CLINICAL RESEARCH

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

Évaluation du traitement hypolipidémiant en France — l’étude CEPHEUS

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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.

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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...
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In order to evaluate this endpoint, blood plasma achieving LDL-C goals according to the 2005 Afssaps guidelines 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...
first level and physicians at the second level. This study had a hierarchical design with a two-tiered structure. Patients were clustered by physician practice, as patients from the same practice were more likely to be treated similarly compared with patients from other practices, and as optimal lipid treatment is likely to reflect a physician’s therapeutic behaviour. A multiple logistic regression model on the combined data assumed observations were uncorrelated. In case of multilevel data, this assumption was unrealistic and failure to take into account the hierarchical data structure may have led to underestimation of standard errors. Hence, the data were analysed by a two-level logistic regression model with the dependent variable (achievement of LDL-C goals according to Afssaps guidelines [yes vs no]) and fixed effects [the potential predictors] and a random effect [physicians]).

Association was appraised by an estimated odds ratio with associated 95% confidence intervals and \( P \) values in the fixed-effects part of the models. All predictors with \( P \) value < 0.10 (using a Wald-type test) in this raw association analysis were then included in an adjusted multilevel logistic regression model, provided that at least 90% of data were available. Multilevel analysis was performed using SAS PROC GLIMMIX (Cary, NC, USA).

## 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, rosvastatin 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>
<thead>
<tr>
<th>LDL-C (mmol/L)</th>
<th>Risk categories according to 2005 Afssaps guidelines</th>
<th>Total (( n = 501 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High risk (( n = 417 )) (%)</td>
<td>≥ 3 risk factors (( n = 24 )) (%)</td>
</tr>
<tr>
<td>2.6–3.4</td>
<td>250 (60.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>3.4–4.1</td>
<td>102 (24.5)</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>4.1–4.9</td>
<td>49 (11.8)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>4.9–5.7</td>
<td>13 (3.1)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>≥ 5.7</td>
<td>3 (0.7)</td>
<td>0 (0.0)</td>
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Of concern, 55% of high-risk patients have LDL-C levels above 1.55 mmol/L. Most physicians reported scheduling cholesterol-monitoring consultations every six months (48.9%) or once a year (35.9%). Only 13.5% of investigators reported scheduling follow-up visits every three months.

Figure 1. Achievement of low-density lipoprotein cholesterol goals according to the 2005 Afssaps guidelines, by risk category.

3.0 mmol/L, 30% had TG values above 1.7 mmol/L, 10% had HDL-C values below 1.1 mmol/L and 40% had HDL-C values above 1.55 mmol/L. Most physicians reported scheduling cholesterol-monitoring consultations every six months (48.9%) or once a year (35.9%). Only 13.5% of investigators reported scheduling follow-up visits every three months.

Among the patients evaluated, 41.8% reached the LDL-C goals recommended in the TJETF guidelines. The percentage of subjects achieving LDL-C goals according to Afssaps guidelines are shown in Fig. 1. In high-risk subjects (44.8% with coronary heart disease, 33.7% with high-risk diabetes [defined as diabetes with at least two classical risk factors] and 37.5% with a Framingham risk score ≥ 20%), more than 55% of patients were above the recommended goal of 2.6 mmol/L. In the subgroup of patients, who did not reach LDL-C goals, we assessed the distribution of LDL-C values within each Afssaps category (Table 3). Patients, who did not reach the target levels had LDL-C values 0.7—1.4 mmol/L higher than the recommended Afssaps goal.

The prognostic factors for achieving LDL-C goals according to the Afssaps guidelines, in an adjusted multilevel logistic regression model, are given in Table 4. When patients were stratified according to risk category, the percentage who reached the target was well correlated with their CVD risk level (i.e. the higher the CVD risk, the lower the percentage of patients on target).

Discussion

The CEPHEUS study, conducted in 2006, conveys new information about the current management of hypercholesterolaemia in France. These data show that the distribution of LDL-C levels in France has not changed since 2003, with 50% of treated patients having levels higher than 3 mmol/L. Of concern, 55% of high-risk patients have LDL-C levels above 2.6 mmol/L. Furthermore in each class, defined according to the Afssaps guidelines, LDL-C levels in subjects not reaching the target were 0.7—1.4 mmol/L higher than the recommended values.

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,
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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