

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Statin utilization by different socio-economic groups of Hungary

by Klára Boruzs



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Head of the **Examination Committee:** Margit Balázs, PhD, DSc

Members of the Examination Committee: Árpád Tószaki, PharmD,
PhD, DSc
Csaba Dózsa, PhD

The Examination takes place at the 2nd floor Meeting room of Department of Preventive Medicine, Faculty of Public Health, University of Debrecen
11 a.m., October 27, 2017

Head of the **Defense Committee:** Margit Balázs, PhD, DSc

Reviewers: Péter Fülöp, MD, PhD
Imre Boncz, PhD

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PhD, DSc
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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
13 p.m., October 27, 2017

1. Introduction

1.1. Cardiovascular disease mortality and morbidity burden

Cardiovascular diseases (e.g. coronary heart disease, stroke, peripheral vascular disease) are the leading causes of mortality in the world despite improvements in outcomes for cardiovascular diseases (CVD). According to World Health Organization (WHO) data, approximately 17.5 million people died of CVDs in 2012, representing 31% of total mortality. It is estimated that by 2020, CVDs will be the leading causes of mortality and morbidity worldwide, and developing countries will be the main contributors to this increase. More than three quarters of CVD mortality occur in low- and middle-income countries, where the people often do not have the benefit of integrated primary health care programs for early detection and treatment of people with risk factors compared to people in high-income countries.

Each year, cardiovascular disease kills about 4 million people in the 53 member states of the World Health Organization European Region and over 1.8 million in the European Union (EU). The health status of the population of the so called EU13 member states of the EU (countries joined the EU by and after May 2004), and especially that of the population of the Central Eastern European (CEE) countries is less favourable than that of those countries which became members before May 2004 (EU15 countries). Although the period of the epidemiological crisis plateaued between 1980 and the early 1990s in the CEE countries and the mortality caused by CVDs is continuously decreasing, even nowadays the relative risk of premature death for the population of the EU13 - among them the CEE - countries is very unfavourable compared to the EU15 countries. According to the latest available data, the average relative risk of premature death caused by CVDs

is 2.86 in the EU13 countries compared to EU15 states, and is particularly high in Bulgaria (4.86), Latvia (4.69), Lithuania (4.29), Romania (3.53) and Hungary (3.35). These data clearly indicate that the effectiveness of preventive interventions against CVDs is not sufficient in these countries; therefore, we need to identify the weaknesses and the potential targets of preventive interventions to significantly decrease CVD-related premature death incidence in this region.

1.2. Preventive interventions against cardiovascular diseases

The main risk factors of CVD-related morbidity and mortality caused by CVDs are high blood pressure, diabetes, obesity, smoking and alcoholism, as well as unhealthy diet and a sedentary lifestyle. However, many additional factors such as genetic susceptibility, socioeconomic determinants, anomalies of health care system, especially that of preventive services, contribute to the development of CVDs and the high rate of premature mortality caused by them. Concerning this background, the WHO recommendations are made for management of major cardiovascular risk factors through changes in lifestyle and preventive medication for CVD prevention is a serious challenge for the whole society, i.e. for the general population, politicians, and healthcare workers alike.

1.2.1. Interventions tackling unhealthy lifestyle

The importance of CVD prevention is indisputable and both primary and secondary preventive measures should be utilized. Promoting healthy lifestyle behaviour in the general population is generally accepted as the most effective primary prevention targeting, as well as interventions tackling unhealthy lifestyle (e.g. unhealthy diet, low physical activity, smoking, uncontrolled alcohol consumption) in case of people with CVD

risk factor(s). The elimination of lifestyle-related risk factors would make it possible to prevent at least 80% of CVD and even 40% of cancers, thus providing added value for other chronic diseases.

1.2.2. Preventive medication

In addition to lifestyle modifying interventions, it is also obvious that considerable benefit can be derived from preventive medication.

In general preventive medications are those used for the prevention of conditions such as high blood pressure, high cholesterol, diabetes, asthma, osteoporosis, heart attack, stroke, certain malignancies and prenatal nutrient deficiency. Concerning prevention of CVDs antihypertensives, platelet-aggregation inhibitors, antithrombotic agents and cholesterol-lowering therapeutics are considered as main categories of medicines used in primary and/or secondary prevention.

The use of preventive medication is supported by international recommendations. These are based mainly on the U.S. Preventive Task Force guidelines. A lot of large insurance companies do cover the expenses of preventive medication under their clients' health plan.

Among preventive medications, lipid-lowering therapy, particularly statin treatment is one of the most widely used interventions. HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors (simvastatin, atorvastatin, rosuvastatin, pravastatin, and fluvastatin), known as statins, can reduce the risk of cardiovascular diseases by lowering blood levels of low-density lipoprotein cholesterol (LDL-C). Statins are generally accepted as effective preventive medicines to reduce mortality and morbidity not just for patients with established CVDs, but also for people who have risk factors for them. Therefore, statins have become the first-line therapy for managing dyslipidaemia and CVD risk, and the most widely used preventive drug on the world. Because statins are very effective in both

primary and secondary prevention of cardiovascular diseases, the guidelines recommend the use of these drugs in both types of prevention.

The meta-analysis of ten randomized studies in which a total of 70,388 persons were registered with an average of 4.1 years of follow-up, clearly showed that statin treatment significantly reduced the risk of all-cause death (OR 0.88), major coronary events (OR 0.70) and major cerebrovascular events (OR 0.81). In patients without established CVD but with cardiovascular risk factors, statin use was associated with significantly improved survival and large reduction in the risk of major cardiovascular events. It was also displayed that every 1 mmol/l reduction in LDL cholesterol results in a 21% reduction in cardiovascular events. Therefore, statins are considered to be the first choice of drugs for patients with hypercholesterolemia to decrease their CVD risk. The use of preventive drugs can only be successful if the doctor prescribes the medicine and the patient redeems it and finally, if the patients' adherence to the medication is adequate. However, if any of the three steps are inaccurate it may contribute to the development of CVDs. By conducting systematic search among the international literature we have found that behind the non-adherence to statin medication several factors may exist. The physicians often do not prescribe statins or prescribe low-intensity statin treatment instead of high-intensity therapy for the patients because they fear the adverse effects of statins. However, patients are also afraid because the information from the media suggests that statins have many serious adverse effects. Therefore certain patients stop taking statins after some time or do not adhere to the prescribed dose. A survey found that 62% of patients discontinued statins because they thought that statins cause adverse effects and one third of them stopped taking statins without consulting doctors. It is well known, that over half of statin users will cease to take the drug within a year, with 62% of those patients citing side effects as the reason. The USAGE survey found

that more effective communication between physicians and patients might grow the persistence of statin usage, especially when the patient has concerns about adverse effects and medication costs. Despite the presently growing number of publications on certain adverse effects (myositis, myopathy, rhabdomyolysis and liver damage) of statin medication, it is accepted that for the vast majority of patients the benefits of statins far outweigh the overall risks.

1.3. Relationship between preventive medication with statins and socioeconomic status

1.3.1. International data

Although with highly contradictory findings, a large number of studies were published on the effect of socioeconomic status (SES) on statin utilization in the most developed countries, but no investigations were performed on the relationship between statin utilization and socioeconomic characteristics of certain population groups in the CEE countries so far.

Studies from certain high-income countries (Australia, Sweden, Denmark and the US) found that statin prescription is more frequent for men with low SES, but among women higher prevalence of statin use with growing SES was observed. A pharmacoepidemiological cohort study in Denmark concluded that the frequency of utilization of statin therapy among patients with high cardiovascular risk differed significantly among different socio-economic groups; statin therapy was primarily linked to high risk individuals within the low-risk socio-economic group. However, a study in the United Kingdom showed that statin prescription was more frequent in more deprived regions. Similarly, in New Zealand, the most frequent use of statins was found in the most deprived socioeconomic regions. Statin utilization was more common among the Maoris than non-Maoris at up to 75-year of age, especially in the middle age group of 45-54 years, where

11.6% of Maoris were treated with statin compared to 8.7% of the non-Maoris. In these studies, the use of statin was characterized by the frequency of prescription for statin, but no information was given about the redemption rate (i.e. no data were published on the rate of primary non-compliance). However, previous studies found that the overall adherence to treatment is low if statins are used for primary prevention, such as for patients with no previous cardiovascular events. A Danish study also found association between the decrease of long-term adherence to preventive statin therapy and decreasing income, particularly for men aged 40-64 years.

In an English survey, it was found that ethnicity, older age and increasing social deprivation were significant predictors of reduced prescribing rates of statins for primary prevention. This study used data from 2006–2007 when the guidelines for prescribing statins for primary prevention were changed, including lowering the 10 year CVD risk threshold to 10%.

In 2013, the PREDIMED study found that socioeconomic differences did not affect the treatment prescribed for primary cardiovascular prevention in elderly patients. In this Spanish study, 7,447 individuals with high cardiovascular risk (57.5% women, mean age 67 years) were involved. Similar results were obtained in Denmark when a cross-sectional study was conducted on a population of 385,879 persons aged 18 years or older. According to the results of a study conducted in Glasgow (Scotland), in the case of patients with CVD, the material deprivation index (MDI) did not correlate with the statin prescription frequency.

At the same time, a recent Swedish study has shown that prescriptions for statins have been significantly higher in those living with more favourable socio-economical conditions.

In a New Zealand study, the frequency of prescriptions for statins was analyzed on a sample of 17,498 patients, who were aged 65 years and

over. According to the results, statins were prescribed significantly more often for women than men aged 79 years and under. Statins were also prescribed more frequently for community services card (CSC) holders than for patients without CSC in all age groups. Finally, studying the effect of socioeconomic status for all general practices between 2004-2005 in England it was found that statin prescription was higher in more deprived areas.

1.3.2. The Hungarian challenge

Although Hungary is among the countries of the EU where the risk of premature death caused by CVDs is very high, no studies on preventive medication by statins in comparison with SES was carried out so far. The relationship between CVD mortality and SES was reported only in a single study analyzing data from the period of 1998-2004.

It is obvious, that to develop targeted interventions against CVD the groups of the population with high risk should be identified. The fact that in the most deprived areas of the country high representation of Roma people can be found indicates the need of studies on this severely vulnerable population.

Roma are the largest ethnic minority group in Europe. It is estimated that approximately 12 to 15 million Roma live in the World Health Organization's European Region including an estimated 10 million that reside in the European Union (EU). Their representation in the population is greatest in Bulgaria, Romania, Slovakia, Hungary, the Czech Republic and Slovenia, but the EU enlargements of 2004 and 2007 have enabled growing numbers to migrate into and to settle in other countries of the EU. The share of Roma without health coverage reaches almost 30% in Bosnia-Herzegovina, over 40% in Bulgaria and Romania and 59.7% and 67.7% in Moldova and Albania, respectively. It was also reported that 8.8% of Roma

has no health coverage in Hungary.

During the history of Hungary, the Roma have mixed with the local populations. However, a significant portion of them settled in the marginal areas where they live in segregated colonies. They can be characterized with low level of education and limited access to the labour market.

The first Roma health behaviour survey indicated that the representation of CVD risk factors as heavy smoking and unhealthy diet were 1.5 to 3 times more prevalent among Roma than in the lowest income quartile of the Hungarian general population. However, no data have been published neither on CVD morbidity nor mortality among Hungarian Roma.

Concerning the international epidemiological research on the health of Roma people it has only recently extended to the field of non-communicable diseases and their risk factors. These studies are limited in number and have severe uncertainties regarding the identification of Roma and are restricted to one or a few indicators. Some studies showed no difference between Roma and non-Roma populations in CVD occurrence, whereas others report substantial evidence on the increased prevalence of various CVD risk factors among Roma people. Concerning statin use among Roma, only a single study was published on a small sample of Slovakian Roma indicating less frequent statin use in Roma compared to non-Roma.

2. Aims

Within the Central Eastern European/ Central, Eastern and South-Eastern European (CEE/CESEE) countries, no study has conducted on the relationship between statin utilization and socioeconomic characteristics of different population groups so far, although epidemiological data have clearly demonstrated that cardiovascular mortality is extremely unfavourable in these countries. Therefore, we decided to analyze the association between statin utilization and socioeconomic status in Hungary.

Based on the existing literature and empirical evidence the following six hypotheses were set up and examined in our study:

- H1: An association exists between the premature mortality caused by CVDs and deprivation.
- H2: A relationship exists between the premature cardiovascular mortality and the relative frequency of statin utilization.
- H3: An association exists between the relative frequency of statin prescription and deprivation.
- H4: An association exists between the relative frequency of statin redeeming and deprivation.
- H5: A relationship exists between the statin prescription/redemption rates and deprivation.
- H6: The Decade of Roma Inclusion targeting the improvement of health and access to health care of this severely vulnerable population may have influence on statin utilization, too.

Our study relied on the following known data and facts:

- The number of prescriptions for statins by general practitioner (GPs).
- The number of statin prescription redeemed by patients.
- The CVD mortality is unequally distributed in Hungary.
- The health status of the population is worse in the more deprived areas of the country.

The aim of the study presented in this thesis was to provide data on statin utilization and its relation to the socioeconomic characteristics of various population groups in Hungary and, as a conceptually new approach on the relationship between redemption and prescription rates, to define the contribution of patient and/or physician factors to the inefficiency of statin utilization, if one exists, on CVD prevention. Because physicians in general practice are the key persons that initiate, coordinate, and provide long-term follow-up for CVD prevention, our study was performed as a cross-sectional analysis utilizing data on statin prescription and redemption rates from all general practices in Hungary. Furthermore, the ratios of the statin prescription and redemption rates were analyzed as functions of deprivation in the areas served. We also aimed to investigate the utilization of cholesterol lowering medication (mainly statin utilization) in the last decade among Roma, living in segregated colonies of the most deprived areas of Hungary. Thus, we investigated whether statin utilisation has any potential impact on the health status of Roma population.

3. Materials and methods

This study focused on the comparative analysis of data on prescriptions by general practitioners (GPs) and redeemed prescriptions for statins in Hungary during 2012. It was the last year for which all data necessary for the analysis were available in validated databases in a district level study design. The ratios between the number of redeemed prescriptions and that of the prescriptions for statins were used to characterize the level of primary non-compliance. The associations between deprivation and premature mortality caused by diseases of the circulatory system (ICD-10: I00-I99), particularly ischemic heart disease (ICD-10: I25), as well as deprivation and statin utilization (prescription, redemption, and their ratio) were also assessed. In addition, in a questionnaire-based survey data were collected – among others – on the prevalence of statin utilization among Roma in 2015. These findings were compared with data obtained about ten years earlier in a Roma health behaviour survey on the same Roma population sample frame by the same instrument.

3.1. Data Sources

Administratively, Hungary is divided into 19 counties plus the capital Budapest; thus, it has 20 European regions at the third level of the Nomenclature of Territorial Units for Statistics (NUTS). The counties are further subdivided into 198 districts constituting Local Administrative Units 1 (LAU1), formerly known as NUTS level 4 of Hungary.

For the year 2012, the mortality data were obtained from the Hungarian Central Statistical Office (HCSO), whereas population data were obtained from the Central Office for Administrative and Electronic Public Services. Both mortality and population data for the districts were stratified by 5-year age bands and sex.

The number of prescriptions for statins and the number of redeemed statin prescriptions were obtained from the National Health Insurance Fund Administration (NHIFA) of Hungary for each primary healthcare practice for the entire year of 2012 from the detailed monthly reports of the general practices and the relevant weekly accounting reports of the pharmacies. Technically, the following data were collated from the monthly reports of the general practices: B303 series of the prescribed medicines, Social Security (SS) numbers of patients and their status in the SS system, identification number of general practitioners (GPs) who prescribed the drugs, as well as that of practices. GPs and practices contracted by the NHIFA for the entire period of 2012 were identified from the NHIFA's database. By combining these two databases the number of prescriptions was defined by ATC-coded groups of medicines. To define the number of redeemed prescriptions these data were linked with the data of the Bréver software containing the weekly accounting reports of the pharmacies. According to the Hungarian regulations, GPs can prescribe only one type of medicine as a 1-month dose for one prescription for people who are taking long-term medications. The data were aggregated at the district level. To define the frequency of prescription and that of redemption, the denominator was the size of the 40+-year-old population that was adjusted for the rate of the 60+-year-old population of the district. Data used to estimate the utilization of cholesterol lowering medicines (mainly statins) among Roma were obtained in the first and second Roma Health Survey.

3.2. Deprivation index calculation

Deprivation index (DI) was used to provide information about socio-economic deprivation at the district level compared to the national average for 2011, the year of the last census in the country. Socio-economic indicators for the DI were selected from available data stored at the Regional

Information System of the Ministry of Local Government and Regional Development. The data were originally obtained from the Hungarian Central Statistical Office (Census, 2011) and the Hungarian Tax and Financial Control Administration (2011).

The method to calculate DI values was described previously and was successfully used in former studies designed to characterize the association between deprivation and mortality amenable to healthcare as well as between deprivation and premature mortality due to alcoholic liver disease in Hungary. Briefly, DI is based on seven elementary socio-economic indicators, including income, level of education, rate of unemployment, rate of one-parent families, rate of large families, density of housing and car ownership. The variables were transformed using the natural log transformation and standardization (z-scores). The district-specific index is a weighted sum of the z-scores, with higher values representing greater deprivation. The weight of each variable was determined on the basis of the standardized scoring coefficients using a principal component analysis. The areas with positive index values are districts with a lower socio-economic status compared with the national average, and the converse is found in districts with negative index values.

3.3. District level study

In Hungary, the number of GP practices operating was 6,658 in 2012. The size of the practices, as the number of clients served, varied widely (800–3000 persons/practice), and the average size was 1,488 persons/practice. Generally, more practices operate in higher populated municipalities, whereas one GP serves more than one municipality in less populated areas. In addition, there are general practitioners with obligations to provide in-area care and those without such duties.

To reduce the risk of misclassification all data were aggregated to the district level for the following reasons:

- the free choice of family physician is a norm in Hungary,
- the detailed population data for practices, as well as the statin utilization data by age group are available, but in only an aggregate form the detailed population data for practices, as well as the statin utilization data by age group are not available due to personal privacy,
- and the DI is not available at the practice level.

The deprivation for each district was calculated using the population weighted average of DI. All districts included in the analysis were classified into three tertiles, ranging from the least deprived (tertile I) to the most deprived (tertile III), with each containing a third of the practices.

In our analyzing we used the Rapid Inquiry Facility (RIF). The RIF embedded in ArcGIS is a freely available software application that supports disease mapping and risk analysis studies. As an integrated information system can be properly used for the assessment of relationships between the environment and health and aims to provide and aims to provide understanding of the links between environmental conditions, health outcomes and risk.

Using the “disease mapping” option within the RIF, spatial patterns of cardiovascular mortality (ICD-10: I00-I99) and mortality due to chronic ischemic heart disease (ICD-10: I25) for the 40+ age group for 2012 were investigated and visualized at the district level. Indirectly, standardized mortality ratios were calculated using sex- and age-specific death rates for the Hungarian population.

The frequency of prescriptions for statins, redeemed statin prescriptions, and the ratios for compliance in relation to the national

average were also mapped using the RIF and their association with deprivation was defined using tertiles of DI as a district-based categorical covariate and the risk analysis capabilities of the RIF.

3.4. Roma Health Surveys

Two surveys (both in segregated colonies of Borsod-Abauj-Zemplén, Szabolcs-Szatmár-Bereg and Hajdú-Bihar counties) were carried out in 2004 and 2015 to characterize health behaviour among Roma in Hungary. Study protocols have been approved by the Ethical Committee of the Hungarian National Scientific Council on Health (TUKEB 445/2003 and TUKEB 47062/2015).

3.4.1. The first Roma Health Survey in 2004

In 2004, the total population of the above counties was 1,877,243 and approximately 62,000 persons lived in Roma colonies. Between 2001 and 2003, a detailed environmental survey was undertaken in the three counties mentioned above; and the researchers identified all settlements in which the population was almost exclusively Roma and recorded the number of people living in them. To create the Roma sample, a 2-stage sampling process was used: towns and villages in the three counties with identified colonies with more than 100 habitants were selected randomly, and then households were selected with the random walk method, based on a map of the settlement. All adults in the households selected were interviewed – among others on medicines they use on a regular basis. The names of medicines were recorded by the interviewers. To maximize the response rate, interviewers were Roma and the survey was supported by local Roma civil society organizations. In this First Roma Health Survey, of the 1000 attempted interviews, 969 interviews were completed successfully (96.9% response rate). Data regarding the use of cholesterol lowering medication

could be obtained from 941 persons younger than 65 years by registering the name of medicines used by the survey participants.

3.4.2. The second Roma Health Survey in 2015

The location of Roma colonies was rechecked before the 2015 survey, and the sampling frame was corrected accordingly. The questionnaire-based data collection was carried out also by Roma interviewers supported by the local Roma self-government. In this survey, the sampling frame contained 123 colonies where 52,099 Roma persons were registered. The sampling method was the same as in the first Roma Health Survey. The sample consisted of 1000 Roma adults and the response rate was 90.5%.

The only difference between the two surveys was that while in the 2004 survey data on cholesterol-lowering medication was collected by registering the names of medicines used by the survey participants, in the 2015 survey questions asked laboratory testing for lipid levels and diet and/or medication used in case of elevated cholesterol level.

4. Results

4.1. Association between deprivation and premature mortality caused by cardiovascular diseases

Deprivation index values defined by districts varied widely from -3.76 to $+5.83$, which indicates a high level of socio-economic inequalities in the country. The tertiles based on the DI values were defined as ranges of $-3.76 \leq DI \leq -0.6$, with an average of -1.32 (tertile I); $-0.6 < DI \leq 0.58$, with an average of -0.04 (tertile II); and $0.58 < DI \leq 5.83$, with an average of 1.59 (tertile III). The least-favoured districts were found in the north eastern and Southwestern parts of Hungary in 2011, whereas the least deprived districts were located in the North-western part of the country as well as in the capital city of Budapest and neighbouring areas.

The spatial distribution of premature mortality due to diseases of the circulatory system and chronic ischemic heart disease in Hungary was also characterized by significant inequalities. The districts with the highest estimated SMRs are localized in the more deprived areas, particularly for chronic ischemic heart disease.

This is supported by the results of the risk analysis showing a significant positive association between the relative risk of premature cardiovascular mortality and deprivation (χ^2 homogeneity = 405.15, $P = 0$, χ^2 linearity = 391.57, $P = 0$) as well as between deprivation and premature mortality caused by chronic ischemic heart disease (χ^2 homogeneity = 443.89, $P = 0$, χ^2 linearity = 412.96, $P = 0$).

4.2. Statin utilization (prescription, redemption, and their ratios)

In Hungary, a total of 10,044,005 statin prescriptions by GPs (simvastatin, atorvastatin, rosuvastatin, pravastatin, and fluvastatin) were prescribed in 2012, and only 63.39% [63.37–63.43%] (6,367,738) were redeemed. The frequency of prescription was 1.971 [1.9701–1.9725] and the frequency of redemption was 1.249 [1.248–1.251] per person aged 40+ years. These values were considered as national average.

The frequency of statin prescriptions in relation to the national average was higher in districts in the North-western and South-eastern parts of Hungary and in the middle of the country. The districts with a higher relative frequency of statin redemption were primarily located in the Southern part of Hungary. Districts with a higher redemption (primary compliance) rate were located along the axis in the North-eastern-to-South-western direction of Hungary, although the spatial distribution did not show clustering.

The results of the risk analysis showed a reverse J-shaped association between the relative frequency of statin prescriptions and deprivation. The areas of highest deprivation showed a low relative frequency of statin prescriptions (1.89 per person). A positive association was observed for the frequency of statin redemption by degree of deprivation. Significantly higher compliance was observed in districts with the highest deprivation (67.88% [67.812–67.951]).

4.3. Statin use among Roma

In the first Roma Health Survey, the total sample number was 941 and 18 of the participants were treated with a cholesterol-lowering medication, i.e. 1.9% of Roma people have taken cholesterol lowering products in 2004. Among men the utilization of cholesterol lowering

therapeutics was more frequent than among women (2.19% vs 1.65%), and for both sexes, the highest prevalence was observed in the age group of 45-64 years (among men 5.2%; among women 5.3%).

In the second Roma Health Survey, the total number of participants was 866 and 46 of them were receiving a cholesterol-lowering medication. In all age groups the prevalence was found higher among women than among men. For both sexes the highest frequency of cholesterol lowering medication was detected in the age group of 45-64 years (men 6.1%; women 11.5%).

Concerning the fact that the prevalence of Roma persons on cholesterol lowering medication was 1.9% in 2004, and 5.3% in 2015 an almost threefold (2.8 times) increase in the prevalence of people on cholesterol lowering medication could be detected in the period spanning the entire Decade of Roma Inclusion.

5. Discussion

In Europe, the East-West life expectancy gap has been a well-known epidemiological phenomenon for a long time. It was clearly demonstrated that the difference of extraordinary magnitude is most strongly related to the high rate of premature mortality from cardiovascular diseases. The inequalities in CVD mortality and that in preventive medication targeting CVD risk factors are very intensely studied in the populations of the high-income EU15 countries. Conversely, reports for the EU13 countries, especially for the most affected CESEE EU member states, are extremely scarce. For the most developed countries, a large number of studies were published on the effect of socioeconomic status on statin utilization, with conflicting results, while these studies are almost completely missing for the EU13 countries.

The 2012 guidelines from the Fifth Joint Task Force of the European Societies on CVD Prevention in Clinical Practice suggest that all hypertensive patients with established CVD or with type 2 diabetes and patients with an estimated 10-year risk of cardiovascular death $\geq 5\%$ based on the SCORE chart should be considered for statin therapy. The 2013 AHA/ACC (American Heart Association/American College of Cardiology) guidelines on the management of elevated blood cholesterol for the primary and secondary prevention of atherosclerotic CVDs suggest appropriate levels of statin therapy for different risk groups.

The WHO guidelines for the prevention of CVDs recommend preventive medication to lower cholesterol level in all individuals with total cholesterol at or above 8 mmol/l, and in those with high cardiovascular risk.

With minor limitations, it is generally accepted, that in those dyslipidemic persons who have not already had a vascular event but are at a higher cardiovascular risk, combined statin therapy substantially reduces the

CVD mortality risk, thereby potentially being an ideal decrease risk factor with added risk reducing by lifestyle changes. Evidence for statins for secondary prevention in individuals after a heart attack is more robust, reducing the risk of a second heart attack by about one-third. Since CVD-related premature mortality is significantly higher in CEE countries including Hungary when compared to the most developed countries of the European Region, one might be reasonable to suggest that preventive interventions, such as preventive medication with statins, have not been considered or implemented sufficiently.

Our present study was designed to answer the question whether a lack and/or ineffectiveness of preventive medication may also exist behind the above mentioned discrepancies; hypothesising that preventive medication is not adequately reaching people characterized by possessing higher risk of CVD, especially those living in socioeconomically deprived conditions. To the best of our knowledge, this is study is the only one from CESEE, analyzing the association between statin utilization and socioeconomic deprivation. In this country-wide analysis, the standardized premature CVD mortality rates, frequency of statin prescriptions, redeemed statin prescriptions, and ratios for compliance compared to the national average were mapped; and their associations with deprivation (tertile of deprivation index as a district-based categorical covariate) were defined.

Based on studies found in international literature there are significant differences between medication prescription and redemption. Behind non-compliance, several factors such as age, gender, degree of deprivation, type of medication, side effects and support of medication may exist. Reason for non-compliance may also be the inadequate function of the health care system: physicians do not want to follow the effect of prescribed drug, while patients will not go back to the doctor to consult about the current status.

All of these might be expected to impact adversely on the health status of the population, especially on that of people living in highly deprived conditions. Many studies have shown the poor health of Roma, the most vulnerable ethnic population in Europe and the high levels of their health needs are unmet due to the impairment of their access to health care. It is reasonable to suppose that their health status is much worse and the average life expectancy is much shorter than that of the majority population. However, it is difficult to assess the size of the problem, because of the limitations of collecting data on health and health care utilization by ethnic status. Consequently, it is necessary to rely on one-off surveys, which consistently show that the health of Roma is much worse than that of the general population, while they face important barriers in accessing health services.

In addition to the EU, many international organizations have also sought to promote Roma inclusion over the past two decades, including the World Bank, the United Nations Development Programme, the Council of Europe, and the Organization for Security and Cooperation in Europe. At the national level, various governmental strategies have been adopted aiming at Roma inclusion. In 2005, international organizations and national governments in the region decided to launch the Decade of Roma Inclusion, i.e. to establish a framework for action to improve the situation of the Roma. The Decade supported progress in targeted sectors such as education, employment, health and housing. Future European policies including the EU's Europe 2020 program as well as other national initiatives also dealt with this issue.

It is known that a relationship exists between health and socio-economic status. In Hungary, researchers developed the deprivation index at the municipality level, which is a multi-dimensional index providing information about the socio-economic deprivation in the country. Indicators

from the 2011 national census were used to calculate the DI. These were income, low education, unemployment, one-parent families, large families, density of housing and car ownership. DI helped to identify large areas of deprivation were detected in the North-eastern, Eastern, and South-western parts of Hungary. The least developed and most underprivileged parts of the country were areas within the counties of Borsod-Abaúj-Zemplén and Szabolcs-Szatmár-Bereg, both located in the North-eastern part of Hungary, and areas within the countries of Somogy and Baranya (that are located in the Southwestern part of Hungary). The most deprived areas were found in the rural, formerly industrial, parts of the country, which currently have small villages.

Our results are consistent with findings on the tremendous effect of socio economic factors on health published for different countries and clearly show that standardized mortality rates caused by CVDs are significantly higher in districts with the highest DIs in Hungary. Although premature mortality caused by ischemic heart disease was found to be highest in the same districts, the frequency of statin prescriptions at the primary care level was significantly lower than the national average. However, the rate of redemption, and consequently, the ratio between redemption and prescription rates were significantly higher. These data clearly indicate that insufficient statin utilization in these districts is highly linked to the so-called physician-factor; i.e., statin prescription, consequently statin treatment is poor and represents significant barriers to mortality reductions, particularly among people living in highly deprived areas of the country.

Reflecting to our hypotheses we have tested the followings can be concluded:

- The risk analysis demonstrated a significant positive association between deprivation and the relative risk of premature cardiovascular mortality.
- The risk analysis demonstrated a significant positive association between the relative risk of premature cardiovascular mortality and the relatively low frequency of statin prescriptions.
- A significant positive association was demonstrated between the relative frequency of statin prescription and deprivation.
- In districts with the highest deprivation significantly higher primary compliance (redemption) was observed.
- Higher statin redemption rates were associated with areas of higher deprivation in Hungary.
- The prevalence of utilization of cholesterol lowering medication among Roma was increased from 1.9% to 5.3% during the entire period of the Decade of Roma Inclusion.

The socio-economic gap in health and mortality is widening in Europe therefore the identification of gaps in preventive services in deprived areas is of the utmost importance. The statement reducing socio-economic inequalities in mortality in Western Europe critically depends upon speeding up mortality declines from CVDs in lower socioeconomic groups, and countering mortality increases from several other causes of death in lower socioeconomic groups can be interpreted as an imperative on how to improve the health of the population for the low- and middle-income countries of the European Region. Our study identifies a gap in current cardiovascular prevention practice by showing that many patients are likely under-treated and others remain untreated.

On the basis of our results obtained in the two Roma Health Surveys, it was demonstrated that the prevalence of cholesterol-lowering preventive medication was extremely low among Roma (1.9%) in 2004, and although it increased significantly between 2004 and 2015 it remained as low as 5.3% in the adult Roma population. Considering the high rate of premature mortality in the most deprived regions of the country, it is reasonable to suppose that the insufficient level of statin medication may also contribute to the unfavourable health status of the most vulnerable Roma population.

Regarding the reasons and remedies for under-treatment, it seems likely that the lack of financial incentives for primary prevention at the level of primary care has a strong effect, particularly if it meets the low health literacy of people living in the most deprived districts. Although a survey (UNDP/World Bank/EC Regional Roma Survey 2011) revealed a high percentage of households unable to afford prescription medication in eleven countries of the CEE region, including Hungary, our results show significantly higher redemption rates in the most deprived districts of the country indicating that primary non-compliance is not the most important factor that contributes to insufficient preventive medication. Based on our results, the importance of determining why GPs do not follow guideline recommendations regarding lipid-lowering treatment should also be emphasized. Benefits provided by the National Health Insurance Fund of Hungary include cost-free healthcare services, such as preventive examinations, primary healthcare, and drug reimbursement on grounds of equity. For persons who have low income or are on social welfare, medical exemption certificates are available, and they are exempt from prescription charges in the case of defined medicaments including the majority of statins.

We can conclude that under-utilization of statins in the most deprived areas is mainly caused by the relatively low prevalence of prescription, but it has to be emphasized that improving prescription rate

alone is not sufficient to solve this problem. Monitoring adherence and defining the reasons of non-adherence in the Hungarian population seem to be very important, because in the international literature even the very sporadic findings are quite contradictory. A report based on data from Finnish healthcare registers showed that low SES was associated with overall and rapidly increasing statin nonadherence among men, while in case of women, associations between SES and nonadherence were weak and inconsistent. Contradictory in a study from Turkey the opposite finding was demonstrated. Namely, discontinuation of statin treatment was decided by patients with higher education more likely than those with lower - only primary – education.

The limitations of our study should also be mentioned. All three factors (patient, physician, and healthcare system) that have an effect on statin utilization cannot be covered in a single study. The effects associated with socio-economic factors may be mediated by other factors that were not included in our analyses. Health system factors were only partially studied; and access to care, especially in case of Roma, requires particular attention in further studies. Information about various elements that may influence a patient's likelihood to take statin medications should also be collected to understand the relatively low redemption rate in areas with the lowest deprivation indices. Concerning preventive medication, statins represent only a single segment of the arsenal, so further studies on the utilization of antihypertensive and antiplatelet drugs are also required.

In the future, we aim to conduct a comparative analysis on statin adherence between Hungary and countries in similar (economic, social and cultural) situation. Furthermore, we are planning to investigate the differences in medication adherence between the Roma and the Hungarian population. Finally, we would like to analyze the relationship between the utilization of other medication and SES in Hungary.

SUMMARY

The risk of premature mortality caused by cardiovascular diseases (CVDs) is about three times higher in the Central Eastern European countries than in the high-income European countries. The aim of the present study was to provide data on the relationship between premature CVD mortality, statin utilization (both prescription and redemption) as a preventive medication and socioeconomic deprivation characterized by Deprivation Index values grouped into tertiles at the district level in Hungary in 2012. To define the prescription and redemption rates data on statin utilization from the National Health Insurance Fund Administration were used, while the denominator was the number of the 40+-year-old population adjusted by the rates of 60+-year-old population of the district. The risk analysis demonstrated a significant positive association between deprivation and the relative risk of premature cardiovascular mortality. A reverse J shaped association was also found between the relative frequency of statin prescriptions and deprivation. Districts with the highest deprivation showed a low relative frequency of statin prescriptions; however, significantly higher primary compliance (redemption) was observed in these districts. Our data clearly indicate that insufficient statin utilization is strongly linked to the so-called physician-factor, i.e., a statin prescription. In two questionnaire-based surveys among Roma, the most deprived population of Hungary, the prevalence of persons on cholesterol lowering medication increased from 1.9 % to 5.3 % between 2004 and 2015, which indicates an almost threefold increase during the Decade of Roma Inclusion. Consequently, it can be stated that statin utilization is poor and represents a significant barrier to reducing CVD mortality, particularly among people living in highly deprived areas of the country.

Keywords

cardiovascular mortality; deprivation; health services research; prescription; redemption; Roma; statin

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