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TREATMENT COMPLIANCE OF PATIENTS WITH HYPERTENSION IN THE FAMILY PHYSICIAN OFFICE "SINU ARST PEREARSTIKESKUS"

Master's thesis

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RAVISOOSTUMUS HÜPERTENSIOONI PATSIENTIDEL SINU ARST PEREARSTIKESKUSES

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

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Abstract

Background: Hypertension is one of the central problems worldwide. It is estimated that every third adult has hypertension. Even more, prevalence of raised blood pressure (BP) is predicted to increase tremendously, especially in societies where population is ageing, such as Estonia. The key factor of adequately controlled BP is compliance to treatment *Aim*: To demonstrate treatment compliance of patients with hypertension and finding its impact to the BP control. *Method:* Quantitative retrospective research 01.01.2014 – 01.01.2016. Evaluation of treatment compliance based on pharmacy refill rates. Determine treatment control based on compliance combined with BP measurements. Data gathering: data obtaining from Estonian Health Insurance Fund and data gathering from the information system Perearst 2. Approval from the Tallinn Medical Research Ethics Committee and Estonian Data Protection Inspectorate was obtained. *Results:* Although 81.9% from the study group had high compliance to antihypertensive medications, yet only 38.6% had their BP under control. Generally, there was relatively low rate of BP control (38.6%), but in high compliance group there were proportionally more patients with controlled BP. Age and the presence of hypercholesterolemia (E78) and/or diabetes mellitus type 2 (E10 – E14) are factors affecting treatment compliance among hypertensive patients. *Conclusion:* Hypertensives in "Sinu Arst perearstikeskus" had relatively high compliance, yet poor BP control. These results can be associated with several reasons, such as *clinician inertia* and *white coat hypertension.* Therefore, further investigation in the field of compliance and BP control among hypertensives is needed.

This thesis is written in English and is 56 pages long, including 7 chapters, 3 figures and 6 tables.

Annotatsioon

Ravisoostumus hüpertensiooni patsientidel

Taust: Hüpertensioon oma tüsistustega on nii Euroopas kui ka Eestis haigestumuse ja surma põhjuste hulgas esikohal. Hüpertensiooni esinemissagedus ülemaailmselt on hinnanguliselt 1/3 täiskasvanutest. Enamasti on hüpertoonia asümptomaatilise kuluga krooniline haigus, seetõttu 1/3 täiskasvanutest, kellel on kõrge vererõhk, ei ole sellest ise teadlikud. Ravimite kasutajatest ühel kolmandikul ei õnnestu vererõhku hoida alla ravijuhistes sätestatud soovitusliku taseme < 140/90 mmHg. Ravisoostumust peetakse üheks peamiseks faktoriks, mis tõhustab vererõhu ohjamist, seega aitab kaasa ka kardio-vaskulaarsete komplikatsioonide vähendamisele. Samuti on ravisoostumuse tõstmisega võimalik vähendada kulusid, mis vastasel juhul kaasneksid täiendavate vastuvõttude, diagnostiliste protseduuride, hospitaliseerimise, suurenenud ravimi dooside või suurenenud ravimihulga puhul nii patsiendile endale, tervishoiusüsteemile, kui ka kogu ühiskonnale.

Eelmainitust tulenevalt planeeriti retrospektiivne uurimustöö. Valim on koostatud Sinu Arsti perearstikeskuse nimistu patsientidest, kellel on esmaseks või kaasuvaks diagnoosiks hüpertoonia (I10 – I13) ajavahemikul 01.01.2014 – 01.01.2016 ning kes on kuni 70 aastat vanad. *Eesmärk*: hüpertensiooni patsientide ravisoostumuse selgitamine ja selle mõju leidmine vererõhu ohjamisele. Lisaks aitab uurimistöö kaasa hüpertensiooni patsientide vererõhu ohjamise parandamisele perearstipraktikas. *Meetodid:* Ravisoostumuse määramise meetodina kasutas autor retseptide täitmise määra. Retseptide täitmise määr: väljaostetud retseptide osamäär väljakirjutatud retseptide kogusummast. Ravisoostumuse määrade alusel jagunesid patsiendid kolme gruppi: Grupp A 80 – 100% (kõrge soostumus); Grupp B 40 – 79% (keskmine soostumus) ja Grupp C 0 – 39% (madal soostumus). Ravisoostumuse mõju hindamiseks vererõhu ohjamisele kogus autor Perearst 2 ravilugudest vererõhuväärtuseid. Autor kõrvutas vererõhuväärtuste aritmeetilise keskmise eelmainitud soostumuse grupiga. *Tulemused:* 166-st patsiendist olid kõrge ravisoostumusega 81,9% ning ohjatud vererõhuväärtustega 38,6%. Kõrge ravisoostumuse grupis oli proportsionaalselt rohkem ohjatud

vererõhuväärtustega patsiente kui keskmise ravisoostumuse rühmas. Vanus ning hüperkolesteroleemia ja diabeet mõjutasid statistilise olulisusega (p) patsientide ravisoostumust. 39 patsiendi kohta puudusid andmed vererõhuväärtuste kohta. *Kokkuvõte:* Kuigi Sinu Arst perearstikeskuse hüpertoonia patsientide seas oli ravisoostumus suhteliselt kõrge, oli vererõhu ohjamine madalal tasemel. Taolisel tulemusel võib olla mitmeid võimalikke seletusi nagu näiteks meditsiinitöötaja tegevusetus (*clinician inertia*) ja valge kitli hüpertensioon *(white coat hypertension*). Seega on tulevikus vajalik leida antud faktorite mõju ravisoostumusele ja vererõhu ohjamisele ning hinnata ravisoostumust, et leida patsientide rühmad, kelle hulgas on ravisoostumus madalam.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 56 leheküljel, 7 peatükki, 3 joonist, 6 tabelit.

List of abbreviations and terms

ABPM	ambulatory blood pressure measurement
BMI	body mass index
BP	blood pressure
CVD	cardiovascular disease
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GP	general practitioner
HBPM	home blood pressure measurement
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
MI	myocardial infarction
mmHg	millimetres of mercury
WHO	World Health Organization

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1 Introduction

Hypertension is one of the central problems both in developed and developing countries [1]. According to the latest statistics provided by World Health Organization (WHO) the prevalence of raised blood pressure (BP), blood pressure ≥ 140/90mmHg, in individuals aged 18 or older worldwide is estimated as follows: 24.0% of men and 20.5% of women. Compared to the prevalence of high BP among the same age in Estonia was quite a lot higher: 38.3% of men and 26% of women [2]. Moreover, the prevalence of raised BP is predicted to increase tremendously [3], especially in societies where population is ageing, such as Estonia. Even more, it is estimated that hypertension causes 7.5 million deaths, which is about 13% of deaths annually [1]. Nevertheless, in spite of numerous guidelines that have been published and other initiatives for preventing and managing hypertension all around the word, population based studies have found that hypertension remains extremely common. It is stated, that around two thirds of people with hypertension are either untreated or inadequately controlled, including a substantial number who remain undiagnosed [4].

Moreover, hypertension is the most common condition seen in primary care and which leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately [5].

Krousel-Wood et al pointed out that the key factor of adequately controlled BP is compliance to treatment; more specifically compliance to medication [6]. Poor compliance contributes worsening of disease, death and increases health care costs [7]. Yet compliance remains poor despite numerous well-tolerated medications available [6].

The extent of non-compliance varies widely, depending on different factors, such as study design and methodology. However, in developed countries compliance rate averages around 50% [8].

In this regard, it is necessary to study what is the current situation, considering treatment compliance and BP control of patients with hypertension, in Estonia. The author focused

on hypertension patients in “Sinu Arst perearstikeskus”, which is general practitioner practice. First, determined treatment compliance rates and secondly evaluated whether there is a correlation between compliance and BP control.

Aim of the research is as follows:

- To demonstrate treatment compliance of patients with hypertension and finding its impact to the BP control.
- In addition, the research will contribute to improving the control of blood pressure of patients with hypertension in the family physician office “Sinu Arst perearstikeskus”.

Approval from the Tallinn Medical Research Ethics Committee and Estonian Data Protection Inspectorate for the research was obtained.

Current thesis involves two main parts. First part gives a theoretical background of the research subject. Second part demonstrates the objectives and questions, methodology, results of the study, discussion and summary.

2 Background of treatment compliance of patients with hypertension

In this chapter, the author firstly clarifies the terminology of compliance, BP and hypertension, so that readers could have common understanding of mentioned terms. Moreover, the most recent recommendations of BP levels for hypertensive patients are described. Also, prevalence of hypertension, the importance of increased compliance, reasons of non-compliance, how to increase compliance and methods of measuring compliance.

2.1 Terminology

When reading several articles about patient medication taking, first a slight confusion about exact understanding of the terminology occurred. There are three main terms - compliance, adherence and concordance – used to describe the extent to which patients are following prescribed treatment. Some authors are using compliance, adherence and concordance synonymously, others feel the need to differentiate these terms and give each of them separate definition. Another term which is sometimes confused with the ones mentioned above is persistence.

2.1.1 Compliance, adherence, concordance

About 2000 years ago, Hippocrates was the first one known to describe the importance of patient compliance. Over the years many studies have been carried out about compliance, which have raised several debates about the terminology. With constant changes in science, medicine, technology and other fields, there is a need for new and specified terminology, in order to understand each other unanimously, so that there would be fewer misunderstandings while communicating “emerging ideas, practices and discoveries” [9]. Just as the issue of compliance, adherence and concordance [9].

According to the definition by Paczkowska et al the term compliance means “the degree to which the patient's behaviour, applying medication or certain lifestyle changes, is

consistent with arrangements communicated to him by a doctor or other healthcare professional" [10].

Comparing words "compliance" and "adherence" literature indicates, that "compliance" is more used to describe that patients are passively following the physician's orders, compared to "adherence" which is indicating the collaborate relationship between patient and physician. Therefore, the treatment plan is based on a therapeutic alliance [11]. Although term "adherence" is preferred by the patients, term "compliance" is still most widely used [12].

Term "concordance" is the most recent term, used mainly in the United Kingdom. Its definition has changed over the time, but it is important to understand that nowadays "concordance" is not synonymous with either "compliance" or "adherence" [13]. "Concordance does not refer to a patient's medicine-taking behaviour, but rather the nature of the interaction between clinician and patient"[13]. Therefore, the main concept is that consultations between physicians and patients are carried out in a way that both are treated equally, more specifically the treatment is patient centred. Thus, physicians should respect patient's decision whether to follow prescribed treatment or not [9], [13]. All in all, though it has been many discussions about the terminology, for now terms compliance and adherence are both used to describe the extent on which patients are following prescribed treatment; first term indicates passive and second term indicates collaborate relationship between patient and physician [14].

Regardless of which term is being used, it is clear that prescribed medications are the most beneficial when patients are following prescribed treatment regimens reasonably closely [7]. Moreover, according to the World Health Organization (WHO) Report medication compliance is the single most important modifiable factor that compromises treatment outcome across diseases [8]. Literature indicates that low compliance to medical recommendations is the key aspect when talking about the effectiveness of antihypertensive therapy [10].

In the current thesis, the term compliance has been selected for describing how precisely the patient is following prescribed treatment regimen.

2.1.2 Definition of treatment compliance and persistence

Term persistence is sometimes mixed up with compliance or adherence. Cramer et al made a literature review about terms and definitions of compliance, adherence and persistence and proposed following definitions [12]. Persistence is "the duration of time from initiation to discontinuation of therapy" [12], compliance and adherence however are described as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [12]. Therefore, persistence is measured in number of days for which medication was taken, whereas compliance and adherence is measured over a period of time and calculated as a percentage of the prescribed doses of the medication actually taken by the patient (Figure 1)[12].

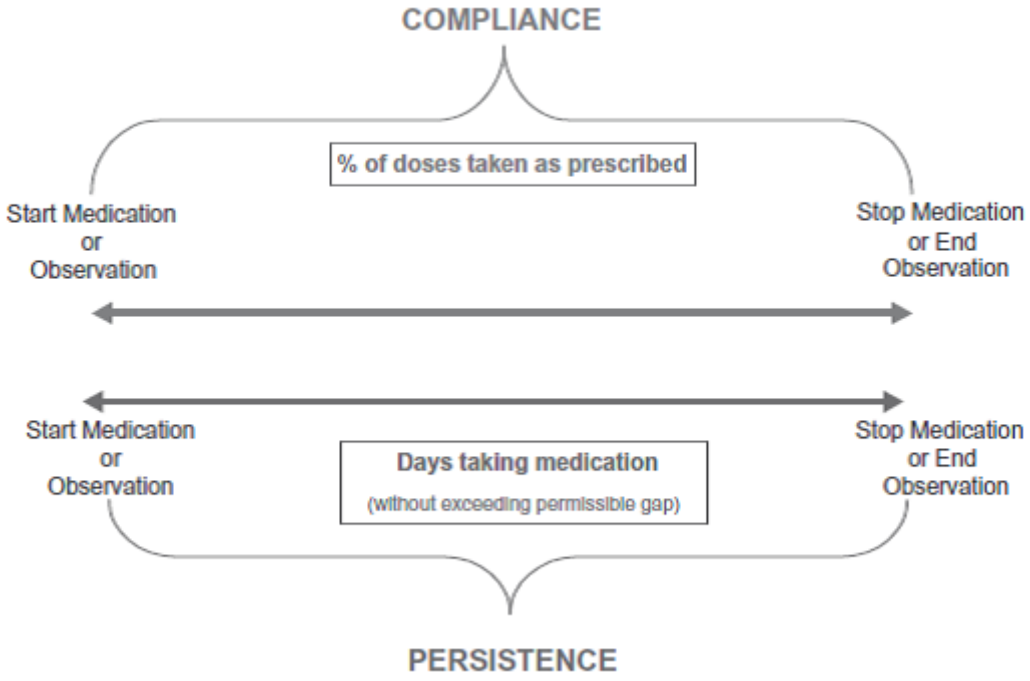

Figure 1. Definition of compliance and persistence [12].

2.2 Definition of blood pressure

BP is the force of blood pushing against the walls of the blood vessels (arteries) as it is pumped by the heart and measured in millimetres of mercury (mmHg) [15]. Therefore, the higher the BP the harder the heart has to pump [1]. According to the guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) optimal BP value for young, middle-aged and elderly are defined as BP less than 120 mmHg when the cardiac muscle contracts (systolic) and less than 80 mmHg when the

heart relaxes (diastolic) (Table 1). Normal values of the BP are: systolic 120 – 129 mmHg and/or diastolic 80 – 84 mmHg and high normal values respectively 130 – 139 mmHg and/or 85 – 89 mmHg (Table 1) [16].

Table 1. Definitions and classifications of office BP levels (mmHg) [16].

Category	**Systolic**		**Diastolic**
Optimal	< 120	And	< 80
Normal	120 – 129	and/or	80 – 84
High normal	130 – 139	and/or	85 – 89
Grade 1 hypertension	140 – 159	and/or	90 – 99
Grade 2 hypertension	160 – 179	and/or	100 – 109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	And	< 90

2.3 Hypertension: definition, causes, symptoms and treatment

According to WHO hypertension is high or raised blood pressure, this is a condition in which the blood vessels have persistently raised pressure, putting them under increased stress [2]. According to ESH and ESC guideline, values of high blood pressure are divided into three grades. When systolic blood pressure is equal to or above 140 mmHg and/or a diastolic blood pressure equal to or above 90 mmHg then the blood pressure is considered to be high or raised and the condition is called hypertension. [2], [16](Table 1).

Hypertension can be classified as primary also called essential hypertension or secondary hypertension. 90 – 95% of high BP cases are caused by primary reasons such as lifestyle factors (overweight, smoking, alcohol abuse and excessive use of salt) and genetics. Over time described lifestyle factors accumulate and cause the predisposition for having hypertension. For example, excessive overweight during the childhood favours the risk of hypertension. 5 – 10% of high BP cases have secondary causes such as disorders in kidneys and in other organs [1].

Hypertension is a chronic condition, yet most hypertensive people have no symptoms, therefore while reading the literature, hypertension was sometimes even called as “silent killer”. The reason above all is because while having no symptoms people ignore the fact

that they have a disease. Therefore, it happens that patient's use antihypertensive treatment only while having symptoms and stopping the treatment while symptoms disappear. However, in case of hypertension, this can be the most common misinterpretation. Moreover, it is even more dangerous, because BP levels can increase tremendously, while the person has no signs or symptoms [1].

Long term elevated BP is a risk factor for stroke, heart attack, heart failure, CVD, renal impairment, peripheral vascular disease, damage of retinal blood vessels, visual impairment and overall mortality. Therefore, lifestyle changes such as weight loss, physical activity, quitting smoking, healthy diet (including decreased amount of alcohol) and decreased salt intake combined with antihypertensive treatment for hypertensive patients are essential [1].

2.4 Recommended BP levels for patients with hypertension

Several studies have shown treatment of hypertension reduces the risk of CVD outcomes, including incident stroke, myocardial infarction, and heart failure. However, the target for blood-pressure lowering is uncertain [17]. Over the years recommended BP levels for patients with hypertension have caused meaningful debates in the field of cardiology. Therefore, recommended BP levels have been changed several times. In 2002, Lewington et al carried out an extensive meta-analysis, where over 1 million patients were enrolled. The study showed that BP is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mmHg [18]. Therefore, for many years clinicians believed, that BP should be decreased as low as possible, to decrease the risk for cardiovascular morbidity and mortality. yet, there is a major difference when talking of BP in people without hypertension compared with those patients who already have the diagnosis. Meaning, that threshold 115/75 mmHg is effective for people without hypertension to decrease cardiovascular morbidity and mortality, but inefficient for patients with hypertension [19].

According to the ESH and ESC 2007 hypertension guidelines the recommended BP levels were $\leq$ 140/90 mmHg in all age groups and $\leq$ 130/80 mmHg of hypertensive patients with higher risk (diabetes, chronic kidney disease, stroke, heart attack) [20]. However, in 2010 ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes BP) study group published their survey, which showed that there is no association in decreasing systolic

BP levels more aggressively (< 120 mmHg) with higher risk hypertensive patients (diabetes mellitus type 2) compared with ordinary systolic BP values < 140 mmHg. Therefore, since 2010 also the recommended systolic BP level for higher risk hypertension patients is < 140 mmHg [21].

Another intensive debate started after 2015, when the SPRINT (The Systolic Blood Pressure Intervention Trial) research group published their trial. The study group investigated over 9000 patients and found that "targeting a systolic blood pressure of < 120 mmHg, as compared with < 140 mmHg, in patients at high risk for cardiovascular events, but without diabetes, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause" [22]. However, there are several aspects why recommended levels in guidelines did not change. First, BP measurements used while the trial were a bit different than the traditional measurements [19]. Investigators used unattended office BP measurements, meaning medical stuff left the room and after 5 min the patient measured her/his BP by herself/himself [22]. Unattended office BP measurements can help to neutralize the "white coat" syndrome, because as measured by the patient's own, the BP values are lower than compared with the traditional cabinet BP measurements [23]. Therefore, in the future unattended office BP measurements might become a new standard giving additional value for disease management, allowing to decrease overtreatment with patients who have "white-coat" syndrome (false positive) [19]. Secondly, though the study population was diverse, SPRINT excluded patients with diabetes mellitus and/or prior stroke [22]. Third, patients with more aggressive treatment in SPRINT trial had also more serious side effects compared with the group of patients received less aggressive antihypertensive treatment [22].

All in all, recommended BP levels for hypertension patients in 2017 are:

- patients aged < 80 years BP < 140/90 mmHg,
- patients aged > 80 years systolic BP < 140 (150),
- patients with diabetes mellitus type 2 < 140/85 mmHg.

With patients who are older than 90 years or are younger than 50 years or have had a stroke the physicians should target lower BP levels. However, in these groups of patients there is little evidence based research done [19].

2.5 Prevalence of hypertension and treatment compliance

According to the latest statistics provided by World Health Organization (WHO) the prevalence of raised blood pressure (BP), blood pressure ≥ 140/90 mmHg, in individuals aged 18 or older worldwide is estimated as follows: 24.0% of men and 20.5% of women. Compared to the prevalence of high BP among the same age in Estonia was quite a lot higher: 38.3% of men and 26% of women [2].

In 2014 Kaldmäe et al published a study, where prevalence of hypertension among Estonian adults was investigated. The study enrolled 1111 randomly selected participants and showed prevalence of hypertension among male 44.2% and among female 28.7%. Though awareness of hypertension was 77.4% among male and 82.6% among female, only 42.3% of male and 38% of female, reported taking antihypertensive medications [24]. Moreover, the prevalence of raised BP is predicted to increase tremendously [1], especially in societies where population is ageing, such as Estonia.

In extensive review of the literature "Adherence to long-term therapies" provided by WHO revealed that in developed countries the compliance rate among hypertensives is approximately 50%. For example, in the United States 51% of patients with hypertension adhere to their antihypertensive medication and in China 43%. In developing countries, such as the Gambia and the Seychelles, treatment compliance rate has been reported somewhat lower, 27% and 26% respectively [8].

Jimmy et al described in their review, that compliance rates are typically higher among patients with acute conditions, as compared against those with chronic conditions. Studies reveal that patients with chronic illnesses take only ~50% of medications prescribed for those conditions [25].

However, the extent of compliance varies widely and can be different depending on several factors, study design can be one of them, more specifically the distribution of compliance. For example, the two studies carried out in Greece had the distribution of compliant and non-compliant [26], [27], compared to a study published by Mazzaglia et al, that separated three different categories: fully compliant, partially compliant and non-compliant [28].

2.6 Importance of increased compliance of patients with hypertension

The positive outcomes of antihypertensive therapy in decreasing BP of patients with hypertension have been shown in several studies. Moreover, decreased BP is associated with reduced risk of stroke, ischemic heart disease, heart failure, CVD, renal failure, peripheral vascular disease, damage of retinal blood vessels, visual impairment and overall mortality [29].

However, the control of hypertension is unsatisfactory [30]. Several studies have shown that about half of hypertension patients discontinue antihypertensive medications within 6 to 12 months [31]. Therefore, adequate treatment compliance combined with persis–tence is shown to decrease BP and in long term also reduce cardiovascular events and other complications in patients with hypertension [30].

It is even more essential, because as mentioned before 90 – 95% of high BP cases are caused by primary reasons such as lifestyle factors (overweight, smoking, alcohol abuse and excessive use of salt) [1]. Therefore, elevated BP is one of the most preventable causes of morbidity and mortality. Furthermore, if BP is controlled, then the whole society can benefit from it, as healthier people can work and pay taxes.

2.6.1 Cardiovascular outcomes

A review provided by Antonakoudis et al found that numerous clinical trials showed that lowering blood pressure (BP) reduces cardiovascular risk by 20 – 25% for myocardial infarction, 35 – 40% for stroke and by 50% for heart failure [32].

In 2009, a relevant study about compliance to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients was published. This study was conducted in Italy with 18 806 patients by 400 primary care physicians and followed up for an average of 4.6 years. Patients included didn´t have cardiovascular disease in the beginning of the study and were at the age of 35 or above. Data was collected from the Health Search/Thales Database and included information about prescriptions, laboratory tests, hospital admissions, cardiovascular events and mortality. Patients were divided into three groups on the bases of compliance: 80 – 100% (high), 40 – 79% (intermediate) and less than 40% (low). However, as the study revealed compliance level among patients was in constant change. For example, in the beginning about 8% of patients had high compliance and 51% low compliance, but at the end

respectively 19% high and 49% low compliance. The main finding of the present study is that high compliance to antihypertensive therapy is associated with a 38% decreased risk of cardiovascular events compared with lower adherence [28].

Only slight differences of as little as 2 – 3/1 – 2 mmHg in blood pressure levels were sufficient to cause beneficial changes in cardiovascular outcomes, therefore long-term compliance and persistence of therapy are important to achieve these objectives [30].

2.6.2 Economic outcomes

Poor compliance to antihypertensive therapy is associated with additional costs due increased number of medical consultation's, diagnostic procedures, hospitalizations, higher doses of drugs, increased number of drugs, decrease in productivity and loss of working days [29]. Eaddy et al made a literature overview where they included 160 articles. The main finding from this review was clear identification of relationships between cost sharing, compliance, and outcomes. From the category of cost sharing and medication adherence 85% showed that an increasing patient share of medication costs was significantly associated with a decrease in compliance. From the other category, the majority noted that increased compliance was associated with a statistically significant improvement in outcomes [33].

Therefore, as stated to the review by Iuga et al medication non-compliance leads to poor outcomes, which is associated with additional health care services, which in term increase overall health care costs. The financial pressure is passed to patients by payers through higher co-payments, or via higher costs to employers for coverage [34]. Increased patient cost can be one of the reasons to decreased medication compliance.

Gaziano et al evaluated that suboptimal blood pressure cost $370 billion globally in 2001. This represents about 10% of the world's overall healthcare expenditures. Even more the same study stated that if current BP levels persist, then over 10-year period elevated blood pressure may cost nearly $1,000 billion globally [35].

2.7 Reasons of non-compliance of patients with hypertension

First of all, in order to improve treatment compliance, it is important to understand the reasons of non-compliance. Based on literature overview provided by Osterberg et al a

model of barriers of compliance was provided (Figure 2) [7]. According to the model barriers of compliance were divided into three groups. Groups formed between three actors - patient, provider and overall healthcare system. Between those actors following barriers occurred:

- Barriers between patient and provider interaction. Poor provider-patient communication can cause patient poor understanding of the disease, therefore also lack of understanding of the need for treatment. Moreover, inadequate communication can lead to poor understanding of benefits for using medication as prescribed. Therefore, physician's ability to adequately explain the benefits of the treatment and possible complications, while also considering patient's lifestyle, cost of medication and the complexity of prescribed regimens, play a great role when considering the barriers for compliance [7].

- Barriers between provider and healthcare system interaction. Poor provider interaction with the health care system can lead to physician's poor knowledge of the drug costs and insurance coverage of different formularies. In addition, physicians, low level of job satisfaction [7].

- Barriers between patient and healthcare system interaction. Healthcare systems can create barriers to patient's compliance by limiting the access to health care, using restricted formulary, switching to different formulary and having high costs for medications and/or co-payments. Therefore, patients have decreased access to appointments and medication [7].

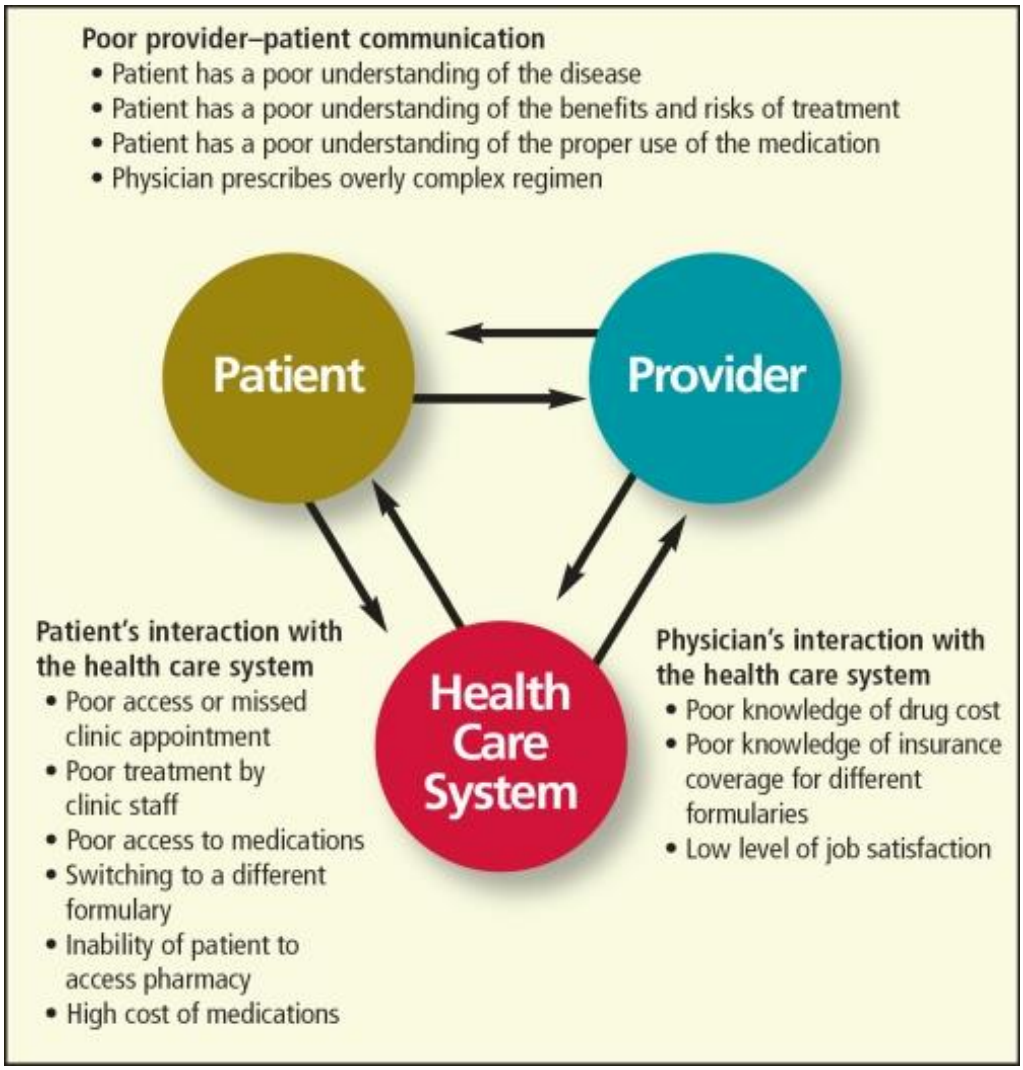

Figure 2. Barriers of compliance [7].

However Manual of Hypertension of the European Society of Hypertension divided causes of non-compliance into six groups: patient related, condition related, social/economic related, health system related, physician related and therapy related [29].

- Patient related - age, gender, ethnicity, socioeconomic status, cognitive function (reasoning, attention, memory, language), patient's insight to the illness, education, responsible physician (private versus public), patients who changed their physician versus those who did not change their physician, medication taking time (evening versus morning), depression, patient-physician relationship and missed appointments.

- Condition related – nature of the condition (asymptomatic), rate of progression and/or severity of the disease, availability of the drugs.

- Social/economic related – socio-economic position, cost of treatment, level of education, unemployment.
- Health system related – care delivery, financing, pharmaceutical management.
- Physician related – failing to explain medication regimen with its beneficial effects and possible side effects, while also considering patient's lifestyle, cost of medication and insurance coverage. Communication. Clinical inertia.
- Therapy related – drug intolerability, side effects, frequent changes in antihypertensive medication, complexity of the treatment regimen, frequency of daily dosage, number of medication, cost of therapy.

When comparing these two models of causes for non-compliance the Manual of Hypertension of the European Society of Hypertension is using "health system" term instead of "healthcare system", therefore indicating on salutogenic approach. Salutogenic model was first described by Aaron Antonovsky who brought the focus from illness and injuries based pathogenic model to the positive health and wellbeing model. Therefore, in addition of asking "what is the cause of illness", it is also important to ask, "what is the cause of health". Moreover, health and illnesses are located at different ends of the same line, therefore health is not only determined through pathogenesis, rather it is a combina–tion of pathogenesis and salutogenesis.

2.8 How to increase treatment compliance of patients with hypertension

According to Hill et al improved compliance can be achieved when two main gaps are filled. First, there is a gap between what researchers have shown to be effective methods to improve compliance and which methods physicians are using in their everyday work. Secondly, gap between what physicians recommend to their patients and what patients actually do at home. In order to close these gaps Hill et all propose four strategies: "focusing on clinical outcomes; empowering informed, activated patients; developing prepared proactive practice teams; and advocating for health care policy reform" [36].

Focusing on clinical outcomes – medication taking has to be respectively to the guidelines, although physicians need to be flexible while also considering patient

characteristics (including ability to pay). Medication regimen adaptation is needed until the BP goal is achieved; moreover, maintenance of goal BP over lifetime is important. If BP remains uncontrolled, then re-evaluation and reviewing treatment options with the patient is needed. An important clinical parameter is compliance; therefore, it is suggested to monitor it. Continuous communication (both verbal and written) with patients about the importance of their medication taking and also providing feedback on progress, using available technologies. Encouraging patients to self-monitor their BP. Moreover, minimizing the number of pills and frequency of administration helps to increase compliance, therefore simple dosing (for example one pill once a day) is suggested. Furthermore, selected drug should be well tolerated by the patient [36].

Empowering informed, activating patients – underlining that patients are eventually responsible for taking their medication, moreover patients themselves have the central role in caring for themselves, therefore motivating patients to ensure that they adhere to treatment. Patients are sometimes facing problems that interfere their maintenance of BP control; therefore, identification of these factors is important. Moreover, evaluation of patient's knowledge, skills, behaviours, confidence, and barriers to compliance, in order to find possible shortcomings. Studies have shown that the most common reason behind low compliance rate is that patients simply forgetting to take medications. Therefore, supporting methods, such as pill boxes, pill organizers and reminders ("alarm clocks"), would be highly appreciated. Moreover, it is suggested to link the medication taking into routine daily activities, for example taking a pill every morning after caring for teeth. Another issue of decreased compliance is sometimes reported ineffective refilling of prescriptions before running out of medication; therefore, patients need guidance how to avoid these situations to happen. Monitoring the cost of medications and patients' ability to pay for them is another important activity to be done. All in all, collaborative care-planning and problem-solving is a key factor when considering effective behavioural changes [36].

Implementation of a team approach – collaborative care-planning, including physicians, nurses, pharmacists and patient's family members. The evidence based (on team approach bases) care should be patient-centred and should provide patient assisting with self-management. Even more, it has been shown previously, that using technology such as remote home monitoring systems, can improve communication, documentation, and BP tracking, which in turn can be effective to increase compliance [36].

Advocating for health care policy reform – recognition that medication compliance is a critical issue, therefore developing policies to support prevention and hypertension management is needed. Another important obstacle is stimulating behavioural aspects of care in communities, therefore financing and structuring in this sector is needed. Finally, as Hill et al pointed out "searching regulatory changes to improve the use of home BP monitors" [36].

To increase compliance, additionally health care practices need to adapt these strategies; also, integration of technology to support clinician's decision making and patient's self-management is needed [29], [36]. Improvements in compliance are likely to be achieved by better education including both verbal and written instructions, supporting patient self-management, a team approach to patient care, including technological possibilities into hypertension management, measuring compliance, and decreasing clinical inertia. All in all, to achieve better compliance collaboration between patients, health care providers and policy makers to redesign healthcare systems is needed [36].

2.9 Methods of measuring compliance

According to the review by Osterberg et al the methods available for measuring comp–liance are divided into direct and indirect methods (Figure 3) [7].

Directly observed therapy, measurement of the level of medicine or metabolite in the blood and measurement of the biologic marker in blood are the direct methods described in Figure 3. Indirect methods for measuring compliance include patient questionnaires, self-reports, pill counts, rates of prescription refills, assessment of the patient's clinical response, electronic medication monitors, measurements of physiologic markers, patient diaries and questionnaires for caregivers and/or teachers in case of children [7].

Each method has its advantages and disadvantages; therefore, no method is considered the golden standard. Although direct methods are considered to be the most precise methods, they can be expensive and inconvenient to the patient. Indirect methods such as patient questionnaires, patient self-repots, patient diaries and questionnaires to the caregiver and/or teacher in case of children, can be easily performable and considerably cheap, but subjective and easily altered by the patient [7].

Pill counts and rates of prescription refills are considered as objective and easily performable methods, however still prone to patient manipulation (pill dumping, pill sharing, buying out the pills but still not taking them) [7].

Assessment of patient's clinical response and measuring physiological markers such as heart rate, are generally easy to perform. Yet, factors other than compliance to medications can affect clinical response such as increased metabolism or poor absorption of medication [7].

Electronic medication monitors, stamping the time of opening bottles, dispensing drops or activating a canister are the methods that provide precise and detailed information about patient medication taking behaviour. Yet, whether the patient actually ingested the correct drug or correct dose, remains unknown. Patients may invalidate the data by opening the container and not take the medication, take the wrong amount of medication or take multiple doses. Moreover, electronic medication monitoring is an expensive method [7].

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

Figure 3. Methods of measuring compliance [7].

3 Research objectives and questions

The author has set the objectives of this thesis project as shortly descripted below:

- To study and determine treatment compliance rates of patients with hypertension in a study population of general practitioner (GP) practice "Sinu Arst perearstikeskus".

- To study treatment compliance rates combined with BP levels and to identify if there is a positive correlation between them.

Accordingly, the author has formulated the following research questions.

Research questions:

- What are the treatment compliance rates among patients with hypertension in a GP practice "Sinu Arst perearstikeskus"?

- Is there a positive correlation between treatment compliance and BP control? Meaning, if the patient is following prescribed treatment regimen relatively closely, is her/his BP levels decreasing?

Research hypothesis:

- Half of the studied patients are in a low treatment compliance group, meaning they are following treatment regimen < 39%.

- There is a correlation between treatment compliance and BP control. Therefore, if the patient is following prescribed treatment regimen relatively closely, then her/his BP levels are decreasing and vice a versa.

4 Materials and methods

Current chapter demonstrates research methodology, details about the sample and finally goes through data collection while explaining how the data was gathered and analysed.

4.1 Research methodology

The quantitative retrospective research was planned. Looking backwards and studying patients with hypertension in the timeframe 01.01.2014 – 01.01.2016. First, to evaluate treatment compliance, based on pharmacy refill rates. Second, to determine treatment control, based on compliance combined with BP measurements. Study population was selected from a GP practice „Sinu Arst perearstikeskus“, in the information system Perearst 2 (study population is described in details under 3.2 Research sample). The GP practice is located at Narva mnt 7, Tallinn, Estonia.

Approval from The Tallinn Medical Research Ethics Committee and Estonian Data Protection Inspectorate was set as a precondition, before initiating data gathering.

Health data is considered to be delicate data, therefore after gaining agreement from the Estonian Data Protection Inspectorate it was possible to request information from Estonian Health Insurance Fund. To link data obtained from Estonian Health Insurance Fund and data gathered by the author from “Perearst 2” identification codes for each individual had to be included into data collection, therefore in addition to approval from Estonian Data Protection Inspectorate data exchange contract and data delivery contract had to be concluded.

4.2 Research sample

The study group has been selected from the patients list of physicians in general practitioner (GP) office “Sinu Arst perearstikeskus”. Subjects were aged ≤ 70 years and diagnosed with hypertension. Disease codes were based on 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD – 10), which is a medical classification list. Patients with primary or also called essential hypertension with ICD – 10 codes I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.1, I13.2, I13.9 were included. Patients who had secondary hypertension with ICD – 10 codes

I15, I15.0, I15.1, I15.2, I15.8, I15.9 were not included. The reason of excluding secondary hypertension is associated with the difficulty to separate antihypertensive treatment compliance with other diseases compliance (as mentioned before, secondary hypertension is a hypertension due to an identifiable cause, meaning some other disease occurred first and resulted in elevated blood pressure). The data originates from the time frame of 01.01.2014 – 01.01.2016. According to the database used in the GP office, Perearst2 version 5.0.0.7 (2003), there were 228 patients with previously described filters. However, after excluding patients who did not have any antihypertensive treatment prescriptions (23 patients), the sample size decreased to 205 patients.

4.3 Data collection

Data about prescribed antihypertensive medications and refilled (bought-out) antihypertensive medications was asked from Estonian Health Insurance Fund, therefore permission was obtained from Estonian Data Protection Inspectorate. Data asked from Estonian Health Insurance Fund included antihypertensive medication names, dates when each medication was prescribed and refilled or not refilled. Antihypertensive medication names were asked based on Anatomical Therapeutic Chemical Classification System (ATC): C02 – C03, C07 – C09.

Patients gender, age, specific hypertension diagnoses (I10 – I13), co-existing risk conditions (E78; E10 – E14), dates of BP measurements and values of BP measurement and the date of first hypertension diagnosis, were manually searched by the author from the "Perearst 2" information system. In the information system used in GP practice, there was an opportunity for medical stuff to use structured field for BP inputs. However, in most cases the field was not used at all or partially used. Therefore, treatment stories for each patient were opened and BP values in the timeframe 01.01.2014 – 01.01.2016 was manually searched from the great number of treatment stories. In total, thousands of treatment stories were read trough by the author in order to find all the available BP measurements.

As, the most common and important coexisting risk factors that can cause cardiovascular complications in patients with hypertension, are diabetes mellitus (E10 – E14) and hypercholesterolemia (E78) [32], [19]. Therefore, these conditions were selected as the conditions that substantially aggravating patient's health condition and BP control.

4.3.1 Data gathering

Data gathering, which was divided into two phases (described in detail under 4.3 Data Collection):

- data obtaining from Estonian Health Insurance Fund;
- data gathering from the information system "Perearst 2".

4.3.2 Data analysing

The beginning of study period, for each patient, was defined as the first antihypertensive treatment prescription date: baseline for the single patient. For example, ages were calculated based on that: if patient "X" (born in 27.08.1966) had her/his first antihypertensive medication prescription in 27.08.2015, then this date was the start of following patient "X" and her/his age was calculated based on the first prescription. In the case of the example patient "X" was 49 years old.

Data analysing was divided into two Phases.

Phase 1 - treatment compliance evaluation.

The rate at which patients refill prescriptions has been the selected method to evaluate treatment compliance. By refilling prescriptions author means the rate at which patients buy-out prescribed medications. Before starting to analyse data, compliance groups were defined. As antihypertensive treatment regimen is normally prescribed for 6 months, which contains 3 prescriptions (one prescription contains doses for 2 months) and prescriptions are valid for 180 days, then 100% compliance was defined as compliance when all the prescriptions are refilled at least 180 days after the prescribing date. During the study period (01.01.2014 – 01.01.2016) the compliance rates for each patient were calculated by using following formula (1):

$$p\% = \frac{a}{A} * 100\% \quad (1)$$

Where p% is compliance rate, a represents refilled prescriptions and A represents all the prescribed antihypertensive medications.

For example: 3 antihypertensive treatment prescriptions for patient "X" were prescribed. 180 days after the prescription date, patient had refilled 2 of 3 prescriptions. Therefore, the compliance for mentioned period is calculated using formula (1):

a = 2 prescriptions

A = 3 prescriptions

$$p\% = \frac{2}{3} * 100\% = 66.6\%$$

Therefore, compliance for the study period ($p\%$) is 66.6%.

According to the compliance, each patient was further classified into one of three compliance groups:

- High treatment compliance (80 – 100%). Defined as patients following treatment regimen as prescribed at least 80%.
- Intermediate treatment compliance (40 – 79%). Defined as patients following treatment regimen as prescribed 40 – 79%.
- Low treatment compliance (< 40%). Defined as patients following treatment regimen as prescribed less than 40%.

Compliance in groups was further classified by gender, age, diagnosis, co-existing risk conditions and the time of first hypertension diagnosis. Described more specifically below:

- Gender: men, women;
- Age: ≤ 50 years, 51 – 60 years, 61 – 70 years;
- Diagnosis: essential hypertension without organ damage (I10), hypertension with organ damage (I11 – I13.9);
- Co-existing risk conditions (E78; E10 – E14): yes, no;
- Time since first hypertension diagnosis: no data, ≤ 10 years, > 10 years.

Phase 2 – determine and evaluation of treatment control, based on compliance combined with BP measurements.

As discussed earlier ("Recommended BP levels of patients with hypertension"), the recommended BP levels are changing over time, as further investigations are done. However, according to Viigimaa, in 2017 recommended BP levels for hypertension patients are [19]:

- patients aged < 80 years BP < 140/90 mmHg,
- patients aged > 80 years systolic BP < 140 (150),
- patients with diabetes mellitus type 2 < 140/85 mmHg.

With patients who are older than 90 years or are younger than 50 years or have had a stroke the physicians should target lower BP levels. However, in these groups of patients there is little evidence based research done [19].

Therefore, because in the current study patients are ≤ 70 years old, the BP control of hypertensive patients is defined through < 140/90 mmHg of patients without diabetes mellitus type 2 and < 140/85 mmHg of patients with diabetes mellitus type 2. Patients were divided into two groups:

- BP under recommended level, BP is controlled,
- BP over recommended level, BP is uncontrolled.

Patients under treatment control groups were further classified by compliance groups.

- High treatment compliance (80 – 100%). Defined as patients following treatment regimen as prescribed at least 80%.
- Intermediate treatment compliance (40 – 79%). Defined as patients following treatment regimen as prescribed 40 – 79%.
- Low treatment compliance (< 40%). Defined as patients following treatment regimen as prescribed less than 40%.

5 Results

The study was conducted retrospectively and the study group was chosen from the patients list of physicians in GP office "Sinu Arst perearstikeskus". Subjects were aged ≤ 70 years and diagnosed with hypertension. The data originates from the time frame of 01.01.2014 – 01.01.2016. Data was manually collected by the author from the information system – Perearst 2 – used in "Sinu Arst perearstikeskus" and asked from Estonian Health Insurance Fund. 228 hypertensive individuals were selected, but data for 23 (10.1%) individuals had to be excluded, because there were no data about prescriptions. Therefore, data for 205 individuals was analysed.

Results are divided into two subgroups:

- 5.1 Results – treatment compliance;
- 5.2 Results – BP control.

5.1 Results – treatment compliance

From 205 subjects, 117 (57.1%) were male and 88 (42.9%) female. Aged 23 – 70 years a mean age of 51.8 years. 43.4% of patients were ≤ 50 years old, 33.2% were 51 – 60 years old and 23.4% were 61 – 70 years old. 157 (76.6%) subjects had only primary (essential) hypertension without organ damage and 48 (23.4%) subjects had primary (essential) hypertension with organ damage. From the subjects analysed, 97 (47.3%) subjects had co-existing risk conditions E78; E10 – E14 and 108 (52.7%) subjects did not have mentioned co-existing risk conditions. Time since first hypertension diagnosis: for 121 (59.0%) subjects the data about first diagnosis was not available (the author had access to Perearst 2 system only and could not have access to Digilugu) and 83 (41.0%) subjects got their first hypertension diagnosis ≤ 10 years ago, and none of the subjects got their diagnosis over 10 years ago (Table 2).

Table 2. Profile of selected patients (n = 205) with hypertension in "Sinu Arst perearstikeskus".

Variables	**Number of patients (n)**	**Percentage (%)**
Male	117	57.1
Female	88	42.9
≤ 50 years	89	43.4
51 – 60 years	68	33.2
61 – 70 years	48	23.4
Primary hypertension without organ damage	157	76.6
Primary hypertension with organ damage	48	23.4
Patients with co-existing risk conditions	97	47.3
Patients without co-existing risk conditions	108	52.7
Time since first hypertension diagnosis: data not available	122	59.5
Time since first hypertension diagnosis: ≤ 10 years	83	40.5
Time since first hypertension diagnosis: > 10 years	0	0

From the study group 166 (81.0%) patients were considered as highly compliant, meaning most of the patients analysed were following prescribed treatment regimen at least 80%. There were 34 (15.6%) patients, who were following prescribed treatment regimen 40 – 79% and only as little as 5 patients from 205 were considered as low compliant, therefore following prescribed treatment regimen less than 40% (Table 3).

Table 3. Treatment compliance among hypertensive patients in "Sinu Arst pereasrtikeskus" between 01.01.2014 – 01.01.2016 (n = 205).

Compliance group	**N**	**%**
High compliance (≥ 80%)	166	81.0
Intermediate compliance (40 – 79%)	34	16.6
Low compliance (≤ 39%)	5	2.4

From the study group (n = 205), 82.9% of male had high compliance (≥ 80%), 15.4% intermediate compliance (40 – 79%) and only 1.7% had low compliance (≤ 39%). Compared to women, whom compliance groups were respectively 78.4%, 18.2% and

3.4%. However, there was no significant association ($p < 0.05$) between gender and compliance groups (Table 4).

The author found significant association with the outcome of interest when comparing patients ≤ 50 years and patients 61 – 70 years old in high compliance group. Between mentioned age groups there is statistically important difference: compliance was highest in the age group of 61 – 70 years, were 91.7% were considered highly compliant and lowest among participants who were ≤ 50 years old. Results showed opposite statistically important association between age groups in intermediate compliance group: there is greater proportion of patients ≤ 50 years in intermediate compliance compared with 61 – 70 years (Table 4). Therefore, patient age is considered to be one of the factors influencing compliance to antihypertensive medication.

When comparing hypertension patients with organ damage and without organ damage, there is statistically important difference in intermediate compliance group. There is a greater proportion of hypertensive patients with organ damage in intermediate comp–liance group compared with hypertensive patients without organ damage in the same group. However, results do not show the same association in high compliance group (Table 4).

The results showed, that 87.6% of hypertensive patients with co-existing risk conditions (E78; E10 – 14) were considered as highly compliant, compared to 75% of hypertensive patients without co-existing risk conditions in the high compliance group. Comparison was found to be statistically relevant, meaning in high compliance group hypertensive patients with co-existing risk conditions are more likely compliant. Moreover, there were proportionally more hypertensive patients with no co-existing risk conditions in the intermediate compliance group compared with hypertensive patients with co-existing risk conditions (Table 4).

Table 4. Influence of demographic and disease related characteristics on treatment compliance among hypertensive patients in "Sinu Arst perearstikeskus" between 01.01.2014 – 01.01.2016 (n = 205).

Variables		**High compliance (≥ 80%) (n = 166)**			**Intermediate compliance (79 – 40%) (n = 34)**			**Low compliance (≤ 39%) (n = 5)**		
		N	**%**	**P**	**N**	**%**	**p**	**n**	**%**	**p**
Gender	Male (n = 117)	97	82.9	0.42	18	15.4	0.60	2	1.7	0.44
	Female (n = 88)	69	78.4		16	18.2		3	3.4	
Age	≤ 50 years (n = 89)	65	73.0	0.11[1]	21	23.6	0.10[1]	3	3.4	0.89[1]
	51 – 60 years (n = 68)	57	83.8		9	13.2		2	3.0	
	61 – 70 years (n = 48)	44	91.7	0.01[2]	4	8.3	0.03[2]	0	0	-
Diagnosis	Hypertension without organ damage (I10) (n = 157)	131	83.4	0.11	21	13.4	0.03	5	3.2	-
	Hypertension with organ damage (I11 – I13) (n = 48)	35	72.9		13	27.1		0	0	
Co-existing risk conditions	Yes (n = 97)	85	87.6	0.02	10	10.3	0.02	2	2.1	0.75
	No (n = 108)	81	75.0		24	22.2		3	2.8	
Time since first hypertension diagnosis	Data not available (n = 122)	101	82.8	0.42[3]	19	15.6	0.64[3]	2	1.6	0.36[3]
	≤ 10 years (n = 83)	65	78.3		15	18.1		3	3.6	
	>10 years	0	0	-	0	0	-	0	0	-

[1]for p value calculation patients ≤ 50 years were compared with patients aged 51 – 60
[2]for p value calculation patients aged ≤ 50 years were compared with patients aged 61 – 71
[3]for p value calculation data not available was compared with the group where first hypertension diagnosis was gained ≤ 10 year

5.2 Results – BP control

From 205 hypertensive patients analysed, 31 patients did not have any data of BP values in the information system (Perearst 2) used in "Sinu Arst perearstikeskus". Therefore, the study group for further analysis decreased to 174 patients. Moreover, after setting the baseline inside the study period for each patient (defined as the first antihypertensive treatment prescription date), BP values for 166 patients was further analysed (BP values for 8 patients were excluded for the reason being measured in the study period but not in the study period for the specific patient). Therefore, total 39 patients (19.0%) from 205 patients did not have any BP measurements within their individual study period.

From the 166 hypertensive patients, 64 subjects (38.6%) had their BP controlled. 102 subjects (61.4%) had their BP over recommended level (uncontrolled).

For the reason of decreased study group, there is a need for re-evaluate compliance groups. From 166 patients, 136 (81.9%) are considered as highly compliant, 25 (15.1%) as intermediately compliant and 5 (3%) as lowly compliant. Therefore, if comparing the results with initially analysed patients (81.0%, 16.6%, 2.4%), the sub-divisions of compliance groups didn't differ significantly. Generally, in all compliance groups there are more patients whose BP is over the recommended level. Comparing patients in high compliance and intermediate compliance there was statistically important association between compliance rates and BP control: among high compliance group, there were proportionally more patients whose BP was under control compared to intermediate compliance group. Therefore, as stated in the hypothesis patients in high compliance group are more likely to have their BP under recommended level compared with patients in the intermediate compliance group (Table 5).

Table 5. Treatment compliance and BP control of hypertensive patients in "Sinu Arst pereasrtikeskus", between 01.01.2014 – 01.01.2016.

Variables	**Controlled**	**Uncontrolled**	**p**
High compliance (≥ 80%) (n = 136)	58 (42.6%)	78 (57.4%)	0.03[1]
Intermediate compliance (79 – 40%) (n = 25)	5 (20%)	20 (80%)	
Low compliance (≤ 39%) (n = 5)	1 (20%)	4 (80%)	0.32[2]

[1]High compliance group was compared with intermediate compliance group
[2]High compliance group was compared with low compliance group

From the 166 hypertensive patients, 144 did not have diabetes mellitus type 2 and 22 had diabetes mellitus type 2. Therefore, as discussed earlier the recommended BP levels for hypertensive patients without diabetes mellitus are as follows: BP < 140/90 mmHg. For hypertensive patients with diabetes mellitus type 2 the recommended BP level is BP < 140/85 mmHg. Therefore, hypertensive patients with diabetes mellitus type 2 had somewhat lower recommended BP levels compared with hypertensive patients without diabetes mellitus type 2. However, lower recommended values in BP did not influence the current study results (BP values of hypertensive patients with diabetes mellitus type 2 whose BP was not under control, were even higher than the recommended BP values for hypertensive patients without diabetes mellitus type 2 – 140/90 mmHg).

From hypertensive patients, who did not have diabetes mellitus type 2 as a co-existing risk condition 57 patients (39.6%) had their BP controlled and 87 patients (60.4%) had their BP over the recommended level. Compared to hypertensive patients with diabetes mellitus type 2: 7 patients (31.8%) had their BP under control, 15 patients (68.2%) had their BP over the recommended level (Table 6). However, there was no statistically important difference, when comparing BP control of hypertensive patients with diabetes mellitus type 2 and hypertensive patients without diabetes mellitus type 2.

Table 6. Treatment control of patients with hypertension and type 2 diabetes in “Sinu Arst perearstikeskus” (n = 166).

Variables	**Controlled (n = 64)**			**Uncontrolled (n = 102)**		
	n	**%**	**p**	**N**	**%**	**p**
Hypertensive patients with diabetes mellitus type 2 (n = 22)	7	31.8	0.49	15	68.2	0.49
Hypertensive patients without diabetes mellitus type 2 (n = 144)	57	39.6		87	60.4	

6 Discussion

In the current chapter, the author discusses research outcomes respectively to the pre-defined research objectives and research questions. As research limitations, the author describes possible shortcomings of the study design. Finally, author sets the possible future perspectives.

6.1 Research outcomes

Findings show that the majority (81% from the initial study group n = 205 and 81.9% from somewhat decreased study group n = 166) of hypertensive patients investigated in "Sinu Arst perearstikeskus" had high compliance to antihypertensive treatment regimen. Therefore, the first hypothesis, that 50% from the hypertensive patients are considered as low compliers, made based on literature overview, did not prove to be true.

One of the reasons associated with high compliance in the family physician office can be the fact that "Sinu Arst perearstikeskus" has been one of the highly-recognized GP office.

Since 2010 The Estonian Family Physician Association evaluates the quality of family physician's offices based on the quality guidelines, this process is named accreditation of the practices. Based on the accreditation the practices are divided into three groups: A, B and C level, where highest quality providers receive A level certificate. According to the Family Physician Association of Estonia "Sinu Arst perearstikeskus" has received the top quality in 2010, 2011, 2012, 2013, 2014 [37].

Therefore, if thinking to the reasons of non-compliance and how to increase it (described in detail under 2.7 and 2.8) then it is evident, that care providers or more specifically physicians and nurses have a great impact on patient's medication taking behaviour. For example, after the patient has received hypertension diagnosis his/her physician is the first one explaining the condition and its treatment.

Therefore, basic knowledge about hypertension, antihypertensive medications and the importance of medication taking should be given clearly and effectively. Also, underlining that patients are eventually responsible for taking their medication, moreover patients themselves have the central role in caring for themselves. Therefore, medical stuff play a major role while motivating patients [36].

Even more, while knowing that the reasons for not taking prescribed medications, can be associated with misunderstanding or ignoring physician's advice [38]. Thus, physician's ability to adequately explain the benefits of the treatment and possible complications, while also considering patient's lifestyle, cost of medication and the complexity of prescribed regimens, play a great role when considering the barriers for compliance [7].

All in all, relatively high compliance (81 – 81.9%) among hypertensive patients in "Sinu Arst perearstikeskus" compared with somewhat lower compliance around the word in developed countries (50%) can be associated with good patient provider interaction. So that the patients understand the nature of the disease, the need for treatment and the benefits for using medications as prescribed [7], [8].

Moreover, higher compliance rate can be associated with differences in study design and a consequence of the distinct characteristics of the sample.

Although hypertensive patients in "Sinu Arst perearstikeskus" had relatively high compliance towards to antihypertensive medications, yet 61.4% had their BP over the recommended level, therefore considered as patients whose BP is uncontrolled.

Quite similar results of BP control among hypertensives in Estonia was published in 2014. The study showed that among participants who were taking medications, only 40% had their BP controlled [24]. However, taking antihypertensive medications in the mentioned study was defined as follows: if the patient had been using antihypertensive medications during the last two weeks before answering the questionnaire. Also, no data about treatment compliance in the mentioned study was gathered.

Moreover, there can be several factors affecting such result. For example, though the rates of prescription refill are considered the most objective and easily performable method, however it is still prone to patient manipulation - pill dumping, pill sharing, buying out the pills but still not taking them [7]. Therefore, the reason of poor BP control can be associated with overestimation of patients following prescribed antihypertensive medications.

Another factor, that could have influenced on the result of BP control, is anxiety and/or conditional response due to an unusual situation. Therefore, BP is elevated in the office BP measurements at repeated visits and normal out of the office, either on ambulatory

blood pressure measurement (ABPM) or home blood pressure measurement (HBPM) [39]. In the literature, there is uncertainly of the exact term, thus several terms are being used such as white coat hypertension, isolated office hypertension and isolated clinic hypertension. Whatever term being used, it has been shown in population based studies, that the prevalence of white coat hypertension among hypertensive patients is about 32% [40]. Thus, also in current study white coat hypertension could have raised BP values for a number of patients.

Even more, the method of measuring BP can cause somewhat different values. Recently it has been suggested that unattended office BP measurements can help to neutralize the "white coat hypertension", because as measured by the patient's own, the BP values are lower than compared with the traditional cabinet BP measurements [23]. Unattended office BP measurements mean that medical stuff leave the room and after 5 minutes the patient measures her/his BP by herself/himself [17]. Therefore, in the future unattended office BP measurements might become a new standard giving additional value for disease management, allowing to decrease overtreatment with patients who have "white-coat hypertension" [19].

Moreover, according to Banegas et al one of the reasons for the low rate of BP control is associated with physician's inertia [41]. The term "physician's inertia" is defined as `lack of therapeutic action when the patients BP is uncontrolled`[16]. The reasons of "physician inertia" are mainly caused by the following concerns from the physician: possibility of side-effects due to greater dosages; doubts about the increased risk when BP in elevated; fear of decreasing the BP as low as it could cause a reduction in vital organ perfusion and lastly scepticism towards to different guidelines [16], [42].

Another possible explanation of low rate BP control, might be associated with those 39 (19%) patients, who had the diagnosis and the prescriptions, yet no data of BP values. More specifically, the explanation might be connected with the possibility that while calling and asking new prescriptions, the nurses usually asking about the HBPM, yet not always recording it, especially when BP is controlled.

However, generally, in all compliance groups there were more patients whose BP was over the recommended level. Yet, patients in high compliance group are more likely to

have their BP under recommended level compared with patients in the intermediate compliance group (statistical significance $p = 0.03$).

Previously studies have shown association between compliance and BP control. For example, short term (7 days) compliance less than 60% raised BP by approximately 12 – 15/7 – 8 mm/Hg compared to 7 days of excellent adherence [43]. Thus, the second hypothesis proved partially to be true when talking about the correlation between compliance and BP control. Yet, the results did not show that straight forward outcomes as stated in the other half of hypothesis (Hypothesis 2: There is a correlation between treatment compliance and BP control. Therefore, if patient is following prescribed treatment regimen relatively closely, then her/his BP levels are decreasing and vice a versa).

In addition to the main findings, the author fund statistically important association when comparing age groups combined with compliance: compliance was highest in the age group of 61 – 70 years, were 91.7% were considered highly compliant and lowest among participants who were ≤ 50 years old.

The association between compliance and patients age has been shown previously in several studies. For example, Tong et al published an extensive survey made in United States, where they gathered data for 4198 study subjects. The survey found clear statistically important association between younger age and non-compliance. More specifically, compliance was shown lowest among participants aged 18 – 44 years [44]. Yet, an extensive literature review, which included 102 articles, concluded that in the majority of the studies age was related to compliance, however results were not always unidirectional. A large proportion of studies showed that elderly have higher compliance, few showed the opposite effect. Moreover, in those few studies, where compliance was higher among younger, there were several cofounders, such as low education level, rural area + tuberculosis and physical disabilities. Therefore, generalization to overall population, based on prementioned studies, cannot be made [45].

All in all, based on the results of current thesis and on the previous researches, younger age is associated with lower compliance to antihypertensive medications. The reasons might be associated with different priorities in their everyday work, compared with older patients. As an example, younger patients are often loaded with work and other

commitments, therefore they may not be able to attend physician/nurse appointments [45], which could lead to underestimation of objective BP control and the importance for antihypertensive treatment.

Moreover, the results showed, that 87.6% of hypertensive patients with co-existing risk conditions (E78; E10 – E14) were considered as highly compliant, compared to 75% of hypertensive patients without co-existing risk conditions in the high compliance group. Comparison was found to be statistically relevant. The reasons why hypertensive patients with co-existing risk conditions are more likely considered as highly compliant compared with hypertensive without co-existing risk conditions, might be associated with the increase of awareness for their disease and/or condition, therefore also acknowledgment for the need and the importance of medications.

All in all, as a result of current thesis age and the presence of hypercholesterolemia (E78) and/or diabetes mellitus type 2 (E10 – E14) are one of the factors affecting treatment compliance among hypertensive patients. Yet, when considering disease management, there are several other factors, though not included to the current research, that could also influence treatment compliance, such as number of pills prescribed, frequency of medication administration etc.

Therefore, when trying to improve compliance and BP control, several factors should be taken into account. First, in order to identify certain subgroups of hypertensive patients who are less likely compliant towards antihypertensive medications and secondly, to plan interventions to support and improve long-term compliance and BP control [44].

Lastly, as mentioned before there was quite substantial number of patients who had: hypertension diagnosis, but no antihypertensive medication prescriptions – 23 patients; hypertension diagnosis and antihypertensive medication prescriptions, but no data about BP values in Perearst 2 – 39 patients. Therefore, treatment management of hypertensive patients should be improved. Thus, already structured BP field could be one of the mandatory fields in the future when talking of management of hypertensive patients. For doing so, it would be possible to collect more BP values, because in order to submit treatment story physician/nurse has to enter BP values. Furthermore, it would allow physicians to see all the BP values for the patient at once. Also, when talking about further

investigations, it enables to collect structured data, instead of reading through all the treatment stories.

6.2 Research limitations

The study had a relatively small sample population. Therefore, further investigations to evaluate the treatment compliance and BP control of patients with hypertension in total population should be carried out in Estonia. In addition, patients from secondary care units and in rural areas should be included to increase the relevance of the findings.

Treatment compliance of patients with hypertension in reality may differ compared with the results presented in the current thesis. For example, in hospitals, where patients with more complex diagnosis are followed by the cardiologist compared to the patients in primary care settings.

Though rates of prescription refills are considered to be objective method when evaluating treatment compliance among hypertensive patients, yet the selected method is still prone to patient manipulation (pill dumping, pill sharing, buying out the pills but still not taking them) [7].

Therefore, in the end there is no certainty whether the patient actually took prescribed treatment regimen or not. Moreover, as discussed in the literature overview, not only the prescribed treatment regimen is relevant, but also the dosage and timing. Therefore, for further investigation understanding compliance a multi-method approach would give more clear and accurate picture of whether and how medical recommendations are being followed [38], [46]. For example, compliance to antihypertensive medications might be assessed by pharmacy refill rates combined with patient self-report, and electronic medication monitors.

Data about the BP values and measurements, in the current study, was collected from the information system “Perearst 2” only. Access to “Digilugu” might give more complete data, because some patients with hypertension diagnosis are followed by the specialist (cardiologist) instead of GP.

6.3 Future perspectives

The future research of treatment compliance of patients with hypertension could be as follows:

- Finding out the reasons of relatively high treatment compliance, but yet poor BP control:
    i. Evaluation of anxiety on BP – traditional BP measurement vs unattended BP measurement;
    ii. Evaluation of the role of clinician's inertia on BP control – blood or urine samples to evaluate the effect of antihypertensive medications;
    iii. Detecting possible other reasons.
- Detecting the reasons for deficient data, especially why there is no data about BP values for quite substantial number of patients.
- Conducting a study to evaluate treatment compliance and BP control of patients with hypertension in total Estonian population:
    i. For treatment compliance evaluation, a multi-method approach is suggested to get more accurate results;
    ii. Identifying sub-groups of hypertensives who are less likely compliant to plan interventions to support and improve long-term compliance and BP control;
    iii. Evaluating the effect of physicians and nurse's appointments to treatment compliance and BP control.
- Usability evaluation of the current information systems used in "Sinu Arst perearstikeskus" to help managing hypertensive patients. Identifying the information can and is needed to be structured in the future.

7 Summary

Poor compliance to medication among patients with hypertension is common, causing cardiovascular diseases (CVD) such as stroke, ischemic heart disease, heart failure and increasing total mortality. In addition, poor compliance is economically a burden to the whole society due to increased healthcare costs [10]. Treatment compliance of patients with hypertension is considered to be one of the main indicators improving treatment results. Therefore, it is important to evaluate compliance systematically and give feed–back to health care providers [14]. Though the reasons of non-compliance are not only connected to health care providers, yet highly motivated and patient centred health care providers can create positive impact improving compliance and therefore also increasing quality of care.

The aim of the master thesis was to demonstrate treatment compliance of patients with hypertension and finding its impact to the BP control. Therefore, data about prescriptions was asked from Estonian Health Insurance Fund and data about BP measurements (date and value), patients gender, age, specific hypertension diagnoses (I10 – I13), co-existing risk conditions (E78, E10 – E14) and the date of first hypertension diagnosis was manually collected from "Sinu Arst perearstikeskus" information system Perearst 2.

The main outcomes and conclusions of the thesis are following:

- Treatment compliance rates among hypertensive patients in "Sinu Arst perearstikeskus" were surprisingly high. Therefore, the first hypothesis: Half of the studied patients are in a low treatment compliance group, meaning they are following antihypertensive treatment regimen < 39% did not prove to be true. Most of the patients studied were in high compliance group: 81.9% from 166 patients.

- Although 81.9% from the study group had high compliance to antihypertensive medications, yet only 38.6% had their BP under control. The second hypothesis proved to be partially true, because generally, in all compliance groups there were more patients whose BP was over the recommended level. Yet, patients in high compliance group are more likely to have their BP under recommended level compared with patients in the intermediate compliance group. The reasons for

these results might be associated with several factors such as *white coat hypertension* and *clinician inertia*.

Therefore, the management of hypertensive patients should be improved. Technology could provide a great support. Currently, in the information system used in GP practice, there was an opportunity for medical stuff to use structured field for BP inputs, yet in most cases the field was not used. Thus, BP could be one of the mandatory fields for managing hypertensive patients.

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