Real-life effectiveness of statins in the prevention of first acute coronary syndrome in France: A prospective observational study

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A R T I C L E  I N F O

Article history:
Received 24 January 2013
Received in revised form 1 May 2013
Accepted 30 August 2013
Available online 7 September 2013

Keywords:
Effectiveness
Statin
Acute coronary syndrome
Case–control study
Epidemiology
Real life

A B S T R A C T

Background: Evidence on the real effectiveness of statins on acute coronary syndrome (ACS) incidence is scarce. We assessed the effectiveness of real-life statins on the risk of first non-fatal ACS in a low-cardiovascular-risk country.

Methods: Systematic case–control study was conducted in 60 cardiology centres and 371 general practices from across France. A total of 2238 cases with first ACS within 1 month from recruitment and 2238 controls without history of ACS were included; controls were matched to ACS cases on sex, age, frequency of visits to GPs, date of recruitment and personal history of chronic diseases. Statin exposure and risk factors were documented through patient telephone interviews and validated against medical records. The index date was the date of ACS for cases. Adjusted odds ratios (OR) of first ACS and statin use were estimated by multiple conditional logistic regression models controlled for risk factors and propensity score for statin exposure.

Results: Statin use was associated with lower ACS risk, with an adjusted matched OR of 0.67; 95% confidence interval (CI): 0.56 to 0.79 for current use (within 2 months) and 0.73; 95% CI: 0.62 to 0.86 for any use within 24 months [atorvastatin: 0.83 (0.63–1.10), fluvastatin: 0.75 (0.43–1.30), pravastatin: 0.98 (0.72–1.34), rosuvastatin: 0.49 (0.35–0.68) and simvastatin: 0.62 (0.46–0.84)]. The preventive effect of statins on non-fatal ACS reached its maximum after one to four years of use.

Conclusion: A similar magnitude of effect for statin use was observed in real life, as compared to randomised clinical trials in France.

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☆ Funding: The present work was supported by an unrestricted grant from AstraZeneca France. The funder had no role in the design, management, data collection, analyses, interpretation, and writing of the article or the decision to publish our findings.

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1 This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
2 Contributing members of the PGRx-Myocardial Infarction study group are listed at the end of the article (Appendix A).
1. Introduction

Lowering low-density lipoprotein (LDL) cholesterol to adequate targets is a major component of international guidelines for the primary and secondary prevention of ischaemic heart events. The role of statins is well established in the Cholesterol Treatment Trialists’ Collaboration meta-analysis, including over 174,149 patients in 27 trials [1,2]. A meta-analysis restricted to participants without vascular disease suggested that reduction in LDL cholesterol decreases the risk of major cardiovascular events and death by 25% and 15%, respectively. Furthermore, risk reduction in non-fatal events showed a bimodal distribution being higher in patients with a low cardiovascular risk score (5-year risk at baseline ≤ 10%), opening the door for reconsideration of European guidelines for those individuals. Indeed, the usefulness of using statins for primary prevention in countries with low baseline risk of acute coronary syndrome (ACS) such as France has been challenged and caution has been urged in prescribing statins for primary prevention in low-risk patients [3].

Besides results from randomised trials (RCTs), little evidence is available on the real effectiveness of statins on MI incidence. Real-life impact can differ from RCTs on a number of factors including interaction between cardiovascular diseases and medications, distribution of risk factors in the population, physicians and patients’ awareness of cardiovascular risks and prevention, physicians’ prescribing habits and patients’ adherence to statin prescriptions [4-8].

The aim of this study was to estimate the impact of statin utilisation on the risk of first non-fatal acute coronary syndrome in the general population of France, a country with a low incidence of coronary artery disease.

2. Methods

This study used two prospective registries of ACS and general practice patients systematically collected in France for pharmacoepidemiology general research (PGRx registries) between 2007 and 2011 [9,10]. ACS patients in these registries were patients presenting with a first recent (≤ 1 month) non-fatal ACS, recruited in a prospective and consecutive manner by participating cardiology centres. General practice registries included all consecutive patients visiting participating general practitioners (GPs) in the same areas as the cases during the same time period. Cases of ACS and controls with no history of ACS considered for inclusion in this study were those agreeing to participate, male and female, aged 18–79 years, living in France, and able to read and answer a telephone interview. Cases and controls were excluded if at least one of these items were present in their medical history: ACS, percutaneous coronary intervention, coronary artery bypass surgery or any other history of coronary artery disease, stroke or heart failure. The confirmation of ACS diagnosis in cases was provided by participating cardiologists based on the presence of at least two of the three following criteria: symptomatic criterion (characteristic pain), electrocardiographic criterion (ECG showing abnormality in at least two adjacent derivations), and biologic criterion (elevation of CK–MB and/or troponin to twice the upper normal values). When the study started, this was called a myocardial infarction and therefore participating cardiologists were asked to recruit cases of first myocardial infarction. Recruiting centres were randomly audited for compliance with recruiting all consecutive eligible cases.

Statin exposure was documented as part of a systematic telephone survey of over 300 drugs through an interview method that has been previously validated against medical prescription or pharmacy records [11]. Interviews also included personal and medical history, socio-demographics and cardiovascular risk factors. Interviews of patients were conducted within 45 days of recruitment by trained interviewers. Statin exposure was documented as part of a systematic telephone survey of over 300 drugs through an interview method that has been previously validated against medical prescription or pharmacy records [11]. Interviews also included personal and medical history, socio-demographics and cardiovascular risk factors. Interviews of patients were conducted within 45 days of recruitment by trained interviewers. Statin exposure was classified as “current” if any statin was used in the 2 months preceding the index date (date of ACS in cases and date of recruitment in controls), or “recent” if any statin was used in the 24 months preceding the index date. Thus, patients who had stopped taking the drug for more than 24 months at inclusion were considered as not exposed. The main analysis considered exposure to any statin as a class versus no use of statin. Secondary analyses were conducted to quantify individual associations of statin molecules (atorvastatin, fluvastatin, pravastatin, rosvastatin, simvastatin) with incidence of ACS versus no use of statin.

2.1. Statistical methods

Cases of ACS were compared to controls for their exposure to statins in a classic case–control analysis. Controls were randomly selected from the general practice registry and matched 1:1 to each case on sex, age (±5 years), number of visits to a GP in the year preceding the index date (0–1, 2–12, 13 + visits), date of consultation closest to the date of ACS for cases (±6 months if possible, otherwise ±1 year, ±2 years, or ±3 years), and personal history of non-cardiovascular (i.e., excluding diabetes, hypertension and obesity that were dealt with in the analyses) chronic disease (yes/no). Analyses were performed using multiple conditional logistic regression with case/control status as the dependent variable. Crude and adjusted odds ratio (OR with 95% confidence interval (CI)) are reported using the following variables for adjustment: smoking habits (current, former, never), body mass index (BMI, weight in kilograms divided by squared height in centimetres and categorised into: 19 or less, 20-24, 25–29, 30 or more), physical exercise (less than 30 minutes per day, 30 minutes or more per day), alcohol consumption (every day or several times a week, occasionally, never), occupation (unemployed, white-collar workers, blue-collar workers), and cardiovascular comorbidities (diabetes mellitus, hypertension, obesity).

Sensitivity analyses were carried out to assess interactions of various risk factors with statin use including age, sex, history of cardiovascular comorbidities (hypertension, diabetes and arterial disease other than coronary) and high vs. low dose of statin (high dose: > 10 mg/day for atorvastatin, > 40 mg/day for fluvastatin, > 20 mg/day for pravastatin, > 5 mg/day for rosuvastatin, > 20 mg/day for simvastatin). The effect of self-reported adherence to the statin regimen was also examined (every day or several times a week vs. less frequent users). Odds ratios were compared between strata using Wald’s test. A sensitivity analysis in the subgroup of patients, with at least one elevated cardiac-specific enzyme for myocardial infarction (troponin or CPKMB elevation exceeding twice the upper limit of normal), was performed to distinguish the risk in patients with atherothrombotic events. In addition, we checked the modification of statin’s effect on the risk of acute coronary syndrome exercised by the variable Northern/Southern region. This has been tested by adding this variable in the model.

Finally, an analysis was conducted among controls that used statins to document a potential indication bias (i.e., whether there were differences in prescribing of statins based on differences in risk factors or not). We calculated a risk score based on all risk factors available, BMI, physical activity, smoking habits, alcohol consumption, hypertension, diabetes, hypercholesterolaemia, and geographical origin of patients. This partial risk score was used to stratify the relationship between statin utilisation and ACS in quartiles of risk, from low to high.

The statistical analysis was conducted using SAS software version 9.2 (SAS Institute, North Carolina, USA).

3. Results

Among centres participating in the PGRx registries, 60 cardiology centres and 371 GP settings participated in this study. The PGRx-ACS registry contained 2,908 cases, of which 2,238 met the inclusion criteria, could be reached for an interview and matched to controls for this study. The general practice registry for controls contained 9,294 patients, of which 2,238 were randomly selected to be matched to cases and met all the eligibility criteria. The final sample included 2,238 matched pairs for the analyses.

The majority of ACS cases were male (76%) with a mean age of 59.0 years which is consistent with the incidence of first lifetime ACS in the French population [12]. ST-segment elevation was present in 75.9% of the cases and elevated (> twice the upper limit of normal) cardiac-specific enzyme for myocardial infarction (troponin 1c, troponin T or CPKMB) in 88.5%. Detailed description of matched cases and controls according to main ACS risk factors is provided in Table 1.

After adjusting for risk factors, current use of any statin (used 2 months before the index date, regardless of use in the 3- to 24-month period) was associated with significant reduction in the occurrence of first non-fatal ACS by 33% (adjusted OR 0.67, 95% CI 0.56 to 0.79; p < 0.0001) (Table 2). Similarly, the use of any statin in the 24 months before the index date was associated with significant reduction in the occurrence of first ACS by 27% (adjusted OR 0.73, 95% CI 0.62 to 0.86; p = 0.0002).

We also repeated the main model in patients with at least one elevated cardiac-specific enzyme for myocardial infarction; and after adjusting for risk factors, current use of any statin was associated with an adjusted OR of 0.69, 95% CI 0.58 to 0.83. Similarly, in this same subgroup, the use of any statin in the 24 months before the index date was associated with an adjusted OR of 0.76, 95% CI 0.64 to 0.90.

In fact, further adjustments in the main model for patients’ region (North vs. South) did not show any region-dependent effect (OR 1.02, 95% CI 0.90 to 1.16) and the OR associated with the use of any statin in the 24 months before the index date was very similar to the main result for the same time window (OR 0.73, 95% CI 0.62 to 0.86) when controlling for the region.
Table 1
Description of matched cases and controls by matching variables and risk factors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>ACS cases N = 2238</th>
<th>No ACS controls N = 2238</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N exposed (%)</td>
<td>N exposed (%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1709 (76.4%)</td>
<td>1709 (76.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>529 (23.6%)</td>
<td>529 (23.6%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.03 (11.64)</td>
<td>58.95 (11.91)</td>
</tr>
<tr>
<td>Median (min–max)</td>
<td>59.23 (23.07–79.99)</td>
<td>59.50 (22.77–80.00)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>970 (43.4%)</td>
<td>457 (20.4%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>652 (29.2%)</td>
<td>874 (39.1%)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>605 (27.1%)</td>
<td>891 (39.8%)</td>
</tr>
<tr>
<td>Rather not say</td>
<td>6 (0.3%)</td>
<td>14 (0.6%)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 minutes a day or less</td>
<td>1732 (78.2%)</td>
<td>1507 (68.1%)</td>
</tr>
<tr>
<td>More than 30 minutes daily</td>
<td>482 (21.8%)</td>
<td>707 (31.9%)</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>64 (2.9%)</td>
<td>90 (4.1%)</td>
</tr>
<tr>
<td>20–24</td>
<td>754 (34.0%)</td>
<td>827 (37.5%)</td>
</tr>
<tr>
<td>25–29</td>
<td>979 (44.2%)</td>
<td>938 (42.5%)</td>
</tr>
<tr>
<td>≥30</td>
<td>418 (18.9%)</td>
<td>350 (15.9%)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every day or several times per week</td>
<td>1061 (47.5%)</td>
<td>1130 (50.5%)</td>
</tr>
<tr>
<td>Occasionally or never</td>
<td>1165 (52.2%)</td>
<td>1090 (49.7%)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>40 (1.8%)</td>
<td>42 (1.9%)</td>
</tr>
<tr>
<td>White-collar workers</td>
<td>1548 (69.3%)</td>
<td>1666 (74.5%)</td>
</tr>
<tr>
<td>Blue-collar workers</td>
<td>645 (28.9%)</td>
<td>528 (23.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1256 (56.4%)</td>
<td>1120 (50.5%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>318 (14.2%)</td>
<td>259 (11.6%)</td>
</tr>
<tr>
<td>Number of cardiovascular-related comorbidities(^a)</td>
<td>761 (34.5%)</td>
<td>925 (42.4%)</td>
</tr>
</tbody>
</table>

\(^a\) Number of cardiovascular-related comorbidities included: diabetes mellitus; hypertension and obesity (BMI ≥30).

Table 3
Assessment of the association between statin use and occurrence of first ACS. Stratified by duration of current statin use and by risk score.

<table>
<thead>
<tr>
<th>Duration of current statin use</th>
<th>ACS cases N exposed (%)</th>
<th>No ACS controls N exposed (%)</th>
<th>Crude matched OR (95% CI)</th>
<th>Adjusted matched(^b) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 year</td>
<td>68 (3.0%)</td>
<td>73 (3.3%)</td>
<td>0.86 (0.61–1.20)</td>
<td>0.82 (0.56–1.19)</td>
</tr>
<tr>
<td>&gt;1 to ≤4 years</td>
<td>212 (9.5%)</td>
<td>275 (12.3%)</td>
<td>0.70 (0.58–0.86)</td>
<td>0.64 (0.51–0.79)</td>
</tr>
<tr>
<td>≥4 years</td>
<td>133 (6.0%)</td>
<td>191 (8.5%)</td>
<td>0.64 (0.51–0.82)</td>
<td>0.63 (0.49–0.82)</td>
</tr>
</tbody>
</table>

\(^b\) Obtained by multiple conditional logistic regression including, smoking, hypertension, body mass index, physical activity, diabetes mellitus and alcohol consumption. Matching by individual risk factors showed differences for age (<65 vs. ≥65) with adjusted OR 0.56 (95% CI 0.45 to 0.69) vs. 0.92 (95% CI 0.72 to 1.17) (p = 0.0022), for sex (males vs. females) with 0.70 (95% CI 0.58 to 0.84) vs. 0.89 (95% CI 0.63 to 1.25) (p = 0.0404), for taking vs. not taking a cardiovascular drug in the previous 2 years with 0.67 (95% CI 0.52 to 0.87) vs. 0.85 (95% CI 0.70 to 1.04) (p = 0.1461), or having vs. not having a cardiovascular comorbidity with 0.64 (95% CI 0.48 to 0.86) vs. 1.07 (95% CI 0.89 to 1.30) (p = 0.003).

3.1. Stratified analyses

There was a significant (p < 0.0001) gradient of risk reduction by duration of statin use (Table 3). Increase in time since the statin was first used was significantly associated with a decrease in occurrence of the first ACS, with adjusted OR ranging from 0.82 (95% CI 0.56–1.19) for ≤1 year since statin first use to 0.64 (95% CI 0.51–0.79) for 1 to 4 years since from statin treatment onset, and levelling off after 3 years. When stratified by quartile of risk score, the reduction in the occurrence of ACS associated with the use of statins (any dose) was monotonously stronger among patients in higher quartiles of cardiovascular risk (Table 3). Exposure to statins did not show any trend with risk score in cases whereas it gradually increased with higher quartiles of risk among controls. Stratification by individual risk factors showed differences for age (<65 vs. ≥65) with adjusted OR 0.56 (95% CI 0.45 to 0.69) vs. 0.92 (95% CI 0.72 to 1.17) (p = 0.0022), for sex (males vs. females) with 0.70 (95% CI 0.58 to 0.84) vs. 0.89 (95% CI 0.63 to 1.25) (p = 0.0404), for taking vs. not taking a cardiovascular drug in the previous 2 years with 0.67 (95% CI 0.52 to 0.87) vs. 0.85 (95% CI 0.70 to 1.04) (p = 0.1461), or having vs. not having a cardiovascular comorbidity with 0.64 (95% CI 0.48 to 0.86) vs. 1.07 (95% CI 0.89 to 1.30) (p = 0.003).

When stratified by dose, the adjusted odds ratio for statin use was 0.56 (95% CI 0.44 to 0.71; p < 0.0001) in low-dose users as opposed to 0.93 (95% CI 0.74 to 1.16; p = 0.4952) in high-dose users (analysis was conducted in a subset of patients with individual drug information made available). Significant higher doses were used in patients less physically active (+49% use) and in patients hospitalised in the previous year (+66%). Otherwise, patients taking statins regularly benefited from a protective effect of statins (adjusted OR 0.69; 95% CI 0.58 to 0.81) compared to a non-significant effect among non-compliant patients (adjusted OR 1.36; 95% CI 0.87 to 2.13).

4. Individual statins

Simvastatin was used more frequently in patients at higher cardiovascular risk compared to all other statins: 45% of simvastatin users in...
the controls belonged to the third and fourth higher quartiles of the cardiovascular-risk score, as opposed to 38% for atorvastatin, 34% for fluvastatin, 33% for pravastatin and 37% for rosuvastatin. Table 4 presents results for use of individual statins (atorvastatin/fluvastatin/pravastatin/rosuvastatin/simvastatin/non-use) and first ACS occurrence after controlling for all cardiovascular risk factors. Overall, 5.8% of statin users self-declared having interrupted their treatment in the 2 years preceding the index date due to perceived adverse effects. Number of self-declared events and lack of validation against medical records did not allow comparison between individual statins.

Finally, in order to assess the possibility of survival bias, 52 of the 2238 ACS cases presenting with resuscitated cardiac arrest (“near-deaths”) were analysed and compared to their 52 matched controls. Previous statin use in near-death patients was similar to that of all MI patients (19.2% vs. 18.6%, respectively) with a reduction in the risk of near-death MI around 35% (crude OR 0.65, 95% CI 0.10 to 4.09; p = 0.6485), in line with the crude estimate for all ACSs (crude OR 0.71, 95% CI 0.61 to 0.82; p < 0.0001) (multivariate adjustment was impossibly due to small numbers).

5. Discussion

This large field clinical study confirmed the real-life impact of statin use on reducing the risk of first acute coronary syndrome in a low-cardiovascular-risk population. It showed that statins were associated with a very similar mean reduction of risk (27% to 33%) to the one observed in meta-analyses of low-risk participants to RCTs presenting with no vascular disease (34% to 39%). Also, the trend towards an increasing effect with increased duration of statin use was consistent with the results from the CTT collaboration meta-analysis published previously [2]. Interestingly, it appeared that most of the effect of statins within our low-risk population was observed in patients at higher baseline risk, such as older patients, males or patients with diabetes, hypertension or obesity. By contrast, patients without these risk factors benefited poorly from statin use. This might be somewhat ascribed to a statistical effect, considering it is more difficult to quantify a risk reduction in a very low risk population. However, results also showed a higher protective effect for patients adhering better to their prescribed statin regimen, independently from their baseline risk.

The similarity in magnitude of the overall effect between this real-life study results and clinical trial results may be attributed to a very consistent effect of the drugs; it may also be due to the convergence of other factors acting in varying directions. Patients treated with statins may also be more health conscious and/or more closely followed by medical practitioners and thus more likely to be treated for other cardiovascular risk factors than patients not treated with statins [13]. This might be positively interpreted from a public health viewpoint, but raises questions on the paternity of statin exposure to explain the observed effect. To address this concern, the analyses were adjusted for the number of annual visits to a physician and several other health behaviour variables (smoking habits, alcohol intake and physical activity). Additionally, given that statins are commonly prescribed to patients with higher baseline risk it was feared this might led to a potential indication bias. In a field study such as this one, such bias would reduce the capacity to show a reduction of ACS in higher risk patients but our observations pointed in the opposite direction.

Compared to RCTs, field study results are likely to be more representative of the target population. The large sample used in this study was carefully planned to reach all regions of France and sampled all types of health centres where first lifetime ACSs could be eventually diagnosed. The general practice registry was previously shown to be highly representative of patients’ visits to general practitioners nationwide [14]. The individual risk factors associated with a first occurrence of ACS in that population were in conformity with the literature: smoking, high BMI, lack of exercise, hypertension and diabetes (treated or not), number of cardiovascular morbidities, blue-collar occupation, NSAID use, and a slightly protective effect from regular alcohol use [10]. For the ACS registry, the distribution of cardiology centres in terms of regional coverage of France, proportion of private/public and university/non-university centres, as well as patient population representation was overall similar to that of France as a whole.

5.1. Study limitations

Compared to a RCT, a field study such as this one presents other methodological challenges. The first concerns recall bias where ACS cases might declare their exposure to statins differently than controls. This possibility was minimised by the utilisation of a standardised data collection methodology, previously validated against physicians’ prescriptions (94% agreement for statin use) [10], and by the systematic collection of all drug utilisation in order to minimise a recall specific to one class of drugs (such as statins). Otherwise, the quality of the information provided by physicians of cases and controls was considered excellent by the audits that have been performed throughout the duration of the study. Another difference between RCTs and the present observational case–control study relates to the intensity of exposure to statins by dose (high vs. low), reflecting previous disease or level of risk which would be higher in patients taking higher doses. This is why our results showing a lack of effect of statins in patients who take high doses is not in conformity with results from meta-analyses on that topic [15].

The study accurately represented patients in close contact with the healthcare system but not those who never seek advice from physicians. This latter population represents only a small proportion of the country’s population given that the availability of GPs is prescribed by the French law; the proportion of adults who have not seen a physician in 2011 was actually low [16].

Finally, this study was limited to survivors of a first ACS and results only apply to the reduction of non-fatal ACS. CTT collaboration meta-analyses of cardiovascular deaths have shown an effect of statins in the order of 15% reduction; thus the effect in survivors appears to be higher. Our analysis of near-death patients, although underpowered, returned results in a similar direction.

In conclusion, prevention of acute coronary syndrome is the subject of scientific recommendations, including from the European Society of Cardiology and the French Society of Cardiology [16–20]. Their recommendations for statin use are based on the results of clinical trials. Our study reflects the real-life impact of statins, reporting a similar magnitude of relative effect to clinical trials in low-cardiovascular-risk populations. These results support the CTT collaboration meta-analyses.
Conclusion that guidelines recommendations should target low-risk populations as suitable for LDL-lowering statin therapy.

Contributors

The work presented here was carried out with the involvement of every author. L.G.-B., M.R., N.D., J.D., E.B., J.B., Y.C., E.A., A.K., J.B., and L.A. conceived both the research theme and the methods, analysed the data and interpreted the results. L.G.-B. was in charge of the study in France, and together with A.K., M.R. and L.A. analysed the data, drafted and revised the paper. All authors have contributed to, read and approved the final manuscript. L.G.-B. is guarantor for the study. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of conflicting interests

L.G.B. was the recipient of a research fellowship from INSERM at the time of the study and is currently employed by LA-SER, the company conducting the study, together with M.R., E.A., and A.K. N.D., J.D., and E.B. received consulting fees or honorarium from LA-SER for the submitted work. N.D. declares to have received research grants from AstraZeneca, Daiichi-Sankyo, Eli-Lilly, Glaxo-Smith-Kline, MSD, Novartis, Pfizer, Sanofi-Aventis, Servier and The Medicines Company; he also received payment for serving in advisory panels or for lecture fees from AstraZeneca, Boehringer-Ingeheim, Bristol-Myers Squibb, Eli-Lilly, Menarini, Merck-Serono, Novo-Nordisk, Servier, and Sanofi-Aventis. E.B. served as a board member for Boehringer-Ingeheim, Ethypharm, MSD, AstraZeneca, Schering-Plough, Sanofi-Aventis, Merck, Danone, Amsterdam Molecular Therapeutics, Lilly, and Amgen: declares to have received research grants from the Institute of Cardiology in Montreal, Genfit, Roche, Danone, MSD, GSK, and Sanofi-Aventis; and has also received payment (to him directly or to his institution) for lectures including service on speakers bureaus from Chugai, Roche, and AstraZeneca. J.D. received research grants from AstraZeneca, Sanofi-Aventis, and Pfizer; and consultant/speaker for AstraZeneca, MSD, Novartis and Danone. J.B. consults for LA-SER, but declares no conflict of interest together with J.B. and Y.C. L.A. is a stockowner and chairman of LA-SER. LA-SER is a private and international scientific organisation that conducts more than 200 studies or consultations annually funded by more than 50 pharmaceutical companies, including AstraZeneca.

Acknowledgements

We are indebted to the following cardiologists that participated in the recruitment of patients: Guy Barberet, Jean-Francois Baron, Jean-Louis Bensoussan, Christian Bourel, Laurent Bremond, Alain Brousse, Claude Burguier, Paul Chiri, Samuel Cohen, Isabelle Cornette, Thierry Coulis, Daniele Delbecque, Dominique Delsart, Michel Delvallez, Philippe Ducamp, Emmanuelle Honnart, Pierre Llor, Gilbert Ohayon, Jacqueline Plot, Christiane Philoctete, Wilfrid Planchamp, Jean-Marc Ponzi, Philippe Regnault, Jean Salvaggio, Bernard Steinberg, Pierre Tran, Philippe Trehou, Philippe Uge, Patrick Vandeveere, and Reine Viallat. We also thank Yann Hamon and Benoît David, data managers/statisticians from LA-SER, for performing the SAS programming for this study.

Appendix A


References


