CLINICAL RESEARCH

Assessment of lipid-lowering treatment in France — The CEPHEUS study

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KEYWORDS
Guidelines; LDL cholesterol; Lipid-lowering drugs; Statins; France

Summary

Objective. — Most evidence-based practice guidelines identify low-density lipoprotein cholesterol (LDL-C) as the primary target of cholesterol-lowering therapy; the optimal LDL-C concentration is based on the patient’s individual risk level. The aim of this study was to determine the proportion of patients on lipid-lowering drugs who reach the LDL-C goals recommended in guidelines.

Methods. — The CEPHEUS study was conducted in eight European countries in patients, who had been treated with lipid-lowering drugs for at least three months, with no dose adjustment for a minimum of six weeks. In France, throughout 2006, 560 general practitioners enrolled 2222 patients into the study, 1966 of whom gave a fasting blood sample. Lipid and glucose parameters were measured centrally.

Results. — Patients had been on treatment for a mean of 5.5 ± 5.7 years. Most patients (90.4%) received a single lipid-lowering drug; 84.9% were treated with statins, and the second most frequently used lipid-lowering drugs were fibrates (13.7%). Among the treated subjects, 50% had LDL-C values >3.0 mmol/L, 30% had triglyceride values >1.7 mmol/L and 10% had HDL cholesterol values < 1.1 mmol/L. In high-risk patients, as defined by French guidelines, over 55% were above the recommended goal of 2.6 mmol/L. In the subgroup of high-risk patients who did not reach the goals, the LDL-C values were 0.7—1.4 mmol/L over the recommended concentration.

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Conclusion. — The results of this survey highlight the suboptimal management of hypercholesterolaemia in France, particularly in the high-risk population, in whom the percentage who achieved the LDL-C goals was the lowest.

Résumé

But de l’étude. — La plupart des recommandations identifient le LDL-cholestérol (LDL-C) comme cible thérapeutique des agents hypolipémiants et recommandent des objectifs de LDL-C basés sur la catégorie de risque à laquelle appartient le patient. Le but de cette étude a été d’évaluer la proportion de patients sous traitement hypolipémiant atteignant les seuils de LDL-C recommandés.


Résultats. — Les patients étaient traités en moyenne depuis 5,5 ± 5,7 ans. La plupart des patients (90,4 %) ont reçu une monothérapie hypolipémiante ; 84,9 % étaient traités par statine, le second hypolipémiant le plus fréquemment utilisé était représenté par les fibrates (13,7 %). Parmi ces sujets traités, 50 % avaient des valeurs de LDL-C au-dessus de 3,0 mmol/L, 30 % avaient des valeurs de triglycérides au-dessus de 1,7 mmol/L et 10 % avaient des valeurs de HDL-cholestérol en dessous de 1,1 mmol/L. Chez les sujets à haut risque défini selon les recommandations françaises, plus de 55 % des patients se situaien au-dessus de la valeur recommandée de LDL-C de 2,6 mmol/L. Dans le sous-échantillon des sujets à haut risque qui n’avaient pas atteint l’objectif recommandé, les valeurs de LDL-C étaient de 0,7 à 1,4 mmol/L plus élevées que les valeurs recommandées.

Conclusion. — Cette étude montre le contrôle sous-optimal de l’hypercholestérolémie en France et ce, plus particulièrement chez les sujets à haut risque cardiovasculaire qui atteignent moins fréquemment les valeurs seuils recommandées.

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Abbreviations

Afssaps Agence française de sécurité sanitaire des produits de santé
CVD cardiovascular disease
HDL-C high-density lipoprotein cholesterol
LDL-C low-density lipoprotein cholesterol
TC total cholesterol
TJETF Third Joint European Task Force

Background

Prevention of cardiovascular disease in an individual patient is based on simultaneous management of all of their risk factors. Preventive actions show the greatest degree of benefit when the risk of cardiovascular events is high. The most recent guidelines from the European Society of Cardiology have reasserted the need to control all risk factors, especially in high-risk patients [1]. These guidelines recommend that the concentration of low-density lipoprotein cholesterol (LDL-C) remains below 3 mmol/L. In France, guidelines on lipid management are published regularly by the Agence française de sécurité sanitaire des produits de santé (Afssaps) [2]. Thus it is important to evaluate contemporary clinical practice patterns relating to these guidelines, in order to ensure that patients benefit from the latest improvements seen in the management of dyslipidaemia-induced cardiovascular risk.

Quantitative evaluation of plasma lipid concentrations is fundamental for the accurate assessment of medical practice and its appropriateness with regard to guidelines. The distribution of lipids levels in a representative sample of the French population on lipid-lowering therapy, and the evaluation of lipid-lowering drugs in relation to the 2000 Afssaps guidelines, became available for the first time in the Suivi des pratiques vers les objectifs thérapeutiques (SPOT) study [3]. A new recommendation for lipid management was issued by Afssaps in March 2005 [2]. Thus, the multinational European CEPHEUS study was carried out to assess the agreement between results obtained with lipid-lowering drugs in France and the Afssaps guidelines issued in 2005, with a precise and centralized quantification of plasma lipids.

Methods

“CEPHEUS” was a multinational survey conducted in eight European countries: Belgium, France, Greece, Ireland, the Netherlands, Finland, Turkey and Luxembourg. To obtain a representative sample of subjects on lipid-lowering treatment, individuals were randomly invited to participate.

In France, the study protocol and informed consent form were approved on 5 May 2006 by the Toulouse-2 Comité consultatif de protection des personnes dans la recherche...
The survey was performed in accordance with the Declaration of Helsinki and was consistent with the International Conference on Harmonisation of Good Clinical Practice guidelines. Signed and dated informed consent was obtained from all participants before conducting any procedures specific to the survey. The principal investigator was responsible for storing the original signed informed consent form and a copy was given to the subject.

Before any patients were recruited, each investigator completed a questionnaire on their experience of and attitude towards the management of hypercholesterolaemia. The form included questions on the diagnosis of hypercholesterolaemia, on guidelines and goals, and on the treatment options available.

Adult (≥ 18 years) men and women were eligible for the study. The inclusion criteria were: lipid-lowering treatment for a minimum of three months before enrolment, with no dose adjustment for at least six weeks; and patients who benefitted from French National Health Insurance. For each subject, the investigator completed a patient record form, which collected the following information:

- screening and demographic data (date of birth, sex and ethnic group);
- results of physical examination (height, weight, waist circumference, blood pressure);
- history of cardiovascular disease (CVD), peripheral artery disease, and cerebrovascular atherosclerotic disease;
- presence of CVD risk factors (current smoking, diabetes, family history of premature coronary heart disease [defined as definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative], arterial hypertension [defined as blood pressure ≥ 140/90 mmHg or current use of antihypertensive medication]);
- hypercholesterolaemia and year drug treatment was started, if known;
- fasting blood sample;
- current lipid-lowering pharmacological treatment; and
- rationale for prescribing current lipid-lowering therapy (familial hypercholesterolaemia, primary or secondary prevention).

A fasting blood sample was also taken. Within 2–5 days after the visit, the investigator received the patient’s results as well as the 2005 Afssaps guidelines (current French guidelines) by fax. This allowed the investigator to determine the patient’s risk profile and take the appropriate measures, if any, with respect to the patient’s future treatment. In addition, the investigator was provided with the patient’s CVD risk profile after the data for that particular individual had been entered in the database.

### Efficacy measurements

The primary efficacy variable was the percentage of subjects achieving LDL-C goals according to the Third Joint European Task Force (TJETF) guidelines [4]. One of the secondary efficacy variables was the percentage of subjects achieving LDL-C goals according to the 2005 Afssaps guidelines [2]. In order to evaluate this endpoint, blood plasma levels were determined for total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, glucose, apolipoprotein A-1 and apolipoprotein B. A total of 5 mL blood was drawn into a gel tube and a further 2 mL into a fluoride tube using the materials provided by the central laboratory. The tubes were mixed by gentle inversion and shipped to the central laboratory by air courier. Laboratory analyses were performed at Quintiles Laboratories Europe (1 Simpson Parkway, Livingston, UK).

### Statistical analysis

The full dataset for this analysis consisted of all patients from the French enrolling centres, who gave their informed consent and underwent a laboratory test. Most investigators (88.8%) used guidelines to establish individual target cholesterol levels; the most frequently used were the Afssaps guidelines (90.9% of investigators). Other, less often used, guidelines were TJETF (17.9%), National Cholesterol Educational Program Adult Treatment Panel III guidelines (16.1%), and individual practice guidelines (21.2%). We therefore analysed LDL-C goals according to the Afssaps guidelines, which are the main tool for evaluating lipid-lowering treatment in France. For each patient, the Afssaps risk category was determined and a dichotomous variable computed indicating whether the patient had achieved their LDL-C goal, corresponding to risk category. The percentage of subjects achieving LDL-C goals according to Afssaps guidelines was then reported.

A two-level logistic regression analysis was performed to determine the prognostic factors for achieving LDL-C goals according to the Afssaps guidelines, with patients at the
Table 2  Distribution of biological parameters in treated subjects (n = 1966) based on central laboratory determination.

<table>
<thead>
<tr>
<th>Percentiles</th>
<th>n</th>
<th>Missing</th>
<th>10th</th>
<th>20th</th>
<th>30th</th>
<th>40th</th>
<th>50th</th>
<th>60th</th>
<th>70th</th>
<th>80th</th>
<th>90th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>1959</td>
<td>7</td>
<td>3.97</td>
<td>4.38</td>
<td>4.64</td>
<td>4.92</td>
<td>5.21</td>
<td>5.44</td>
<td>5.72</td>
<td>6.03</td>
<td>6.62</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mmol/L)</td>
<td>1959</td>
<td>7</td>
<td>1.06</td>
<td>1.16</td>
<td>1.26</td>
<td>1.37</td>
<td>1.47</td>
<td>1.55</td>
<td>1.68</td>
<td>1.83</td>
<td>2.09</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mmol/L)</td>
<td>1957</td>
<td>9</td>
<td>1.91</td>
<td>2.27</td>
<td>2.50</td>
<td>2.76</td>
<td>2.96</td>
<td>3.17</td>
<td>3.43</td>
<td>3.74</td>
<td>4.20</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1959</td>
<td>7</td>
<td>0.77</td>
<td>0.92</td>
<td>1.05</td>
<td>1.19</td>
<td>1.34</td>
<td>1.52</td>
<td>1.75</td>
<td>2.09</td>
<td>2.61</td>
</tr>
<tr>
<td>Apolipoprotein A-1 (g/L)</td>
<td>1938</td>
<td>28</td>
<td>1.25</td>
<td>1.35</td>
<td>1.43</td>
<td>1.50</td>
<td>1.57</td>
<td>1.65</td>
<td>1.72</td>
<td>1.84</td>
<td>1.99</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>1937</td>
<td>29</td>
<td>0.64</td>
<td>0.72</td>
<td>0.79</td>
<td>0.84</td>
<td>0.89</td>
<td>0.94</td>
<td>1.00</td>
<td>1.09</td>
<td>1.22</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>1960</td>
<td>6</td>
<td>4.57</td>
<td>4.79</td>
<td>5.01</td>
<td>5.17</td>
<td>5.34</td>
<td>5.56</td>
<td>5.83</td>
<td>6.27</td>
<td>7.26</td>
</tr>
</tbody>
</table>

Results

In the French arm of the CEPHEUS study, 560 general practitioners enrolled 2222 patients between September and December 2006. Among consenting patients, 256 patients did not undergo a laboratory test. Laboratory data were available for the remaining 1966 patients, who constitute the study population.

Patients’ characteristics are given in Table 1. The prevalences of men older than 50 years or women older than 60 years were 86.4% and 67.2%, respectively. Patients had been on treatment for a mean of 5.5 ± 5.7 years. The most frequent indication for treatment prescription was primary prevention (74.1%), followed by secondary prevention (21.8% patients) and familial hypercholesterolemia (4.1% patients, not included in the French guidelines). Most patients (90.4%) received a single lipid-lowering drug. Of these, the majority (84.9%) were treated with statins. The second most commonly used lipid-lowering therapy was fibrate (13.7%). No patients were treated with bile acid sequestrants, while 25 (1.4%) were treated with ezetimibe as monotherapy. Among the statins used as monotherapy, rosuvastatin was the most frequently used (24.1%), followed by atorvastatin (20.8%) and pravastatin (17.9%). The fibrate most frequently prescribed as monotherapy was fenofibrate (11.4%) followed by bezafibrate (1.0%) and ciprofibrate (1.0%). All patients treated with multiple lipid-lowering therapies (n = 66) received a statin in combination with other drugs.

The average TC values were 5.27 ± 1.06 mmol/L and the LDL-C values were 3.03 ± 0.92 mmol/L. The complete distributions for lipid parameters are shown in Table 2. Among these treated subjects, 50% had LDL-C values above

Table 3  Low-density lipoprotein cholesterol (LDL-C) by risk category in patients who did not reach target levels.

<table>
<thead>
<tr>
<th>LDL-C (mmol/L)</th>
<th>High risk (n = 417) (%)</th>
<th>≥ 3 risk factors (n = 24) (%)</th>
<th>2 risk factors (n = 38) (%)</th>
<th>1 risk factor (n = 17) (%)</th>
<th>No risk factors (n = 5) (%)</th>
<th>Total (n = 501)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6–3.4</td>
<td>250 (60.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>250 (49.9)</td>
</tr>
<tr>
<td>3.4–4.1</td>
<td>102 (24.5)</td>
<td>16 (66.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>118 (23.6)</td>
</tr>
<tr>
<td>4.1–4.9</td>
<td>49 (11.8)</td>
<td>5 (20.8)</td>
<td>28 (73.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>82 (16.4)</td>
</tr>
<tr>
<td>4.9–5.7</td>
<td>13 (3.1)</td>
<td>3 (12.5)</td>
<td>7 (53.1)</td>
<td>14 (82.4)</td>
<td>0 (0.0)</td>
<td>37 (7.4)</td>
</tr>
<tr>
<td>≥ 5.7</td>
<td>3 (0.7)</td>
<td>0 (0.0)</td>
<td>3 (7.9)</td>
<td>3 (17.6)</td>
<td>5 (100.0)</td>
<td>14 (2.8)</td>
</tr>
</tbody>
</table>
Assessment of lipid-lowering treatment in France — The CEPHEUS study

Evidence concerning the efficacy of lipid-lowering treatment, and more particularly of statins, in treating cardiovascular risk is ample in the fields of both secondary and primary prevention [5]. Follow-up studies of randomized controlled trials [6–8] have shown that in patients initially treated with statins, the beneficial effects of the therapy remained even after statin discontinuation. Statins have a large number of targets in atherosclerosis, but their impact on atheroma plaques seems irrefutable [9–11]. The anti-inflammatory pleiotropic effects of statins are still debated and are specifically being investigated [12]. On an epidemiological level, the beneficial effects of lipid-lowering treatment targeting hypertriglyceridaemia and/or low HDL-C levels seem quite compelling but, so far, additional efficacy demonstrations from prospective trials with hard clinical end-points are severely lacking [13–16]. In 2008, lipid-lowering treatment should be based mainly on statins, despite alternative therapies in very specific situations [17].

Compared with the only quantitative evaluation carried out in a French population [3], the French arm of the European CEPHEUS study showed no improvement in LDL-C levels over a three-year period. This goes against the recommendations for optimizing lipid-lowering treatment imparted in international guidelines [1,18], advising aggressive treatment for high-risk patients as well as aiming to decrease overall lipid levels. In France, the situation is complex due to a specific recommendation tolerating relatively elevated LDL-C levels for low-risk subjects (< 4.9 mmol/L and < 5.7 mmol/L). With no absolute cause–effect relationship, the LDL-C distribution did not change between 2003 and 2006. One may wonder about the impact of this overall lack of improvement on the global distribution of cardiovascular risk. In any event, 50% of French patients are treated incorrectly according to European guidelines. The medical and economic impact caused by this situation should be documented further since lifelong low LDL-C is connected with better long-term prognosis [19].

In France, once low-risk patients (correctly treated) are not taken into account since thresholds are rather high (< 4.9 mmol/L and < 5.7 mmol/L), high-risk patients’ conditions are even worse. In March 2005, this category of patients was redefined in the guidelines [2], including all cardiovascular pathologies and subjects with high absolute cardiovascular risk (Framingham risk score > 20% over a 10-year period). In this new context, the LDL-C levels of 55% of high-risk patients were above the recommended threshold of 2.6 mmol/L in the present study. The likelihood of achieving this threshold depends markedly on LDL-C level at baseline in a given subject and on the potency of the statin used. To treat high-risk normolipidaemic subjects, any statin with the dosage used in randomized controlled trials would be adequate. In patients with high LDL-C levels, however, precise assessment of LDL-C levels in the CEPHEUS study showed that to reach the recommended threshold, an additional decrease of 0.7–1.4 mmol/L would be necessary. Consequently, physicians should not hesitate to titrate the current statin or to prescribe a more potent statin to lower LDL-C levels.

In France, very few studies have assessed the results of lipid-lowering drugs in relation to measured LDL-C values. Recently, the EUROASPIRE III study (unpublished data) reassessed the results of lipid-lowering treatment in a sample of 270 coronary patients in the region of Lille (Lille,
Table 4  Predictors of achieving LDL-C goals according to the 2005 Afssaps guidelines: results of multilevel logistic regression.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (vs &lt;40 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–54</td>
<td>0.76</td>
<td>(0.35–1.65)</td>
<td>0.034</td>
</tr>
<tr>
<td>55–69</td>
<td>0.62</td>
<td>(0.29–1.33)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>0.47</td>
<td>(0.21–1.02)</td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>0.44</td>
<td>(0.18–1.06)</td>
<td></td>
</tr>
<tr>
<td>Female (vs male)</td>
<td>1.56</td>
<td>(1.24–1.96)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Current smoker (vs no)</td>
<td>0.48</td>
<td>(0.35–0.65)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes (vs no)</td>
<td>0.56</td>
<td>(0.43–0.73)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypertension (vs no)</td>
<td>0.59</td>
<td>(0.47–0.75)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Family history of premature CVD (vs no)</td>
<td>0.64</td>
<td>(0.5–0.81)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Secondary prevention (vs primary)</td>
<td>0.32</td>
<td>(0.25–0.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>High triglycerides levels (vs no)</td>
<td>0.62</td>
<td>(0.5–0.78)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Lomme, Roubaix, Tourcoing). Since medical practice varies between regions [20], a large population sample would be necessary to draw a relevant conclusion, irrespective of the risk categories defined by the Afssaps. Moreover, declarative data concerning LDL-C may introduce a bias that cannot be rectified by statistical analysis.

**Study limitations**

Despite the rather large sample size, the study population was not representative of all treated patients in France. Moreover, the inclusion criteria required stable treatment over a period of six weeks before entry into the study. The French situation with regard to the Afssaps guidelines is probably worse since the most unstable patients — those not adhering to treatments and patients who are the most difficult to treat — were excluded. Furthermore, blood samples were required for this study, which probably limited the participation of some patients and/or physicians. Conversely, the Afssaps guidelines focused on LDL-C whereas global lipid-related cardiovascular risk goes beyond the evaluation of this sole parameter. In particular, in the CEPHEUS study 30% of treated patients had triglyceride values above 1.7 mmol/L and 10% had HDL-C values less than 1.1 mmol/L. Thus, an over-risk exists due to residual dyslipidaemia in a large number of patients. Lastly, we did not assess medication compliance, which is why, in specific patients, high LDL-C values may reflect poor compliance to lipid-lowering treatment.

**Conclusions**

This is the second study to provide a quantitative evaluation of the results of lipid-lowering treatment in French patients. While low-risk patients were treated in accordance with the guidelines, high-risk patients were inadequately treated. Drug titration and the use of more potent lipid-lowering drugs, combination therapy or a more holistic approach (such as patient education) are avenues worth exploring. In the meantime, patients at very high risk should be treated intensively by physicians, since they are more likely to be at risk of new or recurrent cardiovascular events in the short-term. Further quantitative evaluations of plasma lipids in patients on lipid-lowering treatment are needed to assess French medical practices.

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**References**


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