VILNIUS UNIVERSITY

INGRIDA LISAUSKIENĖ

CHANGES IN CARDIOVASCULAR MEDICINES UTILIZATION AND MORBIDITY AND MORTALITY FROM CARDIOVASCULAR DISEASE IN LITHUANIA

Summary of Doctoral Dissertation
Biomedical Sciences, Medicine (06 B)

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INGRIDA LISAUSKIENĖ

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LIST OF ABBREVIATIONS

A-AB	Alpha- adrenoreceptor antagonist
ACEI	Angiotensin converting enzyme inhibitor
AH	Arterial hypertension
ARB	Angiotensin II antagonist
ATC	Anatomical Therapeutic Chemical (ATC) classification system
BB	Beta bloking agent
BP	Blood pressure
C_{DDD}	Co-payed expenditure for 1 DDD
CCB	Calcium channel blocker
CG_{DDD}	Co-payed expenditure for 1 DDD of generic medicine
CHD	Coronary heart disease
CO_{DDD}	Co-payed expenditure for 1 DDD of originator medicine
CV	Cardiovascular
CVD	Cardiovascular disease
CVM	Cardiovascular medicine
DDD	Defined daily dose
DDD/TID	Number of Defined Daily Doses per 1000 inhabitants per day
DK	Denmark
EAPC	Estimated annual percent change
EE	Estonia
FI	Finland
FIX-D	Fixed-dose combination
FO	Females 65 years of age and older
FY	Females 18-64 years of age
GDP	Gross domestic product
HCT	Hydrochlorothiazide
INN	International Nonproprietary Name of medicine
LT	Lithuania
LV	Latvia
MY	Males 18-64 years of age
MO	Males 65 years of age and older
NHIF	National Health Insurance Fund
NU/TIY	Number of new medicine users per 1000 inhabitants per year
NO	Norway
R_{DDD}	Reimbursed expenditure for 1 DDD
RAS	Renin – angiotensin system
RG_{DDD}	Reimbursed expenditure for 1 DDD of generic medicine
RO_{DDD}	Reimbursed expenditure for 1 DDD of originator medicine
SDR	Age - standardized death rate per 100 000 population
SNS-AH	Antihypertensive acting on sympathetic nervous system
SE	Sweden
WHO	World Health Organization
% change	Percentage change

1. INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of mortality globally (Roth GA, 2015). In Europe, CVD is responsible for 51% and 41% of all women's and men's deaths, respectively (Nichols M. 2014). Striking differences can be observed between the regions and countries: compared to Western Europe and in the Scandinavian countries, CVD death rates have been decreasing over the past 30 years,the age-standardized death rate (SDR) for CVD in Central and Eastern Europe is more than 6,5- and 4,0-fold higher in men and women, respectively. (Nichols M, 2014). This geographical difference in CVD death rate is called the "North-East to South-West gradient" (Müller-Nordhorn J, 2008). Unfortunately, the age-SDR for CVD in Lithuania is one of the highest in the European Union (EU). Based on data from the Lithuanian Statistics department, the main causes of death in Lithuania have remained unchanged for many years, with the primary cause of death being CVD (56,6%). In 2012, CVD was the most common cause of death in men (47,8%) and women (65,6%), and comprised coronary heart disease (CHD; 65,9% and 63,8%, respectively) and cerebrovascular diseases (20,6% and 27,2%, respectively). Additionally, CHD was responsible for the deaths of the majority of working-age men (19,0%) and women (12,1%).

The decrease in mortality from CVD in Europe is attributed to the correction of risk factors, primarily through active preventive practices and proper treatment (Berg J, 2014; Nichols M, 2013; Van Dis I, 2012). In 2012, the European Cardiology Society published guidelines for CVD prevention in clinical practice, which described the following main tools for prevention: smoking cessation, adequate physical activity, healthy nutrition and correction of overweight/obesity, adequate arterial blood pressure (BP), blood lipid metabolism and glycaemic control, and stress management. Arterial hypertension (AH) is the main CVD risk factor, requiring timely treatment. In Lithuania, 51,2% of men and 43,4% of women older than 25 years have BPs higher than 140/90 mm Hg or are using antihypertensive drugs. The prevalence of AH in Lithuania is the third highest based on data from 51 European countries (Nichols M, 2014).

The use of cardiovascular medicines (CVM) is widespread and increasing, with the goal of lowering CVD complications and improving patient outcomes. The increasing

use of CVM and treatment for CVD complications contributes to the increasing costs of treatment. In Lithuania, pharmaceutical expenses make up 28,3% of the total health care costs, the third highest in Europe after Greece (30,5%) and Hungary (30,6%) (OECD, 2014). But in EU countries such as Denmark and Sweden, where the CVD mortality rates are among the lowest, CVD drugs constitute only 6,3−10,1% of total health care costs. Per-person, this amounts to 445 USD in Lithuania, 496 USD in Sweden, and 288 USD in Denmark (OECD, 2015). The increasing use of antihypertensive medicines in Lithuania, measured in Defined Daily Doses for 1000 inhabitants per day (DDD/TID), exceeds that of other countries, but the effects of this increased drug use on the CVD death rate and morbidity have not yet been observed. This begs the question: "Are we using the available resources and medicines rationally?"

More than 30 years ago, the World Health Organization (WHO) presented the concept of rational drug use, which was defined as "the use of drugs, when patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community". Non-rational drug use is considered by WHO to be one of the biggest threats to health care, as approximately 50% of the medicines in the world are prescribed, provided, or distributed without compliance with the rational drug use criteria and approximately 50% of patients are using drugs incorrectly (WHO, 2002).

Administrative databases were created in many of the European countries to collect data regarding the distribution and use of medicines. These databases allow for an analysis of the rationality and actual expenses of treatment and are used to conduct large-scale studies on medical drug use. These studies aim to follow the path of each drug, from the producer to the patient, to form drug policies and to develop adequate intervention strategies to motivate rational drug use (Ferrer P, 2011; Latry P, 2001).

Long-term research on CVM use has not yet been conducted in Lithuania, despite the existence of data regarding reimbursed drugs dating back to the year 2000 (the National Health Insurance Fund [NHIF] database). This research would allow the evaluation of CVM utilization pattern and rationality, its impact on CVD mortality, and provide information on interventional tools to improve CVM use.

2. AIM OF THE RESEARCH

To analyse the pattern of and the changes in cardiovascular medicines utilization in Lithuania between 2003 and 2012 and the impact on mortality from cardiovascular diseases.

3. TASKS OF THE RESEARCH

1. To analyse trends in CVM utilization in Lithuania between the years of 2003 and 2012 and to compare them with data from other countries over the same time period.
2. To evaluate the impact of CVM utilization, CVD risk factors, and the interaction between the two on the CVD mortality rate.
3. To determine age- and sex-related differences in the utilization of reimbursed medicines to treat AH.
4. To evaluate the compliance of AH treatment in Lithuania to the European Society of Hypertension and of the European Society of Cardiology guidelines.
5. To determine the effectiveness of the reimbursed medicines treatment for AH, evaluating the utilization and expense of generic medications.

4. PROPOSITIONS TO BE DEFENDED

1. The utilization of CVM in Lithuania is increasing and reduces CVD mortality rates.
2. The utilization of CVM and the prevalence of CVD risk factors in Lithuania are different from those of the Scandinavian or other Baltic countries, and these factors influence CVD mortality.
3. AH treatment differs by age and sex.
4. AH treatment is not always rational and does not always comply with the European Hypertension treatment guidelines.
5. The utilization of CVM for the treatment of AH in Lithuania is not effective.

5. SCIENTIFIC VALUE AND NOVELTY OF THE RESEARCH

6. This is the first retrospective study reflecting the use of all CVM for the entire Lithuanian population during the years 2003-2012, as well as the influence of CVM use on CVD mortality. This study compares CVM utilization, risk factor prevalence, and the influence of their interaction on the CVD death rates in different Baltic states and Scandinavian countries. This study evaluates the differences in AH treatment between men and women of different ages regarding types of medicines prescribed, treatment initiation, and compliance with AH treatment guidelines of the European Society of Hypertension and the European Society of Cardiology. In addition, this study evaluates the cost effectiveness of treating AH. The findings of this research can inform actions to ensure integration of evidence based medicine principals into everyday clinical practice, the planning of medication policies in Lithuania, and ensure effective use of pharmaceutical expenditure while ensuring high quality health care to every citizen.

6. RESEARCH METHODOLOGY

6.1. Data source

This research was done in Vilnius University Medical Faculty Department of Pathology, Forensic Medicine and Pharmacology in cooperation of with NFIF under the Ministry of Health. The data on dispensed reimbursed CVM was obtained from the population-based electronic database SVEIDRA of the NHIF, which contains information on all dispensed prescriptions of reimbursed medicines since the year 2000, and covers up to 100% of insured population (about 98% of population is covered by health insurance). In the beginning of every month the data about the provided reimbursed medicine is sent from more than 1400 pharmacies, that have agreements made with the Regional Health Insurance funds. In the database SVEIDRA such data is gathered: patient's identification code, age, sex, residence place, primary care institutions and services provided (diagnosed diseases, visits to the general practitioners and specialists), performed diagnostic tests, provided inpatient treatment services, death date.

In this database these data about the reimbursed medicines is gathered: medicines Anatomical Therapeutic Chemical (ATC) classification system code, the International Nonproprietary Name of medicine (INN) and brand name of the medicine as well as the identification code, number of dispensed units (pill, ampoule, inhalator and etc.), dose of the unit, the indications of the medicine provided, naming the disease code according to the International Statistical Classification of Diseases and Related Health Problems 10th revision Australian Modification (ICD-10-AM), date of receipt prescription and issuance, period of treatment, reimbursed and patient co-payed expenditure.

In this database the data about the doctors prescribing of reimbursed medicines is collected: the doctors identification code, the doctors speciality, the medical institution and region, where the doctor is working at.

In this research the inquires formed according to the research objectives were submitted to the administrator of this database. The data received was depersonalized,

providing the changed patient code, preventing from the identification of the person, but only providing patients sex and age data.

6.2. Study population and research material

The study population consisted of all of the citizens of Lithuania, to whom according to NHIF database at least one reimbursed CVM (ATC group C), without evaluating the treatment indications. The utilization of these medicines was analyzed: C01 – cardiac therapy medicines, C02 - antihypertensive medicines acting on sympathetic nervous system (SNS-AHs) and subgroups: C02A - centrally acting antiadrenergic medicines, C02C – alpha adrenoceptor blockers (A-ABs), C03 – diuretics, C04 - peripheral vasodilators, C07 – beta blockers (BBs), C08 - calcium channel blockers (CCBs), C09A – plain angiotensin converting enzyme inhibitors (ACEIs), C09B – ACEIs combinations, C09C - plain angiotensin II receptor blockers (ARBs), C09D – ARBs combinations, C10 – lipid modifying agents (statins).

Analyzing CVM, prescribed for the treatment of AH, utilization, the study population consisted of all citizens of Lithuania, to whom according to the NHIF database, at least one reimbursed CVM for AH treatment was dispensed according to these ICD-10-AM disease codes: I10 – primary (essential) hypertension; I11 - hypertensive heart disease; I12 - hypertensive chronic kidney disease; I13 - hypertensive heart and kidney disease; I15 - secondary hypertension in 2003-2012.

6.3. Research methodology

6.3.1. Total CVM utilization in Lithuania in the year 2003−2012

This data from the Lithuanian NHIF database was retrieved according to the request formed: medicines ATC code, INN and the brand name of the medicine, number of dispensed units (pill, ampoule, inhalator and etc.), dose of the unit, the date of drug prescription.

The drug utilization was calculated using the Anatomical Therapeutic Chemical /Defined Daily Dose (ATC/DDD) methodology, which is standardized methodology used when conducting the comparing research of drug utilization. The data of drug

utilization was expressed as number of Defined Daily Dose for 1000 inhabitants per day (DDD/TID). The total CVM and every group medicines (according to the ATC classification 5th level code) utilization and the percentage of change were calculated.

It is calculated according to the formula:

$$\mathrm{DDD}/_{\mathrm{TID}} = \frac{\text{Dose} \times \text{number of dispened units.}}{\text{DDD according to the ATC} \times \text{number of citizens} \times 365} \times 1000$$

The average number of citizens was retrieved from the Lithuanian Statistic Department database. The drug use through the year 2003-2012 was calculated.

The mostly used medicines list was provided, whose consumption made up of 90% the total CVM utilization (Drug utilization 90 % – DU 90%). The reimbursed expenditure for CVM was calculated, their percentage from all of the expenses indented for the total pharmaceutical reimbursement and the percentage change (% change) in the time of research.

6.3.2. The utilization of CVM for the treatment of AH in Lithuania in 2003-2012

Such data was retrieved from the the Lithuanian National Health Insurance Fund database according to the formed request: the indication of drug prescriptions is indicated with the AH code (I10-I15), drugs ATC code, INN and brand name of the drug, number of dispensed units (pill, ampoule, inhalator and etc.), dose of the unit, the date of drug prescription. The drug utilization was calculated using ATC/DDD methodology, described in the section 6.3.1. The percentage part from all CVM, set for the AH treatment was calculated. The list of most commonly used CVM for AH treatment was provided (DU 90%).

6.3.3. CVM utilization, CVD risk factors and their interaction's influence on CV mortality

The data of CVM utilization, age-standardized death rate (SDR) from CVD and the prevalence of CVD risk factors in three Baltic states – Lithuania (LT), Latvia (LV), Estonia (EE) – and four Scandinavian countries – Sweden (SE) Norway (NO), Denmark (DK) and Finland (FI) was analyzed in this research. CVM utilization data were retrieved from national databases, which description is provided in Table 1.

Table 1. Description of national drug utilization databases and period of available drug consumption data included to the analysis

Country	Database	Type of data	Coverage	Period
LT	Database SVEIDRA of National Health Insurance Fund under the Ministry of Health of Lithuania	Dispensed reimbursed drugs	98% of the population (100% of insured by compulsory health insurance)	2003−2012
LV	Latvian State Medicines Agency (Zāļu valsts aģentūra) [381]	Wholesale trade	100% of the population	2006−2012
EE	Estonian State Medicines Agency (Ravimiamet) [382]	Wholesale trade	100% of the population	2003−2012
SE	Swedish National Health and Welfare Board under the Ministry of Health and Welfare (Socialstyrelsen) [383]	Dispensed reimbursed drugs	100% of the population	2003−2012
NO	Norwegian Prescription Database at the Norwegian Institute for Public Health (NorPD) [384]	Dispensed drugs	100% of the population	2004−2012
DK	Danish Register of Medical Product Statistics under the Danish Health and Drug Administration (Lægemiddelstyrelsen) [385]	Wholesale trade	100% of the population	2003-2012
FI	Finnish Pharmaceutical Agency database (Fimea) [386]	Wholesale trade	100% of the population	2007−2012

The drug utilization was calculated using ATC/DDD methodology. Lithuanian CVM utilization data methodology is given in the section 6.3.1. Latvian, Estonian, Swedish, Danish and Finish CVM utilization was expressed using ATC/DDD methodology in the national databases, Norway's data was presented as a number of dispensed DDD per year in the country. DDD/TID was calculated by dividing a number

of dispensed DDD from the number of citizens given by the Norway's Statistical department.

The statistical analysis of data was carried out using the Statistical Package for the Social Sciences SPSS 22.0 and Microsoft Excel 2007. For a comparison of mean values of CVM utilization time trends in different countries the one-way analysis of variance (ANOVA) was used. POST HOC/LSD criteria was used for exploration of differences among the mean values of CVM utilization in different countries.. The influence of the research period on the dynamics of the indicators was made by linear regression models. The chosen statistically significant p value was $p < 0.05$.

Mortality data were obtained from the WHO Health for All European Mortality Indicator Database (WHO HFA-MDB) and WHO European Region Health for All Database (WHO HFA-DB). These data consisted of age - standardized death rates (SDR) per all ages 100 000 population for CVD (ICD-10 codes I00 –I99), CHD (ICD-10 codes I20 –I25) and cerebrovascular diseases (ICD-10 codes I60 –I69).

Eleven risk factors that may influence CV mortality have been chosen in this study. Selection of factors was based on European guidelines on CVD prevention in clinical practice (version 2012), and on availability of data from publicly available international sources: the WHO, the EUROSTAT, the Food and Agriculture Organization of the United Nations (FAO) databases. These databases contain the aggregated comparable data at the population level over the period of 2003-2012 (Table 2)

Table 2. Classification, description and source of selected risk factors

Factor	Code	Description	Data source
Socioeconomic factors			
Gross Domestic Product (GDP)	F1	GDP, expressed as US$ per capita, is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of the products.	HFA-DB
Unemployment rate	F2	The unemployment rate is the number of people unemployed as a percentage of the labor force. Unemployed persons are all persons 15 to 74 years of age who were not employed during the reference week, had actively sought work during the past four weeks, and were ready to begin working immediately or within two weeks.	EUROSTAT
Crude divorce rate	F3	Crude divorce rate is the ratio of the number of divorces during the year to the average population in that year. The value is expressed per 1 000 inhabitants.	EUROSTAT
Population related risk factors			
Alcohol consumption	F4	Recorded alcohol consumption is defined as the recorded amount of alcohol consumed per adult (15+ years) over a calendar year in a country, in liters of pure alcohol. The indicator only takes into account the consumption that is recorded from production, import, export, and sales data often via taxation.	HFA-DB
Smoking	F5	This indicator is expressed as the percentage of regular daily smokers in the population aged 15 years and above. This indicator is measured using the standard questionnaire during a health interview of a representative sample of the population.	HFA-DB
The energy value of a daily intake of food	F6	The total amount of food converted into kilocalories, which is available for consumption per person per day. It is calculated according to the overall food quantity, produced in the country, adding the imported food, as well as the corrected amounts of stock available from the start of the reporting period.	FAOSTAT

Fruits and vegetables consumption	F7	Consumption of vegetables and fruit expressed in kg per person per year.	FAOSTAT
Personal perception of health condition	F8	The concept is operationalized by a question on how a person perceives his/her health in general using one of the answer categories very good/ good/ fair/ bad/ very bad. The data are expressed by percentage of population, which estimate self-health condition as very good and good.	EUROSTAT
Health care system related factors			
The number of hospital beds	F9	This indicator is expressed as number of available beds in hospitals per 100 000 inhabitants. Total hospital beds are all hospital beds which are regularly maintained and staffed and immediately available for the care of admitted patients.	EUROSTAT
The number of practicing doctors	F10	Number of practicing physicians who provide services directly to patients per 100 000 population.	EUROSTAT
Health care expenditure per capita	F11	Health care expenditure is expressed in euro per capita.	EUROSTAT

The strength of the associations between the use of CVM and CV-SDR in all countries was examined using Pearson's correlation coefficient. The Pearson's correlation coefficient also was used to evaluate the influence of the factors on the use of CVM and on CV-SDR.

The multiple linear regression model, adjusted for multi-collinearity and interaction terms, was used for modelling the outcome – the relationship between CV-SDR and the use of CVM including a series of other changing variables of the risk factors. Regression analysis was performed, using the following equation:

$$CV\text{-}SDR = CVM + F_n + (CVM * F_n)$$

- CV-SDR – CV mortality (dependent variable)
- CVM – utilization of CVM expressed in DDD/TID (independent variable)
- F_n – value of factor, included to analysis (independent variable)

This equation presents variation in CV-SDR induced by changes of the use of CVM while F_n is fixed. Independent variables were centred prior to analysis.

Partial correlation analysis was performed in order to get a correct picture of the relationship between the use of CVM and CV-SDR by controlling the variables, and to study the effect of each variable separately. P value of < 0.05 is considered statistically significant. No extrapolation based on available risk factor trends was made if data was not available in databases.

6.3.4. Sex and age differences in the treatment of AH in Lithuania in 2003-2012

In order to evaluate sex and age differences in AH treatment, patients were classified into four groups: younger (aged 18-64 years) women (FY) and men (MY) and older (aged at least 65 years) women (FO) and men (MO). These groups were compared in terms of use of CV medications. The total CVM and every groups medicine (according to the ATC classification 5th level code) utilization and the percentage of change were calculated. Drug utilization was calculated using ATC/DDD and was expressed as the DDDs per 1000 persons in the population meeting group age and sex

characteristics (DDD/TF_YD, DDD/TM_YD, DDD/TF_OD, DDD/TM_OD). Yearly information about the population was retrieved from the Lithuanian Statistic Department database.

The number of drugs simultaneously used to treat AH was a variable of interest. To estimate the prevalence of monotherapy as well as the use of two, three and four or more drugs for AH treatment, three-month cross-sectional samples were taken from each year (from 1 January to 31 March). Each individual with at least one prescription for an AH medicine (ATC classification group C) was considered a prevalent user. Fixed-dose combinations (FIX-Ds) were considered one prescription in each ATC subgroup. According to the anonymous code provided to every patient, it ensures, that the person is registered only once. It is considered, that the patient is using several drugs, if few receipts for different CVM for AH treatment are issued during the same day. The proportion of different age and sex patients treated with one, two, three and four or more medicines were calculated, presenting the trends of changes and the list of the most commonly used drug combinations.

Data of different group CVM consumption were expressed as DDD/TID and presented as means and the calculated 95% confidence interval (95% CI). The independent Student *t* test was used to evaluate differences in annual medication use between men and women in the same age group. Groups of different age and sex were compared using one-way and two-way analysis of variance (ANOVA) tests followed by multiple-comparison Bonferroni post hoc tests, comparing the means of three or more independent groups. Significance was recognized when the two-tailed P value was less than 0,05.

6.3.5. The initiation of AH treatment – sex and age differences and time trends in 2004−2012

A new patient was described as a person who in 12 months was not prescribed of any AH treatment for the disease codes (I10-I15). For that, all of the people to whom the receipt of AH treatment was prescribed were granted an anonymous code, and they are not included to the research. Since the year 2004, by the principal of each month only new people were fixated. Patients identified, were those who have been prescribed with

medicine on January, then the patients of February were identified, and the patients, but those from January were rejected. New patients were identified again in March, excluding those from January and March. By this model, in 12 months, all new patients that have received CVM were found. Patients were divided by 7 age groups (Table 3):

Table 3. The age groups of the first-time recipients of AH treatment

Patients age	Patients age group code
18−29 years	1
30−39 years	2
40−49 years	3
50−59 years	4
60−69 years	5
70−79 years	6
>80 years	7

It was analyzed:

- Number of people, that have received a reimbursed drug for AH treatment for the first time, the percentage of women, number of new users per 1000 inhabitants per year (NU/TIY) from Lithuania, women, men and between the different age groups, % change and the estimated annual percent change (EAPC). For the calculation of NY/TIY the provided average number of every age and sex of inhabitants from Lithuanian Statistic Department database was used between the years 2004−2012 [376].
- The average age of men and women when the CVM for AH treatment was issued the first time was estimated and the time trends of change were presented.
- The proportion of different age men and women, in whom AH treatment was initiated with one, two, three and four or more was calculated.
- The prescribing rate of different CVM according to ATC groups for the initiation of AH was analyzed, evaluating the differences between men and women of different age groups.

- A list of the most commonly used medicines for women and men is compiled. The proportion of different age men and women, in whom AH treatment was initiated by using FIX-Ds were estimated and the time trends of changes were presented.
- The compliance with AH treatment guidelines of the European Society of Hypertension and the European Society of Cardiology was evaluated. The selection of non-compliance to treatment guidelines criteria are given in Table 4. The percentage of different age and sex newly treated patients in whom AH treatment was initiated in accordance with the criteria indicated was calculated.

Table 4. Definitions of non-compliance with AH treatment guidelines that are used in this study

Number of drugs prescribed for the initiation of AH treatment	Description of non-compliance with treatment guidelines
1 drug	Monotherapy for centrally acting antihypertensive agents (C02A) - moxonidine, rilmenidine. For a woman under 45 years of age the treatment with methyldopa was considered to be compliant with the treatment guidelines
	A-ABs (doxazosin, prazosin) prescribed for monotherapy
	Loop diuretics (furosemide, torasemide)) prescribed for monotherapy
	Aldosterone antagonist (spironolactone) prescribed for monotherapy
	ARBs (losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan medoxomil) prescribed for monotherapy
2 drugs	Treatment was initiated with 2 drugs, second of which was centrally acting antihypertensive agent (C02A)
	Treatment was initiated with 2 drugs, second of which was A-AB
	Treatment was initiated with 2 drugs – ACEI and ARB
	Treatment was initiated with 2 ATC drugs of one group
3 drugs	Treatment was initiated with 3 drugs
	Treatment was initiated with 3 drugs, 2 of which are drugs of the same ATC group
≥4 drugs	Treatment was initiated with 4 drugs
	Treatment was initiated with 5 drugs
	Treatment was initiated with 6 drugs
	Treatment was initiated with ≥4 drugs, 2 of which of the same ATC group

The independent Chi – square test was used to compare the differences in annual medication use and time trend changes between men and women in the same age group and the t-test while using Fisher angular transformation was used for comparison of population proportions. Significance was recognized when the two-tailed P value was less than 0,05.

6.3.6. The evaluation of efficiency of prescribing CVM for AH treatment, analyzing the utilization of generic medicines and changes in pricing policy of medicines in Lithuania

The following impersonalized information was retrieved from the Lithuanian NHIF database: ATC code, INN, name of medicinal product (originator or generic), number of dispensed units, dose of the unit, year of prescription, reimbursed and co-payed expenditure for medicine per year. The data on expenditure was provided in the current Lithuanian currency - litas (LTL). The costs are converted into euro using the official exchange rate ratio of 1 Eur = 3.4528 LTL.

It was evaluated:

- The market share of generics and originators CVM for AH treatment by volume was expressed as a proportion of annually dispensed Defined Daily doses (DDDs) in 2003-2012.
- The market share of generics and originators CVM for AH treatment by value was expressed as a yearly reimbursed expenditure in euros in 2003-2012.
- We calculated these reimbursed prices of one DDD for price comparison analysis: reimbursed expenditure of a class (ATC level 2 or 3) (R_{DDD}), reimbursed expenditure of the originator (RO_{DDD}) and reimbursed expenditures of the generic (RG_{DDD}). These expenditures were calculated by dividing corresponding data on reimbursed expenditures by a total number of dispensed DDDs per year. Calculations were made according to these formulas:

$$R_{DDD} = \frac{\text{Reimbursed expenditure for group medicines per year}}{((\text{Number of dispensed units} * \text{dose})/\text{DDD})}$$

$$RO_{DDD} = \frac{\text{Reimbursed expenditure for group originators per year}}{((\text{Number of originators dispensed units} * \text{dose})/\text{DDD})}$$

$$RG_{DDD} = \frac{\text{Reimbursed expenditure for group generics per year}}{(\text{Number of generics dispensed units} * \text{dose})/\text{DDD})}$$

The % change was calculated in the years 2003−2012 and the time trend changes were estimated.

- We calculated these co-payed prices of one DDD for price comparison analysis: co-payed expenditure of a class (ATC level 2 or 3) (C_{DDD}), co-payed expenditure of the originator (CO_{DDD}) and co-payed expenditures of the generic (CG_{DDD}). These expenditures were calculated by dividing corresponding data on co-payed expenditures by a total number of dispensed DDDs per year. Calculations were made by using the corresponding method presented before. The % change was calculated in the years 2003−2012 and the time trend changes were estimated.
- In order to assess prescribing efficiency, we compared the changes in utilization rate and the changes in reimbursed expenditure over this period. We used three efficiency criteria published in the literature (Table 5) (Godman B, 2011).

Table 5. Criteria for an assessment of drug prescription efficiency

Criteria of medicine prescribing efficiency	Description
Efficient	The rate of increase in utilization is more than double the rate of increase in expenditure
Considerable efficiency	The reimbursed expenditure is decreasing over time despite increasing utilization
No efficiency	The rate of increase in expenditure exceeds utilization

7. RESEARCH FINDINGS

7.1. CVM utilization differences in Scandinavian and Baltic countries

CVM utilization increased in all 7 countries: LT (from 134,6 to 359 DDD/TID, p<0,001), LV (from 129,4 to 293,4 DDD/TID, p<0,001), SE (from 306,9 to 455 DDD/TID, p<0,001), NO (from 306,3 to 394 DDD/TID, p<0,001), FI (from 459,3 to 539,9 DDD/TID, p=0.108) and EE (from 193,6 to 455,3 DDD/TID, p=0,04). The increase in the use of CVM was considerably higher in LT (EAPC 16,7%), LV (EAPC 18,1%) and EE (EAPC 10,4 proc.) meanwhile in three Scandinavian countries EAPC was less than 3,5% (EAPC SE 3,3%, NO 3,2%, FI 2,9%). The highest increase (from 294,7 to 525,1 DDD/TID, EAPC 7,8% (p<0,001)) in CVM consumption was noticed in DK (Figure 1).

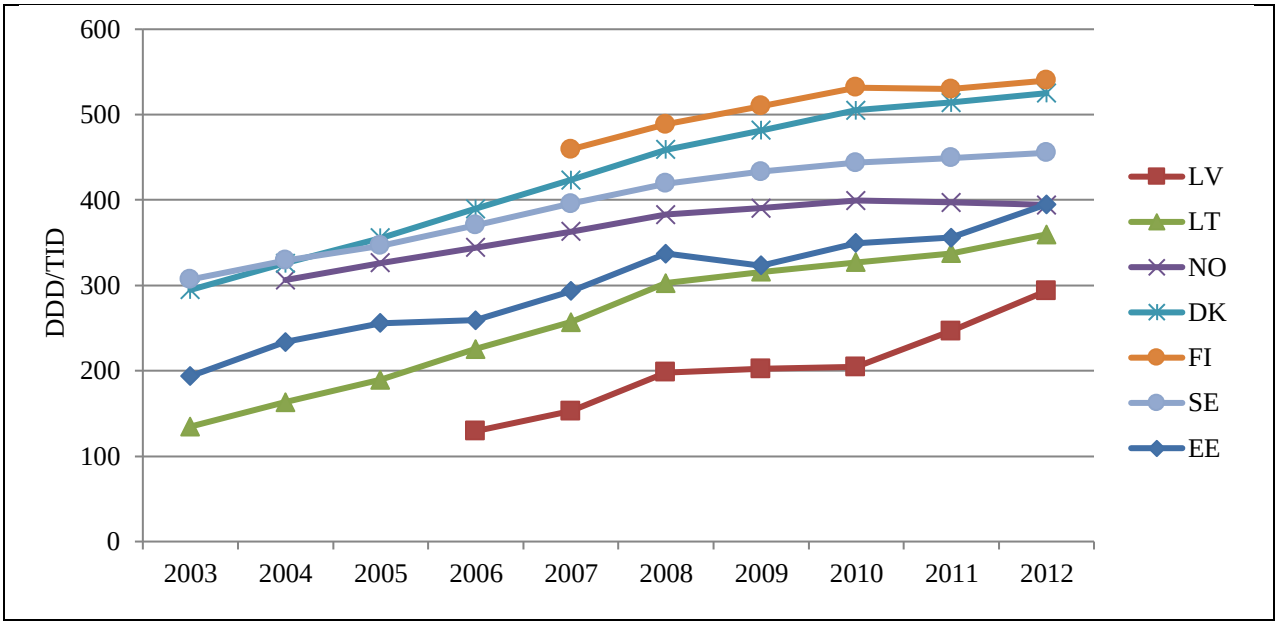
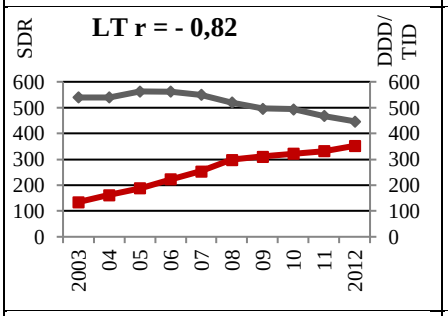
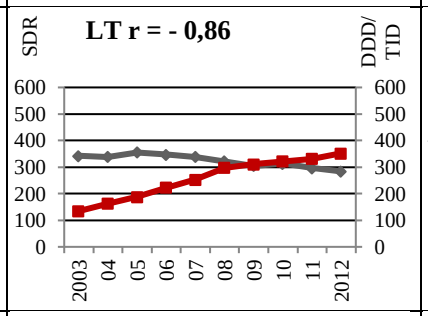
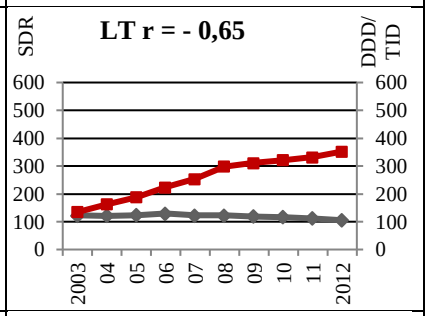
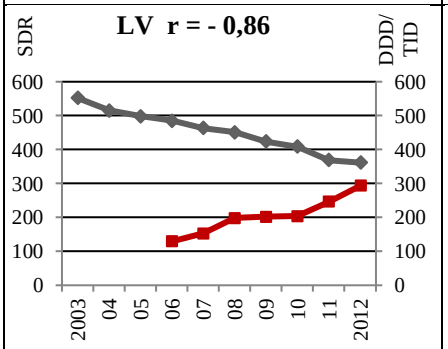
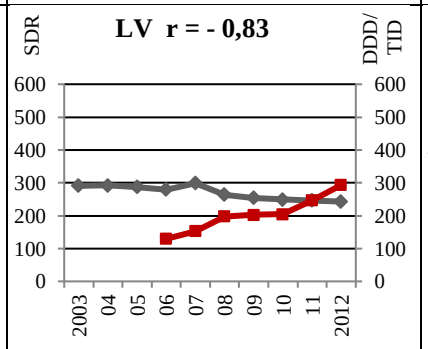
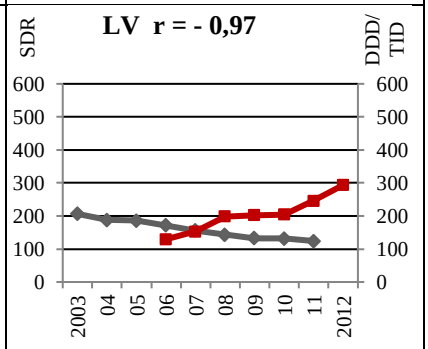
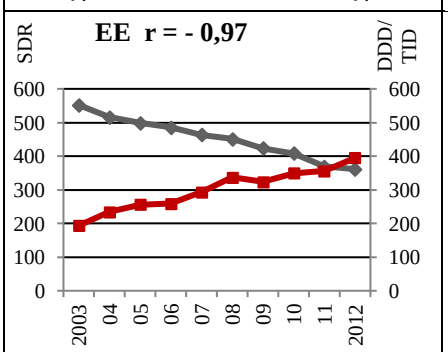
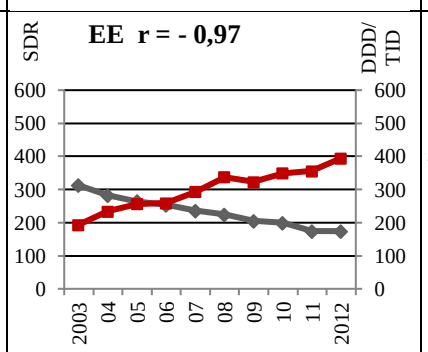
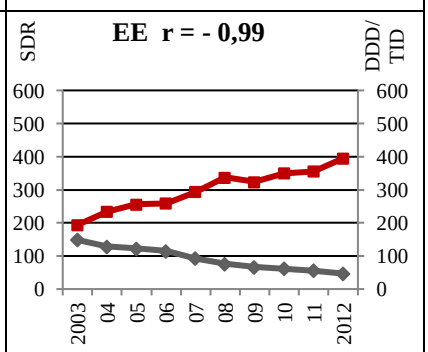
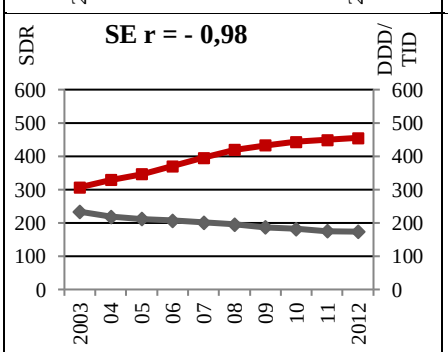
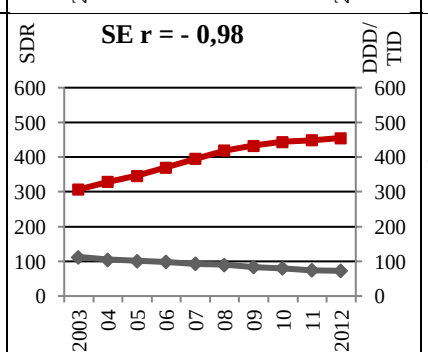
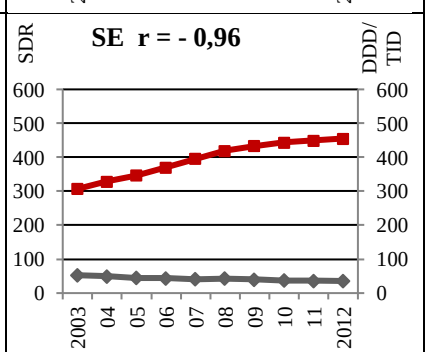
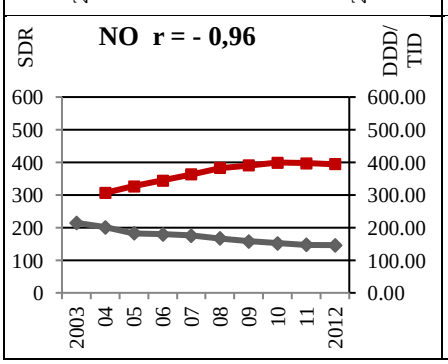
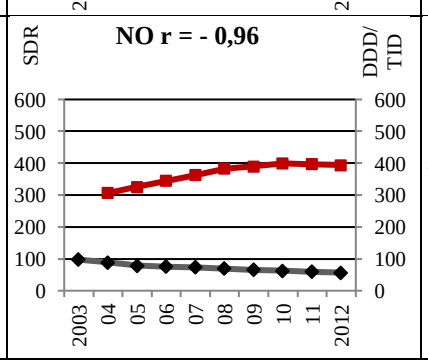
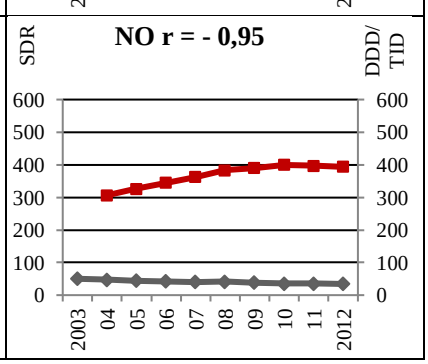


Figure 1. Trends of utilization of CVM, expressed as a number of DDD per 1000 inhabitants per day (DDD/TID) by country and by year

7.2. Correlation between changes in CVD mortality rates and CVM utilization

The significant negative correlation was observed in all countries between CVM utilization and CVD, CHD and cerebrovascular disease SDR. Trends of CVM utilization, SDR and Pearson correlation coefficients' values are presented in Figure 2.

Correlation between CVM utilization and

Cardiovascular SDR	CHD SDR	Cerebrovascular disease SDR
		
		
		
		
		

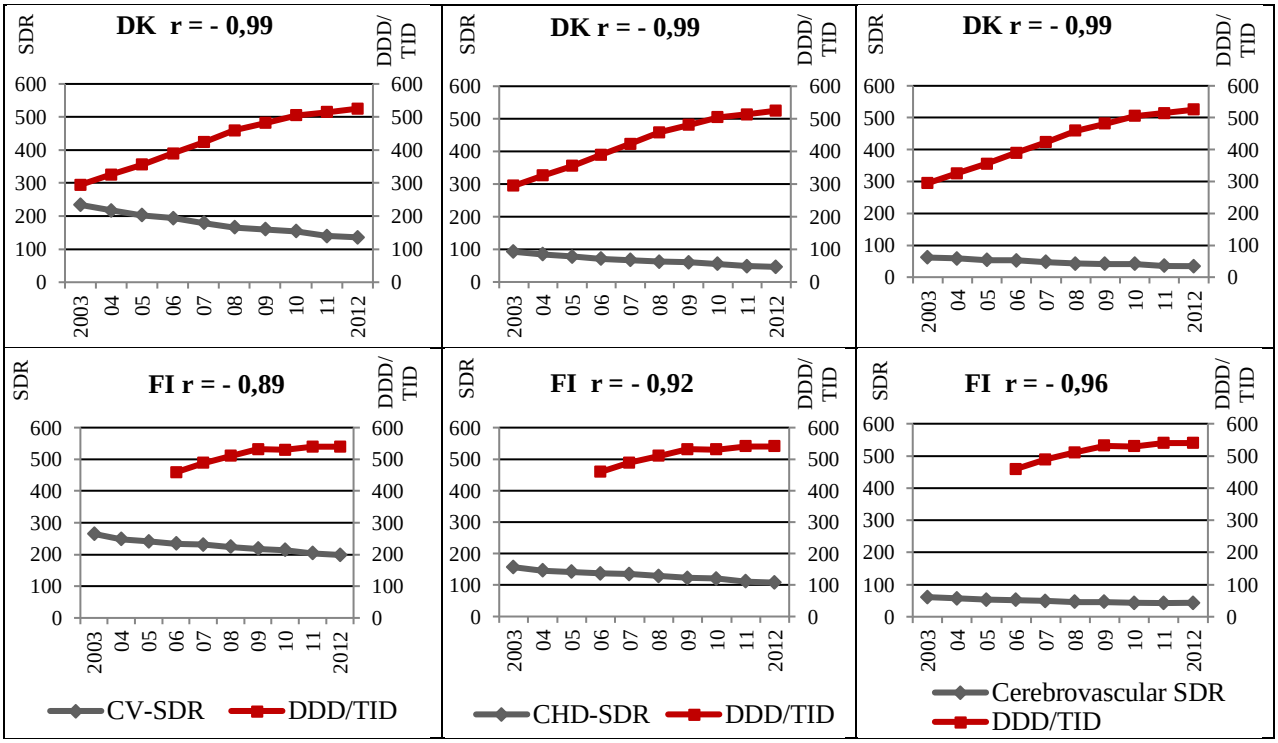


Figure 2. Correlation and trends of CVM utilization, expressed as DDD/TID, and age-standardized death rate per 100 000 population from CVD, coronaty heart disease (CHD SDR) and cerebrovascular disease SDR in different countries

r - Pearson correlation coefficient, LT – Lithuania, LV – Latvia; EE – Estonia; SE – Sweden; NO – Norway; DK – Denmark; FI – Finland

7.3. Utilization of different groups of CVM by countries

Utilization of different groups of CVM by countries is presented in Figure 3.

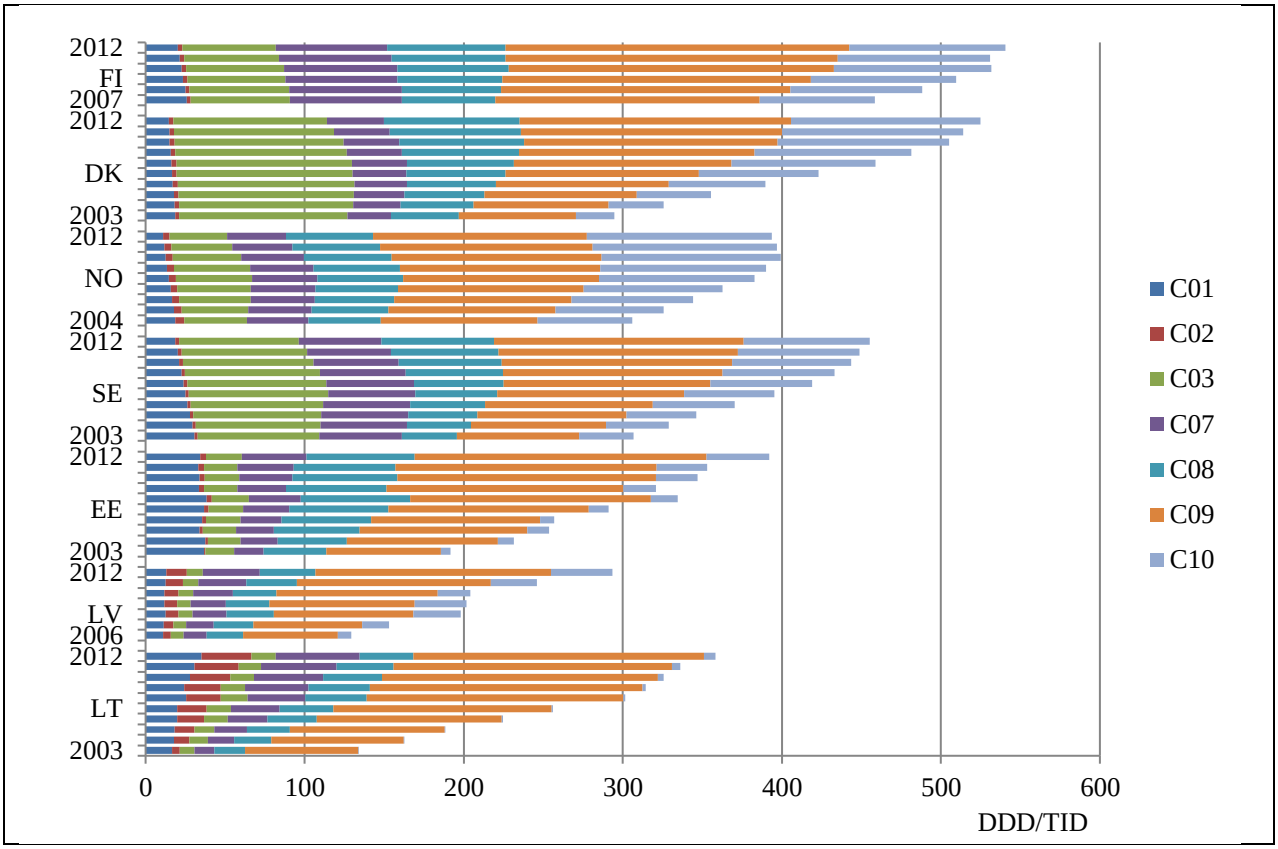


Figure 3. Utilization of different groups of CVM, expressed as a DDD/TID by country and by year (Utilization of peripheral vasodilators (C04) was <1 DDD/TID and it is not presented in the figure)

C01 – cardiac therapy medicines; C02 – SNS-AHs; C03 – diuretics; C07 – BBs; C08 – CCBs; C09A – ACEIs,plain; C09B – ACEIs combinations; C09C – ARBs, plain; C09D – ARBs, combinations; C10 – lipid modifying agents

7.3.1. Differences in cardiac therapy medicines (C01) utilization by countries

The increase in cardiac therapy medicines utilization was seen only in LT (from 16,5 to 35,2 DDD/TID, EAPC=11,3%, p=0,007) and in LV (from 11 to 13,2 DDD/TID, EAPC=2,8%, p=0,652).The highest consumption of cardiac therapy medicines was registered in EE (from 36,6 to 34,3 DDD/TID, EAPC=-0,6%, p=0,781). The use of cardiac therapy medicines decreased in Scandinavian countries (EAPC from -2,2% to -4,5%, time trend change p>0,05). Multiple comparison analysis revealed C01 utilization mean values difference between LT and other 6 countries, also between LV and other 6 countries ($p < 0,05$) (Figure 4).

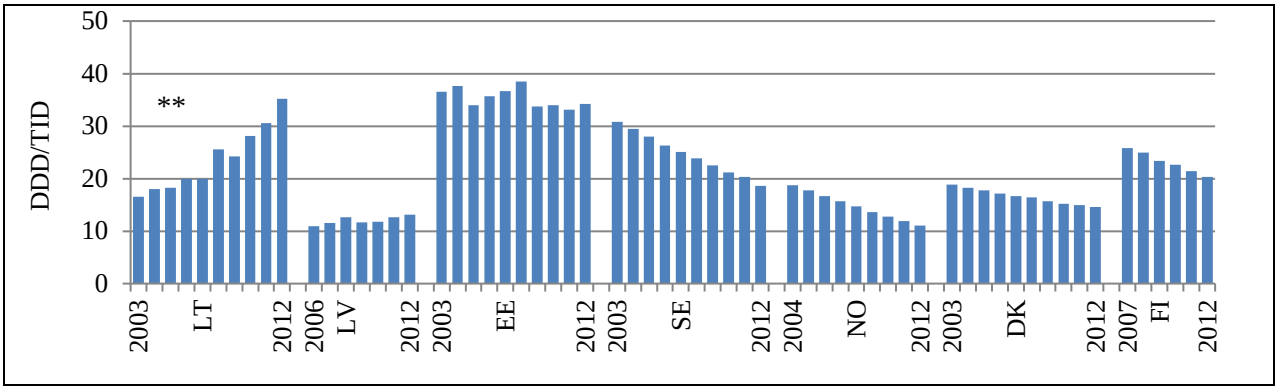


Figure 4. Differences in cardiac therapy medicines (C01) utilization by countries

** − time trend change p<0,01

7.3.2. Differences in SNS-AHs (C02) utilization by countries

The highest and still growing utilization of SNS-AHs was registered in LT (from 4,8 to 31,5 DDD/TID, EAPC =55%, p<0,001) and LV (from 4,8 to 23,9 DDD/TID, EAPC =23.9%, p=0,049). Multiple comparison analysis revealed statistically significant difference between SNS-AHs utilization in LT and other 6 countries and in LV and other 6 countries (p < 0,001). The use of SNS-AHs remained stable (p>0,05) and it was less than 5 DDD/TID in EE and Scandinavian countries during the study period (Figure 5).

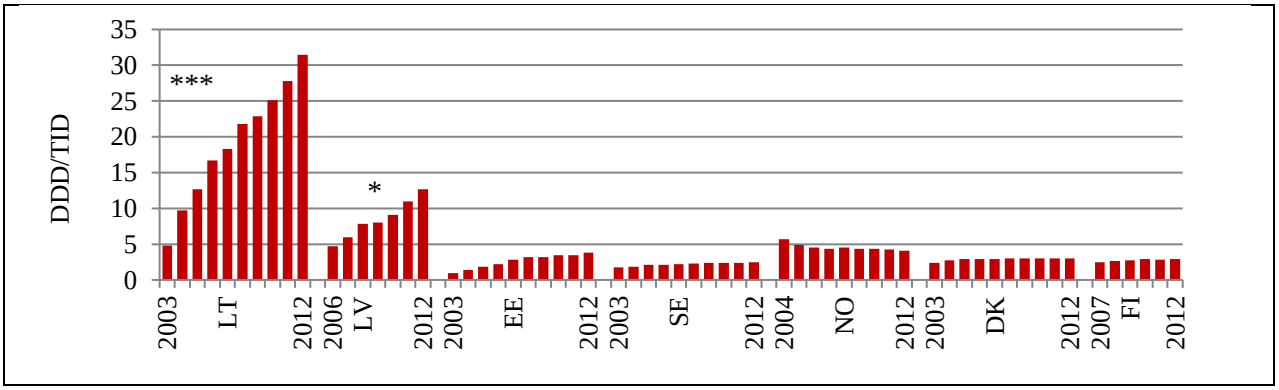


Figure 5. Differences in SNS-AHs (C02) utilization by countries

*** − time trend change p<0,001, * − time trend change p<0,05

7.3.3. Differences in diuretics (C03) utilization by countries

The lowest consumption of plain diuretics was registered in LT (from 9,4 to 15,4 DDD/TID, EAPC =6,2%) and in LV (from 8 to 10,1 NPD/TGD, EAPC =3,6%). The highest utilization of plain diuretics was seen in DK (from 105,9 to 96,6 DDD/TID,

EAPC = -0,9%) and SE (from 76,7 to 75,3 DDD/TID, EAPC = -0,2%). Time trend change p>0,05 in all countries. Multiple comparison analysis revealed that diuretics utilization was not different between DK and SE (p = 0,285), but it was statistically significantly different between other 5 countries (p<0,05) (Figure 6).

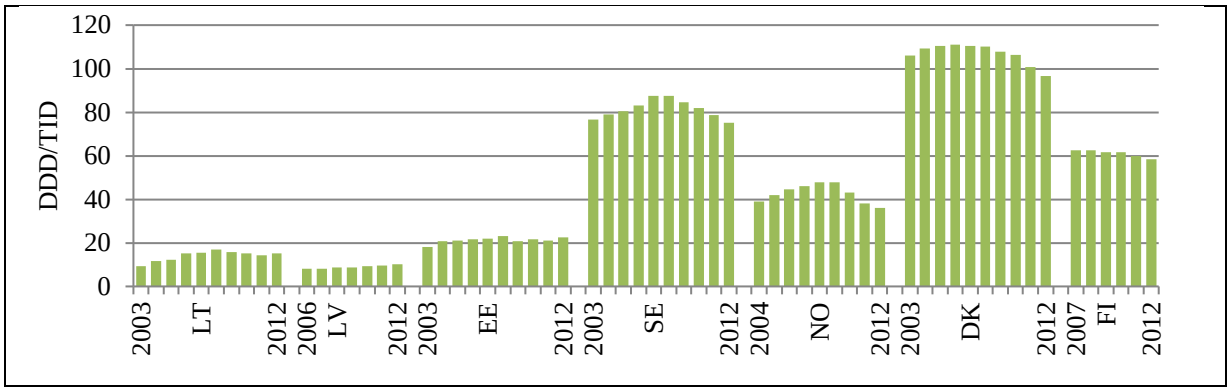


Figure 6. Differences in diuretics (C03) utilization by countries

*** – time trend change p<0,001, ** – time trend change p<0,01, * – time trend change p<0,05

7.3.4. Differences in BBs (C07) utilization by countries

BBs consumption was increasing in all Baltic countries: LT (from 12,5 to 52,6 DDD/TID, EAPC =30,5%, p<0,001), LV (from 14,7 to 35,9 DDD/TID, EAPC=20,4%, p=0,002) and EE (from 18,3 to 40,4 DDD/TID, EAPC=12%, p<0,003). BBs utilization remained unchanged in Scandinavian countries in 2003-2012 (p>0,05). The significantly highest use of this group (p<0,001) was seen in FI (from 70,5 to 70,2 DDD/TID, EAPC=0,38%) and SE (51,8 DDD/TID, EAPC=0%) (Figure 7).

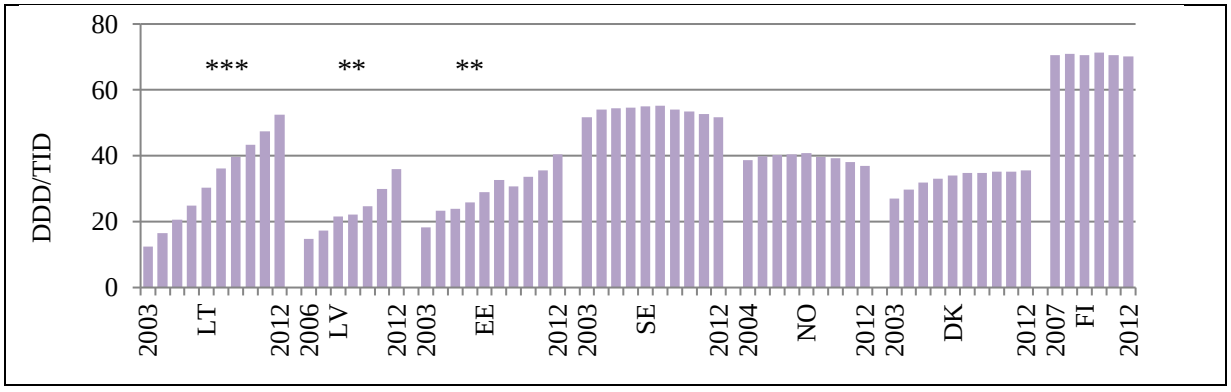


Figure 7. Differences in BBs (C07) utilization by countries

*** – time trend change p<0,001, ** – time trend change p<0,01

7.3.5. Differences in CCBs (C08) utilization by countries

The consumption of CCBs increased in LT (from 19,4 to 33,8 DDD/TID, EAPC=7,4%, p=0,04), EE (from 39,5 to 68,1 DDD/TID, EAPC=7,2%, p=0,004), SE (from 34,5 to 67,8 DDD/TID, EAPC=10,7%, p=0,022) and DK (from 42,7 to 85,2 DDD/TID, EAPC=9,5%, p<0,001). The lowest use of the group medicines was registered in LT and LV as compared with other countries (p<0,001) (Figure 8).

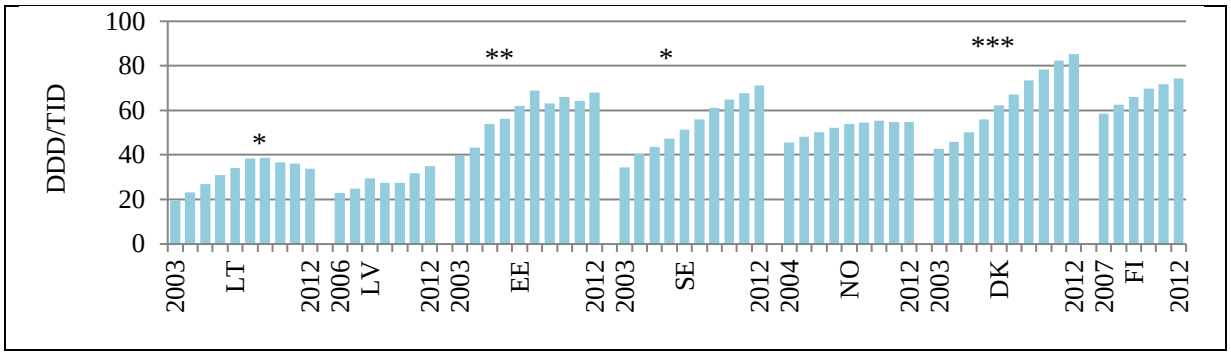


Figure 8. Differences in CCBs (C08) utilization by countries

*** − time trend change p<0,001, ** − time trend change p<0,01, * − time trend change p<0,05

7.3.6. Differences in plain ACEIs (C09A) utilization by countries

The highest utilization of plain ACEIs was seen in LT (from 66 to 89,2 DDD/TID, EAPC=3,5%, p=0,049), FI (from 86,3 to 103,6 DDD/TID, EAPC=3,5%, p=0,184), EE (from 54 to 95,7 NPD/TGD, EAPC=7,7%, p<0,001) and SE (from 48,8 to 83,9 DDD/TID, EAPC=7,2%, p=0,001). No difference between the consumptio of plain ACEIs was registered during the study period (p>0,05) (Figure 9).

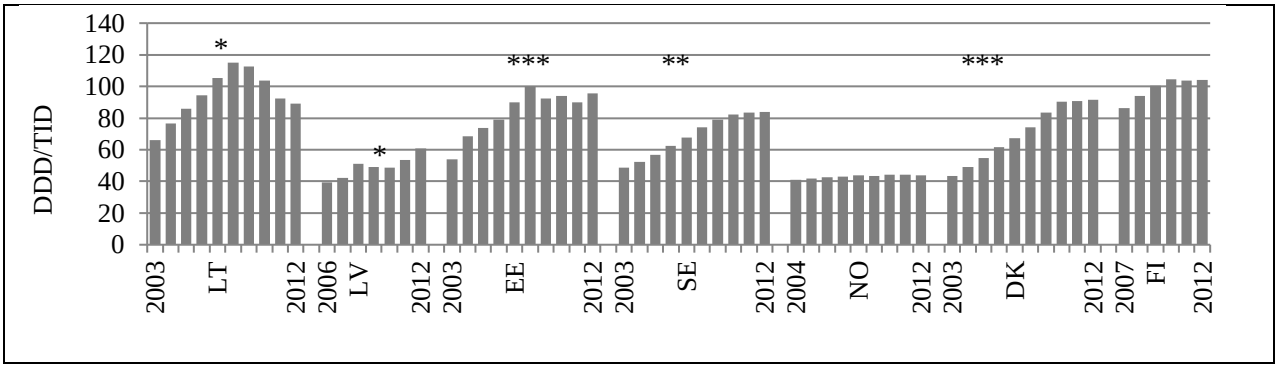


Figure 9. Differences in plain ACEIs (C09A) utilization by countries.*** − time trend change p<0,001, ** − time trend change p<0,01, * − time trend change p<0,05

7.3.7. Differences in ACEIs combinations (C09B) utilization by countries

The highest consumption and the most noticeable increase in the use of ACEIs combinations was seen in Baltic countries: LT (from 5,2 to 38,6 DDD/TID, EAPC=64,9%, p<0,001), LV (from 18,4 to 61,3 DDD/TID, EAPC=33,2%, p<0,001) and EE (from 17,3 to 29,4 DDD/TID, EAPC=7%, p=0,07) differently to Scandinavian countries (p<0,05). The combinations containing ACEI and diuretic were mostly used in all countries, but the increase in consumption of ACEIs and CCBS was registered in Baltic countries: in LT (in 2005 − 0,4 DDD/TID, in 2012 − 12,2 DDD/TID, EAPC=547,8%, p<0,001) and in LV (in 2009 − 3,9 DDD/TID, in 2012. − 20,2 DDD/TID, EAPC=105%, p<0,001) (Figure 10).

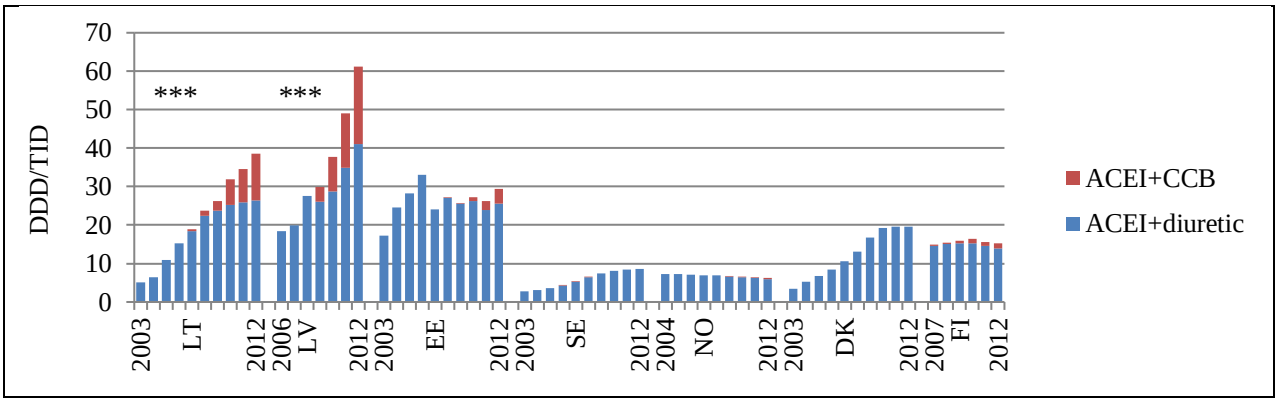


Figure 10. Differences in ACEIs combinations (C09B) utilization by countries

*** − time trend change p<0,001

7.3.8. Differences in plain ARBs (C09C) utilization by countries

The utilization of plain ARBs was increasing in all countries (Figure 11). The highest consumption was registered in FI (from 42,6 to 64,9 DDD/TID, EAPC=8,7%, p=0,026). These medicines were launched into LT market in 2005, and the highest grow up in the utilization was seen in this country (from 0,5 to 42 DDD/TID, EAPC=1077%, p<0,001). There was no significant difference in plain ARBs consumption between FI, SE and NO (p>0,05). In the last years of research, the consumption of this group medicines reached the same level in 5 countries (from 38 to 50 DDD/TID), with exception of FI and LV. In LV the use of plain ARBs remained extremely low (from 1,5 to 10,4 DDD/TID, EAPC=87,7%, p=0,006).

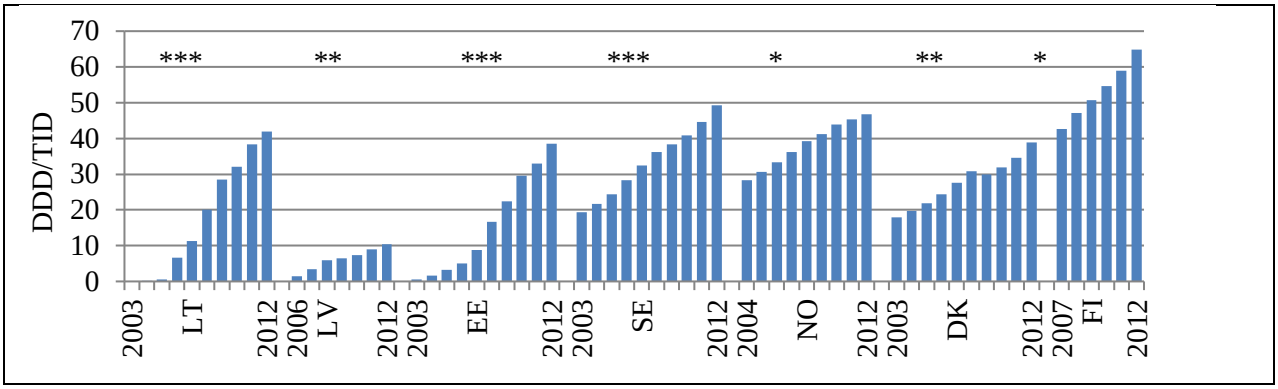


Figure 11. Differences in plain ARBs (C09C) utilization by countries

*** − time trend change p<0,001, ** − time trend change p<0,01, * − time trend change p<0,05

7.3.9. Differences in ARBs combinations (C09D) utilization by countries

ARBs combinations entered Baltic countries markets in 2006-2007, their utilization grew rapidly, but it remained lower than the use in all Scandinavian countries (p<0,001): LT (from 1,4 to 12,9 DDD/TID, EAPC=134,9%, p<0,001), LV (from 0,6 to 15,7 DDD/TID, VMP 366,5%, p<0,001), EE (from 1,5 to 19,8 DDD/TID, EAPC=82,7%, p=0,002). There was no significant difference between the use of ARBs combinations between Baltic countries (p>0,05). The combinations containing ARB and diuretic were mostly used in all countries. The highest consumption of this group medicines was registered in NO (from 22,3 to 37,9 DDD/TID, EAPC=7,8%, p=0,046) (Figure 12).

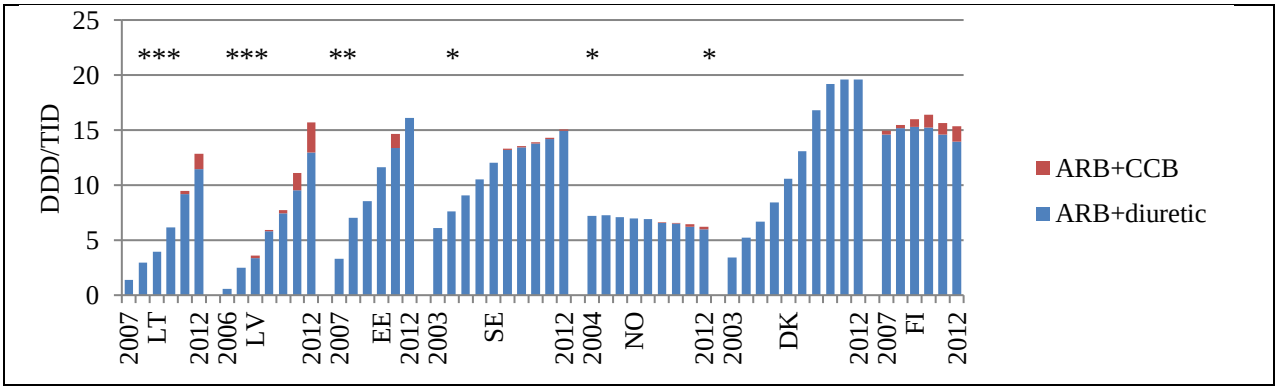


Figure 12. Differences in ARBs combinations (C09D) utilization by countries

*** − time trend change p<0,001, ** − time trend change p<0,01, * − time trend change p<0,05

7.3.10. Differences in lipid modifying agents –statins-(C10) utilization by countries

Lipid modifying agents consumption was increasing in all countries (p<0,05). The lowest consuption was registered in LT (from 0,4 to 7,4 DDD/TID, EAPC=174,9%, p=0,003), differently from other 6 countries (p<0,05). The utilization of these medicines was similar (p=0,495) in EE (from 6,2 to 39,6 DDD/TID, EAPC=54,3%, p<0,001) and LV (from 8,4 to 38,6 DDD/TID, EAPC=51,7%, p<0,001). The highest statins consumption was seen in NO (from 59,6 to 116,3 DDD/TID, EAPC=10,6%, p<0,001) and DK (from 23,9 to 119,3 DDD/TID, EAPC=39,9%, p<0,001). There was no difference between statins utilization between Scandinavian countries (p>0,05) (Figure 13).

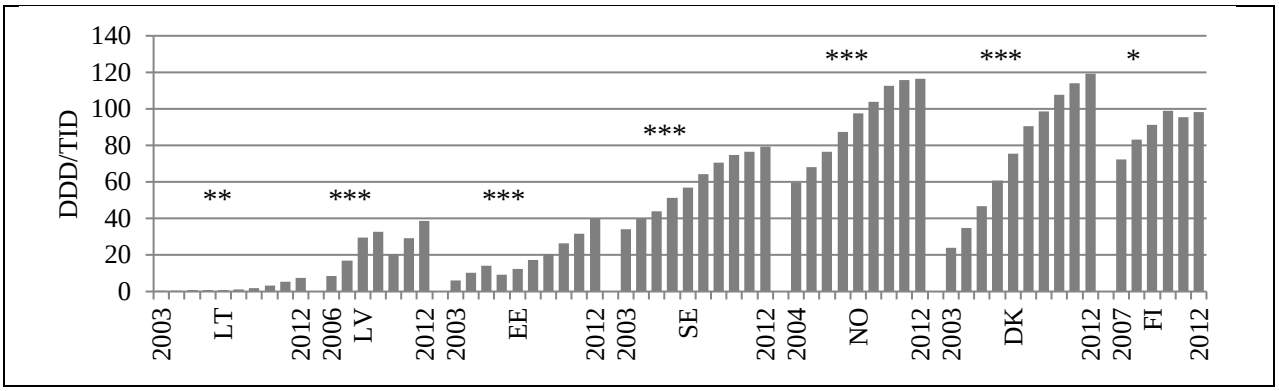


Figure 13. Differences in lipid modifiyng agents- statins- (C10) utilization by countries
*** − time trend change p<0,001, ** − time trend change p<0,01, * − time trend change p<0,05

7.4. CVM utilization, CVD risk factors and their interaction's influence on CV mortality

7.4.1. Correlation between CVD risk factors, CV mortality and utilization of CVM

A strong negative correlation between the CV mortality and CVM utilization (r=-0,89, p<0,001) was registered in our model. Strong and moderate correlation was found between the CV mortality and nine risk factors included to this analysis (Table 6).

Table 6. Pearson correlation coefficients between age-standardized CV death rate and risk factors

*** − p<0,001, ** − p<0,01, * − p<0,05.

Risk factor	Code	Positive correlation	Negative correlation
Socioeconomic factors			
Gross domestic product (GDP)	F1		-0,89 (***)
Unemployment rate	F2	0,53 (***)	
Crude divorce rate	F3	0,64 (***)	
Population related factors			
Alcohol consumption	F4	0,70 (***)	
Smoking	F5	0,67 (***)	
Energetic value of consumed food per day	F6	0,09 (*)	
Fruits and vegetables consumption	F7		-0,64 (***)
Personal perception of health condition	F8		-0,96 (***)
Health care system related factors			
Number of beds in hospitals	F9	0,72 (***)	
Number of practicing physicians	F10		-0,25
Health care expenditure per capita	F11		-0,90 (***)

Strong and moderate correlation was found between CVM utilization and nine risk factors, included to this analysis (Table 7).

Table 7. Pearson correlation coefficients between CVM utilization and risk factors
*** − p<0,001, ** − p<0,01, * − p<0,05.

Risk factor	Code	Positive correlation	Negative correlation
Socioeconomic factors			
Gross domestic product (GDP)	F1	0,63 (***)	
Unemployment rate	F2		-0,27 (*)
Crude divorce rate	F3		-0,54 (***)
Population related factors			
Alcohol consumption	F4		-0,39 (**)
Smoking	F5		-0,7 (***)
Energetic value of consumed food per day	F6	0,15	
Fruits and vegetables consumption	F7	0,37 (**)	
Personal perception of health condition	F8	0,72 (***)	
Health care system related factors			
Number of beds in hospitals	F9		-0,54 (***)
Number of practicing physicians	F10	0,06	
Health care expenditure per capita	F11	0,62 (***)	

7.4.2. CV risk factors' influence on the association between CVM utilization and CV mortality

An analysis of multiple regression models revealed a strong association between the use of CVM and the CV mortality (R^2=0,64; P <0,001), it means that a change of 64% in the CV mortality could be explained by an increased use of CVM. An analysis of an impact of risk factors on the CV mortality showed that socioeconomic factors statistically significantly influence this process: age-standardized CV death rate was lower when there was a higher GDP (F1), lower unemployment rate (F2) and divorce rate (F3). Population related factors decreasing the CV mortality were lower alcohol consumption (F4) and higher consumption of fruits and vegetables (F7). A lower CV mortality was registered in the population with a higher proportion of people who perceived their health as very good or good (F8). Two health care related factors – a smaller number of hospital beds (F9) and higher health care expenditure per capita (F11) - were associated with a lower CV mortality rate (Table 8).

Table 8. Summary of models, which estimate changes of CV age-standardized death rates caused by the use of CVM, risk factors

*** − p<0,001, ** − p<0,01, * − p<0,05, SE - standard error, Coef- coefficient.

Model	DDD/TID Coef	SE	T value	P value	Fn Coef	SE	T value	P value
F1	-0,49	0,08	-5,82	***	-0,004	0,0003	-13,09	***
F2	-1,06	0,08	-12,87	***	22,40	2,61	8,57	***
F3	-0,86	0,12	-6,92	***	159,42	32,91	4,84	***
F4	-0,81	0,09	-9,02	***	32,16	3,43	9,38	***
F5	-0,76	0,22	-3,41	**	6,96	3,84	1,82	0,07
F6	-1,20	0,12	-9,76	***	0,14	0,11	1,31	0,19
F7	-1,04	0,10	-10,46	***	-2,97	0,38	-7,83	***
F8	-0,33	0,08	-4,37	***	-8,88	0,53	-16,74	***
F9	-0,81	0,13	-6,14	***	0,48	0,08	5,97	***
F10	-1,30	0,12	-10,53	***	-0,41	0,30	-1,35	0,18
F11	-0,48	0,07	-6,53	***	-0,05	0,003	-16,29	***

Our model analyzing the impact of factors on the CVM induced decrease in the CV mortality showed a stronger influence in the case of a lower unemployment rate and a higher number of practising physicians. Also CVM utilization influenced the CV mortality more significantly in the countries with a lower GDP and health care expenditure per capita (Table 9). Other factors did not change the impact of CV medicines utilization on the CV mortality in these models.

Table 9. Summary of models, which estimate changes of CV age-standardized death rates caused by the use of CV medicines and risk factors interaction

*** − p<0,001, ** − p<0,01, * − p<0,05, SE - standard error, Coef- coefficient.

Model	DDD/TID* Fn* Coef	SE	T value	P value
F1	0,00001	0,000004	2,608	*
F2	0,162	0,0284	5,707	***
F3	0,412	0,347	1,185	0,241
F4	-0,077	0,063	-1,227	0,226
F5	-0,046	0,035	-1,326	0,193
F6	-0,001	0,001	-0,879	0,384
F7	-0,006	0,005	-1,221	0,228
F8	0,0009	0,005	0,185	0,854
F9	-0,0003	0,0007	-0,470	0,641
F10	-0,008	0,003	-2,590	*
F11	0,0002	0,00005	3,313	**

Partial correlation coefficients were calculated in order to measure the causal relationship between the variables (Table 10). Calculated partial correlation coefficients showed that a correlation between the CVM utilization and the CV mortality was statistically significant by isolating the influence of any risk factor included in the research model.

Table 10. Partial correlation analysis of impact of factors on correlation between CV age-standardized death rates and the use of CV medicines

*** − p<0,001, ** − p<0,01, * − p<0,05.

Controlled variable	Partial correlation coefficient	Coefficient of determination R^2	P value
F1	-0,72	0,52	***
F2	-0,81	0,66	***
F3	-0,69	0,47	***
F4	-0,83	0,69	***
F5	-0,53	0,28	***
F6	-0,82	0,67	***
F7	-0,86	0,73	***
F8	-0,56	0,31	***
F9	-0,73	0,54	***
F10	-0,81	0,66	***
F11	-0,78	0,61	***

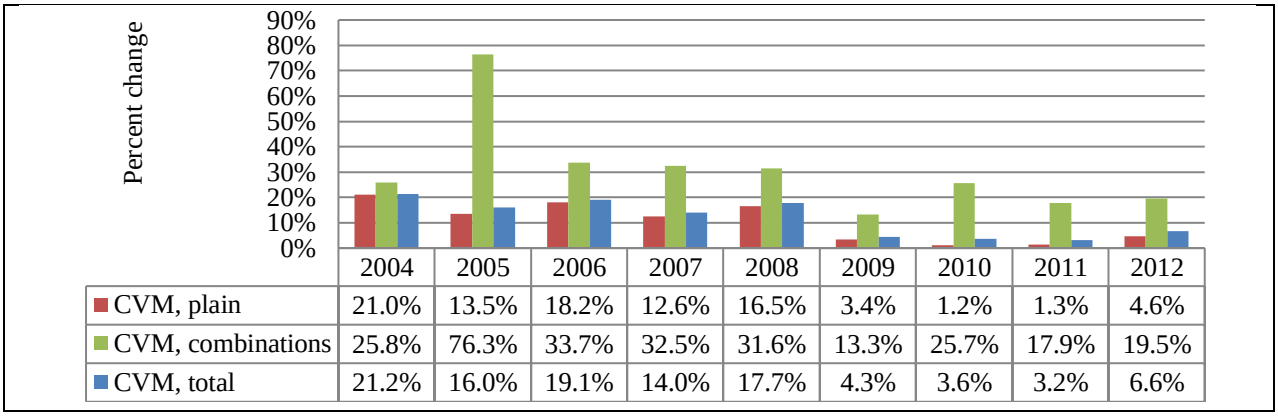
7.5. Trends and patterns of total utilization of CVM in Lithuania in 2003-2012

7.5.1. Total utilization of CVM according to ATC classification

56 485 747 prescriptions issued for the period 2003-2012 were included to this analysis for estimation of the CVM consumption. The utilization of CVM increased every year from 134,6 DDD/TID in 2003 to 359,8 DDD/TID in 2012 (% change= 167,2 %, p<0,001) (Table 11). The consumption of CVM increased in 2003−2008. Since 2009 a significant decrease in the growth of the CVM utilization was observed: in 2008 EAPC was 17,7% and in 2009 EAPC fell to 4,3%, in 2010 – 3,6% and in 2011 – 3,2%. Only in 2012 the increase in the consumption of CVM was more pronounced – 6,6% (Figure 22). An increase of the plain CVM consumption was more modest than CVM combinations introduced on the market in 2002-2007 (Figure 14).

Table 11. Total utilization of CVM, according to ATC classification, expressed as a number of DDD/TID and percentage change in 2003−2012 in Lithuania. RAS – renin angiotensin system

CVM group	Year										% change
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
C01 – Cardiac therapy	16,5	18	18,3	19,9	20	25,5	24,2	28,1	30,6	35,2	113,3
C02 – SNS-AHs	4,8	9,7	12,7	16,7	18,3	21,8	22,9	25,1	27,8	31,5	549,8
C03 – Diuretics	9,4	11,6	12,2	15	15,5	16,9	15,6	15,2	14,3	15,2	62,4
C04 – Peripheral vasodilators	0,4	0,5	0,7	0,9	1,1	1,2	1,3	1,3	1,3	1,4	212,8
C07 – BBs	12,5	16,5	20,6	25	30,3	36,1	39,7	43,4	47,4	52,6	321,3
C08 - CCBs	19,4	23,2	26,9	30,8	34,1	38,5	38,8	36,7	36	33,8	74,3
C09A – ACEIs, plain	66,0	76,8	85,9	94,5	105,5	114,8	112,5	103,7	92,5	89,2	35,1
C09B – ACEIs, combinations	5,2	6,5	11,0	15,3	18,8	23,7	26,3	31,8	34,5	38,6	648,7
C09C – ARBs, plain		<0,1	0,5	6,7	11,3	20,0	28,5	32,1	38,3	42,0	8615
C09D – ARBs, combinations					1,4	2,9	4,0	6,2	9,5	12,9	809,4
C09 – Agents acting on RAS	71,2	83,3	97,4	116,4	137,0	161,5	171,3	173,8	174,8	182,7	156,6
C10 − Lipid modifying agents	0,4	0,4	0,6	0,7	0,8	1,0	1,9	3,4	5,4	7,4	1733
SUM – CVM, plain	129,5	156,7	177,9	210,3	236,8	275,9	285,4	288,9	292,8	306,2	136,5
SUM – CVM, combinations	5,2	6,5	11,5	15,3	20,3	26,7	30,2	38,0	44,8	53,6	937,3
TOTAL	134,6	163,2	189,4	225,6	257,1	302,6	315,6	327,0	337,6	359,8	167,2



	2004	2005	2006	2007	2008	2009	2010	2011	2012
CVM, plain	21.0%	13.5%	18.2%	12.6%	16.5%	3.4%	1.2%	1.3%	4.6%
CVM, combinations	25.8%	76.3%	33.7%	32.5%	31.6%	13.3%	25.7%	17.9%	19.5%
CVM, total	21.2%	16.0%	19.1%	14.0%	17.7%	4.3%	3.6%	3.2%	6.6%

Figure 14. Annual percent change (EAPC) of CVM consumption in 2003-2012

7.5.2. Utilization of cardiac therapy medicines (C01) and peripheral vasodilators (C04) in Lithuania

The utilization of cardiac therapy medicines (C01 group) increased from 16,5 DDD/TID in 2003 to 35,1 DDD/TID in 2012 mainly due to the increasing consumption of trimetazidine. Organic nitrates (C01DA) formed a large part of cardiac therapy medicines group, and their consumption has remained stable during the study period (on average 10.5 DDD/TID) (Table 12).

The utilization of peripheral vasodilators (C04 group) was low during the study period (from 0,4 to 1,4 DDD/TID in 2003-2012) (Table 12).

Table 12. Cardiac therapy medicines (C01) and peripheral vasodilators (C04) utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

ATC code	INN	Year									
		2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
C01	Cardiac therapy	16,5	18,0	18,3	19,9	20,0	25,5	24,2	28,1	30,6	35,2
C01AA05	Digoxin	3,0	3,2	3,3	3,2	3,3	3,0	3,4	3,2	3,1	3,2
C01BC03	Propafenone	0,4	0,5	0,6	0,7	0,8	0,9	1,1	1,2	1,5	1,6
C01BD01	Amiodarone	2,0	2,2	2,3	2,4	2,6	2,8	3,1	3,0	3,1	3,2
C01DA02	Glyceryl trinitrate	6,3	6,0	6,1	5,9	3,5	5,2	2,5	2,2	2,5	2,0
C01DA08	Isosorbide dinitrate	2,0	2,7	1,4	1,5	1,6	1,3	1,4	1,3	1,2	1,2
C01DA14	Isosorbide mononitrate	2,3	2,7	2,8	3,3	3,5	4,7	4,1	6,9	7,1	7,3
C01DX12	Molsidomine	0,3	0,3	0,4	0,4	0,4	0,5	0,6	0,7	0,7	0,8
C01EB15	Trimetazidine		0,4	1,3	2,5	4,4	6,9	8,0	9,6	11,4	13,9
C01EB17	Ivabradine									0,1	2,0
C04	Peripheral vasodilators	0,4	0,5	0,7	0,9	1,1	1,2	1,3	1,3	1,3	1,4
C04AD03	Pentoxifylline	0,4	0,5	0,7	0,9	1,1	1,2	1,3	1,3	1,3	1,4

7.5.3. Utilization of SNS-AHs (C02) in Lithuania

The use of SNS-AHs was increasing every year during the study decade (% change=549,8%) (Figure 15). Three main medicines of this group were used in Lithuania in 2003-2012: imidazoline receptor agonists moxonidine and rilmenidine as well as peripherally acting alpha-adrenoreceptor antagonist doxazosin. The consumption of

methyldopa was <0,1 DDD/TID during the study period. Prazosin and clonidin have not been used in Lithuania since 2007.

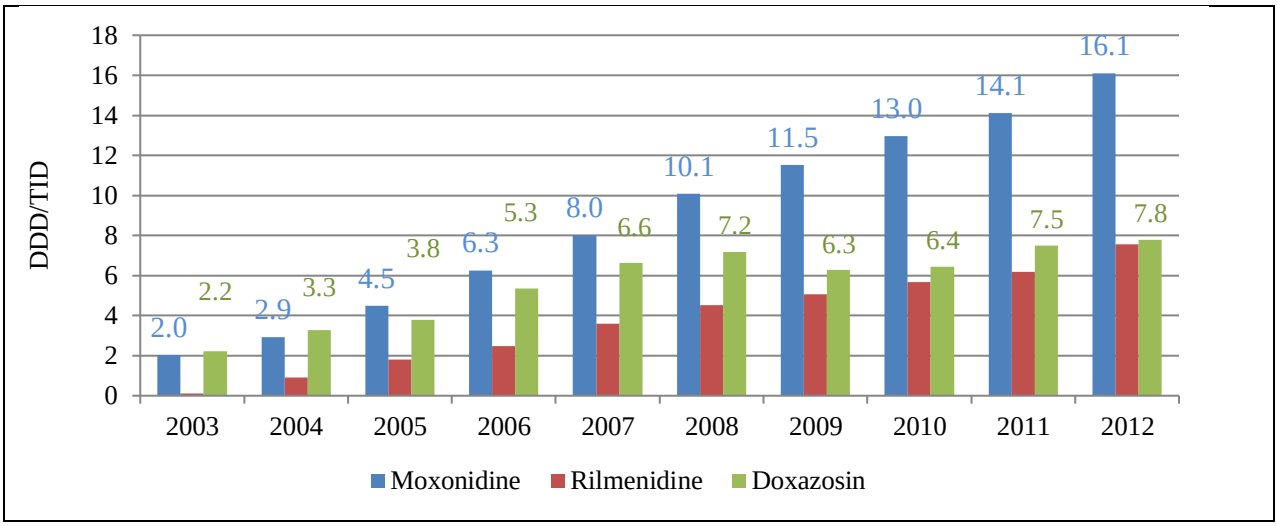


Figure 15. SNS-AH (C02) utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

7.5.4. Utilization of plain diuretics (C03) and diuretics in combinations in Lithuania

The consumption of plain diuretics (C03 group) increased from 9,4 to 15,2 DDD/TID in 2003−2012 (% change= 62,4%) (Figure 16).

The utilization of loop diuretics increased from 1,6 to 6,7 DDD/TID in 2003-2012, mainly due to the increased consumption of torasemide. The utilization of furosemide has remained lower than 0,5 DDD/TID during the study. We registered an extremely low utilization of hydrochlorothiazide (HCT) (from 0,3 to 0,1 DDD/TID), an increasing consumption of indapamide (from 5 to 8,2 DDD/TID) and spironolactone (from 1,2 to 3,4 DDD/TID) during the study decade. A growing use of combinations with diuretics also increased the total utilization of diuretics for the CVD treatment from 14,5 to 55 DDD/TID: HCT and indapamide consumption reached 21,3 DDD/TID and 23,6 DDD/TID in 2012 correspondingly (Figure 16).

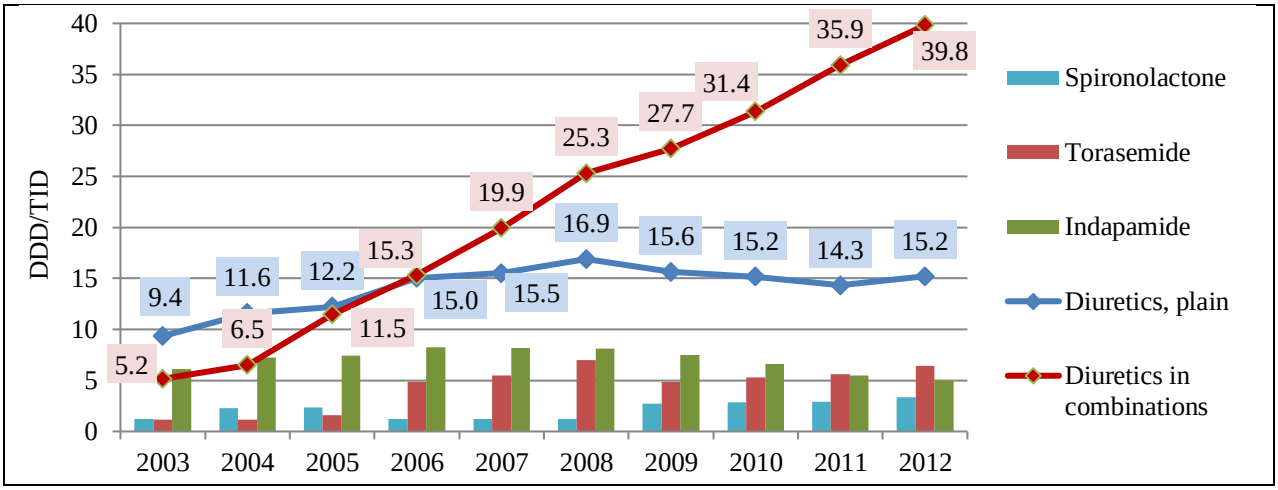


Figure 16. Plain diuretics (C03) and diuretics in combinations utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

7.5.5. Utilization of BBs (C07) in Lithuania

The utilization of BBs grew from 12,4 to 50,5 DDD/TID in 2003−2012, % change=321,3% (Figure 17). The utilization of FIX-Ds of BB and diuretic was higher than 1 DDD/TID only in 2012 when a combination of nebivolol and HCT entered the market. Metoprolol was the most used BB (from 5,3 to 15,7 DDD/TID) and it accounted for 42,8% - 31% during the study period. An increasing use of nebivolol was registered (from 3 to 28,2 DDD/TID), it accounted for 24,1% - 55,7% during the study period. The consumption of propranolol and bisoprolol was <0,1 DDD/TID, of atenolol – from 0,9 to 0,2 DDD/TID and of carvedilol – from 0,7 to 1,7 DDD/TID.

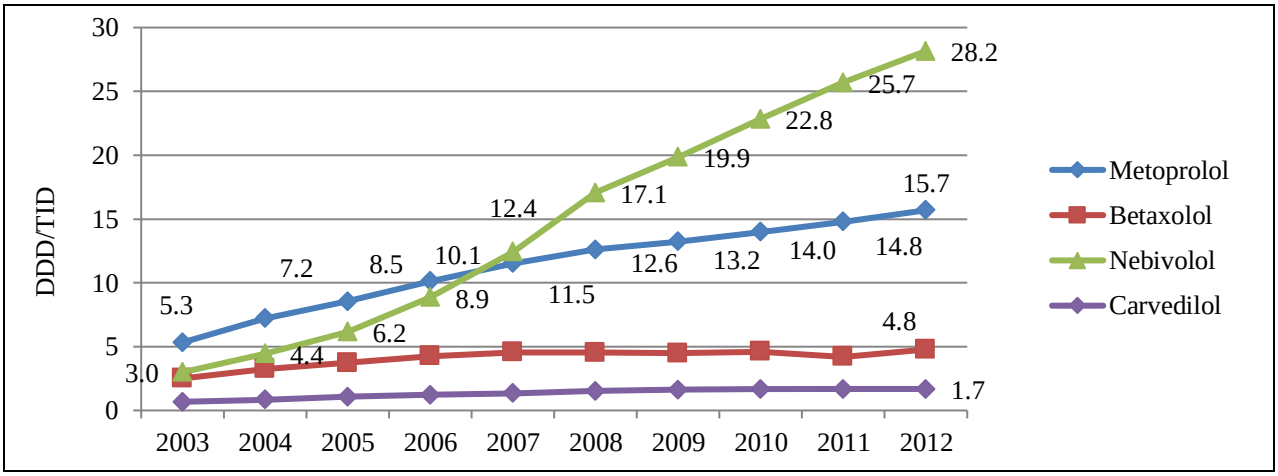


Figure 17. BBs (C07) utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

7.5.6. Utilization of CCBs (C08) in Lithuania

The utilization of CCBs increased from 19,4 to 33,8 DDD/TID in 2003−2012, % change=74,3% (Figure 18).

Amlodipine was the most used CCB (from 7,1 to 13,6 DDD/TID) until 2009 and it accounted for 34,2% - 40,2% of all consumed CCBs. Since 2009 the utilization of amlodipine has decreased to 9,7 DDD/TID in 2012, i.e. 28,8% of all CCBs. It was replaced by lercanidipine whose consumption grew from 0,6 to 14,8 DDD/TID and it accounted for 43,9% of all CCBs in 2012. An increasing utilization of lacidipine (from 3,3 to 6 DDD/TID) and verpamil (from 0,7 to 1,4 DDD/TID) was noticed during the study. A reduction in the consumption of these CCBs was registered: felodipine (from 1,8 to 0,5 DDD/TID), nifedipine (from 0,6 to 0,1 DDD/TID), nitrendipine (from 2,9 to 0,4 DDD/TID), diltiazem (from 2,8 to 1,5 DDD/TID). FIX-Ds with CCBs were prescribed for patients since 2007. Their utilization grew mainly due to the increased utilization of combinations containing ACEI and CCB (up to 12,2 DDD/TID in 2012) (Table 13). Four out of five FIX-D with CCBs contained amlodipine, so it remained the most used CCB (49,3% of all consumed CCBs).

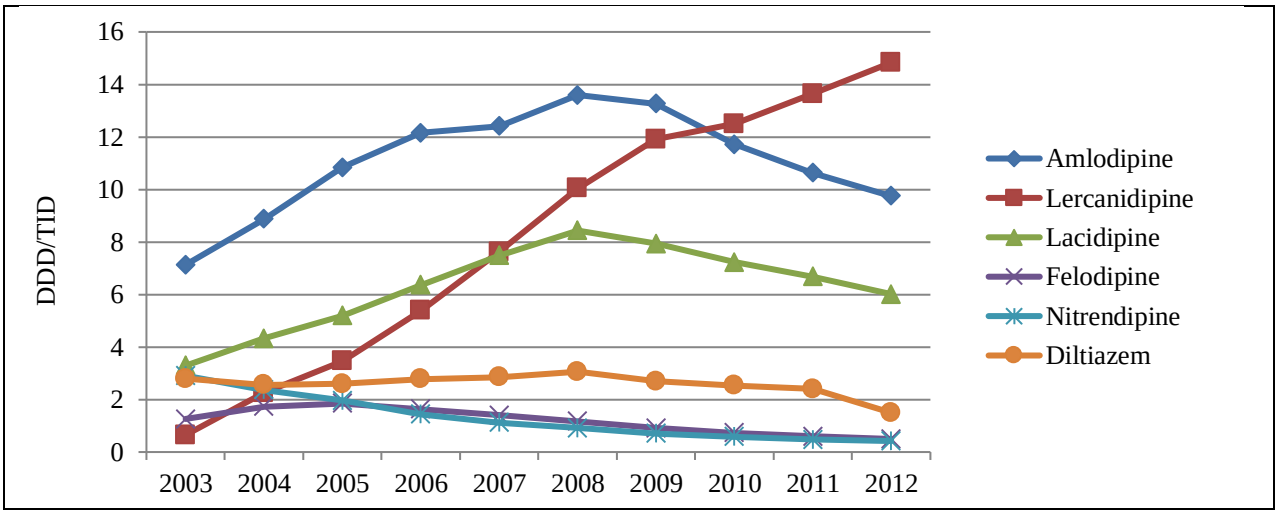


Figure 18. CCBs (C08) utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

Table 13. Plain CCBs (C08) and CCBs in combinations utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

Group	Year									
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
CCBs, plain	19,4	23,2	26,9	30,8	34,1	38,5	38,8	36,7	36,0	33,8
CCBs in combinations					0,4	1,4	2,5	6,6	8,8	13,7
CCBs, total	19,4	23,2	26,9	30,8	34,4	39,9	41,3	43,4	44,8	47,5

7.5.7. Utilization of agents acting on renin – angiotensin system (C09) in Lithuania

Agents acting on renin – angiotensin system (RAS) were the most used CVM in Lithuania in 2003-2012, but we registered changes in the pattern of these medicines use (Figure 19). Plain ACEIs accounted for 49% of all CVM in 2003 and 24,8% in 2012. The highest and increasing consumption of plain ACEIs was noticed in 2003-2008 (from 66 to 114,8 DDD/TID). A decline in these drugs utilization to 89.2 DDD/TID was registered in 2010-2012 followed by a rapid increase in the usage of the ACEIs combinations (from 5,2 to 26,4 DDD/TID), plain ARBs (from 0,5 to 42 DDD/TID). Since 2007 the utilization of ARBs combinations has increased from 1,4 to 12,9 DDD/TID and has accounted for 3,6 % of all CVM.

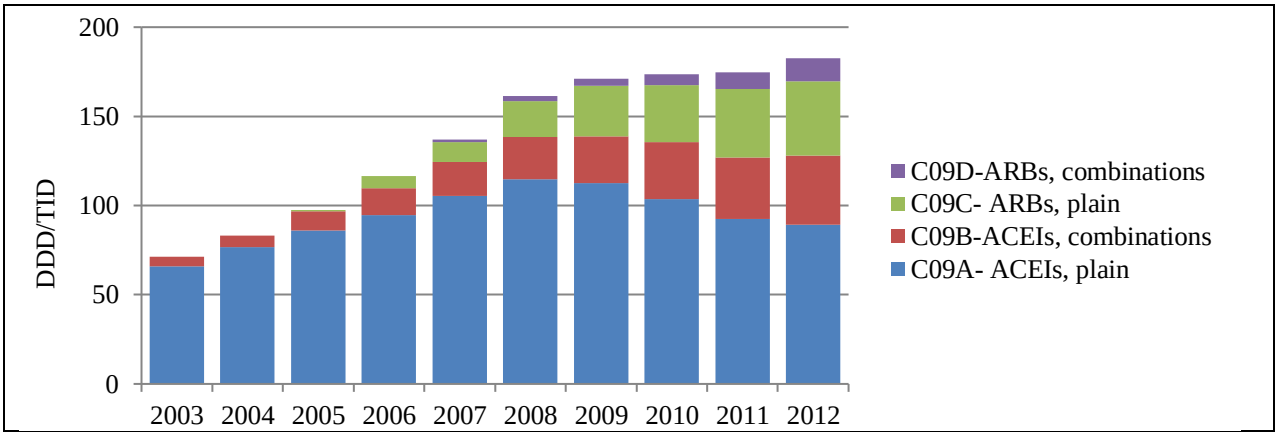


Figure 19. Agents acting on RAS (C09) utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

Enalapril was the most used CVM in 2003 (35,8 DDD/TID, 26,6% of all consumed CVM). Later it was replaced by ramipril, whose utilization was the highest of all CVM – 33,9 DDD/TID, 9,4% of all consumed CVM in 2012) (Table 14). Peridopril/indapamide

was the most prescribed FIX-D, containing ACEI and diuretic (48,2% of all consumed FIX-D with ACEI in 2012). Perindopril/amlodipine was the most commonly used FIX-D, containing ACEI and CCB (27,7% of all consumed FIX-D with ACEI in 2012).

Table 14. Plain ACEIs (C09A) and ACEIs in combinations (C09B) utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

INN	Year									
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
C09AA01 Captopril	1,5	1,4	1,5	1,8	2,1	2,4	2,4	2,4	2,4	2,4
C09AA02 Enalapril	35,8	33,4	28,1	22,3	17,9	14,6	11,3	9,3	7,5	6,1
C09AA03 Lisinopril	1,1	2,6	3,1	3,7	3,9	4,5	5,7	3,9	3,2	2,9
C09AA04 Perindopril	1,5	4,4	7,5	11	16,6	20,6	21,3	21,2	19,1	19,6
C09AA05 Ramipril	14,8	19,4	26,4	34,3	40,2	44,3	42,3	38,8	35,2	33,9
C09AA06 Quinapril	2,2	3,9	5,5	6,6	8,5	10,6	11,6	11,1	9,5	8,4
C09AA09 Fosinopril	8,4	9,5	9,7	8,4	7,9	8,4	8,1	7,1	5,9	5,4
C09AA10 Trandolapril		0,1	0,2	0,6	1,4	1,7	1,8	1,8	2	2
C09AA11 Spirapril	0,8	1,3	0,8	1,3	1,4	0,9	0,6	0,6	0,5	0,3
C09AA15 Zofenopril		0,8	3,1	4,5	5,4	6,9	7,4	7,5	7,3	8,2
C09A ACEIs, plain	66	76,8	85,9	94,5	105,5	114,8	112,5	103,7	92,5	89,2
C09BA02 Enalapril/HCT	5,2	4,6	3,9	2,7	2	1,4	1,1	0,9	0,6	0,4
C09BA04 Perindopril/ indapamide		0,4	3,3	6,6	9,3	11,9	12,8	15	17	18,6
C09BA05 Ramipril/HCT					0,2	0,7	0,8	1,0	1,5	1,4
C09BA06 Quinapril/HCT		0,8	3,1	4,4	5,4	6,2	6,7	6,1	5,2	4,5
C09BA09 Fosinopril/HCT		0,7	0,7	1,5	1,6	2	2,3	2,1	1,7	1,5
C09BA ACEIs + diuretics	5,2	6,5	11	15,3	18,5	22,3	23,7	25,2	26	26,4
C09BB03 Lisinopril/ amlodipine								0,1	1	1,5
C09BB04 Perindopril/ amlodipine							0,6	4,4	7,5	10,7
C09BB10 Verapamil/ trandolapril					0,4	1,4	2	2,1	<0,1	<0,1
C09BB ACEIs+CCBs					0,4	1,4	2,5	6,6	8,5	12,2
C09B ACEIs, combinations	5,2	6,5	11,0	15,3	18,8	23,7	26,3	31,8	34,5	38,6
ACEIs, total	71,2	83,3	96,9	109,8	124,3	138,6	138,8	135,5	127	127,8

Plain ARBs were launched into the market in 2004-2005, and an increase in their consumption was the highest between all CVM (from 0,1 to 42 DDD/TID, % change=8615%) (Table 15). The most prescribed ARB was losartan (15,7 DDD/TID in 2009 and 10,4 DDD/TID in 2012) later replaced by valsartan (18,5 DDD/TID in 2012) and telmisartan (11,8 DDD/TID in 2012). We registered an increasing (up to 12,9 DDD/TID in 2012) utilization of ARBs combinations. The most used medicine from this group was valsartan/HCT (7,3 DDD/TID in 2012.). ARBs combinations with CCBs were introduced to the market in 2011.

Table 15. Plain ARBs (C09C) and ARBs in combinations (C09D) utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

INN	Year							
	2005	2006	2007	2008	2009	2010	2011	2012
C09CA01 Losartan	0,1	5,0	9,4	15,7	17,5	17,0	13,3	10,4
C09CA02 Eprosartan	<0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1
C09CA03 Valsartan	<0,1	0,6	0,7	2,4	8,8	12,6	15,0	18,5
C09CA04 Irbesartan	0,2	0,3	0,1	0,5	0,5	0,4	0,3	0,3
C09CA06 Candesartan	<0,1	0,2	0,2	0,2	0,2	0,2	0,2	0,1
C09CA07 Telmisartanas	<0,1	0,1	0,3	0,5	0,7	1,0	8,7	11,8
C09CA08 Olmesartan	<0,1	0,5	0,5	0,7	0,8	0,9	0,8	0,8
C09C ARBs, plain	0,5	6,7	11,3	20,0	28,5	32,1	38,3	42,0
C09DA01 Losartan/HCT			1,4	2,8	3,5	3,7	3,5	2,7
C09DA02 Eprosartan/HCT					<0,1			
C09DA03 Valsartan/HCT			<0,1	0,1	0,4	2,2	5,1	7,3
C09DA07 Telmisartan/HCT					<0,1	0,1	0,2	1,0
C09DA08 Olmesartan/ HCT				<0,1	0,1	0,3	0,3	0,4
C09DA ARBs + diuretics			1,4	2,9	4,0	6,2	9,2	11,5
C09DB01 Valsartan/ amlodipine							0,2	0,8
C09DB02 Olmesartan/ amlodipine							0,1	0,7
C09DB ARBs + CCBs							0,3	1,4
C09D ARBs, combinations			1,4	2,9	4,0	6,2	9,5	12,9
ARBs, total	0,5	6,7	12,7	22,9	32,5	38,3	47,8	54,8

7.5.8. Utilization of C10 – lipid modifying agents in Lithuania

The consumption of lipid modifying agents was only 0,4 DDD/TID in 2003 and it increased up to 7,4 DDD/TID in 2012 in Lithuania. During the study decade the most prescribed statin was atorvastatin (from 0,2 to 7,1 DDD/TID) (Table 16).

Table 16. Lipid modifying agents (C10) utilization, expressed as a number of DDD/TID in 2003−2012 in Lithuania

INN	Year									
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
C10AA01 Simvastatin	0,14	0,09	<0,1	<0,1	<0,1	<0,1	<0,1	<0,1	<0,1	<0,1
C10AA03 Pravastatin	0,06	<0,1	<0,1	<0,1	<0,1	0,12	<0,1			
C10AA04 Fluvastatin	<0,1	<0,1	0,3	0,3	0,3	<0,1	0,2	0,2	0,1	0,1
C10AA05 Atorvastatin	0,2	0,3	0,3	0,2	0,4	0,7	1,5	3,0	5,0	7,1
C10AA07 Rosuvastatin			<0,1	0,2	0,2	0,2	0,1	0,2	0,1	0,1
C10BX03 Atorvastatin/ amlodipine					<0,1	<0,1	<0,1	<0,1	0,1	0,1
C10 Lipid modifying agents	0,4	0,4	0,6	0,7	0,8	1,0	1,9	3,4	5,4	7,4

7.5.9. The most used CVM in Lithuania

There were 20 and 29 medicines that accounted for 90% of drug prescriptions (DU 90% list) in 2003 and 2012 correspondingly (Table 17). Plain ACEIs prevailed in this list all 10 years. Perindopril/indapamidewas the most commonly used FIX-D in Lithuania during the study period.

Table 17. Drug utilization 90% (DU 90%) list in 2003 and 2012 in Lithuania

No.	DU 90% list in 2003	DDD/ TID		DU 90% list in 2012	DDD/TID
1.	Enalapril	35,75		Ramipril	33,93
2.	Ramipril	14,82		Nebivolol	28,16
3.	Fosinopril	8,37		Perindopril	19,59
4.	Amlodipine	7,13		Perindopril/indapamide	18,60
5.	Glyceryl trinitrate	6,37		Valsartan	18,49
6.	Indapamide	6,14		Moxonidine	16,10
7.	Metoprolol	5,33		Metoprolol	15,69
8.	Enalapril/HCT	5,16		Lercanidipine	14,83
9.	Lacidipine	3,29		Trimetazidine	14,37
10.	Digoxin	3,24		Telmisartan	11,82
11.	Nebivolol	2,99		Perindopril/amlodipine	10,72
12.	Nitrendipine	2,91		Losartan	10,40
13.	Diltiazem	2,79		Amlodipine	9,75
14.	Betaxolol	2,51		Quinapril	8,36
15.	Isosorbide mononitrate	2,30		Zofenopril	8,17
16.	Doxazosin	2,24		Doxazosin	7,79
17.	Quinapril	2,17		Rilmenidine	7,55
18.	Isosorbide dinitrate	2,12		Isosorbide mononitrate	7,36
19.	Amiodarone	2,05		Valsartan/HCT	7,30
20.	Moxonidine	2,04		Atorvastatin	7,07
21.				Torasemide	6,42
22.				Enalapril	6,08
23.				Lacidipine	6,01
24.				Fosinopril	5,37
25.				Indapamide	5,04
26.				Betaxolol	4,78
27.				Quinapril/HCT	4,51
28.				Spironolactone	3,36
29.				Digoxin	3,29

7.5.10. Trends in reimbursed expenditure for CVM in Lithuania

The reimbursed expenditure for CVM was increasing every year until 2009, later EAPC was decreasing until 2012. The reimbursed expenditure for CVM increased from 23,725 M EUR in 2003 to 51,477 M EUR in 2008 and 46,168 M EUR in 2012, contributing to 22,4-26 % of all reimbursed expenditures for pharmaceuticals (Figure 20). The % change of CVM reimbursed expenditure was higher than the change of reimbursed expenditures for all pharmaceuticals (Figure 21).

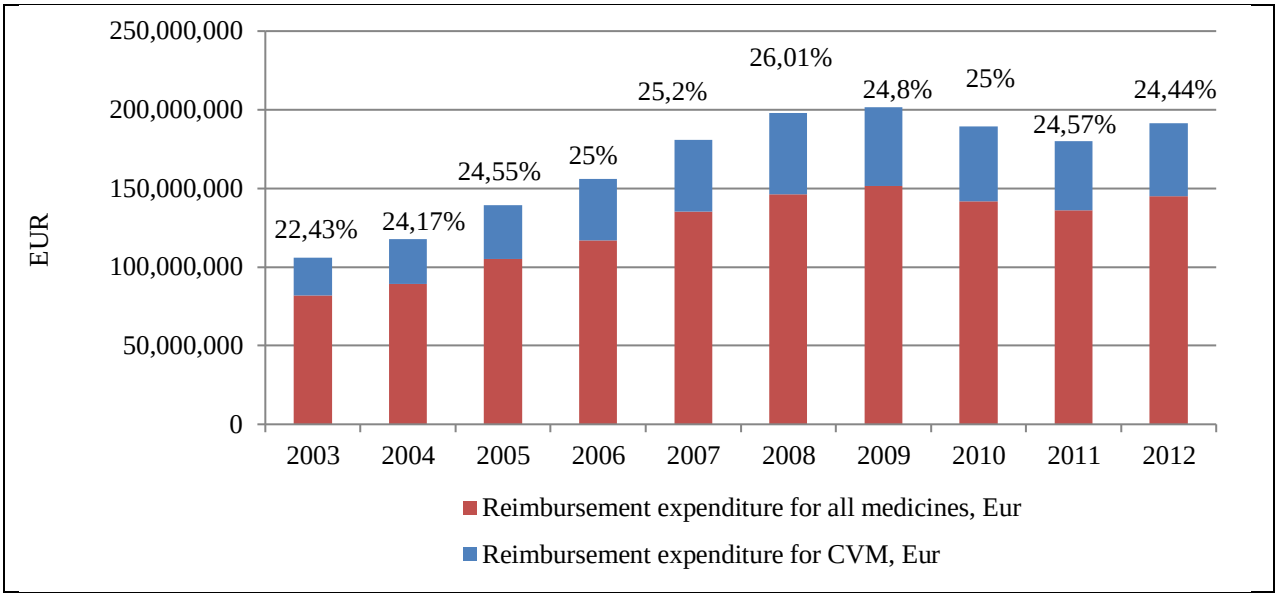


Figure 20. Reimbursement expenditure for all medicines and CVM in 2003−2012 in Lithuania

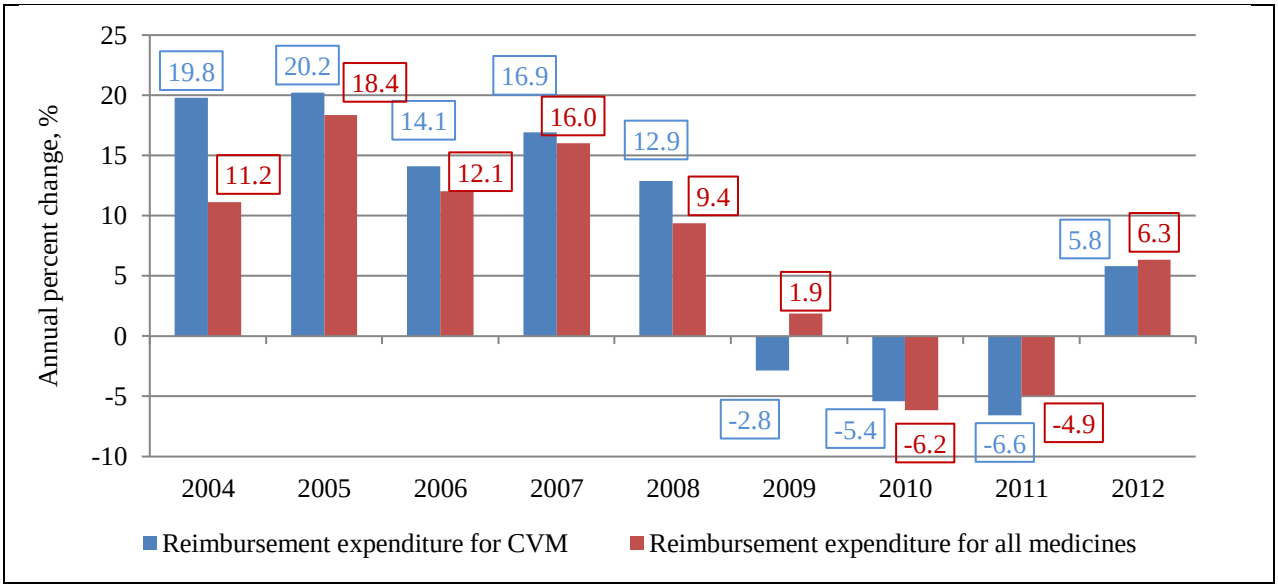


Figure 21. Annual percent change of reimbursement expenditure for all medicines and CVM in 2003−2012 in Lithuania

7.6. The utilization of CVM for arterial hypertension treatment in 2003−2012 in Lithuania

7.6.1. Total utilization of CVM for arterial hypertension treatment

44 346 746 prescriptions, issued for the period 2003-2012, were included in this analysis for estimation of the CVM consumption for AH treatment. The utilization of CVM for AH treatment was increasing every year from 104,8 DDD/TID in 2003 to 295,8 DDD/TID in 2012 (% change= 144,1 %, p<0,001) (Figure 22).

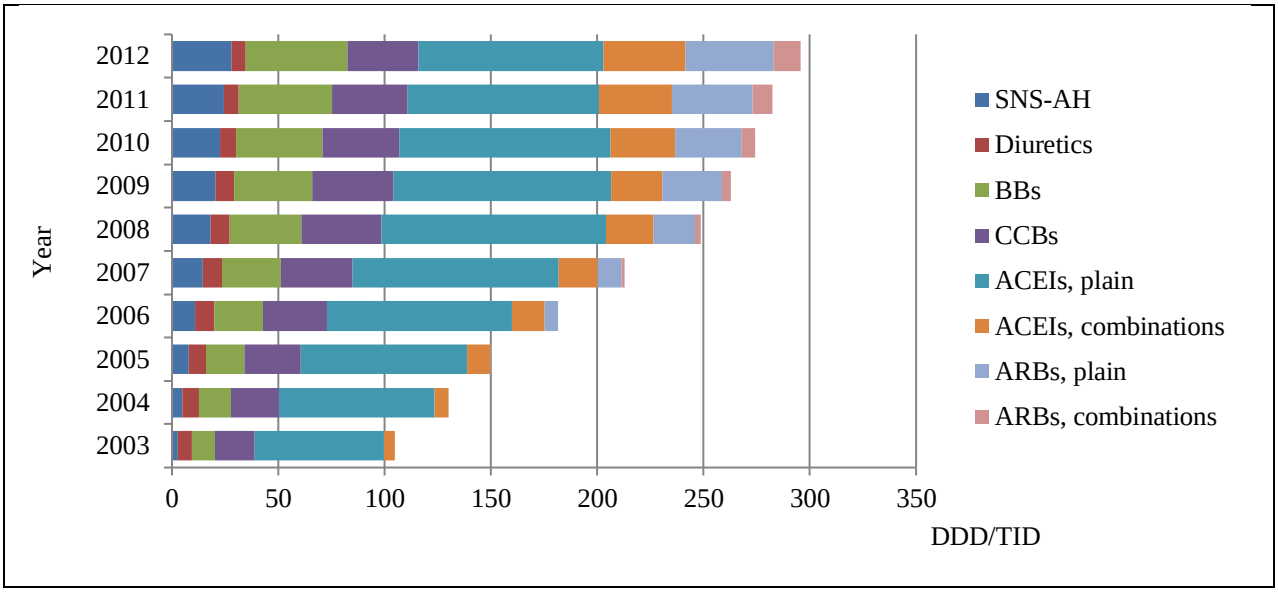


Figure 22. Total utilization of CVM for AH treatment expressed as a number of DDD/TID in 2003−2012 in Lithuania

7.6.2. Utilization of SNS-AHs for AH treatment (C02) in Lithuania

The utilization of SNS-AHs for AH treatment was increasing gradually every year in 2003-2012 (from 2,6 DDD/TID in 2003 to 20,5 DDD/TID in 2012). We registered an increase of moksonidine (from 2 to 16 DDD/TID) and rilmenidine (from 0,1 to 7,6 DDD/TID) utilization for AH treatment. The prescribing of doxazosin for AH treatment also increased from 0,1 DDD/TID to 4,5 DDD/TID during the study decade. Methyldopa consumption was <0,1 DDD/TID every year (Figure 23).

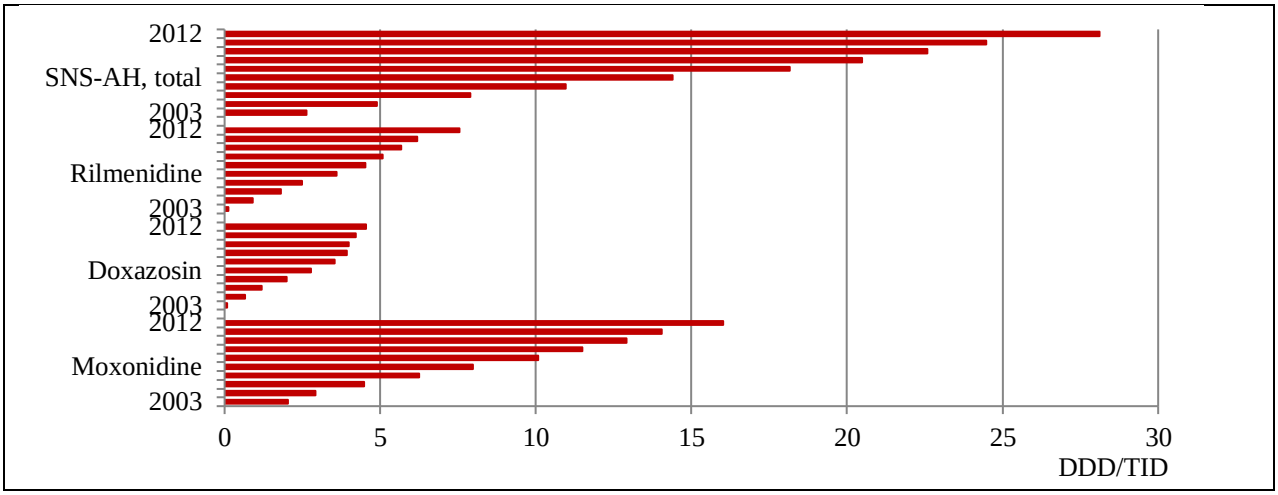


Figure 23. SNS-AHs (C02) utilization for AH treatment expressed as a number of DDD/TID in 2003−2012 in Lithuania

7.6.3. Utilization of plain diuretics (C03) and diuretics in combinations for AH treatment in Lithuania

The consumption of plain diuretics for AH treatment did not changed during the study period (from 6,7 to 6,6 DDD/TID). The utilization of indapamide increased from 5 to 8,1 DDD/TID, this drug was exclusively used for lowering BP. The utilization of loop diuretics furosemide and torasemide for AH treatment was lower than 0,2 DDD/TID. An increase of spironolactone prescribing for AH treatment was noticed (from 0,3 DDD/TID to 1,3 DDD/TID in 2003-2012) (Figure 24).

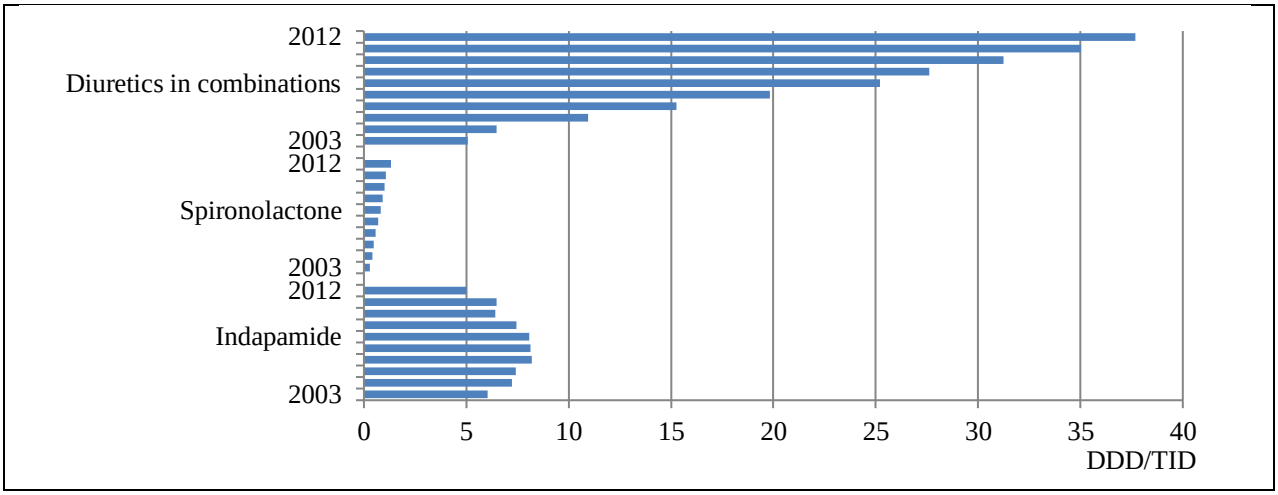


Figure 24. Plain diuretics (C03) and diuretics in combinations utilization for AH treatment, expressed as a number of DDD/TID in 2003−2012 in Lithuania

7.6.4 Utilization of BBs (C07) for AH treatment in Lithuania

The utilization of BBs for AH treatment grew from 10,9 to 47,7 DDD/TID during the study period (Figure 25). Metoprolol (from 4,6 to 14,6 DDD/TID) and nebivoliol (from 2,9 to 28 DDD/TID) utilization for BP lowering was the highest among all BBs. The use of betaxolol for AH treatment increased twice – from 2,4 to 4,8 DDD/TID, meanwhile, the consumption of atenolol decreased from 0,8 to 0,2 DDD/TID. The utilization of carvedilol, propranolol and bisoprolol was <0,1 DDD/TID every year during the study decade.

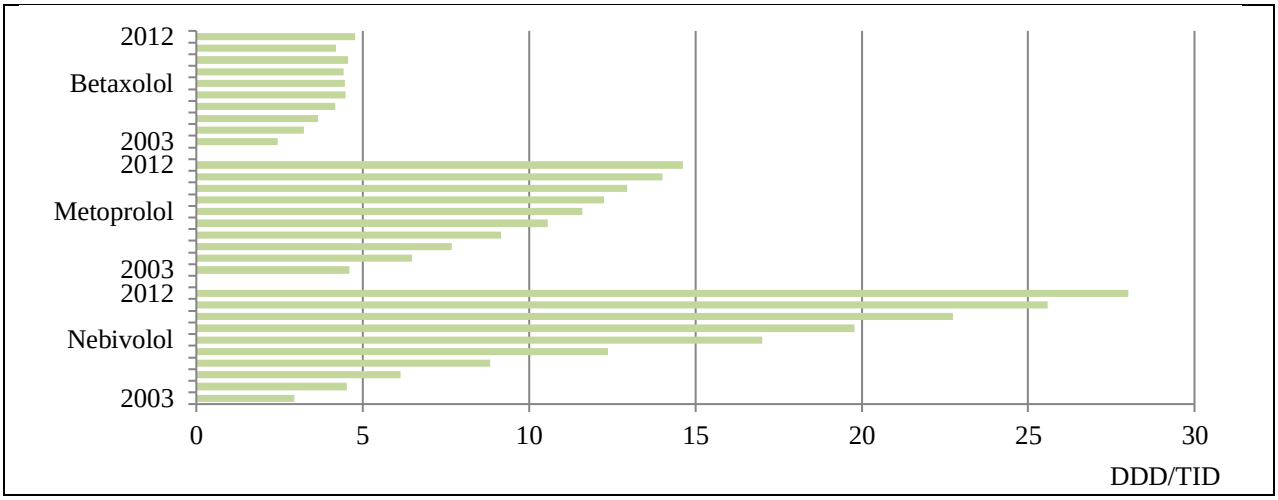


Figure 25. BBs (C07) utilization for AH treatment expressed as a number of DDD/TID in 2003−2012 in Lithuania

7.6.5. Utilization of CCBs (C08) for AH treatment in Lithuania

The utilization of CCBs for AH treatment increased from 18,6 to 33,7 DDD/TID (Figure 26).

All CCBs of dihydropiridine group were used for AH treatment.. The most used CCBs for AH treatment were amlodipine (from 7 to 9,7 DDD/TID), lercanidipine (from 0,6 to 14,8 DDD/TID) and diltiazem (from 2,7 to 1,5 DDD/TID).

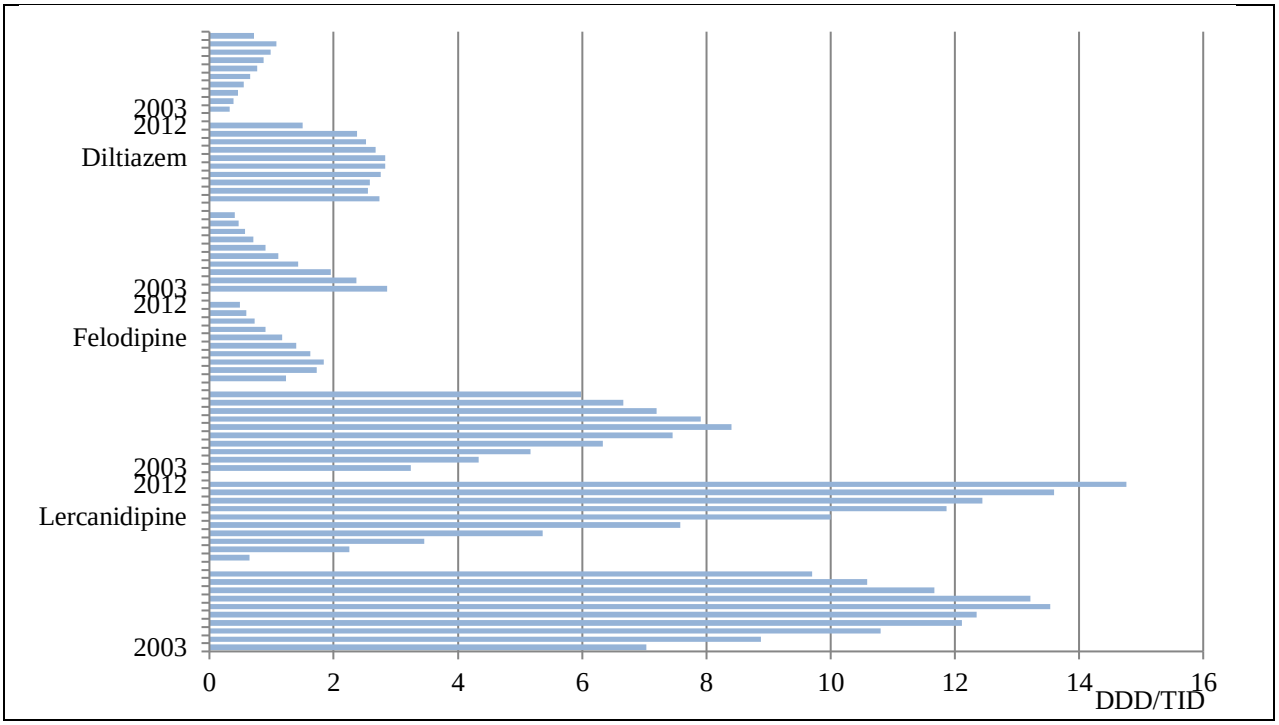


Figure 26. CCBs (C08) utilization for AH treatment expressed as a number of DDD/TID in 2003−2012 in Lithuania

7.6.6. Utilization of agents acting on RAS (C09) for AH treatment in Lithuania

More than 95% of plain ACEIs and more than 99% of plain ARBs, ACEIs and ARBs combinations were prescribed for AH treatment in Lithuania during the study decade (Figure 27).

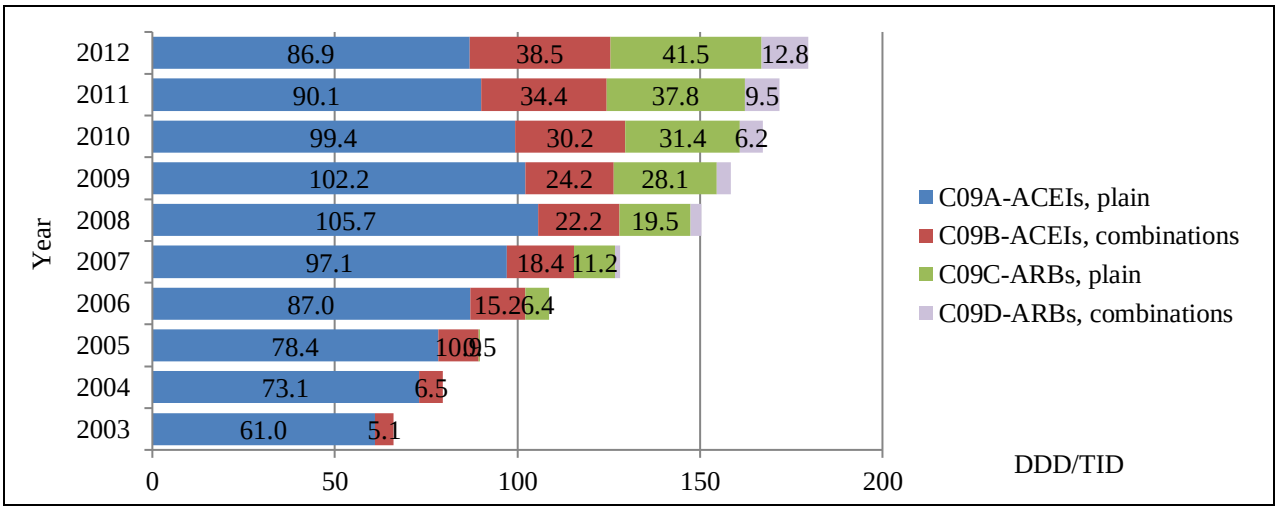


Figure 27. Agents acting on RAS (C09) utilization, for AH treatment, expressed as a number of DDD/TID in 2003−2012 in Lithuania

The data of plain ACEIs utilization is presented in Figure 28. The most used plain ACEIs for AH treatment were ramipril (from 11,3 to 32,3 DDD/TID), perindopril (from 1,2 to 11,2 DDD/TID) and enalapril (from 34,9 to 6 DDD/TID). The use of zofenopril (from 0,8 to 8,1 DDD/TID) and quinapril (from 2,1 to 8,3 DDD/TID) was increasing during the study period.

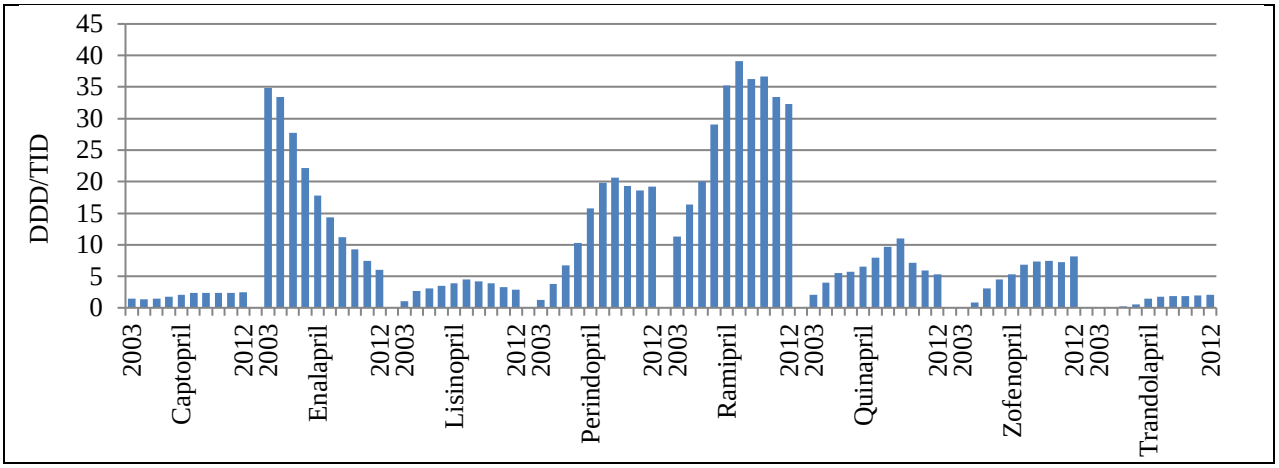


Figure 28. Plain ACEIs (C09A) utilization, for AH treatment expressed as a number of DDD/TID in 2003−2012 in Lithuania

Peridopril/indapamide was the most prescribed ACEIs combination for AH treatment (from 0,4 to 18,5 DDD/TID). The data of ACEIs combinations' utilization is presented in Figure 29.

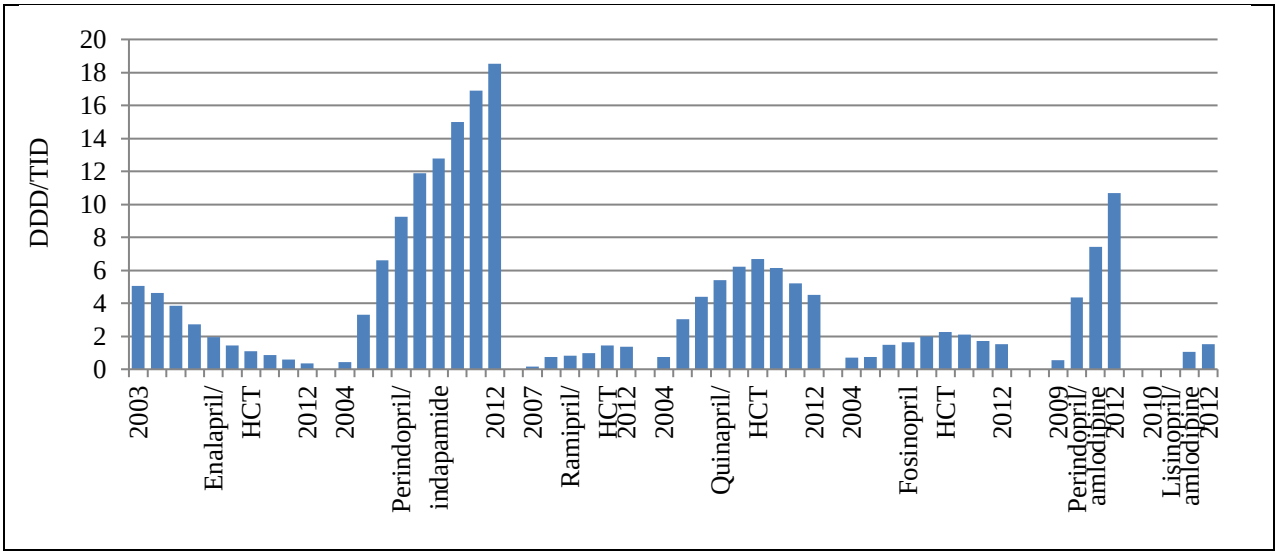


Figure 29. ACEIs in combinations (C09B) utilization for AH treatment expressed as a number of DDD/TID in 2003−2012 in Lithuania

The use of losartans which was the first plain ARB in Lithuanian market decreased because of an increasing consumption of other plain ARBs – valsartan (from 0,4 to 18,4 DDD/TID) and telmisartan (from 0,1 to 11,7 DDD/TID) (Figure 30). The same trends were observed in the utilization of ARBs combinations in 2003-2012.

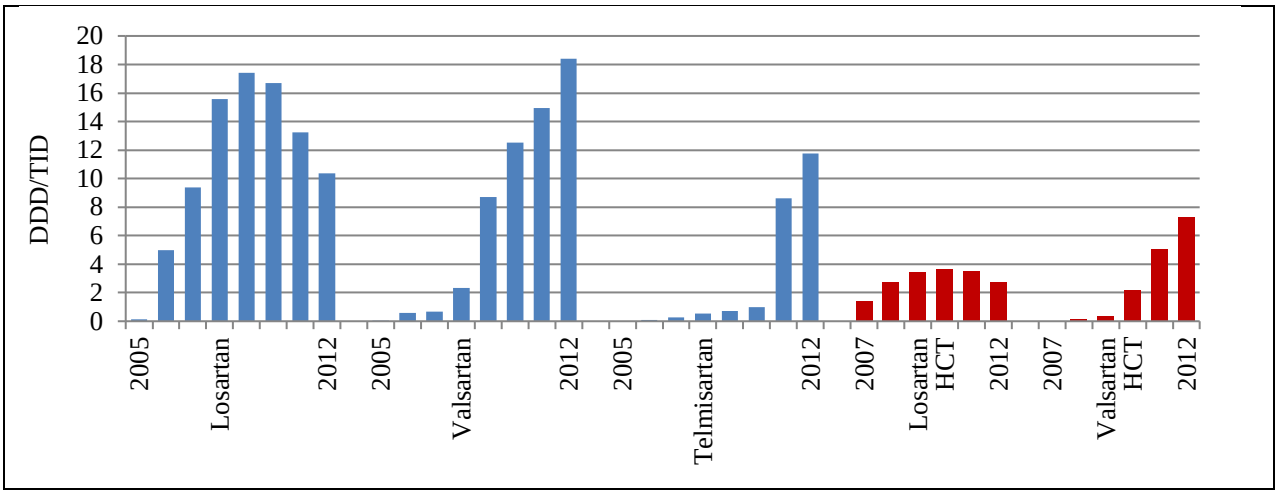


Figure 30. Plain ARBs (C09C) and ARBs in combinations (C09D) utilization for AH treatment expressed as a number of DDD/TID in 2005−2012 in Lithuania

7.6.7. The most used CVM for AH treatment in Lithuania

There were 13 and 22 medicines that accounted for 90% of drug prescriptions (DU 90% list) for AH treatment in 2003 and in 2012 correspondingly (Table 18). Plain ACEIs prevailed in this list all 10 years as the most used CVM group for AH treatment in Lithuania.

Table 18. Drugs for AH treatment utilization 90% (DU 90%) list in 2003 and 2012 in Lithuania

No	DU 90% list in 2003	DDD/TID		DU 90% list in 2012	DDD/TID
1.	Enalapril	34,89		Ramipril	32,30
2.	Ramipril	11,32		Nebivolol	28,02
3.	Fosinopril	8,17		Perindopril	19,20
4.	Amlodipine	7,04		Perindopril/ indapamide	18,52
5.	Indapamide	6,05		Valsartan	18,40
6.	Enalapril /HCT	5,06		Moxonidine	16,02
7.	Metoprolol	4,60		Lercanidipine	14,77
8.	Lacidipine	3,25		Metoprolol	14,62
9.	Nebivolol	2,95		Telmisartan	11,74
10.	Nitrendipine	2,86		Perindopril/amlodipine	10,67
11.	Diltiazem	2,74		Losartan	10,35
12.	Betaxolol	2,45		Amlodipine	9,71
13.	Quinapril	2,11		Quinapril	8,32
14.				Zofenopril	8,11
15.				Rilmenidine	7,55
16.				Valsartan/HCT	7,27
17.				Enalapril	6,04
18.				Lacidipine	5,98
19.				Fosinopril	5,33
20.				Indapamide	5,00
21.				Betaxolol	4,78
22.				Doxazosin	4,54

7.6.8. Trends in reimbursed expenditure and CVM utilization for AH treatment in Lithuania

Trends in reimbursed expenditure and CVM utilization for AH treatment in Lithuania are presented in Figure 31. The utilization of diuretics remained unchaged (from 6,66 to 6,56 DDD/TID), but the reimbursed expenditure decreased nearly twice during the study decade (from 519,9 to 223,5 Eur/1000 inhabitants/year). An increase of CCBs utilization from 18,6 to 33,7 DDD/TID was followed by a decrease of reimbursed expenditure from 1318,8 to 1029,6 Eur/1000 inhabitants/year. We registered that an increased utilization of all other CVM for AH treatment was followed by an increase in the reimbursed expenditure during the study decade. The use of plain ACEIs for AH treatment (from 61 to 86,9 DDD/TID) and reimbursed expenditure (from 2174,4 to 2469

Eur/1000 inhabitants/year) were the highest during the study period comparing with the other CVM. The highest increase of the reimbursed expenditure was seen for plain ARBs (from 30,1 to 1754,2 Eur/1000 inhabitants/year), ACEIs combinations (from 156,4 to 2047,5 Eur/1000 inhabitants/year), SNS-AHs (from 296,7 to 1714,2 Eur/1000 inhabitants/year) and ARBs combinations (from 76,8 to 1171,3 Eur/1000 inhabitants/year).

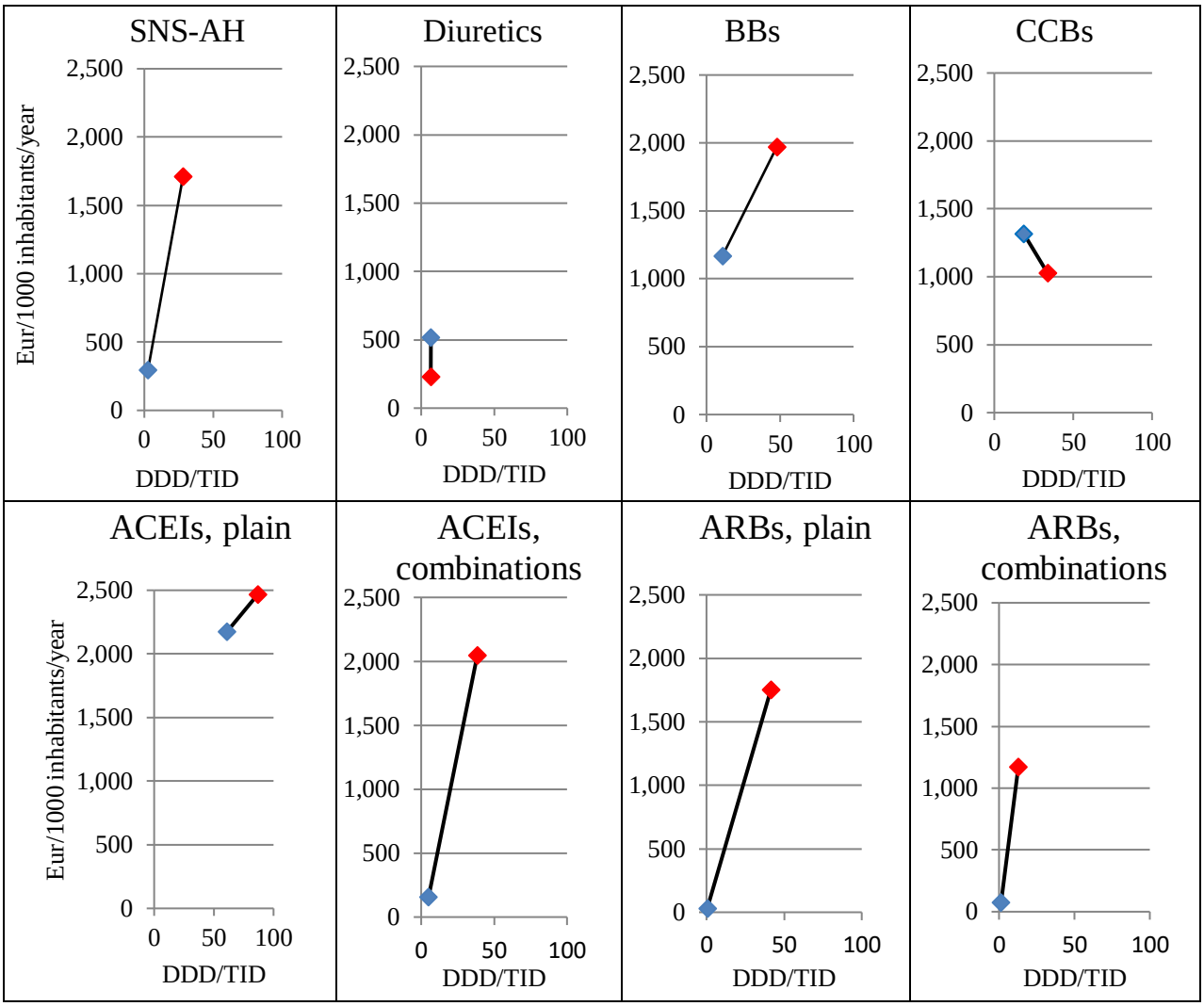


Figure 31. CVM for AH treatment utilization expressed as a number of DDD/TID and reimbursed expenditure expressed as Eur/1000 inhabitants/year in 2003 (blue marker) and in 2012 (red marker) in Lithuania

7.7. Sex and age differences in the treatment of AH in Lithuania in 2003-2012

7.7.1. Sex and age differences in the total consumption of CVM for AH treatment

The use of antihypertensive medicines was increasing annually in every age and sex group (p<0,001). A higher consumption was found in FO than in MO group (p=0,014), however, a greater increase was in MO (% change=184%) than in FO group (% change=147%). Although the use of antihypertensives was considerably lower in younger patients groups, the same trend in drug use has been observed between women and men – a higher use in FY (p=0,031) but a more pronounced increase in MY (% change=218%) than in FY group (% change =117%) (Figure 32).

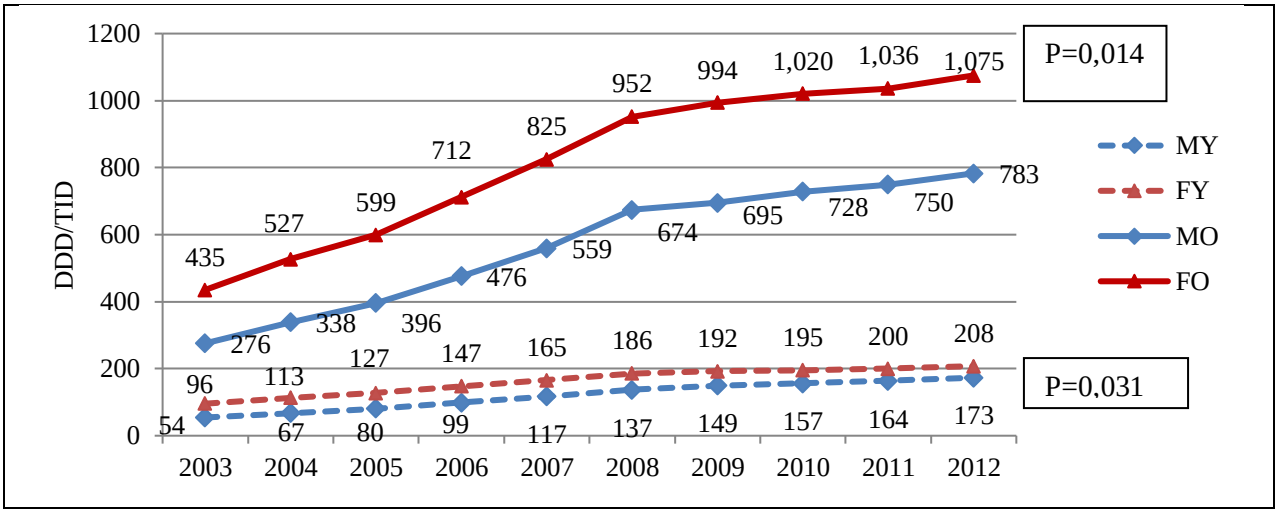


Figure 32. Trends in total utilization of CVM for treatment of AH in various age and sex groups in Lithuania, 2003-2012

7.7.2. Sex and age differences in the total consumption of CVM according to ATC group for AH treatment

A comparison of the use of different groups of CVM between men and women showed a significantly higher use of plain ACEIs (p=0,001), CCBs (p=0,009) and plain diuretics (p<0,001) in FY than in MY and a higher use of plain ACEIs (p<0,001), CCBs (p=0,003), BBs (p=0,039), diuretics (p<0,001) and centrally acting antiadrenergic agents

(p=0,009) in FO than in MO. A-ABs were used more often in both male groups comparing to corresponding female groups (p<0,001) (Table 19).

Table 19. Sex and age differences in consumption of CVM by pharmacological class for treatment of AH in Lithuania from 2003 to 2012.

Group	FY	MY		FO	MO	p value
	Average (95 % CI)	Average (95 % CI)	p value	Average (95 % CI)	Average (95 % CI)	
Antiadrenergic agents, centrally acting	10,7 (7,2-10,8)	5,7 (3,5-7,9)	0,139	53,9 (32,2-75,6)	23,1 (13,4-32,9)	0,009
Moxonidine	7,1(5,2-9)	3,9 (2,6-5,2)	0,015	37,8 (24,6-51)	16,4 (10,4-22,3)	0,012
Rilmenidine	3,5 (2,3-4,6)	1,8 (1,1-2,4)	0,026	15,5 (9,4-21,6)	6,6 (3,2-9,2)	0,022
A-ABs	0,5 (0,3-0,6)	2,4 (1,5-3,4)	<,001	1,7 (1,1-2,3)	27,7 (15,8-39,6)	<,001
Doxazosin	0,4 (0,3-0,6)	2,4 (1,5-2,2)	0,001	1,6 (1-2,2)	27,6 (17,2-38)	<,001
Diuretics	7,2 (6,2-8,2)	3,5 (3,2- 3,8)	<,001	32 (29-35,1)	17,1 (15,6-18,7)	<,001
Indapamide	6,4 (5,5-7,3)	3,1 (2,8-3,4)	<,001	27,9 (25-30,8)	14,2 (12,6-15,8)	<,001
Spironolactone	0,6 (0,4-0,7)	0,3 (0,2-0,4)	0,001	3,2 (2,4-4)	2,2 (1,6-2.9)	0,086
BBs	28,3 (21,5-34,5)	20,5 (13,8-27,2)	0,081	95 (65-123,9)	59,9 (39,3-80,6)	0,039
Metoprolol	8,6 (7,6-9,6)	4,7 (4-5,5)	<,001	41 (32,4-49,6)	25,7 (19,3-32,1)	0,012
Betaxolol	4,8 (4,4-5,3)	2,1 (2-2,3)	<,001	13,4 (11,7-15,2)	6,3 (5,6-7)	<,001
Nebivolol	14,4 (9,6-19,1)	13,4 (8,5-18,3)	0,788	38,4 (22,8-54)	26,9 (15,8-37,9)	0,253
CCBs	20,7 (18,7-22,6)	16,7 (14,2-19,1)	0,009	127,3 (108,2-146,3)	91,8 (77,5-106,1)	0,003
Amlodipine	7,6 (6,7-8,4)	7,4 (6,6-8,2)	0,746	38 (33,6-42,3)	35,6 (31,1-40)	0,460
Felodipine	0,8 (0,5-1,1)	0,6 (0,4-0,8)	0,271	4,9 (3,8-6,1)	3,6 (2,8-4,4)	0,081
Nitrendipine	0,6 (0,2-0,9)	0,4 (0,2-0,7)	0,541	6,5 (3,8-9,1)	4,9 (3-6,8)	0,352
Lacidipine	3,9 (3,4-4,3)	2,6 (2,2-3)	<,001	28,7 (23,8-33,6)	17,1 (14,1-20,2)	<,001
Lercanidipine	5.4 (3,7-7,1)	4,2 (2,7-5,8)	0,341	34 (20,8-47,3)	21 (12,7-29,4)	0,124
Verapamil	0,6 (0,5-0,7)	0,3 (0,2-0,4)	0,001	3 (2,4-3,7)	1,8 (1,3-2,2)	0,007
Diltiazem	1,8 (1,7-2)	1,1 (1,1-1,2)	<,001	11,4 (10,6-12,1)	7,3 (6,9-7,6)	<,001
ACEIs, plain	59,1 (54,9-63,3)	46,8 (40,7-52,8)	0,001	357 (320,4-393,6)	256,4 (222,3-290,4)	<,001
Captopril	1,4 (1,3-1,5)	0,5 (0,5-0,6)	<,001	10,4 (9-11,7)	3,6 (3,2-4,1)	<,001
Enalapril	13,1 (7,3-18,9)	7,6 (4,7-10,6)	0,122	85,1 (54,9-115,3)	48,3 (30,6-66,1)	0,05
Lisinopril	2,7 (2,3-3,1)	1,9 (1,5-2,2)	0,01	12,5 (10,2-14,8)	7,5 (6-91)	0,003
Perindopril	8,6 (5,9-11,2)	8,9 (5,9-11,9)	0,886	48,2 (32,2-64,1)	43,2 (28,6-57,9)	0,661
Ramipril	16,5 (14-18,9)	14 (11,4-16,5)	0,181	122,9 (96,6-149,2)	94,8 (75-114,6)	0,113

Quinapril	5,4 (4,3-6,6)	4,6 (3,6-5,6)	<,001	24,6 (18,3-31)	18,8 (13,8-23,9)	0,176
Fosinopril	5,8 (4,7-6,4)	4,5 (3,9-5,1)	0,071	29,3 (26,6-33,1)	22 (19,9-24)	0,001
Trandolapril	1 (0,6-1,4)	0,8 (0,4-1,2)	0,496	3,7 (2-5,3)	2,9 (1,6-4,2)	0,463
Spirapril	0,7 (0,5-1)	0,5 (0,4-0,6)	0,047	3 (2,1-3,8)	1,9 (1,4-2,4)	0,053
Zofenopril	4,3 (3,3-5,3)	3,9 (2,8-5,1)	0,646	18,8 (14-23,5)	14,8 (10,6-18,9)	0,256
ACEIs, combinations	18,5 (11,9-25,1)	12,1 (6,4-17,8)	0,113	73,6 (46,4-100,8)	45,5 (26-65,1)	0,074
Enalapril/HCT	1,9 (0,9-3)	0,8 (0,4-1,2)	0,075	10,3 (5,7-14,9)	5,5 (3-7,9)	0,089
Perindopril/indapamide	10,4 (7-13,8)	6,6 (4,3-8,9)	0,105	33,9 (21,2-46,5)	20,3 (12,5-28,2)	0,114
Quinapril/HCT	4 (3,1-4,9)	2,3 (1,8-2,9)	0,013	18,3 (13,7-22,9)	10,5 (7,9-13)	0,016
Fosinopril/HCT	1,3 (1-1,5)	0,8 (0,6-0,9)	0,008	6,2 (4,8-7,5)	3,8 (2,9-4,6)	0,014
Ramipril/HCT	0,8 (0,5-1)	0,4 (0,3-0,5)	0,081	3,6 (2,5-4,7)	2,1 (1,5-2,8)	0,119
Perindopril/amlodipine	3,8 (2,1-5,5)	4,8 (2,6-7)	0,132	17,3 (9,3-25,3)	16,2 (8,5-24)	0,905
Verapamil/ trandolapril	1,9 (1,3-2,5)	1,4 (1-1,9)	0,567	5,8 (3,8-7,4)	3,9 (2,7-5,2)	0,454
ARBs, plain	16,2 (6,7-25,8)	11,3 (4,2-18,4)	0,355	70,6 (26,7-114,5)	43,4 (15,6-71,1)	0,244
Losartan	9,4 (6,3-12,5)	5,7 (3,7-7,7)	0,106	41,2 (27,1-55,4)	23,7 (15,5-32)	0,088
Valsartan	5,8 (2,3-9,3)	4,4 (1,8-7,1)	0,601	25,9 (9,6-42,1)	16,6 (6,1-27)	0,415
Telmisartan	2,3 (0,1-4,6)	1,9 (0,1-3,7)	0,819	9,4 (0,1-19)	6,5 (0,1-13,2)	0,672
ARBs, combinations	5,6 (1,7-9,3)	3,1 (0,6-5,7)	0,202	22,5 (6,6-38,4)	11,5 (2,6-20,5)	0,154
Losartan/HCT	2,8 (2,3-3,2)	1,2 (1-1,5)	0,003	11,3 (9,3-13,4)	5,2 (4,3-6,2)	0,005
Valsartan/HCT	2,2 (0,6-3,4)	1,4 (0,4-2,4)	0,554	8,9 (2,3-15,6)	4,8 (1,2-8,5)	0,442
Total	162,9 (134,3-191,5)	119,7 (89,3-150,1)	0,031	810,9 (648,6-973,3)	574 (436,8-711,2)	0,014

7.7.3. Trends of antihypertensive medicines utilization in different age and sex groups in Lithuania in 2003−2012

An increase of plain ACEIs utilization was seen in three patients groups: MY (% change=58%, p=0,041), FO (% change=24,2%, p=0,002) and MO (% change =53,7%, p<0,001) (Figure 33). An increase of the use of centrally acting antiadrenergic agents (p<0,001), BBs (p<0,001), plain ARBs (p<0,001), ACEIs combinations (p<0,001) and ARBs combinations (p=0,003) was observed in FY population. No increase in the use of diuretics (p=0,87) and CCBs (p=0,18) but an increase in the consumption of other CVM (p<0,05) was seen in MY population at the same time.

The utilization of all antihypertensive medicines increased in older patients groups with the only exception in plain diuretics utilization (FO group – % change=0,4%, p=0,98; MO group – % change=8,1%, p=0,82). The utilization of plain ARBs increased more than any other group of medicines in both older patients groups – nearly 150 times.

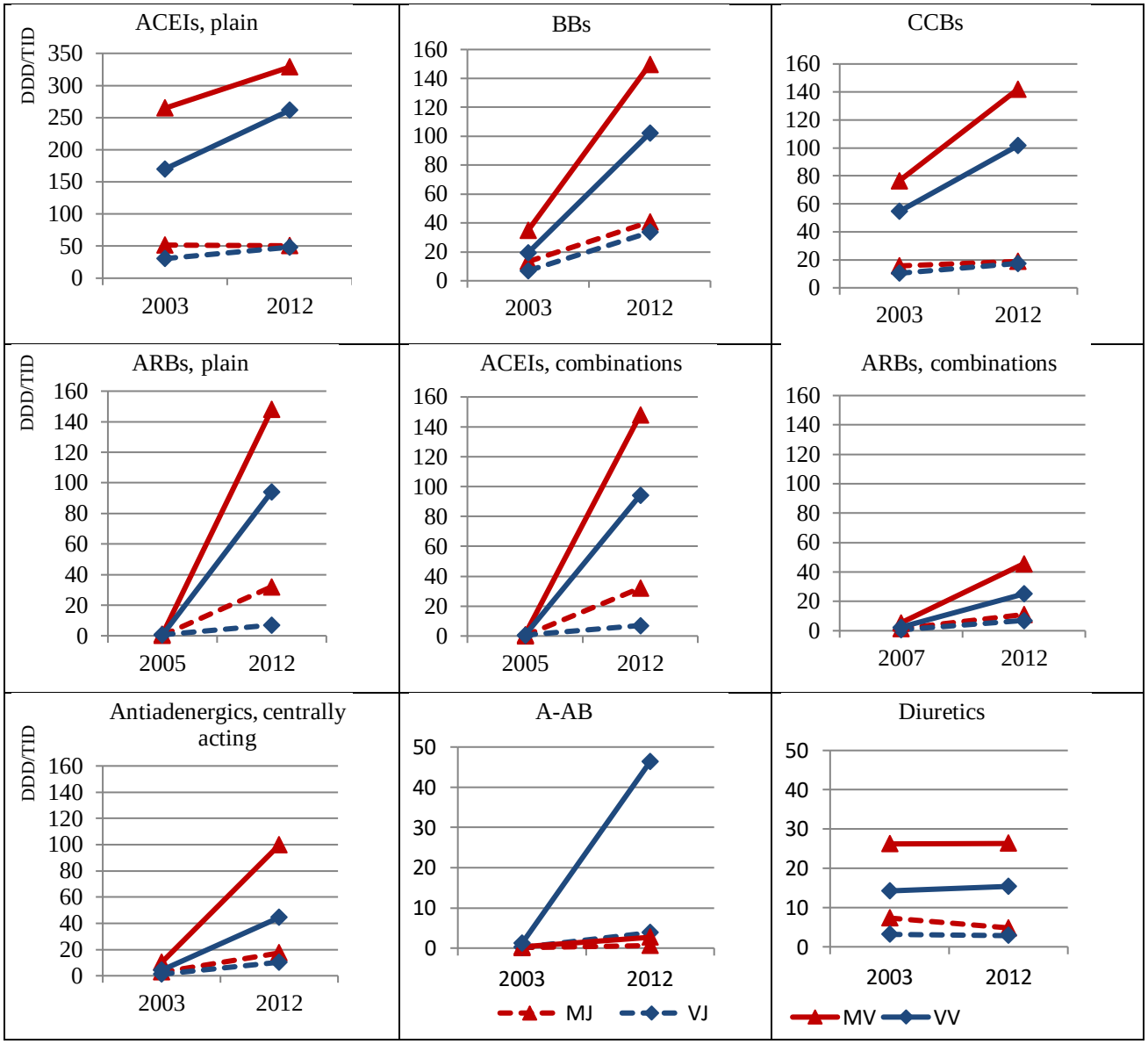


Figure 33. Trends in utilization of CVM for AH treatment in Lithuania from 2003 to 2012

7.7.4. Sex and age differences in the number of CVM simultaneously prescribed for a patient for AH treatment

The proportion of patients receiving monotherapy decreased nearly 2,5 times in both older patients (FO – from 29,1 to 12,7%, MO – from 32 to 12,5%, p<0,001) and 2 times in MY group (from 40,3 to 20,3%, p<0,001) during the study period (Figure 34). The use of two and three medicines increased in all age and sex groups (p<0,001). The proportion of patients receiving four or more drugs increased significantly during the

study decade: FY (from 1 to 2,1%, p<0,001), MY (from 0,9 to 7,3%, p<0,001), FO (from 3,7 to 10,5%, p<0,001) and MO (from 2,5 to 13%, p<0,001). Monotherapy was more often used in FY than in MY (p=0,047) whereas 3 drugs (p=0,047) and ≥4 drugs (p=0,02) were more often prescribed in MY than in FY group. Differences in the number of drugs per prescription were not seen between men and women in the older age range (Table 20).

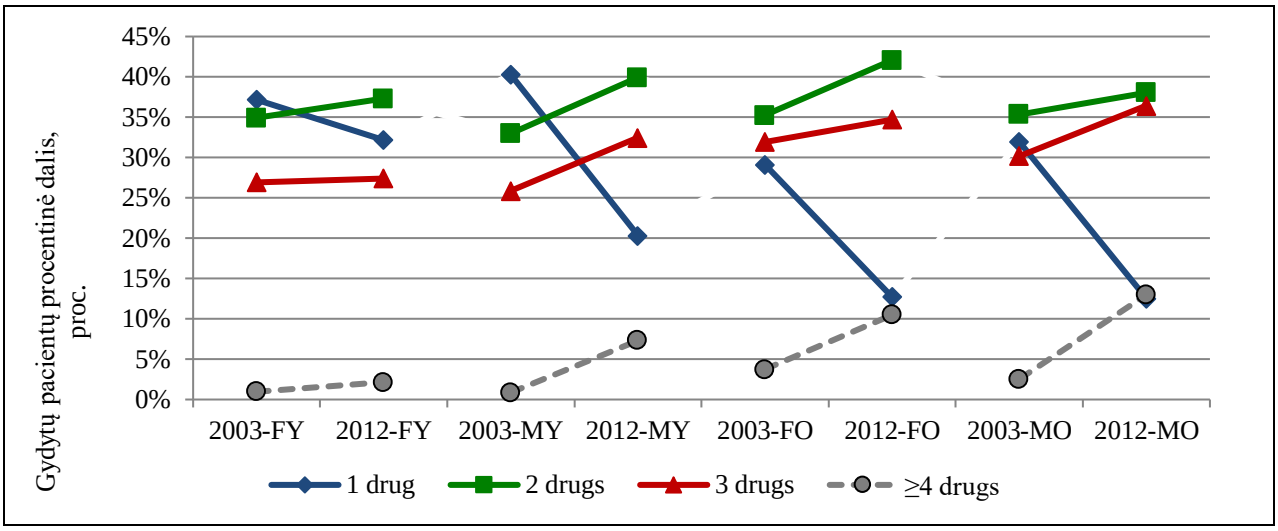


Figure 34. Trends of number of CVM simultaneously prescribed for a patient for the treatment of AH in Lithuania from 2004 to 2012

Table 20. Sex and age differences in the number of CVM simultaneously prescribed for a patient for the treatment of AH in Lithuania from 2003 to 2012

Patients group	FY	MY	p value	FO	MO	p value
	Average (95 % CI)	Average (95 % CI)		Average (95 % CI)	Average (95 % CI)	
1 drug	34,6 (33,6-35,7)	29,9 (25,1-34,8)	0,047	19,3 (15,3-23,2)	20,9 (16,3-25,6)	0,595
2 drugs	36,7 (36,1-37,2)	37 (35,5-38,6)	0,680	39,1 (37,5-40,6)	38,5 (37,4-39,6)	0,.573
3 drugs	26,9 (26,6-27,3)	29 (27,3- 30,7)	0,049	35,1 (33,9-36,3)	33,4 (31,8-34,9)	0,104
≥4 drugs	1,6 (1,3-1,9)	4 (2,4-5,7)	0,018	6,6 (4,9-8,3)	7,2 (5-9,.5)	0,682

7.7.5. Sex and age differences in the utilization of CVM according to ATC group for AH mono and dual therapy

Monotherapy by prescribing centrally acting antiadrenergic agents, A-ABs, diuretics and BBs was more often used in FY than in MY (p<0,001). On the contrary,

monotherapy by prescribing CCBs (p=0,04) and A-ABs (p<0,001) was more often used in MY than in FY group (Figure 35 A). There was no difference in the utilization of plain ACEIs and ARBs as monotherapy, comparing the younger patients groups.

Monotherapy by using CCBs and A-ABs (p<0,001) was more often prescribed for MO than for FO (Figure 35 B).

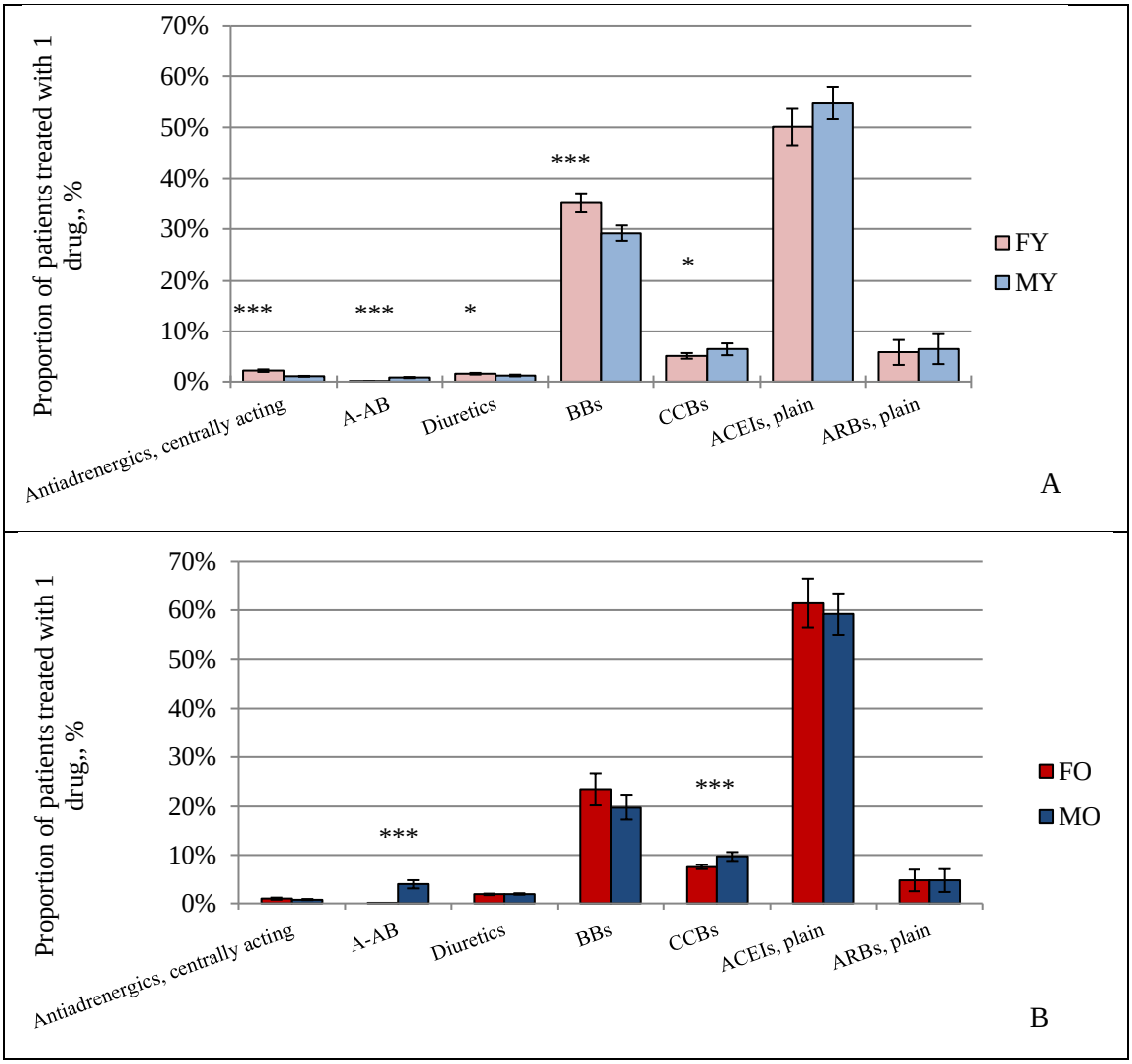


Figure 35. A) Sex differences in 18-64 year age group in consumption of CVM by pharmacological class for monotherapy of AH in Lithuania from 2003 to 2012 (proportion and 95 % CI). B) Sex differences in >65year age group in consumption of CVM by pharmacological class for monotherapy of AH in Lithuania from 2003 to 2012 (proportion and 95 % CI).

*** – p<0,001, ** – p<0,01, * – p<0,05.

The combination of ACEI and diuretic was more often prescribed as a dual therapy for FY than for MY (p=0,02). A dual thearpy with ACEI plus BB (p<0,001), CCB plus

SNS-AH (p<0,001) or BB plus SNS-AH (p<0,001) was more frequently prescribed for MY than for FY (Figure 36 A). The analysis of dual therapy patterns revealed a more frequent prescribing of CCB and diuretic FIX-Ds for FO than for MO (p<0,001) (Figure 36 B). Other differences in dual therapy patterns were not registered between men and women in the older age range.

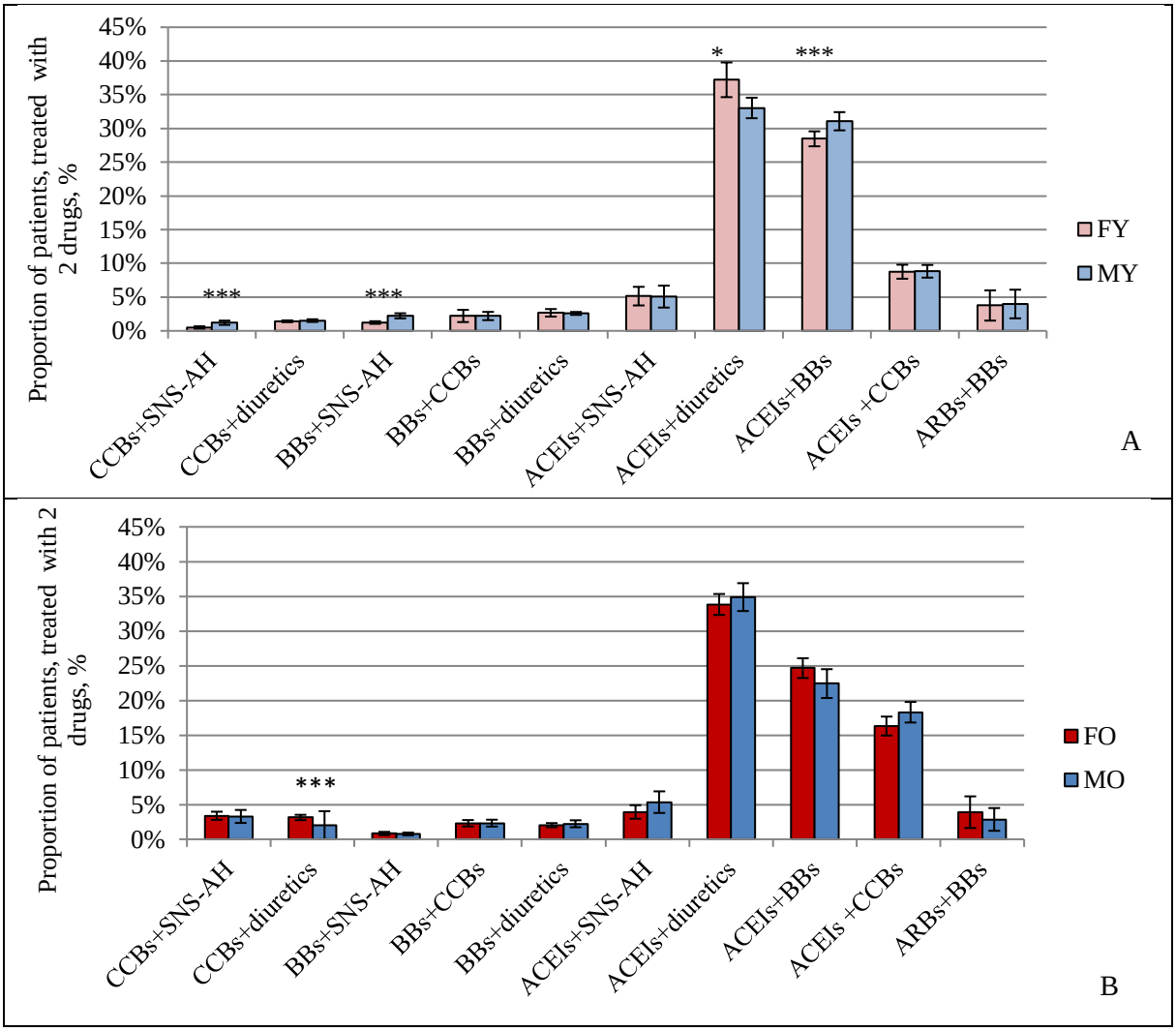


Figure 36. A) Sex differences in 18-64 year age group in consumption of CVM by pharmacological class for 2 drugs therapy of AH in Lithuania from 2003 to 2012 (proportion and 95 % CI). B) Sex differences in >65year age group in consumption of CVM, by pharmacological class, for 2 drugs therapy of AH in Lithuania from 2003 to 2012 (proportion and 95 % CI).

*** – p<0,001, ** – p<0,01, * – p<0,05.

7.8. The initiation of AH treatment – sex and age differences and time trends in 2004−2012

7.8.1. Time trends of incidence and incidence rate of new users of CVM for AH treatment in 2004−2012

A number of people, to whom AH was diagnosed for the first time and the first prescription for the treatment was issued, decreased from 81 736 people (24,2 new users per 1000 inhabitants per year (NU/TIY)) in 2004 to 54 580 persons in 2012 (18,27 NU/TIY, % change =-24,51%, p<0,001). The incidence rate decreased in both sex groups: women – from 26,1 to 17,56 NU/TIY (% change= -37,72%, p<0,001), men – from 22,03 to 18,88 NU/TIY (% change= -13,31%, p<0,001). The proportion of women among new users decreased from 57,59% to 51,84% during the study decade (% change= -9,99%, p<0,001) (Table 21).

Table 21. Incidence and incidence rate of new users of antihypertensives - total, men and women - in 2004-2012 in Lithuania.
NU/TIY- Number of new medicine users per 1000 inhabitants per year
*** – p<0,001, ** – p<0,01, * – p<0,05.

Year	Total number of persons	NU/TIY-total	P value	Women	NU/TIY women	p value	Men	Nu/TIY men	p value	Proportion of women
2004	81 736	24,20		47 075	26,10		34 661	22,03		57,59
2005	80 344	24,18	0,86	46 063	25,92	0,29	34 281	22,18	0,37	57,33
2006	80 483	24,61	***	46 191	26,36	0,09	34 292	22,60	*	57,39
2007	76 735	23,75	***	42 165	24,32	***	34 570	23,09	**	54,95
2008	66 360	20,75	***	35 504	20,67	***	30 856	20,84	***	53,50
2009	65 902	20,84	0,44	34 559	20,32	*	31 343	21,44	***	52,44
2010	57 452	18,55	***	30 679	18,39	***	26 773	18,74	***	53,40
2011	55 501	18,33	*	29 151	17,85	***	26 350	18,88	0,37	52,52
2012	54 580	18,27	*	28 294	17,56	*	26 286	19,10	0,23	51,84
PP		-24,51			-37,72			-13,31		-9,99

The time trends of incidence rate of new CVM users for AH treatment are presented in Figure 37.

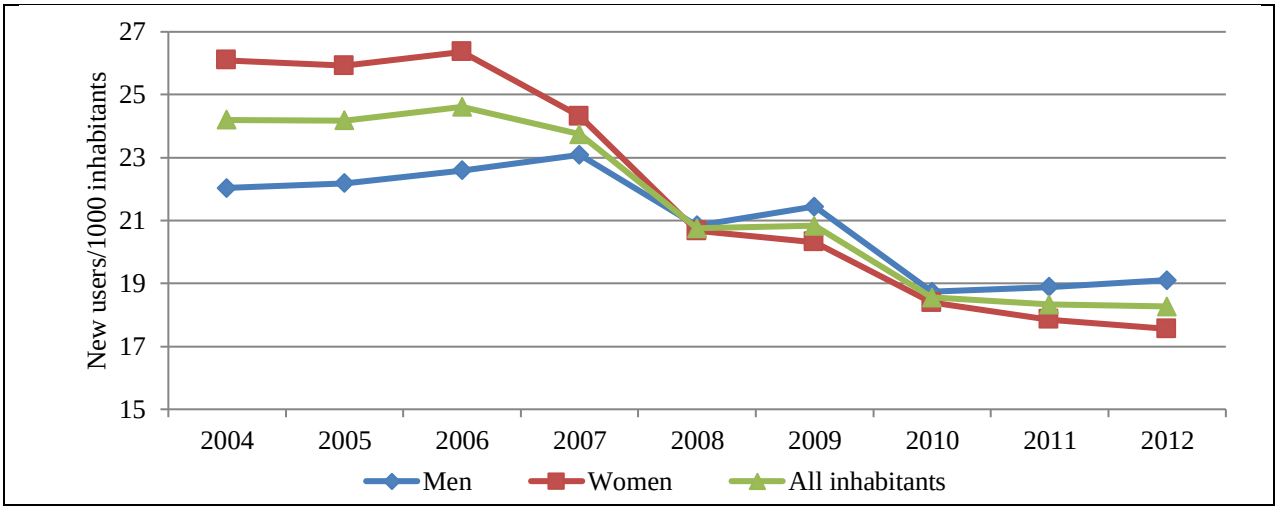


Figure 37. Trends of incidence rate of new antihypertensive drugs users in 2004−2012 in Lithuania.

The incidence rate increased in three age groups: in 18−29 years of age group (from 2,77 to 4,37 NU/TIY, p<0,001), in 30−39 years of age group (from 9,29 to 13,05 NU/TIY, p<0,001) and in 40−49 years of age group (from 24,33 to 28,57 NU/TIY, p<0,001). The incidence rate decreased in the groups of patients aged at least 50 years (Table 22).

Table 22. Trends of incidence rate of new antihypertensive drugs users in different age groups in 2004−2012 in Lithuania.

***- p<0,001, **- p<0,01, * - p<0,05.

Year	1 group 18-29 y.	2 group 30-39 y.	3 group 40-49 y.	4 group 50-59 y.	5 group 60-69 y.	6 group 70-79 y.	7 group ≥ 80 y.
2004	2,77	9,29	24,33	48,51	61,86	66,66	64,40
2005	3,27	11,09	27,52	50,29	58,10	57,40	53,87
2006	3,73	12,41	30,18	52,26	55,64	53,15	47,18
2007	4,30	13,49	31,98	50,32	50,99	45,06	39,28
2008	4,25	12,43	29,21	44,48	42,24	35,88	31,45
2009	4,51	13,70	30,70	44,36	40,83	32,91	27,31
2010	4,15	12,08	27,11	39,47	36,08	27,83	22,52
2011	4,16	12,95	27,72	38,68	33,77	25,61	19,06
2012	4,37	13,05	28,57	38,33	32,97	23,63	16,91
P value	***	***	***	***	***	***	***

The increase of the incidence rate of new antihypertensive drugs users was more evident in the three younger men and women groups (Table 23). The highest % change was registered in 18-29 years of age groups (women group- % change= 66,5%, men

group % change=52,6%). The incidence rate of new antihypertensive drugs users decreased in both sex groups of patients aged at least 50 years. A statistically significant difference in the incidence rate of new antihypertensive drugs users between men and women was registered in all age groups except for the 50-59 years of age group.

Table 23. Trends of incidence rate of new antihypertensive drugs users in different age and sex groups in 2004−2012 in Lithuania.

*** − p<0,001, ** − p<0,01, * − p<0,05, F-females, M -males.

Group	Sex	2004	2005	2006	2007	2008	2009	2010	2011	2012	PP	P-value
18-29	F	1,66	2,09	2,28	2,61	2,61	2,85	2,76	2,85	2,77	66,5	
	M	3,86	4,42	5,14	5,95	5,85	6,13	5,49	5,42	5,90	52,6	***
30-39	F	7,67	9,38	10,67	11,35	10,23	10,90	10,07	10,69	10,63	38,5	
	M	10,95	12,86	14,23	15,71	14,71	16,59	14,16	15,28	15,55	41,9	***
40-49	F	24,23	28,38	31,41	31,99	28,42	29,58	27,29	26,57	26,90	11	
	M	24,44	26,59	28,86	31,97	30,06	31,90	26,93	28,96	30,43	24,5	***
50-59	F	49,84	52,73	54,74	51,09	44,30	43,87	40,20	38,81	38,38	-23	
	M	46,91	47,35	49,30	49,40	44,69	44,95	38,61	38,54	38,33	-18,3	0,87
60-69	F	61,64	57,99	55,55	48,88	40,19	37,94	33,70	32,10	30,59	-50,4	
	M	62,18	58,26	55,77	54,06	45,22	45,05	39,54	36,20	36,50	-41,3	***
70-79	F	64,31	54,01	51,66	42,18	32,21	29,19	24,16	22,06	20,65	-67,9	
	M	62,18	58,26	55,77	54,06	45,22	45,05	39,54	36,20	36,50	-41,3	***
>80	F	61,49	51,69	45,36	36,89	29,14	24,64	19,71	16,50	14,89	-75,8	
	M	72,74	60,26	52,60	46,39	38,21	35,04	30,48	26,24	22,52	-69	***

7.8.2. The age of men and women when the first CVM for AH treatment was prescribed

The age of newly-treated persons was declining every year - the total average age dropped from 60,3 years in 2004 to 54,5 years in 2012. The average age of newly treated women decreased from 62 to 56 years (p<0,001) and men - from 58 to 52,8 years (p<0,001) during the study decade (Figure 38).

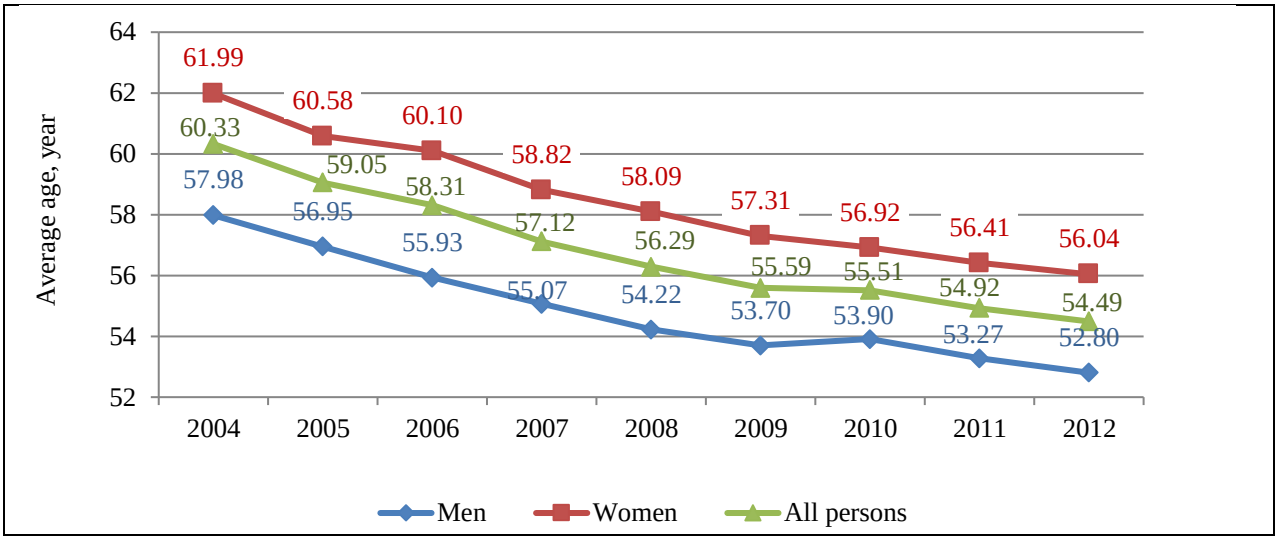


Figure 38. Trends of average age of Lithuanian inhabitants (all, men and women) when the medicines for treatment of AH were prescribed the first time in 2004-2012 in Lithuania.

7.8.3. Prescription of one, two, three and four or more CVM on the initiation of AH treatment – sex and age differences

Monotherapy was more often used for the initiation of AH treatment in all sex and age groups. The proportion of patients using monotherapy for the initiation of treatment was highest in these patient groups: men aged 18-29 years (from 80,2% in 2004 to 77,1% in 2012), women aged 18-29 years (from 79,5% in 2004 to 75,6 % in 2012), men aged at least 80 years (from 77,1% in 2004 to 72,3% in 2012) and women aged at least 80 years (from 72,3 % in 2004 to 65,5% in 2012). A statistically significant difference ($p<0,05$) between men and women in the rate of monotherapy was registered only in 70-79 years and ≥80 years of age patient groups. The proportion of newly treated patients using monotherapy decreased in all patient groups (% change from -2,6% to -9,7%).

The proportion of newly treated patients using a dual therapy increased in all patient groups. The dual therapy was the most often used in both sex groups of patients aged 40−49 and 50−59 years. Three medicines were the most often prescribed for 50−59 years aged men (from 6,9% in 2004 to 8,3% in 2012) and women (from 7,8 % in 2004 to 8,9 % in 2012). The proportion of patients using four and more medicines for the initiation of AH treatment increased in all patient groups. No differences between the

corresponding age men and women groups in the rate of using two, three, four and more drugs were registered (Figure 39).

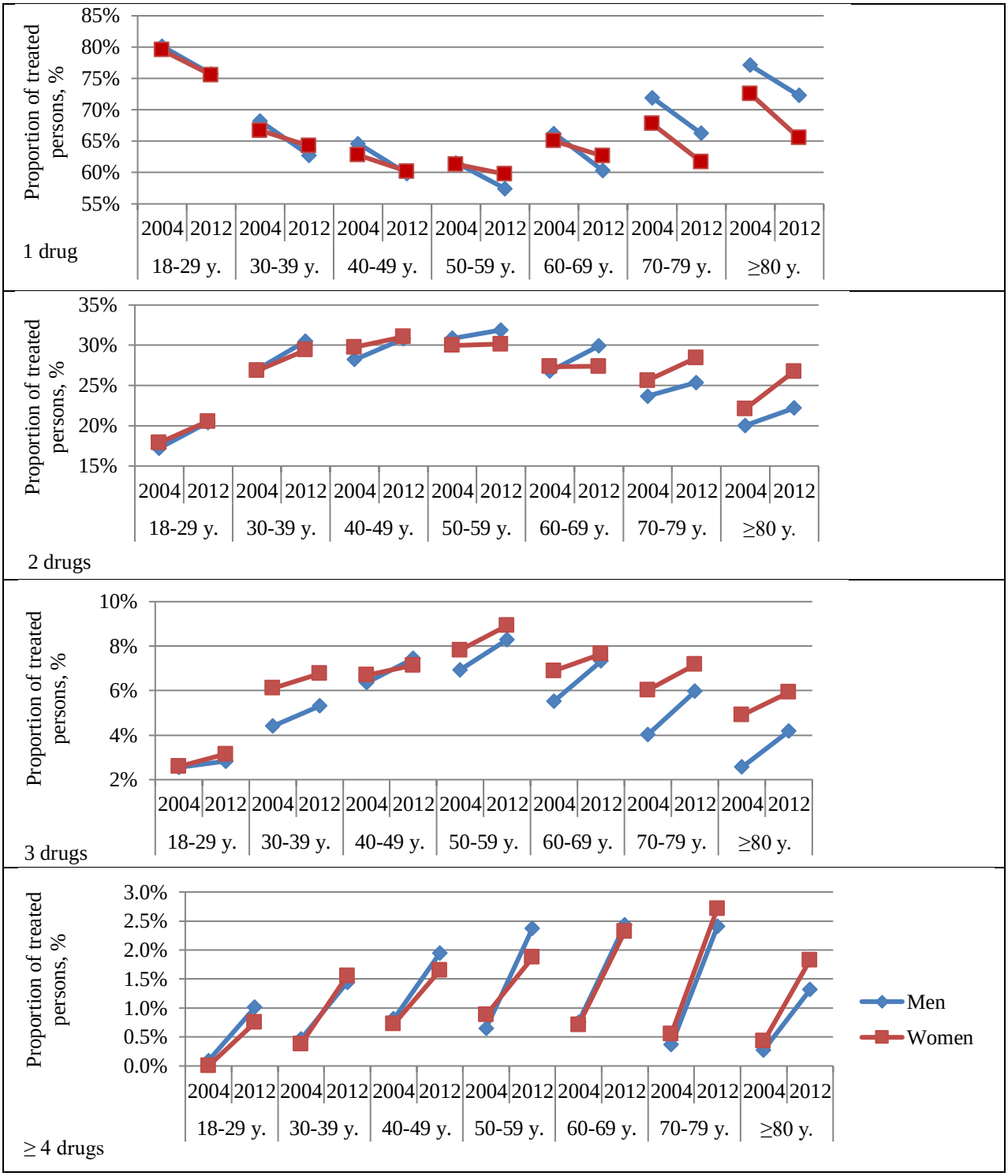


Figure 39. Trends of initiation of AH treatment with 1, 2, 3or ≥4 drugs in different age and sex groups in 2004−2012.

7.8.4. Age and sex differences in the utilization of CVM for monotherapy for the initiation of AH treatment

The most prescribed monotherapies were ACEIs followed by BBs in all patient groups, except for women aged 18−29 years, who were more likely to be treated with BBs (Figure 40). The use of centrally acting antiadrenergic medicines was high in women aged 18−29 years due to the prescription of methyldopa for the treatment of pregnancy induced hypertension. The prescription of A-ABs was more often registered in the groups of men aged at least 50 years.

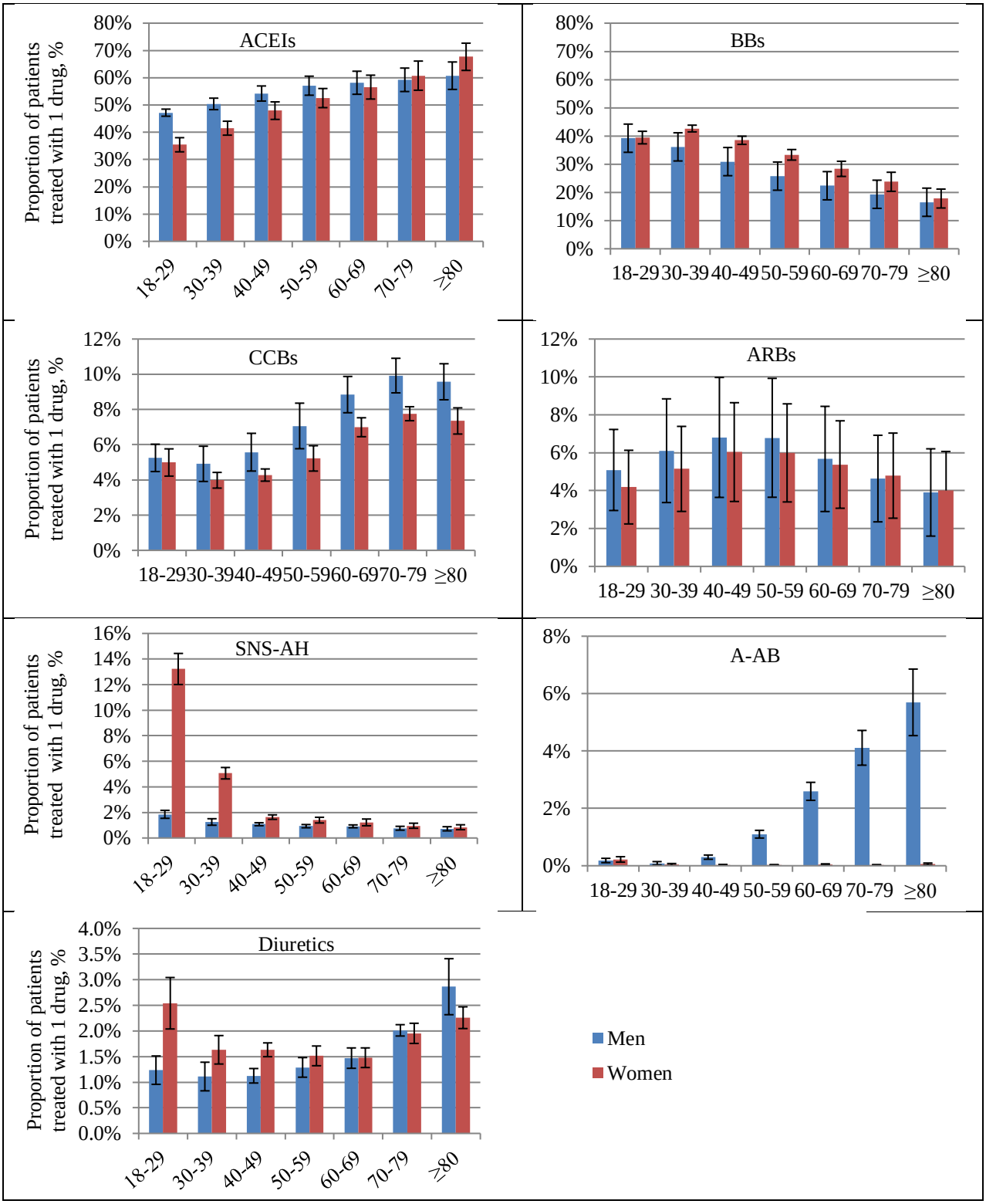


Figure 40. Sex and age differences in the initiation of AH treatment with 1 drug, according to ATC group in 2004-2012 in Lithuania.

7.8.5. The most prescribed CVM for initiation of AH treatment as a monotherapy

In 2004 the first-line drugs for 18-29 and 30-39 years of age women were metoprolol and enalapril. In all other age and sex groups the first choice medicine was enalapril. In 2012 an increased use of zofenopril, perindopril and ramipril replacing enalapril was registered in all patient groups. A list of the most commonly prescribed medicines contained three ACEIs and two BB medicines in almost all patient groups. The only exceptions - 18-39 years of age women, who received methyldopa, and 80 years of age and older men who were often given doxazosin (Table 24, Table 25).

Table 24. Most often for women of different age prescribed medicines for initiation of AH treatment as monotherapy in 2004 and 2012.

Women in 2004						
18-29 y.	30-39 y.	40-49 y.	50-59 y.	60-69 y.	70-79 y.	≥ 80 y.
Metoprolol 24,7%	Metoprolol 32,3%	Enalapril 35,2%	Enalapril 36,3%	Enalapril 39,3%	Enalapril 36,3%	Enalapril 41,7%
Enalapril 22,2%	Enalapril 30,5%	Metoprolol 28,8%	Metoprolol 23,5%	Metoprolol 20,1%	Metoprolol 23,5%	Ramipril 19,4%
Methyldopa 16,8%	Nebivolol 6,2%	Nebivolol 4,7%	Ramipril 7,1%	Ramipril 9,6%	Ramipril 7,1%	Metoprolol 9,2%
Nebivolol 4,9%	Ramipril 3,7%	Ramipril 4,6%	Perindopril 3,5%	Perindopril 4,4%	Perindopril 3,5%	Perindopril 5,8%
Ramipril 4,6%	Methyldopa 3,3%	Perindopril 2,8%	Nebivolol 3,1%	Amlodipine 3,4%	Nebivolol 3,1%	Captopril 3,9%
Women in 2012						
18-29 y.	30-39 y.	40-49 y.	50-59 y.	60-69 y.	70-79 y.	≥ 80 y.
Nebivolol 21%	Nebivolol 22,8%	Nebivolol 20,7%	Nebivolol 19,4%	Metoprolol 18,4%	Metoprolol 18,1%	Ramipril 21,7%
Metoprolol 20,2%	Metoprolol 19,7%	Metoprolol 18,1%	Metoprolol 15,9%	Zofenopril 16,9%	Ramipril 14,5%	Metoprolol 15,9%
Methyldopa 10,1%	Zofenopril 10,3%	Zofenopril 12,4%	Zofenopril 13%	Nebivolol 14,6%	Perindopril 11,4%	Perindopril 11,5%
Zofenopril 9,2%	Perindopril 8,8%	Perindopril 10,3%	Perindopril 11,5%	Perindopril 11,8%	Nebivolol 11,3%	Zofenopril 8,3%
Perindopril 6,3%	Ramipril 5,1%	Ramipril 8%	Ramipril 9,2%	Ramipril 10,6%	Zofenopril 11%	Nebivolol 7%

Table 25. Most often for men of different age prescribed medicines for initiation of AH treatment as monotherapy in 2004 and 2012.

Men in 2004						
18-29 y.	30-39 y.	40-49 y.	50-59 y.	60-69 y.	70-79 y.	≥ 80 y.
Enalapril 23,4%	Enalapril 27,8%	Enalapril 28%	Enalapril 30,4%	Enalapril 30,6%	Enalapril 29%	Enalapril 26,4%
Metoprolol 19,3%	Nebivolol 18%	Metoprolol 17,6%	Metoprolol 15,9%	Metoprolol 14,3%	Ramipril 15,3%	Ramipril 20,6%
Nebivolol 19,3%	Metoprolol 16,1%	Nebivolol 13,2%	Ramipril 9,2%	Ramipril 12%	Metoprolol 13,2%	Metoprolol 9,7%
Fosinopril 6%	Ramipril 5,9%	Ramipril 6,8%	Perindopril 6,5%	Perindopril 7%	Perindopril 7,7%	Perindopril 9,3%
Ramipril 5,5%	Perindopril 4,4%	Perindopril 5,7%	Nebivolol 6,3%	Fosinopril 4,5%	Fosinopril 4,1%	Captopril 6,8%
Men in 2012						
18-29 y.	30-39 y.	40-49 y.	50-59 y.	60-69 y.	70-79 y.	≥ 80 y.
Nebivolol 28,2%	Nebivolol 29,8%	Nebivolol 23,7%	Nebivolol 18,1%	Metoprolol 14,7%	Metoprolol 16,5%	Ramipril 16,5%
Perindopril 12,8%	Zofenopril 13,9%	Zofenopril 15,2%	Zofenopril 15,7%	Nebivolol 12,5%	Ramipril 15,8%	Metoprolol 15,6%
Zofenopril 12,8%	Perindopril 12,7%	Perindopril 13,2%	Perindopril 12,7%	Perindopril 13%	Perindopril 12,7%	Perindopril 11,6%
Metoprolol 10%	Ramipril 7,5%	Ramipril 9,6%	Metoprolol 10,9%	Ramipril 13,1%	Zofenopril 11,4%	Zofenopril 11,2%
Ramipril 7,1%	Metoprolol 6,5%	Metoprolol 8,4%	Ramipril 9,2%	Zofenopril 12%	Nebivolol 8,1%	Doxazosin 7,4%.

7.8.6. Age and sex differences in the utilization of CVM for dual therapy as an initiation of AH treatment

The most commonly prescribed dual therapy was a combination of an ACEI and a diuretic in all patient groups. This combination was prescribed for more than 50% of patients aged 18-29 years and for 30-40% of patients of other age groups treated with a dual therapy (Figure 41).

The second most common combination was ACEI and BB, which was prescribed for nearly 30% of all patients receiving dual therapy.

The third most common combination was ACEI and CCB which was prescribed for 10-12 % of younger patients and for 15-20% of older patients.

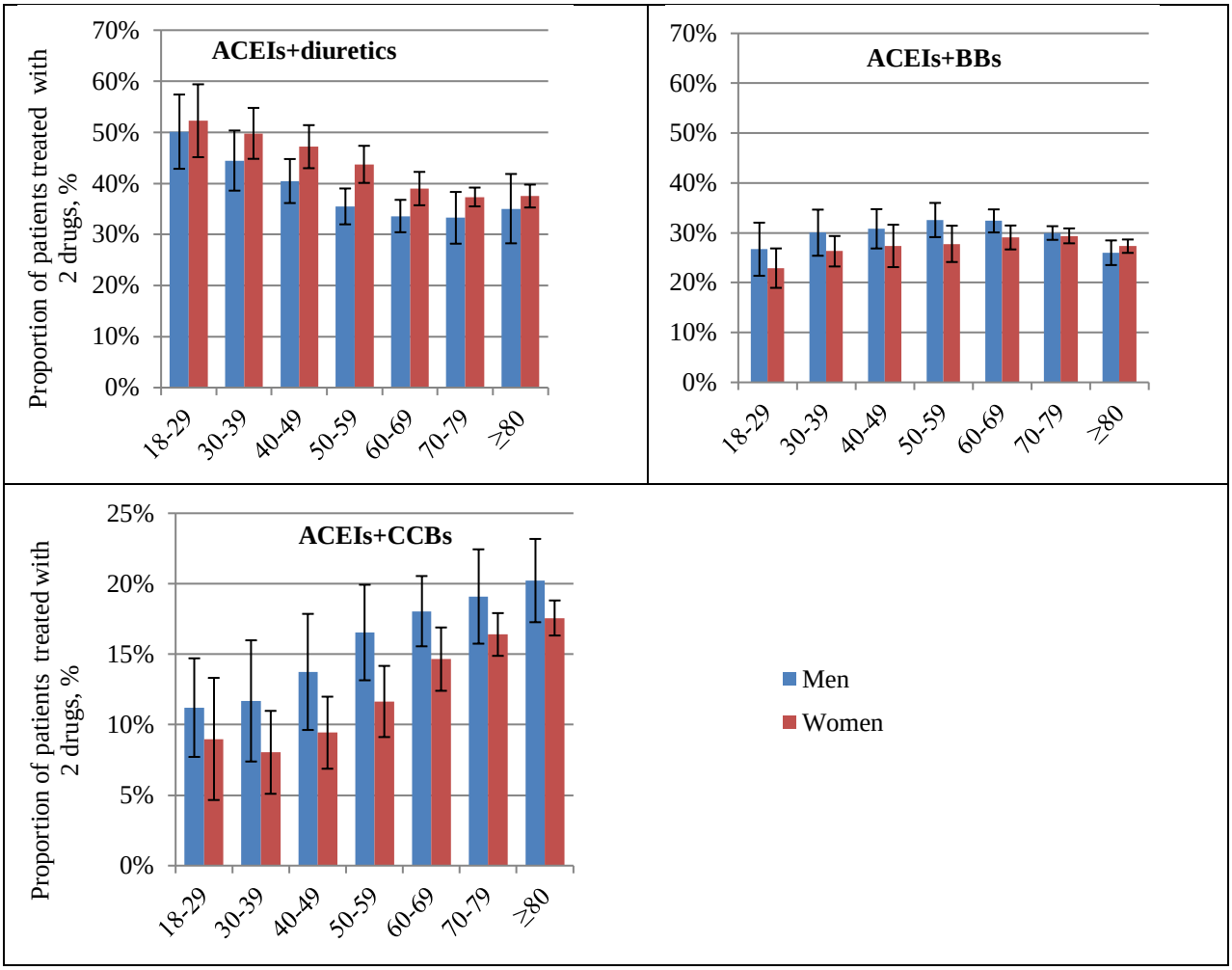


Figure 41. Sex and age differences in the initiation of AH treatment with 2 drugs according to ATC group in 2004-2012 in Lithuania.

In 2004 three the most often used combinations of two CVM for all patients were:

1. Enalapril/HCT
2. Enalapril/metoprolol
3. Perindopril/indapamide

In 2012 three the most often used combinations of two CVM for all patients were:

1. Perindopril/indapamide
2. Perindopril/amlodipine
3. Zofenopril/nebivolol

7.8.7. Age and sex differences in the utilization of CVM for three medicines therapy as an initiation of AH treatment

The most commonly prescribed three medicines therapy was a combination of an ACEI, BB and a diuretic in all patient groups, but the proportion of patients receiving this combination decreased with an increasing age. The second most commonly prescribed three medicines therapy was a combination of an ACEI, CCB and a diuretic in all patient groups. The data about other combinations is presented in Figure 42.

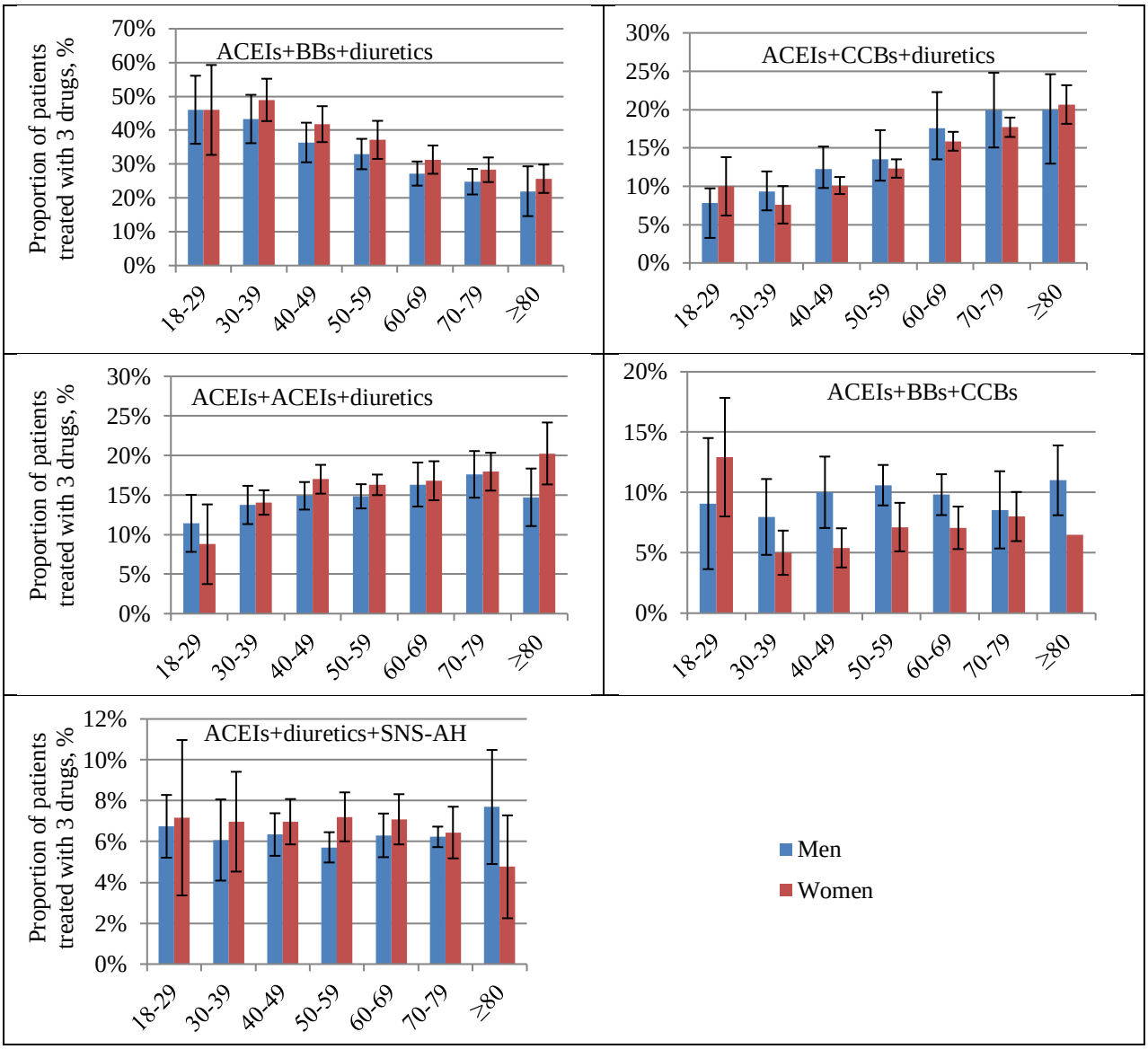


Figure 42. Sex and age differences in the initiation of AH treatment with 3 drugs according to ATC group in 2004-2012 in Lithuania.

In 2004 three the most often used combinations of three CVM for all patients were:

1. Enalapril/HCT (FIX-D) + metoprolol
2. Enalapril/HCT (FIX-D)+ enalapril
3. Enalapril + metoprolol+ amlodipine

In 2012 three the most often used combinations of three CVM for all patients were:

1. Perindopril/ indapamide (FIX-D)+ nebivolol
2. Perindopril/ indapamide (FIX-D)+metoprolol
3. Perindopril/ indapamide (FIX-D)+ rilmenidine for 18−39 years aged patients or perindopril/amlodipine (FIX-D)+ nebivolol for 40−59 years aged patients or perindopril/indapamide (FIX-D)+perindopril for 60 years and older aged patients

No differences in the rate of using combinations of these drugs between men and women groups of corresponding age were registered.

7.8.8. Initiation of AH treatment with four drugs

Four and five the most often used combinations for all patients during the study decade were:

1. 2 ACEIs+BB+diuretic (perindopril/indapamide (FIX-D)+perindopril+ nebivolol)
2. ACEI+BB+diuretic+centrally acting antiadrenergic medicine
3. ACEI+BB+CCB+centrally acting antiadrenergic medicine

7.8.9. Utilization of fixed dose combinations (FIX-D) for initiation of AH treatment

The use of FIX-D for the initiation of AH treatment increased in all age and sex groups during the study period (Figure 43). At the beginning of the study FIX-D were mostly prescribed for women, conversely, in 2012 they became more often used by men.

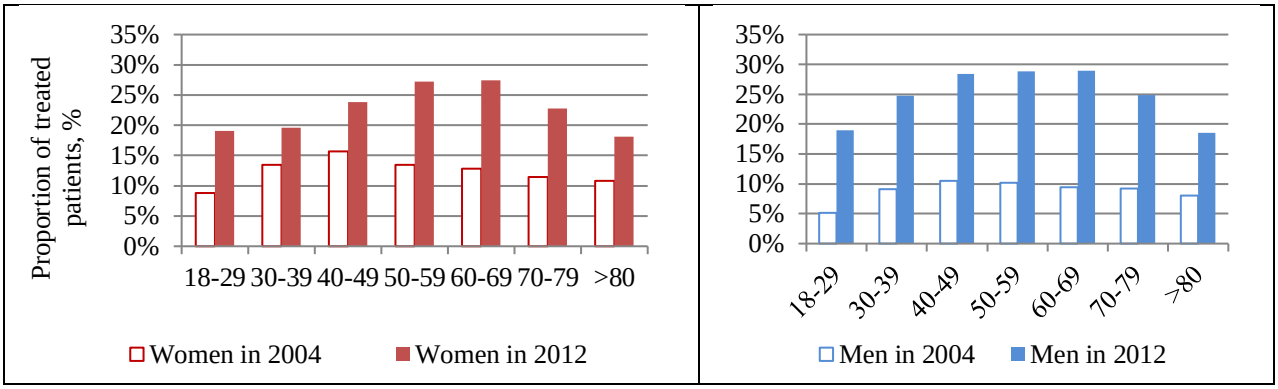


Figure 43. Utilization of fixed-dose combinations in different sex and age groups in the initiation of AH treatment in 2004 and 2012 in Lithuania.

The use of FIX-D as a dual therapy was increasing in all patient groups. The proportion of patients receiving FIX-D when starting treatment with two drugs increased from approximately 20-30% in 2004 to 50-60% in 2014 (Figure 44). The proportion of patients taking FIX-D was higher in young people (> 60% in women aged 18-39 and 46% in women of 80 years of age and older in 2012). In 2012 FIX-D were prescribed for nearly 80% of patients using three medicines.

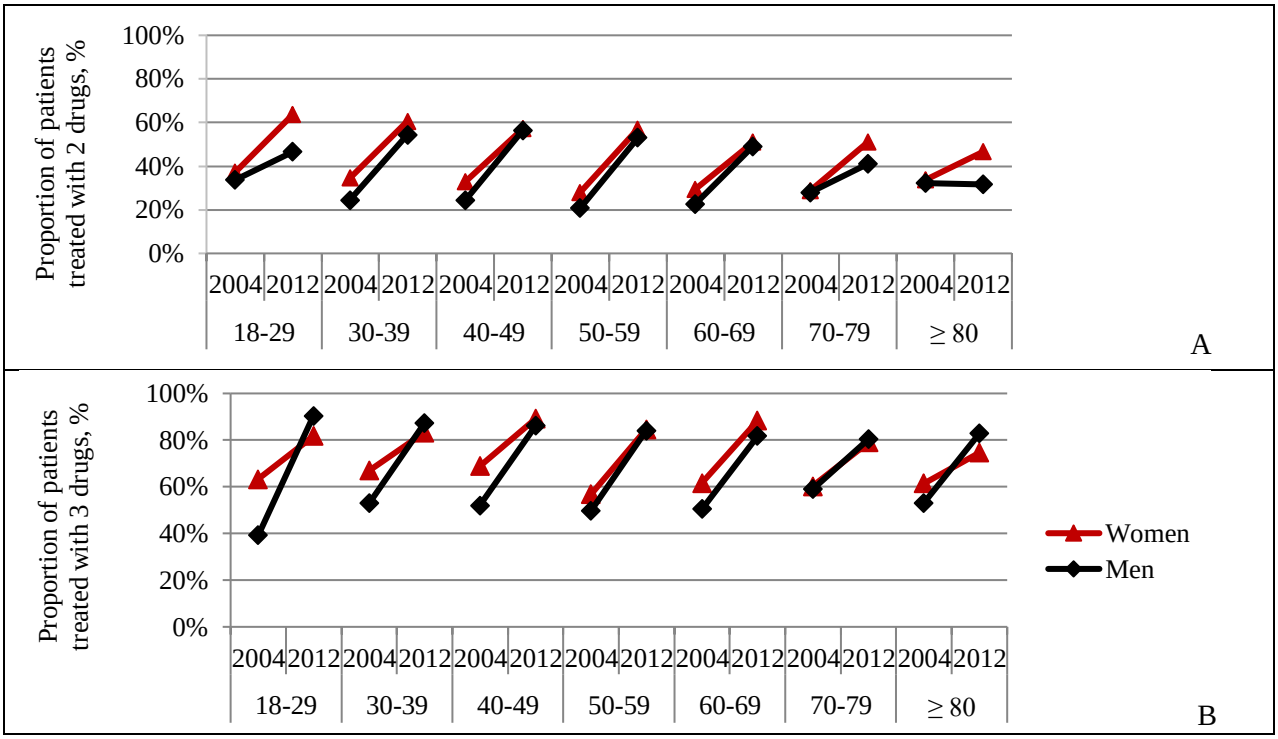


Figure 44. Utilization of fixed-dose combinations in different sex and age groups in the initiation of AH treatment with 2 drugs (A) and 3 drugs (B) in 2004 and 2012

The most commonly used FIX-D was an ACEI/diuretic in all women's age groups. For men ≥70 years old a more frequently prescribed combination was ACEI+CCB (> 40%) (Figure 45).

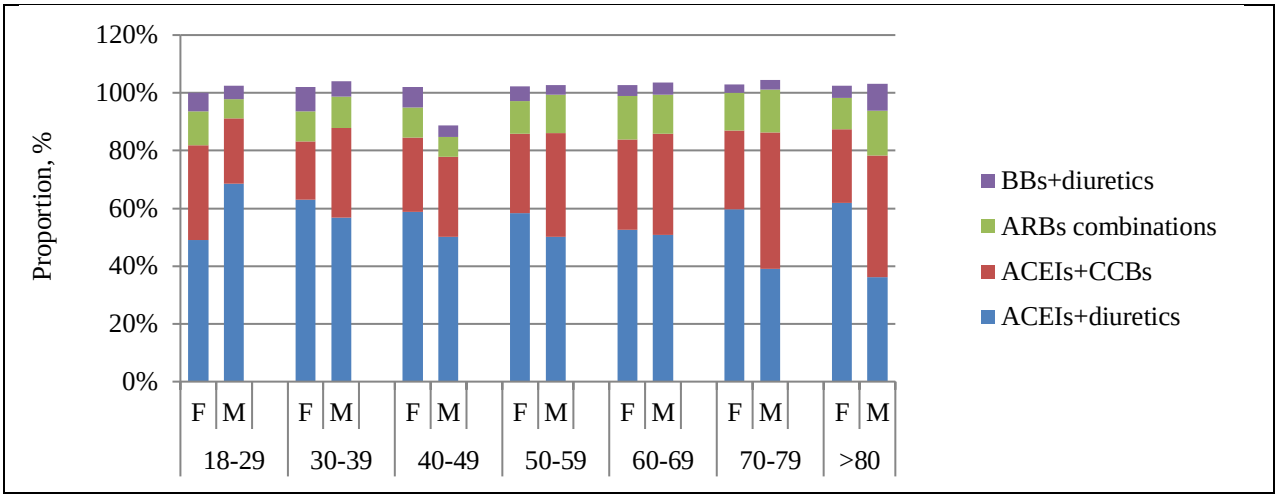


Figure 45. Most often for men of different age prescribed fixed-dose combinations for initiation of AH treatment as monotherapy in 2012.

7.8.10. Compliance with AH treatment guidelines

The selection of non-compliance to treatment guidelines criteria was based on European Hypertension Society Guidelines published in 2013 (Table 12). The proportion of patients receiving a non-compliant treatment increased in all age and sex groups.

At the beginning of the study a non-compliant treatment was usually given for 50-59 years aged women (11,3%) and men (10,2%). At the end of the study such treatment was usually initiated in men ≥50 years of age (22%) (Figure 46). In 2004 the most common non-compliance criteria was a treatment initiation with 3 medicines: from 2,5% in the youngest and oldest patient groups to 8,3% in 50-59 years aged men population. In 2012 an increase in the proportion of all age and sex patients treated with ARBs monotherapy and in women treated with centrally acting antiadrenerics monotherapy was registered.

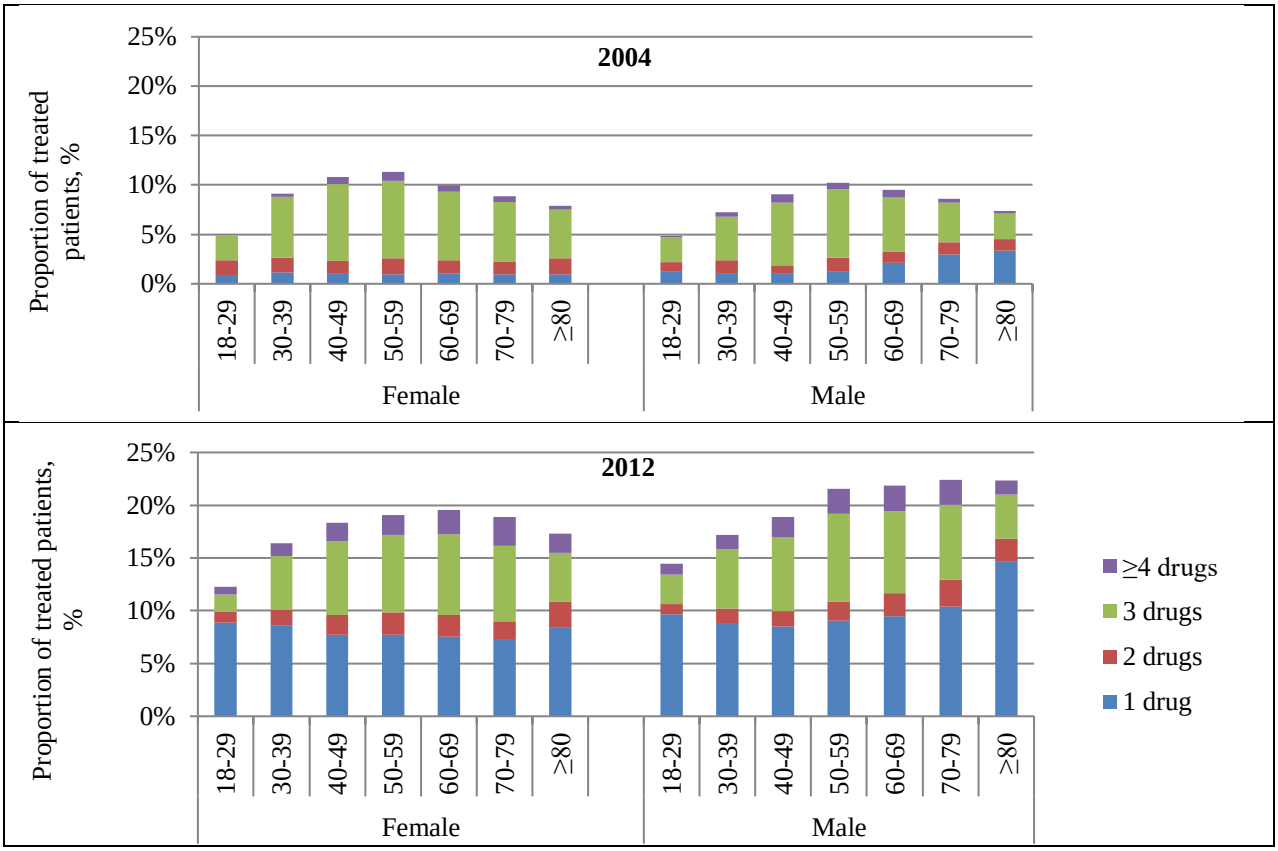


Figure 46. Non adherence to AH treatment guidelines on initiation of treatment in different sex and age groups in 2004 (A) and 2012 (B).

7.9. The efficiency of prescribing CVM for AH treatment, analyzing utilization of generic medicines and changes in pricing policy of medicines in Lithuania

7.9.1. Market share of antihypertensive medicines by volume and by value in 2003-2012 in Lithuania

The market share of antihypertensive generic medicines by volume decreased from 55,6% in 2003 to 35,9% in 2007 but increased up to 44,7% in 2012 (% change = -19,6%). The market share of generics by value dropped from 31,3% in 2003 to 19,3% in 2007 and subsequently grew to 41,8% in 2012 (% change = 33,4%) (Figure 47).

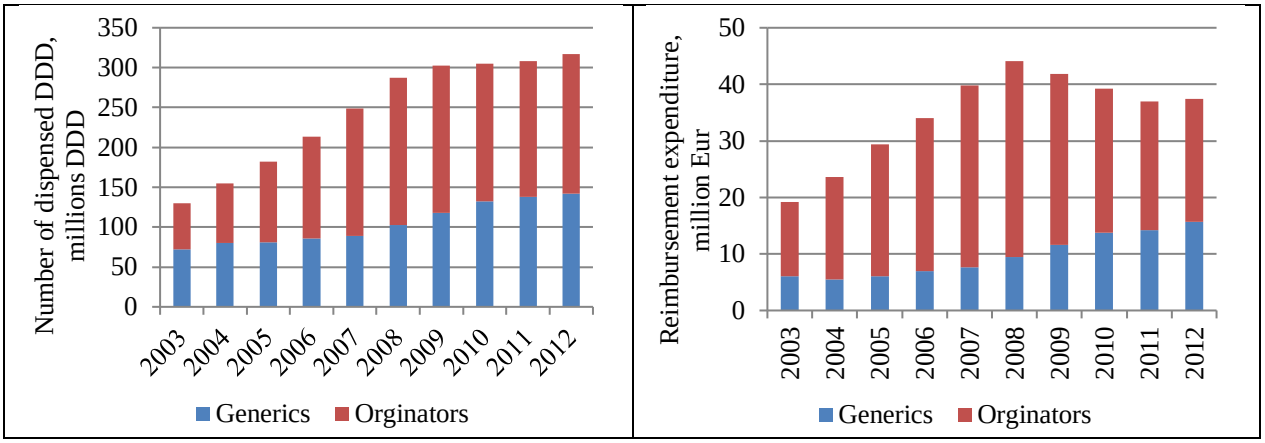


Figure 47. Market share of antihypertensive medicines by volume and by value in 2003-2012 in Lithuania.

Plain ACEIs were the most utilized antihypertensive medicines in Lithuania during the study period. However, a decline in generic ACEIs' market share by volume (% change = -36,4%) and by value (% change = -32,6%) was noticed during the study period. The highest market share by volume was seen for generics of SNS-AHs, plain ARBs, and ARB combinations. Generic medicines of other antihypertensives groups made up less than 40% of dispensed DDDs (Table 34). We registered an increase in the market share by value for generics of SNS-AHs, diuretics, BBs and plain ARBs. The market share of other five classes of antihypertensive medicines by value was lower than 30% (Table 26).

Table 26. Market share of generic antihypertensive medicines by volume and value according to ATC groups in Lithuania in 2003 and 2012.

* − launched in the market in 2005; § − launched in the market in 2007.

CVM group	Proportion of generics, %					
	Market share by volume, %			Market share by value,%		
	2003	2012	PP	2003	2012	PP
SNS-AHs (C02)	4,7	65,6	1307,1	2,8	52,4	1750,3
Diuretics (C03)	30.8	33,6	8,8	17,5	29,3	68
BBs (C07)	24,4	25,2	3,3	10,4	25,6	146,9
CCBs (C08)	57,7	28,2	-51,2	45,5	27,7	-39,1
ACEIs, plain (C09A)	61,3	39	-36,4	36,2	24,4	-32,6
ACEIs, combinations (C09B)	100	30	-70	100	27,5	-72,5
ARBs, plain (C09C) *	54,8	87,8	60,3	34,2	80,2	134,3
ARBs, combinations (C09D)§	97,9	79,2	-19	92,4	68,1	-26,3
Total CVM	55,6	44,7	-19,6	31,3	41,8	33,4

7.9.2. Changes in reimbursed price of 1 DDD

A decrease of R_{DDD}s from 20,4% to 61,8% was seen in all classes of plain antihypertensive medicines during the study period (Table 27). R_{DDD} of SNS-AHs, BBs and plain ARBs decreased by more than 60%. However, we registered an increase of R_{DDD} up to 66,5−70% in all FIX-D.

RO_{DDD} of all classes decreased by 26-67,9%, but in 2003-2012 RG_{DDD} decreased only in plain CVM by 8,7-48,2 %. RG_{DDD} of FIX-D increased by more than 50%.

Table 27. Changes in reimbursed expenditure for 1 DDD of originator and generic antihypertensive medicines in Lithuania in 2003 and 2012.
* − launched in the market in 2005; § − launched in the market in 2007.

	R_{DDD}			RO_{DDD}			RG_{DDD}			Max no of generics
CVM group	2003	2012	PP	2003	2012	PP	2003	2012	PP	
SNS-AHs (C02)	0,36	0,14	-61,3	0,37	0,15	-60,4	0,22	0,13	-39,1	13
Diuretics (C03)	0,21	0,10	-54,7	0,26	0,10	-59,7	0,12	0,08	-30,2	13
BBs (C07)	0,29	0,11	-61,8	0,35	0,11	-67,9	0,13	0,11	-8,7	29
CCBs (C08)	0,19	0,08	-58,4	0,25	0,08	-67,6	0,15	0,08	-48,2	31
ACEIs, plain (C09A)	0,10	0,08	-20,4	0,16	0,10	-40,2	0,06	0,05	-18,4	30
ACEIs, combinations (C09B)	0,08	0,14	66,5	0,26	0,15	-43	0,08	0,13	52,4	9
ARBs, plain (C09C) *	0,31	0,12	-61,3	0,45	0,20	-56,7	0,19	0,11	-43,5	18
ARBs, combinations (C09D)§	0,16	0,27	70,0	0,56	0,41	-26	0,15	0,23	54,8	12
Total CVM	0,15	0,12	-20,3	0,23	0,12	-45,7	0,08	0,11	32,3	155

7.9.3. Changes in reimbursed price of 1 DDD of plain ACEIs

Figure 48 is depicting changes in the reimbursed price of 1 DDD for plain ACEIs after generics were launched in the market. No decrease in RO_{DDD} of medicines without the generics on the market was registered. RO_{DDD} of zofenopril remained unchanged (RO_{DDD} = 0,33 Eur). RO_{DDD} of spirapril decreased by 8 % - from 0,19 to 0,17 Eur.

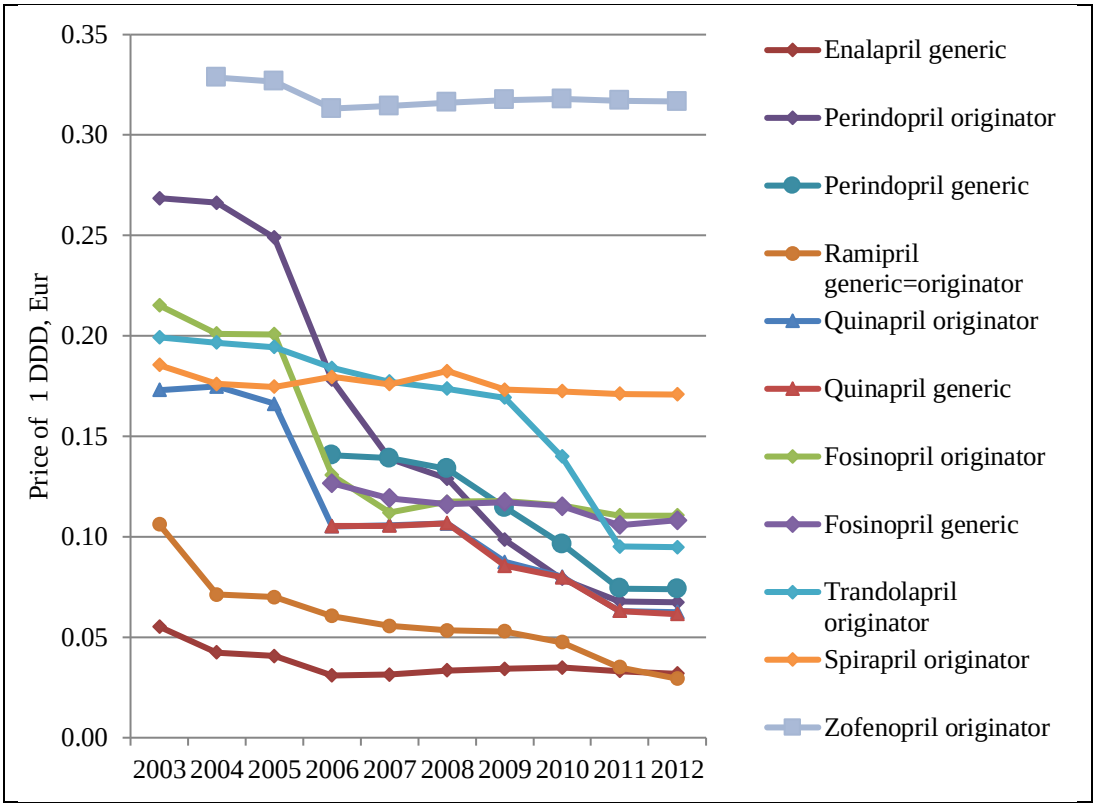


Figure 48. Changes in reimbursed expenditure for 1 DDD of plain ACEIs as the most used CVM group in Lithuania in 2003 - 2012.

7.9.4. Changes in reimbursed price of FIX-Ds

ACEIs and ARBs combinations were in the market during the study period. An increase of 66,5% in the class R_{DDD} and 39,6% in RG_{DDD} of all FIX-Ds was registered despite the decrease in price of separate preparations. Figure 49 is presenting the date of an entry to the market and the reimbursed price of 1 DDD of every combined medicine (originator – color pink, generic – color blue, equal price of generic and originator at the end of the study – color green). The launch and inclusion to the reference system of such originators as perindopril/indapamide, fosinopril/HCT and quinapril/HCT in 2004 influenced an increase in the class R_{DDD} of 131,7% in 2005 and of 194,5% in 2007. The following introduction to the market of generics FIX-Ds caused a price reduction, but by the end of the study R_{DDD} of ACEIs combinations still remained higher than 66,5% despite the decrease in RO_{DDD} of all this class‘s medicines. The same results were

registered in the price analysis of ARBs combinations. We found an R_{DDD} increase of 70 % due to the launch of more expensive originators. (Figure 50).

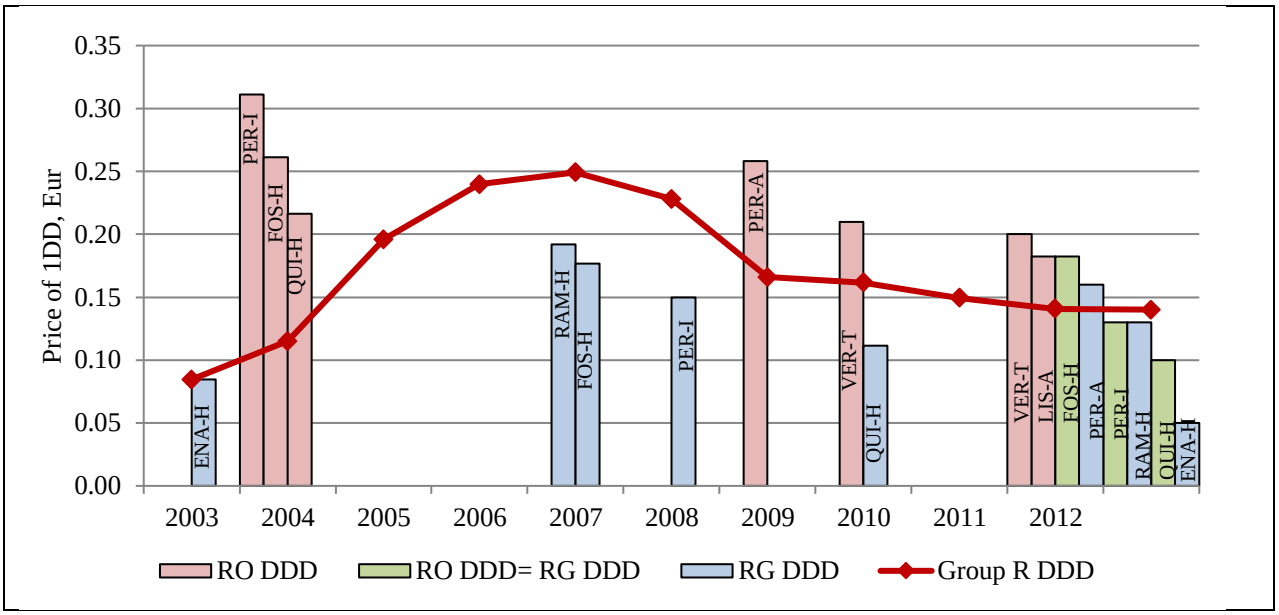


Figure 49. Changes in reimbursed expenditure for 1 DDD of ACEIs combinations in Lithuania in 2003 - 2012.

ENA-H − enalapril/HCT; PER-I − perindopril/indapamide; FOS-H − fosinopril/HCT, QUI-H – quinapril/HCT; RAM-H – ramipril/HCT; PER-A – perindopril/amlodipine, TRA-V – trandolapril/verapamil; LIS-A− lisinopril/amlodipine.

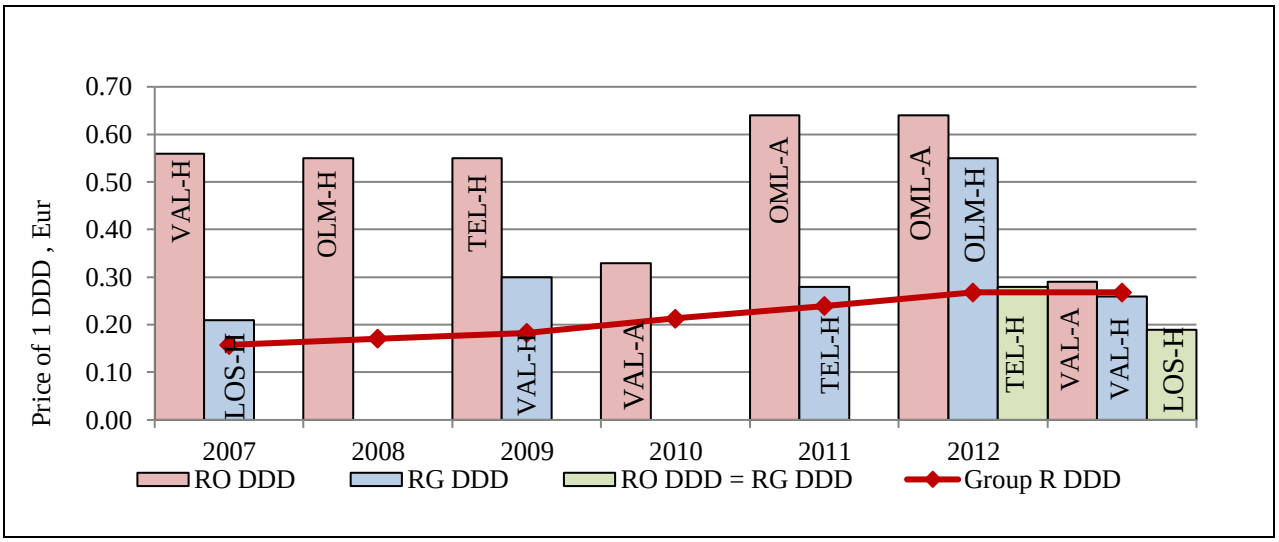


Figure 50. Changes in reimbursed expenditure for 1 DDD of ARBs combinations in Lithuania in 2007 - 2012.

VAL-H − valsartan/HCT; LOS-H − losartan/HCT; OLM-H − olmesartan/HCT; TEL-H − telmisartan/HCT; VAL-A − valsartan/amlodipine; OLM-A − olmesartan/amlodipine.

7.9.5. Changes in co-payed expenditure of 1 DDD

Co-payed expenditure of 1 DDD of all classes of plain antihypertensive medicines decreased during the study (Table 37). The most remarkable decrease in drug class C_{DDD} was seen in the SNS-AHs, BBs, CCBs and plain ACEIs. A decrease in CO_{DDD} was more evident in CCBs (-30,2%) and BBs (-24,6%), but a decrease in CO_{DDD} of other plain CVM groups was lower than 10%. A decrease in plain medicines CG_{DDD} was more noticeable (from 9,1% to 60,7%) during the study period. The group CO_{DDD} and CG_{DDD} of FIX-D increased during the study period (Table 28).

Table 28. Changes in patient co-payment for 1 DDD of originator and generic of antihypertensive medicines in Lithuania in 2003 and 2012

* − launched in the market in 2005; § − launched in the market in 2007.

	C_{DDD}			CO_{DDD}			CG_{DDD}		
CVM group	2003	2012	PP	2003	2012	PP	2003	2012	PP
SNS-AH (C02)	0,12	0,07	-41,7	0,12	0,11	-8,7	0,12	0,05	-60,7
Diuretics (C03)	0,08	0,08	-1,6	0,10	0,10	-5,6	0,04	0,04	-9,1
BBs (C07)	0,11	0,08	-27,1	0,13	0,10	-24,9	0,03	0,03	-16,2
CCBs (C08)	0,10	0,07	-28,7	0,11	0,08	-30,2	0,10	0,06	-43,3
ACEIs, plain (C09A)	0,04	0,03	-22,9	0,04	0,04	-5,5	0,03	0,02	-31,1
ACEIs, combinations (C09B)	0,03	0,17	544,7	0,08	0,19	122,2	0,03	0,11	347,9
ARBs, plain (C09C) *	0,11	0,09	-16,2	0,15	0,14	-4,1	0,08	0,06	-24,4
ARBs, combinations (C09D)§	0,06	0,12	96,2	0,16	0,19	13,8	0,06	0,10	73,5
Total CVM	0,08	0,09	1,6	0,12	0,11	-1,4	0,06	0,06	-3,4

7.9.6. Assessment of prescribing efficiency

Prescribing of all antihypertensive medicines was non-efficient in Lithuania – an increase of 144,1% in their utilization was followed by an increase of 94,6% in reimbursement expenditure (Table 29). Only the prescribing patterns of CCBs and plain ACEIs matched the criteria of considerable efficiency – an increase of 64,3% in utilization of CCBs and of 24,7% in plain ACEIs was followed by a decrease in their reimbursed expenditure of -31,7% and -0,7% correspondingly. Prescribing of BBs and plain ARBs was considered efficient, i.e. the rate of increase in these medicines use was

correspondingly 6 and 2,6 times higher than the rate of increase in reimbursed expenditure. A decrease in diuretics' utilization was followed by a decrease of 4,5 times in reimbursed expenditure.

Table 29. Percentage change in utilization and reimbursed expenditure of antihypertensive medicines in Lithuania in 2003-2012.

* − launched in the market in 2005; § − launched in the market in 2007.

CVM group	Percentage increase in utilization	Percentage increase in reimbursed expenditure	Prescribing efficiency
SNS-AH (C02)	719,7	405,4	Non-efficient
Diuretics (C03)	-13,6	-60,9	Non-efficient
BBs (C07)	285,8	47,4	Efficient
CCBs (C08)	64,3	-31,7	Considerably efficient
ACEIs, plain (C09A)	24,7	-0,7	Considerably efficient
ACEIs, combinations (C09B)	588,1	1045,5	Non-efficient
ARBs, plain (C09C) *	13541,4	5177,7	Efficient
ARBs, combinations (C09D)§	740,3	1328,8	Non-efficient
Total CVM	144,1	94,6	Non-efficient

8. DISCUSSION OF RESULTS

This research represents the first analysis of medicines utilization in Lithuania using the Lithuanian NHIF database. The database contains information regarding all dispensed prescriptions of reimbursed medications and covers up to 100% of the insured population (about 98% of population is covered by health insurance). This research addressed CVD, a current public health care challenge, for which mortality and morbidity rates in Lithuania are some of the worst in Europe. No significant decrease in CVD mortality has been recorded in Lithuania over the past 30 years, despite progress in treatment, efforts of the health care system to ensure quality care, affordability of medicines, and implementation of prevention programs. Reimbursed expenditure for CVM in ambulatory care was the largest component of the total reimbursed pharmaceutical expenditure (from 22,4% to 26% during the period of 2003−2012), a number that is still growing, thus driving the necessity of the current research on CVM use.

9.1. Trends in CVM utilization in Lithuania between the years 2003 and 2012 and comparison with data from other countries

Between the years 2003 and 2012, there was a 167,2% increase in CVM utilization reported in Lithuania, despite the fact that the Lithuanian population fell by 12,5%—from 3,415 million to 2,988 million citizens. Researchers from other countries have also reported trends of increasing CVM use and associated them with increasing CVD morbidity, global human population growth, global population aging, and an increased prevalence of CVD risk factors (Moran AE, 2014; Feigin VL, 2014; Kildemoes HW, 2008).

The Lithuanian Department of Statistics provided data on the increasing CVD prevalence in Lithuania between 2003 and 2012: CVD prevalence increased from 144,6 to 232,0 persons/per 1000 inhabitants; AH prevalence increased from 91,2 to 184,4 persons/per 1000 inhabitants; CHD prevalence increased from 43,0 to 64,3 persons/per 1000 inhabitants, and cerebrovascular diseases increased from 24,2 to 42,3 persons/per 1000 inhabitants. The median age of Lithuanian men (34 to 38 years) and women (39 to

44 years) also increased over this time period. Additionally, the demographic ageing factor, which reflects the number of persons aged 60 years or older per 100 children aged 15 years or younger, increased in Lithuania from 82 to 122 persons in the period of 2003−2012.

During the study period, a two-fold increase (94,6%) in reimbursed CVM expenditure was observed. This increased expenditure was attributed to the continued launch of new and more expensive medicines and the increase in the use and intensity of CVM treatment; ageing of the population and growth tendencies were not thought to be main factors (Gerdtham UG, 2004; Mousnad MA, 2014; Reinhardt UE, 2003). Thus, the increase in CVM use in Lithuania could have been associated with the increase in CVD prevalence and the ageing of the population, despite the fact that the population of Lithuania was decreasing during that time.

We identified the following trends in CVM use in Lithuania during the research period:

- RAS-acting agents were the most common drugs used.
- BBs were the second most common drug used.
- There was an extreme increase in the use of SNS-AHs.
- Utilization of plain diuretics was low.
- Utilization of lipid-modifying agents was extremely low.
- There was an increase in the use of FIX-Ds.
- There was an increase in the use of new CVMs at the expense of the existing "older" CVMs.

The current study used a retrospective approach to compare CVM use among the following countries: Sweden, Norway, Denmark, Finland, Germany, and the Netherlands (Stolk P, 2006). Publicly available data on medication use (reimbursed, dispensed, or wholesale) were used for this comparison, although the data available from each country varied. The selection of medicines utilization data sources from other countries in our research was relied on the data from the literature and national medicines agencies, that the drugs used for the AH treatments are reimbursed in the researched countries. (Ferrer P, 2011; Hedberg N, 2008; Mossialos E, 2008). The drug reimbursement policy in each

country influences the medication use in that country. For instance, atorvastatin was removed from the reimbursement list in Germany when generic simvastatin became available, causing the use of patented atorvastatin to fall to just 2% of overall statin use (Stargardt T, 2010). Although this initiative influenced medicines preferences, it did not change the indicated use of those drugs. According to a previous report, data on the use of ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) differed only by an average of 20 DDD/TID when obtained from a database of dispensed medicines compared to a database tracking wholesale distribution only. Similarly, data on the use of lipid-modifying agents differed only by 1,8−5,6 DDD/TID (Garuolienė K, 2016). Here, we examine the utilization of CVM in geographically neighbouring countries of Northern Europe—four Scandinavian countries (Sweden, Finland, Norway, and Denmark) and three Baltic States (Lithuania, Latvia, and Estonia). We identified the following differences in CVM use between these countries during the study period:

- CVM utilization was 1,5−3,0 times higher in the Scandinavian countries at the beginning of the research period and remained 1,2−1,5 times higher in the year 2012. Compared to the change in total CVM utilization in the Scandinavian countries (from 18% to 78%), the rate of change in the Baltic states was much higher (from 104% to 167%).

- RAS-acting agents were the most common drug used in every country evaluated. In Lithuania, the use of RAS-acting agents increased moderately (by 156,6%); this increase was driven largely by the large increase in the use of plain ARBs (8 615%) and less so by the increase in the use of plain ACEIs (35%). Similar trends were observed in other countries, although no single meta-analysis provided concrete evidence of ARB superiority at lowering CVD mortality rates and controlling BP (Yamano S, 2015; Powers BJ, 2012; Li EC, 2014; Wu HY, 2013; Matchar DB, 2008; Mann JFE, 2008; Xie X, 2016).

- As the number of available FIX-Ds on the market increased, so did their use in every country evaluated. In Lithuania and Latvia, use of FIX-Ds with ACEIs was most common. In 2012, the use of ACEIs combinations in Lithuania was 2,0- to 2,5-fold higher by than that in Denmark or Finland, 4,5-fold higher than that in Sweden, and 6,0-

fold higher than that in Norway. With the exception of Norway and Denmark, the use of ARBs combinations increased in all of the countries evaluated.

- SNS-AHs utilization in Lithuanian was 10-fold higher than that in Scandinavia and Estonia and 2,5-fold higher than that in Latvia. The total use of centrally acting AH medicines in Lithuania increased 12-fold, even though use of these medications is not clearly indicated in the CVD treatment guidelines (Mancia G, 2007; Mancia, 2013). Use of doxazosin (A-AB) increased by 3,5-fold, such that 64% of doxazosin prescriptions are for AH This drug has two registered indications – it is the third and fourth-line antihypertensive treatment and benign prostatic hyperplasia. We do not have supporting data, that the prevalence of benign prostatic hyperplasia was higher in Lithuania than other countries. We also cannot explain the higher prescription rate of SNS-AHs for the patients with hypertension and kidney disease, as less than 0,13% of all antihypertensive medicines were issued for these conditions (codes I12 and I13). Because of a lack of available studies, it is difficult to relate the increase in SNS-AH use to the new clinical evidence showing the benefits of this class on CVD mortality. When performing a literature search in the PubMed/Medline database using the keywords "moxonidine", "rilmenidine," and “arterial hypertension,” only a few studies are identified, and they support the ability of SNS-AHs to lower BP compared to BBs, CCBs, and ACEIs (Jacob S, 2004; Prichard BN, 1992; Prichard BN, 2002; Wolf R, 1992). To date, no randomized, double-blind study has been identified that supports the use of SNS-AHs to lower CVD mortality and morbidity. On the contrary, increasing mortality rates of patients with heart failure have been reported (Swedberg K, 2002; Cohn JN, 2003; Pocock S, 2004).

- Utilization of plain diuretics was lower in all the Baltic States than in Scandinavia. In Lithuania specifically, use of plain diuretics was 3- to 5-fold lower than that of Scandinavia. However, increasing use of FIX-Ds contributed to the increased rate of diuretic use.

- Utilization of CCBs in Lithuania and Latvia was 1,5- to 2,0-fold lower than that in Scandinavian countries and Estonia.

- Extremely low use of lipid-modifying agents was registered exclusively in Lithuania—in 2012 the use of reimbursed statins reached 7,4 DDD/TID, i.e., only 7

persons out of 1000 inhabitants in Lithuania used these medications every day, compared to 166 DDD/TID in Norway. Such low use of statins could be caused by the regulations of reimbursement: statins were reimbursed only for secondary prevention for the first 6 months after a myocardial infarction or an unstable angina episode. In addition, until 2006, statins could only be prescribed by doctors cardiologists for reimbursement. Between 2006 and 2009, a cardiologist had to issue the first prescription for a statin, but general practitioners could continue prescribing afterwards. Since 2009, general practitioners are able to prescribe generic statins. Statin reimbursement for the primary prevention of CVD only began at the end of 2015. Based on wholesale statin data for the period of 2003−2012, use of these medications in Lithuania was exceptionally low, ranging from 2,4 to 12,9 DDD/TID (Garuolienė K, 2016). This is 5-fold lower than use in the neighbouring countries of Latvia and Estonia. The efficacy of statins prescribed for secondary prophylaxis to reduce CVD mortality was confirmed by multiple studies (Cholesterol Treatment Trialists' Collaborators, 2005; Heart Protection Study Collaborative Group, 2011). However, other clinical trials evaluating statin use for the primary prevention of CVD provided contradictory results on the reduction in CVD mortality, raising questions about the efficacy of statin use in patients with a low risk for CVD (Nilsson S, 2011; Cholesterol Treatment Trialists' Collaborators, 2012).

- There was a moderate increase in the use of other drugs for the treatment of CVD, such as cardiac therapy medicines, which increased by 113%, primarily due to increased use of organic nitrates, trimethazidine, and ivabradine. By contrast, trimethazidine and ivabradine were not used in the Scandinavian countries, and use of organic nitrates actively decreased.

- For each drug class, the leading medicines in Lithuania were identified and changes in usage trends resulting from the release of new drugs on the market were evaluated.

Use of the BB metoprolol and the newer BB nebiolol increased by 3- and 7-fold, respectively. Nebivolol became the second most common CVM used by the end of the study. Meanwhile, this drug was not used in the Scandinavian countries.

Use of the most common CCB in the world, amlodipine, increased by 36,7%, whereas use of the new drug lercanidipine increased by 2 184%. In Denmark and Sweden, lercanidipine was used 3- to 10-fold less than amlodipine.

In the ACEI class, an evident change in choice of medication was observed: at the beginning of the study, enalapril was the most common drug used, accounting for 54% of all plain ACEIs used. At the end of the study, enalapril use made up only 6% of the plain ACEIs used. When new drugs enter the market (perindopril, spirapril, or zofenopril), the use of the "older" drugs decreases immediately. The release of ramipril is responsible for the decrease in enalapril usage, and it continues to be the most common ACEI. When analysing the use of ACEIs, plain and in combination, the leader in Lithuania during the research period was perindopril. Such a trend was not observed in the Scandinavian countries. In Denmark, enalapril (42%−52% of all ACEIs during the study period) and ramipril (24%−32% of all ACEIs during the study period), were the two most popular ACEIs. Similarly, enalapril and ramipril were also the most common in Sweden; the use of enalapril increased from 33,4 to 53,1 DDD/TID in 10 years and made up 40%−85% of all ACEIs used. Zofenopril and spirapril were not used in any of the studied Scandinavian countries, and perindopril was only used in Denmark.

ARBs utilization also changed over the study period. The use of the first ARB on the market—losartan—decreased with the increase in use of the newer ARBs valsartan and telmisartan. Meanwhile, use of losartan increased in the Scandinavian countries.

9.2. CVM utilization, CVD risk factors, and the influence of their interaction on CVD mortality

For all countries, a strong negative correlation was measured between CVM use and SDR of CVD, CHD, and cerebrovascular disease. Unfortunately, increasing CVM use in the Baltic states did not cause a significant decrease in CVD mortality, which remained 2- to 4-fold than that in the Scandinavian countries. Using multiple regression models, we determined that the 64% change in CVD mortality could be explained by the increased use of CVM. Although only evaluated by a few studies, underuse of CVM was

found to be associated with increased mortality and hospitalization rates (Beer C, 2011; Meid AD, 2015).

There were also a number of underlying determinants of CVD. In this research, the selection of risk factors was based on the European guidelines on CVD prevention in clinical practice (version 2012), and on the availability of data from publicly available international sources. There was no publicly available data on obesity and physical activity. We instead used indirect factors, such as self-reported health statuses of the population, obtained from the EUROSTAT database. For this indirect data, we identified the percentage of the population who evaluated their own health as good or very good. To indirectly evaluate obesity, we used the energy value of consumed food.

The inclusion of socioeconomic factors as indicators of health care service accessibility and adherence to treatment was based on data from clinical trials and meta-analyses focused on the effect of the socioeconomical state on CVD mortality (Avendano M, 2005; Manrique-Garcia E, 2011; Roelfs DJ, 2011). Socioeconomic conditions are defined as a multivariate concept consisting of material (income, employment) and social (family structure, living arrangements) factors (Alsabbagh MH, 2014). The gross domestic product (GDP) was included as an economic factor, representing the economic states of the countries and partly representing the capacities of the health care systems. Research on the relationship between income level and health status shows that that lower income is associated with worse health conditions (Pickett KE, 2015; Shi L, 2005). The selection of health care-related factors was based on the EUROSTAT-provided official indicators reflecting health care performance.

Currently, there is little data regarding the relationship between the health of the population and the number of beds in hospitals. Hospital usage may be decreased by actively implementing prevention and prophylaxis programs and strengthening ambulatory care (McKee M, 2004; Hamar GB, 2015). Although the significance of the number of working doctors as an impact factor remains controversial, it is clear that a sufficient number of doctors is needed in each country to provide adequate health care (Donohoe MT, 1998; Engstrom S, 2001). Indeed, a negative correlation was found

between the number of doctors per 1000 persons and “premature” mortality or CVD mortality rates (Shi L, 2005).

In some cases, risk factor values were worse in Lithuania compared with the Scandinavian countries. The GDP per capita increased from 5,4 thousand USD in 2003 to 14,2 thousand USD in 2012 in Lithuania, and this increase was rather similar in the Baltic states. In the Scandinavian countries this indicator was 3- to 7-fold higher than in Lithuania (55 thousand USD in Sweden and 99,6 thousand USD in Norway in 2012). Although the *Global Burden of Disease Study 2013* research showed only a weak correlation between the GDP and CVD mortality in high- and middle-income countries, our research demonstrates a strong negative correlation between the GDP and CVD mortality and a strong positive correlation between GDP and CVM utilization (Roth GA, 2015).

The unemployment rate in Lithuania did not decrease during the research period; in 2003 and 2012 the unemployment rates were 11,6% and 11,4%, respectively. The lowest unemployment rate in Lithuania was in 2006 (4,3%), and the highest unemployment rate occurred in 2009 (17,8%). Similar numbers were observed in Latvia and Estonia. In the Scandinavian countries, the unemployment rate was lower, ranging from 2,5% to 4,3% in Norway and from 6,4% to 8,3% in Finland over the course of the research period. We identified an average positive correlation between the unemployment rate and CVD mortality rate and a weak negative correlation between the unemployment rate and CVM utilization.

The divorce rate in Lithuania ranged from 2,9 to 3,5 cases/1000 people in 2003 and 2012, respectively and was 1,2- to 1,8-fold higher than that of any other Scandinavian country. We identified a strong positive correlation between the divorce rate and CVD mortality and a negative correlation between the divorce rate and CVM use.

Alcohol consumption in Lithuania was the highest among all of the countries evaluated during the research period (in 2012 it reached 14,1 L of pure alcohol per 1 person per year) and was 1,2- to 2,3-fold higher than in that of other countries over the course of the research period. The percentage of people smoking in Lithuania decreased from 27,0% in 2003 to 20,5% in 2012. Of the Baltic States, the highest smoking rate was

identified in Latvia (increasing from 30% in 2003 to 34% i 2012). The rate of smoking in the Scandinavian countries decreased during the study period and was 2% to 7% lower than that in Lithuania during the entire 10-year span. We identified strong positive correlations between CVD mortality and both alcohol use and the percentage of people who smoke and an average negative correlation between these two indicators and CVM utilization.

The energy value of the food consumed increased in Lithuania from 3 187 to 3 463 kcal over the course of the study; similar values were identified in Sweden. In other countries evaluated, energy values of food were 100−300 kcal lower. We found only a weak positive correlation between the CVD mortality and food energy value.

Apart from Finland, the amount of fruits and vegetables consumed per person was the lowest in Lithuania —175,6 kg per person per year (i.e., 30−50 kg less than that of the three Scandinavian countries). We identified an average negative correlation between fruit and vegetable consumption and CVD mortality and a positive correlation with CVM use.

The proportion of people who perceived their health to be very good or good ranged from 44% to 46% in Lithuania and Latvia and from 69% to 78% in the Scandinavian countries and was 52% in Estonia. In Lithuania, this indicator did not change over the 10-year period of the study. We identified a very strong negative correlation between this indirect indicator and CVD mortality and a strong positive correlation between this indicator and CVM utilization.

The number of available hospital beds in Lithuania decreased from 777 to 743 beds/1000 citizens between 2003 and 2012. In 2003 a similar number of beds were registered in Latvia (783 beds/1000 citizens) and in Finland (724 beds/1000 citizens). At the end of the research period, this indicator remained the highest in Lithuania—150 beds more than in Latvia, 190 beds more than in Estonia, 213 beds more than in Finland, and 482 beds more than in Sweden, where this indicator was the lowest throughout the research period.

The number of practising doctors increased in all countries over the course of the study and in 2012 was the highest in Lithuania (422 doctors / 1000 citizens) and Norway

(423 doctors / 1000 inhabitants), and the lowest in Finland (300 doctors / 1000 citizens), Latvia (314 doctors / 1000 citizens) and Estonia (328 doctors / 1000 citizens). In Scandinavia, the percentage increase in number of practising doctors ranged from 17% to 29%; in Lithuania -16%, in Estonia-3.9%. We did not identify any significant correlations between the number of practising doctors and CVD mortality or the use of CVM.

Health care expenditure rose in every country evaluated, but was 4- to 10-fold higher in the Scandinavian countries than in Lithuania. In 2012, health care expenditure per person per year measured 731 EUR in Lithuania, 773 EUR in Estonia, 550 EUR in Latvia, and 7 331 EUR in Norway. We identified a very strong negative correlation between health care expenditure and CVD mortality and an average positive correlation between health care expenditure and CVM use.

Using a multiple linear regression model, we determined that CVD mortality was statistically significantly influenced by socioeconomical factors—mortality was lower when the GDP is was higher and the unemployment rate and divorce rate were lower. The population risk factors that correlated with low CVD mortality include decreased use of alcohol, higher intake of vegetables and fruits, and a higher proportion of citizens evaluating their health condition as good or very good. Health care-associated factors associated with low CVD mortality were less hospital beds and higher health care expenditure per person. Moreover, increased CVM utilization was associated with a lower CVD mortality rate in countries with a lower unemployment rate and a higher number of practicing doctors. Also, an increase in CVM use had a stronger influence on CVD mortality in countries with a lower GDP and with less health care expenditure per person.

The aim of AH and CVD treatment is to prevent CVD complications and lower mortality rates. Clinical research has shown that strict BP control lowers the risk of myocardial infarction by 20−25%, stroke by 35−40%, and heart failure by 65%. A primary goal for current medication is to lower the risk of complications among CVD patients by 65% and among society by 80% (Antonakoudis G, 2015; Roth GA, 2015). The question arises as to what rate of CVM utilization is necessary to achieve a

significant decrease in CVD mortality and morbidity? For those who use antihypertensive medications, CVD-related death was prevented in 1 in 125, stroke was prevented in 1 in 67, and myocardial infarction was prevented in 1 in 100 (NNT group, 2014). The results of the current study confirm that proper use of CVM and correction of risk factors are necessary actions to decrease the prevalence of CVD. We have demonstrated a high prevalence of cardiovascular risk factors in the Lithuanian population, which could significantly contribute to CVD mortality. The potential impact of health care system-related factors on CVD mortality must be interpreted with caution because of the limitations related to ecological study design.

9.3. Sex and age differences in the treatment of AH in Lithuania during the period of 2003−2012

We identified the following trends regarding AH treatment in Lithuania over the study period:

- 82% of all dispensed CVM in outpatient care were prescribed for AH treatment. This percentage remained the same throughout the entire research period. The use of antihypertensive medicines increased by 144% over the research period.
- Antihypertensive medicines were used nearly five times more frequently in older patients than in younger patients. This finding was expected, knowing the AH and CVD pathophysiological and statistical data.
- Antihypertensive medicines utilization use was higher in women with AH than in men of corresponding ages, despite the fact that antihypertensive use increased faster in men over the period studied. Based on data from the Lithuanian Statistics department the prevalence of AH in women was 1,5- to 2,0-fold higher than in men; therefore, women with AH are more likely to be treated pharmacologically than are hypertensive men. The data confirming the higher prevalence of AH in women population and the higher consumption of antihypertensive medicines could be influenced by the tendency for women to have increased disease awareness and more often seek medical advice during

their lifetimes, facilitating earlier disease detection and treatment initiation (Reklaitiene R, 2012).

- The increased use of antihypertensive medicines could be the result of increasingly aggressive treatment of AH using combination therapy in Lithuania. In some countries, the rate of monotherapy was ≥60% of all treated patients, regardless of gender (Mori H, 2006; Petrella RJ, 2007). I-SEARCH data, obtained by analysing antihypertensive medicines use in 26 countries, demonstrated that 30% of patients were treated with one drug, 40% of patients were treated with two drugs, and 30% of patients were treated with more than three drugs simultaneously (Thoenes M, 2010). In Lithuania, the rate of monotherapy was similar to the I-SEARCH data for younger patients, but monotherapy was used for for 30% and 12% of older patients in 2003 and 2012 respectively Additionally, among older patients of both genders in the MY group, the monotherapy rate decreased 2,0- to 2,5-fold during the research period; this indicator did not change for patients in the FY group. By contrast, more patients were treated with 2, 3, and especially ≥ 4 drugs in Lithuania. The most aggressive treatment with 2, 3, or ≥4 drugs was initiated in patients aged 40−69 years. These data raise the question, "Why did the more intensive treatment of patients in Lithuania have no significant effect on CVD mortality and why is CVD control still poor?"

- Another factor that contributed to the increasing use of antihypertensive medicines in Lithuania was that the typical AH patient was "getting younger". The average age of patients receiving AH treatment for the first time decreased by more than five years among populations of women (62−56 years) and men (58−53 years). Moreover, antihypertensive drug use increased among patients aged 18−49 years. These data support the previously reported data regarding earlier AH detection and initiation of treatment, trends that we feel are the result of the Lithuanian High Cardiovascular Risk (LitHiR) prevention project, which began in 2006 with the aim of combating CVD morbidity and mortality rates in Lithuania (Laucevičius A, 2012). The primary objective of this project was to estimate and manage CVD risk factors, including AH, in men aged 40−54 years and women aged 50−64 years without overt CVD. Following the project, prevention units were established at primary health centres, where people within the

target age groups were proactively recruited for prophylactic health evaluations. Public awareness regarding the existence and mission of the programme is also increasing—73% of population was aware about the LitHiR project in 2012 (Petronytė G, 2013). Between 2005 and 2012, 27% of the targeted Lithuanian population participated in this programme. According to the recommendations of the European Commission, at least 80% of the population should be included in a preventive program to effectively reduce the mortality rate of that population.

- The pattern of antihypertensive medicines utilization was the same as that of CVM use—ACEIs and BBs were the most frequently used medications across all ages and both sexes. Also observed was the trend for medication use to shift to "newer" drugs as they were introduced to the market. For example, at the beginning of the study, the ACEI enalapril was typically used to initiate AH treatment, and by the end of the study, zofenopril and perindopril were used more frequently.

- The comparison of sex differences in antihypertensive medicines utilization revealed that monotherapy was more prevalent in the FY group than in the MY group, and the MY group used 3 or ≥4 CVM for one patient. There were no significant differences between the number of drugs used per person in the older patient groups. Use of plain ACEIs, CCBs, and plain diuretics was significantly higher in the FY group than in the MY group. Similarly, use of plain ACEIs, CCBs, BBs, plain diuretics, and central-acting antihypertensives was significantly higher in the FO group than in the MO group. In both age groups, A-ABs were used more often for men than for women.

- Compared to women in Lithuania, women in other countries were treated less often with ACEIs, likely due to reports of more frequent adverse reactions in women (Shekelle PG, 2003; Sato A, 2015). Similarly, I-SEARCH data showed that men were treated more often with CCBs than were woman, whereas in Lithuania, these drugs were used more often in women (Thoenes M, 2010). Diuretics were used more often in women than in men, a finding that was consistent with other reports, although use of plain diuretics remained low (Gu Q, 2008; Keyhani S, 2008; Wilkins K, 2012, Loikas D, 2013; Ljungman C, 2011; Ljungman C, 2014; Van der Niepen P, 2011; Fernandez-Liz E, 2008; Lunet N, 2002; Chou CC, 2004; Van den Berg N, 2013). There were no

differences in ARB or FIX-D use between men and women. The reasons for the high use of SNS-AHs are unknown and require further analyses at the patient level to evaluate the indications for such treatment. Older men were more often treated with A-AB monotherapy than were women of a corresponding age. There were no identified differences between men and women in the frequency of initial combination therapy using two or three drugs.

- FIX-D use increased in all patient groups during the course of the study. The most common FIX-Ds used in Lithuania were ACEIs and diuretics.

- At the initiation of treatment, FIX-Ds were commonly prescribed, particularly to younger patients. For combination therapy using three drugs, ~80% of the patients were prescribed FIX-Ds. Meta-analyses and clinical trials show that the use of FIX-Ds was associated with better BP control, a simpler treatment regime (particularly for patients who used multiple drugs to treat comorbidities), and decreased pharmaceutical expenditure (Wald DS, 2009; Corrao G, 2010).

9.4. Compliance with European AH treatment guidelines in Lithuania

For the treatment of AH, Lithuania accepts and actively uses guidelines put forth by the European Hypertension Society and the European Society of Cardiology. Our results show that the proportion of patients who were non-compliant with these guidelines with respect to the initiation of AH treatment increased approximately 2-fold over the course of the study, particularly in the older patient groups. In 2004, non-compliance was found to be highest in the groups treated with combination therapy consisting of three medications and ranged from 2,5% in 18-29 years old men and women groups to 8,3% in the group consisting of 50−59 year-old-men. In 2012, non-compliance was found to be highest in patients treated with monotherapy, primarily in patients treated initially with ARB monotherapy regardless of age and sex, in women treated with centrally acting antiadrenergic monotherapy, and in patients treated with combination therapy consisting of ≥3 drugs. The rate of non-compliant with guidelines treatment from 27 to 46% of cases, depending on criteria evaluated and methodology

used,was demonstrated in other clinical trials, depending on (Theodorou M, 2012; Milchak JL, 2004).

Although the European AH treatment guidelines dictate that ARBs can be used for the treatment of AH, many countries employ ARBs prescription restrictions, based on the high price of ARBs and the fact that other antihypertensive medicines can lower BP equally well. In the United Kingdom, a prescription rule of "80/20" was adopted, which encouraged the use of ACEIs in 80% of the cases and ARBs in 20% of the cases (Baker A, 2015). In Sweden, Croatia, and Austria, recommended prescription restrictions allowed a decrease the use of ARBs without changes in treatment quality (Vogler S, 2013; Vončina L, 2011; Godman B, 2009).

The European AH treatment guidelines recommend use of antihypertensive medicines from any class to treat older adults, depending on the specific needs of those patients; however, CCBs and diuretics are given priority (I1 level recommendation) (Mancia G, 2007; Mancia G, 2013). CCBs were the second common drug class prescribed for patients 65 years and older for the majority of the research period, but use of BBs increased rapidly and in 2012 exceeded use of CCBs. Patients older than 70 years used CCBs 2-fold less than BBs when treated with monotherapy or combination therapy consisting of two drugs. Similar results were found for the initiation of AH treatment—older patients were more often prescribed ACEIs and BBs. However, BBs are not the first choice in antihypertensive drugs for older adult patients, except when treating after a myocardial infarction or certain arrhythmias (Messerli F, 1998; Fleg JL, 2011).

The European guidelines recommend initiating AH monotherapy when there is a mild degree of AH or a low risk for CVD (Mancia G, 2007; Mancia G, 2013). Thus, such a high FIX-Ds use determined amongst groups of young patients in Lithuania could be doubtful. Also, BP control is not achieved immediately after initiating treatment and can take 3,25 months (for monotherapy) or 4,0 months (for combination therapy) (Hong SH, 2013). Only one-third of patients maintained the same treatment regimen as they used at initiation of treatment, and this was less common when FIX-Ds were prescribed (Moser M, 2007). A trend was also noted whereby treatment was initiated with FIX-Ds plus an ACEI and a diuretic, followed by an additional dose of the same ACEI (e.g.,

perindopril/indapamide and perindopril). Such a pattern was identified in 10%−20% of patients receiving combination therapy consisting of three drugs. The rationality of such a combination is questionable, as there is no data available in medical literature.

9.5. The efficiency of prescribing CVM for AH treatment, analyzing use of generic medications and changes in pricing policy of medications in Lithuania

During the period of 2003−2012, CVM for AH treatment were not prescribed effectively—although CVM utilization increased by 144%, CVM reimbursement increased by only 96%. For prescribing to be considered efficient, the increase in drug utilization must be more than double the increase in reimbursement expenditure (Godman B, 2011). An analysis of the different classes of antihypertensive medicines revealed that the most common antihypertensives used—plain ACEIs, ARBs, BBs, and CCBs—were prescribed effectively. By contrast, the prescribing of FIX-Ds, SNS-AHs, and diuretics did not match the criteria for effective prescribing.

Our study demonstrated a noticeable effect of drug pricing policy measures taken by the Lithuania health authorities to decrease the reimbursed price for one DDD of plain medication by 50%−60% and of ACEI by 20% from 2003 to 2012. However, this pricing policy was not effective at decreasing the price of FIX-Ds. Because the reference pricing in Lithuania was based on the principle of molecules and not on principles put forth by the ATC group, new drugs that came onto the market increased the FIX-D class reimbursement expenditure and patients' co-payment price.

Over the 10-year study period, the market share by volume of antihypertensive medications decreased by almost 20%, amounting to only 44,7% in 2012. The increase of the generic part by value was observed, but the more expensive original drugs continued to contribute to the market, requiring higher reimbursement expenditure. A decline in market share by volume of the most commonly used AH classes (plain ACEIs, CCBs, FIX-Ds) and an increase in the use of generic BBs by 3% was identified. Use of the most common generic ACEIs decreased 36% by volume. This change could be partially attributed to the replacement of older medications with new ones just appearing on the market. During the study period, zofenopril was an original, patent-protected

drugine, who's use increased by 10-fold. The price per DDD of zofenopril did not change throughout the entire research period and remained the highest of all of the plain ACEIs—10 times higher than enalapril and ramipril, and 4 times higher than perindopril in 2012. The price of perindopril, another ACEI, decreased 4-fold when the generic version was available on the market, but only 22% of dispensed perindopril DDDs were generic. These changes showed that the prescribing physicians did not take into consideration the price of the drugs they were prescribing (Jacoby A, 2003). Although the newest clinical studies promote increased use of new medications over "older" medicines, Scandinavian countries are reporting better outcomes using the "older" drugs.

An increase in the use of newer medicines could be influenced by the marketing efforts of pharmaceutical companies and limitations in the ability to invest in clinical studies, once generic drugs are released onto the market, by drug policy, the personal decisions of doctors, and recommendations of "opinion leaders" (Lubloy A, 2014). The clinical trials included in this review were conducted in the USA, Western European countries, Scandinavia, Canada, and Australia. No research was conducted in the Eastern European countries.

We acknowledge that this research has several limitations. We did not analyse medicines utilization at the patient level; no information was collected regarding actual daily medicines doses, concomitant disease, factors affecting medication choices, adherence to treatment, and efficacy of the mediations to lower BP. We were also unable to evaluate other factors that influenced the decision of the physician to prescribe certain medications. In addition, we did not study the utilization of antithrombotic agents (antiaggregants, anticoagulants), which can also affect CVD mortality. Nearly all data was obtained from freely accessible databases; therefore, we acknowledge all possible biases related to collection of these data.

In conclusion, this is the first study to analyse the utilization of the most commonly used medicines in Lithuania to such an extent. This work analysed the actual health problems of the Lithuanian society, particularly in those whose treatment results are not satisfactory, compared to other EU countries. The results of this research are useful to promote changes in future drug policies, and serve as tools to encourage rational drug

use. Specifically, these findings are in line with expectations and do provide opportunities to Lithuanian health authorities and medical society to further enhance the quality and efficiency of CVM prescribing, to plan potential drug policy reforms and initiatives for achieving rational medication use.

9. CONCLUSIONS

1. In Lithuania, total CVM utilization and CVM use specifically for AH treatment increased over the course of the study, reaching the rate of use of neighbouring Scandinavian countries; however, a substantial decrease in CVD mortality and morbidity was not observed. Although our analyses revealed a strong association between CVM use and CVD mortality, the high prevalence of CVD risk factors could significantly contribute to CVD mortality.
2. Differences in the pattern of CVM utilization—particularly low statin and diuretic use and high SNS-AH use—could influence the higher rate of mortality for CVD in Lithuania. As well, increased risk factors were identified in Lithuanian populations compared to those in the Scandinavian countries, directly influencing higher CVD mortality. Four factors—GDP, health care expenditure per person, unemployment rate, and the number of practising doctors—influenced the decrease in CVD mortality via an increase in CVM utilization.
3. The utilization of antihypertensive medications increased in both sex and all age groups. Although women used antihypertensive medications more frequently than men, the increase in AH medication utilization was more pronounced in men. The age of new antihypertensive medicines users has lowered by five years in Lithuanian men and women. Differences in the use of antihypertensive treatment by sex were only observed amongst the younger population, but no sex differences existed at the initiation of the AH treatment.
4. AH treatment does not always conform to the rational drug use concept—during the period of 2003−2012, the rate of non-compliance with AH treatment guidelines increased 2-fold.
5. Although the most common antihypertensives medications—plain ACEIs, ARBs, BBs, and CCBs—were effectively prescribed, not all antihypertensive prescriptions were efficient. Market shares by volume of the generic drugs did not increase. National drug policy reforms and initiatives in Lithuania have been successful at reducing reimbursement expenditure and patient co-payments for antihypertensive medications used in monotherapy but not for FIX-Ds.

10. PRACTICAL RECOMMENDATIONS

The results of this research clearly describe the real situation of the CVD and AH treatment in Lithuania. It provide the opportunity for Lithuanian health authorities an medical society to plan further reforms and initiatives to promote the rational use of medicines in treatment facilities, groups of doctors, counties, or country-based extent.

This research provides clear proof that tools to promote generic drug use among doctors, pharmacists, and patients are necessary when seeking to lower treatment costs and increase CVM prescribing effectiveness.

The results of this work can be useful when considering drug reimbursement policy changes, particularly when the reference drug group is determined by the principals of the ATC group and not by the drug's molecular makeup.

This work confirms the necessity of CVD prevention via correction of risk factors and pharmacological treatment of AH and CVD.

The presented results should initiate more detailed research on medication use focused on different aspects of care—the patient, the doctor, the medical institution, etc., —specifying the factors influencing the CVM prescription patterns.

11. PUBLICATIONS AND REPORTS BY THE AUTHOR OF THE DOCTORAL DISSERTATION

11.1. Publications

1. Lisauskienė I, Garuolienė K, Gulbinovič J. Utilization of cardiovascular medicines and cardiovascular mortality in Lithuania, Sweden and Norway in 2003–2012. Medicina (Lithuania). 2017 Jun (Accepted for publication).

2. Lisauskienė I, Garuolienė K, Gulbinovič J. Trends and pattern of the utilization of cardiovascular medicines in Lithuania in 2003–2012. Acta Medica Lituanica 2014; vol. 21, no. 3, p. 143–150.

11.2. Scientific reports

1. Lisauskienė I, Garuolienė K, Gulbinovič J. Comparison of Cardiovascular Medicines Utilization and Mortality from Cardiovascular Diseases in Baltic countries, Norway and Sweden 2007–2012. Tarptautinė konferencija „Evolutionary Medicine: Perspectives in Understanding Health and Disease“, Vilnius University, Vilnius, Lithuania, 2014 May 27–30.
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