Comparative Analysis of the Use of Lipid Modifying Agents in the Republic of Serbia and Nordic Countries in the Period 2015-2017

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SUMMARY

Introduction: Cardiovascular diseases are the leading cause of death both in Serbia and in the rest of the world. It has been shown that as many as 80% of them are preventable. Control of serum lipid levels is one of the most important tasks of cardiovascular diseases prevention.

Aim: The aim of the study was to analyze the use of serum lipid-modifying drugs in Serbia, Norway and Finland in the period 2015-2017.

Methods: Data on drugs use during 2015, 2016 and 2017 were taken from the official websites of national drug regulatory authorities: the Serbian Medicines and Medical Devices Agency, the Norwegian Institute of Public Health and the Finnish Medicines Agency. Use was expressed as DDD/1000 inhabitants/day according to the Anatomical Therapeutic Chemical classification.

Results: The share of drugs used for treatment of cardiovascular diseases in total drugs use was the largest in all three countries during the observed period. The use of lipid-modifying agents was 3-4 times lower in Serbia than in Norway or Finland. Of all lipid-modifying drugs, statins are most commonly prescribed in all three countries. Atorvastatin and rosuvastatin are the most widely used in Serbia, and simvastatin and atorvastatin in Norway and Finland.

Conclusions: Use of lipid-modifying drugs in Serbia is lower than in Norway and Finland, but it is constantly increasing. This use in Serbia still represents the smallest share of all drugs for the treatment of cardiovascular diseases.

Keywords: Cardiovascular Disease Prevention, Hypolipidemic Agents, Statins, Fibrates
INTRODUCTION

According to the World Health Organization (WHO), cardiovascular diseases (CVD) are the leading cause of death in the world. In 2016, 17.9 million deaths from CVD were recorded, which represents 31% of the total mortality in the world [1]. WHO data on the European region show that CVD are the cause of more than a half of deaths [2]. Similar data were also recorded in Serbia, where CVD were the cause of 51.8% of deaths of all causes in 2018. However, a decrease of 4.5% in women and 1.7% in men in the mortality rate due to CVD was noted in Serbia in the period from 2009 to 2018, although in the same period an increase in the general mortality rate was also observed [3].

Even though CVD are the dominant cause of death in modern times it can be prevented in as many as 80% of cases. Prevention of CVD means eliminating or reducing risk factors, and it is believed that decreasing of cholesterol level, smoking prevalence and blood pressure level can have the greatest benefits [2]. It is estimated that these three risk factors are responsible for the development of 75% of all CVD in the world [4].

Hyperlipoproteinemias (HLPs) are metabolic disorders of increased blood lipid levels. The positive effects of lowering blood lipid levels on the occurrence of CVD are well documented. Small changes in lipid levels have a major impact on health. An increase in total cholesterol by 1% increases the risk of developing ischemic heart disease by 2-3%. It has also been shown that only by reducing low-density lipoproteins (LDL), mortality and morbidity from ischemic heart disease can be reduced by 40% [4]. This is the precise reason why the treatment of HLPs is the most important tasks of CVD prevention.

There are several classes of drugs used as monotherapy or, if necessary, in combination for the treatment of HLP. The most important groups of hypolipidemic drugs are: 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), fibrates, anionic-exchange resins, nicotinic acid and cholesterol absorption inhibitors [4]. Numerous randomized studies have shown that the use of statins reduces cardiovascular risk. Statins cause a reduction in serum total cholesterol level and a reduction in the risk of major adverse cardiovascular events in various patients, for example those with high and low risk, both women and men, younger and older [5-10]. Despite all this knowledge, serum cholesterol-lowering therapy is insufficiently used in the population of patients with high risk of heart attack and CVD. In the PURE study that included 22 countries in 2016, 66% of people aged 35 years – 70 years with CVD use statins in high-income countries (Sweden and Canada), 27% in middle-income countries (Poland, Turkey and Brazil) and about 5% in low-income countries (China and India) [11,12]. In the SHARE study in 2013, only 42% of people over the age of 50 years with previous CVD taking serum cholesterol-lowering therapy with large variations between different countries (55% - 56% in Belgium, Denmark and Norway; 27% - 29% in Estonia and Slovenia) [11,13]. The study examining the use of hypolipidemic drugs in Serbia in the period 2004-2008 showed that their use is 6 - 8 times lower than in the Scandinavian countries. An inversely proportional relationship between the use of this group of drugs and CVD mortality was also observed [14]. Insufficient use of hypolipidemic drugs can cause a high incidence of CVD and complications associated with CVD, which includes and a high mortality rate [15 - 17].

AIM

The aims of this study were:
1. An analysis of the use of drugs in the treatment of HLPs in the Republic of Serbia during 2015, 2016 and 2017.
2. When comparing the use of the same drugs between Republic of Serbia and the Kingdom of Norway and the Republic of Finland, two countries that have well-developed pharma-cotherapeutic practices, in the mentioned period.

METHODS

The analysis was designed as a comparative, pharmaco-economic, retrospective, time series study. Data on drugs use during 2015, 2016 and 2017 were observed. Drugs use data in the Republic of Serbia were taken from the official website of the Medicines and Medical Devices Agency of Serbia (ALIMS) [18-20]. Drugs use data in the Kingdom of Norway
were downloaded from the official website of the Norwegian Institute of Public Health (NIPH) [21]. Drugs use data in the Republic of Finland were downloaded from the official website of the Finnish Medicines Agency (FIMEA) [22].

Use of drugs is calculated by the methodology of Defined Daily Doses (DDD) according to the Anatomical Therapeutic Chemical (ATC) classification. DDD is a statistical unit of measure of drug use, the value of which represents the average daily dose of drug use in an adult and does not depend on the price, dosage form and packaging size of the drug. The number of DDD per 1000 inhabitants per day (DDD/1000 inh/day) provides an insight into how many inhabitants (from 1000) used a certain drug and were exposed to its action during the day. Evaluation of drug use over time at the national and international levels has been simplified and improved through the use of DDD [23].

RESULTS

Use of ATC group C drugs is most dominant in all three countries, during three years of observation. The share of use of lipid-modifying agents (C10) in ATC group C has a growth trend during the observed period in all countries. However, the use of ATC group C10 drugs was 3-4 times lower in Serbia than in Norway or Finland. By far the most common C10 representatives were monocomponent statins (C10AA) in all countries during the entire observation period. These data are shown in Table 1.

The share of hypolipidemic drugs in the use of all drugs from group C can be seen in the example from 2017. During 2017, the

Table 1. Use of drugs from selected ATC groups expressed in DDD/1000 inh/day and percentages (%) in Serbia, Norway and Finland during 2015, 2016 and 2017

| ATC group | DDD/1000 inh/day | Serbia | Norway | Finland |
|-----------|------------------|--------|--------|---------|
| C9        | 2015             |        |        |         |
| C         | 1609.01          | 701.41 (43.59) | 417.74 (30.73) | 557.75 (31.34) |
| C10       | 37.53 (5.35)     | 128.92 (30.86) | 105.41 (18.90) |
| C10AA     | 34.29 (91.37)    | 123.20 (95.56) | 101.35 (96.15) |
| C10       | 2016             | 635.12 (39.25) | 421.08 (31.31) | 105.77 (19.02) |
| C10       | 35.27 (5.55)     | 131.84 (31.31) | 101.27 (95.74) |
| C10AA     | 31.44 (89.14)    | 124.50 (94.43) | 107.64 (95.60) |
| C10       | 2017             | 624.32 (41.09) | 424.49 (30.27) | 568.49 (31.78) |
| C10       | 38.59 (6.18)     | 135.56 (31.93) | 112.63 (19.81) |
| C10AA     | 34.56 (89.56)    | 127.17 (93.81) | 107.64 (95.60) |

Table 2. Distribution of drug use in group C expressed as DDD/1000 inh/day and as a percentages for 2017 between the three observed countries

| ATC group | DDD/1000 inh/day | Serbia | Norway | Finland |
|-----------|------------------|--------|--------|---------|
| C         | 624.32           | 100.00 | 100.00 | 100.00 |
| C01       | 50.41            | 8.07   | 2.36   | 2.67    |
| C02       | 2.01             | 0.32   | 0.94   | 0.52    |
| C03       | 33.03            | 5.29   | 7.54   | 9.09    |
| C04       | 3.22             | 0.52   | 0.07   | 0.11    |
| C07       | 67.01            | 10.73  | 8.18   | 11.14   |
| C08       | 82.70            | 13.25  | 13.65  | 14.37   |
| C09       | 347.35           | 55.64  | 35.37  | 42.37   |
| C10       | 38.59            | 6.18   | 31.93  | 19.81   |
total use of hypolipidemic drugs in the territory of the Republic of Serbia amounted to 38.59 DDD/1000 inh/day (6.18%) and was in fifth place in terms of use of drugs in group C. In the Kingdom of Norway and the Republic of Finland, hypolipidemic drugs are much more represented in the total use of drugs for the treatment of CVD. In the Kingdom of Norway, in 2017, the use of hypolipidemic drugs amounted to 135.56 DDD/1000 inh/day (31.93%) and was in second place in terms of use of drugs in group C. In the Kingdom of Norway and the Republic of Finland, hypolipidemic drugs are much more represented in the total use of drugs for the treatment of CVD. In the Kingdom of Norway, in 2017, the use of hypolipidemic drugs amounted to 135.56 DDD/1000 inh/day (31.93%) and was in second place in terms of use of drugs in group C. In the Kingdom of Norway, in 2017, the use of hypolipidemic drugs amounted to 135.56 DDD/1000 inh/day (31.93%) and was in second place in terms of use of drugs in group C. In the Kingdom of Norway, in 2017, the use of hypolipidemic drugs amounted to 135.56 DDD/1000 inh/day (31.93%) and was in second place in terms of use of drugs in group C. In the Kingdom of Norway, in 2017, the use of hypolipidemic drugs amounted to 135.56 DDD/1000 inh/day (31.93%) and was in second place in terms of use of drugs in group C. In the Kingdom of Norway, in 2017, the use of hypolipidemic drugs amounted to 135.56 DDD/1000 inh/day (31.93%) and was in second place in terms of use of drugs in group C. In the Kingdom of Norway, in 2017, the use of hypolipidemic drugs amounted to 135.56 DDD/1000 inh/day (31.93%) and was in second place in terms of use of drugs in group C. In the Kingdom of Norway, in 2017, the use of hypolipidemic drugs amounted to 135.56 DDD/1000 inh/day (31.93%) and was in second place in terms of use of drugs in group C.

In the Republic of Serbia, in the observed period, statins (C10AA) recorded a share of 91.37% in 2015, 89.47% in 2016 and 90.31% in 2017 of the total use of hypolipidemic drugs (C10A). During the same period, the share of statins in the Kingdom of Norway and the Republic of Finland accounted for over 95% of total hypolipidemic drugs use. Statin use in the Kingdom of Norway and the Republic of Finland shows a slight positive trend of several DDD/1000 inh/day, but is present from year to year. In the Republic of Serbia, among the statins, the three most used drugs are atorvastatin, rosuvastatin and simvastatin. Use of simvastatin in the Republic of Serbia during the observed period is quite low and this drug is in third place in terms of statin use. The most used drug from the group of statins in the Republic of Serbia during the observed three years was atorvastatin. Use of atorvastatin in the Kingdom of Norway shows a positive trend. Use of simvastatin in the Kingdom of Norway during the observed period recorded a negative trend, although this drug is in the second place in terms of statin use during all three observed years. Use of rosuvastatin in the Kingdom of Norway during the observed period recorded a fairly low level (about 4% of total use of hy-

| Country          | Republic of Serbia                                      |
|------------------|--------------------------------------------------------|
| **ATC group**    | **2015** | **2016** | **2017** |
| C10A             | 37.53   | 100.00  | 35.14   |
| C10AA            | 34.29   | 91.37   | 31.44   |
| C10AA01          | 3.37    | 8.98    | 3.41    |
| C10AA02          | -       | -       | -       |
| C10AA03          | 1.47    | 3.92    | 1.30    |
| C10AA04          | -       | -       | -       |
| C10AA05          | 20.98   | 55.90   | 16.25   |
| C10AA07          | 8.47    | 22.57   | 10.48   |
| C10AB            | 3.24    | 8.63    | 3.70    |
| C10AB02          | -       | -       | -       |
| C10AB04          | -       | -       | -       |
| C10AB05          | 2.60    | 6.93    | 3.15    |
| C10AB08          | 0.64    | 1.71    | 0.55    |
| C10AC            | 0.00    | 0.00    | 0.00    |
| C10AC01          | -       | -       | -       |
| C10AC02          | -       | -       | -       |
| C10AC04          | -       | -       | -       |
| C10AX            | -       | -       | 0.01    |
| C10AX06          | -       | -       | 0.01    |
| C10AX09          | -       | -       | 0.01    |
| C10AX14          | -       | -       | -       |
| C10AX15          | -       | -       | -       |
to the group of other hypolipidemic drugs (group C10AX). It is used as monotherapy or in a fixed combination with simvastatin. Its use in the Republic of Serbia during the observed three years was not registered. In the Kingdom of Norway, ezetimibe use in 2015 was 3.98 DDD/1000 inh/day or 3.11%, in 2016 4.45 DDD/1000 inh/day or 3.43% and in 2017 it was 4.91 DDD/1000 inh/day or 3.69% of total hypolipidemic drugs use. A similar situation, when it comes to the use of ezetimibe, is in the Republic of Finland. Ezetimibe use in the Republic of Finland in 2015 was 3.48 DDD/1000 inh/day or 3.30%, in 2016 3.78 DDD/1000 inh/day or 3.58% and in 2017 it was 4.21 DDD/1000 inh/day or 3.74% of total hypolipidemic drugs use.

Use of hypolipemic drugs in the observed countries during 2015-2017 is shown in Tables 3-5.

**DISCUSSION**

In all three investigated countries, the use of drugs for the treatment of CVD (group C)
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Table 5. Comparative overview of use of lipid modifying agents, plain (group C10A) in the Republic of Finland in the period from 2015 to 2017, expressed by the DDD/1000 inh/day and percentages (%)

| Country                        | 2015 DDD | 2015 % | 2016 DDD | 2016 % | 2017 DDD | 2017 % |
|--------------------------------|----------|--------|----------|--------|----------|--------|
| **C10** - lipid modifying agents |          |        |          |        |          |        |
| C10AA - HMG CoA reductase inhibitors |          |        |          |        |          |        |
| C10AA01 - simvastatin          |          |        |          |        |          |        |
| C10AA02 - lovastatin           |          |        |          |        |          |        |
| C10AA03 - pravastatin          |          |        |          |        |          |        |
| C10AA04 - fluvastatin          |          |        |          |        |          |        |
| C10AA05 - atorvastatin         |          |        |          |        |          |        |
| C10AA07 - rosuvastatin         |          |        |          |        |          |        |
| C10AB - Fibrates               |          |        |          |        |          |        |
| C10AB02 - bezafibrate          |          |        |          |        |          |        |
| C10AB04 - gemfibrozil          |          |        |          |        |          |        |
| C10AB05 - fenofibrate          |          |        |          |        |          |        |
| C10AB08 - ciprofibrate         |          |        |          |        |          |        |
| C10AC - Bile acid sequestrants |          |        |          |        |          |        |
| C10AC01 - colesteryamine       |          |        |          |        |          |        |
| C10AC02 - colestipol           |          |        |          |        |          |        |
| C10AC04 - colestevam           |          |        |          |        |          |        |
| C10AX - Other lipid modifying agents |          |        |          |        |          |        |
| C10AX06 - omega-3-triglycerides incl. other esters and acids |          |        |          |        |          |        |
| C10AX09 - ezetimibe            |          |        |          |        |          |        |
| C10AX14 - alirocumab           |          |        |          |        |          |        |
| C10AX15 - bempedoic acid       |          |        |          |        |          |        |

Note: The use of statins has increased in all three countries. The use of hypolipidemic drugs is more commonly prescribed in all three countries. Of all hypolipidemic drugs, statins are most commonly prescribed in all three countries. The use of statins has increased in Western societies since the publication of the Scandinavian Simvastatin Survival Study (4S) in 1994 [25]. After the intensive growth of statin use at the beginning of the 21st century, their use has stabilized in recent years and recorded a slight growth of this group of drugs from year to year. Compared to the previous research, use of statins in Serbia has increased about 24 times from 2004 [15]. In addition to evidence of efficacy and safety, changes in national prescribing requirements are needed to further increase statin use [26]. One of the reasons for significantly lower prescribing of statins in Serbia compared to other countries may be the differences in the legislation on prescribing these drugs [15]. The Republic of Serbia has very strict criteria for reimbursement of statin costs. Indications for which statins can be prescribed at the expense of the RFZO in the Republic of Serbia are the prevention of secondary myocardial infarction and stroke and the familial form of HLP. For the first indication, the share of the RFZO is 15-25% of the price of the medicine, while for the second indication it is 50 RSD [25,26]. In...
CONCLUSION

During the observed period (2015-2017), the Republic of Serbia was the country with the lowest use of hypolipidemic drugs in relation to the Kingdom of Norway and the Republic of Finland. In the Republic of Serbia, the use of these drugs still represents a low share in the use of all drugs for the treatment of CVD (group C). Although use has increased compared to the previous study, additional pharmacoeconomic steps are needed to match use in Serbia with use in Norway and Finland.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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Uporedna analiza upotrebe lekova u terapiji hiperlipoproteinemija u Republici Srbiji i Nordijskim zemljama u periodu 2015 - 2017. godine

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KRATAK SADRŽAJ

Uvod: Kardiovaskularne bolesti su vodeći uzrok smrti u Srbiji i svetu. Pokazano je da su čak 80% njih preventibilne. Regulisanje nivoa lipida u serumu je jedan od najznačajnijih zadataka prevencije kardiovaskularnih bolesti.

Cilj: Cilj ove studije bio je da se analizira potrošnja lekova za smanjenje nivoa lipida u Srbiji, Norveškoj i Finskoj u periodu 2015-2017.

Metodologija: Podaci o potrošnji lekova tokom 2015, 2016 i 2017 preuzeti su sa zvaničnih veb sajtova nacionalnih regulatornih autoriteta u oblasti lekova: Agencije za lekove i medicinska sredstva Srbije, Norveškog instituta za javno zdravlje i Finske agencije za lekove. Potrošnje su izražene u DDD/1000 stanovnika/dan u skladu sa anatomsko-terapijsko-hemijskom klasifikacijom.

Rezultati: Udeo lekova za kardiovaskularne bolesti u ukupnoj potrošnji lekova bio je najveći u sve tri zemlje tokom posmatranog perioda. Upotreba lekova za smanjenje lipida bila je 3-4 puta manja u Srbiji nego u Norveškoj ili Finskoj. Od svih hipolipemika, statini su najčešće propisivani u sve tri države. Atorvastatin i rosuvastatin su najšire korišćeni u Srbiji, a simvastatin i atorvastatin u Norveškoj i Finskoj.

Zaključak: Potrošnja hipolipeminih lekova u Srbiji je manja nego u Norveškoj i Finskoj, ali se neprestano povećava. Potrošnja lekova za smanjenje lipida u Srbiji i dalje zauzima najmanji udeo od svih lekova za kardiovaskularne bolesti.

Ključne reči: prevencija kardiovaskularnih bolesti, hipolipidemici, statini, fibrati

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