

# Trends and pattern of the utilization of cardiovascular medicines in Lithuania in 2003–2012

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**Background.** Despite the wide use of cardiovascular (CV) drugs, CV diseases are still the leading cause of mortality and morbidity. Analysis of drug utilization gives a possibility to evaluate effectiveness of interventions.

**Materials and methods.** The aim of the study was to evaluate CV medicines consumption in Lithuania in 2003–2012. Data was retrieved from the SVEIDRA database of the National Health Insurance Fund. Utilization of the following groups of CVM (ATC group C) was analyzed: C02 – antihypertensive drugs, C03 – diuretics, C07 – beta blocking agents (BBs), C08 – calcium channel blockers (CCBs), C09 – agents acting on the renin–angiotensin system, C10 – lipid modifying agents. ATC/DDD methodology was used. Data was expressed as a number of DDD per 1 000 inhabitants per day (DDD/TID).

**Results.** Consumption of CVM went from 134.5 DDD/TID in 2003 to 352.2 in 2012. Angiotensin converting enzyme inhibitors (ACEI) were the most consumed ones (66–114.8 DDD/TID), followed by CCBs (19.4–38.8 DDD/TID) and BBs (12.5–52.6 DDD/TID). There was high consumption of antihypertensives (4.7–23.9 DDD) and low consumption of diuretics (9.4–16.9 DDD/TID) and lipid modifying agents (0.4–7.4 DDD/TID). Increasing utilization was noticed in the angiotensin II antagonist (ARBs) group (42 DDD/TID), ACEI combinations (38.6 DDD/TID) and ARBs combinations (12.9 DDD/TID) in 2012.

**Conclusions.** Utilization of CV medicines increased in Lithuania in 2003–2012. ACEI held the first position. An extremely low utilization of lipid modifying agents, diuretics and high consumption of alpha-receptor blockers showed the need of actions on changing the prescribing pattern of CV drugs.

**Key words:** drug utilization (trends), cardiovascular medicines, hypertension medication, Lithuania

## INTRODUCTION

Cardiovascular diseases (CVD) remain the main cause of death in the majority of countries (1, 2).

European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012) have promoted the treatment of all the reversible risk factors identified and the appropriate management of the raised blood pressure (BP) *per se* (3). The recent decrease in cardiovascular mortality in high-income countries is associated with a rise in the numbers of patients living with cardiovascular disease and the wider use of preventive drugs.

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In the past decades most European countries have developed administrative databases to monitor drug utilization by measuring volume and expenditures of medicines and the quality of prescribing on a national level. The ultimate goal of drug utilization research is an assessment of drug therapy rationality. Only few data were published on prevalence, awareness and management of CVD in Lithuania. The aim of our study was to evaluate the trends and pattern of the use of cardiovascular (CV) medicines in Lithuania in 2003–2012.

## MATERIALS AND METHODS

The use of reimbursed medicines, acting on the cardiovascular system, during the period of ten years – 2003–2012 was studied. CV drugs were classified according to the Anatomical-Therapeutic-Chemical (ATC) classification.

The list of analysed CV medicines groups and cardiovascular drugs is presented in the Table.

The data of purchased reimbursed medicines was retrieved from the SVEIDRA database of the National Health Insurance Fund (NHIF). Drug utilization was calculated using the Anatomical Therapeutic Chemical / Defined Daily Dose (ATC/DDD) methodology, and data was expressed as a number of DDD per 1 000 inhabitants per day (DDD/TID), using the ATC/DDD Index 2014 (4, 5, 6).

## RESULTS

The utilization of CV drugs in Lithuania during the period 2003–2012 is shown in Fig. 1. The data indicates continuous growth in the use of CV drugs over the time, from 134.5 DDD/TID in 2003 to 352.2 DDD/TID in 2012 (growth percentage per

**Table.** The list of analysed CV drugs groups and cardiovascular drugs

ATC grp. code and name	Medicines name and ATC code
C02 – Antihypertensives	Methyldopa (C02AB01); clonidine (C02AC01); moxonidine (C02AC05); prazosin (C02CA01); doxazosin (C02CA04).
C03 – Diuretics	Hydrochlorothiazide (HCT) (C03AA03); indapamide (C03BA11); furosemide (C03CA01); torasemide (C03CA04); spironolactone (C03DA01).
C07 – Beta blocking agents (BBs)	Propranolol (C07AA05); metoprolol (C07AB02); atenolol (C07AB03); betaxolol (C07AB05); bisoprolol (C07AB07); nebivolol (C07AB12); carvedilol (C07AG02); bisoprolol and HCT (C07BB07); nebivolol and HCT (C07BB12).
C08 – Calcium channel blockers (CCBs)	Amlodipine (C08CA01); felodipine (C08CA02); nifedipine (C08CA05); nitrendipine (C08CA08); lacidipine (C08CA09); lercanidipine (C08CA13); verapamil (C08DA01); diltiazem (C08DB01).
C09A – Angiotensin converting enzyme inhibitors, plain (ACEI)	Captopril (C09AA01); enalapril (C09AA02); lisinopril (C09AA03); perindopril (C09AA04); ramipril (C09AA05); quinapril (C09AA06); fosinopril (C09AA09); trandolapril (C09AA10); spirapril (C09AA11); zofenopril (C09AA15).
C09B – ACEI, combinations	Enalapril and HCT (C09BA02); perindopril and indapamide (C09BA04); ramipril and HCT (C09BA05); quinapril and HCT (C09BA06); fosinopril and HCT (C09BA09); lisinopril and amlodipine (C09BB03); perindopril and amlodipine (C09BB04); verapamil and trandolapril (C09BB10).
C09C – Angiotensin II antagonists, plain (ARB)	Losartan (C09CA01); eprosartan (C09CA02); valsartan (C09CA03); irbesartan (C09CA04); candesartan (C09CA06); telmisartan (C09CA07); olmesartan medoxomil (C09CA08).
C09D – ARB, combinations	Losartan and HCT (C09DA01); eprosartan and HCT (C09DA02); valsartan and HCT (C09DA03); telmisartan and HCT (C09DA07); olmesartan medoxomil and HCT (C09DA08); amlodipine and valsartan (C09DB01); olmesartan medoxomil and amlodipine (C09DB02).
C10 – Lipid modifying agents	Simvastatin (C10AA01); pravastatin (C10AA03); fluvastatin (C10AA04); atorvastatin (C10AA05); rosuvastatin (C10AA07).

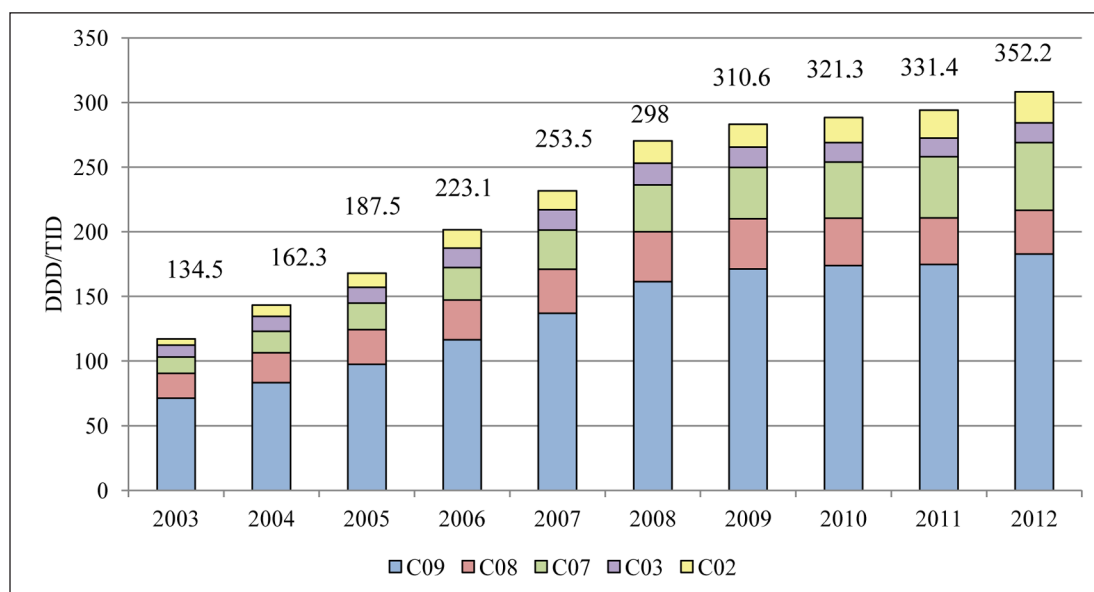


Fig. 1. Changes by year of utilization of CV medicines (ATC group C), presented in DDD/TID

study period (G%) = 162%; annual growth percentage (AG%) = 16.2%).

The most used medicines were the agents acting on the renin-angiotensin system (RAS), followed by beta blocking agents (BBs) and calcium channel blockers (CCBs).

The consumption of antihypertensive medicines went from 4.7 to 23.9 DDD/TID (G% = 406%). The utilization of moxonidine grew by between 2 to 16.1 DDD/TID. The utilization of doxazosin also increased 3.5 times during the study period (2.2–7.8 DDD/TID). The consumption of methyldopa (<0.01 DDD/TID) and prazosin (<0.1 DDD/TID) was very low.

The consumption of plain diuretics was stable and low in Lithuania (9.4–15.2 DDD/TI). The utilization of indapamide was rather stable during the study period (5–8.2 DDD/TID); on the contrary, the augmentation of consumption of torasemide (1.1–6.4 DDD/TID) and spironolactone (1.2–3.4 DDD/TID) was noticed. The consumption of furosemide and hydrochlorothiazide (HCT) was <0.6 DDD/TID.

The consumption of BBS increased gradually every year (12.5–52.6 DDD/TID; G% = 321.3). The most often prescribed medicines were metoprolol (5.3–15.7 DDD/TID), nebivolol (3–28.2 DDD/TID), betaxolol (2.5–4.8 DDD/TID) and carvedilol (0.7–1.7 DDD/TID). The combined preparation of nebivolol and HCT was introduced in 2011 and its consumption achieved 2 DDD/TID in 2012.

The highest consumption of CCBs (38.5–38.8 DDD/TID) was noticed in 2008–2009 and the decline in these drugs utilization to 33.8 DDD/TID was registered in 2010–2012 (G% = 74.3). The most often prescribed CCBs were amlodipine (7.1–13.6 DDD/TID), lercanidipine (0.6–14.8 DDD/TID), and lacidipine (3.3–6 DDD/TID). The following reduction was registered in the consumption of other CCBs during the study period: felodipine – 1.8–0.5 DDD/TID; nitrendipine – 2.9–0.4 DDD/TID; verapamil – 1.4–0.7 DDD/TID; diltiazem – 3.1–1.5 DDD/TID; nifedipine – 0.6–0.1 DDD/TID.

The group of agents acting on RAS was the most consumed CV medicines. We analyzed separately the utilization of ACEI and ARB, plain and combinations. The utilization of the plain ACEI increased from 66 DDD/TID in 2003 to 114.8 DDD/TID in 2008 followed by the reduction to 89.2 DDD/TID in 2012 (G% = 35.1). This decrease was compensated by an augmentation in consumption of combined preparations with ACEI (5.2–38.6 DDD/TID; G% = 648.7), plain ARB (0.5–42 DDD/TID; G% = 8 615.7) and ARB combinations (1.4–12.9 DDD/TID; G% = 809.4) (Fig. 2).

Ramipril was the most consumed medicine of all CV drugs (14.8–44.3 DDD/TID). The utilization of previously very popular enalapril decreased from 35.8 to 6.1 DDD/TID. This study showed an increasing utilization of perindopril (1.5–19.6 DDD/TID), quinapril (2.2–11.6 DDD/TID) and zofenopril

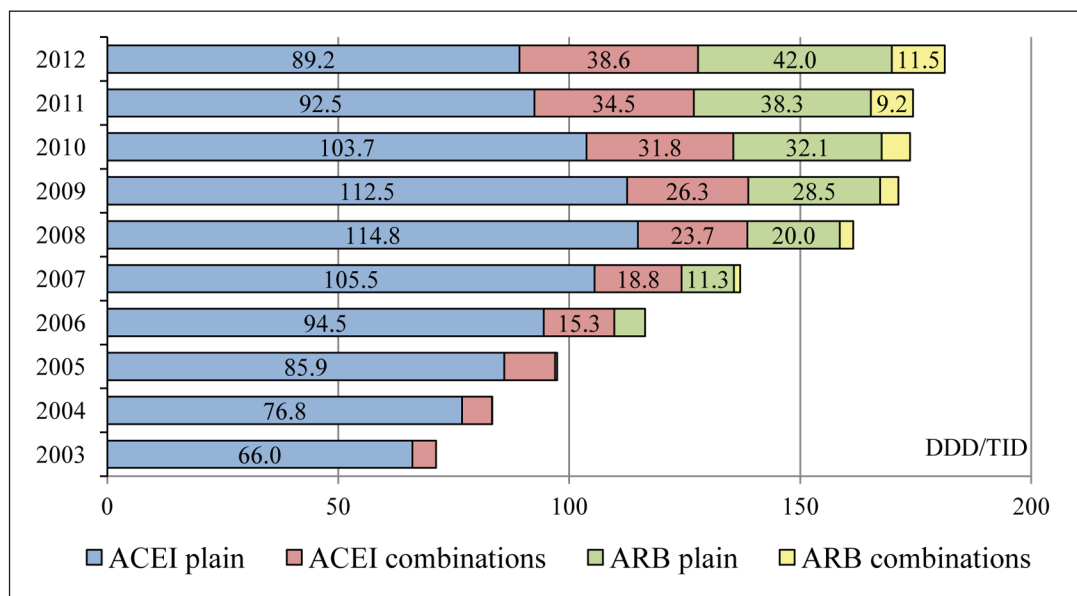


Fig. 2. Total utilization of ACEI and ARB, plain and combined preparations by year

(0.8–8.2 DDD/TID). The consumption rate of other ACEI such as lisinopril,trandolapril and spirapril was low (<2 DDD/TID).

ARBs were introduced in the Lithuanian market in 2006 and their utilization increased quickly influencing the utilization of the ACEI group. Losartan was a very popular drug until 2010 (5 DDD/TID in 2006 – 17.5 DDD/TID in 2010 – 10.4 DDD/TID in 2012). The prescription of other ARB drugs increased as follows: valsartan – 0.6–18.5 DDD/TID and telmisartan – 0.1–11.8 DDD/TID.

Combined preparations of ACEI and diuretics became very popular in Lithuania. The most consumed combined preparations were combinations of enalapril and HCT (5.2–0.4 DDD/TID), perindopril and indapamide (0.4–18.6 DDD/TID), quinapril and HCT (0.8–6.7 DDD/TID). ARB and diuretics combinations were started to use from 2006. Valsartan and HCT consumption reached 7.3 DDD/TID in 2012 and losartan and HCT consumption was 3.7 DDD/TID in 2010. The combinations of agents acting on RAS and CCBs were not so popular during the study period, but their utilization increased from 2008. The most popular such combination was perindopril and amlodipine, which utilization reached 10.7 DDD/TID in 2012.

The utilization of lipid modifying agents was extremely low – 0.4 DDD/TID in 2003 and 2004, 0.6 DDD/TID in 2005, 0.7 DDD/TID in 2006, 0.8 DDD/TID in 2007, 1 DDD/TID in 2008,

1.9 DDD/TID in 2009, 3.4 DDD/TID in 2010, 5.4 DDD/TID in 2011 and 7.4 DDD/TID in 2012. Only one drug – atorvastatin was widely used during the study period. The utilization of other lipid modifying drugs was <0.1 DDD/TID.

## DISCUSSION

The aim of this study was to evaluate the trends and pattern of utilization of CV medicines in Lithuania in 2003–2012. The idea was that the total amount and pattern of CV drugs used in Lithuania can relatively reflect the aggressiveness in arterial hypertension and other CVD treatment. Evidence favouring the administration of BP-lowering drugs to reduce the risk of major clinical CV outcomes (fatal and nonfatal stroke, myocardial infarction (MI), heart failure and other CV deaths) in hypertensive individuals results from a number of RCTs, recent meta-analysis (7–11). In the 2007 and 2013 versions of the Guidelines of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) it was concluded that the main benefits of antihypertensive treatment are due to lowering of BP *per se* and are largely independent of the drugs employed (12, 13).

Only few data was published on prevalence, awareness and management of arterial hypertension, and impact on health-related quality of life in Lithuania (14, 15). Previous studies found out

that the most frequently prescribed drugs had been ACEI (75.3% of patients), BBs (61.1%), diuretics (47.6%), CCBs (36.1%), alpha-receptor blockers (8.4%) (16). In addition, our data showed high consumption of centrally active antihypertensive agents and alpha-receptor blockers in Lithuania (3.51–6.79% of all prescribed CV drugs). A similar trend could be observed in Latvia where the utilization of these drugs also reached 3.7–5% of all CV drugs (17). On the contrary, the utilization of alpha-receptor blockers is very low in Scandinavian countries – less than 1% in Sweden, Denmark and Finland – and in Estonia (18, 19, 20, 21, 23). Alpha-receptor blockers are recommended as the third-line therapy or in multiple drug combinations when other treatment options failed (24). None of studies have shown superiority of these medicines compared to others. Future analysis on the patient level has to be performed for the explanation of this phenomenon in Lithuania.

Diuretics remain the cornerstone of antihypertensive treatment and are recommended by the ESH/ESC Guidelines as the first-choice drugs used either as monotherapy or in some combinations (13). The evidence proves that thiazides reduce mortality (RR 0.89, 95% CI 0.83, 0.96), incidence of stroke (RR 0.63, 95% CI 0.57, 0.71), coronary heart disease (CHD) (RR 0.84, 95% CI 0.75, 0.95) and cardiovascular events (RR 0.70, 95% CI 0.66, 0.76) (9). The use of plain diuretic medicinal products was not frequent in Lithuania despite guidelines on hypertension treatment. The use of plain diuretics made up about 5.75% of all prescribed CV drugs DDD/TID compared with 22.5–16.5% in Sweden in 2006–2012 (18) and 36–18.4% in Denmark (19) in 2003–2012. We found out that the reduction of plain diuretics utilization was compensated by increased use of the combined preparation of diuretics and other antihypertensive agents, reaching on the average 11.3% of all used CV drugs DDD/TID in Lithuania in 2012. The same trend of increased utilization of the combinations was observed in Norway, Denmark, Estonia and Finland (8.9–11% of all CV medicines DDD/TID) (19–22). Only in Sweden the utilization of combined preparations remained low and stable (4% of all CV medicines DDD/TID) in 2006–2012 (18).

The increasing utilization of beta blockers was registered during the study period (on the average 9.3–14.9% of all CV drugs). A similar utilization

rate was observed in Scandinavia and other Baltic countries (7–15%) (17–23).

The utilization of calcium antagonists was decreasing in Lithuania from 2008 composing 14.4–9.6% of used all DDD/TIDs. The use of CCBs was higher and is still increasing in all Scandinavian countries (12.8–16.3%) and in Latvia (16.8–20.1%) (17–23). Some data shows that CCB may reduce incidence of cardiovascular events (RR 0.71, 95% CI 0.57, 0.87), but not CHD (RR 0.77 95% CI 0.55, 1.09) or cardiovascular mortality (RR 0.86, 95% CI 0.68, 1.09) (9), cardiovascular complications in hypertensive diabetics (25) and in patients with metabolic syndrome (26).

The ACEI are the most popular CV medicines. Clinical trials showed that they have not only lower BP, but also improve outcomes and survival in patients with heart failure, with prior MI, and in patients with diabetes type 1 and kidney diseases (9, 27, 28). Our data showed that ACEI were the mostly prescribed CV drugs in Lithuania (49.1%–36.3% of all CV drugs DDD/TID), although decrease in the use of plain ACEI was noticed that was compensated by using combined ACEI preparations (10.97% of all CV drugs in 2012). The same tendency was observed in Latvia and Estonia: plain ACEI made up 20.7–30.3% and ACEI combination 6.5–20.9% of all CV drugs DDD/TID (17, 21). Data from other countries confirmed lower utilization of plain ACEI (14.7–18.4% of all CV medicines DDD/TID in Scandinavia) and combined ACEI (1–1.5% in Sweden, 1.2–3.8% in Denmark, Finland and Norway) (18, 19, 20, 22).

The consumption of ARB, plain and combinations was increasing in our country. The plain ARBs compose 11.9% and ARB combinations make up 3.3% of all CV drugs DDD/TID. An increase in the use of ARB is also noticed in other countries despite prescribing restrictions by the authorities (29).

An extremely low use of lipid modifying agents in Lithuania is difficult to explain. On the contrary, the utilization of statins in Western Europe was 10–15 times higher, e. g. it is more than 100 DDD/TID in Scandinavian countries. Although the recent guidelines recommend prescribing statins very early for the primary prophylaxis, debates are ongoing whether such “statinization” of population is rational and justifiable (30, 31, 32). Furthermore, an ecological study performed in Sweden did not show that increase in the use of statins has any impact on CV mortality (33).

Our study has a number of limitations. We have not analyzed the utilization of the CVM at the patient level, thus we are not able to say whether all purchased medicines were utilized, whether patients were compliant, and whether drugs were prescribed according to the guidelines. We also have not analysed what indications CV drugs were prescribed for. Nonetheless, despite the limitations our study shows the trends and patterns of CV drug use. Further studies are needed to find out whether changes in the use of CV medicines has any impact on mortality from CV diseases.

## CONCLUSIONS

The utilization of CV medicines increased in Lithuania in 2003–2012. The ACEI group held the first position during the study period, but utilization of combined preparations is growing every year. An extremely low utilization of lipid modifying agents, plain diuretics and high consumption of alpha-receptor blockers showed the need of some actions on changing the prescribing pattern of CVM in order to achieve better quality of care.

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### **ŠIRDIES IR KRAUJAGYSLIŲ SISTEMA VEIKIANČIŲ VAISTŲ SUVARTOJIMAS LIETUVOJE 2003–2012 M.**

#### *Santrauka*

**Įvadas.** Nepaisant didėjančio širdies ir kraujagyslių sistemą veikiančių vaistų (ŠKSV) vartojimo širdies ir kraujagyslių ligos išlieka dažniausia mirštamumo ir sergamumo priežastimi. Vaistų suvartojimo tyrimai leidžia įvertinti gydymo efektyvumą.

**Medžiaga ir metodai.** Tyrimo tikslas yra įvertinti ŠKSV vartojimo pokyčius Lietuvoje 2003–2012 m. Duomenys gauti iš Valstybinės ligonių kasos duomenų bazės SVEIDRA. Tirtas šių ŠKSV suvartojimas (ATC klasifikacija C grupė): C02 – antihipertenziniai vaistai, C03 – diuretikai, C07 – beta blokatoriai (BBs), C08 – kal-

cio kanalų blokatoriai (CCBs), C09 – renino – angiotenzino sistemą veikiančys vaistai, C10 – riebalų apykaitą reguliuojantys vaistai. Tyrime naudota ATC/numatytos paros dozės (DDD) metodika. Duomenys pateikti DDD skaičiumi 1 000 gyventojų per dieną (DDD/TID).

**Rezultatai.** ŠKSV suvartojimas didėjo nuo 134,5 DDD/TID 2003 m. iki 352,2 DDD/TID 2012 m. Daugiausia suvartota angiotenziną konvertuojančio fermento inhibitorių (ACEI) (66–14.8 DDD/TID), CCBs (19.4–38.8 DDD/TID) ir BBs (12.5–52.6 DDD/TID). Stebėtas itin didelis antihipertenzinių vaistų (4.7–23.9 DDD), mažas diuretikų (9.4–16.9 DDD/TID) ir riebalų apykaitą reguliuojančių vaistų (0.4–7.4 DDD/TID) suvartojimas. 2012 m. registruotas didėjantis angiotenzino II antagonistų (ARBs) (42 DDD/TID), kombinuotų preparatų su ACEI (38.6 DDD/TID) ir ARBs (12.9 DDD/TID) suvartojimas.

**Išvados.** 2003–2012 m. Lietuvoje didėjo ŠKSV suvartojimas, didžiausias – ACEI. Mažas riebalų apykaitą reguliuojančių vaistų, diuretikų ir didelis alfa receptorių blokatorių vartojimas atskleidė, kad reikalingos poveikio priemonės siekiant racionalizuoti ŠKSV vartojimą.

**Raktažodžiai:** vaistų suvartojimas (tendencijos), širdies ir kraujagyslių sistemą veikiančių vaistų suvartojimas, arterinės hipertenzijos gydymas, Lietuva