

High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: The French Familial Hypercholesterolemia Registry

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Abstract: Background and aims: Cardiovascular risk is high in heterozygous familial hypercholesterolemia (HeFH). The objective of this study was to describe recurrent cardiovascular events in selected patients with HeFH attending lipid clinics in France.
Methods: We included 781 patients with a clinical (Dutch Lipid Clinic Network score ≥ 6) or genetic diagnosis of HeFH who had experienced a first cardiovascular event (myocardial infarction, percutaneous coronary intervention or coronary bypass, unstable angina, stroke, peripheral arterial revascularization or cardiovascular death) and were enrolled in the French Familial Hypercholesterolemia Registry (November 2015 to March 2018).
Results: The first cardiovascular event occurred at the mean age of 47 years (interquartile range 39-55) in a predominantly male population (72%); 48% of patients were on statin therapy. Overall, 37% of patients had at least one recurrent cardiovascular event (mean of 1.8 events per patient), of which 32% occurred in the 12 months after the index event; 55% of events occurred >3 years after the first event. Mean LDL-C at the last clinic visit was 144±75 mg/dL (132±69 mg/dL for patients on high-potency statin therapy and 223±85 mg/dL for untreated patients).
Conclusions: The rate of recurrent cardiovascular events was high in French patients with HeFH in secondary prevention. The detection of FH in the childhood is crucial to prevent CV events at a young age by early initiating statin therapy. There is a clear urgent need to expand the actual very small target population which can be treated with PCSK9 inhibitor in France.

Highlights

One in two HeFH patients is not treated with statins at the time of the first CV even

37% of HeFH patients have CV recurrences after a first CV event

Nearly half of the CV recurrences occurred more than 3 years after the first event

High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: the French Familial Hypercholesterolemia Registry

Short title: Cardiovascular recurrences in familial hypercholesterolemia

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Key words: familial hypercholesterolemia, registry, cardiovascular disease, cardiovascular recurrences, cardiovascular events

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ABSTRACT

Background and aims: Cardiovascular risk is high in heterozygous familial hypercholesterolemia (HeFH). The objective of this study was to describe recurrent cardiovascular events in selected patients with HeFH attending lipid clinics in France.

Methods: We included 781 patients with a clinical (Dutch Lipid Clinic Network score ≥ 6) or genetic diagnosis of HeFH who had experienced a first cardiovascular event (myocardial infarction, percutaneous coronary intervention or coronary bypass, unstable angina, stroke, peripheral arterial revascularization or cardiovascular death) and were enrolled in the French Familial Hypercholesterolemia Registry (November 2015 to March 2018).

Results: The first cardiovascular event occurred at the mean age of 47 years (interquartile range 39–55) in a predominantly male population (72%); 48% of patients were on statin therapy. Overall, 37% of patients had at least one recurrent cardiovascular event (mean of 1.8 events per patient), of which 32% occurred in the 12 months after the index event; 55% of events occurred >3 years after the first event. Mean LDL-C at the last clinic visit was 144±75 mg/dL (132±69 mg/dL for patients on high-potency statin therapy and 223±85 mg/dL for untreated patients).

Conclusions: The rate of recurrent cardiovascular events was high in French patients with HeFH in secondary prevention. The detection of FH in the childhood is crucial to prevent CV events at a young age by early initiating statin therapy. There is a clear urgent need to expand the actual very small target population which can be treated with PCSK9 inhibitor in France.

Keywords:

Familial hypercholesterolemia

Registry

Cardiovascular disease

Cardiovascular recurrences

Cardiovascular events

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant hereditary disease caused by mutations in genes involved in the catabolism of low-density lipoprotein cholesterol (LDL-C): *LDLR*, *APOB* and *PCSK9* [1,2]. FH is one of the most common genetic diseases, with an estimated prevalence of 1 in 250 for heterozygous FH (HeFH) and 1 in 300,000 for homozygous FH [3-5]. People with FH have very high circulating levels of LDL-C from birth, leading to a lifelong exposure of the arteries to elevated levels of cholesterol and a high cardiovascular risk [6,7]. Young adults with FH have an up to 13-fold higher risk of myocardial infarction compared to similar young adults without the condition [3,4]. As placebo-controlled randomized trials with cardiovascular endpoints are unethical in FH, the reduction in cardiovascular risk with lipid-lowering treatment has to be extrapolated from trials in the general population or from observational studies [8-10].

The current burden of cardiovascular disease in patients with HeFH in France is unknown. We sought to evaluate the typical features of cardiovascular disease (mean age at the time of the event, type and number of events, use of lipid-lowering therapies) in HeFH patients in secondary prevention in the French Familial Hypercholesterolemia Registry.

2. Patients and Methods

2.1. Settings

In 2015, the New French Society of Atherosclerosis established a national multicenter registry to identify patients with FH in France, with the objective of assessing screening practices, treatments, and clinical and patient-reported outcomes. Eligible patients were those who visited a participating lipid clinic and were diagnosed, either clinically (Dutch Lipid Clinic Network score ≥6) or genetically, with homozygous or heterozygous FH.

Sixteen sites contributed data to the registry, as of March 2018. Adult patients received an information leaflet about the registry before being evaluated for inclusion. Informed consent from both parents was required in the case of minors. The cohort was declared to the ANSM (the French National Agency for Medicines safety) and received a declarant number [unique number identifying a particular research protocol, issued by the ANSM in France]: 2014-A01549-38. The protocol of this study was assessed by two different committees: French advisory committee on the processing of information for medical research (CCTIRS) and the National Commission for computer technology and

freedom (CNIL) respectively in May and November 2015. This research is conducted in accordance with good clinical practices.

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. To obtain data from first contact, retrospective data extraction from the patients' medical records was done for patients who were already being treated at the site.

Sociodemographic, clinical and biological data (age, height, weight, blood pressure, smoking status, cardiovascular events, use of lipid-lowering drugs) were collected, along with family history (hypercholesterolemia or any cardiovascular disease), standard laboratory results (total cholesterol, LDL-C) and cardiovascular imaging data. Where available, genetic data (presence of known FH-related mutations) were collected. Information on cardiovascular history included the date of diagnosis and the type of event. Cardiovascular events included coronary heart disease (acute coronary syndromes, encompassing myocardial infarction and unstable angina, defined according to the European Society of Cardiology/American College of Cardiology [11], percutaneous coronary intervention or coronary artery bypass graft), stroke or transient ischemic attack, peripheral artery disease (defined as carotid endarterectomy, carotid angioplasty, peripheral artery angioplasty or bypass), resuscitated sudden death and cardiovascular death.

2.2. Patients and Outcomes

The present analysis involved patients with either a Dutch Lipid Clinic Network score ≥6 or an FH-causing mutation, plus a history of at least one cardiovascular event. Cardiovascular event and recurrences of cardiovascular events were defined as: coronary heart disease (myocardial infarction, coronary angioplasty or bypass and unstable angina), stroke, transient ischemic attack, peripheral artery disease (carotid endarterectomy, carotid angioplasty, and peripheral arterial bypass), resuscitated sudden death or cardiovascular death. A recurrent cardiovascular event was defined as a second cardiovascular event, regardless of the type of the first or the second event. Coronary revascularization (i.e. percutaneous coronary intervention or coronary artery bypass graft) and myocardial infarction occurring <30 days after the index event were not considered as recurrences.

Overall follow-up duration was defined as the time from the first cardiovascular event to the last available visit at the lipid clinic. The length of time between the first and the last available visit was also

assessed. Exclusion criteria were a diagnosis of homozygous FH and the occurrence of minor cardiovascular events such as silent ischemia and stable angina when not followed by coronary revascularization.

2.3. Statistical analysis

Data are presented as frequency and percentage for categorical variables and as mean (standard deviation [SD]) or median with interquartile range (IQR) for continuous variables. A descriptive analysis was performed for cardiovascular event history. The characteristics of patients with and without at least one recurrence were compared using Student's *t* test or the Wilcoxon rank-sum test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. *P* values were associated with a significance level of 0.05 for all tests. All analyses were performed with SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Between November 2015 and March 2018, 4682 patients were enrolled in the registry, of which 781 (16.7%) met the inclusion criteria. The characteristics of the population (at the last clinic visit) are detailed in Table 1. Median follow-up was 7 (IQR: 2-17) years from the time of the first cardiovascular event until the last available clinic visit, totaling 5779 patient-years of follow-up. The population was predominantly male (72%) with a mean age of 60 years, and 64% had a family history of any cardiovascular event. Over half (55%) of the patients had a history of smoking, 36% had hypertension and 13% had type 2 diabetes. Data on maximum lifetime cholesterol and lipoprotein(a) were available for 535 (69%) and 414 (53%) patients, respectively; mean (SD) lifetime cholesterol was 420 (19) mg/dL and lipoprotein(a) was 55 (56) mg/dL. Overall, 75% patients underwent genetic testing, of which 437 (75%) had a mutation, with some patients having mutations in more than one gene. Median age at the first visit to a lipid clinic was 51 (IQR: 41-60) years.

3.2. Index and recurrent cardiovascular events

Information on history of cardiovascular events, collected at the last clinic visit, is shown in Table 2. Median age at the first cardiovascular event was 47 (IQR 39-55) years. The most frequently observed first events were coronary revascularization procedure (64%) and myocardial infarction (27%).

Overall, 511 recurrences were observed, yielding an average incidence rate of 9 per 100 patient-years after the first cardiovascular event. During follow-up, 37% of patients had at least one recurrence, 14% had two or more recurrences and 7% had three or more recurrences. The most frequent recurrences were coronary revascularization (65%) and peripheral artery disease (15%). The median time between the first and the second event was 4 years (49 months), with a median duration of 3 years (38 months) between recurrences. For 3% of patients, the recurrence occurred during the first 30 days after the first event and 29% in the first year. Approximately half of the patients had a second cardiovascular event >3 years after the first event. Median age at the time of the second event was 49 years (IQR: 42-57). A Kaplan-Meier curve showing freedom from recurrent cardiovascular events is shown in Figure 1.

3.3. Patients with recurrent cardiovascular events

Compared with patients who did not have a recurrent cardiovascular event, those with a recurrent event were more likely to be male (81% vs 67%, $p < 0.0001$) and to be older (62 vs 59 years, $p < 0.0001$) (Table 3). No differences were found in terms of genetic mutations, lipoprotein(a) levels, and maximum lifetime total cholesterol.

In patients with a recurrent event, the first cardiovascular event had occurred 7 years earlier ($p < 0.0001$), at a median age of 42 years (IQR 37 - 51) (Table 3). The type of first cardiovascular event was more often myocardial infarction (28% vs 18%, respectively) and less often stroke or TIA (6% vs 13%, respectively) in patients with at least one recurrence ($p = 0.0070$).

3.4. Treatment patterns in patients with or without cardiovascular recurrences

Median duration of statin therapy was 19 years (IQR: 10-27), starting at a median age of 41 years (IQR: 33-50); 48% of patients were treated with statin at the time of the first cardiovascular event (Table 4). Patients with at least one recurrence were less likely to be on statin treatment at the time of

the first event (39% vs 53%, $p = 0.0084$). The mean length of exposure to statins before the first event was shorter in patients with a cardiovascular recurrence (6.2 years vs 8.6 years, $p = 0.0191$).

At the time of the last clinic visit, 83% of patients were receiving statin therapy (alone or in combination with other lipid-lowering therapy); 58% were on a high-potency statin, as defined by Law et al. [12], and 57% were on statin plus ezetimibe (Table 4). No difference in treatments were found between patients with or without cardiovascular recurrences ($p = 0.0690$).

At the last clinic visit, mean LDL-C was 144±75 mg/dL for all patients (n=714), 132±69 mg/dL for patients on high-potency statin therapy (n=456) and 223±85 mg/dL for untreated patients (n=58). When reported (52%, 44/84), reasons for not taking statin therapy were muscle symptoms (44%, 37/84), patient refusal (4%, 3/84) and hepatic intolerance (4%, 3/84).

4. Discussion

The results from this contemporary French multicenter registry demonstrate the high burden of cardiovascular disease in HeFH. One in two patients was not receiving statin treatment at the time of their first cardiovascular event, which occurred at a mean age of 47 years, and only 58% were on a high-potency statin. Recurrent events occurred in 37% of patients, with almost two events (first and recurrent) per patient.

4.1. Statins in primary prevention

In FH, initiation of statin treatment early in life decreases long-term exposure of the arteries to high cholesterol levels and is highly beneficial in the prevention of cardiovascular events [13]. US and European guidelines recommend starting statins before the age of 10 years in FH [1,2,14]. French pediatric and atherosclerosis societies also promote the initiation of statins during childhood in FH [15,16]. In our study, approximately 40% of patients started statin therapy in primary prevention, suggesting that the hypercholesterolemic status of the remaining patients before the first event was either unknown or ignored by patients and/or their general practitioners. Furthermore, the mean age at which statin treatment was started was 41 years, by which time these patients have been exposed to elevated cholesterol levels for many years, placing them at high cardiovascular risk [1,15,16].

4.2. Recurrent events

Recurrent cardiovascular events are associated with poor quality of life as well as high costs due to hospitalization and physician visits [17]. In a Swedish national registry of patients post myocardial infarction, the probability of a recurrent event (defined as non-fatal myocardial infarction, non-fatal stroke or cardiovascular death) in patients aged <60 years within 12 months of the index event was 6.5%, and the rate remained relatively stable to 3 years [18]. In the UK cohort of the GRACE UK–Belgium registry, published in 2010, recurrent myocardial infarction occurred in 15.5% of patients with an acute coronary syndrome up to 5 years after the first cardiovascular event [19]. Rapsomaniki et al. reported a 9.7% incidence of recurrent cardiovascular events (myocardial infarction or coronary heart disease death) at 5 years in a population with stable coronary artery disease [20]. The recurrence rates in these studies, albeit in different populations and with different endpoints, are markedly lower than in our registry of HeFH (9 per 100 patient-years).

Contemporary data on recurrent cardiovascular events in HeFH are scarce. Recently, a Swiss study reported a high risk of recurrent coronary events (odds ratio of 2–3.5 versus non-FH, depending on the criteria used for the clinical diagnosis of FH) in HeFH patients after an acute coronary syndrome [21]. In an analysis using data from two Danish registries, Rerup et al. demonstrated that patients with a possible diagnosis of FH (based on the Dutch Lipid Clinic Network criteria) had a higher risk of recurrent myocardial infarction than those without FH (16% vs 11%, respectively, over a period of 3.3 years) [22]. In 2018, Galema-Boers et al. reported a 30% rate of subsequent cardiovascular events in a Dutch cohort of 102 patients with HeFH (diagnosed using the same criteria as in our study), despite maximum-tolerated lipid-lowering therapy [23].

The design of our study may in part explain the high rate of recurrent cardiovascular events. First, data were collected over a period exceeding 7 years, versus 1 year in the Swiss study [21] and 3.3 years in the Danish study [22]. Second, 75% of the patients were diagnosed using genetic testing; among those diagnosed clinically, a Dutch Lipid Clinic Network score of ≥6 was used (indicating a probable or definite diagnosis). Third, our population may be biased towards patients with more-severe FH, as it was restricted to those referred to lipid clinics.

4.3. Cardiovascular events

The majority of first and subsequent cardiovascular events (approximately 80%) were coronary in origin, with peripheral artery disease and ischemic stroke occurring in roughly equal proportions

(approximately 10% each). In a Spanish study, Mata et al. described a higher proportion of coronary heart disease (93.4%) in HeFH patients with prior cardiovascular disease [24]. Few data are available on cardiovascular events other than coronary events in FH studies [3]. Most recurrences (65%) were new revascularization procedures, which is in line with other studies in distinct populations. For example, 58% of recurrent events were coronary revascularization in the IMPROVE-IT trial in patients after an acute coronary syndrome [25].

4.4. Cardiovascular risk factors

More than half of our patients were current or former smokers. In a previous study in 734 patients with HeFH (with or without cardiovascular events), 75% had at least one additional risk factor, of which 31% was tobacco smoking [26]. These results emphasize the importance of identifying ways in which to encourage smoking cessation in these high cardiovascular risk patients.

The results of our study confirm that patients with FH in secondary prevention are undertreated with lipid-lowering therapy and are not achieving the recommended LDL-C target of 70 mg/dL [7]. Despite the very high cardiovascular risk of these patients, the mean LDL-C value was 144±77 mg/dL. These findings are in concert with our previous work, in which LDL-C levels remained elevated despite maximal therapy with a high-potency statin plus a non-statin lipid-lowering drug (mainly ezetimibe) [27], and show that even when managed by lipid specialists, the majority of patients with HeFH have LDL-C levels that are above the recommended target. Whereas the high levels of LDL-C in HeFH reflect the disease itself, statin intolerance – primarily manifesting as muscle symptoms – can also lead to inability to take statins or to tolerate only low doses. In France, the PCSK9 inhibitors have been reimbursed since February 2018 for two conditions: alirocumab for HeFH requiring lipoprotein apheresis; and evolocumab for homozygous FH. In France, the criteria for apheresis are LDL-C >200 mg/dL on maximum-tolerated oral lipid-lowering therapy in secondary prevention, and LDL-C >300 mg/dL on maximum-tolerated oral lipid-lowering therapy in primary prevention.

4.5. Limitations

Whereas registries provide data from the spectrum of patients treated in everyday clinical practice, several limitations must be acknowledged. First, as we collected data from patients referred to lipid centers, our population may be biased towards more severe patients with HeFH. However, the

prevalence of comorbidities are consistent with data from other FH registries. Second, we could not verify the reason for recurrent revascularization, whether ischemia-driven, urgent or due to the presence of silent ischemia. Third, it is important to note that data regarding the initiation of statin therapy before the first event were absent for almost half of the patients, so the results on exposure on statins may not be representative of the entire population.

4.6. Conclusions

The rate of recurrent cardiovascular events was high in this retrospective, contemporary French study of HeFH. A substantial proportion of these high-risk patients were undertreated with lipid-lowering therapies and were not achieving the recommended LDL-C target. Detection of FH in the childhood is crucial to prevent cardiovascular events at a young age, through early initiation of statin therapy. There is also clear and urgent need to ensure that non-statin lipid-lowering therapies, such as the PCSK9 inhibitors, are considered in patients with HeFH who are unable to achieve the recommended LDL-C target with their current therapy alone.

Author's contributions: SB and EB are the principal investigators of the French FH registry; they contributed to the design and the setting of the registry. SB and EB wrote the manuscript. AV performed the statistical analyses. FB, BC, AC, JF, MF, MK, MV, SC, NP and JPR are coinvestigators, and made critical revisions to the manuscript. SB and EB are the guarantors of this work and, as such, had full access to all of the data and take responsibility for the integrity of the data.

Conflicts of interest

SB, EB, BC, FB, AC, JF, MF, MK, MV, SC, NP and JPR have received honoraria from Sanofi and Amgen for board, conferences, clinical trials, or congresses. AV has no conflict of interest to declare.

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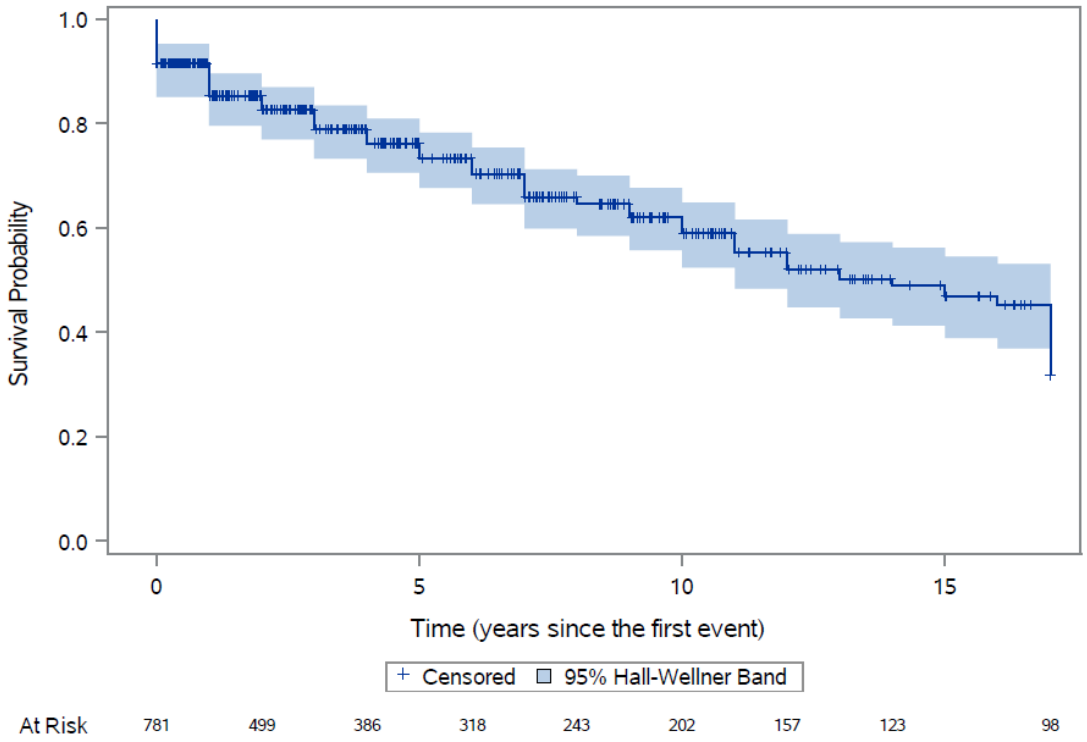
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Fig. 1. Kaplan–Meier curve of freedom from recurrent cardiovascular event.

Coronary heart disease recurrences were censured when they were <30 days after a first coronary event. The shading shows 95% Hall-Wellner confidence interval.



REBUTTAL LETTER TO THE EDITOR AND THE REVIEWERS:

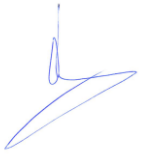
Dear Professors von Eckardstein and Ray,

Thank you for reviewing our manuscript, entitled "**High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: the French Familial Hypercholesterolemia Registry**" (Ms. No. ATH-D-18-00445).

We again thank the reviewers for their overall positive comments and the pertinent points raised. Our responses to these comments are provided below, and the changes are marked in the manuscript.

We believe that the manuscript has benefited significantly from the reviewers' critiques, and hope that you will now find it acceptable for publication in your journal.

Yours sincerely,
Dr SOPHIE BELIARD, MD, PhD
Marseille, the 15 June 2018,



Reviewers' comments:

Reviewer #1:

The manuscript entitled "High burden of recurrent cardiovascular events in Familial Hypercholesterolemia: data from the French FH Registry" has been evaluated and got the following comments. First of all, your work is interesting,and needs to be published. However, I found many flaws when revising the manuscript, and I think you should consider re-writing and re-submitting the article. One example is that you use mg/dL to describe lipid values (1,5 mg/dL, 0,70 mg/dL), when these values should be in g/L. In the Tables the values are correctly presented, but not in the text. Indeed, we usually use lipid values in mg/dL or in mmol/L. But, OK, they are in g/L, but stated as mg/dL. That gives a totally different picture of your results.

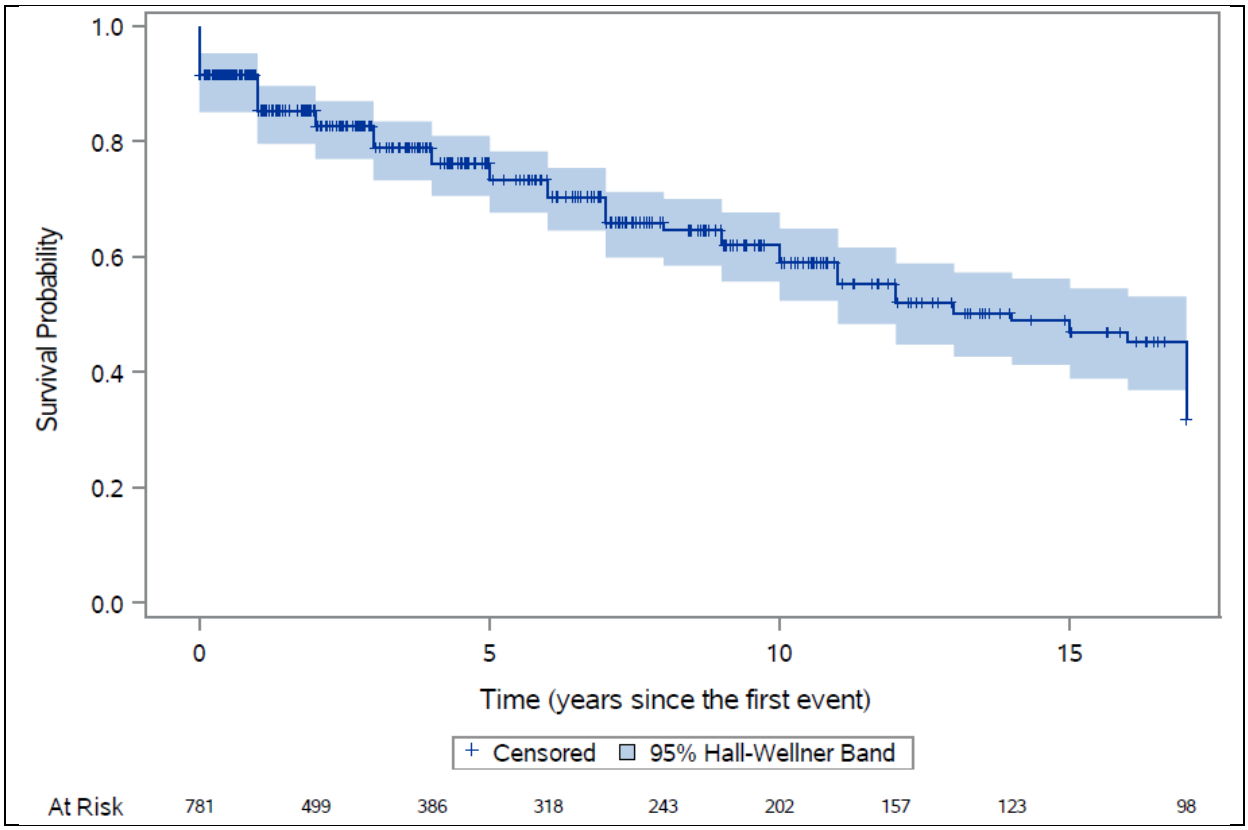
Response: We thank the reviewer for his/her very positive and encouraging assessment of our manuscript and the pertinent points raised. First, we sincerely apologize for the errors in the units for the lipid values, which have now been corrected and presented in mg/dL.

It would be nice to have a cumulative event rate curve (Kaplan-Meier) illustrating your recurrent events.

Response: As suggested, we have included a Kaplan-Meier curve (Figure 1).

Figure 1: Kaplan–Meier curve of freedom from recurrent cardiovascular event.

Coronary heart disease recurrences were censured when they were <30 days after a first coronary event. The shading shows 95% Hall-Wellner confidence interval.



The English language must be carefully reviewed by a native English.

Response: As suggested, a native English speaker has reviewed the manuscript and corrected the language.

Reviewer #2:

The study is very well designed, analyzed and presented. However, the main finding is the recurrence of CV events in heFH patients, which has been reported before in several studies and populations. The observation of increased CV event recurrences in French heFH is very important for French clinicians in order to modify the therapeutic approaches for this disease (e.g. expand the group of patients that are eligible for PCSK9 prescription).

Response: We thank the reviewer for his/her very positive and encouraging assessment of our manuscript.

The high CV risk of the HeFH population is indeed well known, and has been studied in many cohorts (Benn et al. JCEM 2012, Do et al. Nature 2015, Mundal et al. J Am Heart Assoc 2014, Wallas Krogh et al. Eur Heart J 2015). However, we have found only 3 recent studies in the literature that present the

recurrence of CV events in this specific population of patients with HeFH. We discuss this point on page 9:

"Contemporary data on recurrent cardiovascular events in HeFH are scarce. Recently, a Swiss study reported a high risk of recurrent coronary events (odds ratio of 2–3.5 versus non-FH, depending on the criteria used for the clinical diagnosis of FH) in HeFH patients after an acute coronary syndrome [20]. In an analysis using data from two Danish registries, Rerup et al. demonstrated that patients with a possible diagnosis of FH (based on the Dutch Lipid Clinic Network criteria) had a higher risk of recurrent myocardial infarction than those without FH (16% vs 11%, respectively, over a period of 3.3 years) [21]. In 2018, Galema-Boers et al. reported a 30% rate of subsequent cardiovascular events in a Dutch cohort of 102 patients with HeFH (diagnosed using the same criteria as in our study), despite maximum-tolerated lipid-lowering therapy [22]."

The results of the study though do not add substantially new knowledge for CV events and FH to the international scientific community

Response: The strengths of this national study are the multicenter design (16 clinical reference centers for FH diagnosis and care) and the long follow-up (median 7.4 years). We believe that our article offers new insights to the scientific community, with the longest follow-up of FH patients with CVD. Other studies had shorter follow-up periods (1 year for the Swiss cohort, Nanchen D et al. Circulation 2016; 134:698-709) and 3.3 years for Rerup SA et al (Am Heart J 2016; 181:35-42); duration of follow-up was not mentioned in the paper by Galema-Boers et al (J Clin Lipidol 2018; 12:409-416).

We observed that 68.3% of the recurrences occurred after the first year, emphazing the need for long-term cardiovascular follow-up in this population. Finally, as you acknowledge, we hope that our results will provide support to extend the criteria for reimbursement of PCSK9 monoclonal antibodies in patients with severe FH in France.

Reviewer #3:

The absence for ethical reasons of clinical trials in familial hypercholesterolemia (FH) makes the information derived from registers have a special value. The French registry recruits subjects with FH from 18 different units of France and in this work presents information on recurrences of events. This issue is especially important among other things because the lipid-lowering treatment in these and other subjects depends on the baseline CVD risk, considering the price of some drugs. The work provides new information of clinical interest that, nevertheless, has to clarify several aspects.

Response: We thank the reviewer for his/her positive and encouraging review of our manuscript.

-It is not clear in the article the temporal distribution of information. The data in Table 1 should be better explained. It is difficult to know if the information refer to the diagnosis of FH, to the

first visit in the lipid unit, at the time of inclusion in the register, at the time of the event or during the follow-up.

-The same applies to the information in Table 2. Are the data at the time of recurrence, during follow-up, or the last visit?

Response: We have clarified the information presented in Tables 1 and 2. These data were collected during the patients' last visits to the lipid clinic.

-The definition of event is not very solid. The high number of peripheral arterial disease is striking. What criteria were used for its diagnosis?

Response: We have now included the definition for acute coronary syndrome in the manuscript (Alpert JS, et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000; 36:959-969). We have also modified our definition of peripheral artery disease (PAD), so that it includes only PAD that required intervention, such as carotid endarterectomy, carotid angioplasty, and peripheral arterial bypass. Therefore, the number of PAD events decreased from 99 to 76. All these changes are in red in the manuscript (page 5).

-The inclusion of valvulopathy is very debatable and it should be defined what criteria was used. Any valve of any etiology?

Response: We agree with the reviewer: valvulopathy may not be due to atherosclerosis and should not be included in the analysis. We have therefore excluded the data from patients who had valve replacement or aortic intervention. Twenty events were excluded from the analysis, leading to 781 events instead of 801.

- 40% of the events occur after the first year of follow-up, and a large part of them in the first month.

Response: We have recalculated the number of events, excluding coronary events (recurrent MI, recurrent coronary revascularization) that occurred within 30 days after the index event. All these changes are in red in the manuscript (page 5).

This type of events is complicated to attribute to recurrence since they are possibly intimately related to the index event.

Response: We have censured coronary events that occurred less than 30 days after the index event, to exclude any that could be attributed to the index event.

- In relation to the previous comment, 61% of the recurrences are coronary revascularizations, when they were 32% of the first event. These differences should be explained carefully, and possibly discard all early revascularizations.

Response: We believe that our high rate of recurrent coronary revascularization procedures is in line with other studies in this distinct population. As stated in the original version, "*Most recurrences (65%)*

were new revascularization procedures, which is in line with other studies in distinct populations. For example, 58% of recurrent events were coronary revascularization in the IMPROVE-IT trial in patients after an acute coronary syndrome [24]." To address this issue, we have now excluded any coronary revascularization recurrences that occurred within 30 days of the index event.

- It would be better to clarify precisely the reasons for revascularization.

Response: Unfortunately we did not collect this information, which is included as a limitation of the study (page 10). We have also excluded any coronary revascularization recurrences that occurred within 30 days of the index event.

-The mortality data are not of interest because they refer only to patients who have survived. While this information is prospective, only survivors can be studied, the rest of the information is retrospective.

Response: This is indeed another limitation of our retrospective study, but we believe that the number of deaths is interesting and we would prefer to retain it.

- Authors should define what they consider high intensity regime.

Response: The definition for high-intensity regimens has been included in the manuscript. The definition is based on the percentage reduction of LDL-C concentration with a daily dose of statin: >45% (i.e. atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg) (Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003 Jun 28; 326: 1423).

We replaced the term "high intensity regimen" with the more obvious term "high-intensity statin".

-The units in the article contain many errors and are not homogeneous, sometimes, mg / dL, other g / L, and data are mixed.

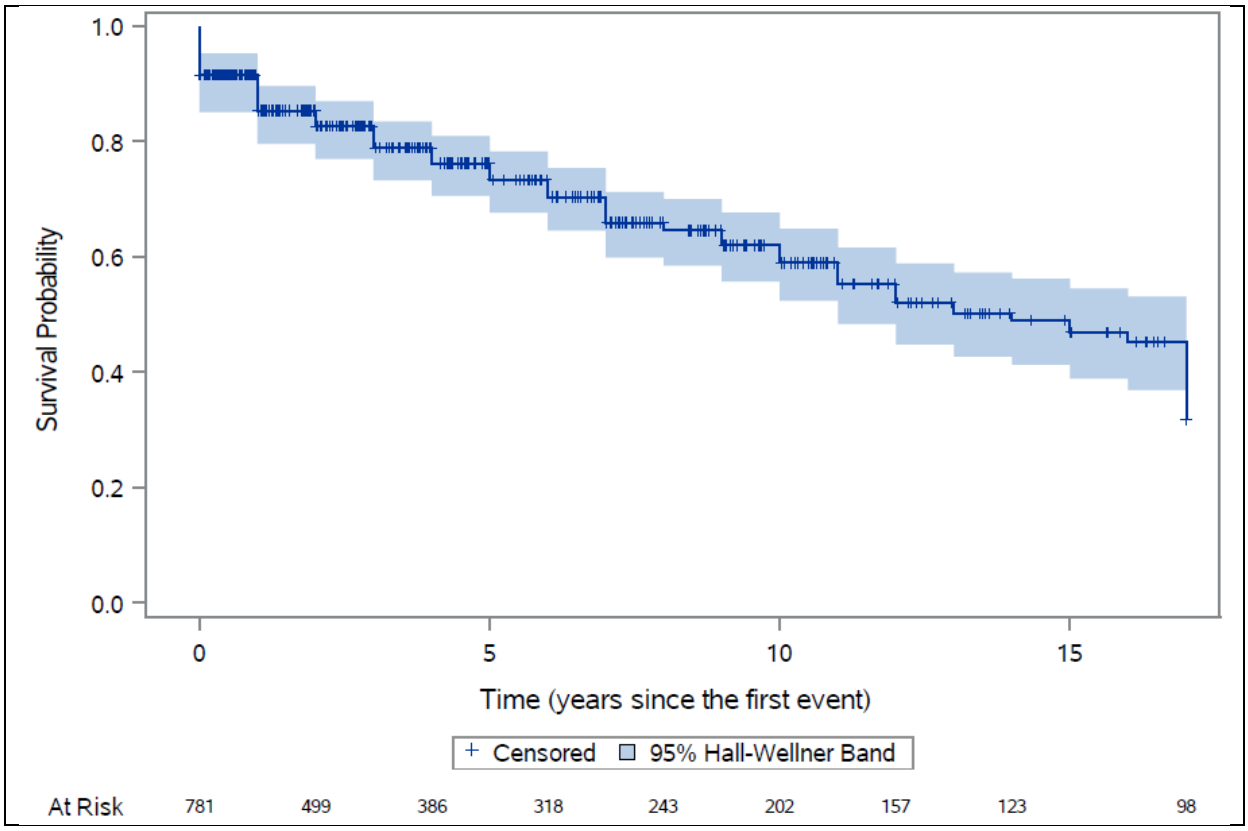
Response: We sincerely apologize for the errors in the units for the lipid values, which have now been corrected and presented in mg/dL.

- Given that the time between the first event and the recurrence is very variable, the authors should present a table or char with the data per year, in this way it would be easier to calculate the post-event risk in the long term.

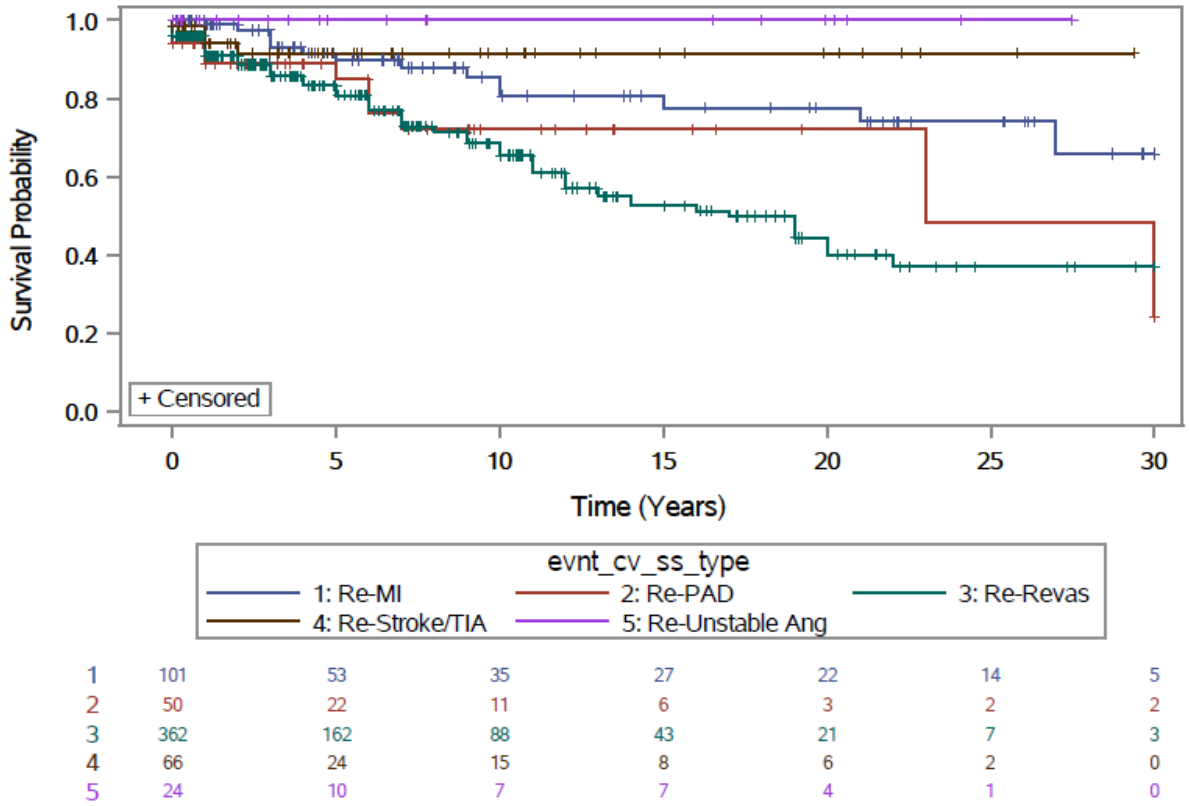
Response: We have included a Kaplan-Meier curve (figure 1), with the cumulative events per year. We have also added the data in Table 2.

Figure 1: Kaplan–Meier curve of freedom from recurrent cardiovascular event.

Coronary heart disease recurrences were censured when they were <30 days after a first coronary event. The shading shows 95% Hall-Wellner confidence interval.



We could eventually also include another Kaplan-Meier curve, showing the freedom from recurrent cardiovascular events regarding the type of recurrent event (coronary revascularization, stroke, PAD, unstable angina and myocardial infarction). .



- A very important limitation is that information about medication is absent in half of the patients at the time of the event. This means that the data in Table 4 must be analyzed with caution.

Response: The reviewer has raised an important point: the absence of information on the lipid-lowering therapy at the time of the event for nearly half of patients (45%) is a limitation, and the data in the Table 4 must be interpreted with caution.

We have added the following sentence on pages 10−11: *"Third, it is important to note that data regarding the initiation of statin therapy before the first event were absent for almost half of the patients, so the results on exposure on statins may not be representative of the entire population."*

- In the discussion, the comparison of recurrences with other cohorts is very biased since the definition of recurrences is very different. In fact, without removing the events of the first year, the recurrences of major events: IAM and stroke is very low, less than expected in other populations. All the discussion and the title itself is somewhat biased magnifying the risk.

Response: We agree that the definitions for events and recurrent events vary between studies. We have commented on this crucial point (page 9 in the discussion): "*The recurrence rates in these studies, albeit in different populations and with different endpoints, are markedly lower than in our registry of HeFH (9 per 100 patient-years).*"

However, recurrences of CV events are frequent in the present cohort, even after the first year following the event. Indeed, 60% of HeFH patients had a CV recurrence >1 year later. We do not think that we are magnifying the risk. For example, in a Swedish registry, the prevalence of recurrent CV events in young patients (<60 years; nevertheless older that the HeFh population of 46 years) was very low compared with our cohort: respectively 10% vs 42% (Jernberg, Eur Heart J 2015; 36:1163-1170).

We have now added a Kaplan-Meier curve (Figure 1) to clarify the point on the time of recurrences.

-There are multiple typographical errors in the quotes within the text, and typos that should be thoroughly reviewed.

Response: Thank you for raising this point. A native English speaker has reviewed the manuscript and corrected the language.

Marseille, April 5th 2018,

Dr A. von Eckardstein

Editor in Chief

Statement of originality:

Dear A. von Eckardstein,

I certify that the data of the present study are my own work and have not been published in this or any substantially similar form, nor accepted, nor is it under consideration for publication elsewhere.

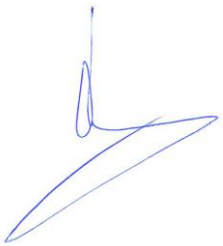
All authors have contributed to the preparation and development of this manuscript, and have approved the final draft prior to submission.

Thank you for considering the manuscript and I look forward to hearing from you.

Yours sincerely

Sophie BELIARD-LASSERRE, MD, PhD

APHM, Aix Marseille University, France



REBUTTAL LETTER TO THE EDITOR AND THE REVIEWERS:

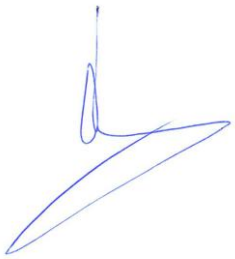
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We again thank the reviewers for their overall positive comments and the pertinent points raised. Our responses to these comments are provided below, and the changes are marked in the manuscript.

We believe that the manuscript has benefited significantly from the reviewers' critiques, and hope that you will now find it acceptable for publication in your journal.

Yours sincerely,
Dr SOPHIE BELIARD, MD, PhD
Marseille, the 15 June 2018,



***Conflict of interest form**

Marseille, April 5th 2018,

Dr A. von Eckardstein

Editor in Chief

Dear A. von Eckardstein,

<u>This is the conflict of interest form for the present work:</u>

SB, EB, FB, AC, JF, MF, MK, MV, SC, NP and JPR have received honoraria for boards, and/or conferences, and/or clinical trial and/or congress from Sanofi or Amgen.

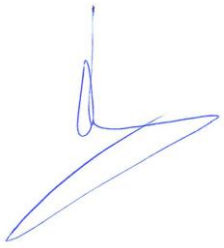
AV has no conflict of interest to declare.

Thank you for considering the manuscript and I look forward to hearing from you.

Yours sincerely

Sophie BELIARD-LASSERRE, MD, PhD

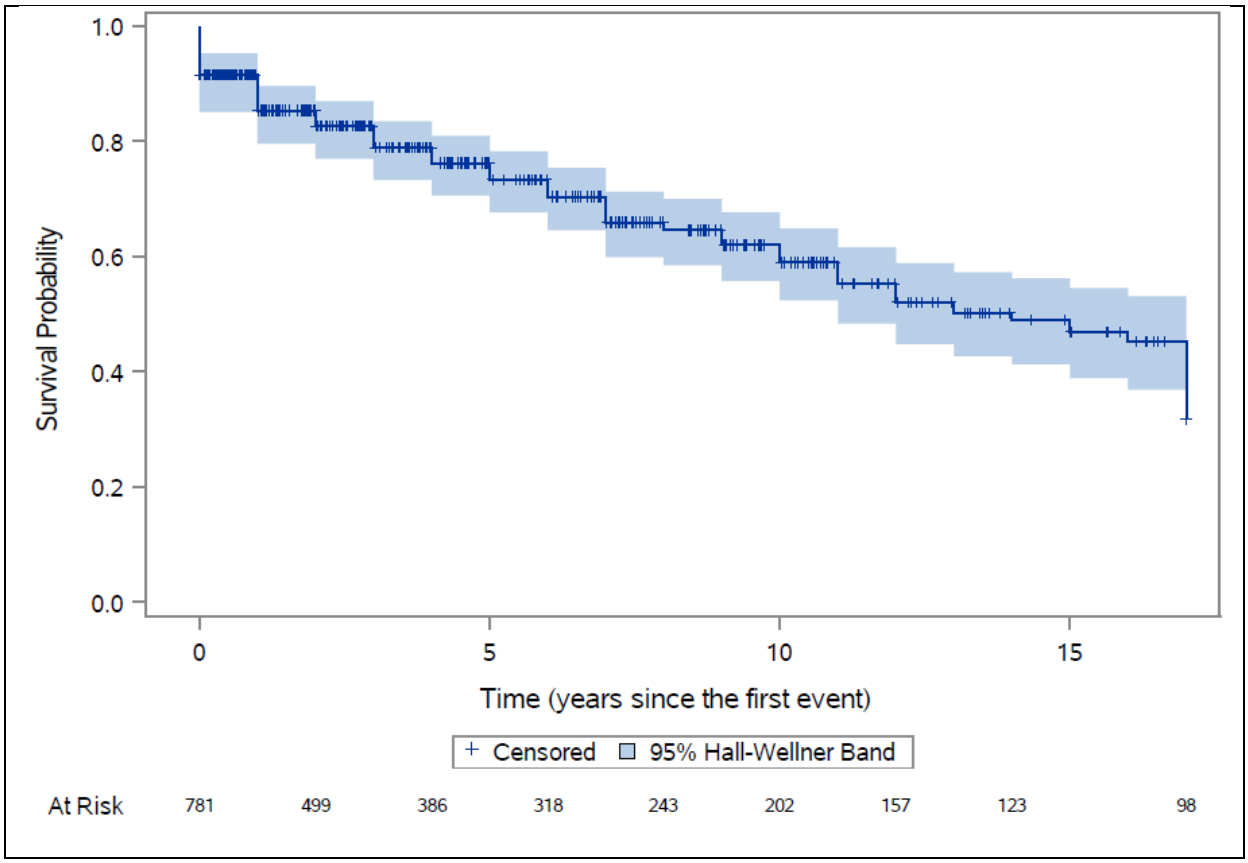
APHM, Aix Marseille University, France



Figure(s)

<u>Figure 1:</u> Kaplan–Meier curve of freedom from recurrent cardiovascular event.

Coronary heart disease recurrences were censured when they were <30 days after a first coronary event. The shading shows 95% Hall-Wellner confidence interval.



Table(s)

Table 1 : Demographic and clinical characteristics of patients with heFH in secondary prevention (at the last visit to the lipid clinic).

Variables	Total (n=781)
Men, n (%)	565 (72)
Age, years, mean (SD)	60 (13)
Length of follow-up (from first cardiovascular event to last clinic visit), years, median (IQR)	7 (2–17)
Patient-years of follow-up	5779
Cardiovascular risk factors, n (%)	
Smoking status	(n=706)
Current	111 (16)
Former	277 (39)
Never smoker	318 (45)
Type 2 diabetes	93 (13) (n=704)
Hypertension	255 (36) (n=705)
Lipoprotein(a), mg/dL, mean (SD)	55 (56) (n=414)
Familial history of CVD	501 (64) (n=781)
Maximal total cholesterol, mg/dL, mean (SD)	420 (190) (n=535)
Patients who underwent genetic testing	583 (75)
Results not available	126 (16)
No mutation	20 (3)
Mutation[a]	437 (75)
LDLR	401 (92)
APOB	40 (9)
PCSK9	13 (3)

APOB, apolipoprotein B; CT, maximum lifetime total cholesterol; heFH, heterozygous familial hypercholesterolemia; IQR, interquartile range; LDLR, low-density lipoprotein receptor; SD, standard deviation.

[a] Some patients had more than one mutation.

Table 2: Index and recurrent cardiovascular events (at the last visit to the lipid clinic).

Variables	Total (n=781)
Age at first event, years, median (IQR)	47 (39 - 55) (n=756)
Type of first cardiovascular event, n (%)	**(n=778)**
Coronary heart disease	628 (80)
Coronary angioplasty or bypass	403 (64)
Myocardial infarction	167 (27)
Unstable angina	50 (6)
Undefined	11 (1)
Stroke or transient ischemic attack	80 (10)
Peripheral artery disease[a]	68 (9)
Resuscitated sudden death	2 (<1)
Type of subsequent events, n (%)	**(n=511)**
Coronary heart disease	400 (78)
Coronary angioplasty or bypass	332 (65)
Myocardial infarction	36 (7)
Unstable angina	31 (6)
Undefined	1 (<1)
Stroke or transient ischemic attack	30 (6)
Peripheral artery disease[a]	76 (15)
Resuscitated sudden death	2 (<1)
All-cause death, n (%)	18 (2)
Cardiovascular death, n (%)	8 (1)
Patients with recurrences, n (%)	
≥1[b]	289 (37)
≥2[b]	111 (14)
≥3[b]	53 (7)
Recurrences per patient, mean (SD)	1.8 (1.4)
Number of total recurrences	*n=511*
Delay between initial event and first recurrence, months, median (IQR)	49 (8 - 122) (n=281)
≤30 days, n (%)	8 (3)
>30 days to <1 year, n (%)	81 (29)
1–3 years, n (%)	37 (13)
>3 years, n (%)	155 (55)
Delay between recurrences, months, median (IQR)	38 (9 - 104) (n=503)

IQR, interquartile range; SD, standard deviation.

[a] Carotid endarterectomy, carotid angioplasty, peripheral arterial bypass.

[b] Recurrence of any cardiovascular event.

Table 3 : Comparison of patients with and without a recurrent cardiovascular event.

Variable	No recurrence (n=492)	≥1 recurrence (n=289)	*p*-value
Men, n (%)	332 (67)	233 (81)	<0.0001
Age, years, mean (SD)	59 (13)	62 (12)	<0.0001
Age at first visit to the lipid clinic, years, median (IQR)	50 (41 - 59)	51 (42 - 61)	0.1600
Age at first event, years, median (IQR)	49 (40 - 57) (n=475)	42 (37 - 51) (n=281)	<0.0001
Cardiovascular risk factors			
Smoking status	(n=433)	(n=273)	0.2000
Never	195 (45)	123 (42)	
Current or former	238 (55)	150 (60)	
Familial history of CVD	304 (62)	197 (68)	0.0730
Lipoprotein(a), mg/dL, mean (SD)	53 (58) (n=266)	58 (53) (n=231)	0.5400
CT max, mg/dL, mean(SD)	417 (345) (n=351)	423 (132) (n=191)	0.9327
Patients with a genetic diagnosis	368 (75)	215 (75)	0.9000
Results not available	82 (22)	44 (20)	
No mutation	14 (4)	6 (3)	
Mutation[a]	272 (74)	165 (77)	0.6200
LDLR	249 (91)	152 (92)	0.4400
APOB	23 (8)	17 (10)	
PCSK9	11 (4)	2 (1)	
Type of first cardiovascular event			
Coronary heart disease	385 (78)	243 (84)	0.0070
Coronary angioplasty or bypass	264 (54)	136 (47)	
Myocardial infarction	87 (18)	80 (28)	
Unstable angina	24 (5)	26 (9)	
Undefined	10 (2)	1 (<1)	
Stroke or transient ischemic attack	62 (13)	18 (6)	
Peripheral artery disease[b]	41 (8)	27 (9)	
Resuscitated sudden death	1 (<1)	1 (<1)	

APOB, apolipoprotein B; CT, maximum lifetime total cholesterol; IQR, interquartile range; LDLR, low-density lipoprotein receptor; SD, standard deviation.

[a] Some patients had more than one mutation.

[b] Carotid endarterectomy, carotid angioplasty, peripheral arterial bypass.

Table 4: Treatments patterns in heFH patients and LDL-c levels, overall and with and without recurrent cardiovascular event, at the last clinic visit.

Variable	Total (n=781)	No recurrence (n=492)	≥1 recurrence (n=289)	*p*-value
History of statin exposition	(n=430)	(n=275)	(n=155)	
Age at start of statin treatment, years, median (IQR)	41 (33–50)	41 (32–50)	41 (34–49)	0.7912
Overall exposure, years, median (IQR)	19 (10-27)	16 (8-26)	23 (15-28)	0.0001
Exposure to statins before first event, n (%)	208 (48)	147 (53)	61 (39)	0.0084
Duration of exposure to statins before first event, years				0.0191
Median (IQR)	4 (0 - 17)	5 (0 - 15)	3 (0 - 10)	
Mean (SD)	7.9 (9.9)	8.6 (10.5)	6.2 (8.0)	
Treatment at last visit				
Statins (alone or in combination)	650 (83)	416 (84)	234 (81)	0.0690
High-potency statin[a]	456 (58)	287 (58)	169 (58)	
Statin alone	162 (21)	116 (24)	46 (16)	
Statins + ezetimibe	448 (57)	281 (57)	167 (58)	
Statin + PCSK9 inhibitor	15 (2)	6 (1)	9 (3)	
Statin + ezetimibe + PCSK9 inhibitor	25 (3)	13 (3)	12 (4)	
Ezetimibe alone	22 (3)	14 (3)	8 (3)	
PCSK9 inhibitor alone	15 (2)	8 (2)	7 (2)	
Apheresis (alone or in combination)	64 (8)	33 (7)	31 (11)	
Other treatment[b]	23 (3)	17 (3)	6 (2)	
No treatment	58 (7)	31 (6)	27 (9)	
LDL-c levels at last visit, mg/dL, mean (SD)	(n=714)	(n=460)	(n=254)	
All patients	144 (75)	148 (78)	136 (68)	0.0343
Patients on high-potency statin[a]	132 (69)	136 (74)	125 (58)	0.0725
Patients without treatment	223 (85)	230 (84)	211 (87)	0.3627

heFH, heterozygous familial hypercholesterolemia.

[a] Atorvastatin 40–80 mg, rosuvastatin 20–40 mg, simvastatin >40 mg.

[b] Fibrates, niacin, cholestyramine, yeast red rice, phytosterols.

***Atherosclerosis style guide checklist**

I did it off line