CLINICAL RESEARCH

Suboptimal achievement of low-density lipoprotein cholesterol targets in French patients with coronary heart disease. Contemporary data from the DYSIS II ACS/CHD study

Difficulté d’atteinte des cibles de LDL cholestérol chez les patients coronariens français : données récentes de l’étude DYSIS II ACS/CHD

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Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; DYSIS, Dyslipidemia International Study; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; EUROASPIRE, European Action on Secondary and Primary Prevention by Intervention to Reduce Events; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; L-TAP, Lipid Treatment Assessment Project; SD, standard deviation.
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† A complete list of the DYSIS II French investigators is included in Appendix A.
Summary

Background. — European guidelines recommend a low-density lipoprotein cholesterol (LDL-C) target of < 1.8 mmol/L (70 mg/dL), and/or a ≥ 50% reduction when the target level cannot be reached, for patients at very high cardiovascular risk, and high-potency lipid-lowering therapy (LLT) in patients with an acute coronary syndrome (ACS). Aim. — To document the prevalence of lipid abnormalities and the achievement of lipid targets among patients surviving an ACS and in patients with stable coronary heart disease (CHD), using data from the DYSIS II study.

Methods. — DYSIS II was an observational cross-sectional study conducted in 21 countries (2012—2014). We report data from the French cohort, comprising patients hospitalized with an ACS and patients diagnosed with stable CHD. Data on patient characteristics, risk factors, treatments and lipid profile were collected. LDL-C target achievement was assessed based on the European guidelines endorsed by the French Society of Cardiology.

Results. — Of the 468 ACS patients, 277 (59.2%) were receiving LLT at admission to hospital; 22.6% were hospitalized for a recurrent event. Statins were used in 96.6% (450/466) of patients at discharge and in 95.1% (310/326) at 120-day follow-up, at which time 50.6% (80/158) of patients with available data achieved the LDL-C goal. Most of the 436 patients with stable CHD (97.2%) were on LLT (56.8% on high-intensity therapy); 29.2% of patients on LLT met the LDL-C treatment target < 1.8 mmol/L (70 mg/dL).

Conclusion. — These observational data show the progress made in the treatment of ACS from the acute phase up to 3 months, and highlight key areas for improvement in the prevention of recurrent events in patients with CHD in France. The use of higher intensity or combination LLT as recommended in secondary prevention are needed to increase the achievement of LDL-C treatment targets and reduce the risk of morbidity and mortality due to CHD.

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Background

Hypercholesterolemia is a major contributor to the development of atherosclerosis and coronary heart disease (CHD), with all-cause mortality rising in association with increasing concentrations of low-density lipoprotein cholesterol (LDL-C) [1,2]. A large prospective meta-analysis involving over 90,000 individuals, almost half of whom had pre-existing CHD, showed that every 1 mmol/L reduction in LDL-C achieved with statin therapy resulted in a 21% reduction in major vascular events [3]. Guidelines from the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommend an LDL-C target of < 1.8 mmol/L (70 mg/dL), and/or a ≥ 50% reduction from baseline when this target cannot be reached, for patients at very high cardiovascular risk, and the administration of high-potency statin therapy as the first choice in patients presenting with an acute coronary syndrome (ACS) [4]. Not all patients achieve these lipid goals, and require the addition of a non-statin lipid-lowering therapy (LLT) such as ezetimibe, while others are intolerant of statin therapy [4]. Ezetimibe, when combined with a statin, results in an additional 20–25% reduction in LDL-C compared with statin monotherapy [5,6]. The recently published IMPROVE-IT trial also demonstrated that ezetimibe, on top of statin therapy, improved cardiovascular outcomes [7].

In a previous examination of the first 12 countries (11 European countries and Canada) included in the DYSIS study [8], conducted between April 2008 and February 2009, half of the 22,063 statin-treated patients age ≥ 45 years did not achieve their therapeutic LDL-C goal, highlighting a gap between evidence-based recommendations and clinical practice. Among the patients enrolled in France, only 39.6% achieved the target lipid values [9]. We sought to document the prevalence of lipid abnormalities and the achievement of lipid targets among patients who have had an ACS and in patients with stable CHD in France, using data from the global Dyslipidemia International Study (DYSIS) II ACS/CHD study.

Methods

Study design and population

DYSIS II was a cross-sectional observational study conducted in 21 countries in Asia-Pacific, Europe and Middle East/Africa between 2012 and 2014. Two distinct patient populations were enrolled: those hospitalized with an ACS (DYSIS II ACS) and those diagnosed with stable CHD (DYSIS II CHD). The study design is shown in Fig. 1.

Patients who were eligible for enrolment in DYSIS II ACS were:

- ≥ 18 years of age;
- had been hospitalized for an ACS (ST-segment elevation myocardial infarction, left bundle branch block, non-ST-segment elevation myocardial infarction or unstable angina) at the time of enrolment;
- had a full lipid profile performed on blood drawn within 24 hours of admission;
- had either been on LLT for ≥ 3 months or were not taking any LLT.

Patients were given a booklet at enrolment and instructed to take it with them when they next visited their physician following discharge from the index event. The booklet was retained by the patient and was completed by their physician during subsequent consultations, capturing the patient’s lipid profile and other basic characteristics. The purpose of the booklet was to gather accurate information that could be reported by the patient during the follow-up telephone interview, which was carried out with patients (or their next of kin) 120 ± 15 days after the index event.

DYSIS II CHD enrolled patients ≥ 18 years of age with stable CHD during a single visit to their physician on an outpatient basis. Physicians were representative of the general population of clinicians managing patients for secondary prevention in France, and included general practitioners or family physicians, internists and cardiologists. Stable CHD was defined as one or more of the following:

- > 50% stenosis on coronary angiography or computed tomography;
- previous percutaneous coronary intervention; previous coronary artery bypass graft;
- history of ACS ≥ 3 months previously.

Patients were required to have had a fasting lipid profile done within the previous 12 months, either while on LLT for ≥ 3 months or not on any LLT. Patients with a history of ACS within the previous 3 months were not eligible for enrolment in DYSIS CHD.

To avoid selection bias, centres participating in DYSIS II were strongly encouraged to enrol all consecutive patients who fulfilled the inclusion criteria. Patients enrolled in clinical trials involving medication were not eligible.

Data on patient characteristics, risk factors, treatments (LLT and selected concomitant pharmacological therapies) and laboratory values were collected using an electronic case report form. LDL-C target achievement was assessed based on the 2011 ESC/EAS guidelines for patients at very high cardiovascular risk (LDL-C < 1.8 mmol/L [70 mg/dL]) [4].

DYSIS II was strictly observational in nature and the protocol did not recommend or discourage any treatments, procedures, diagnostics or examinations that were not part of those delivered in routine medical care. As such, the study served to comprehensively document current secondary prevention practices in patients with CHD or ACS, regardless of current treatment.

This study was conducted in accordance with good epidemiological and clinical practice, and all applicable laws, rules and regulations, and was approved by the authorities in all participating countries. All subjects provided written informed consent to participate.

Objectives

The primary objective in the French cohort of this observational study was to document real-life lipid concentrations relative to the targets in the 2011 ESC/EAS guidelines for the management of dyslipidaemias [4] in patients hospitalized with an ACS and in those with stable CHD, who had either been on LLT for ≥ 3 months or were not taking any LLT. Key secondary objectives were to describe the
patient characteristics and risk profiles, to document drug usage patterns and to determine lipid goal achievements.

**Study management**

A site management team (Institut für Herzinfarktforschung Ludwigshafen, Ludwigshafen, Germany) was responsible for training the site personnel on all aspects of the study and was a resource for data-collection questions and query resolution. This team closely monitored patient enrolment and data submission at each site and performed calls, as necessary, to stimulate enrolment or data submission.

Standardized data management procedures were undertaken to ensure the integrity and analytical utility of the study data, including handling rules for missing or incomplete data, range checks and data transformations. Data quality checks were carried out at the time of data entry and before creation of the analysis dataset. Data were anonymized to protect patient confidentiality. Source documentation and data accuracy were verified in 25% of cases.

**Statistical analysis**

Categorical variables are described using count (percentage) and continuous quantitative variables as mean ± standard deviation (SD) or median (interquartile range [IQR]). Treatment patterns, healthcare usage patterns, and all other documented variables were compared among prespecified subgroups using the chi-square test or Mann-Whitney-Wilcoxon test, as appropriate. In all analyses, a value of \( P \leq 0.05 \) was considered statistically significant. All analyses were performed using SAS software version 9.3 (Cary, NC, USA).

**Results**

**DYSIS II ACS**

DYSIS II ACS was conducted in 24 coronary care units in France. Of the 468 patients enrolled, half (50.6%) had ST-segment elevation myocardial infarction or left bundle...
<table>
<thead>
<tr>
<th>Variable</th>
<th>ACS All ACS (n = 468)</th>
<th>Incident ACS (n = 362)</th>
<th>Recurrent ACS (n = 106)</th>
<th>Stable CHD All CHD (n = 436)</th>
<th>No LLT (n = 12)</th>
<th>LLT (n = 424)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No LLT (n = 181)</td>
<td>LLT (n = 181)</td>
<td>No LLT (n = 10)</td>
<td>LLT (n = 96)</td>
<td>No LLT (n = 12)</td>
<td>LLT (n = 424)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 12</td>
<td>60 ± 12</td>
<td>68 ± 11</td>
<td>69 ± 11</td>
<td>65 ± 13</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>Men</td>
<td>375 (80.1)</td>
<td>154 (85.1)</td>
<td>134 (74.0)</td>
<td>5 (50.0)</td>
<td>82 (85.4)</td>
<td>349 (80.0)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>138 ± 24</td>
<td>140 ± 26</td>
<td>139 ± 24</td>
<td>133 ± 19</td>
<td>135 ± 23</td>
<td>132 ± 13</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80 ± 16</td>
<td>82 ± 16</td>
<td>80 ± 16</td>
<td>73 ± 14</td>
<td>75 ± 13</td>
<td>76 ± 9</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>106 (22.6)</td>
<td>0</td>
<td>0</td>
<td>10 (100)</td>
<td>96 (100)</td>
<td>236/435 (54.3)</td>
</tr>
<tr>
<td>CKD</td>
<td>18 (3.8)</td>
<td>5 (2.8)</td>
<td>6 (3.3)</td>
<td>2 (20.0)</td>
<td>5 (5.2)</td>
<td>22 (5.0)</td>
</tr>
<tr>
<td>Diabetes mellitus type 2β</td>
<td>102 (21.8)</td>
<td>23 (12.7)</td>
<td>46 (25.4)</td>
<td>3 (30.0)</td>
<td>30 (31.3)</td>
<td>117/434 (27.0)</td>
</tr>
<tr>
<td>Hypercholesterolaemiaβ</td>
<td>312/463 (67.4)</td>
<td>62 (34.3)</td>
<td>162/177 (91.5)</td>
<td>6 (60.0)</td>
<td>82/95 (86.3)</td>
<td>323/426 (75.8)</td>
</tr>
<tr>
<td>PAD</td>
<td>43/466 (9.2)</td>
<td>7 (3.9)</td>
<td>20/179 (11.2)</td>
<td>2 (20.0)</td>
<td>14 (14.6)</td>
<td>64/431 (14.8)</td>
</tr>
<tr>
<td>Stroke (ischaemic or haemorrhagic)</td>
<td>28/463 (6.0)</td>
<td>5/179 (2.8)</td>
<td>15/179 (8.4)</td>
<td>0</td>
<td>8 (8.3)</td>
<td>16/425 (3.8)</td>
</tr>
<tr>
<td>Type of ACS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST elevation/LBBB MI</td>
<td>237 (50.6)</td>
<td>77 (42.5)</td>
<td>3 (30.0)</td>
<td>39 (40.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ST elevation MI</td>
<td>191 (40.8)</td>
<td>81 (44.8)</td>
<td>6 (60.0)</td>
<td>45 (46.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>40 (8.5)</td>
<td>23 (12.7)</td>
<td>1 (10.0)</td>
<td>12 (12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors for CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>131 (28.0)</td>
<td>36 (19.9)</td>
<td>4 (40.0)</td>
<td>18 (18.8)</td>
<td>33 (7.6)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Family history of premature CVD</td>
<td>146/418 (34.9)</td>
<td>52/171 (30.4)</td>
<td>59/156 (37.8)</td>
<td>3/8 (37.5)</td>
<td>32/83 (38.6)</td>
<td>129/338 (38.2)</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>139/322 (43.2)</td>
<td>52/115 (45.2)</td>
<td>4/7 (57.1)</td>
<td>25/66 (37.9)</td>
<td>178/428 (41.6)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Metabolic syndrome (NCEP-ATP III)</td>
<td>56/122 (45.9)</td>
<td>18/40 (45.0)</td>
<td>0</td>
<td>11/17 (64.7)</td>
<td>55/217 (25.3)</td>
<td>2/7 (28.6)</td>
</tr>
<tr>
<td>Hypertensionβ</td>
<td>395 (84.4)</td>
<td>169 (93.4)</td>
<td>8 (80.0)</td>
<td>91 (94.8)</td>
<td>428 (98.2)</td>
<td>10 (83.3)</td>
</tr>
<tr>
<td>Central obesity</td>
<td>113/135 (83.7)</td>
<td>38/42 (90.5)</td>
<td>2/2 (100)</td>
<td>19/22 (86.4)</td>
<td>207/290 (71.4)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m²</td>
<td>115 (24.6)</td>
<td>46 (25.4)</td>
<td>2 (20.0)</td>
<td>29 (30.2)</td>
<td>88 (20.2)</td>
<td>2 (16.7)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation, n (%) or n/N (%), where data are missing. ACS: acute coronary syndrome; BMI: body mass index; BP: blood pressure; CHD: coronary heart disease; CKD: chronic kidney disease; CVD: cardiovascular disease; LBBB: left bundle branch block; LLT: lipid-lowering therapy; MI: myocardial infarction; NCEP-ATP: National Cholesterol Education Program Adult Treatment Panel; PAD: peripheral artery disease.

a Previously diagnosed or current treatment of fasting plasma glucose ≥ 7 mmol/L (≥ 126 mg/dL).
b Known history of hypercholesterolaemia or currently taking lipid-lowering therapy or low-density lipoprotein cholesterol > 4.1 mmol/L (160 mg/dL).
c Parent, brother or sister with myocardial infarction or sudden death before age 55 years (male) or age 65 years (female).
d Defined as < 20–30 minutes of walking on 3–4 days each week.
e BP ≥ 140/90 mmHg, antihypertensive medication, previously diagnosed hypertension.
f Waist circumference ≥ 94 cm in men or ≥ 80 cm in women.
Table 2  Chronic treatments in patients with ACS or stable CHD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACS&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th>Stable CHD&lt;sup&gt;b&lt;/sup&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (&lt;i&gt;n&lt;/i&gt; = 468)</td>
<td>Incident ACS (&lt;i&gt;n&lt;/i&gt; = 362)</td>
<td>Recurrent ACS (&lt;i&gt;n&lt;/i&gt; = 106)</td>
<td>All patients (&lt;i&gt;n&lt;/i&gt; = 436)</td>
<td>No LL T (&lt;i&gt;n&lt;/i&gt; = 12)</td>
<td>LL T (&lt;i&gt;n&lt;/i&gt; = 424)</td>
</tr>
<tr>
<td></td>
<td>No LL T (&lt;i&gt;n&lt;/i&gt; = 181)</td>
<td>LL T (&lt;i&gt;n&lt;/i&gt; = 181)</td>
<td>No LL T (&lt;i&gt;n&lt;/i&gt; = 10)</td>
<td>LL T (&lt;i&gt;n&lt;/i&gt; = 96)</td>
<td>No LL T (&lt;i&gt;n&lt;/i&gt; = 12)</td>
<td>LL T (&lt;i&gt;n&lt;/i&gt; = 424)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>173/467 (37.0)</td>
<td>16 (8.8)</td>
<td>77 (42.5)</td>
<td>5 (50.0)</td>
<td>75/95 (78.9)</td>
<td>349/435 (80.2)</td>
</tr>
<tr>
<td></td>
<td>92 (19.7)</td>
<td>9 (5.0)</td>
<td>37 (20.4)</td>
<td>4 (40.0)</td>
<td>42 (43.8)</td>
<td>171 (39.2)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>217/466 (46.6)</td>
<td>43 (23.8)</td>
<td>103 (56.9)</td>
<td>4 (40.0)</td>
<td>67/94 (71.3)</td>
<td>336 (77.1)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>169/465 (36.3)</td>
<td>15 (8.3)</td>
<td>80 (44.2)</td>
<td>5 (50.0)</td>
<td>69/94 (73.4)</td>
<td>336 (77.1)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>98/465 (21.1)</td>
<td>16 (8.8)</td>
<td>51/180 (28.3)</td>
<td>3 (30.0)</td>
<td>28/94 (29.8)</td>
<td>131 (30.0)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>25/467 (5.4)</td>
<td>4 (2.2)</td>
<td>10 (5.5)</td>
<td>1 (10.0)</td>
<td>10/95 (10.5)</td>
<td>38 (9.0)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>21/466 (4.5)</td>
<td>2 (1.1)</td>
<td>11 (6.1)</td>
<td>1 (10.0)</td>
<td>7/94 (7.4)</td>
<td>55 (12.6)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>82/465 (17.6)</td>
<td>12 (6.6)</td>
<td>44/180 (24.4)</td>
<td>4 (40.0)</td>
<td>22/94 (23.4)</td>
<td>119 (27.3)</td>
</tr>
<tr>
<td>Oral antidiabetic drug</td>
<td>103 (22.0)</td>
<td>22 (12.2)</td>
<td>51 (28.2)</td>
<td>3 (30.0)</td>
<td>27 (28.1)</td>
<td>120 (27.5)</td>
</tr>
</tbody>
</table>

Data are expressed as <i>n</i> (%) or <i>n</i>/<i>N</i> (%), where data are missing. ACE: angiotensin-converting enzyme; ACS: acute coronary syndrome; ARB: angiotensin II receptor blocker; CHD: coronary heart disease; LL T: lipid-lowering therapy.

<sup>a</sup> On admission.

<sup>b</sup> At the time of latest lipid test.
branch block, 40.8% had non-ST-segment elevation myocardial infarction, and 8.5% had unstable angina (Table 1). The mean age of the ACS population was 65 ± 12 years and 80.1% were men. More than one-fifth (22.6%) had been hospitalized for a recurrent ischaemic event; these patients had a more severe medical history, including a higher prevalence of chronic kidney disease, type 2 diabetes mellitus, and peripheral artery disease, than patients with a first (incident) ACS, and 90.6% were on LLT compared with 50.0% of those with an incident ACS. Patients with an incident ACS who were receiving LLT were older than those not on LLT and had a more severe medical history (Table 1).

Chronic non-LLT treatments being taken at hospital admission are detailed in Table 2. The rate of aspirin use was 37.0% overall (19.7% of patients received a P2Y₁₂ inhibitor), driven by higher rates among patients with recurrent ACS and, to a lesser extent, in patients with an incident ACS on LLT. The use of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers was higher in the population with a history of ACS and in patients with incident ACS on LLT.

Of the 468 patients, 260 (55.6%) were taking a statin, 40 (8.5%) were taking a non-statin LLT, and 191 (40.8%) were receiving no LLT at admission to hospital (Table 3). The most frequently taken statins were atorvastatin (35.4% of 260 patients on a statin) and rosuvastatin (32.7%). Ezetimibe (55.0% of 40 patients on non-statin LLT) was the most frequently taken non-statin LLT. The most common treatment at admission was statin monotherapy (50.6%); 4.3% were on combination LLT with a statin plus ezetimibe (Fig. 2A). Rates of use of statin monotherapy had increased to 91.4% at discharge. Use of statin plus ezetimibe did not change between admission (4.3%) and discharge (3.0%) (Fig. 2A).

### Table 3 Lipid-lowering treatments in patients with an ACS or with stable CHD.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACS patients</th>
<th>CHD patientsᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At admission (n = 468)</td>
<td>At discharge (n = 466)</td>
</tr>
<tr>
<td>No lipid-lowering therapy</td>
<td>191 (40.8)</td>
<td>14 (3.0)</td>
</tr>
<tr>
<td>Statin</td>
<td>260/468 (55.6)</td>
<td>450/466 (96.6)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>92 (35.4)</td>
<td>273 (60.7)</td>
</tr>
<tr>
<td>Dose potency, mg/day</td>
<td>40 (10, 40)</td>
<td>80 (40, 80)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>85 (32.7)</td>
<td>133 (29.6)</td>
</tr>
<tr>
<td>Dose potency, mg/day</td>
<td>10 (5, 20)</td>
<td>20 (10, 20)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>34 (13.1)</td>
<td>21 (4.7)</td>
</tr>
<tr>
<td>Dose potency, mg/day</td>
<td>20 (20, 20)</td>
<td>20 (20, 40)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>41 (15.8)</td>
<td>23 (5.1)</td>
</tr>
<tr>
<td>Dose potency, mg/day</td>
<td>20 (20, 20)</td>
<td>20 (20, 40)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.2)</td>
<td>—</td>
</tr>
<tr>
<td>Non-statin lipid-lowering treatment</td>
<td>40/468 (8.5)</td>
<td>26/466 (5.6)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>22 (55.0)</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Otherᵇ</td>
<td>18 (45.0)</td>
<td>10 (38.5)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%), median (interquartile range), or minimum, maximum. ACS: acute coronary syndromes; CHD: coronary heart disease.

ᵃ At time of latest lipid test.

ᵇ Omega 3 or fibrate.

**Figure 2.** A. LLT on hospital admission, at discharge and at 120-day follow-up in all ACS patients (data on non-statin LLT available in 466/468 patients at discharge). B. Intensity of statin treatment (mean statin dose calculated in atorvastatin dose equivalents) in ACS patients on admission, during hospitalization, at discharge and at 120-day follow-up. ACS: acute coronary syndrome; LLT: lipid-lowering therapy; mono: monotherapy.
Table 4  Lipid profile<sup>a</sup> and proportion of patients who achieved the 2011 ESC/EAS targets threshold values [4].

<table>
<thead>
<tr>
<th>Lipid profile (mmol/L)</th>
<th>ACS</th>
<th></th>
<th></th>
<th>Stable CHD</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ACS (n = 468)</td>
<td>Incident ACS (n = 362)</td>
<td>Recurrent ACS (n = 106)</td>
<td>All CHD (n = 436)</td>
<td>No LLT (n = 12)</td>
<td>LLT (n = 424)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No LLT (n = 181)</td>
<td>LLT (n = 181)</td>
<td>No LLT (n = 10)</td>
<td>LLT (n = 96)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.86 ± 1.12</td>
<td>3.49 ± 1.04</td>
<td>2.50 ± 0.97</td>
<td>3.66 ± 1.32</td>
<td>2.27 ± 0.87&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.26 ± 0.79</td>
<td>3.50 ± 0.63&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.74 ± 1.27</td>
<td>5.37 ± 1.22</td>
<td>4.41 ± 1.10</td>
<td>5.49 ± 1.47</td>
<td>4.09 ± 1.09&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.23 ± 0.92</td>
<td>5.49 ± 0.71&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.19 ± 0.37</td>
<td>1.21 ± 0.39</td>
<td>1.21 ± 0.33</td>
<td>1.21 ± 0.59</td>
<td>1.10 ± 0.34</td>
<td>1.28 ± 0.38</td>
<td>1.36 ± 0.29</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.50 (1.04, 2.03)</td>
<td>1.51 (1.03, 2.20)</td>
<td>1.40 (1.04, 1.85)</td>
<td>1.88 (1.51, 2.44)</td>
<td>1.54 (1.06, 2.05)</td>
<td>1.26 (0.90, 1.70)</td>
<td>1.15 (0.80, 1.66)</td>
</tr>
<tr>
<td>Non—HDL-C</td>
<td>3.58 ± 1.23</td>
<td>4.21 ± 1.17</td>
<td>3.20 ± 1.06</td>
<td>4.28 ± 1.27</td>
<td>3.02 ± 1.10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.95 ± 0.89</td>
<td>4.12 ± 0.80&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total cholesterol/HDL-C ratio</td>
<td>1.8</td>
<td>2.5</td>
<td>2.0</td>
<td>2.5</td>
<td>2.0</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>LDL-C &lt; 1.8 mmol/L (&lt; 70 mg/dL)</td>
<td>79 (16.9)</td>
<td>8 (4.4)</td>
<td>39 (21.5)</td>
<td>1 (10.0)</td>
<td>31 (32.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>124 (28.4)</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Distance to LDL-C &lt; 1.8 mmol/L (mmol/L)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.35 ± 0.99</td>
<td>1.78 ± 0.96</td>
<td>1.00 ± 0.86</td>
<td>2.10 ± 1.11</td>
<td>0.86 ± 0.75&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.80 ± 0.62</td>
<td>1.69 ± 0.63</td>
</tr>
<tr>
<td>LDL-C &lt; 2.5 mmol/L (&lt; 100 mg/dL)</td>
<td>215 (45.9)</td>
<td>37 (20.4)</td>
<td>111 (61.3)</td>
<td>2 (20.0)</td>
<td>65 (67.7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>295 (67.7)</td>
<td>1 (8.3)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Distance to LDL-C &lt; 2.5 mmol/L (mmol/L)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.10 ± 0.82</td>
<td>1.27 ± 0.81</td>
<td>0.87 ± 0.80</td>
<td>1.51 ± 1.03</td>
<td>0.72 ± 0.60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.57 ± 0.52</td>
<td>1.04 ± 0.48&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non—HDL-C &lt; 2.6 mmol/L (&lt; 100 mg/dL)</td>
<td>106/465 (22.8)</td>
<td>10/179 (5.6)</td>
<td>55 (30.4)</td>
<td>0</td>
<td>41/95 (43.2)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>161 (36.9)</td>
<td>1 (8.3)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation, median (interquartile range) or n (%). ACS: acute coronary syndrome; CHD: coronary heart disease; EAS: European Atherosclerosis Society; ESC: European Society of Cardiology; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy.  
<sup>a</sup> Lipid profile and lipid parameters measured within 24 hours of admission for an ACS event and at the time of latest lipid test for stable CHD.  
<sup>b</sup> P < 0.0001.  
<sup>c</sup> P < 0.05.  
<sup>d</sup> P < 0.01.  
<sup>e</sup> In patients who have not achieved the target.
Suboptimal patients, 49 equivalent a on goal follow-up dose of lipoprotein event (> and < value 70 <.

At follow-up statin 1.8 (<28 <1.8 mmol/L (25.3%) admission, LDL-C discharge, 3.3 mmol/L (70 mg/dL). Among patients with a recurrent ACS, a higher number had the LDL-C value of <1.8 mmol/L (70 mg/dL).

At hospital discharge, 96.6% (450/466) of patients were on statin therapy (Table 3), but nearly one-third (30.2%) of the patients were on ≤20 mg/day atorvastatin dose equivalent (Fig. 2B). The mean ± SD atorvastatin dose equivalent increased from 22±18 mg/day at admission to 49±28 mg/day at discharge (Fig. 2B).

Follow-up data at 120 days were available in 333 (71.2%) patients, at which time 95.1% (310/326 with data on medications) were still on statins. The mean ± SD atorvastatin dose equivalent decreased to 41±28 mg/day by the 120-day follow-up (Fig. 2B) and 50.6% (80/158) achieved the LDL-C goal (<1.8 mmol/L (70 mg/dL)) (Fig. 3A). The percentage of patients with LDL-C <1.8 mmol/L (70 mg/dL) had increased relative to those at admission in all subgroups, with the greatest improvement observed among patients with an incident ACS who were not on previous chronic LLT. Of the 136 patients on low-to-moderate-intensity statin treatment at discharge, 127 (93.4%) remained on this dose, compared with 183/314 (58.3%) patients remaining on high-intensity statin treatment.

**DYSIS II CHD**

In DYSIS II CHD, 436 patients with CHD were enrolled by 27 cardiologists and general practitioners in France during 2013 and 2014. Most patients (97.2%) were on chronic LLT at the time of the latest lipid test (Table 1). The use of chronic non-LLT treatments was high, particularly antihypertensive medications (97.5% of patients), with diuretics used in 27.3% of patients (Table 2). Oral antidiabetic drugs were used in 27.5% of patients. Aspirin was used in 80.2% of patients and a P2Y12 inhibitor in 39.2%.

Of the 424 patients on LLT, 404 (95.3%) were taking a statin and 75 (17.7%) were taking a non-statin LLT (Table 3). The most frequently used statin was atorvastatin (45.0% of 404 patients on statins), followed by rosuvastatin (25.5%); the most frequently used non-statin LLT was ezetimibe (77.3% of 75 patients on LLT). Eighty per cent of patients were on statin monotherapy and 10.3% were on statin plus ezetimibe (Fig. 4A). Only one-third (32.0%) of the patients were on ≥40 mg/day atorvastatin dose equivalent (Fig. 4B).

The mean ± SD LDL-C concentration at the time of the latest lipid test was 2.26 ± 0.79 mmol/L (87.4 ± 30.5 mg/dL), and was lower among patients on LLT (Table 4). Of the patients on LLT, 29.2% met the LDL-C

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**Figure 3.** Percentage of ACS patients with LDL-C value <1.8 mmol/L (<70 mg/dL) at admission for the index event and at 120 days according to: A. Chronic LLT at admission; and B. LLT treatment at admission. aWith LDL-C > 1.8 mmol/L (>70 mg/dL). ACS: acute coronary syndrome; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy.

At admission, 16.9% of patients had an LDL-C value of <1.8 mmol/L (70 mg/dL), driven primarily by the group on LLT (25.3%) (Fig. 3A, B; Table 4). Among patients with a recurrent ACS, a higher number had the LDL-C value of <1.8 mmol/L (70 mg/dL).

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**Figure 4.** A. LLT (n = 436) and B. Statin treatment in atorvastatin dose equivalents at time of latest lipid test in 403 patients with stable coronary heart disease. Atorva: atorvastatin; LLT: lipid-lowering therapy; mono: monotherapy.
rate of non-ST-elevation ACS than patients not taking statin therapy (44.8% vs 32.6%, respectively). While these data are unadjusted for differences in baseline characteristics, they support the hypothesis that chronic use of statins could alter the presentation of ACS, resulting in fewer ST-segment elevation myocardial infarctions, a smaller infarct size and a lower mortality [10—12].

Three-quarters of the patients with stable CHD had hypercholesterolaemia. A minority (28.4%) achieved the LDL-C treatment goal of <1.8 mmol/L (70 mg/dL). Most of the CHD patients were taking LLT, with four out of five patients receiving statin monotherapy, and 43.2% were on a low- or moderate-intensity dose. Of concern, one-quarter of the patients with CHD were being treated with rosuvastatin, which is not indicated for secondary prevention [13]. The mean LDL-C value in our population of stable CAD patients is marginally lower (2.26 ± 0.79 mmol/L vs 2.5 ± 0.8 mmol/L) than that reported in the multicentre CORONOR study [14], conducted between 2010 and 2011 in the Nord Pas-de-Calais administrative region of France and involving 4184 patients with stable CAD enrolled by cardiologists. In both this study and in the CORONOR study, the use of statins was very high (92.7% overall in DYSIS II vs 92% in CORONOR), and a similar percentage of patients achieved the LDL-C therapeutic target of <2.5 mmol/L (67.7% vs 70—71% in CORONOR).

The Lipid Treatment Assessment Project (L-TAP), conducted initially in the United States between 1996 and 1997, and subsequently in nine countries in 2006 to 2007, demonstrated improvements in the use of LLT in adult dyslipidaemic patients [15]. Overall, 73% of patients (75% of whom were on a statin, 8% on other LLT, and 16% on non-pharmacological LLT) achieved the national treatment goals in L-TAP 2, versus 38% in L-TAP, but this percentage decreased to 67% in high-risk patients (versus 18% in L-TAP). The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) surveys, which started in 1995—1996, have shown a large proportionate increase in the prescribing of LLT, most frequently statins, and a corresponding reduction in LDL-C in patients aged <80 years with CHD in Europe [16]. However, the surveys also revealed that most patients were not achieving the LDL-C treatment targets. In an analysis from EUROASPIRE IV of nearly 8000 patients (conducted between May 2012 and April 2013), 80.5% of the population had LDL-C ≥1.8 mmol/L despite the fact that 85.7% were on statin medication, and 65% of men and 55% of women had achieved the conservative target of <2.5 mmol/L [16]. In a further analysis from EUROASPIRE IV of adults aged ≤80 years with a first or recurrent CHD discharged from hospital, 90.4% were discharged on statin therapy (37.6% were on a high-intensity statin), but this figure had dropped to 86% by the follow-up interview (conducted at least 6 months after hospitalization), at which point 32.7% were still on a high-intensity statin [17]. Only 19.3% of the patients achieved an LDL-C value of <1.8 mmol/L at follow-up interview. In the 332 EUROASPIRE IV patients enrolled in France, 93.1% were discharged on a statin, which is similar to the rate of 96.6% in DYSIS II ACS. However, a greater proportion of patients in DYSIS II ACS were discharged on high-intensity statin therapy (69.8% vs 56.9%). This difference persisted at follow-up (59.0% vs 48.2% in EUROASPIRE IV), perhaps reflecting differences in the populations, geographical reach and durations.
of follow-up. Together, however, the findings from these studies clearly demonstrate the need for better lipid control through the use of more intensive or combination LLT.

Limitations

As an observational cohort study, this analysis is subject to several limitations, including missing data and loss to follow-up. While investigators were strongly encouraged to enrol consecutive patients to avoid selection bias, we are unable to verify to what extent this was achieved. Some of the subpopulations were small and the findings should be interpreted with caution. Patients who were lost to follow-up at 120 days (approximately one-quarter of the population) may have been less compliant with their LLT than patients who were available.

Conclusions

These data from DYSIS II highlight key areas for improvement in the primary and secondary prevention of CHD in France and better adherence to evidence-based clinical practice guidelines. A sizable proportion of patients without a history of CHD — but who are at very high risk of an ischaemic event — do not receive LLT. Among patients with CHD, higher intensity LLT, or a combination of a statin and a non-statin LLT, is needed to increase the achievement of LDL-C treatment targets and reduce the risk of morbidity and mortality.

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Sophie Rushton-Smith, PhD (MedLink Healthcare Communications Ltd, UK) provided writing support and was funded by the sponsors.

Disclosure of interest

J. F. Received honoraria from Aegerion, Amgen, Merck, and Sanofi.
A.K.G. Received research support and honoraria for lectures from a number of pharmaceutical companies producing lipid-lowering drugs including Merck & Co., Inc., the sponsor of this study.

Appendix A. DYSIS II French Investigators

DYSIS II ACS (24 centres):

- Linda Aissou, hôpital Avicenne, Bobigny;
- Franck Albert, centre hospitalier Louis-Pasteur, Le Coudray;
- Denis Angoulvant, CHR Tours, Tours;
- Emmanuel Boiffard, centre hospitalier départemental Vendée Site de la Roche, La-Roche-Sur-Yon;
- Yves Cottin, hôpital du Bocage central, Dijon cedex;
- Nicolas Delarche, centre hospitalier de Pau, Pau;
- Raphaële Arrouasse, Philippe Le Corvoisier, hôpital Henri-Mondor, Creteil;
- Emile Ferrari, Hôpital Pasteur, Nice;
- Alain Furber, CHU d’Angers, Angers;
- Sylvain Ranc, Centre Hospitalier Saint-Joseph Saint-Luc, Lyon;
- Michel Galinier, hôpital Rangueil - pôle cardiovasculaire et Toulouse;
- Jean-Louis Georges, centre hospitalier de Versailles, Le Chesnay;
- Christophe Piot, clinique Millenara, Montpellier;
- Florence Leclercq, hôpital Arnaud-de-Villeneuve, Montpellier;
- Thierry Lefevre, institut Jacques-Cartier, Massy;
- Marc Goralski, CHR De La Source, BP 6709, Orleans;
- Gilles Levy, clinique du Millenaire, Montpellier;
- Nicolas Mansencal, hôpital Ambroise-Pare, Boulogne-Billancourt;
- Franck Paganelli, hôpital Nord—Pavillon Mistral, Marseille;
- François, Paillard, CHU de Rennes—hôpital Pontchaillou, Rennes;
- Patrick Peycher, clinique Axiom, Aix-en-Provence;
- Gilles Rouault, hôpital Laennec—site de Quimper, Quimper;
- François Schiele, CHU Besançon—hôpital Jean-Minjoz, Besançon;
- Jacques Berland, clinique Saint-Hilaire, Rouen.

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- Philippe Boisson, Bedoin;
- Loic Boucher, cabinet médical, Murs Erigne;
- Alain Rostane, Velizy-Villacoublay;
- Jean Ferrieres, CHU Rangueil, Toulouse;
- Adib Dabboura, cabinet médical, Villefranche-sur-Saone;
- Bernard Doucet, cabinet médical, Chambery;
- Christian Duray, cabinet médical, Laval;
- Dominique Edet, Bretteville L’orgueil;
- Ghazaleh Esna Ashari, cabinet médical, Rambouillet;
- Jean Philippe Fleury, Velines;
- Daniel Gombaud, cabinet médical, Angers;
- Yves Bermond, Vannes;
- Roland Greffe, Firminy;
- Macario Sorrias, Sete;
- Patrick Leprince, cabinet médical, Tours;
- Jean-Louis Long, cabinet médical, Vichy;
- Benoouda Mahdjoub, cabinet médical, Thouars;
- Hamid Makki, cabinet médical, Chatillon-Sur-Seine;
- Denis Marin, cabinet médical, Briollay;
- Christophe Marocco, Les-Pennes-Mirabeau;
- Jean-Luc Mougeolle, cabinet médical, Sedan;
- Philippe Mureau, cabinet médical, Belabre;
- Philippe Remaud, cabinet médical, Angers;
- Dominique Renard, cabinet médical, Calvi;
References


