3ST-POL trial: standards of statin use in Poland in the context of the European Society of Cardiology guidelines

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ABSTRACT

INTRODUCTION Statins play a crucial role in modern cardiological pharmacotherapy. For the patient, as the beneficiary of an effective pharmacotherapy, it is of utmost importance that his or her physician can take maximum advantage of the whole potential of the available medications.

OBJECTIVES The aim of the study was to analyse the effectiveness of statin treatment in Polish patients treated in an ambulatory setting, in view of the European Society of Cardiology guidelines.

PATIENTS AND METHODS The study was conducted on 49,950 ambulatory patients from Poland (women – 53%, men – 47%). The questionnaire consisted of 43 questions and was completed by a physician based on the results of physical examination, medical records, lipid profile, and additional tests. Twenty-eight per cent of the patients were obese, 37% were overweight, and more than 26% were smokers. The mean blood pressure was 142.9/84.0 mmHg (± 18.5/11.6 mmHg). The target objectives of the pharmacological treatment of arterial hypertension were achieved in less than 25% of the study population. Nearly 50% of the patients had coronary artery disease, 20% had myocardial infarction, and 10% had transient ischemic attack or cerebral stroke. More than 30% of the patients had diabetes mellitus.

RESULTS The most commonly used statins were atorvastatin and simvastatin (49.1% vs. 44.8%, respectively; P < 0.05). Almost 71% of the patients received the daily statin dose of <20 mg. Mean total cholesterol (TC) was 244.9 mg/dl, low-density lipoprotein (LDL) cholesterol – 155 mg/dl, and triglycerides – 180 mg/dl. TC levels of <190 mg/dl were achieved in 1 in 6 patients, and LDL levels of <115 mg/dl in less than 21% of the patients.

CONCLUSIONS Despite the recommendation to administer statins at higher than minimum doses in primary and secondary prevention of coronary heart disease, this drug class is still underestimated by general practitioners.

KEY WORDS atherosclerosis, dyslipidemia, hyperlipemia, ischemic heart disease, pharmacoeconomics
that a properly adjusted statin dose reduces not only low-density lipoprotein (LDL) cholesterol but also the C-reactive protein (CRP) levels, and, as demonstrated by the JUPITER study,\(^2\) it is crucial for reducing the risk of cardiovascular events. In addition, it is associated with a reduction in CRP levels in patients who have achieved the desired LDL levels. The usefulness of statins is also indicated in the primary prevention of cardiac diseases, particularly in individuals with familial genetic predisposition.

In terms of pharmacoeconomy, an effective statin treatment, combined with hypotensive and antinicotine therapies, can significantly reduce the number of cardiovascular complications. Furthermore, it may also reduce the number of patient visits, hospitalizations, and percutaneous transluminal coronary interventions.

The role of statins in modern pharmacology cannot be undermined. Their history began in the 1970s with the synthesis of mevastatin by a Japanese scientist, Akira Endo. The 1990s witnessed a real revolution in statin research. Initially, the inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) were known as agents lowering cholesterol levels, precisely the LDL cholesterol fraction, but subsequent research demonstrated the pleiotropic effects of statins.

The aim of our study was to analyze the efficacy of statin treatment in an outpatient setting in Poland, in view of the 2007 ESC guidelines, considering the limited number of reports demonstrating the effectiveness of this therapeutic approach to dyslipidemia.

**PATIENTS AND METHODS** The 3ST-POL study was conducted on 49,950 Polish patients (women – 53%, men – 47%) aged 59.4 ±10.8 years, scheduled to undergo a medical examination in order to modify their treatment regimen for arterial hypertension and dyslipidemia. In the studied group, 28% of patients were obese, over 37% were overweight, and 26.5% were smokers.

The mean blood pressure (BP), measured with the traditional method, was 142.9/84.0 mmHg (±18.5/11.6 mmHg) with the administration of 1.96 hypotensive drugs. The recommended BP values were achieved in approx. 25% of the examined individuals. One in 2 patients had ischemic heart disease, 1 in 5 experienced a cardiovascular event, while 1 in 10 had a history of transient ischemic attack or stroke. One in 3 patients received treatment for diabetes (TABLE 2).\(^3\)

The highest percentage of the studied patients came from the Silesian and Mazovian Provinces (14.8% and 14.2%, respectively), and the lowest (2.4%) from the Świętokrzyskie and Opole Provinces.

The study was conducted in the form of a survey. Patients were treated by general practitioners (38,805; 77.7%), cardiologists (7859; 15.7%), and diabetes specialists (2498; 5%). All patients participating in the study had their heart rate, BP, weight, height, waist circumference, and lipid profile monitored. The obtained values were entered into the Microsoft Office Excel 2007 spreadsheet. Statistical analysis was performed using the Microsoft Office Excel 2007 software. The Pearson’s \(\chi^2\) test and Fisher’s exact test were used to analyze the results.

**RESULTS** Statin administration In ¾ of the examined patients, the diagnosis of dyslipidemia was made during the 12 months prior to the study, while ¾ of all patients had been treated with statins for less than a year (TABLE 3). The most commonly administered statins were atorvastatin and simvastatin (49.1% vs. 44.8%, respectively;
significant difference between the doses of the 2 most commonly used statins in the group of patients who achieved the desired LDL levels as well as in subjects with LDL levels exceeding the recommended values. This was true for both the general population (TABLE 5) and patients with a history of a vascular event (TABLE 6).

**DISCUSSION** Nowadays, it is possible to identify the risk factors for cardiovascular diseases, and the pharmacological treatment options are safe, cheap, convenient, and widely available. Statins are recommended by all the leading societies of cardiology worldwide for the primary and secondary prevention of coronary artery disease. Hyperlipidemia as well as arterial hypertension and diabetes are independent cardiovascular risk factors. The reports published by the World Health Organization (WHO) in 2002 indicated that hypercholesterolemia accounted for 8% of all diseases in the developed countries, including 56% of coronary events and 18% of strokes. In order to reduce the risk of cardiovascular events associated with coronary heart disease by 20%, plasma LDL levels should be reduced by 1 mmol/l (38.5 mg/dl).

The international WHO MONICA project demonstrated that dyslipidemia affected 8% to 53% of men (Russia and Switzerland) and 15% to 40% of women (Russia and Lithuania). As indicated by the Polish scientists participating in the MONICA project, elevated TC and LDL cholesterol levels were lower than 190 mg/dl, while in 3 in 5 patients, the LDL levels were lower than 115 mg/dl (FIGURE 1).

The target serum LDL levels was achieved only in a small percentage of the general population or high cardiovascular risk subpopulation (FIGURE 2). Despite the above, in both these groups as well as in patients with serum LDL levels above the recommended values, no significant increase in the statin dose was introduced. There was no significant difference between the doses of the 2 most commonly used statins in the group of patients who achieved the desired LDL levels as well as in subjects with LDL levels exceeding the recommended values. This was true for both the general population (TABLE 5) and patients with a history of a vascular event (TABLE 6).

**TABLE 4** Administered statins according to their type and dose

<table>
<thead>
<tr>
<th>Type of statin international name</th>
<th>%</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>49.1</td>
<td>17.6</td>
<td>63.4</td>
<td>18.0</td>
<td>0.8</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>3.1</td>
<td>42.5</td>
<td>43.7</td>
<td>10.7</td>
<td>1.0</td>
</tr>
<tr>
<td>lovastatin</td>
<td>2.4</td>
<td>16.7</td>
<td>59.9</td>
<td>20.7</td>
<td>1.8</td>
</tr>
<tr>
<td>pravastatin</td>
<td>0.6</td>
<td>7.6</td>
<td>39.7</td>
<td>34.4</td>
<td>12.2</td>
</tr>
<tr>
<td>simvastatin</td>
<td>44.8</td>
<td>5.4</td>
<td>65.9</td>
<td>26.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

P <0.05); other agents from this class were used only in 1 in 20 patients.

In 81% of the patients treated with atorvastatin and almost 71% of those receiving simvastatin, the dose used did not exceed 20 mg daily (TABLE 4). The average dose of atorvastatin was 20.86 mg daily, and simvastatin – 24.5 mg daily.

**The effects of treatment** The median total cholesterol (TC) levels were 244.9 mg/dl, LDL – 155 mg/dl, and triglyceride – 180 mg/dl. In 1 in 6 patients, TC levels were lower than 190 mg/dl, while in 1 in 5 patients, the LDL levels were lower than 115 mg/dl (FIGURE 1).

The target serum LDL levels was achieved only in a small percentage of the general population or high cardiovascular risk subpopulation (FIGURE 2). Despite the above, in both these groups as well as in patients with serum LDL levels above the recommended values, no significant increase in the statin dose was introduced. There was no significant difference between the doses of the 2 most commonly used statins in the group of patients who achieved the desired LDL levels as well as in subjects with LDL levels exceeding the recommended values. This was true for both the general population (TABLE 5) and patients with a history of a vascular event (TABLE 6).

**FIGURE 1** A Percentage of patients with recommended levels of particular lipid fractions, B Percentage of women with recommended levels of particular lipid fractions, C Percentage of men with recommended levels of particular lipid fractions

Abbreviations: see TABLE 1

**FIGURE 2** A Percentage of patients with recommended levels of particular lipid fractions among patients after vascular incident (myocardial infarction or transient ischemic attack) or/influenced by type 2 diabetes, B Percentage of women with recommended levels of particular lipid fractions, C Percentage of men with recommended levels of particular lipid fractions

Abbreviations: see TABLE 1
levels are observed in nearly 7 of 10 adults. An epidemiological program conducted in Poland, the Cracovian Program for Secondary Prevention of Ischaemic Heart Disease, provided similar results. High cholesterol (>200 mg/dl) was observed in 71.7% of the examined patients, and the elevated levels of other lipid fractions were also frequently noted.

As evidenced by the EUROASPIRE II survey (European Action on Secondary Prevention through Intervention to Reduce Events), conducted in clinical centers and concerning patients undergoing pharmacotherapy, the treatment of hyperlipidemia appeared to be successful in 51% of the examined cases. However, in a British study involving patients on statin treatment, the recommended levels of individual cholesterol fractions had not been achieved: 27.4% – LDL, 68.2% – high-density lipoprotein (HDL), 57.6% – TG, as evidenced by the treatment results reported by British general practitioners.

In the 3ST-POL study, cholesterol levels above 190 mg/dl were observed in 1 in 6 patients, while LDL below 115 mg/dl – in 1 in 5 patients. In the whole group, the levels of TC, and particularly the LDL fraction (155 mg/dl), exceeded those included in the ESC guidelines (115 mg/dl). It is also worth noting that only 20% of the individuals undergoing outpatient dyslipidemia treatment, LDL cholesterol levels were lower than 115 mg/dl. Similar findings have been reported by the POLKARD-SPOK investigators who examined the efficacy of treatment in an outpatient setting in patients at a higher risk for cardiovascular events. The levels of TC below 175 mg/dl and LDL below 115 mg/dl were achieved in 1 in 10 patients (9.84%) with coronary artery disease. In the 3ST-POL study, similar values were observed for TC, while the maintenance of LDL below 100 mg/dl proved to be more effective (11.6% vs. 15.64% in POLKARD-SPOK and 3ST-POL, respectively).

The results of the study conducted by Cooney et al. on a population of more than 100,000 healthy individuals from 7 European countries have indicated that low HDL levels are an independent risk factor for death due to cardiac diseases. Moreover, it has been shown that the protective effects of the HDL fraction are more strongly marked in women than in men. In the 3ST-POL study, over 50% of all patients achieved the recommended HDL values. Notably, they were lower in women than in men (64.2% vs. 72%, respectively; FIGURE 1A and 1B), and a similar trend was observed in patients suffering from cardiovascular diseases (FIGURE 2A and 2B).

The results of the 3ST-POL study have shown that atorvastatin (49%) and simvastatin (44.8%) were the most often administered medicines, while the contribution of other drugs proved insignificant. The applied dose regimen in the case of both of the above agents was found to be approx. 4-fold smaller than the maximum recommended doses and amounted to ≤20 mg daily in 70% of the examined patients. The hypolipidemic effects of statins have been described by Roberts as following the rule that each doubling of a statin dose results in the lowering of LDL cholesterol and TC levels by 7% and 5%, respectively. However, in view of the fact that statins exert numerous effects on the human body, the efficacy of HMG-CoA reductase inhibitor treatment cannot be evaluated solely on the basis of cholesterol level lowering. The benefits from statin use in patients after acute coronary event have been confirmed by the PROVE-IT study. The endpoint occurrence rate was reduced by 16% in the group of patients receiving atorvastatin at a dose of 80 mg daily and pravastatin at a dose of 40 mg daily. It should also be noted that among 2099 patients taking atorvastatin, no single case of rhabdomyolysis was detected. The TNT (Treating to New Targets) study has demonstrated that administration of maximum statin doses (atorvastatin at 80 mg daily vs. 10 mg daily) statistically significantly lowers the risk of death due to a cardiovascular event. It has also been observed that hypolipidemic therapy results in a reduction of the risk of cardiovascular events in primary and secondary prevention as well as in a reduction of endpoint occurrence rates. Similar findings have been reported by the Cholesterol Treatment Trialists analysis of statins as safe and easily dosed medicines. Notably, the incidence rate of serious complications due to statin administration is smaller than in the case of the commonly used acetylsalicylic acid.

Promising results have been delivered by the JUPITER trial examining rosuvastatin vs. placebo and showing, in the statin group, a reduction by 50% in the occurrence of primary endpoints.
TABLE 6 Percentage of patients correctly and incorrectly treated, average doses of the two of the most commonly used statins in patients after a cardiovascular event (myocardial infarction or transient ischemic attack) or diagnosed with type 2 diabetes and/or cardiovascular disease

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>LDL</th>
<th>TG</th>
<th>HDL, women</th>
<th>HDL, men</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>9.8</td>
<td>90.2</td>
<td>15.6</td>
<td>58.6</td>
<td>67.2</td>
</tr>
<tr>
<td>average dose</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: see TABLE 1

among the patients with baseline LDL cholesterol below 130 mg/dl and CRP above 2. It should also be emphasized that in 50% of all the enrolled patients, the lowering of LDL levels from 108 mg/dl to 55 mg/dl after treatment was observed. Due to the study design, it cannot be stated to what degree the reduction in cardiovascular events results from the lowering of LDL levels and not from the anti-inflammatory effect of statins. Nevertheless, the JUPITER study has demonstrated that statins play a significant role in the primary prevention of cardiovascular diseases.

In terms of future advances in cardiological pharmacotherapy, a polypill (one pill containing hypotensive drugs, statins, acetylsalicylic acid, and folic acid) seems to be an interesting option, as demonstrated by POLYCAP.15 The trial showed a 62% reduction in the incidence of heart diseases and 48% in the incidence of strokes. It is estimated that a monthly cost of such therapy is 1 United States dollar, thus indicating it as a more efficient solution as far as pharmacoeconomy is concerned.

Limitations The 3ST-POL study has a number of limitations. Due to the lack of lipid profile results obtained prior to statin administration, the efficacy of this drug class in patient treatment cannot be fully estimated. The results presented in this report show the overall therapeutic effectiveness in patients with dyslipidemia. However, the study does not provide specific data on the patients’ compliance with physicians’ recommendations.

Conclusions In terms of the benefits for the patient, it should be of paramount importance for the general practitioners to be able to take full advantage of the whole potential of the available therapeutic agents.

The findings of the 3ST-POL study presented in this report can be summarized as follows are summarized below: hypolipidemic treatment is not satisfactory; statins are administered in inadequate doses and are still underestimated by physicians, despite strong indications for their use at higher doses than minimum, which helps achieve lower TC and LDL cholesterol levels, and despite clear benefits from their use in the primary and secondary prevention of ischemic heart disease. The study presented here demonstrates a significant therapeutic potential of statins and indicates how they can be used for the benefit of patients.

Currently, a continuation of the 3ST-POL study is being prepared. It should enable a detailed analysis of the factors limiting statin prescription rate in Poland, as well as help design an educational program for general practitioners in Poland.

REFERENCES

ARTYKUŁ ORYGINALNY

Badanie 3ST-POL: stosowanie statyn w Polsce na tle wytycznych Europejskiego Towarzystwa Kardiologicznego

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SŁOWA KLUCZOWE
choroba niedokrwienna serca, dyslipidemia, farmakoekonomika, hiperlipemia, miażdżyca

STRESZCZENIE

Wprowadzenie Statyny odgrywają ważną rolę w nowoczesnej farmakoterapii kardiologicznej. Dla pacjenta, jako głównego beneficienta korzyści płynących z efektywnej farmakoterapii, najważniejsze jest, aby jego lekarz potrafił w pełni wykorzystać potencjał leków, którymi dysponuje.

Celem badania była analiza efektywności leczenia statynami w populacji polskich pacjentów leczonych ambulatoryjnie, na tle wytycznych Europejskiego Towarzystwa Kardiologicznego.

Pacjenci i metody W badaniu wzięło udział 49 950 pacjentów objętych w Polsce ambulatoryjną opieką medyczną (kobiety – 53%, mężczyźni – 47%). Ankiety, składające się z 43 pytań, wypełniał lekarz prowadzący na podstawie badania fizykalnego, historii choroby, wyników pełnego lipidogramu oraz innych badań laboratoryjnych. W całej grupie badanych 28% było otyłych, 37% miało nadwagę, >26% palo tytoń. Średnie ciśnienie tętnicze wyniosło 142,9 mm Hg/84,0 mm Hg (±18,5/11,6 mm Hg). U <25% populacji osiągnięto cele terapeutyczne w leczeniu nadciśnienia tętniczego. Blisko 50% pacjentów miało zdiagnozowaną chorobę niedokrwienną serca, 20% przeżyło zawał serca, 10% – przemijający atak niedokrwienny lub udar mózgu. Ponad 30% chorowało na cukrzycę.

 Wyniki Najczęściej stosowanymi statynami były atorwastatyna oraz simwastatyna (49,1% vs 44,8% P <0,05). Blisko 71% pacjentów zażywało statynę w dawce <20 mg/dobę. Średni poziom cholesterolu całkowitego wynosił 244,9 mg/dl, lipoprotein a małej gęstości (low-density lipoprotein – LDL) – 155 mg/dl, triglicerydów – 180 mg/dl. Poziom cholesterolu całkowitego <190 mg/dl osiągano u co szóstego pacjenta, a LDL <115mg/dl – u mniej niż 21% badanych.

Wnioski Pomimo zaleceń stosowania większych niż minimalne dawek statyn w prewencji pierwotnej i wtórnej choroby niedokrwiennej serca, leki z tej grupy są wciąż niedoceniane przez lekarzy opieki ambulatoryjnej.