VILNIUS UNIVERSITY

FACULTY OF MEDICINE

Institute for Biomedical Sciences (Pharmacy and Pharmacology Center)

MASTER'S THESIS

DIAGNOSES BEHIND PRESCRIBING OF ANTIHYPERTENSIVES IN LITHUANIA: A
CROSS-SECTIONAL STUDY

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LIST OF ABBREVIATIONS

ACEI or **ACE inhibitors** - Angiotensin-Converting Enzyme Inhibitors

ARB - Angiotensin II receptor blockers

ATC - Anatomical Therapeutic Chemical classification system

BMI - Body Mass Index

BP - Blood Pressure

BPH - Benign Prostate Hyperplasia

CCB - Calcium Channel Blockers

CVD - cardiovascular disease

ESC/ESH - European Society of Cardiology/European Society of Hypertension

EU - European Union

GLP1-RA - Glucagon-Like Peptide-1 Receptor Agonists

ICD - International Statistical Classification of Diseases and Related Health Problems

LDL-C - Low-density lipoprotein-cholesterol

LUTS - Lower Urinary Tract Symptoms

TC - Total Cholesterol

MPP - Medical aids (Medicinos Pagalbos Priemonės)

NHIF or **VLK -** National Health Insurance Fund (Valstybinė Ligonių Kasa)

NHANES - National Health and Nutrition Examination Survey

PTSD - Post Traumatic - Stress Disorder

PSDF - Compulsory health insurance fund (Privalomas Sveikatos Draudimo Fondas)

RAS - Renin-Angiotensin-System

SBP - Systolic Blood Pressure

1 INTRODUCTION

Antihypertensive drugs were originally developed for high blood pressure reduction and their original use is well known. A few decades of research have shown that most of these drugs also have beneficial effects for the treatment of other disorders. Today, there are large randomized clinical trials demonstrating the efficacy of different antihypertensive drug classes in addressing various medical conditions, extending their utility to ailments such as heart failure, ischemic heart disease, atrial fibrillation, migraines, prostate hyperplasia, type 2 diabetes, paranoid schizophrenia, involuntary tremors, and others.

These topics hold significant importance. Cardiovascular diseases (CVD) rank high in terms of global prevalence (1), even though they are manageable health conditions nowadays. According to the World Health Organization (WHO) in total 1.28 billion people, aged 30 to 79 and mostly in lower-to-middle income countries, have been diagnosed with hypertension (2). According to 2015 data high blood pressure was linked to 8.5 million deaths, with 88% occurring in nations with low to moderate income levels (3). A worldwide study conducted in 2021 revealed that the prevalence of hypertension among individuals aged 30 to 79 years doubled from 1990 to 2019 (4). An ecological study on CVD mortality rates, spanning from 2003 to 2012, in Lithuania, Sweden, and Norway, indicated a consistent increase in utilization of most cardiovascular drugs, while the CVD mortality decreased slightly (5). This study also noted that data from other sources revealed that only 12.6% of men and 16.6% of women in Lithuania achieved optimal blood pressure control, in contrast to 52–58% of patients in Sweden and 71% of patients in Norway (5). Also, a 2021 retrospective study on antihypertensive medication use in the Baltic States between 2008 and 2018 showed an overall increase of medication for hypertension utilization in Lithuania, Latvia, and Estonia (6). This information underlines that the CVD situation in Lithuania is less than ideal.

Throughout the decades of development of effective hypertension treatment it was noticed that antihypertensive drugs from specific cardiovascular system drug classes could be used for the treatment of cardiovascular comorbidities or other non-hypertensive diseases. Prior to the year 2000, clinical researches consistently supported prescribing of a propranolol (ATC C07AA05) dosage ranging from 80 to 240 mg per day for the prevention of migraine (7). A study on "Treatment of Benign Prostatic Hyperplasia in Hypertensive Men" analyzed the use of alpha-adrenergic blocker doxazosin (ATC code C02CA04) in the treatment of benign prostate hyperplasia (BPH), a disease which often goes as a comorbidity with hypertension in men (8). Additionally, there is a shortage of research on antihypertensive drug prescribing for cardiovascular diseases, especially hypertensive and non-hypertensive health conditions.

Furthermore, there are even less studies written using electronic prescriptions that have most of the information displayed as data source.

Aim: this study's main objective is to provide a deeper understanding of the usage of hypertensive drugs for other health conditions in Lithuania by analyzing data on prescriptions. With guidance from supervisors, I have independently analyzed the literature, gathered data, and research objectives throughout the process of writing this master's thesis. Also, the goal with this study was to answer the following research questions:

1. To assess to which extent antihypertensive drugs are prescribed for the treatment of hypertension.
2. To evaluate for which diseases, hypertensive and non-hypertensive, antihypertensive drugs are prescribed.
3. To determine the distribution of antihypertensive drug usage according to sex and age.
4. To determine which specialty health professionals prescribed antihypertensive drugs most frequently for the treatment of hypertension-related diseases.

In this study focus was to select specific antihypertensive drug classes and assess their prescribing for different health conditions which include CVD and diseases that are not related to circulatory diseases. The selected drug classes were: centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C), and angiotensin II receptor blockers, combinations (C09D). The collected prescription data was analyzed according to patients' age, sex, disease code (ICD code), drug class (ATC code) and which specialty doctors write prescriptions. The underlying diagnoses behind the antihypertensive drug prescriptions were assessed.

2 LITERATURE REVIEW

Hypertension, or high blood pressure, occurs when the force of blood against the walls of the blood vessels is elevated, repeatedly reaching 140/90 mmHg (2)(9). Even though it is a common health problem, it can pose serious health risks if left untreated. Individuals with hypertension may not experience noticeable symptoms, but it is important to check blood pressure regularly for detecting and monitoring this disease (2). In cases where people get very high blood pressure, symptoms such as nausea, anxiety, dizziness, confusion, chest pain, blurred vision and headaches can occur. Factors that elevate the risk of developing high blood pressure encompass advancing age, genetic predisposition, excess weight, sedentary lifestyle, a high-sodium diet, and excessive alcohol consumption (2). Study on modifiable risk factors, cardiovascular disease, and mortality in different income countries showed that metabolic factors were the main risk factors for cardiovascular diseases, especially hypertension (10). In middle-income and low-income, household air pollution, poor diet, low education, and low grip strength had stronger effects on cardiovascular disease or mortality than in high-income (10).

As for treatment, at the moment, the advised treatment thresholds are set at ≥140/90 mmHg for individuals aged 18−79 years and ≥160/90 for those aged ≥80 years (11). However, for individuals with a history of cardiovascular events, especially myocardial infarction, the threshold is reduced to ≥130/85 mmHg (11).

2.1 Hypertension types and comorbidities

Hypertension can be two types: primary and secondary. The difference between these types is their causes.

Primary or essential hypertension may appear due to unhealthy lifestyle and other specific factors such as obesity, genetics, extensive alcohol consumption, irregular sleep schedule, high sodium level diet, age, and lack of physical activities. In most cases this type of hypertension is the cause of elevated blood pressure (12)(13).

Secondary hypertension is caused by another health problem. It usually occurs to patients that have endocrine disorders, renovascular disorders, vascular disorders, obstructive sleep apnea, polycystic ovarian syndrome, preeclampsia and most commonly to individuals that have renal parenchymal disease (13)(14).

Quite frequently patients with hypertension have comorbidities. In a study done in Korea in 2016 among 58,423 participants hypertensive patients with two or more comorbidities were 42.2% and those with three or more diseases were 17.7% (Figure 1) (15). The age- and sex-specific prevalence of three or more comorbidities among male hypertension patients was significantly

higher than those patients in the 30 - 59 age group (15). Most common comorbidities to hypertension were obesity, diabetes mellitus, dyslipidemia, cardiovascular disease, chronic kidney disease, and thyroid disease (15).

Type of comorbid diseases	Normal (Male 4916, Female 8251)		Prehypertension (Male 3785, Female 3315)		Hypertension (Male 4657, Female 5168)		p
	N	Percent (95% CI)	N	Percent (95% CI)	N	Percent (95% CI)	
Male							
Obesity	1471	29.8 (28.3–31.2)	1576	43.4 (41.6–45.3)	2445	59.9 (57.8–62.0)	<.001
Diabetes mellitus	379	8.2 (7.3–9.1)	406	9.3 (8.3–10.4)	988	15.4 (14.1–16.7)	<.001
Impaired fasting glucose	1280	26.5 (25.1–28.0)	1433	35.7 (33.9–37.6)	2519	48.1 (45.9–50.2)	<.001
Dyslipidemia	1768	47.3 (45.4–49.2)	1487	50.0 (47.8–52.2)	2235	60.2 (57.6–62.8)	<.001
Cardiovascular disease	113	2.4 (1.9–2.9)	112	2.3 (1.8–2.8)	356	4.0 (3.4–4.5)	<.001
Chronic kidney disease	4	0.1 (0.0–0.1)	5	0.1 (0.0–0.3)	17	0.4 (0.04–0.7)	<.01
Liver function test abnormality	865	17.4 (16.2–18.7)	893	23.7 (22.1–25.4)	1130	31.7 (29.6–33.9)	<.001
Thyroid disease	32	0.5 (0.3–0.7)	24	0.5 (0.2–0.7)	23	0.3 (0.1–0.5)	0.49
Anemia	174	3.5 (2.9–4.1)	127	2.7 (2.1–3.2)	269	3.2 (2.6–3.8)	<.001
Number of comorbid disease							
0	2447	50.0 (48.3–51.6)	1616	44.3 (42.4–46.2)	1560	37.1 (34.9–39.4)	<.001
1	1256	25.1 (23.7–26.5)	991	25.3 (23.6–26.9)	1050	20.4 (18.6–22.1)	<.001
2	863	18.0 (16.8–19.3)	764	19.8 (18.3–21.3)	1137	23.5 (21.7–25.3)	<.001
≥3	350	6.9 (6.1–7.7)	414	10.6 (9.4–11.8)	910	19.0 (17.3–20.8)	<.001
Female							
Obesity	2042	26.5 (25.3–27.8)	1355	39.4 (37.0–41.8)	2924	55.5 (51.6–59.5)	<.001
Diabetes mellitus	315	4.6 (4.0–5.2)	312	8.2 (7.0–9.5)	1082	14.7 (12.3–17.1)	<.001
Impaired fasting glucose	1321	17.8 (16.7–18.9)	995	28.5 (26.3–30.6)	2394	41.3 (37.2–45.3)	<.001
Dyslipidemia	2093	31.9 (30.6–33.2)	1251	40.6 (38–43.2)	2625	50.3 (46.0–54.6)	<.001
Cardiovascular disease	74	1.3 (0.9–1.6)	75	1.5 (1.1–1.9)	375	3.6 (2.6–4.6)	<.001
Chronic kidney disease	7	0.1 (0.0–0.2)	3	0.1 (0.0–0.1)	26	0.3 (0.1–0.5)	<.001
Liver function test abnormality	399	4.8 (4.2–5.4)	308	9.3 (7.8–10.8)	560	11.2 (8.8–13.5)	<.001
Thyroid disease	256	3.1 (2.7–3.6)	112	2.9 (2.1–3.6)	172	4.4 (2.1–6.7)	0.61
Anemia	1252	15 (14–15.9)	340	12.1 (10.5–13.7)	623	10.9 (8.8–13.1)	<.001
Number of comorbid diseases							
0	4333	50.6 (49.3–52.0)	1342	44.0 (41.5–46.5)	1362	31.8 (28.1–35.5)	<.001
1	2496	30.2 (28.9–31.4)	969	28.0 (25.8–30.2)	1398	29.5 (25.6–33.4)	0.02
2	1093	14.5 (13.6–15.5)	708	19.8 (17.9–21.7)	1451	25.3 (21.8–28.8)	<.001
≥3	329	4.7 (4.1–5.3)	296	8.2 (6.9–9.5)	957	13.4 (11.1–15.7)	<.001

Figure 1. The prevalence of comorbid diseases among participants, stratified by gender (29)

The number of comorbid diseases was defined by the number of diseases among diabetes mellitus, obesity, dyslipidemia (hypercholesterolemia, hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia), cardiovascular disease (stroke, myocardial infarction, or angina), CKD, thyroid disease, anemia, and liver function test abnormalities. HDL: high density lipoprotein, LDL: low density lipoprotein, CKD: chronic kidney disease

A similar research on drug treatment of hypertension in Sweden has shown among men, most common comorbidities included diabetes mellitus, ischemic heart disease, and atrial fibrillation

(16). However, in women, most common comorbidities were diabetes mellitus, asthma/chronic obstructive pulmonary disease, and ischemic heart disease (16).

Obesity affects one-third of adults in the United States (32.9% in the 2003–2004 US National Health and Nutrition Examination Survey (NHANES) and is a major risk factor for the development of HTN, CVD, and chronic renal disease (17). The risk of left ventricular hypertrophy (LVH) and concomitant heart failure increases with increasing BMI (17). The effect of obesity on CVD risk may be because of its impact on the risk of associated metabolic abnormalities, such as diabetes and hyperlipidemia, which are themselves risk factors for CVD (17). According to Lithuania's 2019 statistics, 41% of individuals aged 18 and above had normal body weight, while 57% were classified as above normal weight, with 38% falling into the overweight category and 19% categorized as obese (18). The prevalence of obesity was higher among women (21%) compared to men (17%). However, 43% of men and 33% of women were classified as overweight (18).

Patients with *diabetes mellitus* experience increased peripheral artery resistance caused by vascular remodeling and increased body fluid volume associated with insulin resistance-induced hyperinsulinemia and hyperglycemia (19). Both of these mechanisms elevate systemic blood pressure. Moreover, insulin stimulates obesity through fat accumulation and this leads to obesity-induced hypertension in association with type 2 diabetes mellitus (19). Since 2018 in Lithuania the number of diabetes mellitus diagnosis has increased (Figure 2) (20).
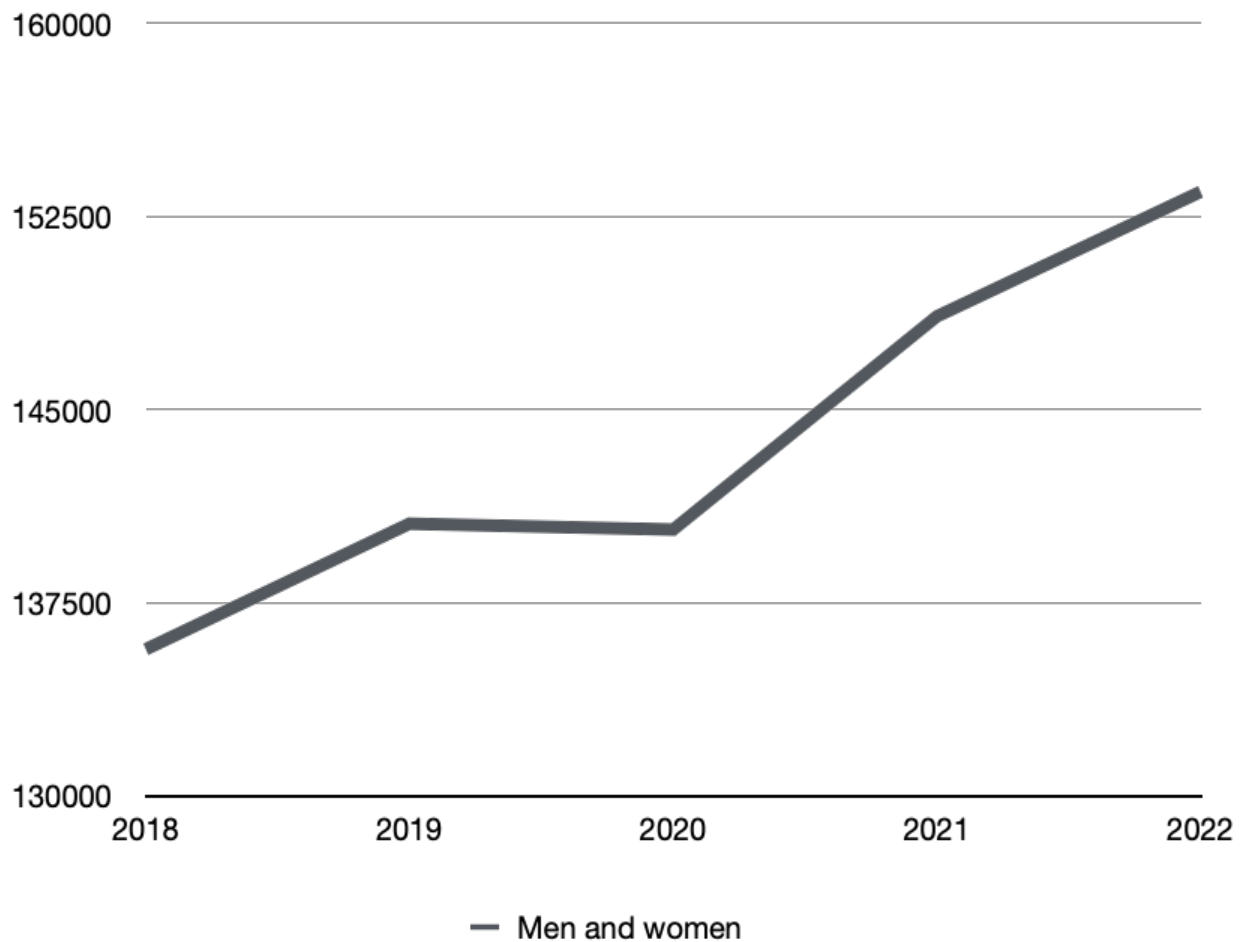
Figure 2. Diabetes mellitus prevalence in Lithuania among men and women (20)

Dyslipidemia is also a common comorbidity. The issue with this health condition lies in its prevalence and lack of awareness. Based on data from 1989 to 1997 showing 32 populations across 19 countries on three continents, within the 35–64 age group, the prevalence of hypercholesterolemia (total cholesterol 6.5 mmol/l or taking lipid-lowering drugs), in men, prevalence ranged from 3% to 53%, while in women, it ranged from 4% to 40% (21). Awareness of hypercholesterolemia was ranging from 1% to 33% in men and from 0% to 31% in women across different populations (21). Population-based epidemiological studies have reported that gradual increases in blood pressure (BP) or prevalence of hypertension are associated with increases in blood lipid levels. The study proposed an explanation suggesting that hypertension and dyslipidemia have shared underlying causes in their physiological mechanisms (22). These common factors include conditions like obesity and the subsequent disruption of adipocytokine release from adipose (fat) tissue (22). In a study at a Japanese electrical equipment manufacturing company, 17,885 male workers (mean age 38±9 years) underwent annual checkups (22). During the follow-up, 1,483 participants developed hypertension. Adjusting for

various factors, those with a total cholesterol (TC) level ≥222 mg/dL had a significantly higher risk of developing hypertension compared to those with TC ≤167 mg/dL (22).

Established *cardiovascular disease (CVD)* is also a common comorbidity as well as a consequence of poorly treated hypertension. Large cohort studies have demonstrated that high BP is an important risk factor for heart failure, atrial fibrillation, chronic kidney disease, heart valve diseases, aortic syndromes, and dementia, in addition to coronary heart disease and stroke (23). High BP is a major risk factor for development of CVD. Prevention of the age-related increase in BP would substantially reduce the vascular consequences usually attributed to aging (23). Other risk factors, including lipid abnormalities, cigarette smoking, physical inactivity, and dietary influences other than sodium, may also lead to CVD progression (23). Although elevated BP impacts greatly on population health, prevention of CVD is best achieved by improving CVD risk factors at any stage of life (23).

Chronic kidney disease (CKD). The healthcare burden is highest in the initial stages, primarily because of the rising prevalence, impacting approximately 35% of individuals aged 70 and above (24). Hypertension is both a contributing factor and a consequence of chronic kidney disease (CKD) (25). Majority of CKD patients are affected by hypertension, which means that managing hypertension is crucial for individuals with CKD, as it not only slows down the progression of the disease but also decreases the risk of cardiovascular disease (CVD) (25).

Thyroid disease. A research investigation on hypertension in thyroid disease noted that previous studies indicated the occurrence of heart failure in 6–16% of individuals with hyperthyroidism (26). Those with pre-existing hypertension or predisposing factors for coronary artery disease face an elevated risk of experiencing hemodynamic alterations that can lead to the development of chronic heart failure (26). A common complication associated with hyperthyroidism, atrial fibrillation, indicates the increased chronic heart failure risk (26).

2.2   Epidemiology of hypertension

According to the World Health Organization (WHO) hypertension is one of the leading causes of premature deaths worldwide. It is estimated that hypertension is found in every 1 in 4 men and 1 in 5 women (27). Approximately 31.1% of adults globally, 1.39 billion individuals in total, were reported to have hypertension in the year 2010 (28).

High blood pressure is more commonly found in low-income and middle-income nations compared to their high-income countries (29). In 2015, 8.5 million deaths were linked to hypertension, 88% occurring in low-income and middle-income countries (29). Implementing population-wide strategies, such as enhancing access to fresh fruits and vegetables at reasonable

prices and reducing the sodium content in processed foods, can effectively lower blood pressure across entire communities (29).

Between 1990 and 2019, the number of individuals aged 30–79 with hypertension doubled from 331 million women and 317 million men in 1990 to 626 million women and 652 million men in 2019, despite a stable global age-standardized prevalence (4). In 2019, Canada and Peru exhibited the lowest age-standardized hypertension prevalence for both genders, while Taiwan, South Korea, Japan, and select countries in western Europe including Switzerland, Spain, and the UK demonstrated lower rates among women (4). Several low-income and middle-income nations such as Eritrea, Bangladesh, Ethiopia, and the Solomon Islands reported lower prevalence rates among men (4).

In 2017, a cross-sectional study was carried out in Sweden, encompassing the entire population of 292,623 individuals aged 20 years or older. The study focused on those with recorded primary or secondary diagnoses of hypertension at any point between 2009 and 2013 in the larger Stockholm region, Sweden (16).

According to the Official Statistics Portal in Lithuania coronary artery disease (ICD code I25. 1), congestive heart failure (ICD code I11. 0), atrial fibrillation (ICD code I48. 11), cerebrovascular disease (ICD code I67. 9), peripheral arterial disease (ICD code I73. 9), aortic aneurysm (ICD code I71. 9) and chronic kidney disease (ICD code N18. 9) affected 804,555 habitants in 2022 and 787,407 habitants in 2021 (20). These numbers include both men and women (20).

2.3 Economic impact of hypertension and its comorbidities

CVD imposes a substantial economic burden on the European Union (EU), estimated at €282 billion annually. Health and long-term care expenses contribute €155 billion (55%), which equals 11% of the EU's total health expenditure (30). Productivity losses make up 17% (€48 billion), while informal care costs reach €79 billion (28%) (30)[34]. On average, CVD costs €630 per person, ranging from €381 in Cyprus to €903 in Germany (30). Coronary heart disease and cerebrovascular diseases each represent 27% of CVD costs, totaling €77 billion and €76 billion, respectively (30). In high-income countries, total health expenditure represented 12.3% of the gross domestic product (GDP) in 2014 (31). Though newly introduced pharmaceuticals may pressure a given healthcare budget, patent expiration and associated price decreases may offset this burden (31). After a patent expiry or loss of other exclusivity rights, generic copies of the originator can be produced and marketed without a license from the originator company (31). According to National Health Insurance Fund (NHIF) statistics, drugs for the cardiovascular system come in second place as the most funded drugs for patients. In 2022 for this drug group 68.6 million euros were paid (32). This number includes both compulsory health insurance fund

(PSDF) budget expenditures for medicines and MPP, including the premium paid by the patient (Figure 3) (32).

2018 – 2022 m. PSDF biudžeto išlaidos vaistams ir MPP, įskaitant padengiamą pacientų priemoką, pagal ATC klasifikacijos I lygį (mln. Eur)

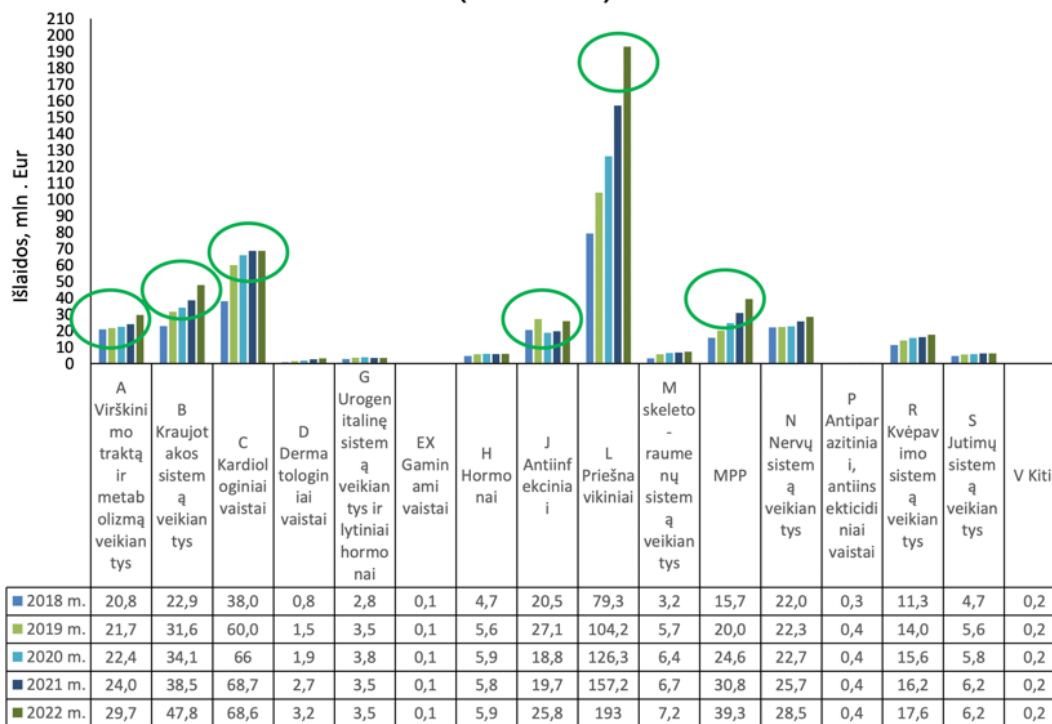|	A Virškinimo traktą ir metabolizmą veikiantys	B Kraujotakos sistemą veikiantys	C Kardiologiniai vaistai	D Dermatologiniai vaistai	G Urogenitalinę sistemą veikiantys ir lytiniai hormonai	EX Gaminami vaistai	H Hormonai	J Antiinfekciniai	L Priešnavikiniai	M skeleto-raumenų sistemą veikiantys	MPP	N Nervų sistemą veikiantys	P Antiparazitiniai, antiinsekticidiniai vaistai	R Kvėpavimo sistemą veikiantys	S Jutimų sistemą veikiantys	V Kiti
2018 m.	20,8	22,9	38,0	0,8	2,8	0,1	4,7	20,5	79,3	3,2	15,7	22,0	0,3	11,3	4,7	0,2
2019 m.	21,7	31,6	60,0	1,5	3,5	0,1	5,6	27,1	104,2	5,7	20,0	22,3	0,4	14,0	5,6	0,2
2020 m.	22,4	34,1	66	1,9	3,8	0,1	5,9	18,8	126,3	6,4	24,6	22,7	0,4	15,6	5,8	0,2
2021 m.	24,0	38,5	68,7	2,7	3,5	0,1	5,8	19,7	157,2	6,7	30,8	25,7	0,4	16,2	6,2	0,2
2022 m.	29,7	47,8	68,6	3,2	3,5	0,1	5,9	25,8	193	7,2	39,3	28,5	0,4	17,6	6,2	0,2

Figure 3. 2018 - 2022 PSDF budget expenditures for medicines and MPP, including covered premium, according to ATC classification I measures (million EUR)(32)

A - drugs affecting the digestive tract and metabolism, B - drugs affecting circulatory system, C - drugs for cardiovascular system, D - dermatological drugs, G - drugs acting on the urogenital system, EX - extemporaneous drugs, H - hormonal drugs, J - anti-infective drugs, L - antineoplastic agents, M - musculoskeletal medicines, MPP - medical aids, N - drugs for the nervous system, P - antiparasitic, anti-insecticidal drugs, S - drugs affecting the sensory system, V - others

2.4 Pharmacological management of hypertension and its comorbidities

Obesity and hypertension. The correlation between body mass index (BMI) and blood pressure (BP) follows an almost linear pattern (33). An increase of 1.7 kg/m2 in BMI or 4.5 cm in waist circumference corresponds to a 1 mmHg increase in systolic blood pressure (SBP). According to the European Society of Cardiology/European Society of Hypertension (ESC/ESH) hypertension guidelines, lifestyle modifications such as regular physical activity are recommended to achieve a normal weight. Individuals with severe obesity (BMI >40 kg/m2) often require multiple antihypertensive medications (33). Glucagon-like peptide-1 receptor agonists (GLP1-RA) have been shown to reduce body weight and exhibit effects to the cardiovascular system, including modest reductions in SBP (33).

Diabetes mellitus and hypertension. Combination therapies involving RAS blockers, calcium channel blockers (CCB), or diuretics are advised. According to an individual participant data meta-analysis involving 145,939 participants, RAS blockers decreased the relative risk of new-onset diabetes by 16%. Conversely, CCBs had a neutral effect, while beta-blockers and thiazide diuretics were associated with an increased incidence of diabetes (33). In cases of resistant hypertension and diabetes, spironolactone (at doses of 25–50 mg daily) has been shown to reduce blood pressure and albuminuria. Beta-blockers should be avoided in individuals with pre-diabetes unless there is a compelling cardiovascular indication, as they may affect insulin sensitivity, induce lipid alterations, and lead to weight gain (33).

Dyslipidemia. Recent European guidelines for dyslipidemia suggested, if LDL-cholesterol control is not achieved, ezetimibe (C10AX09) is recommended as another treatment, preferably as a single-pill combination to enhance treatment adherence(9). Concerning antihypertensive therapy, beta-blockers (BBs) and diuretics may be deemed less preferable in cases of challenging-to-treat dyslipidemia due to their modest effects on lipid profiles, especially when used in combination treatments (9). Nevertheless, their effectiveness in reducing cardiovascular risk through blood pressure regulation far outweighs their metabolic drawbacks, and they should be utilized when necessary to control blood pressure (9).

Chronic kidney disease and hypertension. The ESC/ESH hypertension guidelines recommend lowering office SBP in CKD patients to 130–139 mmHg based on a systematic review and meta-analysis (9). Renin–angiotensin system blockers are highlighted as more effective in reducing albuminuria and are suggested to be combined with either a calcium channel blocker (CCB) or a diuretic. Enhanced blood pressure control can be achieved by utilizing potent, long-acting thiazide-like diuretics like chlorthalidone and indapamide. Notably, chlorthalidone demonstrated efficacy even in stage 4 CKD and hypertension that was poorly controlled (with 60% of patients receiving loop diuretics), resulting in a reduction of 24-hour SBP by 10.5 mmHg. Additionally, studies showed that dapagliflozin decreases the risk of estimated glomerular filtration rate (eGFR) decline, end-stage CKD, or death from renal or cardiovascular causes in CKD patients, irrespective of whether they had diabetes (33).

Cardiovascular diseases and hypertension. There are quite a lot of variations for applying antihypertensives for both hypertension and cardiovascular disease treatment (34). Diuretics are suitable for the treatment of both hypertension and heart failure (34). Beta adrenoceptor blockers are suitable for hypertension and after myocardial infarction, for patients with angina pectoris and for patients with atrial fibrillation. Alpha adrenoblockers are used when prostate hypertrophy occurs (34). ACE inhibitors are used to treat hypertension, left ventricular dysfunction, and diabetic nephropathy (34).

2.5 Guidelines for hypertension management in Lithuania

When diagnosing hypertension and the specific disease code, the level of blood pressure, risk factors, organ damage caused by hypertension, and co-morbidities aggravating the condition are evaluated.

There are five categories of increased blood pressure: normal (<120mmHg/<80mmHg), normal - high (120-139mmHg/80-89mmHg), First (I) degree increase (140-159mmHg/90-99mmHg), Second (II)-degree increase (≥160mmHg/≥ 100mmHg), isolated systolic hypertension (≥140mmHg/<90mmHg) (35)(36).

According to Lithuanian guidelines, the risk factors for arterial hypertension are(36):

- type II diabetes.
- dyslipidemia.
- abdominal (visceral) obesity.
- microalbuminuria.
- smoking.
- insufficient physical activity.
- a positive family history of cardiovascular disease or premature death.

It is explained that hypertension, especially if it's untreated, can cause damage to one of these organs: heart, brain, kidneys, or arteries (35)(36). After finding the damage localization further diseases can be identified. For example, if the damage is in the heart, hypertension can be the cause of systolic, diastolic, or mixed heart failure, heart rhythm disorders, left ventricular hypertrophy. In cases where the brain is damaged, chronic cerebral ischemia, cerebral hemorrhage or stroke may occur (35)(36). If hypertension affects the kidneys, chronic renal failure, glomerular and/or stromal sclerosis may develop. Also, lesions in the arteries can lead to aortic aneurysm, plaques or stenosis or the development of hypertensive Angio retinopathy.

After evaluating the state of health according to the available data, the diagnosis of the disease and the code of the disease are established, according to which the treatment is selected. Main hypertensive diagnoses and their ICD-10-codes include (35):

- Primary hypertension (I 10). Coded in the absence of target organ damage.
- Hypertensive heart disease (I 11). Also referred to as hypertensive cardiopathy.
- Hypertensive kidney disease (I 12). Also referred to as hypertensive nephropathy.
- Secondary hypertension (I 15).
- Arterial hypertension diseases, which are not directly reflected by the codes (I 10, I 11, I 12, I 15).

After assessing the magnitude of the risk, it is decided when to start medical treatment of arterial hypertension, to what extent to reduce blood pressure, and how quickly the target blood pressure should be reached (36). At moderate risk, risk factors are adjusted, patients are observed for 2-3 weeks before prescribing drugs, but if necessary, drugs are prescribed immediately after diagnosis. For high- and very-high-risk patients, it is also important to target risk factors and prescribe drugs immediately after diagnosis (35)(36).

If low and moderate BP can be treated with one drug (36). At high and very high risk, treatment starts immediately with a combination of two antihypertensive drugs in lower doses. In the absence of the required effect, monotherapy should not last long (up to 3 months). Treatment with combinations of two or three antihypertensive drugs is used in about 70% of cases.

Patients with arterial hypertension. If more than three antihypertensive drugs are needed for treatment, the doctor of general practice or internal medicine patient is guided to a specialist consultation (cardiologist, nephrologist, etc.), after which he can prescribe three or more antihypertensive drugs for a maximum of 1 year (36). Next, it is sent again for a doctor's specialist consultation (36).

Antihypertensives are usually picked for one of two lists of drugs that are reimbursed from the PSDF (36):

- The first list of drugs are reimbursed drugs for the initial correction of arterial blood pressure, until the tests and clinical conditions necessary for prescribing the drugs of the second list are determined (Table 1).

Table1. The first list of reimbursed drugs

Drug group	Drug examples
Calcium channel blockers	Diltiazem, Nifedipine (modified release)
ACE inhibitors	Enalapril, Captopril
Beta blockers	Atenolol, Metoprolol
Others	Hydrochlorothiazide, Clonidine, Prazosin
Fixed combinations	Enalapril and hydrochlorothiazide

- The second list of drugs are drugs that are prescribed for the long-term treatment of arterial hypertension after at least one clinical condition has been confirmed by the necessary tests to prescribe the drug from this list. The list is compiled based on clinical conditions confirmed by clinical studies and when there are complications of arterial

hypertension ("target organ damage") and/or accompanying clinical conditions and/or risk factors (Table 2 - 5).

Table 2. The second list of drugs (Calcium channel blockers - C08)

Drug group	Drug examples (and comorbidity examples)
Calcium channel blockers (CO8)	**Amlodipine** - hypertensive cardiopathy without heart failure, accompanied by coronary heart disease, accompanied by diabetes mellitus.
	Diltiazem (modified effect) - hypertensive cardiopathy accompanied by coronary heart disease, hypertensive nephropathy.
	Felodipine - hypertensive cardiopathy without heart failure, accompanying coronary heart disease, hypertensive nephropathy, accompanying diabetes, hypertension in the elderly ($\geq$ 65 years).
	Lacidipine - Hypertensive cardiopathy without heart failure with associated coronary heart disease, Hypertensive arteriopathy, Hypertensive nephropathy
	Lercanidipine - hypertensive cardiopathy without heart failure; hypertensive arteriopathy accompanying diabetes mellitus.
	Nitrendipine - hypertensive cardiopathy without heart failure; hypertension in the elderly ($\geq$ 65 years).
	Verapamil (modified action) - hypertensive cardiopathy

Table 3. The second list of drugs (ACE inhibitors - C09A)

Drug group	Drug examples (and comorbidity examples)
ACE inhibitors (C09A)	**Fosinopril** - hypertensive cardiopathy without or with heart failure.
	Quinapril - hypertensive cardiopathy without or with heart failure accompanied by coronary heart disease (angina and/or myocardial ischemia and/or recurrent myocardial infarction and/or after catheter/surgical treatment), hypertensive arteriopathy accompanied by diabetes mellitus (and/or metabolic syndrome).
	Lisinopril - hypertensive cardiopathy without heart failure, hypertensive nephropathy, accompanying diabetes mellitus.
	Perindopril - Hypertensive cardiopathy without or with heart failure, after recurrent stroke and/or transient ischemic attack (TIA).
	Ramipril - hypertensive cardiopathy without or with heart failure; accompanying coronary heart disease.
	Spirapril - hypertensive cardiopathy without heart failure.
	Trandolapril - hypertensive cardiopathy without heart failure; accompanied by coronary heart disease (myocardial infarction).

Table 4. The second list of drugs (Beta blockers - C07)

Drug group	Drug examples (and comorbidity examples)
Beta blockers (C07)	**Betaxolol** - hypertensive cardiopathy without heart failure. **Metoprolol** (modified effect) - hypertensive cardiopathy without or with heart failure, accompanying coronary heart disease, accompanying tachyarrhythmias, accompanying diabetes mellitus, hypertensive arteriopathy. **Nebivolol** - hypertensive cardiopathy without heart failure with concomitant coronary heart disease (angina and/or myocardial ischemia) requiring BAB and concomitant diabetes mellitus.

Table 5. The second list of drugs (Other antihypertensive drugs, which includes C0A - antihypertensive drug class, C03 - diuretic drug class)

Drug group	Drug examples (and comorbidity examples)
Others antihypertensive drugs	**Doxazosin** (modified effect) - AH accompanied by benign prostatic hyperplasia; accompanying diabetes mellitus (and/or metabolic syndrome). **Indapamide** - hypertensive cardiopathy without heart failure; hypertensive nephropathy. **Indapamide** (modified effect) - hypertensive cardiopathy without heart failure; hypertensive nephropathy accompanying diabetes mellitus (and/or metabolic syndrome). **Clonidine** - for the treatment of AH in the third trimester of pregnancy. **Labetalol**, **methyldopa** - arterial hypertension and pregnancy (prescribing labetalol in the first three months of pregnancy to assess the benefit-risk ratio). **Rilmenidine**, **Moxonidine** - hypertensive cardiopathy without heart failure, accompanied by diabetes. **Spironolactone** - for the treatment of AH with heart failure.

2.6 Reimbursement of drugs in Lithuania

Residents who are covered by compulsory health insurance can receive reimbursed medicines or medical devices in Lithuania (37). Doctors can prescribe medicines and medical aids reimbursed by the Compulsory Health Insurance Fund (PSDF) for outpatients. In 2016, more than 217 million euros have been earmarked for these purposes (37).

Pharmacies must have a full range of reimbursable drugs with a price close to the base price (38).

Necessary medicines and medical aids, the purchase costs of which are reimbursed from the State Social Insurance Fund or the Lithuanian state budget and municipal budgets, are issued in pharmacies in the same district and city where the institution that issued the prescriptions is located, or in the patient's residential area (38).

Only those drugs that are included in the list of diseases and compensable drugs for their treatment (A) and the list of compensable drugs (B) can be purchased with reimbursement. Compensatory medical aid measures are recorded in a separate list of Compensatory medical aid measures (C) (37). As in other countries, only the base price of the drug is reimbursed in Lithuania. The list of compensable drugs (A) is intended for all those covered by compulsory health insurance. Medicines from this group are prescribed only for the treatment of certain diseases.

The list of compensable drugs (B) is intended for patients of individual social groups, whose financial ability to purchase certain drugs is lower, for example children, pensioners, disabled. But there is also a third case of drug reimbursement (37).

In all cases, if the patient is diagnosed with a chronic disease for the first time or a new drug is prescribed for the treatment of a chronic disease for the first time, drugs are prescribed for a treatment course of up to 1 month (it can be prescribed for one or several days) (37). If the medication is effective, it can be given for up to 3 months. lasting course of treatment (except for narcotic and psychotropic drugs) (37). Also, a doctor can write prescriptions for compensatory drugs marked "Continue treatment" for a period of up to 6 months for a patient with a chronic disease, when his health condition is stable and there is no need to visit the doctor more often (37).

Until the middle of 2015, only paper prescriptions for medicines were issued to patients in Lithuania. However, on May 28, 2015, Order No. 112, specifying all the requirements regarding the preparation and issuance of a prescription for prescription, reimbursed medicinal products or drugs, was changed. In the new version, doctors were allowed to write prescriptions electronically (39).

Additionally, according to 31 January 2024. Order No V-137, general practice nurses can prescribe certain drugs in the case of a stable state of health of the patient, to continue the treatment of a chronic disease prescribed by a doctor for a maximum period of 1 year by prescribing medicinal products which the patient has already been taking for at least 3 months (40).

2.7   Antihypertensive drug classification

Antihypertensive drugs are classified and well recognized by the The Anatomical Therapeutic Chemical (ATC) codes (41). Each drug group is distinguished by the first three digits of the code - the first digit is a letter, and the other two are numbers. Later, individual drugs are distinguished according to the following signs. According to the first letter, it is distinguished which body system, organ, drug group or drug works. Antihypertensive drug codes always begin with the letter C - drugs affecting cardiovascular conditions. Main antihypertensive classes are: C02 - Antihypertensives, C03 - Diuretics, C07 - Beta blocking agents, C08 - Calcium channel blockers and C09 - Agents acting on the renin-angiotensin system (Table 6) (41).

Class C09 can also be in four groups: C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - ARBs and C09D - ARBs, combinations (41).

Table 6. Examples of ATC classes and codes with names of active substances from the Lithuanian reimbursed drug list(36)(41).

Drug group name	ATC class	ATC code	Name of the drug
Centrally acting antihypertensives	C02A	C02AC01	Clonidine
		C02AC05	Moxonidine
Diuretics	C03	C03AA03	Hydrochlorothiazide
		C03BA11	Indapamide
Beta blockers	C07	C07AB02	Metoprolol
		C07AB12	Nebivolol
Calcium channel blockers	C08	C08CA01	Amlodipine
		C08DB01	Diltiazem
ACE inhibitors	C09A	C09AA01	Captopril
		C09AA05	Ramipril
ARBs	C09C	C09CA06	Candesartan
		C09CA08	Olmesartan medoxomil

2.8   Other diseases that antihypertensives are used for

The underlying mechanisms of migraines result from nerve cells, glial cells, blood vessels, and inflammatory interactions, signals (42). These interactions give rise to a severe neurological condition marked by recurring one-sided headaches lasting between 4 to 72 hours (42). These headaches are often accompanied by symptoms like nausea, sensitivity to light, and sensitivity to sound. Medications meant for prevention of migraines act by inhibiting CSD through diverse mechanisms, including the blocking of calcium and sodium channels, gap junctions, and matrix metalloproteinases (43).

In a 2022 study it has been mentioned that certain antihypertensives can be applied for the treatment of some mental disorders (44). For example, propranolol, atenolol can be used for post

traumatic - stress disorder (PTSD) symptom treatment (44). Enalapril and captopril showed a positive effect by improving mood and decreasing depression, anxiety (44). Spironolactone, candesartan, perindopril showed anxiolytic properties (44).

Benign prostatic hypertrophy (BPH) and hypertension often coexist, with around 25%–30% of men aged over 60 experiencing both conditions at the same time (8). The treatment of BPH commonly involves the use of doxazosin, an effective α blocker (8). However, achieving relief from lower urinary tract symptoms (LUTS) might require titrating the dosage to relatively high levels (≥8 mg daily) (8). Clinical trials focusing on men with BPH demonstrated that tamsulosin (0.4 mg/d) enhances urinary flow rates and helps to relieve BPH symptoms without causing clinically significant impacts on blood pressure or heart rate (8).

Also, antihypertensive drugs can potentially decrease the risk of fractures resulting from falls (45). Statistics indicate that around one-third of adults aged 65 years or older experience at least one fall annually, with 6% of these individuals sustaining a fracture as a consequence. Several studies suggest that thiazide diuretics and β-blockers may contribute to reducing the risk of fractures among older adults (45).

According to research examining the effects of antihypertensive medications on cognitive decline and dementia prevention, it's suggested that these drugs could potentially lower the risk of not only vascular dementia but also Alzheimer's disease (46). Four randomized controlled trials have shown a positive effect of antihypertensive treatment for these health conditions: SYST-EUR I and II demonstrated a 55% reduction in dementia risk (3.3 vs. 7.4 cases per 1,000 patient years; $p < 0.001$); HOPE showed a 41% decrease in cognitive decline related to stroke (95% confidence interval [CI] 6–63); and PROGRESS exhibited a 19% reduction in cognitive decline (95% CI 4–32; $p = 0.01$) (46).

3   METHODS

3.1   Setting

The study took place in the Republic of Lithuania (population - 2.8 million). The proportion of sexes in Lithuania is 1.499 million women to 1.307 million men. Population by age distribution is as follows: 0 to 14 - 14,9%, 15 to 64 - 65,1%, 65 and over - 20,0% of the population (47). The prescription data was collected from the State Enterprise Registry Center, of which drug prescriptions from March 2022 were analyzed. Examined electronic prescriptions contained details of the specialty of the physician who prescribed the medication, the diagnoses for which the prescription was made, as well as the sex and age group of the patient. Lithuanian drug policies allow urologists, cardiologists, internal medicine, geriatricians, occupational medicine, and family doctors, to prescribe antihypertensive drugs.

3.1.1   Study design

This study is a cross - sectional research to analyze the prevalence of antihypertensive drug utilization and their prescribing for hypertension and other conditions, in a specific time frame. The statistical information will be gathered from a database.

3.1.2   Data collection

Information for the theoretical part of this study will be gathered from various available articles and research papers. Most of the research data was obtained from the National Library of Medicine website. Sources for the information on ATC classification and codes for the antihypertensives were collected from the World Health Organization (WHO) website. The data on antihypertensive medication prescription will be collected through electronically prescriptions found on the State Enterprise Registry Center (ESPBI IS e. prescription subsystems data on prescribed drugs (48). Each prescription contains information on patient's sex, age group, the specialist of the physician who prescribed the medication, the city where the prescription was made, the ATC code of the antihypertensive drugs and the disease code from the International Statistical Classification of Diseases and Related Health Problems (ICD) (49). Antihypertensive drugs with the following ATC codes were selected for analysis: C02A, C03, C07, C08 and C09A, C09B, C09C and C09D.

3.1.3 Method of analysis

The collected data for this analysis contained 1,855,031 prescriptions from March 2022. The results were observed through pivotal tables and diagrams created in Microsoft Excel. In the Central Registry database, there were three files that contained electronically prescribed medication collected from a 10-day period in March. The first file (from March 1st to March 10th) contained 634,318 prescriptions for all prescribed medication for different health problems. In the second file (from March 11th to March 21st) there were 569,361 prescriptions. Lastly, the third file (from March 21st to March 31st) contained 651,352 prescriptions (48). Microsoft Excel was used to filter the prescribed drug data. Only drugs which ATC code started with C02A, C03, C07, C08, C09A, C09B, C09C and C09D were used for the analysis. Secondly, the data was filtered by the disease ICD code. First, all health conditions that received antihypertensive drug prescriptions were analyzed. Then for non-hypertensive disease analysis, prescriptions that had ICD codes that started with chapter I (diseases of the circulatory system) and D (diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism) were excluded to make it easier to determine for which non-hypertensive diseases antihypertensive drugs were prescribed. Later the selected data was analyzed by filtered by age groups, sex, health specialists who wrote the prescriptions. This made it possible to determine antihypertensive drug usage tendencies in Lithuania.

3.1.4 Ethical considerations

During the investigation, the analyzed prescription records from the State Enterprise Central Registry were depersonalized, to exclude any personal patient or health specialist information. The data had already been gathered before this study. No permits or signed documents were required to comply with data collection laws.

Even though health specialists commonly prescribe antihypertensive drugs for the treatment of diseases other than hypertension, there has not been sufficient research done regarding this topic in Lithuania. This study may give a start for new research to take place and to analyze this topic further.

4   RESULTS AND DISCUSSION

The total number of prescriptions issued between January and December 2022 was 18,390,697. In the same year, the total number of prescriptions for centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C), and angiotensin II receptor blockers, combinations (C09D), was 4,596,196. Consequently, the cardiovascular drugs included in the study, together accounted for 25% of all prescriptions (Figure 4).

Among all cardiovascular drug prescriptions (C class drugs), 34.7% of them were prescriptions for renin-angiotensin system (RAS) - acting agents (C09) which made it the most prescribed antihypertensive drug class (Appendix 1). Clinical evidence suggests that ARBs play a significant protective role against cardiovascular and renal damage, as well as reducing the occurrence of major adverse cardiovascular events, in patients with hypertension (50). Also, neutral metabolic effect has been reported upon ARBs administration, in contrast to other antihypertensive agents, such as beta-blockers and diuretics (50). Therefore current US and European guidelines recommend ACEi and ARBs as a suitable first choice for hypertension treatment together with calcium channel blockers (CCBs) and thiazide diuretics (50).

In comparison, among the drug classes selected for this analysis, beta-blockers (C07) were prescribed the most (29.4%) (Appendix 2). In 2023, guidelines were updated to position beta-blockers as beneficial options at any stage of the treatment algorithm, provided there is a guideline-directed indication or other conditions where their benefits are apparent (9). Previously, beta-blockers were not commonly recommended as a first-choice antihypertensive medication (9). However, clinical practice has demonstrated their positive effects on various clinical conditions that often accompany hypertension (9). Consequently, their use, either as monotherapy or in combination with other medications, has become more common in clinical practice (9).
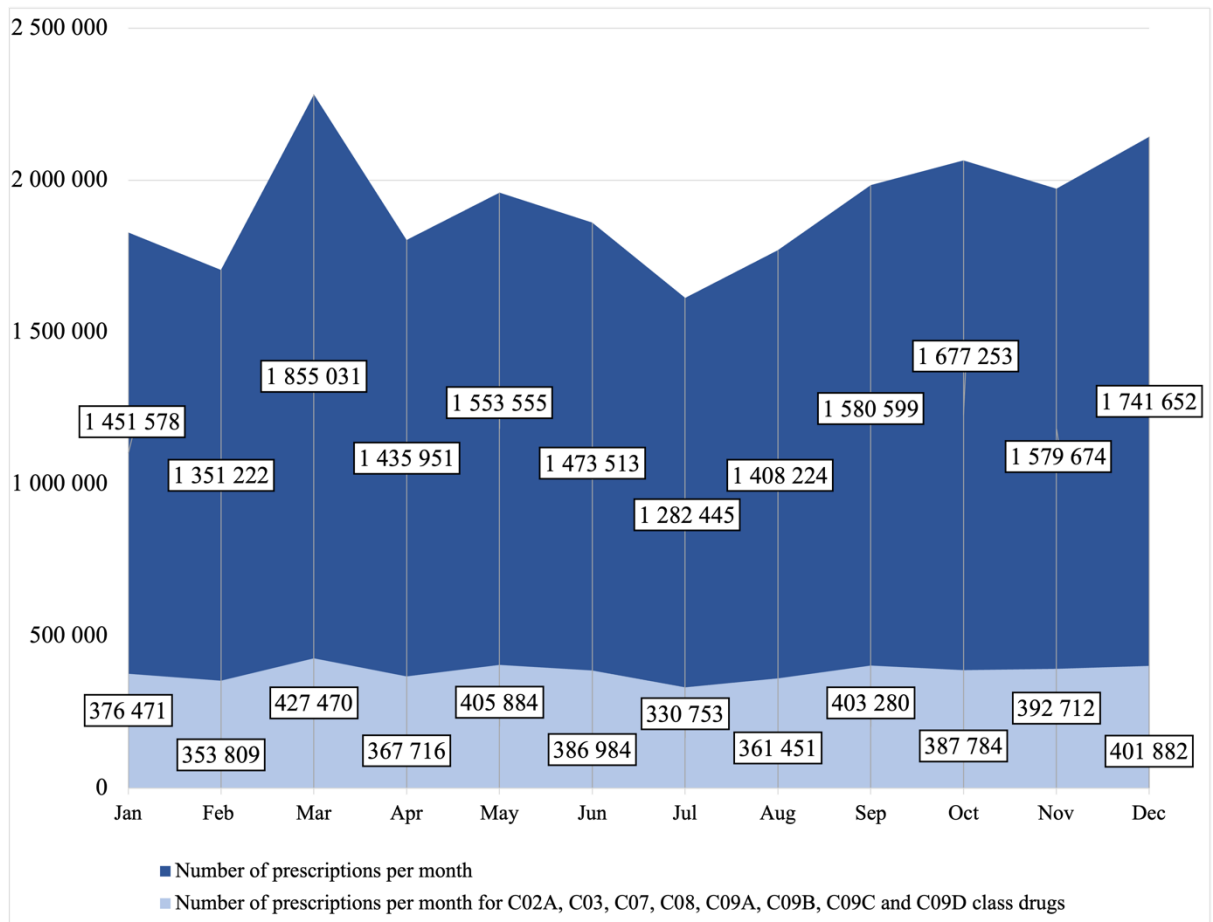
Figure 4. Number of prescriptions for antihypertensive drugs in 2022 each month

In 2022, the months of March, October, and December had the highest overall prescription numbers: 1,855,031, 1,677,253, and 1,741,652 prescriptions, respectively (Figure 1). However, when considering the selected cardiovascular drugs specifically, March, May, and September recorded the highest numbers of prescriptions: 434,580 in March, 412,653 in May, and 409,847 in September (Figure 4). Detailed numbers for all included drug classes are presented in Table 7.

Table 7. Number of prescriptions in each month of 2022

Month	Number of prescriptions per month*	C02A	C03	C07	C08	C09A	C09B	C09C	C09D
22-Jan	376,471	25,114	41,183	110,955	22,412	49,193	79,989	18,075	29,550
22-Feb	353,809	23,641	38,886	103,964	21,166	45,661	75,341	17,103	28,047
22-Mar	427,470	28,041	47,468	125,974	25,541	55,306	90,241	20,752	34,147
22-Apr	367,716	24,064	42,096	108,253	21,757	45,891	77,627	18,053	29,975
22-May	405,884	26,323	47,052	117,937	23,993	51,136	85,710	20,060	33,673
22-Jun	386,984	25,155	46,425	113,027	22,396	47,554	81,064	19,168	32,195
22-Jul	330,753	21,442	40,147	98,562	18,858	39,281	69,570	15,891	27,002
22-Aug	361,451	22,861	43,555	107,843	20,485	43,149	75,708	17,545	30,305
22-Sep	403,280	26,204	45,882	119,146	23,610	49,879	84,575	19,795	34,189
22-Oct	387,784	25,127	43,791	114,192	22,720	47,878	81,496	18,978	33,602
22-Nov	392,712	24,946	45,130	114,626	23,090	49,178	82,017	19,552	34,173
22-Dec	401,882	26,092	45,811	117,467	23,664	49,632	83,648	19,720	35,848

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

In March, May, and September, the main classes of cardiovascular drugs used for treating hypertension exhibited the highest prescription rates (Table 7).

Given the findings of the study, which revealed that the highest numbers of prescriptions for these drugs occurred in March, a decision was made to conduct a more in-depth investigation into this specific month (Table 7).

In March 2022 in total there were 427,470 prescriptions for all the selected antihypertensive drugs (Table 7). Out of these prescriptions, 29.5% were for beta-blockers (C07); therefore, it was the most frequently prescribed cardiovascular drug during this month (Table 1). Lithuanian guidelines recommend beta-adrenergic blockers (C07) as an initial treatment for patients with recurrent myocardial infarction, as well as those without a history of myocardial infarction,

provided there are no contraindications (36) . They are also prescribed for conditions such as angina pectoris and heart failure (36).

All antihypertensive drugs were primarily prescribed for diseases of the circulatory system (disease code starts with ICD-chapter I) - in total 422,437 prescriptions. The second most common diagnoses were diseases of the genitourinary system (ICD chapter N) (Table 2), for which 604 diuretics (C03) prescriptions were prescribed. There were 716 prescriptions for beta-blockers to treat nervous system diseases (ICD-chapter G). Calcium channel blockers (C08) - 45 prescriptions, and angiotensin II receptor blockers (C09C) - 38 prescriptions, were sometimes prescribed for endocrine, nutritional, and metabolic diseases (ICD-chapter E). ACE inhibitors (C09A) were occasionally prescribed for ICD-chapter R, i.e., 'symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified' - 307 prescriptions.

In March 2022, 98.8% of prescriptions of antihypertensive drugs were prescribed for diseases of the circulatory system (ICD - Chapter I). The remaining 1.2% of prescriptions were for other disease groups. Figure 2 illustrates the distribution of prescriptions among all disease groups (ICD-chapters) excluding circulatory system diseases (ICD - Chapter I) (Figure 5).
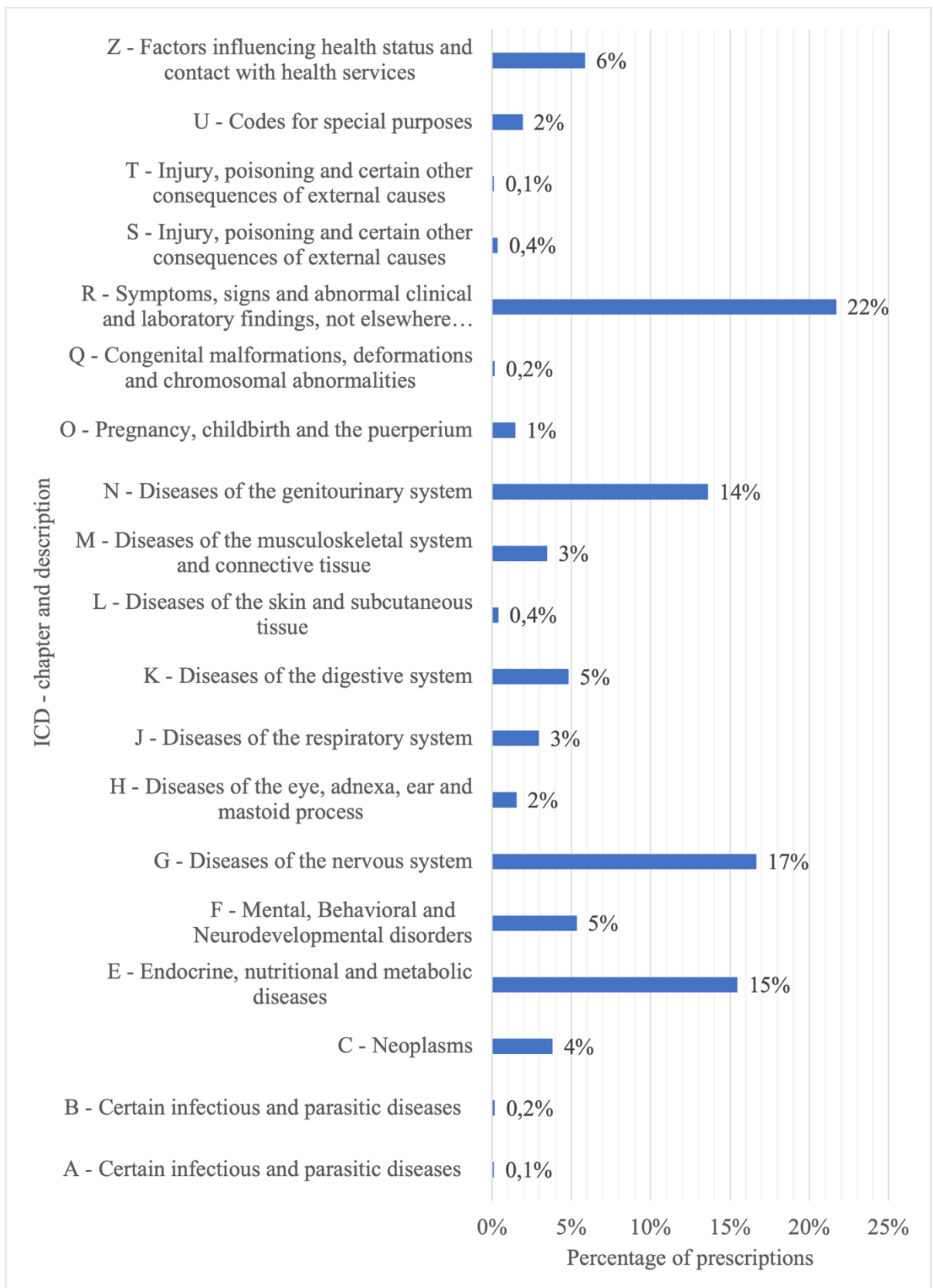
Figure 5. Distribution of prescriptions of antihypertensives on other ICD-chapters than cardiovascular diseases (I) in March 2022.

Table 8. Number of prescriptions for other extrapyramidal and movement disorders, such as essential tremor, drug-induced tremor, other specified forms of tremor, other specified and unspecified extrapyramidal and movement disorders (G25) treatment in 2022.

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
G25	Other extrapyramidal and movement disorders, such as essential tremor, drug-induced tremor, other specified forms of tremor, other specified and unspecified extrapyramidal and movement disorders.	476	0.0% - C02A 0.0% - C03 100.0% - C07 0.0% - C08 0.0% - C09A 0.0% - C09B 0.0% - C09C 0.0% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

One of the diseases for which many prescriptions for antihypertensives were prescribed in March 2022 fall under the ICD - chapter G25 (Other extrapyramidal and movement disorders, such as essential tremor, drug-induced tremor, other specified forms of tremor, other specified and unspecified extrapyramidal and movement disorders) (Table 8). For this disease treatment only diuretics (C07) were prescribed.

The preferred medications for treating essential tremor (ET) are β-blockers, typically propranolol, and primidone. Both of these medications have received a level A recommendation and can be selected as initial treatments for ET based on factors such as comorbidities and possible side effects (51). Approximately 50%–60% of patients experience improvement, with hand tremors showing the most significant improvement and head or voice tremors demonstrating the least improvement (51). Twelve controlled studies have revealed the effectiveness of the beta blocker Propranolol (C07) in managing limb tremor in ET, with accelerometry showing a reduction of around 50%. Treatment with beta blockers leads to improvement in two-thirds of patients with ET (52).

Table 9. Number of prescriptions for Essential (primary) hypertension (I10) treatment in 2022.

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I10	Essential (primary) hypertension	7,206	1.9% - C02A 1.7% - C03 32.7% - C07 4.0% - C08 33.0% - C09A 20.4% - C09B 4.1% - C09C 2.2% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

For the treatment of essential (primary) hypertension the most prescribed antihypertensives were beta blockers (C07) and ACE inhibitors (C09A) (Table 9).

For monotherapy ACE inhibitors, ARBs, calcium channel blockers, beta-blockers, diuretics, or alternative medications if none of the antihypertensive drugs prove effective, can be used (36). When treating with multiple drugs, the recommended approach involves combining drugs that target the renin-angiotensin system (such as ACE inhibitors or ARBs, known as RAS blockers) with a calcium channel blocker or diuretic (36). If the desired blood pressure target is not achieved with a two-drug combination, a three-drug combination (RAS blocker, calcium channel blocker, and diuretic) may be prescribed (36).

Table 10. Number of prescriptions for Hypertensive heart disease (I11) treatment in 2022.

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I11	Hypertensive heart disease	379,898	7.3% - C02A 6.0% - C03 29.7% - C07 6.4% - C08 13.6% - C09A 23.2% - C09B 5.3% - C09C 8.5% - C09D

. for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

While treating hypertensive heart disease (I11), beta blockers (C07) and ACE inhibitors, combinations (C09B) were prescribed the most (Table 10).

According to Lithuanian guidelines for the treatment of hypertensive heart disease and its comorbid medical conditions, beta-blockers (C07), ACE-inhibitors (C09A), and combinations thereof (C09B), as well as calcium-channel blockers (C08) may be prescribed (53).

Table 11. Number of prescriptions for Secondary hypertension (I15) treatment in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I15	Secondary hypertension	722	1.7% - C03 32.7% - C07 4.0% - C08 33.0% - C09A 20.4% - C09B 4.1% - C09C 2.2% - C09D 5.7% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

According to data for the treatment of secondary hypertension (I15), beta blockers (C07) and ACE inhibitors (C09A) were prescribed the most (Table 11). A study suggests that ACE inhibitors and ARBs are preferred antihypertensive medications for individuals with unilateral renal artery stenosis (14). Nevertheless, their usage is contraindicated in cases of bilateral renal artery stenosis due to the potential for precipitating rapid renal dysfunction. Alternative pharmacological treatment choices include calcium channel blockers (C08) and thiazide diuretics (C03) (14). Maintaining proper blood pressure levels is crucial in managing chronic kidney disease (CKD), and modern recommendations suggest renin-angiotensin (RA) antagonists as the primary pharmacological approach to treating hypertension in CKD (14).

Table 12. Number of prescriptions for Angina pectoris (I20) treatment in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I20	Angina pectoris	2,109	1.0% - C02A 7.2% - C03 83.5% - C07 2.1% - C08 2.0% - C09A 2.8% - C09B 0.4% - C09C 1.0% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

For angina pectoris (I20) treatment beta blockers (C07) were prescribed the most (Table 12). According to Lithuanian guidelines, calcium channel blockers (C08) and beta blockers (C07) are recommended as treatments for angina pectoris (34).

Table 13. Number of prescriptions for Acute myocardial infarction (I21) treatment in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I21	Acute myocardial infarction	359	0.0% - C02A 9.8% - C03 65.5% - C07 0.0% - C08 20.9% - C09A 3.3% - C09B 0.0% - C09C 0.6% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

While treating acute myocardial infarction (I21) beta blockers (C07) were prescribed the most. ACE inhibitors (C09A)were the second most prescribed antihypertensive for this disease (Table 13).

Combining beta blockers (BABs) (C07) with a medication from other primary classes of antihypertensive drugs present as an option for a specific clinical indication treatment such as angina pectoris, post-myocardial infarction, heart failure, and additional conditions (34). Examples of pairings different class antihypertensives: ACEIs (or ARBs) (C09) with BABs (C07) or CCBs (C08), CCBs (C08) with diuretics or BABs (C07), and BABs (C07) with diuretics (C03) (34).

Table 14. Number of centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C), and angiotensin II receptor blockers, combinations (C09D) class drug prescriptions for Paroxysmal tachycardia (I47) treatment in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I47	Paroxysmal tachycardia	408	0.0% - C02A 0.0% - C03 73.8% - C07 25.0% - C08 0.5% - C09A 0.5% - C09B 0.3% - C09C 0.0% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

For the treatment of paroxysmal tachycardia (I47), beta blockers (C07) were prescribed the most, followed by calcium channel blockers (C08) as the second most prescribed antihypertensive for this disease (Table 14).

As one of the treatment options drugs like ivabradine, beta-blockers, or calcium channel blockers can be prescribed to lower the pulse (54).

Table 15. Number of prescriptions for Atrial fibrillation and flutter (I48) treatment in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I48	Atrial fibrillation and flutter	2,810	0.4% - C02A 5.7% - C03 84.9% - C07 4.5% - C08 1.4% - C09A 2.3% - C09B 0.2% - C09C 0.6% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

For the treatment of atrial fibrillation and flutter (I48) beta blockers were prescribed the most (Table 15).

For the treatment of atrial fibrillation and flutter, two groups of drug combinations can be applied: ACEI (C09A) or ARB (C09C) + BAB (C07) or non-dihydropyridine CCB (C08), and BAB (C07) + dihydropyridine CCB (C08) (36).

Table 16. Number of prescriptions for Other cardiac arrhythmias (I49) treatment in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I49	Other cardiac arrhythmias	1,374	0.1% - C02A 0.4% - C03 84.9% - C07 13.5% - C08 0.4% - C09A 0.3% - C09B 0.2% - C09C 0.2% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

Beta blockers (C07) were the most prescribed medication for the treatment of other cardiac arrhythmias (I49), followed by calcium channel blockers (C08) as the second most prescribed antihypertensive for this disease (Table 16).

European guidelines recommend treating arrhythmias with antiarrhythmics (C01B), beta blockers (C07), and calcium channel blockers (C08) (55).

Table 17. Number of prescriptions for Heart failure (I50) treatment in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
I50	Heart failure	26,768	<0.1% - C02A 83.7% - C03 9.5% - C07 0.1% - C08 1.4% - C09A 0.1% - CO9B <0.1% - C09C 5.1% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

For heart failure (I50) treatment diuretics (C03) were prescribed the most (Table 17). According to the 2021 ESC Guidelines acute and chronic heart failure should be treated with ACE inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), beta-blockers, and sodium-glucose co-transporter 2 (SGLT2) inhibitors to decrease mortality resulting from heart failure and sudden cardiac death (SCD) (55).

Table 18. Number of prescriptions Chronic kidney disease (CKD) treatment in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
N18	Chronic kidney disease (CKD)	584	0.2% - C02A 97.1% - C03 0.3% - C07 0.2% - C08 0.9% - C09A 0.2% - C09B 0.9% - C09C 0.3% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

For the treatment of chronic kidney disease (CKD) (N18) diuretics (C03) were prescribed the most (Table 18). Reducing salt intake and using diuretics are key strategies for managing blood pressure in chronic kidney disease (CKD).

The guidelines suggest starting treatment with a ACEi or ARB and CCB for both diabetic and non-diabetic chronic kidney disease (CKD) patients (56).

The recent CLICK trial has provided evidence of the effectiveness of chlorthalidone, a long-acting diuretic similar to thiazides, in controlling high blood pressure in stage 4 CKD patients with poorly managed hypertension (57).

Table 19. Number of prescriptions for Abnormalities of heart beat (R00) in 2022

ICD-chapter	ICD code description	Total number of prescriptions	Distribution of prescriptions for antihypertensives*
R00	Abnormalities of heart beat	514	0.0% - C02A 0.6% - C03 93.8% - C07 3.5% - C08 1.6% - C09A 0.6% - C09B 0.0% - C09C 0.0% - C09D

* for C02A, C03, C07, C08, C09A, C09B, C09C and C09D class drugs

C02A - centrally acting antihypertensives, C03 - diuretics, C07 - beta blockers, C08 - calcium channel blockers, C09A - ACE inhibitors, C09B - ACE inhibitors, combinations, C09C - angiotensin II receptor blockers, C09D - angiotensin II receptor blockers, combinations.

While treating abnormalities of the heart beat (R00) beta blockers were prescribed the most (C07) (Table 19).

In case of tachycardia according to European guidelines beta blockers (C07) are recommended for treatment (58).

Findings reveal that, out of all prescriptions for antihypertensive drugs in March, 90.7% were for diseases heavily associated with hypertension, such as hypertension (essential and secondary) - around 1.9%, and 88.9% were for prescriptions for hypertensive heart disease (I11). Within the 1.9% of prescriptions for hypertension (essential and secondary), 2.9% were for antihypertensives (C02A), 2.0% for diuretics (C03), 32.3% for beta blockers (C07), 5.0% for calcium channel blockers (C08), 31.8% for ACE inhibitors (C09A), 19.1% for ACE inhibitor combinations (C09B), 4.4% for angiotensin II receptor blockers (C09C), and 2.5% for angiotensin II receptor blocker combinations (C09D) (Table 9) (Table 11). Regarding the 88.9% of prescriptions for hypertensive heart disease (I11), 7.3% were for centrally acting antihypertensives (C02A), 6.0% for diuretics (C03), 29.7% for beta blockers (C07), 6.4% for calcium channel blockers (C08), 13.6% for ACE inhibitors (C09A), 23.2% for ACE inhibitor combinations (C09B), 5.3% for angiotensin II receptor blockers (C09C), and 8.5% for angiotensin II receptor blocker combinations (C09D) (Table 10).

4.1.1 Distribution of cardiovascular drug prescriptions by sex

The statistical data showed that out of all 427,470 prescriptions for antihypertensive drugs in March 2022, 65% were prescribed for women and 35% for men. Within the total number of prescriptions for cardiovascular drugs in March, 0,1% did not specify the patient's sex (Figure 5) (Table 20).
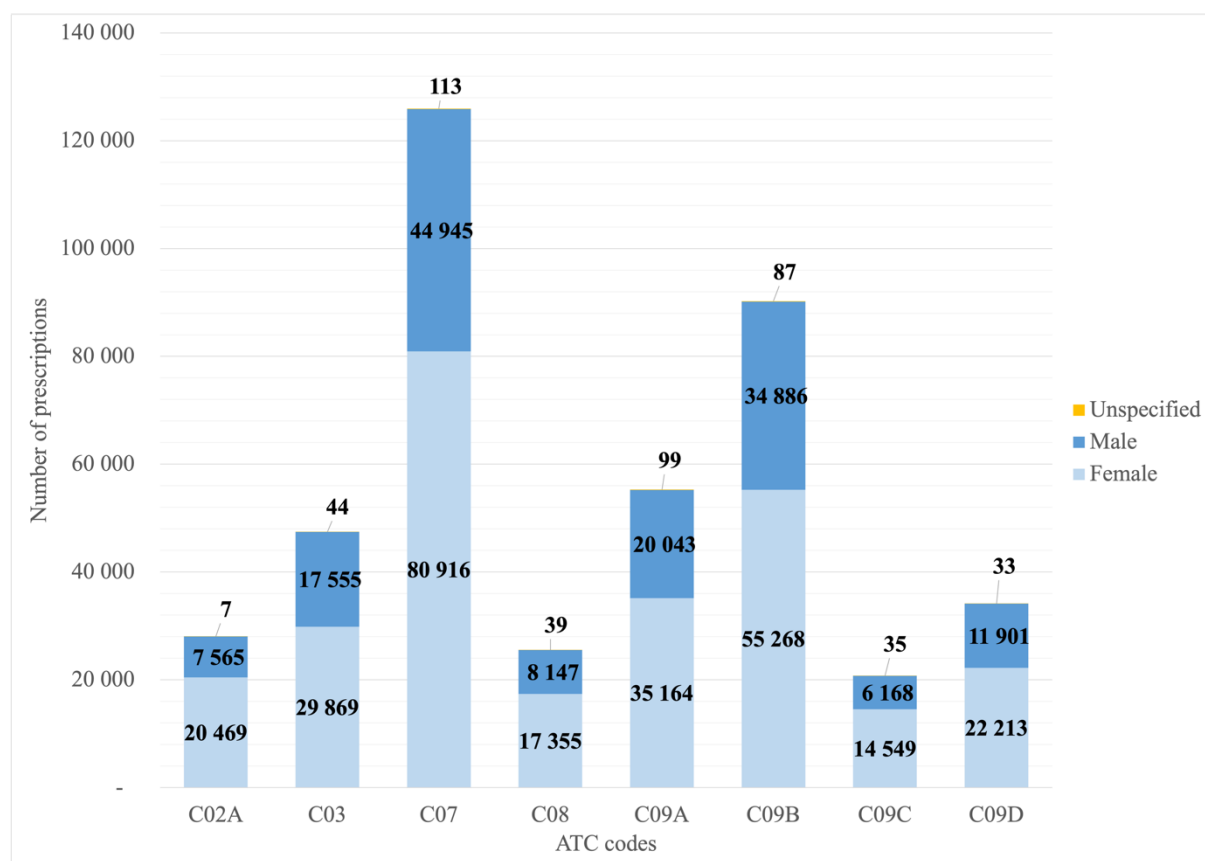

Figure 6. Number of prescriptions for different antihypertensive drug classes by gender in March 2022.

Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C), and angiotensin II receptor blockers, combinations (C09D) class drugs.

Table 20. Number of prescribing among men and women in March 2022

Sex (female, male)	C02A*	C03*	C07*	C08*	C09A*	C09B*	C09C*	C09D*
Female	73,0%	62,9%	64,2%	67,9%	63,6%	61,2%	70,1%	65,1%
Male	27,0%	37,0%	35,7%	31,9%	36,2%	38,7%	29,7%	34,9%
Unspecified	0,0%	0,1%	0,1%	0,2%	0,2%	0,1%	0,2%	0,1%

* Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C), and angiotensin II receptor blockers, combinations (C09D) class drugs

For women the most prescribed centrally acting antihypertensive (C02A) was Metildopa (C02AB01). For men Moxonidine (C02AC05) was the most prescribed centrally acting antihypertensive. Rilmenidine (C02AC06) was prescribed for women the most (Table 21).

Out of diuretic (C07) class Indapamide (C03BA11) was prescribed for women the most. For men the most prescribed diuretic was Torasemide (C03CA04). Spironolactone (C03DA01) was prescribed for females the most (Table 21).

Thiazides can reduce the risk of osteoporotic fractures, which often afflict women. They are also a primary choice in treating patients, often men, with recurrent calcium oxalate nephrolithiasis and hypercalciuria. However, thiazides can lead to hypokalemia and hyponatremia, particularly affecting women, while men may experience hyperuricemia and gout. Men are also prone to sexual dysfunction, notably erectile dysfunction, during thiazide therapy. Thiazides are rarely prescribed during pregnancy due to concerns regarding decreased placental perfusion and reduced plasma volume, which are associated with preeclampsia.

For men the most prescribed beta blocker (C07) was Nebivolol (C07AB12). For women Metoprolol (C07AB02) was prescribed the most. Bisoprolol (C07AB07) was prescribed for women more often than for men (Table 21).

Beta blockers (C07) can cause erectile dysfunction (59).

Data shows that for women the most prescribed calcium channel blocker (C08) was Lercanidipine (C08CA13). For men Amlodipine (C08CA01) was prescribed the most. Amlodipine and diuretics (C08GA02) combination was more often prescribed for women (Table 21).

Women are more prone to experiencing side effects such as dizziness, flushing, headache, and tibial edema from calcium channel blockers (C08) (60). However, despite these potential side effects, calcium channel blockers are considered safe for use during pregnancy and can serve as a treatment option for Raynaud phenomenon, a condition that affects women more often (60).

Out of ACE inhibitors (C09A) for women Captopril (C09AA01) was prescribed the most. For men Zofenopril (C09AA15) was prescribed the most. Perindopril (C09AA04) was prescribed for women more often than for men (Table 21).

For women the most prescribed ACE inhibitors, combinations (C09B) Perindopril Arginine/Indapamide (C09BA04) was prescribed the most. For men Perindopril Arginine/Indapamide/Amlodipine (C09BX01) was prescribed the most. Bisoprolol

fumarate/Perindopril arginine (C09BX02) was more often prescribed for women than men (Table 21).

Out of Angiotensin II receptor blockers (C09C) for men Telmisartan (C09CA07) was the most prescribed. For women Olmesartan medoxomil (C09CA08) was the most prescribed. Valsartan (C09CA03) was prescribed for women more often.

For men the most prescribed Angiotensin II receptor blockers, combinations (C09D) was Olmesartan medoxomil/Amlodipine (C09DB02). For women Valsartan/Hydrochlorothiazide (C09DA03) was prescribed the most (Table 21).

Olmesartan Medoxomil/Amlodipine/Hydrochlorothiazide (C09DX03) combination was prescribed for women more often (Table 21).

ACE inhibitors and angiotensin receptor blockers (ARB) are commonly prescribed for both women and men, but they have more adverse effects on women than on men (5). ACE inhibitors more often cause coughing as a side effect for women than men (5). Both ACE inhibitors and angiotensin receptor blockers (ARB) are contraindicated in pregnancy (5).

Additionally, one of the most prescribed antihypertensives (C02) for men was Doxazosin (C02CA04) (Appendix 4). Alpha blockers are not considered to be a primary treatment, but they play a pivotal role in managing lower urinary tract symptoms in men with benign prostatic hyperplasia (BPH). This is because they alleviate smooth muscle tension not only in blood vessels but also in the urethra and bladder neck. Additionally, doxazosin has the potential to alleviate symptoms of erectile dysfunction.

Table 21. Most commonly antihypertensives* by sex in March 2022

ATC code	Drug name	Female	Male	Unspecified	Total
Centrally acting antihypertensive drugs (C02A)					
C02AB01	Metildopa	99.3%	0.7%	<0.1%	146
C02AC05	Moxonidine	72.5%	27.5%	<0.1%	15,556
C02AC06	Rilmenidine	73.4%	26.6%	<0.1%	12,338
Diuretics (C03)					
C03CA04	Torasemide	60.7%	39.2%	0.1%	19,19
C03DA01	Spironolactone	63.7%	36.2%	0.1%	22,026
C03BA11	Indapamide	70.1%	29.7%	0.2%	4,877
Beta blockers (C07)					
C07AB02	Metoprolol	66.7%	33.3%	<0.1%	47,579
C07AB07	Bisoprolol	63.1%	36.6%	0.4%	17,354
C07AB12	Nebivolol	61.8%	38.1%	0.1%	37,229
Calcium channel blockers (C08)					
C08CA01	Amlodipine	62.7%	37.0%	0.3%	8,491
C08CA13	Lercanidipine	71.8%	28.1%	0.1%	7,983
C08GA02	Amlodipine and diuretics	63.6%	36.4%	<0.1%	3,081
ACE inhibitors (C09A)					
C09AA01	Captopril	77.2%	22.6%	0.2%	8,883
C09AA04	Perindopril	61.6%	38.3%	0.1%	21,316
C09AA15	Zofenopril	58.0%	42.0%	<0.1%	11,733
ACE inhibitors, combinations (C09B)					
C09BA04	Perindopril Arginine/Indapamide	67.0%	32.9%	0.1%	19,974
C09BX02	Bisoprolol fumarate/Perindopril arginine	59.9%	40.1%	0.1%	2,113
C09BX01	Perindopril Arginine/Indapamide/Amlodipine	57.0%	43.0%	0.1%	15,303
Angiotensin II receptor blockers (C09C)					
C09CA03	Valsartan	70.0%	30.2%	0.2%	9,046

C09CA07	Telmisartan	68.6%	31.3%	0.1%	4,395
C09CA08	Olmesartan medoxomil	72.0%	28.1%	<0.1%	3,84
Angiotensin II receptor blockers, combinations (C09D)					
C09DA03	Valsartan/Hydrochlorothiazide	72.2%	27.7%	0.1%	7,58
C09DX03	Olmesartan medoxomil/Amlodipine/Hydrochlorothiazide	62.9%	37.1%	<0.1%	6,022
C09DB02	Olmesartan medoxomil/Amlodipine	60.7%	39.2%	0.1%	3,813

Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C), and angiotensin II receptor blockers, combinations (C09D) class drugs

4.1.2 Distribution of cardiovascular drug prescriptions by age groups

Among the main classes of prescriptions for antihypertensive drugs analyzed in this study, angiotensin II receptor blockers (C09C) were the least often prescribed, accounting for 4.9% (Figure 7).
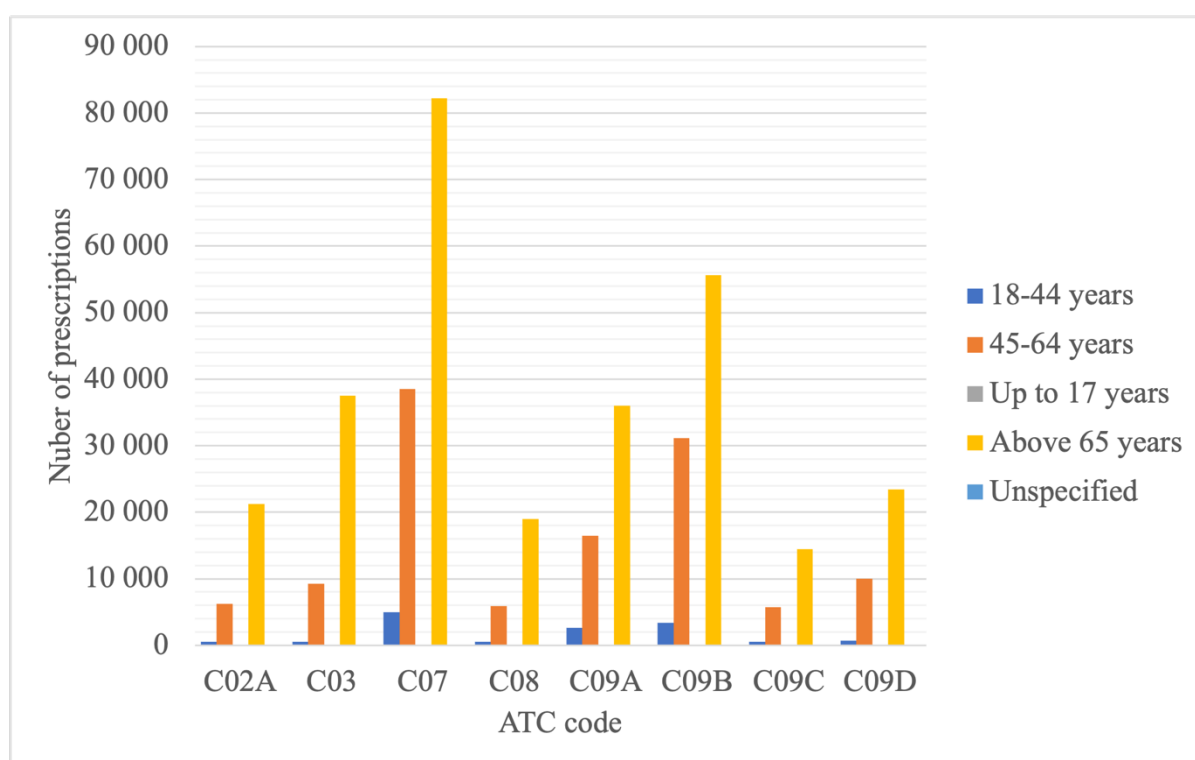

Figure 7. Number of prescriptions among different age groups in March 2022

Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

Out of all prescriptions of antihypertensives, 0.1% were prescribed for patients aged up to 17 years, 3.3% for those aged 18-44 years, 28.8% for patients aged 45-64 years, and 67.7% for patients aged 65 years and above. 0.1% of prescriptions did not specify the patient's age group.
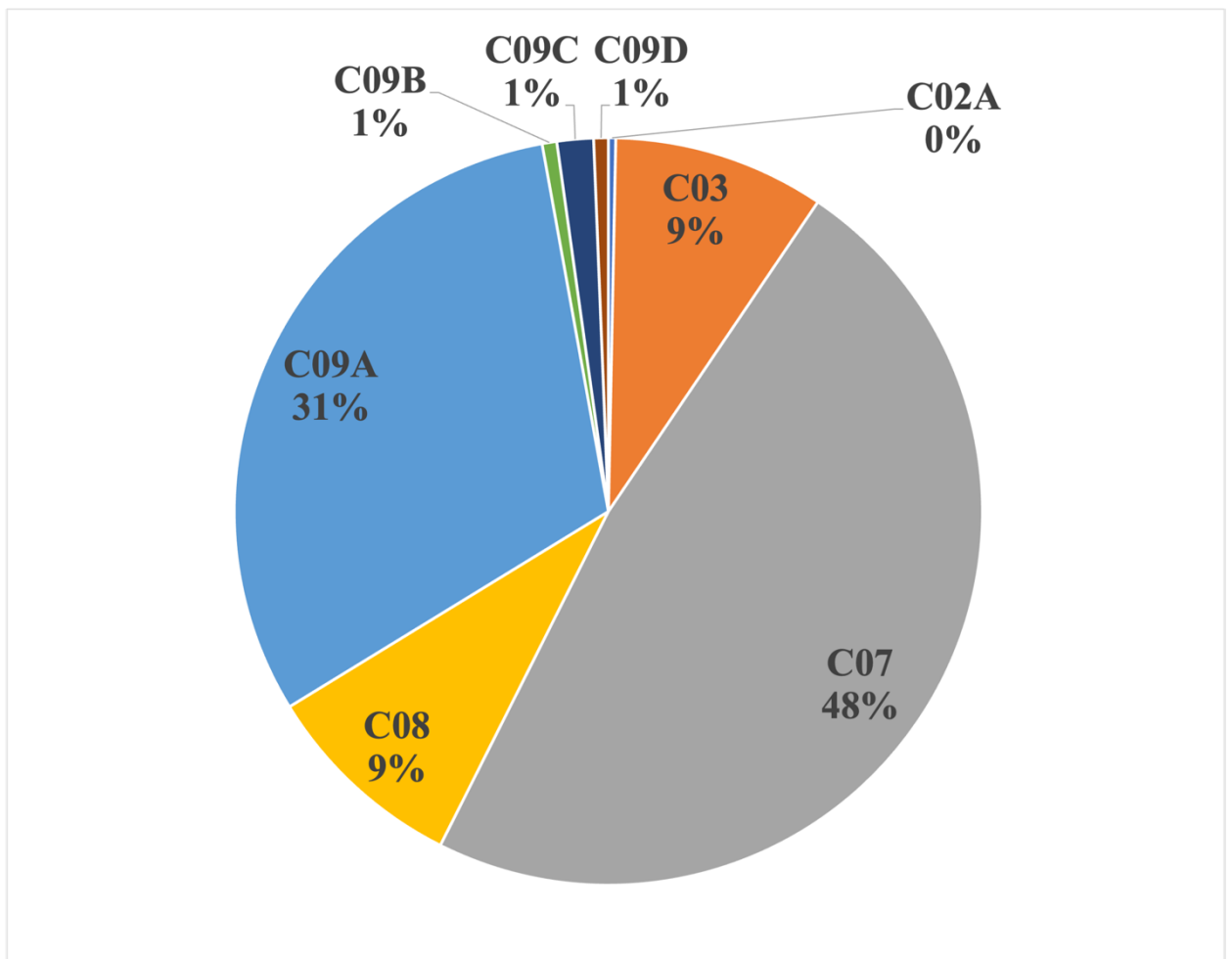
Figure 8. Percentages showing the number of prescriptions dispensed for a given class of antihypertensive medicines for up to 17 age group compared to the total number of prescriptions dispensed in March 2022 for the corresponding drug classes.

Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

For people aged up to 17 years most commonly prescribed antihypertensives were beta blockers (CO7) and ACE inhibitors (C09A). In general this age group received the least amount of prescriptions out of all the other age groups (Figure 8).
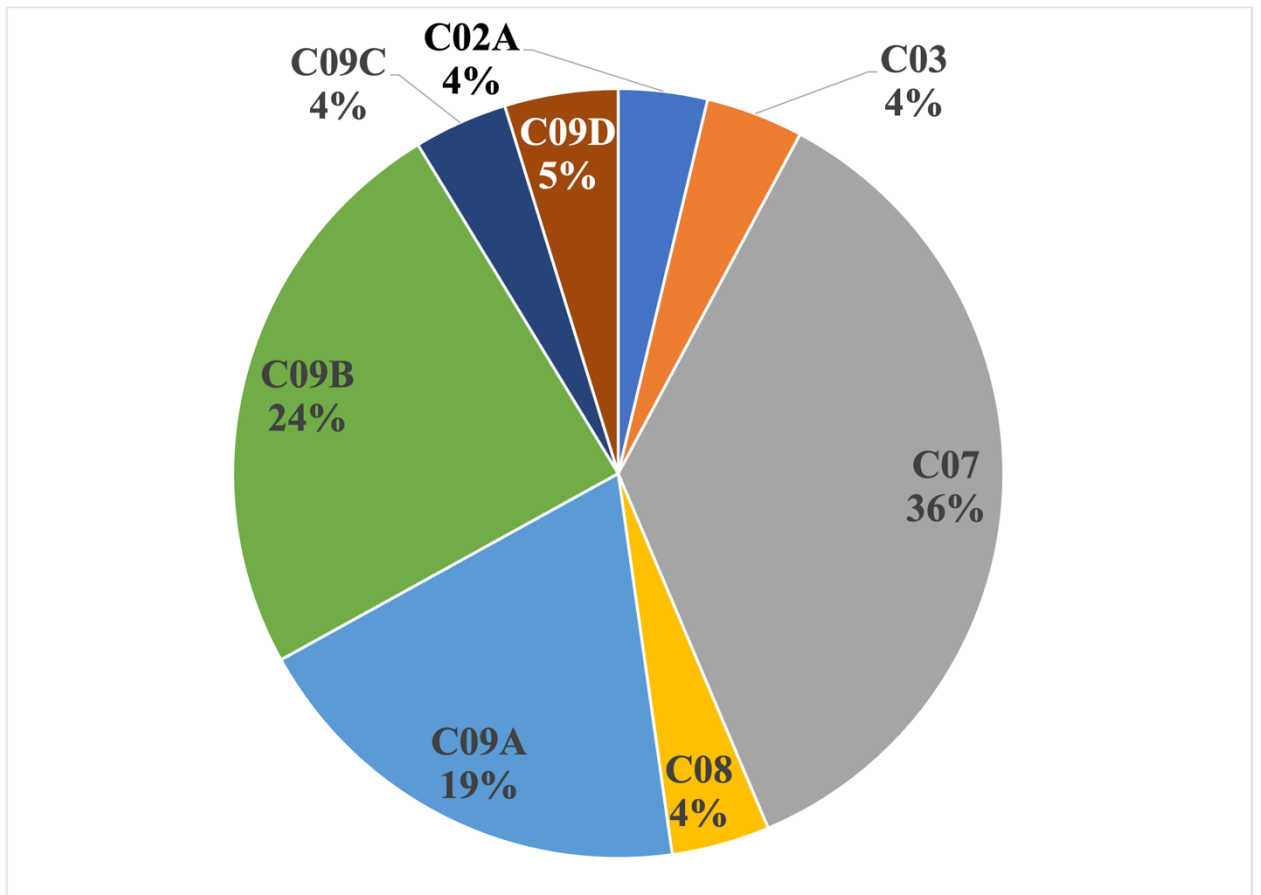
Figure 9. Percentages showing the number of prescriptions dispensed for a given class of antihypertensive medicines for the 18-44 age group compared to the total number of prescriptions dispensed in March 2022 for the corresponding drug classes.

Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

For people aged from 18 to 44 the most common antihypertensive drug prescriptions were ACE inhibitors, combinations (C09B) and beta blockers (C07) (Figure 9).
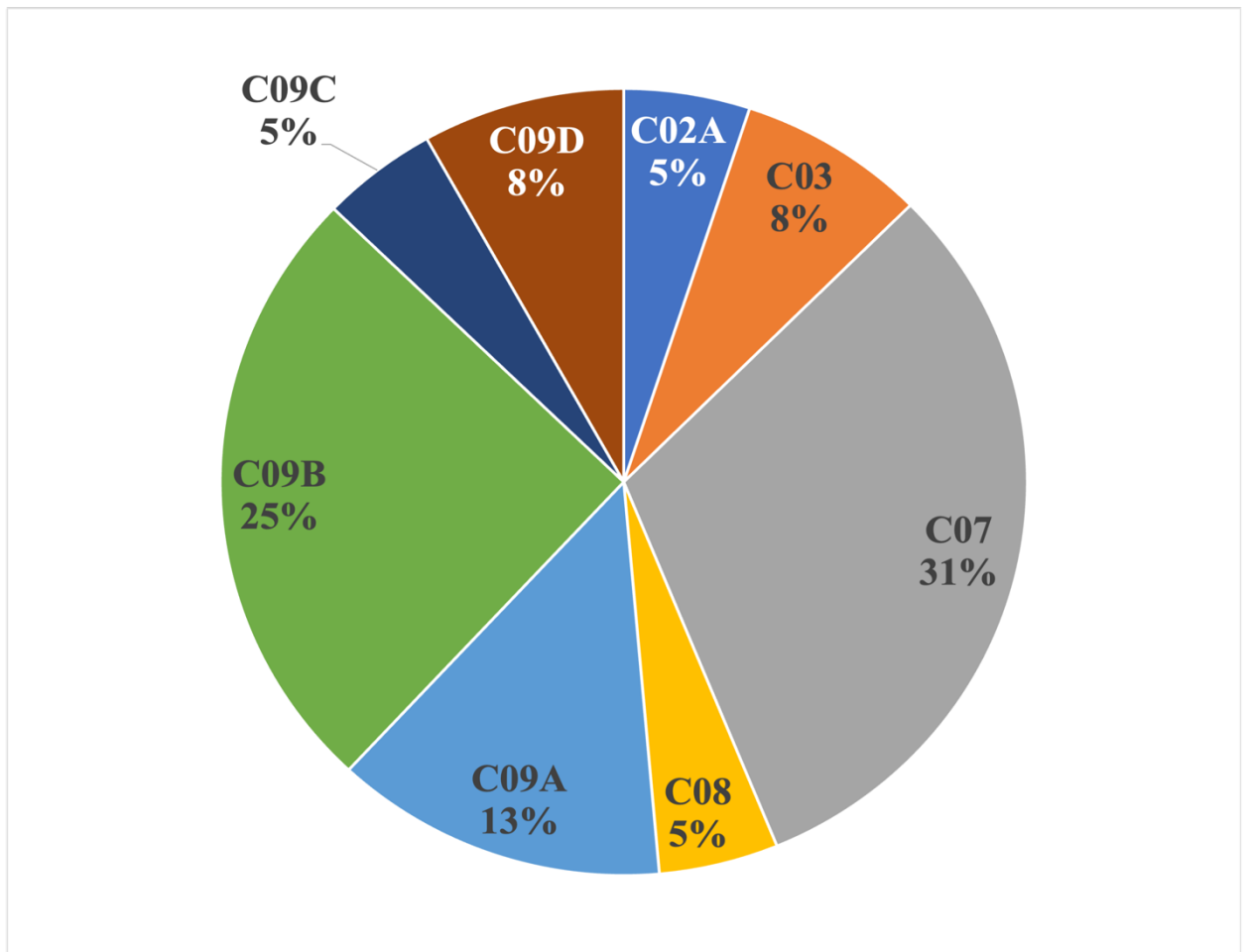
Figure 10. Percentages showing the number of prescriptions dispensed for a given class of antihypertensive medicines for the 45 - 64 age group compared to the total number of prescriptions dispensed in March 2022 for the corresponding drug classes

Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

For patients in the 45 - 64 years age group the most prescribed antihypertensive class was ACE inhibitors, combinations (C09B). The second most prescribed class for this age group was beta blockers (C07) (Figure 10).
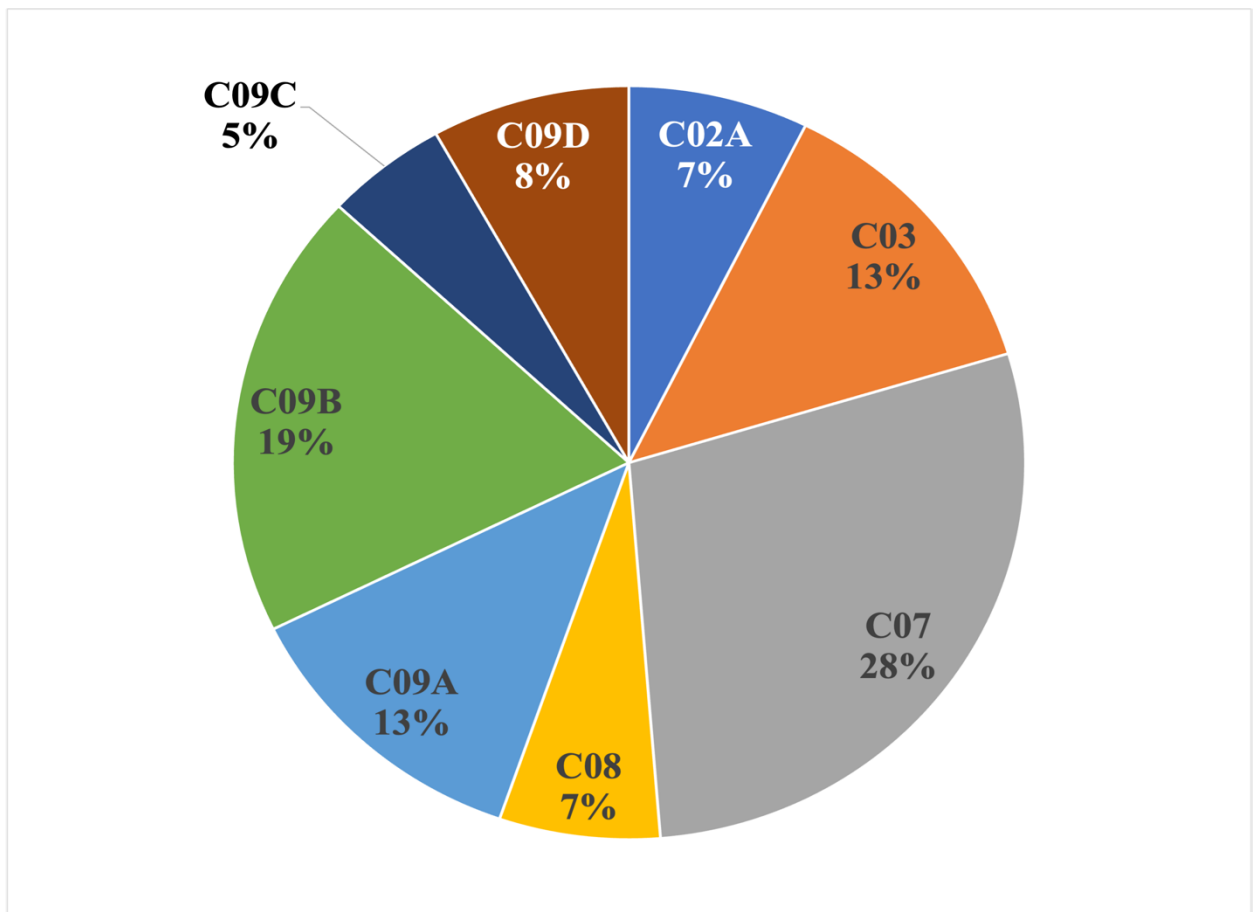
Figure 11. Percentages showing the number of prescriptions dispensed for a given class of antihypertensive medicines for above 65 age group compared to the total number of prescriptions dispensed in March 2022 for the corresponding drug classes.

Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

For patients who were above 65 years beta blockers (C07), ACE inhibitors, combinations (C09B) were prescribed the most (Figure 11).

The remaining percentages for each antihypertensive drug class represent prescriptions that did not specify the age group of the patient. Specifically, for diuretics (C03), beta blockers (C07), ACE inhibitors combinations (C09B), and angiotensin II receptor blockers combinations (C09D), 0.1% of prescriptions did not specify age group of the patient. For calcium channel blockers (C08), ACE inhibitors (C09A), and angiotensin II receptor blockers (C09C), this figure was 0.2%. All prescriptions for centrally acting antihypertensives (C02A) included patient age group specifications.

4.1.3 Other disease treated with antihypertensives in March 2022

Upon excluding the ICD-chapters cardiovascular (I) and hematology (D)N class diseases from the remaining chapters, many chapters had very few prescriptions. Those with more than 49 prescriptions for any of the selected drug classes are presented in Table 22 and Appendix 3.

In March 2022, antihypertensives drugs were occasionally prescribed for other diseases, such as chronic kidney disease (CKD) (N18), abnormalities of heart beat (R00), other extrapyramidal and movement disorders, such as essential tremor (G25), and type 2 diabetes mellitus (E11) (Table 22).

Table 22. Other diagnoses, beyond hypertension, treatment in March 2022

ICD code	Disease name	Prescribed drugs		
		ATC code	Number of prescriptions	Percentage %
E11	Type 2 diabetes mellitus	C02A	32	7.6%
		C03	35	8.3%
		C07	109	26.0%
		C08	30	7.1%
		C09A	48	11.4%
		C09B	92	21.9%
		C09C	28	6.7%
		C09D	46	11.0%
G25	Other extrapyramidal and movement disorders, such as essential tremor	C07	476	100.0%
N18	Chronic kidney disease (CKD)	C02A	1	0.2%
		C03	567	97.1%
		C07	2	0.3%
		C08	1	0.2%
		C09A	5	0.9%
		C09B	1	0.2%
		C09C	5	0.9%
		C09D	2	0.3%
R00	Abnormalities of heart beat	C03	3	0.6%
		C07	482	93.8%
		C08	18	3.5%
		C09A	8	1.6%
		C09B	3	0.6%

* Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

Almost all, 97% of prescriptions for chronic kidney disease (CKD) (N18) treatment, were for diuretics (C03). A total of 94% of prescriptions for abnormalities of heart beat (R00) were for

beta blockers (C07). All prescriptions for other extrapyramidal and movement disorders, such as essential tremor (G25) treatment were prescribed for beta blockers (C07). One fourth of prescriptions for type 2 diabetes mellitus (E11) treatment were for beta blockers (C07), around one fifth, 22% of prescriptions, were for ACE inhibitors, combinations (C09B), 11 for ACE inhibitors (C09A), and 11% were for angiotensin II receptor blockers, combinations (C09D).

Other non-hypertensive diseases presented in Appendix 3. In the management of hyperthyroidism (E05), 91.2% of prescriptions were for beta blockers (C07). Diuretics were predominantly utilized for other conditions related to fluid, electrolyte, and acid-base balance (E87). Beta blockers (C07) were frequently prescribed for the treatment of schizophrenia (F20). Similarly, beta blockers (C07) were the primary pharmacological intervention for managing migraines (G43). In cases of liver fibrosis and cirrhosis (K74) and ascites (R18), diuretics emerged as the most commonly prescribed medications.

4.1.4   Speciality of physicians who prescribed antihypertensive drugs in March 2022

In March 2022, prescriptions for antihypertensive drugs were most commonly prescribed by primary care (80.8%) and internal medicine (18.3%) doctors (Figure 12).
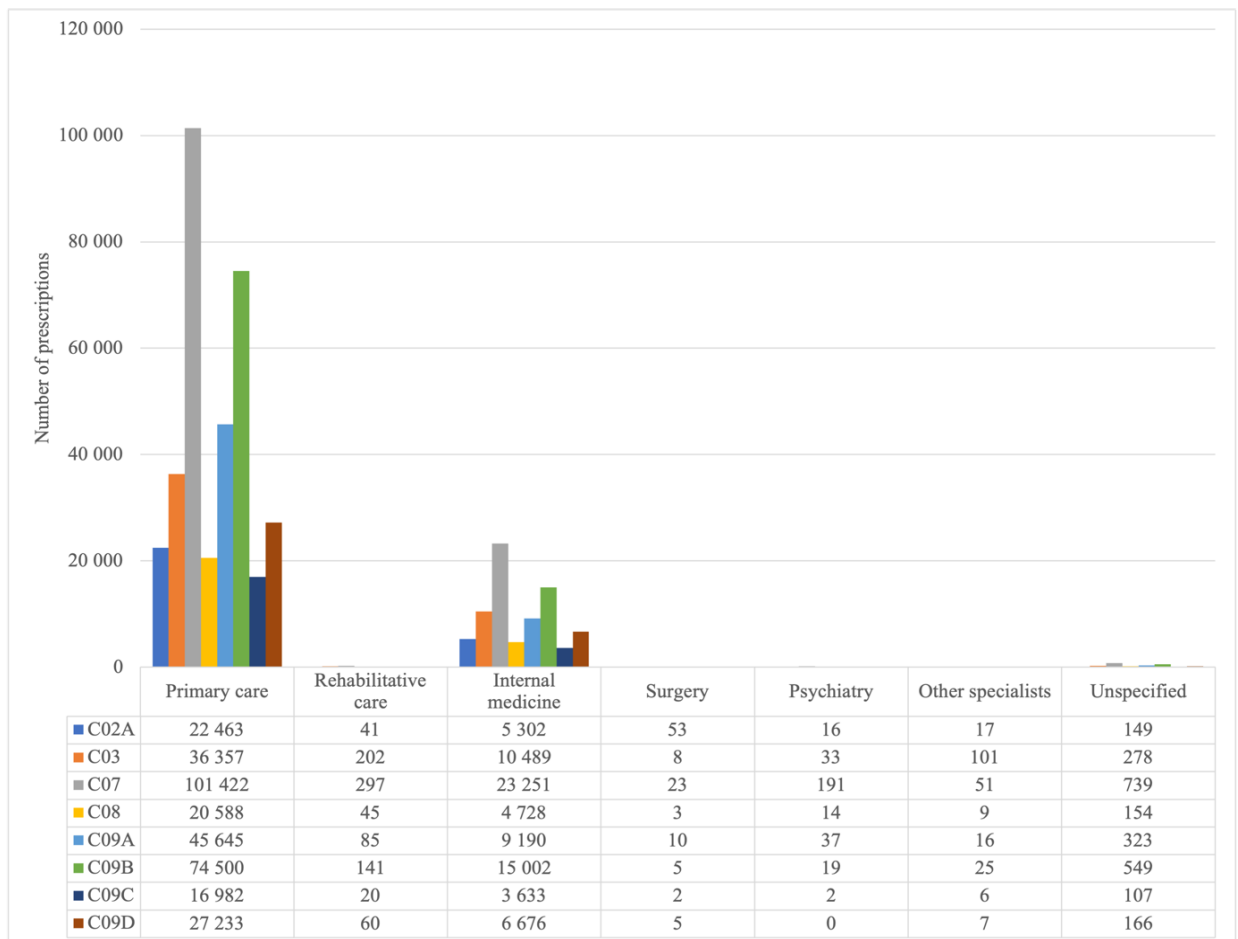
	Primary care	Rehabilitative care	Internal medicine	Surgery	Psychiatry	Other specialists	Unspecified
■ C02A	22 463	41	5 302	53	16	17	149
■ C03	36 357	202	10 489	8	33	101	278
■ C07	101 422	297	23 251	23	191	51	739
■ C08	20 588	45	4 728	3	14	9	154
■ C09A	45 645	85	9 190	10	37	16	323
■ C09B	74 500	141	15 002	5	19	25	549
■ C09C	16 982	20	3 633	2	2	6	107
■ C09D	27 233	60	6 676	5	0	7	166

Figure 12. Number of prescriptions prescribed by different specialization doctors in March 2022

Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

71.0% of prescriptions were prescribed by family doctors, 6.4% were prescribed by internal medicine doctors, 5.7% prescribed by family doctors specializing in internal medicine and 5.1% prescriptions were prescribed by general practice nurses (appendix 5)(appendix 6) .

5   GENERAL DISCUSSIONS

This study aimed to determine for which diagnoses, including hypertension and beyond hypertension, antihypertensives are used and to examine the prescribing tendencies of different antihypertensive drug classes in Lithuania. After analyzing results several points can be noted.

The findings of this study have the potential to stimulate further research in an area that has not received sufficient attention. This research will not only show the extent to which antihypertensive drugs are utilized for managing hypertension but also for other medical conditions. Currently, there is a notable absence of studies that explore the various applications of antihypertensive medications and their prevalence while using electronic prescriptions as data, especially in Lithuania. The research will extend its analysis to investigate the prevalence of antihypertensive drug usage among various age groups, different sex patients in Lithuania. Additionally, it will delve into the examination of which healthcare specialists are responsible for prescribing these medications to patients. In summary, this study aims to encompass a comprehensive array of aspects related to this topic.

Firstly, even though European guidelines suggest ACE inhibitors and ARBs as first choice medications for cardiovascular diseases, in March 2022 beta blockers (C07) were the most prescribed antihypertensive drugs in Lithuania, regardless of sex and age category. Beta blockers (C07) used to be considered an important drug class for treating cardiovascular diseases. But in recent years there have been debates on whether this drug class should remain as first line treatment for cardiovascular conditions (61). Doubts about this drug class efficacy were raised due to the fact that there have been trials that show beta blocker lesser effect in reducing the risk of stroke and mortality related to cardiovascular conditions, when compared to other first line antihypertensives for hypertension treatment (61). But in the 2023 ESH guidelines, it is noted that beta-blocker treatment shows efficacy not only in various cardiac conditions closely linked to hypertension but also in numerous vascular and non-vascular conditions that often occur alongside hypertension. These include post-myocardial infarction, angina pectoris, heart failure, atrial fibrillation, patients with elevated heart rate, and aortic aneurysm, among others. Other conditions would be migraine, hypothyroidism or tremor. This leads to the possibility of treating multiple health conditions with one medication.

Most antihypertensive drug prescriptions were prescribed for hypertensive heart disease (I11) while hypertension (essential and secondary) received around 1.9% prescriptions. A number of trials have shown that structural, functional, and neurohumoral abnormalities of the heart,

involving the ventricular and atrial myocardium as well as the epicardial and intramural coronary arteries - hypertensive heart disease, can be caused by sustained hypertension (56). This could mean that patients often get treatment for hypertension only when it has had complications and caused other more significant cardiovascular health problems. Another study involving 41,455 participants revealed the issue of undiagnosed hypertension (62). According to European ESC/ESH standards for diagnosing hypertension, 21.4% of individuals (or 47% based on American ACC/AHA criteria) exhibited an average blood pressure surpassing the diagnostic threshold for Stage 1, 2, or 3 hypertension (62). Furthermore, 5% of the participants showed an average blood pressure exceeding the ESC/ESH criteria (or 13% based on ACC/AHA criteria) for hypertension, despite lacking a prior diagnosis of hypertension or a prescription for antihypertensive medication while being hospitalized (62).

Majority of the prescriptions were for diseases of the circulatory system (ICD - chapter I) and other coexisting health conditions. At times antihypertensives can be used for other disease treatments that are not necessarily related to hypertension. This study showed that in Lithuania according to the prescription numbers the most frequent non circulatory system disease groups to receive antihypertensive drug treatment can be considered as common hypertension comorbidities. This includes chronic kidney disease, essential tremor, type 2 diabetes (ICD - chapter) which often coexist with hypertension.

During this analysis it was noticed women receive much more prescriptions for antihypertensives than men, even though years ago studies would show the opposite result. But the reason for that used to be that there would be more men than women participants in research. Reasons why now women receive more medications could be that women adhere more to the treatment they are prescribed (63) or they are more prone to having specific diseases, adverse reactions to treatment more often (64). A study conducted on drug treatment of hypertension in Sweden in relation to sex, age, and comorbidity has shown that women were prescribed less antihypertensive drugs compared to men (1.9 ± 1.3 vs. 2.1 ± 1.5, $P < .001$). Women tended to use diuretics, angiotensin receptor blockers, and β-blockers more frequently, while men were more likely to use angiotensin-converting enzyme inhibitors and calcium channel blockers (all $P < .01$). Additionally, among women, a lower proportion of those with diabetes mellitus (66%) and heart failure (72%) used angiotensin-converting enzyme inhibitors/angiotensin receptor blockers compared to men (76% and 79%, respectively; all $P < .001$, adjusted for age and comorbidity) (16).

5.1 Strengths and limitations:

This study helps to overview what class antihypertensive drug classes are prescribed in Lithuania the most. It also allows us to take a look at what are the trends on prescribing specific drug classes for different age groups and different sex patients.

For this research electronic prescriptions were used as a new accessible data source. Not many studies have used this method before, so this research shows how it can be done and what insight it can provide. Electronic prescriptions offer convenient accessibility and furnish comprehensive information, including patient demographics, disease codes, information on prescribed medications, physician specialization, and prescription location. Therefore, this study serves as an illustrative example of the opportunities presented by integrating emerging data sources into scientific inquiry. A positive aspect is that using this data not only confirmed information already known from other studies but also revealed new findings that warrant further investigation, potentially stimulating additional research emergence.

In terms of limitations, each prescription was considered as one patient during this study, therefore the exact number of participants included in this analysis remains unknown. In certain instances, a single patient might have received a polypharmaceutical treatment comprising multiple antihypertensive drug prescriptions for cardiovascular diseases and/or other comorbidities. Information on which prescriptions were prescribed for a single patient was not provided. In order to reduce statistical bias due to the undefined number of patients in the analysis, the study chose to analyze only one month of the year. This decision was based on the assumption that the patient would withdraw the medication one time during the month.

Another limitation is the lack of studies utilizing electronic prescriptions as a data source. This presents challenges when comparing statistical data and results with those of other studies, particularly in Lithuania, where more research on cardiovascular diseases and their treatment is needed.

At the moment electronic prescription usage as data can be considered as a limitation due to the fact that not a lot of similar studies have been made. This type of data source is a rather new way leading into understanding drug utilization and prescribing tendencies in Lithuania, but while there are not many similar studies to compare to, it is hard to exactly determine the significance of analysis findings.

6 CONCLUSIONS

1. Findings show that antihypertensive drug usage varies throughout the year, with March being the month in which the highest number of prescriptions for these drugs is written.

2. In 2022, beta blockers were the most commonly prescribed antihypertensive drug class. Occasionally, antihypertensives are prescribed for diseases beyond hypertension, such as Type 2 diabetes mellitus, essential tremor, and chronic kidney disease (CKD).

3. According to the research findings, antihypertensive drugs were prescribed to women more often than to men.Antihypertensive drugs were more frequently prescribed to people aged 65 and above.

4. In March 2022, the majority of prescriptions were issued by primary care doctors and other health specialists. The primary prescribers were family doctors and general practice nurses.

7 SUMMARY

Hypertension is a global risk factor for cardiovascular disease (CVD) as well as several other related diseases, thus contributing to the global burden of disease. CVD ranks high in terms of global prevalence. This study aims to provide a deeper understanding of antihypertensive drug usage for hypertensive and non-hypertensive disease treatment in Lithuania. There is limited amount of research done on cardiovascular diseases using electronic prescriptions as a data source. Furthermore, there is a lack of studies on tendencies of antihypertensive drug usage for hypertensive and non-hypertensive diseases.

With this study it was important to assess how many antihypertensive drugs are prescribed for different health conditions in March 2022. Then the differences of prescribing antihypertensive drugs according to patients age and sex were evaluated. Also, the study overlooked which specialty health professionals prescribed antihypertensive drugs most frequently for the treatment of hypertension-related and non-hypertensive diseases.

The collected data for this analysis contained 1,855,031 prescriptions from March 2022. The results were observed through pivotal tables and diagrams created in Microsoft Excel. In the State Enterprise Centre of Registers database, there were three files that contained electronically prescribed medication collected from a 10-day period in March. Information for the theoretical part of this study will be gathered from various available articles and research papers. In this study, each prescription is treated as one patient.

Each prescription contained information on the patient's sex, age group, the specialist of the physician who prescribed the medication, the ATC code of the antihypertensive drugs and the disease code from the International Statistical Classification of Diseases and Related Health Problems (ICD). The analyzed prescription records from the State Enterprise Central Registry were depersonalized, to exclude any personal patient or health specialist information.

Findings show that antihypertensive drug usage varies throughout the year, with March being the month in which the highest number of prescriptions for these drugs is written. In 2022, beta blockers were the most commonly prescribed antihypertensive drug class. Occasionally, antihypertensives are prescribed for diseases beyond hypertension, such as Type 2 diabetes mellitus, essential tremor, and chronic kidney disease (CKD). In some cases they were prescribed for migraines, hyperthyroidism, etc.

According to the research findings, antihypertensive drugs were prescribed to women more often than to men. Additionally, patients aged 65 and above received more antihypertensive drug prescriptions. In March 2022, the majority of prescriptions were issued by primary care specialists, with family doctors and general practice nurses being in first place.

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9 APPENDICES

Appendix 1. Percentage of prescriptions of all antihypertensive drugs prescribed in 2022

Month	C01	C02	C03	C04	C05	C07	C08	C09	C10
All months of 2022	7,4%	6,1%	8,5%	0,9%	0,4%	21,8%	4,4%	34,7%	15,8%

Appendix 2. Percentage of prescriptions in 2022

Month	C02A	C03	C07	C08	C09A	C09B	C09C	C09D
All months of 2022	6,5%	11,5%	29,4%	5,9%	12,5%	21,0%	4,9%	8,3%

* Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drug

Appendix 3. Percentage of prescriptions for non-hypertensive diseases in March 2022

ICD code	Disease name	Prescribed drugs		
		ATC code	Number of prescriptions	Percentage %
E05	Thyrotoxicosis (hyperthyroidism)	C02A	1	1,75%
		C03	1	1,75%
		C07	52	91,23%
		C08	1	1,75%
		C09A	1	1,75%
		C09D	1	1,75%
E87	Other disorders of fluid, electrolyte and acid-base balance	C02A	1	1,20%
		C03	82	98,80%%
F20	Schizophrenia	C07	51	98,08%
		C09A	1	1,92%
G43	Migraine	C07	133	94,33%
		C09A	3	2,13%
		C09B	1	0,71%
		C09C	4	2,84%
K74	Fibrosis and cirrhosis of liver	C03	128	85,33%
		C07	21	14,00%
		C08	1	0,67%
R18	Ascites	C03	51	100,00%

* Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

Appendix 4. Percentage of prescriptions for antihypertensive drug Doxazosin (C02CA04) prescribed for men and women in March 2022

ATC code	Drug name	Women	Men	No data on sex	Grand Total
Antihypertensives (C02)					
C02CA04	Doxazosin	17,2%	82,7%	28,4%	7,043

Appendix 5. Number of prescriptions prescribed by primary care health care specialists in March 2022.

Doctor groups	EN	C02A	C03	C07	C08	C09A	C09B	C09C	C09D
Primary care	Obstetrician	0	0	1	2	0	5	0	0
	General practice nurse	1,424	2,109	6,299	1,334	2,717	5,002	1,032	1,855
	Medical doctor	229	654	1,214	286	693	796	153	239
	Medical doctor, Family doctor	719	1,229	3,245	683	1,45	2,412	545	957
	Medical doctor, Pediatrician	1	1	2	1	0	4	0	1
	Medical doctor, Internal medicine doctor	16	83	75	8	31	33	4	10
	Family doctor	19,769	31,769	88,917	18	40,038	64,891	14,984	23,729

* Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs

Appendix 6. Number of prescriptions prescribed by internal medicine doctors in March 2022.

Doctor groups	EN	C02A	C03	C07	C08	C09A	C09B	C09C	C09D
Internal medicine	Doctor hematologist	2	11	9	0	2	1	0	1
	Hematologist, Medical doctor	0	7	0	0	0	0	0	0
	Cardiologist doctor	868	3,001	5,746	1,082	1,578	2,657	777	1,842
	Doctor cardiologist, Doctor pediatric cardiologist	11	15	36	10	24	21	5	7
	Cardiologist, Medical Doctor	64	354	465	81	152	279	59	136
	Cardiologist, internal medicine doctor	107	406	625	129	183	301	114	190
	Endocrinologist doctor	6	37	78	12	26	28	4	9
	Endocrinologist, Medical Doctor	1	1	13	16	5	0	0	1
	Endocrinologist, Family doctor	60	83	208	53	106	146	41	65
	Doctor endocrinologist, doctor of internal medicine	30	44	110	19	50	69	14	30
	Rheumatologist doctor	2	13	8	9	2	5	2	1
	Rheumatologist, internal medicine doctor	0	1	2	1	0	0	0	0

* Centrally acting antihypertensives (C02A), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), ACE inhibitors (C09A), ACE inhibitors, combinations (C09B), angiotensin II receptor blockers (C09C) and angiotensin II receptor blockers (C09D) class drugs