

Evaluation of statin utilization in the Republic of Macedonia during 2013–2016

Zorica Naumovska¹
Aleksandra K Nestorovska¹
Aleksandra Grozdanova¹
Kristina Hristova²
Aleksandar Dimovski¹
Ljubica Suturkova¹
Zoran Sterjev¹

¹Department of Pharmaceutical Chemistry, Faculty of Pharmacy, SS “Cyril and Methodius”, Skopje, Republic of Macedonia; ²Department of Health Insurance Fund of R. Macedonia, Skopje, Republic of Macedonia

Purpose: A rational use of statins has a major and increasing importance in public health and allocation of financial resources by the health insurance funds (HIFs). The aim of this study was to evaluate the market share and utilization trends of statins in the Republic of Macedonia (R. Macedonia) from 2013 to 2016.

Materials and methods: A retrospective analysis and data comparison for the utilization of HMG-CoA inhibitors (C10AA) in R. Macedonia from 2013 to 2016 were conducted. The data obtained from HIF, IMS Health, pharmaceutical industry and marketing authorization holders (MAHs) were evaluated through defined daily doses per 1000 insurers per day (DDD/TID).

Results: Cardiovascular drugs are the most commonly prescribed and utilized drugs in R. Macedonia. The HIF cost for cardiovascular disease (CVD) increased to €2,243,777.00 in the period from 2013 to 2016. Since 2012, the reimbursement shows that atorvastatin accounts for the highest expenditure reaching €2,162,958.00 while rosuvastatin reached €1,645,860.00 in 2016. The increased consumption of statins is confirmed from the records obtained from IMS Health databases in the evaluated period in R. Macedonia suggesting increased expenditures with total growth of 35.65% reaching €4,421,280.24 in 2016. Evident growth of statin consumption is confirmed from the data obtained from the pharmaceutical industry and MAH. The statin use increased from 42.347 DDD/TID in 2013 to 71.697 DDD/TID in 2016, although it is lower in comparison to other European Union (EU) countries (1.1–2.5-fold).

Conclusion: The rapid increase in the consumption of statins can be attributed mostly to an increase in the consumption volume. It is inevitable to widen the price reduction concept with initiatives that may control statin consumption amounts with measures such as educational programs for rational drug utilization and targeting eligible population.

Keywords: statins, cardiovascular prevention, expenditures for statin utilization prescription drug expenditure

Introduction

The risk factors for coronary heart disease (CHD) could be classified into two groups: not modifiable (age over 65 years and hereditary positive family history) and modifiable (hypertension, hypercholesterolemia, type 2 diabetes, cigarette smoking, alcohol consumption, obesity and physical inactivity). The clinical trials have confirmed that a decrease in the cholesterol level up to 10% lowers the risk of death from CHD by approximately 15%.¹

Cardiovascular diseases (CVDs), such as stroke and ischemic heart disease, are still the main cause of death (40%) in the European Union (EU), especially in Central and Eastern Europe. Heart diseases account for approximately 25% of all deaths in

Correspondence: Zorica Naumovska
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, SS “Cyril and Methodius”, Street Mother Theresa 47, Skopje 1000, Republic of Macedonia
Tel +389 75 49 7751
Email zose@ff.ukim.edu.mk

people aged 65–84 years and approximately 33% of deaths for people aged 85 years and older.^{1–4} Moreover, the cost to the EU economies linked to CVD is not decreasing and is currently estimated to be €196 billion a year, i.e., 54% is due to health care costs, 24% is due to productivity losses and 22% is due to the informal care of people with CVD. In the Republic of Macedonia (R. Macedonia), diseases of the cardiovascular system (with 57.8% of total deaths) are the most common cause of death. From the 19,000 deaths, 11,000 are a consequence of a CVD. Each year in R. Macedonia, more than 3,000 CVDs are registered in 10,000 residents and about 160 are being treated in hospital. In an effort to reduce the CVDs, which cause 18 million deaths globally per year and affect more than 1 billion adults worldwide, researchers and physicians according to relevant facts and evidence-based medicines are suggesting the daily usage of cholesterol-lowering drugs. The point of these recommendations is accepted and implemented in evidence-based guidelines for clinical practice, such as the latest guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) 2013, updated on January 25, 2016.

HMG-CoA reductase inhibitors (statins) reduce the incidence of coronary events significantly, in both primary and secondary prevention, being the most efficient hypolipidemic compounds that have reduced the rate of morbidity and mortality in coronary patients. The addition of 40 mg simvastatin to the existing treatment of patients with coronary disease, occlusive arterial disease and diabetes was confirmed as a beneficial approach associated with the reduction in myocardial infarction, stroke or revascularization by one-quarter to one-third depending on the patient compliance in comparison to the placebo group in large randomized trial, irrespective of the patients' initial cholesterol concentrations.⁵ Statins have been shown to lower “bad” low-density lipoprotein (LDL) cholesterol levels by 21–63% and to raise “good” high-density lipoprotein (HDL) cholesterol levels by 4–16%. Clinical studies have confirmed that, in certain people, statins reduce the risk of heart attack, stroke and even death from a heart disease by 25–35%.^{1,5} Many studies revealed that there are negligible differences in the effectiveness between the various statins applied with appropriate doses, which encouraged the generic prescription of these drugs, a measure that is especially important in low-income countries.^{5,6} In addition, statins are drugs with favorable safety profiles with a rare but serious and potentially fatal side effect rhabdomyolysis. Adverse events and tolerability are equivalent among statins and are dose dependent. All

statins are recommended as once-daily oral dose and are equivalent when comparing convenience.^{7,8} Evolving clinical guidelines result in a higher number of patients eligible for statin therapy and market increase.^{2,9}

Financial expenditure of national insurance funds (NIFs) is constantly increasing owing to the rapidly growing proportion in health care costs due to the high prices of drugs. The availability of low-cost generic statins in low- and middle-income countries (LMICs) increases the medicine access and treatment adherence for patients.

Many drugs are attributed to demand-side measures, such as specific obligatory prescription or indication conditions. Statins have dominated the global dyslipidemia therapeutic market for the past few decades, but the global statin market has been continuously decreasing since 2004. In 2011, it was valued at \$20.5 billion, with a trend of decline for approximately 7.2% each year, so it is estimated to reach \$12.2 billion by 2018. The most noticeable decline was obtained in 2012 with the patent expiries of Lipitor (atorvastatin calcium), Vytorin (ezetimibe/simvastatin), Lescol (fluvastatin) and Crestor (rosuvastatin), followed by severe generic erosion. Rational prescribing of statins, acceptable co-payment policy and higher generic availability of statins have a major and increasing importance for the public health, appropriate patient compliance and allocation of financial resources by the health insurance funds (HIFs).

To control the health care expenditure, USA and European countries are developing and employing various cost containment policies, such as pricing and reimbursement regulation, i.e., supply-side initiatives.³ A price-regulated system with established rules for generic pricing was implemented in Croatia, Belgium, France, Norway and Poland, and a free pricing was introduced in Germany, the Netherlands, Sweden, Scotland and UK, whereas a mixed approach was used in Austria. Since various statins at therapeutic doses were seen as essentially similar by the health authorities in EU countries, multiple demand-side measures were implemented as International Nonproprietary Name prescribing resulting in considerable savings by the utilization of generics instead of originator drugs and incentive use of lower price generics by switching patients from rosuvastatin to atorvastatin and prescribing of simvastatin and atorvastatin as a first-line therapy.^{5,6,10–13}

R. Macedonia provides almost universal health care coverage including reimbursement of prescription drugs to its citizens and permanent residents (2.1 million people) via a mandatory public health insurance system. The reimbursement is based on a list of fully or partially paid

medicines. The overall drug expenditure in R. Macedonia approaches about 30% of the total health care costs, with 5.9% on statins alone (reaching €11.7 million in 2016), so a special attention is inevitable, because of the current economic problems in the country. In R. Macedonia, statins are prescribed exclusively by specialized cardiologists and doctors of internal medicine, and also general practitioners (GPs) are allowed to prescribe statins for some indications. Co-payments for all the below-mentioned statins available in R. Macedonia are low, and they could not influence considerably the patients' adherence, as it was discussed in the literature review by Simoens and Sinnaeve.¹⁴ Although 22 different brands of generic statins (atorvastatin [8], rosuvastatin [7], simvastatin [5], fluvastatin [1] and lovastatin [1]) are marketed in R. Macedonia, almost 99% of the market share accounts for atorvastatin, rosuvastatin and simvastatin. According to the official data from the HIF for the previous 5 years, the utilization of statins is higher and is constantly increasing with a serious economic burden on the Macedonian health care system.

The aim of our retrospective study was to evaluate the market share and utilization trends of statins in R. Macedonia in the period from 2013 to 2016. The evaluation was performed using the official data for statin utilization from the national HIF (NHIF), IMS Health (Skopje, Macedonia), pharmaceutical industry and marketing authorization holders (MAHs).

Materials and methods

Data source and collection

A retrospective analysis and data comparison for the utilization of HMG-CoA reductase inhibitors (C10AA) in R. Macedonia were conducted. The number of prescriptions for statins, pricing and reimbursement information were collected from the publicly available annual reports published by the Macedonian HIF. The data related to comparative analyses were obtained from IMS Health, pharmaceutical industry and MAHs. The exchange rate between Macedonian denar (MKD) and one unit of the common European currency (MKD/€) was 61.5 MKD in the evaluated period. The data on utilization were measured in defined daily doses per 1000 insurers per day (DDD/TID) in the period from 2013 to 2016. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.¹⁵ The unit prices were calculated per DDD according to World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology,¹⁶

which are 30 mg for simvastatin, 20 mg for atorvastatin and 10 mg for rosuvastatin since these statins account for almost 99% of the market share in R. Macedonia.

Results

R. Macedonia has 2.07 million citizens with 1.85 health insurance insurers. The Fund Total HIF's budget for 2017 is around €438 million, and around 10% of this budget (€45 million) is planned to be spent on prescription medicines in the primary health care. According to the obtained data from the WHO, the gross domestic product (GDP) per capita according to data amounts to US\$5,020 for the year 2016, and 4.5% of GDP is allocated for the health.

Expenditures for drugs on the reimbursement list show a constant growth in the past decades. For comparison, in 2002, the expenditures were €19,512,195.12 for 8 million prescriptions, and in 2008, they were €21,138,211.38 for 10 million prescriptions reaching the twofold increase in the budget in 2016. The number of prescriptions in 2016 grew by 5.4% in comparison to 2015.

According to the official data from HIF, the number of dispensed prescriptions in R. Macedonia is increasing approximately between 1 and 1.7 million each year in the period from 2013 to 2016, reaching 22,274,288 prescriptions in 2016.

The total expenditure for drugs was €34,536,246.6 in 2013, whereas in 2016 it was €42,701,143.38. The expenditure growth increased for about 6.5% from 2013 to 2015 with the highest increase of 8.2% in 2016 compared to 2015 (Figure 1).

Cardiovascular drugs are the most commonly prescribed and used drugs in R. Macedonia (43.4% of all prescriptions in 2016 account for CVD drugs). Cardiovascular drugs amount to 28% of the total expenditure for drugs from HIF. The average HIF costs for this group of drugs was €10.8 million in the period from 2013 to 2015 with an increasing trend of approximately 6.5–7.1% each year. The expenditure growth for this group of drugs was 6.7% for 2016 compared to 2015 amounting to €11,674,471.54 (Figure 2).

Regarding the official data from HIF, atorvastatin is constantly on the list of 10 most commonly utilized drugs in R. Macedonia since 2012, and it accounts for the highest expenses from the reimbursement, reaching €2,162,958.00 in 2016 (Figure 3).

Rosuvastatin is also one of the 10 drugs that manifest the highest costs from the NHIF with €1,645,860.00 in 2016. The presented results revealed that 5–5.9% of the budget

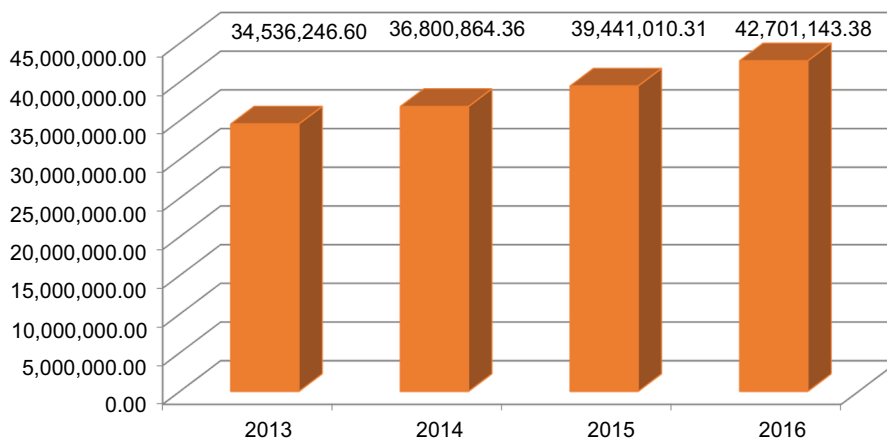


Figure 1 Total expenditure for prescription drugs for primary health care in euros.

Note: Data from the NHIF.²⁸

Abbreviation: NHIF, national health insurance fund.

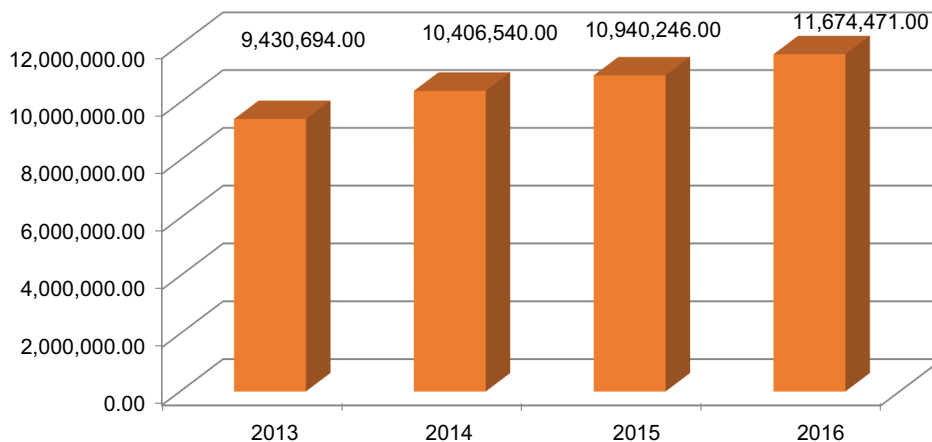


Figure 2 Expenditures for CVD in euros.

Note: Data from the NHIF.²⁸

Abbreviations: CVD, cardiovascular disease; NHIF, national health insurance fund.

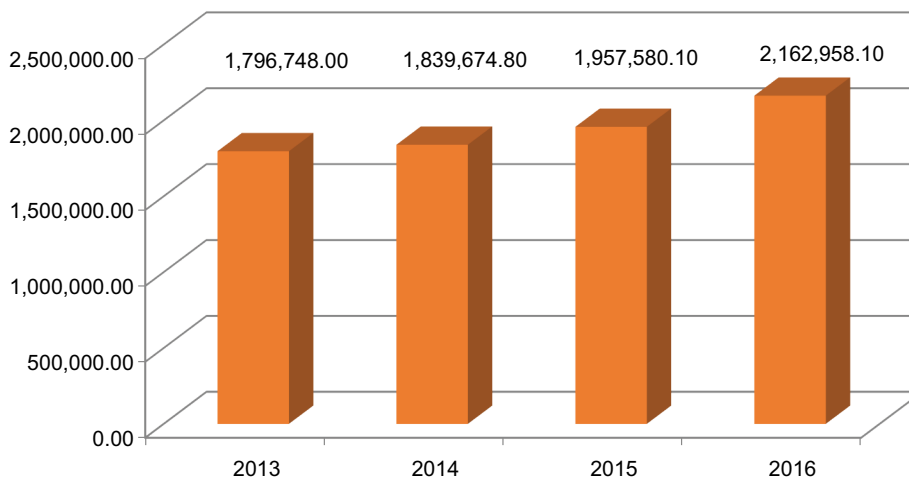


Figure 3 Expenditures for atorvastatin in euros.

Note: Data from the NHIF.²⁸

Abbreviation: NHIF, national health insurance fund.

expenditures for all drugs in R. Macedonia are accounted for atorvastatin followed by 3.2–3.86% for rosuvastatin.

To evaluate the volumes and expenditures associated with statins, data from IMS Health were obtained to help assess some differences which could be an indicator for the out-of-pocket use of statins. According to the official data from IMS Health in R. Macedonia, over 95% of the market share for lipid-modifying agents refers to statins in the period from 2013 to 2016.

The expenditure evaluation of both hospital and pharmacy channels shows a continuous trend for increasing outflows. In R. Macedonia, statins are most commonly obtained from community pharmacies ranging between 97% and 99% in the period from 2013 to 2016, and only a small percentage is dispensed in hospitals. The official data suggested that more than 88% of all statins utilized in R. Macedonia in the evaluated period are covered and reimbursed by HIF. The sum expenditures for statin utilization from hospital and pharmacy channels (commercial and reimbursed) according to the data obtained from IMS Health are constantly rising: 14% in 2014 compared to 2013, 15% from 2014 to 2015 and 12.15% from 2015 to 2016, or in total 35.65% growth is observed in this period amounting to €4,421,280.24 in 2016 (data are shown in Figure 4).

In comparison to the official HIF data, noticeable differences are observed for the dispensed generic drugs and variations in their average costs of 10% in 2013 and 2014 and 8% in 2015, a fact that indicates a potential out-of-pocket expenditure and possible irrational use of these lipid-lowering drugs (Figure 5).

The data obtained from the pharmaceutical industry and MAHs for statin utilization in R. Macedonia have confirmed that simvastatin is the only lipid-lowering drug that has trend of declined lowered costs for 25% from 2013 to 2014 and 19% from 2014 to 2015, i.e., the total decrease accounts for 40% in the 2-year period. A slight increase in simvastatin expenditures was observed only in 2016 (6.2% compared to 2015), reaching €76,432.36 last year. Almost 98% of the market share for simvastatin came from the local generic company such as Alkaloid AD (Skopje, Macedonia; brand name Holesta).

Mirroring the observed trends in other low-income countries, a remarkable increase in statin consumption in R. Macedonia was observed after their patent expiry when generics become available. Five different brand names in six different doses from 10 to 80 mg for atorvastatin are accessible in our country. Krka (Novo Mesto, Slovenia)

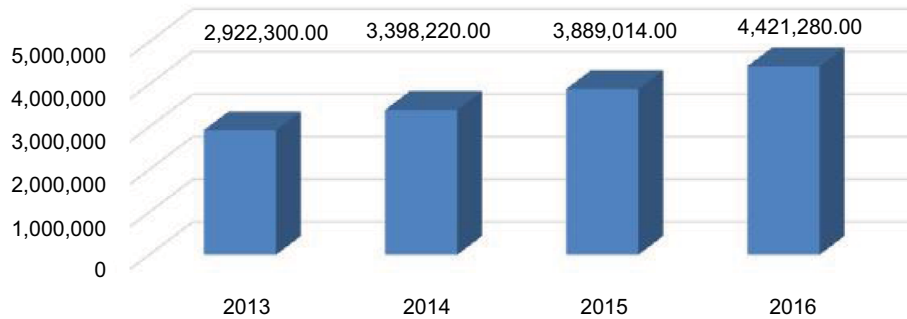


Figure 4 Sum expenditure in euros for statins (IMS Health).

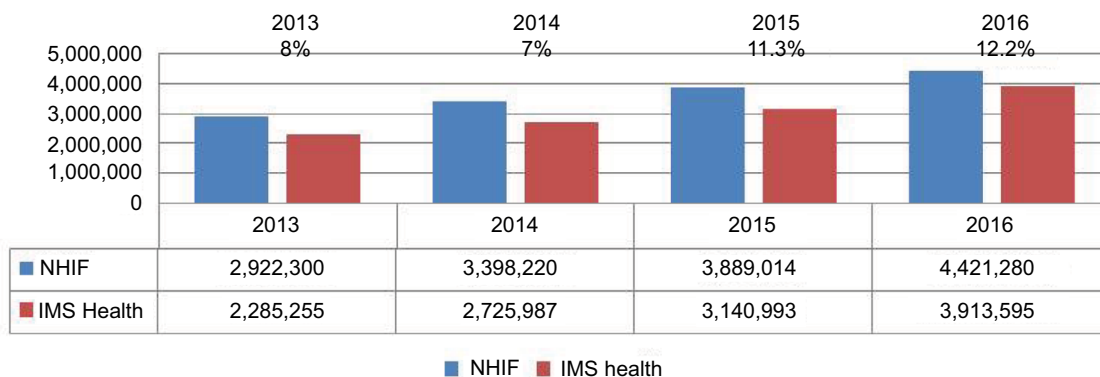


Figure 5 Comparison of data for statin utilization in euros according to IMS Health and NHIF.

Abbreviation: NHIF, national health insurance fund.

followed by Lek-Sandoz (Ljubljana, Slovenia) has the biggest percentage of the market share for atorvastatin, and only a small percent accounts for Alkaloid and Pliva-Teva (Zagreb, Croatia). A high increase in the number of prescriptions which resulted in 31.8% total enlargement of the costs is established in the evaluated period.

Rosuvastatin is marketed in six doses ranging from 5 to 40 mg. Almost a doubling in sales is confirmed for rosuvastatin in the period from 2013 to 2015, so this drug has reached the sixth place in the list of the most utilized drugs in R. Macedonia. A considerable increase in the number of prescriptions which resulted in a 59.7% increase in the total increase of costs (39% for 2014 compared to 2013 and a large elevation of 17% for 2015 compared to 2014, which continued in 2016 with 20% increase compared to 2015) is established in the evaluated period.

According to the data gathered from the pharmaceutical industry and MAH, there were 14.78% lower expenses in 2013 for statin utilization according to the NHIF of R. Macedonia. This trend, continued in 2014 and 2015, and the difference in costs was only 1% higher according to the available official data obtained from NHIF in 2016 (Figure 6).

Statin utilization as DDD/TID

The total drug utilization in R. Macedonia is in a constant growth in the past 15 years. As it was already mentioned, the financial expenditures and drug utilization for statins

expended in the analyzed period. The use of statins increased from 42.347 DDD/TID in 2013 to 50.220 DDD/TID in 2014, 57.546 DDD/TID in 2015 and 71.697 DDD/TID in 2016. The use of simvastatin in the 4-year period expressed as DDD/TID has a tendency of decline (decrease of almost 55%). On the other hand, the use of atorvastatin has an increase from 28.273 DDD/TID in 2013 to 40.802 in 2016 (a total increase by 31%). The highest increase was observed for rosuvastatin available since 2010, from 12.02 DDD/TID in 2013, 19.4 DDD/TID in 2014, 23.16 DDD/TID in 2015 and 29.505 in 2016 (total increase by 59.25%; Figure 7A and B).

The utilization of statins in R. Macedonia has been rising steadily, and it is gradually approaching the utilization in terms of DDD and patient number in other European countries. Although R. Macedonia belongs to the group of countries with a high risk for CVD, the usage of statins is still not comparable with other countries in this group and is 1.1–2.5-fold lower (Table 1). This fact correlates with higher incidence of CVD and mortality rates from CVD. In that line, we are expecting a proceeding enlargement of prescribing and dispensing of CVD drugs in the R. Macedonia.

Discussion

The reference pricing system for drug utilization in R. Macedonia was introduced in 2009 giving the patients the opportunity for the selection of the prescription drug from the positive drug list. In 2010, the authorities effectuated new reference prices for the drugs on reimbursement list using a

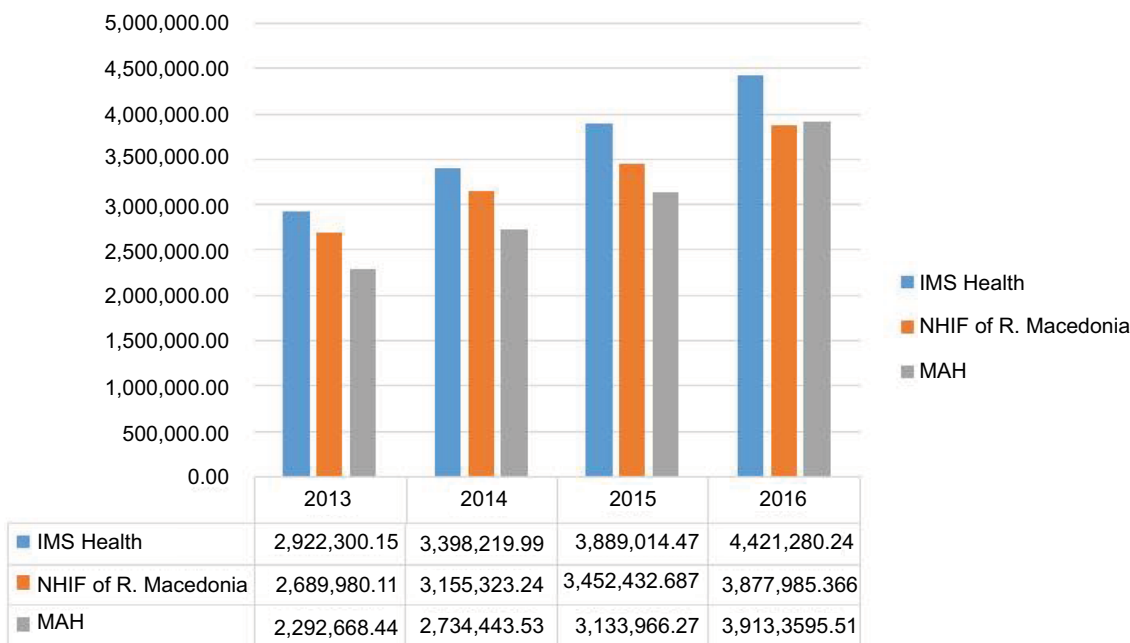


Figure 6 Comparison of statin expenditures according to IMS Health, NHIF and MAH.

Abbreviations: MAH, marketing authorization holder; NHIF, national health insurance fund; R. Macedonia, Republic of Macedonia.

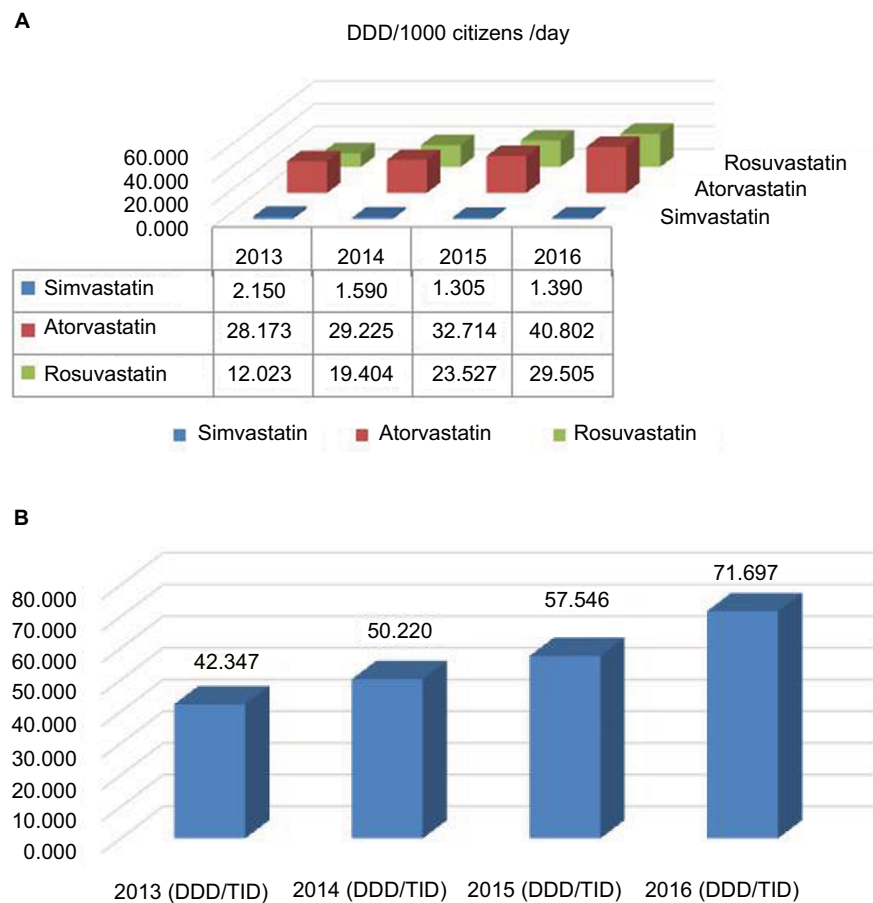


Figure 7 Utilization of statins in the R. Macedonia (2013–2016).

Notes: (A) DDD/TID of different statin generics in R. Macedonia. (B) DDD/TID of statins in R. Macedonia (2013–2016).

Abbreviations: DDD/TID, defined daily doses per 1000 insurers per day; R. Macedonia, Republic of Macedonia.

Table I DDD/TID of statin utilization in EU countries

EU countries	Year 2000 DDD/TID	Year 2012 DDD/TID
Finland	17	94.9
Scotland	17.2	142.8
Germany	21.4	70.5
Sweden	21.8	76.3
Norway	30.9	114.6
Denmark	8.6	117.3
The Netherlands	35.6	99.9
Italy	6.4	64.5
Belgium	50.9	112.7
Spain	14.7	91.6
Portugal	11.1	98.9
France	32.3	66
Mean	22	95

Note: Data from Vancheri et al.¹⁷

Abbreviations: DDD/TID, defined daily doses per 1000 insurers per day; EU, European Union.

new comparative methodology. These interventions resulted in a fourfold increase in the number of prescription drugs in 2016 in R. Macedonia compared to 2009. On the other hand, the authorities keep on introducing, so called, demand-side initiatives to control the prescription drug expenditures in

terms of prescription and usage limitations. All the available statins in R. Macedonia are prescription-only drugs and are eligible for reimbursement by HIF. In the reimbursement restriction criteria for statin utilization unlike other countries, such as Finland,¹⁸ Norway,¹⁹ Austria,¹⁹ Germany,²⁰ or countries with co-payment policies (USA, Canada²¹) in the R. Macedonia similar to the Czech Republic,² there are no measures that would recommend a prescription from one statin to another in opposite direction to the market evolution and generic erosion. In Finland, a restriction for more expensive statins was implemented as a reimbursement limitation in the period before the patent expiry. In Norway, Austria and the Netherlands, the reimbursement regulations supported by educational interventional measures suggest mandatory use of simvastatin as first-line therapy, which resulted in increase in its utilization and decrease in the overall expenditures. Nevertheless, some clinical trials have shown that the reduction in LDL cholesterol with rosuvastatin, atorvastatin and simvastatin is about 46%, 43% and 39%, respectively, so the use of the more potent statins could result in a larger

reduction in LDL with a smaller increase in DDDs. In Germany, to encourage a generic drug prescription, a target prescription, as a cost-saving method, was introduced. France, Portugal, Turkey and the Republic of Ireland are characterized with more limited demand-side measures for counteracting pharmaceutical market pressures resulting in increased use of patented statins following generic simvastatin. New approaches are introduced in France and Spain (Catalonia) to rationalize prescribing generics with targeted prescriptions and financial incentives.²² An interesting approach was introduced by the authorities in Korea, where the number of individuals with chronic illnesses is constantly rising. They developed demand-side initiatives in addition to supply-side initiatives, such as lowering prices to effectively constrain prescription drug expenditure increases, by introducing the incentive prescribing scheme, a system in which doctors are offered 30% of the saved drug cost if they voluntarily improve their prescription behavior and save drug costs.²³

Because of the confirmed influence of social, cultural and economic factors in the epidemiology of CVD as well as the great complicity of the pathology background, a more appropriate evaluation and disease sub-stratifications have to be performed on the population level. All relevant data suggest that the effectiveness of statin utilization is directly dependent on patient compliance. Differences in the discontinuation rate of statins among countries might have a role in the relation between statin utilization and CHD mortality. Unfortunately, in R. Macedonia, there are no studies conducted for the evaluation of accuracy in terms of dosing and adherence to medicinal treatment with these lipid-lowering drugs. Although many clinical studies support the beneficial effects of statin utilization in the prevention of CVD, we are facing real problems related to the justified growing trend for statin utilization and expenditures worldwide. In everyday clinical practices, it has been observed that there is an irrational use of statins, i.e., sometimes they are overused by individuals with a low CVD risk, or underused by high-risk patients.¹⁷ Despite the development of specific tools for risk assessment, most commonly, the risk estimate for a single patient is usually made subjectively.²⁴ Additional problems in the evaluation of the benefits of statins are associated with their use in the secondary prevention as the patients with hypertension and diabetes type 2 are considered as eligible for statin treatment. In that manner, we have to consider the fact that according to official data in the developing countries such as Croatia,^{25,26} only about 50-63% of hypertensive patients and 22.30-34.7% of diabetic patients have managed disease with the utilized drugs. A similar situation is present in R. Macedonia, and

broad interventions with incorporated biological, social and behavioral factors on personal and population level should be introduced to succeed in lowering the mortality and morbidity rate associated with CVD. Additional assessment is needed for determining whether the statin utilization growth is associated with the increased number of statin prescriptions for primary or secondary prevention. Different tendencies are confirmed in different countries, i.e., in Italy, statin utilization is linked dominantly with the primary prevention, and in Sweden it is equally distributed between the primary and secondary prevention, whereas a Danish study showed an increasing use of statins in asymptomatic individuals, and in patients with diabetes or peripheral atherosclerosis.²⁷ After the appropriate spotting of the problems, the authorities are obliged to introduce educational interventions and disease management programs that will encourage the rational use of statins especially in high-risk groups, including the patients with diabetes and a history of stroke in the clinical practice.

Conclusion

Rapid increase in statin use worldwide and in R. Macedonia can be attributed mostly to an increase in the consumption volume which led to a substantial growth in statin expenditures. One of the reasons for irrational use of statins in the R. Macedonia is they are easily available for the patients resulting in confirmed out-of-pocket outflow. Statin utilization in R. Macedonia presented as DDD/TID is lower in comparison to other countries (1.1–2.5 times) which correlates with a higher incidence of CVD and mortality rates from CVD. To evaluate drug expenditure effectively when chronic diseases remain on the rise globally, it is inevitable to widen the price reduction concept with initiatives that may control statin consumption amounts, such as educational programs for rational drug utilization and targeting eligible population.

Acknowledgments

The authors would like to acknowledge the help of IMS Health, Alkaloid, Krka-Farma, Dooel (Skopje, Macedonia) and Pliva-Teva for the provision of the data related to volumes of statins dispensed in the evaluated period. The study was exempted from institutional review board (IRB) approval, but it was part of the regular activities of the ISPOR Chapter (Macedonia) which has agreements with these companies for the provision of data for the purposes of ISPOR activities. This study has no sponsorship or funding, and there are no relationships to be declared. No assistance in the preparation of this article is to be declared.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

- Gorevski E, Bian B, Kelton CM, Martin Boone JE, Guo JJ. Evidence-based prediction of statin use with lipid-panel data from the National Health and Nutrition Examination Survey. *Value Health*. 2012;15(1):32–38.
- Fuksa L, Vocelka M, Vytrisalova M. The impact of changes in national prescribing conditions for statins on their public expenditure and utilization in the Czech Republic 1997–2013. *Health Policy*. 2015;119(9):1255–1264.
- Manova M, Stoimenova A, Savova A, Peikov P, Petrova G. Utilization and price trends in some reimbursed cardiovascular medicines. *Biotechnol Biotechnol Equip*. 2011;25(2):2424–2431.
- Vojvodić Z, Stimac D. Trends in statin consumption and cardiovascular mortality in Croatia 2004–2012. *Coll Antropol*. 2014;38(suppl 2):73–78.
- Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. *Lancet*. 2003;361(9374):2005–2016.
- Godman B, Baker A, Leporovski A, et al. Initiatives to increase the prescribing of low cost generics; the case of Scotland in the international context. *Med Res Arch*. 2017;5(3):1–34.
- Littman J, Halil R. Potential effects of rational prescribing on national health care spending: more than half a billion dollars in annual savings. *Can Fam Physician*. 2016;62(3):235–244.
- Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. *J Clin Pharm Ther*. 2010;35(2):139–151.
- Pedersen TR, Faergeman O, Kastelein JJ, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294(19):2437–2445. Erratum in: *JAMA*. 2005;294(24):3092.
- Bennie M, Godman B, Bishop I, Campbell S. Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland. *Expert Rev Pharmacoecon Outcomes Res*. 2012;12(1):125–130.
- PrescQIPP. Switching Rosuvastatin to Atorvastatin, 2014, Bulletin 81. Accessed March 6, 2018.
- Usher-Smith J, Ramsbottom T, Pearmain H, Kirby M. Evaluation of the clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a primary care setting: 2 years on. *Int J Clin Pract*. 2008;62(3):480–484.
- Fraeyman J, Van Hal G, Godman B, Beutels P. The potential influence of various initiatives to improve rational prescribing for proton pump inhibitors and statins in Belgium. *Expert Rev Pharmacoecon Outcomes Res*. 2013;13(1):141–151.
- Simoens S, Sinnaeve PR. Patient co-payment and adherence to statins: a review and case studies. *Cardiovasc Drugs Ther*. 2014;28(1):99–109.
- WHO Collaborating Centre for Drug Statistics Methodology. *ATC/DDD index 2018*. 2018. Available from: https://www.whocc.no/atc_ddd_index/. Accessed April 30, 2018.
- WHO Collaborating Centre for Drug Statistics Methodology [webpage on the Internet]. Available from: http://www.whocc.no/atcdddindex_. Accessed September 22, 2014.
- Vancheri F, Backlund L, Strender LE, Godman B, Wettermark B. Time trends in statin utilisation and coronary mortality in Western European countries. *BMJ Open*. 2016;6(3):e010500.
- Martikainen JE, Saastamoinen LK, Korhonen MJ, Enlund H, Helin-Salmivaara A. Impact of restricted reimbursement on the use of statins in Finland: a register-based study. *Med Care*. 2010;48(9):761–766.
- Sakshaug S, Furu K, Karlstad Ø, Rønning M, Skurtveit S. Switching statins in Norway after new reimbursement policy: a nationwide prescription study. *Br J Clin Pharmacol*. 2007;64(4):476–481.
- Godman B, Schwabe U, Selke G, Wettermark B. Update of recent reforms in Germany to enhance the quality and efficiency of prescribing of proton pump inhibitors and lipid-lowering drugs. *Pharmacoeconomics*. 2009;27(5):435–438.
- Damiani G, Federico B, Anselmi A, et al. The impact of regional co-payment and national reimbursement criteria on statins use in Italy: an interrupted time-series analysis. *BMC Health Serv Res*. 2014;14:6.
- Godman B, Shrank W, Andersen M, et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. *Expert Rev Pharmacoecon Outcomes Res*. 2010;10(6):707–722.
- Bae G, Park C, Lee H, Han E, Kim DS, Jang S. Effective policy initiatives to constrain lipid-lowering drug expenditure growth in South Korea. *BMC Health Serv Res*. 2014;14:100.
- Eichler K, Zoller M, Tschudi P, Steurer J. Barriers to apply cardiovascular prediction rules in primary care: a postal survey. *BMC Fam Pract*. 2007;8:1.
- Croatian Institute for Public Health. *Croatian health-statistical annals, 1990-2012*. Zagreb: Croatian Institute for Public Health; 1991-2013. Croatian.
- Delija I, Vrdoljak D, Bergman-Markovikj B. How well do family physicians record cardiovascular risk factors? *Med Jadertina*. 2012;42(3–4):129–137.
- Ferrajolo C, Arcoraci V, Sullo MG, et al. Pattern of statin use in southern Italian primary care: can prescription databases be used for monitoring long-term adherence to the treatment? *PLoS One*. 2014;9(7):e102146.
- Health Insurance Fund of Macedonia [webpage on the Internet]. Annual reports for the expenditures in denars for the drugs that are on the positive list in The Republic of Macedonia. Available from: <http://genet.sickkids.on.ca/app>. Accessed May 28, 2018. Macedonian.

ClinicoEconomics and Outcomes Research

Publish your work in this journal

ClinicoEconomics and Outcomes Research is an international, peer-reviewed open-access journal focusing on health technology assessment, pharmacoeconomics and outcomes research in the areas of diagnosis, medical devices, and clinical, surgical and pharmacological intervention. The economic impact of health policy and health systems

Submit your manuscript here: <https://www.dovepress.com/clinicoeconomics-and-outcomes-research-journal>

organization also constitute important areas of coverage. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.