Residual dyslipidaemia after statin treatment in France: Prevalence and risk distribution

Prévalence des anomalies lipidiques résiduelles sous traitement par statines en France

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Summary

Background. — Residual dyslipidaemia in patients treated with statins needs to be addressed to reduce the prevalence of cardiovascular disease in primary and secondary care.

Aims. — To estimate the prevalence of residual lipid abnormalities in statin-treated patients in France.

Methods. — Plasma concentrations of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides were recorded in patients classified by cardiovascular risk according to guidelines from Agence française de sécurité sanitaire des produits de santé. Recruitment took place between September 2008 and February 2009, and involved patients aged \textgreater 45 years who had been on statin therapy for \textgreater=3 months.

Results. — Overall, 39.6\% of the 4335 statin-treated patients had lipid values within desirable levels. Low-density lipoprotein cholesterol was not at goal more often (51.8\%) in higher risk patients than in all patients averaged (37.2\%). Also, high-risk patients with low-density lipoprotein cholesterol not at goal had additional lipid abnormalities (low high-density lipoprotein cholesterol and/or high triglycerides) more frequently (25.6\%) than all patients averaged (18.4\%).

Conclusion. — We conclude that a significant proportion of dyslipidaemic patients at high cardiovascular risk in France are not achieving treatment goals after statin treatment. A significant

Abbreviations: Afssaps, Agence française de sécurité sanitaire des produits de santé; BP, blood pressure; CV, cardiovascular; DYSIS, Dyslipidemia International Study; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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proportion of these patients might benefit from alternative therapies targeted at improving low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels. More attention to the management of these patients is needed to use public health resources more effectively.

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Background

Lowering the prevalence of modifiable risk factors such as dyslipidaemia, smoking or sedentary lifestyle has contributed to reducing cardiovascular-related mortality [1–3]. In urban France, cardiovascular disease is the most frequent cause of death in women and the second most frequent in the general population, only recently surpassed by cancer [4,5].

It is estimated that reduction of plasma cholesterol alone prevented 24% of cardiovascular-related deaths between 1980 and 2000 in the United States [6]. Many other studies have similarly shown the benefits of lipid-lowering treatments not only on mortality [1–3] but also on morbidity [7]. High circulating low-density lipoprotein (LDL) cholesterol levels are most successfully treated with statins [8]. Every 1 mmol/L reduction in LDL cholesterol is linked to a 24% decrease in mortality [3,9].

Residual dyslipidaemia remains for a significant number of treated patients. Some patients do not reach the intended therapeutic goals for LDL cholesterol [10,11]. Significant risk associated with other lipid parameters represents additional normal levels to be achieved. Thus, another group of dyslipidaemic patients at risk despite treatment are those with low levels of high-density lipoprotein (HDL) cholesterol and/or high levels of triglycerides [12–14]. Low HDL cholesterol is in itself an established independent risk factor [15–17] and high triglycerides may be too, although this is controversial [18–21]. Statins are known to mildly augment blood levels of HDL cholesterol (4–8%) and to reduce triglycerides (10–35% depending on baseline triglyceride levels) [8,22].

The Dyslipidemia International Study (DYSIS) was an epidemiological study recently conducted in Europe and Canada with the objective of evaluating the prevalence of residual lipid abnormalities in patients receiving statin therapy. In the present report, we perform a separate analysis on the DYSIS cohort from France. The aim was to estimate the prevalence of different types of dyslipidaemia according to the guidelines of the Agence française de sécurité sanitaire des produits de santé (Afssaps).

Methods

Study population

As part of DYSIS, subjects were enrolled at 740 sites in France. The sample included outpatients managed by a family practitioner or referred to a specialist (endocrinologist or cardiologist) for the treatment of dyslipidaemia.

Eligible subjects were individuals older than 45 years, who had been on statin therapy for 3 months or longer and had at least one fasting blood lipid profile within the past 6 months available while receiving statin therapy. Patients participating in other clinical studies were excluded from our study. Each site was allowed to enrol up to 10 consecutive patients.

Study design and data collection

This was a cross-sectional study designed to estimate the prevalence of different types of dyslipidaemia in statin-
treated patients. The study protocol was approved by the relevant local ethical review committees. Patients who visited physician(s), irrespective of the reason, and fulfilled the inclusion criteria were invited to participate. They were informed of both the aims of the study and its protocol. Data were collected from a single clinical examination and from medical charts.

Information was recorded on patient demographic data (sex, age), type of medical practice and location. Other clinical variables collected were: history of premature cardiovascular disease in first-degree relatives, smoking history, hypertension, ischaemic heart disease, diabetes mellitus, cerebrovascular disease, peripheral artery disease, height, weight, waist circumference, level of physical activity, alcohol consumption, fasting plasma glucose and HbA1c. Following the definition of the International Diabetes Federation, metabolic syndrome was considered to be present if a person had central obesity (waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity specific values for other groups) plus any two of the following: triglycerides ≥ 1.7 mmol/L (150 mg/dL) or specific treatment for this lipid abnormality; HDL cholesterol < 1.0 mmol/L (40 mg/dL) in men and < 1.29 mmol/L (50 mg/dL) in women or specific treatment for this lipid abnormality; systolic blood pressure (BP) ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension; and fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL) or previously diagnosed type 2 diabetes.

For this evaluation of the French population, patients were distributed into five risk categories, following the criteria set forth by the Afssaps [23]. Each category is defined by the sum of risk factors applicable to an individual: 0, 1, 2, ≥ 3 or high risk. High-risk patients were considered as those with either proven coronary disease, or with diabetes plus two other cardiovascular risk factors. Cerebrovascular and peripheral arterial diseases, considered here as separate disease entities, were present only in patients at high risk.

Information collected on statin therapy included the name and daily dose of the statin and any other lipid-modifying therapies used at the time of the blood lipid tests. Laboratory results from patients, who had been on statin therapy for 3 or more months, were included in the analyses. Plasma lipid tests included in this study were: total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, all expressed in mmol/L and in mg/dL. The results were analysed in the light of specific targets for every risk level, as recommended by the French guidelines for prevention of cardiovascular risk (see below). The percentages of patients within the therapeutic normal levels (i.e., at goal) for single and combined lipid measurements are presented in Venn diagrams.

The recommendations from the Afssaps [23] to define the LDL-cholesterol targets were: in the absence of other risk factors, the target LDL cholesterol for an individual is 5.7 mmol/L (220 mg/dL); for patients with 1, 2, or ≥ 3 risk factors, it is 4.9, 4.1 and 3.4 mmol/L (190, 160 and 130 mg/dL), respectively; and for high-risk patients, the target is 2.6 mmol/L (100 mg/dL). HDL cholesterol below 1.0 mmol/L (40 mg/dL) is a risk factor for both men and women. By contrast HDL cholesterol values > 1.5 mmol/L (60 mg/dL) are considered protective and computed as (−1) in the risk calculation equation. As no recommended threshold for plasma triglyceride concentrations is given in the Afssaps guidelines, the one recommended (1.7 mmol/L [150 mg/dL]) by the European Society of Cardiology [24] was used.

Statistical analysis

Sample-size estimations for a binomial proportion of prevalence of dyslipidaemia between 20 and 60% indicated that a survey on 4000 individuals would allow prevalence estimations with precisions of between 1 and 2.5%.

Continuous variables, including patient characteristics, are reported using descriptive statistics (mean ± standard deviation [SD] or median with Q1–Q3 interquartile range, as appropriate). Categorical variables are presented as percentage and absolute number. The percentages of patients classified in the five risk categories were used to stratify the results for LDL cholesterol, HDL cholesterol and triglycerides by risk category. Post-hoc analyses compared subgroups of combined lipid abnormalities (i.e., LDL cholesterol not at goal, low HDL cholesterol and/or high triglycerides) by risk level. Distributions of single and multiple combined lipid abnormalities were obtained and the prevalence of each lipid profile was calculated.

All analyses were performed with the Statistical Analyzing System, version 9.1 (SAS Institute Inc., Cary, NC, USA). Patients who did not have values for the appropriate lipid parameters were not included in the lipid analyses.

Results

Patient characteristics

A total of 4335 patients were recruited between September 2008 and February 2009, 69.5% of whom came from primary care centres. Mean age was 64.7 years and 65.3% were men. According to the risk-category classification of the Afssaps, 61.6% of the participants were considered at high risk, whereas only 5.9% had no additional risk factor (Table 1). The most frequent clinical feature was hypertension (69.5% of patients), with a mean systolic and diastolic BP in this cohort of 134.0 ± 12.4 and 77.9 ± 8.3 mmHg, respectively. Metabolic syndrome was seen in 59.6% of the patients, coronary heart disease in 34.0%, diabetes in 32.9%, family history of premature cardiovascular disease in 26.9% and obesity in 26.8%. The mean waist circumference of the group was 98.9 ± 13.4 cm and the body mass index was 27.9 ± 4.8 kg/m². Clinical characteristics and their distribution across risk groups are given in Table 1.

Treatment

Most patients were on atorvastatin treatment (32.4%), simvastatin (26.7%), rosuvastatin (19.0%) or pravastatin (17.5%; Table 2). All the other lipid-modifying treatments were used in combination with a statin. Among these, ezetimibe was the most common, in 12.1% of patients; and fibrates, nicotinic acid and bile-acid sequestrants were less commonly used.

The statin dose potency used by most (74.2%) of the patients was equivalent to simvastatin 20–40 mg/day (Fig. 1).
Lipid profiles by risk category

Mean average plasma concentrations of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides are given in Table 3. In absolute terms, little difference in lipid parameters was seen across the various risk categories. However, the therapeutic targets for LDL cholesterol vary with the number of risk factors, as detailed in the previous section [23]. When the LDL-cholesterol results were examined, taking into consideration the Afssaps target values, most patients with 0 or 1 risk factor had their LDL cholesterol at the recommended level (Table 4). The proportion of patients with elevated LDL cholesterol increased steadily with the number of additional risk factors. In the high-risk group, 51.8% of the patients had LDL-cholesterol concentrations above those recommended.

The distribution of patients with low HDL cholesterol followed a similar trend, with proportions increasing in the higher risk groups. In the high-risk group, 22.8% of the

Table 1  Patient characteristics according to risk category.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Patients with risk factors or at high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>0 RF (5.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 RF (12.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 RF (12.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 3 RF (12.7)</td>
</tr>
<tr>
<td>Agea (years)</td>
<td>64.7 (10.1)</td>
<td>551 (12.7)</td>
</tr>
<tr>
<td>SBPa (mmHg)</td>
<td>134.0 (12.4)</td>
<td>78.4 (7.9)</td>
</tr>
<tr>
<td>DBPa (mmHg)</td>
<td>77.9 (8.3)</td>
<td>134.3 (11.2)</td>
</tr>
<tr>
<td>Waist circumferencea (cm)</td>
<td>98.9 (13.4)</td>
<td>97.6 (12.3)</td>
</tr>
<tr>
<td>BMIb</td>
<td>27.9 (4.8)</td>
<td>77.0 (7.7)</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m² b (%)</td>
<td>26.8</td>
<td>28.4 (4.1)</td>
</tr>
<tr>
<td>Womenb (%)</td>
<td>34.7</td>
<td>31.2</td>
</tr>
<tr>
<td>Family history of premature CV diseaseb,c (%)</td>
<td>26.9</td>
<td>66.7</td>
</tr>
<tr>
<td>Current smokerb (%)</td>
<td>11.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Hypertensionb (%)</td>
<td>69.5</td>
<td>72.2</td>
</tr>
<tr>
<td>Ischaemic heart diseaseb (%)</td>
<td>34.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Diabetes mellitusb (%)</td>
<td>32.9</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular diseaseb (%)</td>
<td>7.5</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral artery diseaseb (%)</td>
<td>13.4</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic syndromeb (%)</td>
<td>59.6</td>
<td>42.8</td>
</tr>
</tbody>
</table>

BMI: body mass index; DBP: diastolic blood pressure; RF: risk factor; SBP: systolic blood pressure.

a Mean ± SD.

b Percentages calculated from total number of patients in each risk group.

c At least one first-degree relative with myocardial infarction/sudden death before age 55 (men) or 65 (women).

Table 2  Lipid-modifying therapies.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>All patients (n = 4335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin treatment (%)</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>26.7</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>32.4</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>19.0</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>17.5</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>4.1</td>
</tr>
<tr>
<td>Unknown statin</td>
<td>0.3</td>
</tr>
<tr>
<td>Other lipid-modifying treatment (%)</td>
<td>13.3</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>12.1</td>
</tr>
<tr>
<td>Fibrate</td>
<td>0.7</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>0.5</td>
</tr>
<tr>
<td>Bile-acid sequestrant</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Figure 1. Statin use by dose potency in French patients. Potency equivalence for different statins is shown in the table.
patients had low HDL cholesterol (Table 4). In comparison with low HDL cholesterol, larger proportions of patients had triglycerides in excess of 1.7 mmol/L (150 mg/dL): from 18.7% of patients with 0 risk factors to 37.3% of the patients in the high-risk group.

Combined lipid abnormalities were stratified by risk group (Table 4). The percentages of patients with LDL cholesterol not at goal plus low HDL cholesterol and/or high triglycerides increased from 0.8% in the group with 0 risk factors to 25.6% in patients at high risk.

### Prevalence of abnormal lipid profiles

When all of the patients were considered together, 62.8% had LDL cholesterol at goal, 39.6% had normal levels for all the lipid parameters and 23.2% had low HDL cholesterol and/or high triglycerides and LDL cholesterol at goal (Fig. 2). Globally, 37.2% of patients had LDL cholesterol not at goal, and 18.4% had low HDL cholesterol and/or high triglycerides and LDL cholesterol not at goal.

Proportions of patients with all of the individual and the combined lipid abnormalities are represented in Fig. 3. In 4.7% of the overall patients all three parameters were abnormal (Fig. 3a). Among high-risk patients, 48.2% had LDL cholesterol at goal; 26.8% had all lipid parameters normalized and 21.3% had at least one other lipid parameter abnormal (Fig. 3b). Among all high-risk patients not attaining the LDL cholesterol goal, 25.6% had at least another lipid abnormality, and in 6.7% all three lipid parameters were abnormal.

### Discussion

DYSIS set out to estimate the prevalence of residual dyslipidaemia in statin-treated patients across Europe and Canada.
Table 4  Prevalence of patients whose lipid profiles were not at goal or were abnormal, by risk category.

<table>
<thead>
<tr>
<th>Lipid status</th>
<th>All patients</th>
<th>Patients with risk factors or at high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 4335</td>
<td>n = 257 n = 552 n = 551 n = 186 n = 2669</td>
</tr>
<tr>
<td>LDL cholesterol not at goal (%)</td>
<td>37.2</td>
<td>1.6 6.2 15.3 42.0 51.8</td>
</tr>
<tr>
<td>(≥ 5.7/4.9/4.1/3.4/2.6 mmol/L) (≥ 220/190/160/130/100 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HDL cholesterol (%)</td>
<td>17.6</td>
<td>0.0 1.8 9.5 41.4 22.8</td>
</tr>
<tr>
<td>(≤ 1.0 mmol/L; ≤ 40 mg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High triglycerides (%)</td>
<td>33.9</td>
<td>18.7 22.8 33.5 41.4 37.3</td>
</tr>
<tr>
<td>(≥ 1.7 mmol/L; ≥ 150 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol not at goal plus low HDL cholesterol and/or high triglycerides (%)</td>
<td>18.4</td>
<td>0.8 1.9 6.7 27.8 25.6</td>
</tr>
</tbody>
</table>

HDL: high-density lipoprotein; LDL: low-density lipoprotein; RF: risk factor.

in the light of revised and unified criteria, and the lipid recommendations of the European Society of Cardiology [24]. The results of the study are expected to provide additional information for future guidelines for the management of dyslipidaemia, in particular for patients at high cardiovascular risk. However, risk variables are not homogeneously distributed throughout countries, and algorithms to stratify cardiovascular risk have not been universally validated. France, for example, has consistently been shown to have a lower prevalence of cardiovascular disease than most European countries [25], attributed in part to dietary habits and lifestyle [26,27]. Variations exist in the pharmacokinetics, half-lives and active metabolites of the different statins, as well as in their effects on plasma lipids [8,28]. In spite of this, the statin potency, normalized to that of simvastatin [28,29], was estimated to be in a narrow range, and the treatment intensity across the 4335 patients can be considered rather homogeneous.

Figure 3. Distribution of single and multiple combined lipid abnormalities in French patients with total lipid profile: (a) all patients; (b) high-risk patients.
Together with possible differences in genetic predisposition [30], the aforementioned characteristics of the French cohort might significantly change the cardiovascular risk map with respect to the overall DYSIS population. It seems therefore sensible to analyse the lipid profile of the French population separately, according to its regional peculiarities, to obtain a more realistic depiction of the lipid status of each risk group. The representativeness of the French DYSIS sample is questionable. However, the distribution of statin use in 2008 in the French representative Étude permanente de la prescription médicale (EPPM) survey (unpublished observations) was quite similar (atorvastatin 32%, pravastatin 22.5%, rosuvastatin 20.7%, simvastatin 19%, fluvastatin, 7%) to that observed in the DYSIS study.

The stratification into five risk categories, based on the addition of risk factors in the Afssaps guidelines, delineates a more gradual distribution of risk than the one used in other guidelines (i.e., low, high). Lipid abnormalities could therefore be allocated with greater precision to individuals at different levels of cardiovascular risk. As expected, patients in low-risk groups were more frequently at goal than the ones at high risk. Roughly half of the high-risk patients were at the recommended levels for LDL cholesterol. This figure is very close to the 44.8% recorded in the CEPHEUS study performed at the end of 2006 in France [11]. This highlights that despite the population and risk stratification peculiar to this study, secondary cardiovascular prevention in France could be improved substantially. Reducing further the population at risk either by improving compliance or intensifying treatment could help to achieve lower LDL-cholesterol levels in those patients who need them most. It was also remarkable that about one in four patients at high risk also had low HDL cholesterol and high triglyceride concentrations. This prevalence is in agreement with percentages of 21.2—26.9% observed in a European survey of 8545 dyslipidaemic patients [15]. Statin therapy is unlikely to correct such abnormalities as it has only mild effects on these lipid parameters [8]. Such patients would potentially benefit from alternative lipid-modifying therapies such as nicotinic acid (which has an effect on the three main lipid parameters) or fibrates (which have an effect mostly on triglycerides). An additional group of patients, those with ≥3 risk factors, not strictly considered ‘high-risk’, would also benefit from treatment to increase low HDL cholesterol and reduce their triglyceride concentrations. This group comprises a special type of patient, however, who can be considered ‘borderline’ between low and high risk.

Whether moderately high triglyceride levels are an independent cardiovascular risk factor is difficult to ascertain and the Afssaps does not provide specific recommendations in this respect. Although claims in support of this have been made [18—20], no interventional study has been able to associate lowering specifically triglyceride levels with reductions of cardiovascular morbidity. Triglycerides also present pronounced intra-individual variation and high levels often accompany low HDL cholesterol, so that they may represent just an alternative index of a common metabolic disturbance [21]. Notwithstanding this, we used the European Society of Cardiology cut-off value of 1.7 mmol/L (150 mg/dL), which is consistent with the reference values in our population, but we did not regard it as an independent risk factor in our study.

Conclusions

Nearly 40% of statin-treated patients in France could still benefit from LDL cholesterol reduction. Among patients at high cardiovascular risk, half of them had higher LDL cholesterol levels than recommended and an additional quarter had low HDL cholesterol and high triglyceride levels. One in four high-risk patients had LDL cholesterol not at goal combined with additional lipid abnormalities. More comprehensive lipid management strategies in this population may decrease the prevalence of lipid abnormalities and contribute to further decreases in cardiovascular risk. Improvements in the lipid management of high-risk patients should be a priority to help reduce the burden on public health resources.

Conflict of interest statement

Oliviu Crisan is currently employed by Merck Sharp and Dohme-Chibret.

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