 1 delivery of lipid-lowering treatment. Adherence was defined by the proportion of days covered by the lipid-lowering treatment in the 6 months preceding clinical examination. Prevalence of hypercholesterolemia in France was 23.3% (27.8% in men, 19.0% in women). Mean low density lipoprotein cholesterol was 3.38 mmol/l in French participants. Among them, 7.2% were treated (8.5% of men, 5.8% of women), while 16.1% of adults went untreated (19.3% of men, 13.2% of women). Only 29.7% of secondary prevention adults had a delivery of lipid-lowering treatments in the 6 months preceding clinical examination. Fewer than 1 in 3 treated adults were adherent, i.e. more than 80% of days covered by a

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JB has received research support or has served on advisory boards or as a speaker for Abbott, Amgen, Astellas, Astra-Zeneca, Bayer, Boehringer Ingelheim, Bouchara-Recordati, Daiichi Sankyo, Ferring, Gilead, Icomed, Medexact, Medtronic, Novartis, Novo Nordisk, Quantum Genomics, Saint Jude, Sanofi Aventis, and Servier.

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IRB Approval: The study was registered in the French National Agency for Medicines and Health Products Safety (No. 2012-A00456-34) and was approved by the Advisory Committee for Protection of Persons in Biomedical Research.

All patients provided written consent for participation in the registry in accordance with local ethics committee requirements.

JB and VO were at the origin of the conception and design of the work. VO, AV and AG performed the acquisition and analysis of the data. All authors made substantial contributions to the interpretation of data. JB and VO drafted the manuscript and all authors revised it critically for important intellectual content. All authors have read and gave final approval and agree to be held accountable for all aspects of work ensuring integrity and accuracy.

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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treatment. This proportion reached 37.4% in the high-risk group, with no significant difference of adherence in people with or without a personal history of cardiovascular disease in this group.

This study showed that hypercholesterolemia is a common metabolic disease in France, affecting 23.3% of the population. Lipid-lowering prescriptions diverged greatly from current recommendations, with less than a third of eligible patients being treated.

**Abbreviations:** BMI = body mass index, EAS = European Atherosclerosis Society, ESC = European Society of Cardiology, HDL = high density lipoprotein, LDL-c = low density lipoprotein cholesterol, SAS = Statistical Analysis Software, SCORE = systematic coronary risk evaluation, SNDS = *Système national de données de santé*.

**Keywords:** adherence, cardiovascular risk, cholesterol, guidelines, statins

## 1. Introduction

Cardiovascular disease is the leading cause of death worldwide.<sup>[1]</sup> The last 4 decades have seen continued improvement in cardiovascular morbidity and mortality, at least in developed countries.<sup>[1]</sup> From 2004 onwards, cardiovascular diseases moved from being the first to the second leading cause of death in France, after cancer.<sup>[2]</sup> The reasons for this improvement include better patient care thanks to fundamental changes in therapeutic practices and strategies in the recent decades and better control of cardiovascular risk factors at the population level.<sup>[3]</sup> Low density lipoprotein cholesterol (LDL-c) has been well-established as a major risk factor for cardiovascular diseases<sup>[4–6]</sup> and current guidelines have set LDL-c goals according to cardiovascular risk. Prescription of a lipid-lowering treatment, especially statin, has been shown, with a high level of evidence, to have an impact in terms of both primary and secondary cardiovascular prevention.<sup>[7,8]</sup> However, several studies have demonstrated under-prescription of statin and non-optimal adherence to these treatments.<sup>[9–11]</sup> Physician inertia, patient unwillingness and the real or alleged side effects of statins may be implicated in the suboptimal management of dyslipidemia.<sup>[10–12]</sup> In France, this therapeutic class has been challenged in the lay press and, as a consequence, generates fears with recurring suspicions about its safety and its usefulness.<sup>[12]</sup> Very few French data are available on the prevalence and management of hypercholesterolemia at the population level.<sup>[11]</sup>

Esteban was a cross-sectional epidemiological study comprising a clinical examination. Conducted in 2014 to 2016, it provided a wide range of health information on a representative sample of the French population.<sup>[13]</sup> The objectives of the present analysis were to assess the prevalence of hypercholesterolemia according to cardiovascular risk profiles, to evaluate the modalities of prescription of lipid-lowering treatment, to compare the prescriptions with the European recommendations for the management of patients with dyslipidemia (European Society of Cardiology/European Atherosclerosis Society (ESC/EAS), 2011),<sup>[14]</sup> and to measure patient adherence to lipid-lowering treatments.

## 2. Methods

### 2.1. Study design

Esteban survey was a cross-sectional study incorporating a clinical examination, representative of the whole population of French adults. The study protocol has been published elsewhere.<sup>[13]</sup> One of the study objectives was to estimate the prevalence of vascular risk factors, and to describe their management. The design of the Esteban survey was a multistage stratified random sample. In the first stage, a stratified sample of

geographical primary units was created. At the second stage, households were sampled by random generation of landline and mobile telephone numbers. At the third level, a single adult was selected by lot from among the eligible household members according to Kish's method. Considering the sample design, an initial set of weightings was calculated based on the number of eligible individuals in the household, multiplied by the inverse probability of dwelling selection in the stratum. To account for individuals who dropped out of the study between the first visit and the clinical examination, we estimated a new set of weightings. Calibration was then made separately for each gender according to national census data on age, diploma and whether the household included or did not include at least 1 child and the season. Calibration was carried out using the Statistical Analysis Software (SAS) macro program CALibration on MARGins. This methodology ensured our sample's representativity among the non-institutionalized French population.

Data comprised dietary intake description, clinical and biochemical marker measurements, physical activity (Recent Physical Activity Questionnaire) and complementary items in questionnaires. Individual participant-provided data were linked to the *Système National des données de santé* (SNDS; French National Health Insurance Information System) database, which provides exhaustive data on reimbursements for healthcare expenditures such as drugs and outpatient medical care prescribed or provided by health-care professionals.<sup>[15]</sup> The study was registered with the French National Agency for Medicines and Health Products Safety (No. 2012-A00456-34) and approved by the Advisory Committee for Protection of Persons in Biomedical Research.

### 2.2. Study population

A total of 3,021 adults were included between April 2014 and March 2016. After exclusion of participants without a clinical examination (n = 518) and those who did not provide consent to data linkage with the SNDS database (n = 387), 2,011 participants with available lipid measurements were included in the analyses (Fig. 1).

### 2.3. Data collection

Sociodemographic data were collected by dedicated personnel with face-to-face questionnaires during the first home visit. Self-declared smoking status was classified into 3 categories: current smoker, former smoker and non-smoker. Participants were considered diabetic if they reported that they had been diagnosed as diabetic by a physician in the past, if they were currently taking anti-diabetic treatment (oral agents or injections), or if their fasting blood glucose was  $\geq 7$  mmol/l. Otherwise, they were

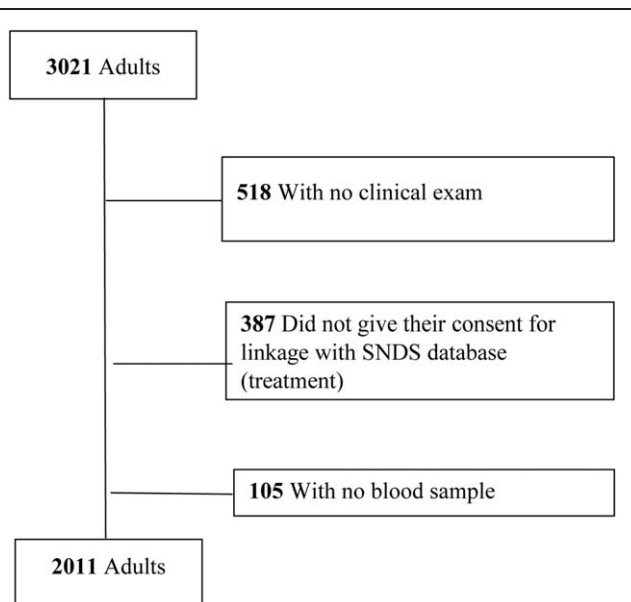


Figure 1. Flow chart of the study population.

considered non-diabetic. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg on clinical examination, or the delivery of at least 1 antihypertensive treatment during the year preceding the clinical examination. Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared.

First-degree family history of premature coronary heart disease (myocardial infarction or sudden death before 55 years in men and before 65 years in women) and personal history of cardiovascular disease were declarative. Chronic kidney disease was defined as known macroproteinuria or decreased renal function (creatinine clearance  $< 60$  mL/min calculated by the Cockcroft-Gault equation) for more than 3 months.

#### 2.4. Lipid profile

A blood sample was taken during the clinical examination. Participants had to fast for at least 12 hours before the examination. Total cholesterol, high density lipoprotein cholesterol (HDL-c) and triglycerides were all measured within hours of sampling by laboratories attached to health examination centers or by private laboratories. LDL-c was calculated using the Friedewald formula when triglycerides were less than 3.8 mmol/L. Lipid-lowering treatment information (name and date of delivery) was obtained by matching the individual adult data included with the data from the SNDS database. An adult was considered treated if he or she had received at least 1 delivery of a lipid-lowering treatment during the 6 months preceding the clinical examination.

#### 2.5. European guidelines for management of patients with dyslipidemia

In line with the 2011 ESC/EAS guidelines,<sup>[14]</sup> adults in the Esteban survey with a calculated 10-year risk score of cardiovascular death  $\geq 10\%$  (using the systematic coronary risk evaluation (SCORE) scale, low risk chart<sup>[16]</sup>), patients with established cardiovascular disease, patients with type 2 diabetes

with another markedly elevated risk factor, patients with type 1 diabetes with target organ damage (such as microalbuminuria) and patients with moderate to severe chronic kidney disease (creatinine clearance  $< 60$  mL/min/1.73m<sup>2</sup>) were all classified in the very high-risk group. Patients with a calculated 10-year risk score between 5 and 10%, patients with markedly elevated single risk factors such as familial dyslipidemias and severe hypertension were classified in the high-risk group. In the Esteban survey, patients were considered as having a familial hypercholesterolemia if their LDL-c level or pre-treatment LDL-c level was above 7.8 mmol/L. Patients with a calculated 10-year risk score between 1 and 5% were classified in the moderate risk group. Finally, patients with a calculated 10-year risk score  $\leq 1\%$  were classified in the low risk group.

Furthermore, according to the same 2011 guidelines, the level of LDL-c used to consider normal values for LDL-c was 4.9 mmol/L in patients with low and moderate risk, 2.6 mmol/L in patients with high cardiovascular risk and 1.8 mmol/L in patients with very high cardiovascular risk. In Esteban, patients who had an LDL-c level above the normal value or who had received a lipid-lowering drug in the 6 months before the clinical examination were considered as having hypercholesterolemia.

#### 2.6. Treatments prescribed according to guidelines

For each patient treated with a lipid-lowering drug, we first evaluated the pre-treatment level of LDL-c, by adding the mean LDL-c decrease achieved by treatment to the current LDL-c, taking into account type and dose of each treatment.<sup>[17]</sup> Using this pre-treatment LDL-c level, we then classified patients according to the class of recommendation and level of evidence as defined in the 2011 guidelines. Patients treated with a lipid-lowering medication who had a pre-treatment LDL-c level corresponding to an I/C category were considered to be treated outside of recommendations.

#### 2.7. Adherence definition

Adherence was defined by the proportion of days covered by the lipid-lowering drug between the first treatment delivery in the 6 months preceding the clinical examination and the date of examination itself. The number of days covered was calculated by number of medication deliveries multiplied by number of pills delivered. A patient was considered adherent if the proportion of days covered was greater than 80%.

#### 2.8. Statistical analysis

A descriptive analysis, using SAS survey analysis procedures, was performed for the entire population and for each gender using weighted mean  $\pm$  standard deviation for quantitative variables, and weighted percentages for categorical variables for the entire population and for each gender. Confidence intervals were reported with a 95% bilateral confidence level. A  $P < .05$  was considered statistically significant. Statistical analyses were performed using SAS software version 7.1 (SAS Institute, Carry, NC).

### 3. Results

The characteristics of the 2,011 included participants (903 men and 1,108 women) stratified by gender are displayed in Table 1.

**Table 1**  
**Characteristics of adults included in Esteban study.**

Characteristics	All	Men	Women	P value
N	2 011	903	1108	
Age (yr), mean (SD)	47.3 (14.6)	47.8 (14.2)	46.8 (14.9)	.27
Education level, %				.8
<high school diploma	9.3%	9.3%	9.2%	
high school diploma	47.0%	46.0%	48.0%	
>high school diploma	43.7%	44.7%	42.8%	
BMI (kg/m <sup>2</sup> ), mean (SD)	25.9 (5.1)	26.1 (4.5)	25.7 (5.5)	.18
BMI class, %				<.0001
<25	50.9%	45.2%	56.2%	
25–30	31.9%	38.1%	26.1%	
>30	17.2%	16.7%	17.7%	
Score Alcohol, %				<.0001
Never/light drinker	8.9%	7.0%	10.6%	
Moderate drinker	85.1%	82.6%	87.4%	
Heavy drinkers	6.0%	10.4%	2.0%	
Tobacco, %				<.0001
Non-smoker	51.2%	42.6%	59.3%	
Former smoker	28.1%	32.5%	23.9%	
Current smoker	20.7%	24.8%	16.8%	
Physical Activity, %				<.0001
Low	38.6%	28.9%	47.6%	
Moderate	51.1%	56.3%	46.3%	
High	10.3%	14.9%	6.2%	
Diabetes, %	5.5%	8.0%	3.2%	.0006
Hypertension, %	30.9%	37.2%	25.0%	<.0001
Personal history of CV diseases, %	3.6%	4.9%	2.4%	.007
Total cholesterol (mmol/l), mean (SD)	5.42 (1.05)	5.39 (1.03)	5.42 (1.16)	.47
HDL-c (mmol/L), mean (SD)	1.52 (0.39)	1.39 (0.33)	1.64 (0.39)	<.0001
LDL-c (mmol/l), mean (SD)	3.36 (0.92)	3.42 (0.92)	3.31 (0.92)	.11
Triglycerides (mmol/L), mean (SD)	1.18 (0.60)	1.29 (0.67)	1.06 (0.50)	<.0001

BMI=body mass index, CV=cardiovascular, HDL-c=high density lipoprotein cholesterol, LDL-c=low density lipoprotein cholesterol, SD=standard deviation.

The mean age of adults was 47.3 years and mean BMI was 25.9 kg/m<sup>2</sup>. The distribution of men and women by BMI classes differed with higher prevalence of overweight men as compared to women (38.1% vs. 26.1%, respectively). The proportions of heavy drinkers and current smokers were greater in men (10.4% and 24.8%, respectively) than in women (2.0% and 16.8%). The level of physical activity was greater in men, with 71.2% of men reporting a moderate or high-level of physical activity versus 52.5% in women. Prevalence of diabetes and hypertension were 5.5% and 30.9% respectively, in the whole study population, with higher prevalence in men than women (8.0% vs 3.2%, respectively, for diabetes and 37.2% vs 25.0%, respectively, for hypertension). Mean total cholesterol, HDL-c and LDL-c were 5.42, 1.52 and 3.38 mmol/L respectively with HDL-c significantly higher in women than in men (1.64 vs. 1.39 mmol/l in men). Distribution of adults according to their individual cardiovascular risk level showed that 55.2% of the Esteban population had a low level of risk (Table 2). One tenth (10.3%) of the Esteban population had a very high cardiovascular risk (3.6% of the Esteban population due to personal history of cardiovascular disease). Men had a less favorable cardiovascular risk profile than women with 41.3% of the former in the low cardiovascular risk group (vs. 68.4% of women), and 11.7% in the group at very high cardiovascular risk group (vs. 9.1% in women). The proportion of adults treated with lipid-lowering drug increased with the level of cardiovascular risk: from 1.4% in the low cardiovascular risk group to 21.9% in the very high cardiovas-

cular risk group (Fig. 2). The very high cardiovascular risk group included adults who had a personal history of cardiovascular disease. Among those adults specifically, the proportion of patients treated with lipid-lowering drug was 29.7%. In the latter group, the proportion of men treated by lipid-lowering treatments (26.6%) was higher than in women (16.2%). All in all, 7.2% of the study population was treated by lipid-lowering treatments (8.6% for men and 5.8% for women), 85.7% of them being treated with statins.

Mean LDL-c was 3.38 mmol/l and did not differ significantly between men and women ( $P=.11$ ) (Table 2).

Average adherence to lipid-lowering treatments, estimated by the proportion of days covered by treatment in the 6 months before the clinical exam, was 65.7%. Fewer than 1 in 3 treated adults (30.8%) presented adherence exceeding 80% (Table 2). While adherence did not differ significantly between men and women ( $P=.61$ ), rate of adherence by cardiovascular risk level was higher in the very high-risk group (Table 2). In the high-risk group, adherence did not differ significantly between people with or without history of cardiovascular disease (34.2 vs 40.9% of people with more than 80% of days covered by treatment respectively). Prevalence of hypercholesterolemia -estimated as the proportion of adults presenting with LDL-c level higher than normal value or having received lipid-lowering treatments in the 6 months before the clinical examination- was 23.3% (Fig. 2). It was higher among men (27.8%) than women (19.0%). Prevalence of hypercholesterolemia increased (non-linearly) with

**Table 2**  
**Breakdown of Esteban population, lipid lowering drugs, mean LDL-c level and adherence according to cardiovascular risk level\*.**

Total	Low	Moderate	High	Very High	Total
Esteban population (%)	55.2 [52.4–54.8]	30.5 [27.9–33.1]	3.9 [2.9–5.0]	10.3 [8.7–12.0]	100.0
LDL-c level					
Mean LDL-c (mmol/l)	3.22 [3.16–3.28]	3.64 [3.56–3.73]	3.78 [3.54–4.02]	3.35 [3.22–3.49]	3.38 [3.34–3.43]
Average adherence to lipid lowering drugs					
Proportion of days covered (%)	62.3 [50.1–74.5]	62.8 [55.7–69.8]	70.3 [61.0–79.6]	71.4 [64.6–78.1]	65.7 [60.8–70.7]
Proportion of patients with adherence>80% (%)	27.1 [1.3–54.0]	28.4 [16.5–40.3]	22.1 [0.0–53.5]	37.4 [19.4–55.3]	30.8 [21.5–40.2]
Men	Low	Moderate	High	Very High	Total
Esteban population (%)	41.3 [37.3–45.34]	40.3 [36.2–44.3]	6.8 [4.8–8.8]	11.7 [9.0–14.3]	100.0
LDL-c level					
Mean LDL-c (mmol/l)	3.31 [3.21–3.40]	3.59 [3.48–3.70]	3.65 [3.48–3.83]	3.18 [2.97–3.39]	3.43 [3.36–3.49]
Average adherence to lipid lowering drugs					
Proportion of days covered (%)	72.9 [65.4–80.5]	65.3 [58.9–71.8]	71.5 [59.8–83.1]	73.8 [65.8–81.8]	69.1 [64.6–73.6]
Proportion of patients with adherence>80% (%)	33.7 [0.0–94.0]	27.3 [11.2–43.4]	27.0 [0.0–65.9]	43.4 [21.5–65.4]	33.4 [21.4–45.4]
Women	Low	Moderate	High	Very High	Total
Esteban population (%)	68.4 [64.9–71.8]	21.3 [18.2–24.3]	1.3 [0.5–2.1]	9.1 [7.1–11.1]	100.0
LDL-c level					
Mean LDL-c (mmol/l)	3.74 [3.10–3.24]	3.17 [3.61–3.86]	4.42 [3.31–5.54]	3.56 [3.40–3.71]	3.34 [3.28–3.40]
Average adherence to lipid lowering drugs					
Proportion of days covered (%)	59.2 [44.3–74.0]	59.1 [45.2–73.0]	65.0 [65.0–65.0]	66.6 [57.4–75.7]	61.1 [52.6–69.6]
Proportion of patients with adherence>80% (%)	25.2 [0.0–53.4]	29.9 [11.0–48.8]	0.0 [0.0–0.0]	25.3 [52.8–96.7]	27.3 [14.0–40.6]

ESC/EAS=European Society of Cardiology/European Atherosclerosis Society, LDL-c=low density cholesterol.

\* according to risk level stratification of the ESC/EAS guidelines for the management of dyslipidemias.

the level of cardiovascular risk, from 4.9% in the low cardiovascular risk group (LDL-c normal value=4.9 mmol/l) to 96.8% in the very high cardiovascular risk group (LDL-c normal value=1.8 mmol/l).

Over 16% of adults, who according to the 2011 guidelines should have been treated, went untreated (10.3% and 5.8% with I/A and IIa/A treatment category, respectively) (Fig. 3). While the proportion was marginal in the low cardiovascular risk group (3.5%), it reached 74.9% in adults with very high cardiovascular risk (Fig. 2). The proportion of patients treated outside recommendations was very low (0.6% of the total population). Non-implementation of the 2011 recommendations was higher for men than for women, 19.3% of the former not being treated despite being eligible (vs 13.2% of women,  $P < .01$ ).

#### 4. Discussion

The Esteban study showed that, according to the current guidelines, in 2015 hypercholesterolemia affected 23.3% of the French population. Furthermore, the management of LDL-c deviated substantially from the ESC/EAS guidelines with under a third of hypercholesterolemic subjects being pharmacologically treated. In addition, the average number of pills delivered over the year corresponded to daily treatment received for less than 8 months/year, which would strongly suggest that many patients are giving themselves therapeutic windows or a lower dosage than prescribed. According to the guidelines, 16.1% of the population should have been treated but were not, while 0.6% were treated outside of existing recommendations. Finally, the lack of difference in mean LDL-c levels, in groups defined by their cardiovascular risk, suggests that baseline LDL-c level is a stronger determinant of being treated than the overall cardiovascular risk level.

The mean level of LDL-c found in our study was similar to the mean level of non-HDL-c reported in a recent analysis of 1,127

patients in a pooled population-based study (3.3 mmol/l).<sup>[18]</sup> Our results therefore are not in favor of a French specificity in terms of lipids (basis of the “French paradox”). Although the role of cholesterol serum levels as potential risk factor for ischemic stroke has been reported as conflicting, with complex relations,<sup>[19–21]</sup> cholesterol is undoubtedly a major cardiometabolic risk factor.<sup>[22]</sup>

The larger proportion of subjects treated in secondary prevention (vs. primary prevention) may suggest that recommendations are more closely followed in these high-risk patients. Nevertheless LDL-c goals are lower for secondary prevention subjects, and our results showed that they were achieved less frequently in the high-risk population than in other groups. Only 29.7% of secondary prevention adults were treated with lipid-lowering treatments, even though 92.8% were eligible for treatment according to the 2011 guidelines. Insufficient management and poor adherence to lipid-lowering treatment has been described in other studies with a large proportion of high- and very high-risk individuals failing to attain their LDL-c goals.<sup>[9–11,23–25]</sup> The proportion of people receiving lipid-lowering treatment in the high-risk group in our study is 1 of the lowest described in the literature. This finding could be partially explained by the pronounced distrust among patients in France regarding this therapeutic class. In France, recurring suspicions and controversies about the safety and usefulness of statin have gone far beyond the limited scope of the scientific world in France and have spread among the general public with very wide coverage not only on the traditional audiovisual media, including newspapers, but also on numerous websites.<sup>[12]</sup>

As regards women, management seems even worse for women; in secondary prevention, only 19.6% of them were receiving lipid-lowering treatment (data not shown). This result is consistent with previous studies showing that the lower use of

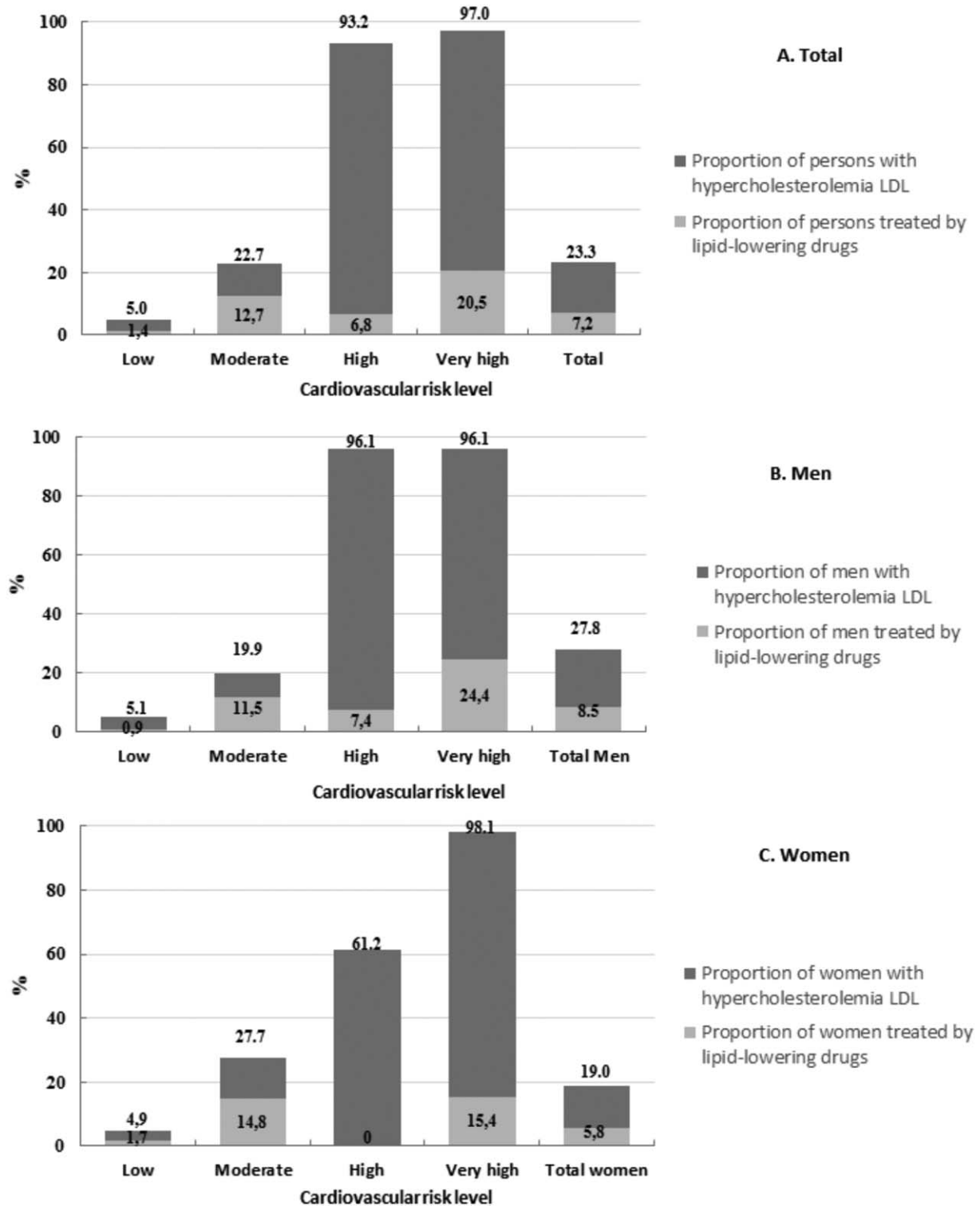
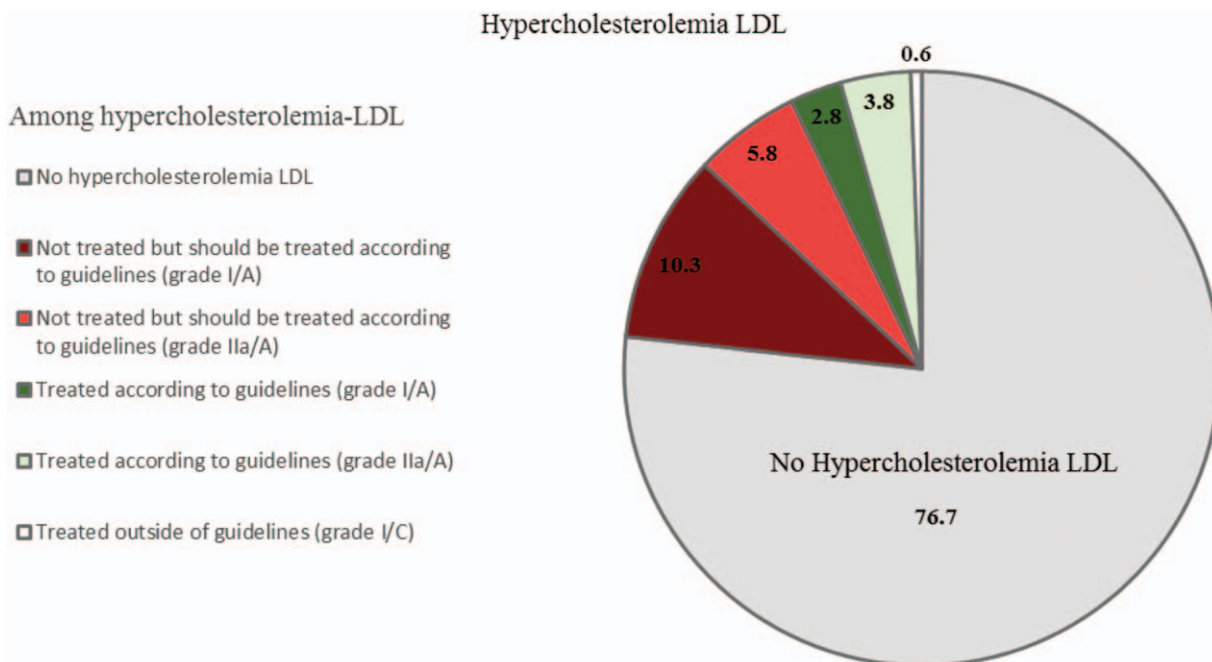


Figure 2. Prevalence of hypercholesterolemia and treated persons in each cardiovascular risk level group in all (A), men (B) and women (C).

cardiovascular prevention drugs in women is probably related to underestimation by clinicians of women's cardiovascular risks.<sup>[26]</sup>

It has previously been reported that French care providers prescribed too many lipid-lowering drugs.<sup>[27]</sup> Based on reasonable assumptions about the effect of statin treatments on LDL-c,

we estimated a spontaneous LDL-c level using data on the LDL-c level achieved following treatment. It appears that among the 7.2% of the population receiving lipid-lowering treatments, more than 91% (ie, 6.6%) were treated in accordance with the recommendations for practice, while 0.6% of treatments were outside the recommendations. Given that strict application



**Figure 3.** Distribution of treated and non-treated adults according to grade of 2011 ESC/EAS guidelines for the management of dyslipidemias.

of the practice recommendations would mean that 23.3% of the population should have been treated, we can therefore conclude that this class of cardiovascular prevention drugs is underprescribed in the French population.

Other authors have shown that negative messages on statins may also impact antihypertensive treatments, further decreasing the effectiveness of cardiovascular prevention.<sup>[28]</sup> This phenomenon has been observed in France with a significant decrease in hypertensive treatments over the same period.<sup>[29]</sup>

#### 4.1. Strengths and Limitations of this study

The main strength of our study is that participants in the ESTEBAN survey were representative of the general French population. Data were collected in accordance with standardized protocols, adding validity to our study results. In addition, use of the exhaustive SNDS database to retrieve data on treatments for each adult enabled us to avoid memory bias and social desirability bias along with under or overdeclaration regarding treatments. Our adherence estimation was consequently more reliable than declarative estimation.

However, some limitations are present in our study. First, some of the data collected were declarative, particularly personal and family history. Self-administered questionnaires may lead to memory biases, which could alter patient answers. That said, only medically established diagnoses of previous cardiovascular events were considered in our analysis. Another study limitation regarded assessment of cardiovascular risk. More specifically, according to European recommendations, while microalbuminuria is 1 of the risk factors included in assessment of very high cardiovascular risk, it was not measured in the Esteban study, and could consequently not be taken into consideration. Furthermore, our design did not enable us to differentiate absence of medical prescription from a non-fulfilled prescription.

#### 4.2. Future directions

Although numerous controlled trials and meta-analyses have demonstrated that a reduction in LDL-c according to degree of cardiovascular risk yields a significant benefit on morbidity and mortality, our results, which show that only a minority of patients reach the LDL-c goal set by the guidelines, raise a number of questions. Management guidelines for dyslipidemia always take time to be integrated and implemented by physicians in clinical practice. New strategies designed to change medical practices more quickly and in depth and to improve patient compliance need to be devised to improve the management of patients' cholesterol and cardiovascular risk profiles.

#### 5. Conclusion

Hypercholesterolemia may be viewed as a common metabolic condition in France, affecting 23.3% of the population in 2015. However, management has been suboptimal, with a lower level of prescription for lipid-lowering treatments than what the guidelines suggest and with a poor level of adherence to treatment.

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## References

- [1] Naghavi M, Abajobir AA, Abbafati C. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390:1151–210.
- [2] Aouba A, Eb M, Rey G, et al. Mortality data in France: the main causes of death in 2008 and trends since 2000. *Bull Epidemiol Hebd* 2011;2: 49–55.
- [3] Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 2007;356:2388–98.
- [4] Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenings of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; 256:2823–8.
- [5] Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med* 1990; 322:1700–7.
- [6] Wong ND, Wilson PW, Kannel WB. Serum cholesterol as a prognostic factor after myocardial infarction: the Framingham Study. *Ann Intern Med* 1991;115:687–93.
- [7] Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;388:2532–61.
- [8] Akyea RK, Kai J, Qureshi N, et al. Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease. *Heart* 2019;105:975–81.
- [9] Kim S, Han S, Rane PP, et al. Achievement of the low-density lipoprotein cholesterol goal among patients with dyslipidemia in South Korea. *PLoS One* 2020;15:e0228472.
- [10] Athyros VG, Stavropoulos K, Imprialos KP, et al. Suboptimal management of dyslipidemia in everyday clinical practice: Alarming signals from real-world data. *Int J Cardiol* 2020;316:240–1.
- [11] Bongard V, Dallongeville J, Arveiler D, et al. Attainment of low-density lipoprotein cholesterol target in the French general population according to levels of cardiovascular risk: Insights from the MONA LISA study. *Arch Cardiovasc Dis* 2013;106:93–102.
- [12] Blacher J. The disturbing state of affairs of hypertension in France: a replica of the cholesterol/statins tsunami? *Presse Med* 2018;47:497–8.
- [13] Balicco A, Oleko A, Szego E, et al. Esteban design: a cross-sectional health survey about environment, biomonitoring, physical activity and nutrition (2014–2016). *Toxicologie Analytique et Clinique* 2017;29:517–37.
- [14] European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, et al. ESC Committee for Practice Guidelines (CPG) 2008–2010 and 2010–2012 2012 Committees 2011 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J* 2011;32:1769–818.
- [15] Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the systeme national d'information interregimes de l'Assurance Maladie (SNIIRAM) to the systeme national des donnees de sante (SNDS) in France. *Rev Epidemiol Sante Publique* 2017;65(Suppl 4):S149–67.
- [16] Conroy R, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24:987–1003.
- [17] Weng TC, Yang YH, Lin SJ, et al. A systematic review and meta-analysis on the therapeutic equivalence of statins. *J Clin Pharm Ther* 2010;35:139–51.
- [18] Collaboration NCDRF. Repositioning of the global epicentre of non-optimal cholesterol. *Nature* 2020;582:73–7.
- [19] Pinto A, Tuttolomondo A, Di Raimondo D, et al. Risk factors profile and clinical outcome of ischemic stroke patients admitted in a department of internal medicine and classified by TOAST classification. *Int Angiol* 2006;25:261–7.
- [20] Di Raimondo D, Tuttolomondo A, Buttà C, et al. Metabolic and anti-inflammatory effects of a home-based programme of aerobic physical exercise. *Int J Clin Pract* 2013;67:1247–53.
- [21] Della Corte V, Tuttolomondo A, Pecoraro R, et al. Inflammation, endothelial dysfunction and arterial stiffness as therapeutic targets in cardiovascular medicine. *Curr Pharm Des* 2016;22:4658–68.
- [22] Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;38:2459–72.
- [23] De Luca L, Arca M, Temporelli PL, et al. Current lipid-lowering treatment and attainment of LDL targets recommended by ESC/EAS guidelines in very high-risk patients with established atherosclerotic cardiovascular disease: Insights from the START registry. *Int J Cardiol* 2020.
- [24] Breuker C, Clement F, Mura T, et al. Non-achievement of LDL-cholesterol targets in patients with diabetes at very-high cardiovascular risk receiving statin treatment: Incidence and risk factors. *Int J Cardiol* 2018;268:195–9.
- [25] da Silva PM, Aguiar C, Morais J, et al. Suboptimal lipid levels in clinical practice among Portuguese adults with dyslipidemia under lipid-lowering therapy: data from the DISGEN-LIPID study. *Rev Port Cardiol* 2019;38:559–69.
- [26] Bird CE, Manocchia M, Tomblin B, et al. Mapping the Gaps: gender differences in preventive cardiovascular care among managed care members in four metropolitan areas. *Womens Health Issues* 2018; 28:446–55.
- [27] Ravnskov U, de Lorgeril M, Diamond DM, et al. LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. *Expert Rev Clin Pharmacol* 2018;11:959–70.
- [28] Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. *Eur Heart J* 2016;37:908–16.
- [29] Vallée A, Gabet A, Grave C, et al. Patterns of hypertension management in France in 2015: the ESTEBAN survey. *J Clin Hypertension* 2020;22:663–72.