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KUOPIO STUDY 75+ : THE PREVALENCE OF ORTHOSTATIC HYPOTENSION

Diplomová práce

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CONTENT

1 INTRODUCTION

„Ageing is a privilege and a societal achievement".
"Human life shows an unavoidable tendency to physical and mental deterioration, with death as the end-point."

The world is fast ageing. There is a high level of awareness in developed countries that people of advanced years constitute more of population than hitherto and that the processes which have given rise to this state seem to continue indefinitely. The distribution of population according to the age groups is changing in turn for older part of population (table 1 and 2). Fewer children are born in developed countries and the lifespan is increasing in general in all countries. In 2000, there were 600 million people aged 60 and over; there will be 1.2 billion by 2025 and 2 billion by 2050. Today, about two thirds of all older people are living in the developing world; by the year 2025, it will be by estimation 75% (Council of Europe 2001 Recent Demographic Developments in Europe 2001).

Ageing is a normal physiological process which could be found in different levels of life, in cells, tissues and organs. While losing body cells and decreasing of organ's functions, most of older adults continue leading a full and active life. On the other hand we can observe progressive restriction of physical and mental abilities in some of them (Armour and Cairns 2002). We all are becoming less capable of productive employment and living qualitatively during aging process, it is just a question of time. Some of us will experience the results of aging earlier than the others. There are differences within individuals and these can be partly explained by different genetic information and partly by lifestyle. The physiology of aging can give us ideas about differences between young and old body of human being.

Our knowledge improved in every part of health care system. The prevention, the diagnosis and the treatment are more powerful nowadays in comparison to the past. The possibility of cure arose for many people suffering from different health problems which couldn't be solved in last decades. According to the tendency of aging world we are forced to be ready for providing more health and social services for older part of population. As we know, the life of elderly is accompanied with many different disorders and illnesses, which are frequently combined together. It is rare to find any old person who doesn't suffer from any health

problem. The availability of drugs increases on the market and the exposure to medicine is growing in individuals and in society. The danger of different interactions and adverse effects becomes nowadays attentions worthy.

All systems of body are involved in aging process. Our area, which we are interested in, is cardiovascular system where many changes occur. The structure of heart and veins don't remain the same. There are taking part particular processes which affect the work of both. In general, the heart has to produce more work to reach the same effectiveness as young heart and on the other hand veins are less capable in regulation of blood flow. The ability to maintain haemodynamic homeostasis during orthostatism (changing position from lying position to standing position) becomes problematic in older people. Certain volume of blood which is located in thoracic area during lying moves to pelvic area during standing. There are complex processes which maintain this situation but they seem to be impaired during aging from different reasons. The aged people are predisposed to significant decline in blood pressure so called orthostatic hypotension. The reason is a decrease of physiological functions, increase of intake medications which influence cardiovascular system or underlying illness which affect haemodynamic homeostasis.

The prevalence is of wide range and differs between home-dwelling elderly (lower rate) and elderly living in institution (higher rate). The conditions for developing orthostatic hypotension are not the same. Elderly living in institution are supposed to have different lifestyle (bed rest) and also medicine intake is higher. Detection of this phenomena is important. There is higher risk of falls and higher cardiovascular risk associated to this disorder. It decreases quality of the life and it is often accompanied with symptoms as dizziness, headache and syncope.

Table 1: Aging of population in advanced countries in Europe 2000-2050 (Council of Europe 2001; Recent Demographic Developments in Europe 2001)

Region	**Proportion of human beings in age of 65 and more (in %)**			
	2000	**2015**	**2030**	**2050**
Europe	13,9	16,4	22,1	27,6
North America	12,3	14,6	20,4	21,4
Australia/New Zealand	12,2	15,1	20,2	22,5
Czech republic	13,9	18,7	24,4	32,7

Table 2: Progress in all groups of age in Europe 2000-2050 (Council of Europe 2001. Recent Demographic Developments in Europe 2001)

Group of age	**2000**	**2015**	**2030**	**2050**	**2015**	**2030**	**2050**	**2000**	**2015**	**2030**	**2050**
	Total number in millions				**Index (2000=100)**			**Proportion in population (%)**			
0-14	150	120	113	106	80	75	70	18,6	15,0	14,5	14,7
15-64	546	549	493	414	101	90	76	67,5	68,6	63,4	57,7
65+	112	132	172	198	117	153	176	13,9	16,4	22,1	27,6
Total	808	801	778	718	99	96	89	100,0	100,0	100,0	100,0

2 AIM OF STUDY (WRITTEN IN CZECH)

Studie Kuopio 75+ byla provedena ve Finsku v roce 1998. Vzorek populace byl vybrán ze záznamů o sčítání lidu, provedené v oblasti Kuopia podle náhodného principu, tedy randomizovaně. Byla vybrána populace ve věkové kategorii 75 let a více. Naše data pocházejí z roku 2003, kdy bylo provedeno pokračování studie u přeživších..

Cíle této práce byly následující:

1. Stanovení prevalence ortostatické hypotenze. Zajímá nás, zda se prevalence pohybuje v obdobném měřítku, jaké bylo zaznamenáno v jiných studiích. Určit frekvenci jednotlivých typů OH, tedy OHS 1/3 min a OHD 1/3 min.

2. Zhodnocení spojitosti mezi výskytem ortostatické hypotenze a pohlavím, vyšším věkem, zvýšeným krevním tlakem a polyfarmacií.

3. Dalším cílem je získání celkového přehledu o krevním tlaku. Chtěli bychom porovnat hodnoty mezi sebou v jednotlivých polohách, hledat rozdíly ve stanovených věkových skupinách a taktéž mezi muži a ženami.

4. Zpracování dat o pravidelné a nepravidelné medikaci a určení tak úrovně polyfarmacie ve studované populaci s ohledem na pohlaví, věk a krevní tlak.

3 LIST OF ABREVIATIONS

AAS/AAN	American Autonomic society and the American Academy of Neurology
ACEI	Angiotensin converting enzyme inhibitor
ADME	Acronym for absorption-distribution-metabolism-elimination
ADR	Adverse drug reactions
ATC	Anatomic therapeutical chemical classification
BP	Blood pressure
COI	Chronic orthostatic hypotension
CR	Creatinine
DPB	Diastolic blood pressure
GIT	Gastrointestinal tract
ID	Intermediate postural drop of blood pressure
LBPN	Lower body suction
LA	Left atrium
MAOI	Monoamine oxidase inhibitors
OH	Orthostatic hypotension
OHD 1 min/ 3 min	Orthostatic hypotension diastolic after 1 or 3 minutes
OHS 1 min/ 3 min	Orthostatic hypotension systolic after 1 or 3 minutes
PRA	Plasma rennin activity
PVR	Peripheral vascular resistance
SA (node)	Sinoatrial (node)
SBP	Systolic blood pressure
SSRI	Selective serotonin reuptake inhibitors
SSS	Sick sinus syndrome
TCA	Tricyclic antidepressants

4 CHANGES IN ORGANISM DURING AGING

4.1 Impairment of homeostasis

Homeostasis is the maintenance of a constant internal environment, necessary for effective physiological activity. Homeostasis involves a complex series of physiological and biochemical changes and responses. Nearly all organs and systems are involved in this process (Redfern SJ, Ross FM 2001). Aging is associated with marked and sustained increases in sympathetic nervous system (SNS) activity to several peripheral tissues, including the heart, the gut-liver circulation, and skeletal muscle. These include chronic reductions in leg blood flow and vascular conductance, increased tonic support of arterial blood pressure, reduced limb and systemic alpha-adrenergic vasoconstrictor responsiveness, impaired baroreflex buffering, and decreased vascular and cardiac responsiveness to beta-adrenergic stimulation. These effects of chronic age-associated SNS activation on the structure and function of the cardiovascular system, in turn, may have important implications for the maintenance of physiological function and homeostasis, as well as the risk of developing clinical cardiovascular and metabolic diseases in middle-aged and older adults (Seals and Dinenno 2004).

Postural control

Postural stability is normally achieved by static reflexes, which involve sustained contraction of the musculature, and phasic reflexes, which are dynamic, short term and involve transient corrective movements. With ageing, the frequency and amplitude of corrective movements increase and an age-related reduction in dopamine D2 receptors in the striatum has been suggested as the probable cause. Drugs which increase postural sway, e.g. hypnotics and tranquilizers, have been shown to be associated with the occurrence of falls in the elderly (Armour and Cairns 2002)

Orthostatic circulatory responses

In normally elderly subjects there is blunting of the reflex tachycardia that occurs in young subjects on standing or in response to vasodilatation. Structural changes in the vascular tree

that appear with ageing are believed to contribute to this observation although the exact mechanism is unclear. Antihypertensive drugs, drugs with α receptor blocking effects (e.g. TCA, phenothiazines and some butyrophenones, drugs which decrease sympathetic outflow from the central nervous system (e.g. barbiturates, benzodiapines, antihistamines and morphine) and antiparkinsonian drugs (e.g. levodopa and bromocriptine) are therefore more likely to produce hypotension in the elderly (Armour and Cairns 2002).

Thermoregulation

We can observe impaired thermoregulatory mechanism in the elderly; of course it is not universal. An event of hypothermia can be produced by drugs which are able to cause sedation, impaired subjective consciousness of temperature, decreased mobility and muscular activity, vasodilatation (Ewing 2002).

Cognitive function

Many structural and neurochemical changes take place during ageing. Cholinergic system is linked to normal cognitive function, and in the elderly there is reduced activity of choline acetyltransferase in some areas of the cortex and limbic system (Armour and Cairns 2002).

Visceral muscle function

There is a decline of gastrointestinal motility in geriatrics. The constipation is common problem. Anticholinergic drugs, opiates, TCA and antihistamines are more likely to cause constipation or ileus in the elderly. Anticholinergic drugs may cause urinary retention in elderly men, especially those who suffer from prostatic hypertrophy. Bladder instability is also common and urethral dysfunction more prevalent in elderly women (Armour and Cairns 2002).

4.2 Aging and cardiovascular system

There are changes in aging cardiovascular system in progress, which lead to altered cardiovascular physiology. It appears in every individual but not in the same rate. Those

alterations have to be differentiated from the effects of pathology, such as coronary artery disease, that occur with increasing frequency as age increases (Cheitlin 2003). Blood pressure is unstable and sensitive to changes in position, meals, and physical activity. Accentuation of SBP is the main determinant in problems of postural hypotension. Hypertension and alterations in the afferent pathway of the baroreflex, adrenergic receptors, structure of the arterial wall, and intravascular volume appear to participate in the changes of blood pressure variability observed in the elderly (Girard 1999).

4.2.1 The main changes in arteries during aging

Large artery stiffness is determinant of aging. Central arteries stiffen progressively with age, whereas peripheral muscular arteries change little with age. Increase of central artery stiffness with age is responsible for earlier wave reflections and changes in pressure wave contours, whereas the aortic stiffness is a potential risk factor for increased cardiovascular morbidity and mortality. (Benetos et al 2002) It can be observed in normotensive as in hypertensive people (Safar and Smulyan 2007). It is result of many changes in the arterial media, which will be discussed later. The consequence is reduction of arterial distensibility with the increase of pulse wave. Common finding is dilation of arteries. Especially, this process affects aorta. The result is becoming less compliant, which influences the blood flow and its handling. Impaired endothelial release of nitric oxide is the reason of increase PVR, particularly observed by older hypertensive women. The reduction in intravascular volume is observed. Cardiac output and peripheral vascular resistance (PVR) determine mean arterial blood pressure. A rise in peripheral vascular resistance and the increase in artery stiffness, both lead to increase in systolic blood pressure, while the decrease in PVR or increase of large artery stiffness will result in fall diastolic blood pressure. Circulating levels of catecholamines increase with the age (Cheitlin 2003).

Afterload

Afterload is the pressure which the ventricle ejects blood against. Arteries determine afterload. As we know, arteries become dilated with the less compliance during aging (Gerstenblith et al 1977).The cause is progressive thickening of the aortic media and intima (Safar 1990). Increase in arterial stiffness results from changes in the arterial media such as

thickening of the smooth muscle layers, increased fragmentation of elastin, increased amount and different characteristics of collagen and increased calcification (Bilato and Crow 1996). The consequence of increased stiffness of aorta and reduction of its distensibility is the increase of pulse wave velocity. These structural changes in the arterial wall are independent of arteriosclerosis (Avolio et al 1985). The aged-associated increase of stiffness and decrease of distensibility don't concern distal arteries (Boutouyrie et al 1992). Impedance spectral patterns have shown an age-related increase in characteristic aortic impedance and in peripheral vascular resistance. The reduction in arterial compliance contributes more to the age- related increase in afterload than does the loss of peripheral vascular beds (Rodeheffer et al 1984)

With aging, there is an increase in systolic BP pressure and widening of pulse pressure in general**.** A slight reduction of diastolic BP occurs after 6th decade (Landahl et al 1986). The increase of systolic BP is consequence of interaction of many factors: aging, cardiovascular disease, and lifestyle factors such as dietary intake of sodium, level of physical activity, body weight. As aortic compliance is decreasing during the age, there is a decrease of transfer kinetic energy from the blood ejected during left ventricular systole to potential stored energy in the elasticity of the aortic wall, so there is a decreased return of potential energy stored in the wall of aorta to the kinetic energy of blood flow during the diastole. The left ventricle now has to eject its stroke volume into the less compliant aorta with the greater pressure and force to achieve an adequate cardiac output. The increased pulse wave velocity also causes the pressure in the aorta to increase and peak later in systole (Aronow 2006). The aging process is accompanied with an increased prevalence of hypertension and cardiovascular disease (Blacher and Safar 2005).

The changes in heart structure and heart work

The increase of systolic load demands bigger excess mechanical strains on the left ventricle, that's leads to the hyperplasia of the wall of left ventricle. The hypertrophy of the left ventricle is caused by increased volume of cardiac myocytes, not by increased number of them. Fibroblasts undergo hyperplasia and collagen is deposited in the myocardial interstitium. The hypertrophy is not unfortunately accompanied with increased coronary perfusion. A coronary perfusion is dependent primarily on the diastolic pressure and the duration of diastole (Aronow 2006). The heart work is influenced also by dropout of atrial pacemaker cells

resulting in a decrease in intrinsic heart rate. With fibrosis of the cardiac skeleton there is calcification at the base of the aortic valve and damage to the His bundle as it perforates the right fibrous trigone. Finally there is decreased responsiveness to ß - adrenergic receptor stimulation (Cheitlin 2003).

The main features of heart work in aged body are decrease of cardiac output and reduction in heart rate. Reduction in heart rate is usually caused by cardiac disorder, which occurs by aging. The rhytmicity of SA node declines in age, so called Sick sinus syndrome (SSS). Its initial manifestations range from asymptomatic to nonspecific and include palpitations, fatigue, confusion, and even syncope and sudden death. The result is bradyarrhytmia, which can interfere with tachyarrhytmia, especially atrial fibrilation. Medications such as digoxin, beta-blockers, and calcium blockers may initiate or worsen the manifestations of SSS (Rodriguez and Schocken 1990)

Preload

Preload is the filling volume of left ventricle; determined by many factors. During aging resting left ventricular end-diastolic volume does not change but the left ventricular early diastolic filling shows decrease during aging. Left ventricular filling during early diastole decreases 50% from age 20 years to 80 years (Bryg, Williams and Labovitz 1987;Gerstenblith et al 1977;Iskandrian and Hakki 1986).

Stiffness and less compliance, impaired relaxation, passive filling decrease of LA may lead in hypotension if preload is reduced. An age related increase of systolic blood pressure also impairs early diastolic filling, it can also lead to hypotension, if the preload is reduced. Preload is maintained because of more vigorous left atrial contraction for increasing late diastolic filling of the left ventricle (Iskandrian and Hakki 1986) (Bryg, Williams and Labovitz 1987). Augmentation of late diastolic filling of the left ventricle prevents a decrease in end diastole volume with aging. An age related increase in left atrial size resulting from increased wall stress due to increased left atrial pressure counteracts the effect of decreased left ventricular compliance with aging. A reduction of preload is not well tolerated in elderly people. Reduced intravascular volume, decreased venous return to the heart, vasodilatation by drugs or disease states, drugs as nitrates or diuretics can reduce preload and decrease cardiac output and cause the hypotension in elderly people (Aronow 2006). Decreased compliance of

the left ventricle and reduced cardiac and vascular responsiveness to β-adrenergic stimulation (Lakatta 1980) predispose elderly to be greatly dependent on the Franklin-Starling mechanism to increase cardiac output. They are more susceptible to develop orthostatic hypotension (Robbins and Rubenstein 1984). Impaired baroreceptor reflex sensitivity, loss of arterial compliance and decreased venous return due to increased venous distensibility, all contribute to developing of orthostatic hypotension (Aronow and Ahn 1994;Lipsitz et al 1983). Compensatory mechanisms for maintenance of fluid volume and electrolyte balance are impaired. Changes in the control of both water intake and excretion accompany aging and may predispose the elderly to disturbances in sodium and water balance (Rolls and Phillips 1990). Both renal plasma flow and plasma rennin activity (PRA) are decreased. PRA decrease is observed markedly more in hypertensives than in normotensives.

Since the artrial contraction may contribute up to 50% of left ventricular filling in a poorly compliant left ventricle, development of atrial fibrilation may cause a marked reduction in cardiac output because of the loss of left atrial contribution to the late diastolic filling. The incidence of chronic atrial fibrilation increases with the age (Aronow 2006).

Contractility

The intrinsic ability of the heart to generate force does not change with the age in healthy people. Prolongation of left ventricular ejection time and of the pre-ejection period with aging in healthy persons indicates that prolongation of contraction occurs with aging. Age associated reductions in maximal heart rate and in left ventricular contractility during maximal exercise are manifestations of decreased β-adrenergic responsiveness with aging (Swine 1992).

4.3 Changes in response to drug administration

Advancing age is accompanied by pharmacokinetic and pharmacodynamic changes, together with impairment of homeostasis and coexisting diseases make this part of population particularly sensitive and frail e.g. to adverse drug reactions ADRs.

4.3.1 Pharmacokinetics in old age

Pharmacokinetics is a branch of pharmacology dedicated to the study of the time course of substances and their relationship with an organism or system. Pharmacokinetics has been broadly divided into two categories of study: absorption and disposition. Disposition is further subdivided into the study of the distribution, metabolism and elimination or excretion of a drug. Thus, pharmacokinetics is sometimes referred to as ADME.

Drug absorption

To reach the blood stream, the drug has to pass certain barriers (except intravenous dosage forms). The most common dosage form is oral dosage form nowadays. The gastrointestinal environment influences the dissolution rate and the rate of absorption. Although the overall surface of the intestinal epithelium, gut motor function, splanchnic blood flow and possibly gastric acid secretion decrease with age, absorption of most drugs that permeate the gastrointestinal epithelium by diffusion is not diminished in the elderly. An age dependent reduction of the extent or rate of absorption was shown for only a few drugs (indomethacin, prazosine, digoxin). Agents that impede propulsive gut motility (antimuscarinic drugs, antihistamines, tricyclic antidepressants, opioids) retard intestinal absorption to a greater extent that does aging. Compounds that permeate the intestinal epithelium by carrier-mediated transport mechanisms may be absorbed at a lower rate in the elderly; examples are calcium, iron, and vitamins. Gabapentin and some nucleoside drugs are also absorbed by mediated transport, but it is unclear if their absorption is retarded in old age (Turnheim 1998). In conclusion, there is no evidence of serious problems with handling the drugs in comparison with the drug metabolism and elimination. The doses of most drugs need not to be altered because of the altered gastrointestinal environment.

Table 3: Changes in absorption in aging (Armour and Cairns 2002)

Summary of absorption changes in GIT
1. Reduced amount of saliva
2. Increasing gastric Ph
3. Reduced gastric acid secretion
4. Increased gastric emptying time
5. Decreased gastric surface area
6. Decreased gastrointestinal motility
7. Decreased active transport mechanisms

Although there is atrophy of the epidermis and dermis in the aged with a reduction in barrier function of the skin, the rate of transdermal drug absorption may be diminished in elderly because of reduced tissue blood perfusion (Trautinger 2001). The decrease in blood flow is often caused by replacement of well-perfused tissue by connective tissue and fat (Ewing 2002). This holds also true for absorption from the subcutaneous and muscular tissue. Intramuscular injections should be avoided generally in this age group because of erratic absorption and the high risk of sterile infiltrates (Turnheim 2003).

Drug distribution

There appear changes in distribution in older people connected to changed volume of body fat and water. There is also the reduction in total body protein. A decrease in skeletal muscle is the most noticeable manifestation of this change but there is also a reduction in other physiologic proteins such as organ tissue, blood components, and immune bodies (Chernoff 2004). As cardiac output is lower in elderly people and peripheral resistance is increased, these changes follow into reduction of organ's perfusion. The kidneys and liver are receiving reduced amounts of blood, so that it affects also their capability of metabolism and excretion (Armour and Cairns 2002).

Body water content falls by 10–15% until the age of 80. The volume of distribution of hydrophilic drugs therefore decreases; the equivalent doses given to younger individuals will result in higher plasma concentrations. This, for instance, is the case for aspirin, tubocurarine, edrophonium, famotidine, lithium, but also ethanol (Turnheim 1998). Use of diuretics may

reduce the extracellular space even further, leading to accentuation of toxic drug effects. Body fat, on the other hand, increases on average from 18 to 36% in men and from 33 to 45% in women (Vestal 1997). Thus, although the fat content is higher in women than in men, the relative change in the volume of distribution for lipophilic drugs is more marked in men than in women. Examples for drugs with increased volumes of distribution in old age are amiodarone, diazepam, teicoplanin, and verapamil (Turnheim 1998).

Acidic drugs tend to bind to plasma albumin, whilst basic drugs bind to α_1–acid glycoprotein. Plasma level of albumin is decreasing with age, the result is that free fraction of acidic drugs is increasing, e.g. warfarin, cimetidin, furosemid. Plasma level of α_1–acid glycoprotein could remain the same or slightly rise; the result is increased free fraction of basic drugs, e.g. lignocaine. Disease can change more in case of glycoprotein in comparison to the impact of the age (Armour and Cairns 2002).

Very old individuals lose weight and become frail. It isn't frequently taken into consideration as low weight patients frequently receive higher doses per unit body weight than heavier patients. Hence low body weight, in addition to advanced age, constitutes a risk factor for over medication (Campion et al 1987)

Table 4: Changes in distribution during aging (Armour and Cairns 2002)

Summary of changes in distribution
1.Reduced cardiac output
2.Increased peripheral vascular resistance
3.Decreased renal and hepatic blood flow
4.Reduced body water
5.Increased body fat
6.Altered serum levels of proteins

Drug metabolism

Drug metabolism is mainly taking place in liver; other less important places of metabolism are organs as kidney, lungs and gut. Two basic impacts of senescence are reduced hepatic blood flow up to 40% (Tregaskis and Stevenson 1990) and reduced mass of cells. No consistent relationship has been found between age and the activity of microsomal

cytochrome CYP450, which are responsible for the Phase I – metabolism. The metabolic clearance of some drugs is decreased by 20–40% (examples are amiodarone, amitriptyline, triazolam, fentanyl, nifedipin, warfarin, and verapamil), whereas that of others is unchanged (for instance alfentanil, diazepam, paracetamol [acetaminophen], celecoxib, diclofenac, citalopram, and risperidone), apparently irrespctive of which CYP enzyme is involved (Turnheim 2003). This discrepancy has been attributed in part to the property of high or low extraction of the drug by the liver. Drugs that are extensively 'cleared' from the blood by the liver display an age-related decrease in metabolic clearance as blood flow through the liver declines in the elderly (Le Couteur and McLean 1998). After absorption in intestine, drugs are transported via the portal circulation to the liver, where is taking place first pass metabolism. Many lipid soluble drugs are extensively metabolized (more than 90-95%). This markedly is diminishing their bioavalibility in organism. This category includes morphine, propranolol and many of the calcium channel antagonists. Their decreased clearance can lead in clinically significant problems. The metabolic clearance of drugs with low hepatic extraction, on the other hand, is usually not altered, since it is not dependent on hepatic hemoperfusion but on the tissue content of metabolizing enzymes (Le Couteur and McLean 1998). The nutritional status of a patient has a marked influence on the rate of drug metabolism. In frail elderly, drug metabolism is diminished to a greater extent than in elderly with normal body weight (Vestal 1997;Walter-Sack and Klotz 1996).

Table 5: Changes in metabolism during aging (Armour and Cairns 2002)

Summary of metabolic changes
1. Reduced mass of hepatic cells
2. Altered first pass effect
3. Increased steady-state levels of certain drugs
4. Increased half-lives

Drug elimination

The most important pharmacokinetic change in the elderly is the reduction in renal drug elimination. Glomerular filtration rate, tubular secretion, and renal blood flow are reduced. Disregarding the reduction in drug elimination by the kidney in the elderly will result in increased drug serum levels. In fact, the decline in renal function is closely related to the

incidence of adverse drug reactions ((Lindeman 1992;Muhlberg and Platt 1999)). Many drugs are fully or mainly excreted via kidney, some of them in unchanged active form, for instance digoxin, gentamicin. After the age of 40 there is progressive development of glomerulosclerosis in the kidney, the number of functioning glomeruli is reduced. Renal blood flow decreases by approximately 1% per year, among other factors increased angiotensin-II and endothelin levels and decreased prostaglandin concentrations may contribute to this effect. Glomerular filtration rate declines by 25–50% between the ages of 20 and 90. Tubular secretion falls in proportion to the loss of glomeruli, so that the glomerulotubular balance is preserved (Lindeman 1992;Muhlberg and Platt 1999).

Renal elimination of most drugs is closely correlated with the endogenous creatinine clearance CL_{CR}. The influence of the age, weight and serum concentration of creatinine was taken into account by Cocroft and Gault equation (1976):

$$CL'_{CR} = \frac{(140 - \text{age}) \cdot \text{bodyweight(kg)}}{72\, C_{CR}}.$$

This equation give the result for clearance in men, for women it has to be multiplicated with 0, 85. The reason of that lies in lower skeletal muscle mass in women. It should be considered, using this equation, we receive average values. The only way to be certain about the value is to measure it in a given person. Elderly people may have normal plasma creatinine (CR) levels but still have a reduced $CL_{CR,}$ because serum CR concentrations are result of a balance between production CR by muscle tissue and clearance of CR of kidney. Production is less and decreased renal excretion is compensated, what can give the “normal” serum level of CR (Rowe et al 1976)

4.3.2 Pharmacodynamics in old age

Pharmacodynamics is the study of the biochemical and physiological effects of drugs and the mechanisms of drug action and the relationship between drug concentration and effect. It is often summarily stated that pharmacodynamics is the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug. Molecular and cellular changes in the old age occur naturally, that is cause of the different response to drug

in comparison to young organism. Most of the drugs are not enough lipid-soluble and can't go trough the cell membrane, so they exert their effect through the interaction drug-receptor. Number of receptors, drug affinity to the receptor, receptor membrane environment and mechanism of binding, postreceptor signal´s way as signal amplification or control mechanisms can be altered fat (Armour and Cairns 2002).

There is a profound decrease in cardiac beta-adrenergic responsiveness with aging. This occurs by multiple mechanisms including downregulation and decreased agonist binding of β 1-receptors, uncoupling of β2-receptors, and abnormal G protein-mediated signal transduction (White et al 1994). Generally, β -adrenoreceptor function is thought to decline with age, while α -adrenoreceptor function is usually unchanged or even increased. For example, airway β 2-adrenoreceptor responsiveness is diminished in the elderly, suggesting that airway β -adrenoreceptor dysfunction may be implicated in late-onset asthma (Connolly et al 1995). An age-related decline in β -adrenergic responsiveness has been proposed as a causative factor of reduced bladder compliance in the elderly (Li et al 2003). These authors propose reduced β -adrenoreceptor density and adenylyl cyclase activity as the underlying molecular mechanism for the changes observed. Reduced β -adrenoreceptor-mediated vascular smooth muscle relaxation in the aged has been demonstrated using the dorsal hand vein technique. Maximal dilatation induced by isoprenaline was reduced in elderly subjects, but maximal dilatation induced by adenosine was not. It is important to note that these results indicate that the age-associated receptor down-regulation is receptor specific and not due to a general loss in the ability to vasodilate (Ford et al 1992). The decline in β -receptor function just described does not occur with α -adrenoreceptors. Rudner et al. has shown that arterial α 1-adrenoreceptor expression increases with age at the mRNA and protein levels. α 1-Adrenoreceptor expression doubles with age (<55 versus ‡ 65 years) and is mainly due to an increase in α 1b-adrenoreceptor expression (Rudner et al 1999). Hogikyan et al. 1994 conclude that there is appropriate desensitization of arterial α -adrenergic responsiveness among the older relative to the young subjects that is specific for the alpha-adrenergic system (Hogikyan and Supiano 1994). What is more, samples obtained from older subjects are more responsive to α -agonists. Taken together, these studies seem to show that ageing vascular smooth muscle is more responsive to vasoconstricting α -agonists and less responsive to vasodilating β -agonists. In summary, the ageing process produces subtle changes in adrenoreceptor expression, up-regulating some, leaving others unchanged and down-regulating others. What

is not happening is a general decline in receptor function due to a general decline in tissue viability (Burton et al 2005).

5 ORTHOSTATIC HYPOTENSION

5.1 Definition

Orthostatic hypotension was defined in 1995 by a consensus statement by American Autonomic society and the American Academy of Neurology AAS/AAN. OH is assessed when following criteria are fulfilled, a drop of 20mm Hg or more in the systolic BP or a drop of 10mm Hg in the diastolic BP within 3 minute after standing up from a lying position or passive head-up tilt position at 60 degrees (Consensus statement 1996a; Consensus statement 1996b). Studies differ frequently in timing of passive head-up tilt (Lipsitz et al 1996;Nieminen et al 2005;Timoteo et al 2005;Ylitalo et al 2005), for instance study done by Nieminen et al. 2005 in Finland, there results were measured after 8 min provocation, in another studies (Timoteo et al 2005;Ylitalo et al 2005) there was blood pressure reported after 3 min of tilt provocation at 60 degrees. Different concerned timing of active orthostatic tests is also common (Boddaert et al 2004;Robertson, DesJardin and Lichtenstein 1998).

Definition stated by consensus is not ideal, it cannot include elderly, who demonstrate OH after longer period of standing or who have postural symptoms at decreases of <20/10mmHg (Consensus statement 1996b). There could be problem by those frail elderly who are not able to stand longer than 1 min. Weiss et al. 2004 conducted in Israel study which considered drop of blood pressure under the threshold of definition. They defined intermediate postural drop (ID) in BP as a decrease of 10-19 mmHg in systolic BP and/or of 5-9 mmHg in diastolic BP. The measurements were implemented in the morning, afternoon and evening in 502 elderly patients. The intermediate drop of blood pressure was associated with OH during the day. Elderly, who experienced ID in the morning, had 57% probability to experience OH during the day. Monitoring values under the threshold seem to be important too. Orthostatic hypotension was defined as a drop of 20mm Hg or more in the systolic BP and a drop of 10mm Hg in the diastolic BP either 1 minute or 3 minutes after standing up from a lying position in our study, this definition was conducted also in another studies (Saez et al 2000).

5.2 Mechanism and nosology

Orthostatic hypotension develops if the compensatory mechanisms fail to resist the approximately 500 ml reduction of blood coming to the heart as a person stands up from a lying position. When cardiac output decreases, baroreceptors located in heart, aorta, and carotid artery are stimulated to increase the heart rate and cause peripheral vasoconstriction to maintain the blood pressure (Hajjar 2005).

As many systems are involved in mechanism of haemodynamic homeostasis, there can be found many causes of OH. The classification is not ideal, because there are occurring overlaps in individual conditions causing OH and sometimes OH is a symptom of underlying disease or pathophysiological process. It is distinguished primary versus secondary and acute versus and chronic OH (table 6). Primary is related to postural haemodynamics as the main manifestation of OH. Mostly it is connected to primary autonomic dysfunction. On the other hand underlying illness causes secondary OH. Acute OH develops over a very short time and in general it needs immediate attention (Hajjar 2005).

Orthostatic hypotension is the most incapacitating symptom of autonomic failure. This disorder occurs with both central autonomic neurodegenerative disorders, such as multiple system atrophy and Parkinson's disease, and peripheral autonomic disorders, such as the autonomic peripheral neuropathies and pure autonomic failure. The hallmark of both central and peripheral causes of neurogenic orthostatic hypotension is the failure to release norepinephrine appropriately upon standing (Freeman 2003).

Table 6: Types of orthostatic hypotension (Hajjar 2005)

ACUTE			
	Primary	Acute dysautonomia	
	Secondary	Volume	Volume depletion Acute blood loss
		Neuromuscular	Spinal cord lesions Acute stroke
CHRONIC			
	Primary	Pure autonomic failure Idiopathic orthostatic hypotension Multiple system atrophy Baroreflex failure Carotid sinus hypersensitivity Neurocardiogenic syncope Paroxysmal orthostatic tachycardia Syndrome/orthostatic intolerance	
	Secondary	Nervous system	Stroke Tumor Multiple sclerosis Neuropathy (diabetic autonomic) Guillain-Barré Syndrome Labes dorsalis Amyloidosis HIV Parkinson's disease Lewy body dementia
		Endocrine	Hypothyroidism Adrenal insufficiency
		Muscular disease	Bed rest Atrophy
		Drugs	

5.3 Pathophysiology of OH

Maintenance of blood pressure and heart rate during postural changes is proceeding by cardiovascular, musculoskeletal, renal, endocrinological and autonomic nervous system. These systems take control under haemodynamic balance that included blood volume, cardiac function and peripheral resistance during active (stand-up from supine position) or passive (head-up tilt) postural changes (Hajjar 2005).

In supine position there is 30% of blood occurring in chest. During process of changing position from lying to standing, all involved systems have to maintain 500 ml of blood, which pools into the pelvic and lower circulatory system, otherwise the orthostatic hypotension will occur. On the acute orthostatic hypotension there is a response from baroreceptors in carotid, decrease of vagal tone and increase of sympathetic flow, which leads to increase of heart rate, peripheral resistance, stroke volume and the blood pressure is increased. Active position causes muscular contraction in pelvic area, which helps with blood homeostasis. The renin-angiotensin system and vasopresin partake of long-term maintenance. Although heart rate is not included in AAS/AAN definition for OH, it can be monitored easily. The increase of heart rate can show the compensatory process for decreased stroke volume (Bradley and Davis 2003). Any abnormality in this chain can lead to presence of orthostatic hypotension.

Baroreceptor's sensitivity declines (Amery et al 1978;Mukai et al 2003) and β-adrenoreceptor mediated response decreases during aging (Hogikyan and Supiano 1994). Vascular stiffness is increasing (Izzo and Mitchell 2007;Laurent et al 1996;Mukai et al 2003), an increase in peripheral vascular resistance is common and a decrease in plasma renin-angiotensin-aldosterone levels occurs (Amery et al 1978).

Investigation whether arterial stiffening, one of the characteristics of the aging vascular system, is associated with orthostatic hypotension, was subject of some studies. Two small studies with less than 100 participants were conducted. In the first study there was upper-limb arterial wall stiffness significantly greater in elderly patients with OH than in patients without OH and was significantly related to blood pressure changes after standing (Boddaert et al 2004). The second study does not support the association between arterial stiffness and postural change of blood pressure (Sengstock, Vaitkevicius and Supiano 2005). Cross-

sectional cohort study in elderly men and women (3362 subjects aged 55 and older) investigated the relationship between arterial stiffness and orthostatic hypotension within the framework of Rotterdam study, it was confirmed the association between arterial stiffness and orthostatic hypotension (Mattace-Raso et al 2006).

Lucini et al.2004 tested the hypothesis that baroreflex and autonomic responses to graded lower body suction could be altered in COI (chronic orthostatic intolerance) patients. Patients with chronic orthostatic intolerance show distinct signs of altered baroreflex and autonomic regulation of the SA node and of the vasculature in response to graded LBNP (Lucini et al 2004). Changes in RAS and decline in thirst mechanism in elderly can lead to great blood pressure changes and cause OH (Stachenfeld et al 1997;Tajima et al 1988); volume depletion, immobility are conditions for developing OH too (Luukinen et al 1999).

The association between supine hypertension and OH presence was assessed, the underlying mechanisms could be vascular stiffness and baroreflex' sensitivity decline (Goldstein et al 2003). As we mentioned in nosology of orthostatic hypotension, there are chronic disorders which can cause OH by different mechanisms. Diabetic autonomic neuropathy (Hilsted et al 1981), Parkinson's disease, high BP, stroke, transient ischemic attack, a past myocardial infarction, they all belong to disorders, which are associated with OH (Luukinen et al 1999).

Many antihypertensive medications influence various places in the mechanism of maintaining blood pressure during postural changes. Cross-sectional studies are not able to clear the relationship between OH and treatment with antihypertensives. The short- term and long-term use can differ in causing hypotension; first-dose hypotension effect of ACE inhibitors is well-known and it disappears with long-term use. Prospective longitudinal studies can show more details (Hajjar 2005). It is not easy to generalize the pharmacological effect for the whole group of antihypertensives, for instance the group of calcium channel blockers involves nifedipine and nicardipine, which possess different power to develop OH. Moreover the treatment of hypertension seems to have positive influence on OH presence (Ooi et al. 1997). Antidepressants, antipsychotics and vaso-active drugs produce OH as an adverse effect. The whole chapter is devoted to drug-induced hypotension. It is very difficult to assess the causation of OH in elderly. As there is increasing incidence and prevalence of systemic diseases, especially chronic diseases, among older adults, and also increasing concomitant medication use (Heft and Mariotti 2002) the assessment is even more difficult. The orthostatic

hypotension can be symptomatic or asymptomatic. Among symptoms are referred dizziness, lightheadedness, blurred vision, and higher rate of falls.

5.4 Epidemiology of OH

Published reports suggested the wide range from 5% to 60% of OH prevalence. Prevalence is higher in institutionalized elderly, where almost half of them are suffering from OH, compared to home-dwelling elderly, where 5-15% rate of OH was reported (Hajjar 2005). The wide range is caused by different attitude to the definition, the technique is not following one model; especially different timing of measuring is problem as we mentioned in the definition already. OH is not stable phenomenon; short-term variability is one of the features of orthostatic hypotension. There can be seen intraindividual and intraobserver differences in many studies. Study done by Italian general practinioners, conducted in Milano (Alli et al 1992), 3858 elderly outpatients aged 65 years or more were randomized and examined. The OH was assessed according three definitions twice 7 days apart, (1) decrease in systolic BP greater than 20 mmHg (SOH); (2) a decrease in both systolic (greater than 20 mmHg) and diastolic (greater than 10 mmHg) BP (SDOH); (3) any decrease in systolic BP associated with symptoms (SyOH). Prevalence figures for SOH were 13.8% at the first and 12.6% at the second visit, and respectively 5.3 and 4.8% for SDOH, 14.1 and 11.8% for SyOH. The diagnosis of OH was confirmed at both visits in 36.3% of cases for SOH, in 25.7% for SDOH, and in 43.9% for SyOH. This fact contributes to difficulty of determining the prevalence of OH.

Studies are not giving consistent information about association of different conditions with OH presence. Their opinions are sometimes antagonistic. The advanced age was associated with OH (Nardo et al 1999;Rutan et al 1992); other studies didn't find any relationship between age and OH (Raiha et al 1995;Robertson, DesJardin and Lichtenstein 1998). Low body mass index was confirmed to have an association in some studies (Applegate et al 1991;Ooi et al 1997;Rutan et al 1992), in other studies not (Raiha et al 1995;Robertson, DesJardin and Lichtenstein 1998). No sex difference between participants with OH and without OH was found (Raiha et al 1995), on the other hand there was found association OH with male sex (Ooi et al 1997). Smoking was linked to higher blood pressure decline (Nardo

et al 1999). Other factors connected to OH were bed rest (Tonkin 1995) and hypokalemia with hyponatremia.

In Finland there was conducted population study (Luukinen et al 1999) which consisted of all persons aged 70 years or older living in 5 rural municipalities, the final number of participants was 833. Orthostatic hypotension was defined the same way as in our study. They were looking for associations separately for diastolic OH 1 min and systolic OH 3 min. There was found an association between diastolic OH 1 minute after standing up and dizziness when turning the neck (odds ratio [OR], 2.44), the use of a calcium antagonist (OR, 2.31); the use of a diuretic medication (OR, 2.29), a high systolic BP (OR, 2.23), and a low body mass index (OR, 2.26). Systolic OH 3 minutes after standing up was associated with male sex (OR, 1.52), with diabetes mellitus (OR, 1.92), a high systolic BP (OR, 2.91), and a low body mass index (OR, 1.68).

OH is variable over time within day. There are studies, which are observing the patterns of OH concerning daytime and meal (Ooi et al 1997;Puisieux et al 1999). Study by Puisieux et al. examined the influence of time of day and of meals on postural blood pressure (BP) changes in older adults. A total of 126 inpatients from short-stay department clinic (91 women and 35 men; mean age: 81.4+/-7.9 range 61-95 years) were observed. Two measurements were assessed, the first one in the mid morning and the second one within 30-60 minutes after lunch. Orthostatic hypotension (OH) was defined as a systolic blood pressure (SBP) decline > or = 20 mm Hg within 3 minutes after standing. Sixty-one participants (48%) experienced significant orthostatic BP decline on at least one reading; 46 (37%) had OH in the mid-morning, and 32 (25%) had OH after lunch. The obtained results show need of repeating measurements at best under circumstances, when OH symptoms are occurring (Puisieux et al 1999).

Differences in observed population are also common. Some studies are focused on particular cohort of people; obtained values of OH prevalence are not comparable among them. In a cohort study of 4,736 persons suffering from isolated systolic hypertension were followed –up to determine the impact of treatment ISH. It was a randomized multi-center double-blind outpatient clinical trial. The criteria were the age greater than or equal to 60 years, the systolic blood pressure (SBP) greater than or equal to 160mm Hg and diastolic blood pressure (DBP) less than 90mm Hg. OH was found in 10.4% of participants at 1 minute and in 12.0% of

participants at 3 minutes (Applegate et al 1991). Patients with Parkinson disease (PD) often have signs or symptoms of autonomic failure, including orthostatic hypotension. It reflects sympathetic neurocirculatory failure. Study conducted in was interested in prevalence of orthostatic hypotension in Parkinson's disease, 91 patients with diagnosis of Parkinson's disease participated measurements. They stated high prevalence of 58, 2 %, OH was asymptomatic in 38, 5 %. Symptomatic orthostatic hypotension was related to duration and severity of the disease and with the use of higher daily levodopa and bromocriptine doses (Senard et al 1997). Another study of 159 participants with Parkinson disease stated OH in 80 subjects (50.3%) had OH. These subjects were older, more likely to be male, and taking larger doses of dopaminergic medications than those without OH (Allcock, Kenny and Burn 2006).

6 DRUG-INDUCED ORTHOSTATIC HYPOTENSION

One of factor, which can increase the risk or aggravate orthostatic hypotension is medication. We distinguish drugs with an antihypertensive action (diuretics, calcium antagonists, beta-blockers, ACE inhibitors, alpha 1-blockers, and centrally acting antihypertensives) have a more pronounced effect in the elderly and drugs with hypotension as a known adverse effect (Nitrates, antiparkinsonian drugs, antidepressants and antipsychotics) (Verhaeverbeke and Mets 1997). Although there are many studies considering contribution of antihypertensive therapy to orthostatic hypotension, results are conflicting. The first problem is that they are cross-sectional, longitudinal studies are scarce. And as the orthostatic hypotension is common also among elderly who don't receive antihypertensive therapy, the causality of this event is then hard to be concluded (Hajjar 2005). Indirect proof between antihypertensives and OH is high correlation between OH and supine hypertension, which is associated with use of antihypertensives (Applegate et al 1991)

Another problem is different pharmacological and haemodynamic properties of drugs within class and among different classes of antihypertensive medications. Many studies grouped together more drugs from various classes. Then it is hard to compare results. In the end, there are variations among methods of measuring blood pressure and heart rate, timing, positional change and cuff location during standing (Hajjar 2005). Prospective, randomized trials give us more reliable and accurate results. Such studies are scarce. Study of Masuo et al.1996 suggests that lowering of blood pressure is not associated with OH, even can improved OH. In the beginning there were 50 untreated elderly patients, they received thiazide diuretic, calcium channel antagonist (nifedipine), beta adrenoreceptor antagonist (metoprolol), ACE inhibitor (enalapril) or α-adrenoreceptor antagonist (prazosin). There was statistical decline in prevalence OH in 2-year follow-up, except α-adrenoreceptor antagonist and thiazide diuretics. In control group there was no decline (pre-treatment - 4%, post-treatment - 4%) (Masuo et al 1996).

6.1 Drugs with desired hypotensive effect

First-line of hypertension treatment consist of following drugs - Diuretics, Calcium channel blockers, β-blocking agents, ACE inhibitors and Angiotensin II receptor antagonists.

6.1.1 Diuretics

Diuretics are drugs that are increasing the excretion of Na^+ and water from the body by an action on kidney. Their primary effect is decrease of the reabsorption of Na^+ and Cl^- from filtrate and the water loss is the secondary effect. They act directly on the cells or they change the content in the filtrate. Diuretics which affect the cells of nephron directly are loop diuretics and diuretics acting on the distal tubule (thiazides and related drugs), potassium-sparing agents. Diuretics that act indirectly by modifying the content of urine are osmotic diuretics and diuretics acting on the proximal tubule. The main diuretics are loop diuretics and thiazides, those were taken by study's participants.

Thiazide-type diuretics are used plain or in combination with potassium sparing agents. They have moderately powerful diuretic action (Rang 2003). The effect is caused by binding to the Cl^- of the electroneutral Na^+/Cl^- co-transport system in lumen of tubule and thiazides inhibite its action. The precise mechanism how they reduce blood pressure is unknown (Wright 2000). Although some metabolic changes may occur with higher dosages of these medications, they seem to be of limited clinical significance. They are well tolerated. K^+ depletion is the most important. We can mention also other as metabolic alkalosis, hyperglycemia, hyperuricemia, hyperlipidemia.

Other used diuretics are loop-diuretics. They are the most powerful of all diuretics. The known mechanism is inhibition of sodium-potassium-chloride co-transport at the thick ascending loop of Henle, the effect appears rapidly and the decline of BP is vigorous. They appear to have a venodilator action, directly and/or indirectly through the release of a renal factor. The adverse effects are common, potassium loss occurs; metabolic alkalosis is caused by excretion of H^+. Depletion of Mg^{2+} and Ca^{2+} are common too. Hypovolemia and hypotension occur in elderly and can be followed with collapse (Rang 2003).

Diuretics and OH

Studies about the association between diuretics intake and OH incidence are not consistent. The interpretation is difficult; there is high prevalence of OH also in control groups. The first study consisted of participants in age 55-99 years; this is different range of age than in our study. The result was 4, 6 % of those receiving diuretics and 3, 6 % of those not receiving diuretics demonstrated OH (Myers et al 1978). In a study of 70–years old frail elderly patients, the incidence of OH was 60% in those receiving thiazide diuretics, 20% of those receiving loop diuretics and 37% in those non-treated with diuretics. Poon and Braun 2005 described the prevalence of symptomatic and asymptomatic OH in veterans aged 75 years and older attending a geriatric clinic, and assessed the association between OH and the number of potentially causative medications used. Receiving hydrochlorothiazide was associated with the highest prevalence of OH (65%), furosemide was associated with lower prevalence (56%) (Poon and Braun 2005). There was also reported higher prevalence of hypokalaemia in thiazide diuretics cured patients, which has been reported as association with OH presence (Heseltine and Bramble 1988).

6.1.2 Calcium Channel Blockers

Calcium antagonists block the Ca^{2+} entry by preventing opening of voltage-gated L-type calcium channels. There are three main L-type antagonists typified by verapamil, diltiazem and dihydropyridines (e.g. nifedipine). The main effect is performed in heart tissue and smooth muscle. They differ selectively in place of action. Verapamil is relatively cardioselective, nifedipine is relatively smooth-muscle selective and diltiazem is intermediate. They produce vasodilator effect on resistance of vessels, which reduces afterload (mainly dihydropyridines). They dilate coronary vessels too. The effect on heart is antidysrhytmic, which is caused by impaired atrioventricular conduction and reduced contractility. The clinical use is of big importance; their effect is used in treatment of hypertension, dysrhytmia and angina. The most of unwanted effects are extensions of their pharmacological actions. The adverse effects include headache, flushing, constipation (verapamil), ankle oedema (dihydropyridines). No postural hypotension is described (Rang 2003).

Calcium Channel Blockers and OH

Before administering a calcium channel antagonist to an elderly person, orthostatic hypotension has to be investigated. Association with a diuretic results in high risk due to hypovolemia that can enhance the vasodilatory effect of calcium antagonists (Le Jeunne et al 1991). Arteriolar vasodilatation and possible increased glomerular pressure by affecting afferent arteriole can lead to increased risk of OH. Nifedipine has been found to increase nocturnal natriuresis, which worsens orthostatic blood pressure decline (Jordan et al 1998). Verapamil may cause less OH, since it may improve baroreflex sensitivity and improve PBP changes (Chamontin, Montastruc and Salvador 1987). Nicardipine was tested in double-blinded trial the tolerance and antihypertensive effect of nicardipine versus placebo in 32 elderly patients (mean age: 84 years). Orthostatic hypotension was never observed (Forette et al 1984).

6.1.3 β-Blockers

β-adrenoreceptor antagonists are heterogenous group, they consist of different drugs which vary in their pharmacological effect. The distinction between β_1- and β_2 - adrenoreceptors is very important, the first ones are found mainly in heart and they are responsible for positive inotropic and chronotropic effect, which is followed with increased cardiac rate, force of contraction and higher consumption of oxygen. The latter is responsible for smooth muscle relaxation in many organs, e.g. bronchodilatation, vasodilatation, relaxation of visceral smooth muscle. Their pharmacological effects vary depending on the degree of intrinsic sympathomimetic activity, lipid solubility and receptor's selectivity and membrane stabilisation activities. The receptor' selectivity is rather relative than absolute. We distinguish β- blocking agents non-selective, β-blocking agents selective and α- and β-blocking agents. The mechanism is complex and it involves cardiac output reduction with decrease of myocardial contractility, reduction of renin release from juxtaglomerular cells of kidney and reduction of sympathetic activity. The adverse effects are resulting from blocking adrenoreceptors. It involves bronchoconstriction (block of β_2 – adrenoreceptors), cardiac failure and bradycardia (block of β_1 – adrenoreceptors), hypoglycaemia (block of β_2 – adrenoreceptors), fatique (probably result of blocking β_1 – adrenoreceptors), cold extremities (more likely caused by block of β_2 – adrenoreceptors, not clear) (Rang 2003).

β-Blockers and OH

Data of influence β-blocking agents on prevalence OH is scarce and it can vary from the type of β – adrenoreceptor antagonist and their properties. β – adrenoreceptor with intrinsic sympathetic activity can even have positive effect on orthostatic hypotension. β – adrenoreceptor antagonists with β_2 – adrenoreceptor blockage activity can increase peripheral resistance by blocking the peripheral β_2 – adrenoreceptors with no effect on the α_2 adrenoreceptors, leading to an increase in peripheral vascular resistance. This pressor effect is transient and more pronounced upon standing, but can be exaggerated in elderly patients with underlying increased sympathetic activity or with OH (Cleophas et al 2002). Large studies have been completed indicating that the depressor effect on pulse pressure upon standing in this category of patients can be offset and turned into a pressor effect by long-term beta-blocker treatment. In elderly patients beta-blockers may, therefore, be the most appropriate antihypertensive agents as they protect the elderly from orthostatic hypotension (Cleophas and van Marum 2003;Masuo et al 1996)The incidence of first dose postural hypotension has been reported in pharmacokinetic studies as being as high as 40% with carvedilol (Louis et al 1987;Rittinghausen 1988). The incidence of orthostatic hypotension after administration of carvedilol is connected to the dose (Krum et al 1994). In a recent report Cleophas et al. reported that in 1971 patients treated with nebivolol for 6 months the original decrease in blood pressure upon standing for 1 minute was reserved (Cleophas et al 2002). A cross-sectional study in a primary geriatrics practice demonstrated that elderly receiving beta-blocking agents showing larger drop in blood pressure upon standing compared with other hypertensives (Catoe, Sixta and Hajjar 2003).

6.1.4 Angiotensin Converting Enzyme (ACE) inhibitors

ACE inhibitors belong to indirectly acting vasodilator drugs. They inhibit conversion of angiotensin I and that leads to decreased level of angiontensin II and increased kinnin level, both leading to vasodilatation. ACEIs affect capacitance and resistance vessels and reduce cardiac load as well as arterial pressure. They don’t influence cardiac contractility and the cardiac output doesn’t increase. They show selectivity in acting just on angiotensin-sensitive vascular beds, those include kidney, heart and brain. They are used widely and each of them differs from duration of action and tissue distribution. The adverse effects are hypotension

(especially after first dose), dry cough (accumulation of bradykinin), renal failure in patients with bilateral renal artery stenosis, headache, hyperkalaemia etc (Rang 2003).

Angiotensin Converting Enzyme (ACE) inhibitors and OH

OH is relatively uncommon during use ACE inhibitors, apart from the first-dose effect (Romero et al 1995). A postmarketing study from England of 4676 participants suggested the rate 0,25% of those who were receiving lisinopril developed OH (Fareeduddin and Abelmann 1969). A prospective, double blinded, cross-over study was conducted to compare the effect of enalapril with long-acting nifedipine on orthostatic hypotension in older patients. 39 patients aged 65 years or older with systolic blood pressure (SBP) of 140-190 mm Hg and diastolic blood pressure (DBP) of 90-110 mm Hg were followed up 20 weeks in cross-over design. Supine and standing 0-, 1-, and 5-minutes blood pressure was recorded before and at the end of each treatment period. The cross-over of enalapril and nifedipine reproduced the hypotensive effect and reversed the postural effect. Enalapril reduced the number of orthostatic episodes significantly, whereas nifedipine aggravated this phenomenon. At the end of enalapril phase, no one experienced OH versus 15% at the end of the nifedipine phase (Slavachevsky et al 2000). Lisinopril improved baroreflex sensitivity in their study, which has positive effect on occurrence of orthostatic hypotension (Egan et al 1993).

6.1.5 Angiotensin II receptor antagonists

The mechanism is based on antagonism specific receptor and blocking the effect of angiotensin II. They are reserved for patients, who experience and are unable to tolerate dry cough in use of ACEI. There is still missing evidence if this class is equivalent to the class of ACEI (Rang 2003).

Angiotensin II receptor antagonists and OH

They showed low rate of orthostatic hypotension in studies. In an 8 week open-label study including 6465 patients (mean age of 58 years) with untreated or uncontrolled hypertension, 0, 2 % of those receiving candersartan cilexetil alone and 0, 8 % of those receiving combination therapies with candesartan cilexetil demonstrated OH (20). In a 4-week study of

valsartan, 14% of 97 patients developed OH, compared with 8% in the placebo group (Pool et al 1998)

6.1.6 α -adrenoreceptor antagonists: Selective α_1 – antagonists

This class of drugs doesn't belong to the first line of treatment of hypertension. The mechanism is based on highly selective antagonism of α_1 receptor. The effect is arteriolar and venous vasodilatation and fall in blood pressure (Hardman et al 2001). The advantage of them is that they are causing also relaxation of the bladder neck and prostate capsule, which is useful in treatment of benign prostate hypertrophy. The clinical use is cure of mild hypertension. The postural hypotension can occur (Rang 2003).

α -adrenoreceptor antagonists: Selective α_1 – antagonists and OH

Peripheral vasoconstriction is part of managing orthostatism stress; the patients receiving drugs from this class are in higher risk of developing OH. The rapidity of drug's onset influences the risk of this phenomenon. The latest medications has slower onset, so they are more tolerated (Hajjar 2005). There was a double-blind randomized study comparing the efficacy of two alpha 1-antagonists, bunazosin retard and prazosin retard, in 185 patients with mild to moderate essential hypertension. Specific orthostatic tolerance was evaluated by a standardized test. A comparison of blood pressure profiles during specific orthostatic tolerance tests did not show any significant difference between the two groups. However, the symptoms of orthostatic hypotension were significantly less frequent and less severe with bunazosin compared with prazosin (Rieckert 1996).

6.2 Drugs with hypotensive effect as an adverse effect

6.2.1 Organic nitrates

This class belongs to antianginal drugs. Their effect is caused by relaxation of vascular smooth muscles. They produce marked venorelaxation with a consequent reduction pre-load (decrease of central venous pressure). Venous pooling occurs during standing and can cause orthostatic hypotension. There is a big effect on large muscular arteries in comparison to the

effect on small-resistance arteries that reduce pulse wave reflection of arterial branches and leads to decreased pre-load. Additionally, myocardial consumption is decreased. There is a redistribution of coronary flow and relief of coronary spasmus. Adverse effects include headache, postural hypotension and occasionally psychotic symptoms (Rang 2003).

Organic nitrates and OH

The risk of developing orthostatic hypotension caused by use of nitrates is particularly great in elderly (Cherin et al 1997), as the response to nitrates doesn't decline during aging and as the pharmacokinetics is changed in elderly patients for longer half-life, there is need of dose reduction (Cahalan et al 1992;Eichler et al 1987). Double-blind, randomized crossover comparison of nicardipine (20 mg by mouth t.i.d.) versus isosorbide (20 mg by mouth t.i.d.) was conducted to determine mechanisms of postural blood pressure regulation in elderly patients with coronary artery disease. 15-minute 60-degree head-up tilt test were conducted on no study medications and then after successive 3-week treatment periods with nicardipine or isosorbide. Isosorbide treatment was associated with a higher prevalence of symptoms of cerebral hypoperfusion and a failure to increase systemic vascular resistance during tilt (Lipsitz et al 1996). Acute and initial treatment with ISDN provokes arterial hypotension and orthostatic dysregulation which may persist over a period of 10 h. On the other hand chronic medication, there cannot longer be seen nitrate-induced drop in arterial blood pressure and orthostatic hypotension even after high-dose application of ISDN (Haussinger and Bachmann 1983). The hypotension can be provoked in combination nitrates with alcohol (Mets 1995).

6.2.2 Anti-Parkinsonian Drugs

Drug used in Parkinson's disease act by counteracting the lack of dopamine in basal ganglia or by blocking muscarinic receptors. The most common is levodopa given with an inhibitor of peripheral dopa decarboxylase to minimise side-effects. Among unwanted effects are involuntary movements, on-off effects, nausea and postural hypotension. Other drugs used in treatment are selegiline, bromocriptine, amantadine and benzetropin (Rang 2003).

Anti-Parkinsonian Drugs and OH

The causation of orthostatic hypotension in intake of levodopa, selegiline, bromocryptine and anticholinergics were described (Mehagnoul-Schipper et al 2001;Mets 1995;Verhaeverbeke and Mets 1997).

6.2.3 Antidepresants

Antidepressants are prescribed for diverse therapeutic reasons, including a variety of psychiatric disorders, pain control, insomnia, smoking cessation, substance abuse and eating disorders (Keene, Galasko and Land 2003). This group is rich of different drugs. The practicing clinician now has five distinct classes of antidepressant medications that may be used for treating depression in the elderly: tricyclic antidepressants (TCAs; e.g., desipramine, nortriptyline), monoamine oxidase inhibitors (MAOIs; e.g., isocarboxazid, tranylcypromine), selective serotonin reuptake inhibitors (SSRIs; i.e., fluoxetine, sertraline, and paroxetine), aminoketones (i.e., bupropion), and triazolopyridines (i.e., trazodone) (Spina and Scordo 2002).

Antidepresants and OH

Antidepressants are known to cause orthostatic hypotension as an adverse effect (Verhaeverbeke and Mets 1997). A retrospective study was conducted of 1,800 randomly selected patient records and evaluated the prevalence of using antidepressants and other medications concurrently. They analyzed also potentional complication as orthostatic hypotension. The result was that not all antidepressants potentate orthostatic hypotension. There are differences among drugs within this class. For example, most SSRIs and venlafaxine do not cause OH according the results. (Keene, Galasko and Land 2003)The classical group of TCA contains drugs, which produce orthostatic hypotension frequently, occurring in 10% to 50% of the patients (Mets 1995;Preskorn 1993). Amitriptyline and imipramine are metabolized by liver and their metabolites are removed by kidney, as both processes are decreased in elderly, their metabolites accumulate. It tends to higher risk of OH presence (Mets 1995). Stage et al. proved orthostatic hypotension caused by clomipramine intake to be more pronounced in elderly patients in comparison to younger (Stage, Kragh-

Sorensen and Danish University Antidepressant Group 2002). Another prospective, randomized clinical trial evaluated the effects of clomipramine and moclobemide on orthostatic blood pressure during treatment for depression. One hundred and fifteen depressed inpatients, age up to 70 years, were randomized to treatment with either moclobemide (400 mg/day) or clomipramine (150 mg/day) after 1 week of placebo treatment. The orthostatic hypotension was measured weekly in 6-week period. This study indicates that moclobemide does not induce orthostatic side effects, which is a significant problem in treatment with TCAs (Stage and Danish University Antidepressant Group 2005).

Most human clinical studies with SSRIs such as fluoxetine, fluvoxamin, paroxetine, sertraline and citalopram showed significant advantages over TCAs in producing fewer cardiotoxic, anticholinergic and antihistaminergic side effects in the treatment of major depressive disorders. These newer compounds exhibited a lower risk of inducing hypotension . The SSRI drugs were reported as to be free of orthostatic hypotension (Mets 1995). Surprisingly, an increasing number of case reports have demonstrated that the use of SSRIs and new antipsychotics (e.g. clozapine, olanzapine, risperidone,sertindole, aripiprazole, ziprasidone, quetiapine) is associated with cases of arrhythmias, prolonged QTc interval on electrocardiogram (ECG) and orthostatic hypotension in patients lacking cardiovascular disorders, raising new concerns about the putative cardiovascular safety of these compounds (Pacher and Kecskemeti 2004;Pacher and Ungvari 2001). A multicenter case control study has shown that in the elderly the consumption of fluoxetine was significantly associated with an excess risk of syncope and orthostatic hypotension (Cherin et al 1997). Triazolopyridines (e.g. trazodone) produce OH frequently by blocking α1 receptor (Poon and Braun 2005;Preskorn 1993). Monoamino oxidase inhibitors (e.g. phenelzin, isocarboxazid...) may cause also orthostatic hypotension, they are not recommended for use in elderly patients (Mets 1995)

6.2.4 Antipsychotics

Antipsychotics are widely used in geriatric psychiatric disorders; many of them are approved for use in treating other conditions as well, such as behavioral problems. The classification of antipsychotics is following, first group is consisting of originally developed drugs called clasical or typical antipsychotic drugs (haloperidol, chlorpromazine) and the second group is

called atypical antipsychotic drugs, consisting of recently developed drugs (risperidone, clozapine) (Rang 2003). Most available antipsychotic agents block dopamine type 2 postsynaptic receptors. Antipsychotics also bind to cholinergic, alpha-adrenergic, histamine type 1, and serotonin receptors. The affinities of a given agent for receptors determine its adverse effects and probably its efficacy. Adverse effects frequently observed in the elderly are orthostatic hypotension, anticholinergic effects, pseudoparkinsonism, and tardive dyskinesia (Zaleon and Guthrie 1994). Lower dosages and more frequent assessments are necessary in elderly patients.

Antipsychotics and OH

Randomized controlled trials were conducted for different druha (Callaghan et al 1997;Swift et al 1999). They proved orthostatic hypotension as an adverse effect. In study (Swift et al 1999) there showed haemodynamic measures orthostatic reductions in blood pressure with thioridazine which were particularly marked in the older group. These results indicate potential problems with orthostatic hypotension with thioridazine in older patients.

7 METHODS AND MATERIALS

This project is part of the study, which is following up the population-based Kuopio 75+ study from year 1998. It was a multidisciplinary health study, which was designed for elderly persons aged 75 and more. The survey focused on their diseases, medication and functional capacity.

7.1 Study population

The targeted population was obtained of all inhabitants of the city Kuopio, in eastern Finland, who were aged 75 or more on January 1, 1998 (N = 4518). A random sample was drawn from this population. Five persons couldn't be contacted, 15 died and 79 refused participating. The remaining 601 participants attended a structured clinical examination and an interview which was undertook by a geriatrician and a trained nurse.

In follow - up study there were 339 survivors aged 80 years and more, that means 56, 4 % population from year 1998 (n= 601); all of them participated our blood pressure assessment. The main condition, which had to be fulfilled to be accepted to our project, was a status as home-dwelling persons (n=289). Elderly, who were in residential care, were not considered (n=50).

Gender and age

In our study, there were 78 men (27%) and 211 women (73%).
We divided them into 3 age groups, first group aged 80-84 years consisted of 157 participants (54, 3%), the second group aged 85-89 years consisted of 93 participants (32, 2%) and the third group aged ≥ 90 years consisted of 39 participants (13,5%) (table 1)

Table 7: Gender distribution in age groups

Age	Men	%	Women	%	Total n (%)
80-84	41	52,6	116	54,5	157 (53,6)
85-89	27	34,6	66	31,3	93 (33,0)
90+	10	12,8	29	13,7	39 (13,4)
Total	78	100,0	211	100,0	289 (100,0)

Blood pressure level

We stated 3 categories of systolic blood pressure in sitting position to compare different potential for drop blood pressure during orthostatism. First group consisted of 26 participants with systolic BP less than 120 mmHg (hypotensive group). The second group consisted of 60 participants with systolic BP = 120-139 mmHg (normotensive group). The last group contained 155 participants with systolic more than 140 mmHg (hypertensive group).

7.2 Definition and measurements OH

Orthostatic hypotension was defined as a drop of 20mm Hg or more in the systolic BP and/or a drop of 10mm Hg in the diastolic BP either 1 minute or 3 minutes after standing up from a lying position. We considered in study these definitions.

Our study contained 289 participants, who attended measurements of blood pressure. Unfortunately not everyone has been measured in all positions, which we demand for orthostatic hypotension's assessment. The required condition for orthostatic testing was measurement of blood pressure in lying position and in standing position after 1 min and/or after 3 min. OH 1 min assessment, there are required values of BP, which are obtained in lying position (A) and in standing position after 1min (C), **OH 1 min = A - C**. The values of A and C position were carried out in 241 patients. OH 3 min assessment is counted as a difference of BP in lying position (A) and standing position after 3 min (D): **OH 3 min =A - D**. We obtained just 152 measurements in A and D position. The measurements were carried out just once. A calibrated mercury column sphygmomanometer was used.

7.3 Data of drug use and health status of participants

The data was collected through interviews, clinical examinations and clinical tests. A trained nurse interviewed our participants about their medication and recorded the regularly taken medicines. They were also asked for bringing their prescription forms and medicine containers with them. If there occurred any problem with obtaining the particular information, the relatives or caregivers were asked for completing. There were available medical records from municipal health center, home nursing service, local hospitals and the Kuopio University Hospital.

The medicines were classified according to the most used system, the Anatomic Therapeutic Chemical (ATC) classification system, and version 2004, recommended by the World Health Organization (WHO) for drug utilization studies. The use of regular and irregular medicines, prescribed and non-prescribed was recorded. The regular medicine use was regarded in case, if it was taken daily or in regular intervals. On the other hand as irregular use was regarded when medicine was taken in time of need. We stated 3 categories of medicine use (Jyrkka 2006). Non-polypharmacy is use of 0-5 medicines, polypharmacy is use of 6-9 medicines and excessive polypharmacy is use of 10 and more medicine.

SPSS 14.0 for windows provided the statistical part of thesis. Fisher's exact test, Man-Whitney test and Anova one way test were used for testing hypothesis. The written informed consent was obtained from each participant or from his or her relatives. The ethics committee of the Hospital District of Nothern Savo and the University Hospital of Kuopio approved the study.

8 RESULTS

8.1 Blood pressure overview

Study sample was ranked according to BP values obtained in sitting position into the classification from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (table 8). Men and women were separated. We were interested in that, how the blood pressure is controlled in participants. Assessing BP in sitting position belongs to common standard. The values obtained in other positions are not comparable among themselves because there is produced stress of different level for the body.

Study participants have big disproportion between systolic and diastolic BP, low diastolic and very high systolic BP. 49% of men and 52 % of women are suffering from isolated systolic hypertension (1).

Table 8: Distribution of values according to the classification

		Sitting position	
	BP (mmHg)	**Men %**	**Women %**
Optimum	Sys≤119	7	12
	Dia≤79	57	59
Prehypertension	Sys 120-139	28	22
	Dia 80-89	26	24
Hypertension 1 stage	Sys 140-159	36	31
	Dia 90-99	8	14
Hypertension 2 stage	Sys ≥160	29	35
	Dia ≥100	9	3
Isolated systolic hypertension (1)	Sys ≥140 Dia ≤90	49	52
Isolated systolic hypertension (2)	Sys ≥160 Dia ≤90	5	18

(1) JNC 7th report 2003

(2) Kocemba et al. 1998

8.1.1 Blood pressure measurements

The trained nurse carried out 4 measurements. Systolic and diastolic blood pressure (BP) have been measured in lying position, sitting position, standing position after 1 minute and in the end in standing position after 3 minutes. Every measurement was unfortunately implemented just once. The number of patients, who participated in every test, differs significantly (table 9). We observed large drop out, especially in the standing position after 3 min.

Table 9: Number of participants in different measurements (n=289)

Position	Valid	Missing	Inclusion (%)
BP lying	252	37	87,2
BP sitting	270	19	93,4
BP standing 1 min	259	30	89,6
BP standing 3 min	169	120	58,5

The values of BP are changing with aging, typical features are higher systolic blood pressure and fall in diastolic blood pressure, which are connected to different changes in cardiovascular system. This was fully confirmed in our study. There was a wide range for values from minimum to maximum in blood pressure in all positions. The distribution in different levels of blood pressure (systolic and diastolic) was changing according to the specific position (appendix 9 and 10). Values of blood pressure in specific position were quite heterogeneous among participants (appendix 2-7). The reasons could be individual health status, attitude to the cure, e.g. compliance, the level of controlling blood pressure through medicines. Standard deviation is quite high (table 10). This is probably connected to the small number of participants in testing.

Table 10: The main description of BP (mm Hg) in different positions (n=289)

	Systolic	Min-Max	Diastolic	Min-Max
Lying	152,7 ± 25,8	59-260	76,5 ± 11,1	48-110
Sitting	149,7 ± 25,7	98-227	77,0 ± 11,8	52-110
Standing 1min	147,1 ± 26,1	87-221	77,5 ± 12,5	44-120
Standing 3min	153,6 ± 26,6	90-226	80,7 ± 13,2	52-131

8.1.2 Gender and age differences in blood pressure

We were interested in differences of BP's values in genders and age groups. This can give us the picture of blood pressure generally in our sample. If we compare values of systolic BP in different positions, we will notice decrease from A to C position and increase from C to D position step by step. In diastolic BP there are values very **close** to each other among positions; except D position, there is a small increase of BP. In both systolic and diastolic there weren't found significant differences in values between genders. The mean of BP and CI 95% (of group next to) overlaps (table 11 and 12).

Table 11: The mean and CI 95% of systolic BP in different position according to the gender (n=289)

Systolic BP	**Men**		**Women**	
	Mean (CI 95%)	**Total**	**Mean (CI 95%)**	**Total**
Lying (A)	152 (146,6-157,4)	70	153 (149,0-157,0)	182
Sitting (B)	148 (142,5-154,0)	75	150 (146,5-153,9)	195
Standing 1min (C)	145 (139,2-151,3)	71	148 (144,0-151,6)	188
Standing 3min (D)	151 (143,4-158,2)	46	155 (149,8-159,5)	123

Table 12: The mean and CI 95% of diastolic BP in different position according to the gender (n=289)

Diastolic BP	**Men**		**Women**	
	Mean (CI 95%)	**Total**	**Mean (CI 95%)**	**Total**
Lying	77 (74,2-79,9)	70	76 (74,7-77,8)	182
Sitting	77 (73,6-79,6)	75	77 (75,6-78,7)	195
Standing 1min	77 (74,3-80,4)	71	78 (75,8-79,3)	188
Standing 3min	81 (76,7-85,2)	46	81 (78,3-82,9)	123

We observe the decreasing tendency of the mean BP (systolic and diastolic) according to increase of the age in all positions. In summary, the values of systolic and diastolic BP differ from each other between 80-84 aged group and 90+ aged group. The systolic BP values in both standing positions have enough wide CI 95% that they don't differ significantly in age groups occurring next to. The mean of diastolic BP with CI 95% don't overlap between 80 -

84 aged group and 85 – 89 aged group, they differ significantly in all positions (table 13 and 14).

Table 13: The mean of systolic BP in different position according to the age (n=289)

	80-84 Mean (CI 95%)	85-89 Mean (CI 95%)	90+ Mean (CI 95%)
Lying	156 (151,4-160,3)	151 (145,3-157,6)	144 (139,2-149,1)
Sitting	154 (150,1-158,8)	148 (142,2-152,9)	136 (130,3-142,0)
Standing 1min	152 (147,0-156,1)	145 (139,0-150,2)	136 (129,9-142,4)
Standing 3min	158 (152,3-162,8)	149 (141,5-157,2)	142 (132,3-151,1)

Table 14: The mean of diastolic BP in different position according to the age (n=289)

	80-84 Mean (CI 95%)	85-89 Mean (CI 95%)	90+ Mean (CI 95%)
Lying	79 (77,4-81,4)	75 (72,8-77,2)	69 (66,8-71,5)
Sitting	81 (78,5-82,6)	74 (72,3-76,2)	70 (67,2-72,8)
Standing 1min	82 (79,6-84,0)	74 (71,5-75,8)	70 (67,2-72,8)
Standing 3min	85 (82,4-87,5)	75 (71,6-78,0)	71 (67,6-74,7)

We observe in every position the tendency of decreasing BP according to the increase of age in both genders. This confirms results from tables 12 and 13. The CI 95% is wide enough almost in every case, that the mean of BP of group 1(men) can be found in CI 95% of group 2 (men) and other way round too. That shows, there is no significant difference. It concerns always the group next to. It doesn't concern group 1 x 3 difference (Notes: AGE group 80 - 84 = group 1, AGE group 85 - 89 = group 2 , AGE group 90+ = group 3). The blood pressure is decreasing during orthostatism, changing position from lying to standing 1 min, the values obtained after 3 min are higher than the values after 1 min standing. That shows adapting of body to the stress during standing. The biggest drop of systolic BP was found in 90+ aged. The range of values is becoming narrow according to the increase of age and standard deviation is becoming smaller. This can be caused by small-represented sample in the oldest group.

We didn't find significant difference in genders. The only exception is women and men in 80-84 aged. Women experienced smaller drop in BP than men. All systolic BP values belong to prehypertension stage or hypertension stage I, when we don't consider SD (table 15)

Table 15: Systolic BP in certain position according to the gender

	80-84		85-89		90+	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Lying position	155±24,7	156±26,5	150±21,8	152±30,9	144±13,5	144±15,0
Standing 1 min	148±27,6	153±26,9	145±25,3	145±26,4	135±14,0	136±19,7
Standing 3 min	153±25,8	159±27,7	150±27,2	149±26,5	139±12,2	143±21,3

Values of diastolic blood pressure are similar in different position. We noted only tendency of BP decrease in increase of age (table 16).

Table 16: Diastolic BP in certain position according to the gender

	80-84		85-89		90+	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Lying position	79±13,6	79±10,9	77±9,8	74±10,1	70±8,3	69±6,4
Standing 1 min	80±14,1	82±12,8	76±11,3	73±9,5	69±8,0	70±8,4
Standing 3 min	84±14,6	85±12,8	76±13,2	74±9,9	71±8,3	71±7,1

8.2 Orthostatic hypotension

It is required BP values from lying position and standing position 1 and/or 3 min for assessing OH. Two hundred eighty nine persons were attending blood pressure measurements, 251 persons obtained required BP values for OH assessment. Out of 251, 10 participants were in residential care, 241 home-dwelling persons were involved in OH 1 min assessment and 152 home-dwelling persons were involved in OH 3 min assessment. The most represented age group is the youngest from 80 – 84, they constitute more than 50% in both assessment. Female gender constitutes more than 70% of sample (table 17).

Table 17: The participant's distribution in age groups and gender

Age group	**A + C measured**	**A + D measured**	**Gender**	**A + C measured**	**A + D measured**
80-84	125 (51,9%)	93 (61,2%)	Male	67 (27,8%)	42 (27,6%)
85-89	83 (34,4%)	43 (28,3%)	Female	174 (72,2%)	110 (72,4%)
90+	33 (13,7%)	16 (10,5%)			
Total	241 (100%)	152 (100%)	Total	241 (100%)	152 (100%)

Notes: A = lying position , C = standing position 1 minute, D = standing position 3 minutes

8.2.1 Prevalence of OH

We assessed the prevalence of orthostatic hypotension to be **23, 7 %** in home-dwelling persons in study. **57 participants** experienced one or more types of orthostatic hypotension. Every patient was counted just once, even though he could have had more than one type of OH.

We separately counted at first prevalence of OHS or OHD after 1min together (241 participants in measurement) and at second prevalence of OHS or OHD after 3 min together (152 participants in measurement). The reason was different number of participants. We received the same result, **19, 1%.** Systolic OH is more prevalent 18, 3 % (44 persons) than diastolic OH 9, 1% (22 persons). Just **1, 2%** of participants had all types of considered OH; 3 persons of 241 (table 18).

Table 18: The overall prevalence of OH in study patients (n= 241)

	N	**%**
The prevalence of any type of OH	57 (n=241)	**23, 7**
The prevalence of OHS 1min or OHD 1 min	46 (n=241)	19, 1
The prevalence of OHS 3min or OHD 3min	29 (n=152)	19, 1
The prevalence of OHS 1 or 3 min	44 (n=241)	18, 3
The prevalence of OHD 1 or 3 min	22 (n=241)	9, 1
The prevalence of all type of OH	3 (n=241)	1, 2

We ascertained different types of OH in participants. The OHS positivity is more presented than the OHD positivity. The highest prevalence is prevalence of OHS after 1 minute standing (**16, 2 %)**. Even though there is 37 % decrease of participant's number, the percentage is still high in OHS after 3 min (**12, 5%).** We noticed an increase of percentage in OHD 3 min (**8, 6%**) in comparison to OHD 1 min (**6, 2%**).

We distinguished intervals of systolic and diastolic BP drop, which was higher than the threshold for orthostatic hypotension. The most of cases occur near threshold in interval from 20-29mm Hg for systolic and 10-15mm Hg for diastolic BP drop. There is a decrease in

case's frequency in the same interval of Δ **BP** between OH 1min and OH 3 min. We find an exception when we compare OHD 1 min and 3 min. There was a slight increase of cases in the stage Δ **BP** 15+ mmHg (table 19 and 20).

Table 19: The frequency OHS 1 min and OHS in 3 min in intervals of drop in BP

	OHS 1min (n=241)		OHS 3min (=152)	
Δ BP	Frequency	%	Frequency	%
20-29	21	8,7	13	8,6
30-39	13	5,4	3	2,0
40+	5	2,1	3	2,0
Total	39	16,2	19	12,5

Table 20: The frequency OHD 1min and OHD 3 min in intervals of drop in BP

	OHD 1min (n=241)		OHD 3min (n=152)	
Δ BP	Frequency	%	Frequency	%
10 -15	13	5,4	8	5,3
15+	2	0,8	5	3,3
Total	15	6,2	13	8,6

8.2.2 Age and OH prevalence

We stated OH prevalence to be **24, 0% in age group 80-84** (30 of 125 participants), **25, 3% prevalence in age group 85-89** (21 of 83 participants) and **18, 2% prevalence in age group 90+** (6 of 33 participants).

The prevalence of OHS 1min is represented almost equally in all age groups and the percentage is quite high. There is a decrease in prevalence of OHS in time. This trend concerns all age groups. The prevalence of OHD is lower in general and OHD 3 min was observed more often than OHD 1 min. In 90+ aged participants, there is the lowest prevalence of OHD 1 min. We find patients suffering just from OH after 1 min standing; no patient was suffering from OH after 3 min standing, in both systolic and diastolic as well in the oldest group (table 21). The reason is probably small number of 90+ aged participants in assessment of OH after 3min.

Table 21: The prevalence of certain OH in age categories (n=241)

Age (years)	OHS 1 min % (n)	OHS 3 min % (n)	OHD 1 min % (n)	OHD 3 min % (n)
80-84	16,0 (20)	15,1 (14)	4,8 (6)	8,6 (8)
85-89	16,9 (14)	11,6 (5)	8,4 (7)	11,6 (5)
90+	15,2 (5)	0,0 (0)	0,8 (2)	0,0 (0)

Notes: The percentage was counted from the number of participants according to age and specific measurement (table 17)

The lowest drop out was noticed in the youngest group of participants, 93 of 125 persons (74, 4 %) participated both measurements in standing position. In the other groups, there were drop out almost in half of participants for BP measurement after 3 min (table 22).

Table 22: The drop out in measurements according to the age (n=241)

Age (years)	Measurement 1 min % (n)	Measurement 1 + 3 min % (n)
80-84	25,6 (32)	74,4 (93)
85-89	48,2 (40)	51,8 (43)
90+	51,5 (17)	48,5 (16)
Total	100,0 (89)	100,0 (152)

8.2.3 Gender and OH prevalence

The prevalence OH in gender was **22, 4% in men** (15 men of 67 participants) and **24, 1 % prevalence of OH in women** (42 women of 174 participants). No significant difference was found p=0,866 (two-sided p- value obtained by Fisher's exact test).

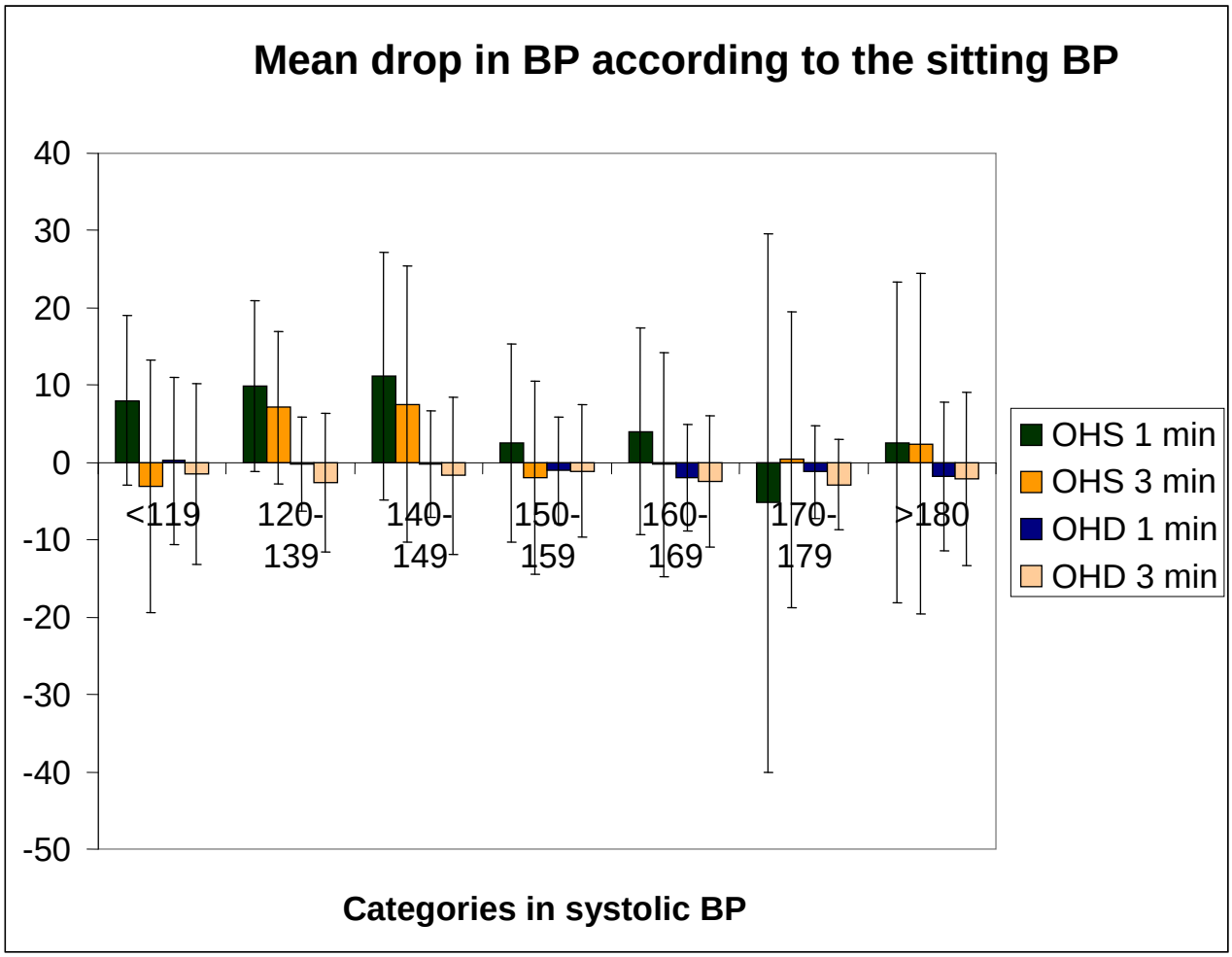
If we compare men and women in certain OH assessment, there are 2 differences, in prevalence of OHS 1min and OHD 3 min. We tested it by Fisher's exact test, OHS 1 min p=0,172 and OHD 1 min p = 0,190 (both two-sided). The difference wasn't significant. We found out higher prevalence of OHS after 1min standing in women, 18, 4% (versus 10, 4% in men). There is a triple increase in prevalence of diastolic OH in time in men. The disadvantage of all presented percentages is small number of cases, which makes the results less reliable (table 23).

Table 23: The prevalence of certain OH in genders (n=241)

Gender	OHS 1 min	OHS 3min	OHD 1 min	OHD 3 min
	% (n)	% (n)	% (n)	% (n)
Men	10,4 (7)	11,9 (5)	4,5 (3)	14,3 (6)
Women	18,4 (32)	12,7(14)	6,9 (12)	6,4 (7)

There was no difference in drop out of participants during measuring between genders. Twenty five men (37, 3 %) and 64 women (36, 8 %) didn't undergo BP measuring after 3 min.

Figure 1: Mean BP drop according to the BP intervals in the sitting position



8.2.4 BP categories and OH prevalence

We stated 3 categories of systolic blood pressure in the sample according to the values obtained in sitting position:

- participants with systolic BP less than 120 mmHg (hypotensive group)
- participants with systolic BP = 120-139 mmHg (normotensive group)
- participants with systolic more than 140 mmHg (hypertensive group)

26 (10, 8%) participants belonged to the hypotensive group according to the values of their blood pressure (5 men and 21 women). The BP values of 60 participants (24, 9%) fell to the group of normotonics (19 men and 41 women). The biggest group consisted of hypertonics. One hundred fifty five participants were classified as hypertonics (64, 3%) participants (43 men and 112 women). Description of blood pressure and OH prevalence in groups is presented (table 24). Groups don't differ in diastolic BP, the values overlap, when we take SD into consideration.

Table 24: Main description of groups (n=241)

	Hypotensive (n=26)	**Normotensive (n=60)**	**Hypertensive (n=155)**
Sys BP (mean ±SD)	110, 4 ± 7, 3	127, 6 ± 6, 1	163, 8 ± 19, 4
Dia BP (mean ±SD)	65, 7 ± 7, 0	69, 6 ± 6, 8	81, 6 ± 10. 9
Age (mean)	84, 7	85, 1	83, 3
OH prevalence % (n)	23, 1 (6)	25, 0 (15)	23, 2 (36)

The ratio between men and women is 1:3 in the study, this ratio changed at the most in the group of normotensive to 1:2, it changed to 1:4 in the group of low blood pressure and stayed in the hypertensive group 1:3.

We tested distribution of age in defined groups. We found no difference in age between hypotensive (mean 84, 7 years; min-max 80 – 95 years) and normotensive (mean 85, 1 years; min-max 80-95 years), **p= 0,103** (Man-Whitney test for not normally distributed variables). We found significant difference in age between the group of normotensive and hypertensive group (mean 83, 3 years; min-max 80-93 years) **p= 0, 001**. The difference between group with

low BP and hypertensive wasn't significant; **p=0, 095**. The follow-up in measurements was significantly different among groups (**p= 0, 003**; Anova one way test). There was drop out of 53, 8% (14) of participants in the group with low BP, 50, 0% (30) in the group normotensive and 29, 0% (45) in the group hypertensive. This can be connected to the smaller size of hypotensive and normotensive.

We observed distribution (%) in different levels of drop in systolic blood pressure. We were interested in BP drop occurring near the threshold from the definition for orthostatic hypotension (table 25 and 26). We took into consideration defined intermediate drop in systolic BP 10-19 mmHg and diastolic BP 5-9 mmHg (Weiss et al 2004). We found many cases occurring in this range of values, especially in OH assessment after 1 min, in systolic BP there was 21 % (hypertensive group), 27 % (hypotensive group) and 37 % of participants (normotensive group) and diastolic BP 15 % (hypertensive group), 17 % (normotensive group) and 27% of participants (hypotensive group). Intermediate drop of BP after 3 minutes standing was less frequent, in systolic BP there was 0% (hypotensive group), 12 % (hypertensive group) and 22 % of participants (normotensive group); in diastolic BP there was 5% (normotensive group) and 15 % (hypertensive and hypotensive group).

Table 25: Distribution in categories of systolic BP drop (n=241)

	Hypotensive		**Normotensive**		**Hypertensive**	
Δ BP	**OHS 1min % (n)**	**OHS 3min % (n)**	**OHS 1min % (n)**	**OHS 3min % (n)**	**OHS 1min % (n)**	**OHS 3min % (n)**
Less than 0 mmHg	15,4 (4)	19,2 (5)	15,0 (9)	13,3 (8)	29,0 (45)	26,5 (41)
0 – 9mmHg	42,3 (11)	23,1 (6)	28,3 (17)	10,0 (6)	34,8 (54)	23,2 (36)
10 – 14mmHg	19,2 (5)	0 (0)	25,0 (15)	15,0 (9)	18,7 (29)	9,0 (14)
15 – 19mmHg	7,7 (2)	0 (0)	11,7 (7)	6,7 (4)	2,6 (4)	2,6 (4)
20+ mmHg	15,4 (4)	3,8 (1)	20,0 (12)	5 ,0(3)	14,8 (23)	9,7 (15)
Missing cases	0 (0)	53,8 (14)	0 (0)	50,0 (30)	0 (0)	29,0 (45)
Total	100,0 (26)	100,0 (26)	100,0 (60)	100,0 (60)	100,0 (155)	100,0 (155)

Table 26: Distribution in categories of diastolic BP drop (n=241)

	Hypotensive		Normotensive		Hypertensive	
Δ BP	OHD 1 min % (n)	OHD 3 min % (n)	OHD 1 min % (n)	OHD 3 min % (n)	OHD 1 min % (n)	OHD 3 min % (n)
Less than 0 mmHg	50,0 (13)	26,9 (7)	38,3 (23)	20,0 (12)	45,8 (71)	36,8 (57)
0 – 4mmHg	11,5 (3)	3,8 (1)	45,0 (27)	25,0 (15)	39,4 (61)	18,7 (29)
5 – 9mmHg	26,9 (7)	3,8 (1)	10,0 (6)	3,3 (2)	9,7 (15)	9,7 (15)
10+ mmHg	11,5 (3)	11,5 (3)	6,7 (4)	1,7 (1)	5,2 (8)	5,8 (9)
Missing CASE	0 (0)	53,8 (14)	0 (0)	50,0 (30)	0 (0)	29,0 (45)
Total	100,0 (26)	100,0 (26)	100,0 (60)	100,0 (60)	100,0 (155)	100,0 (155)

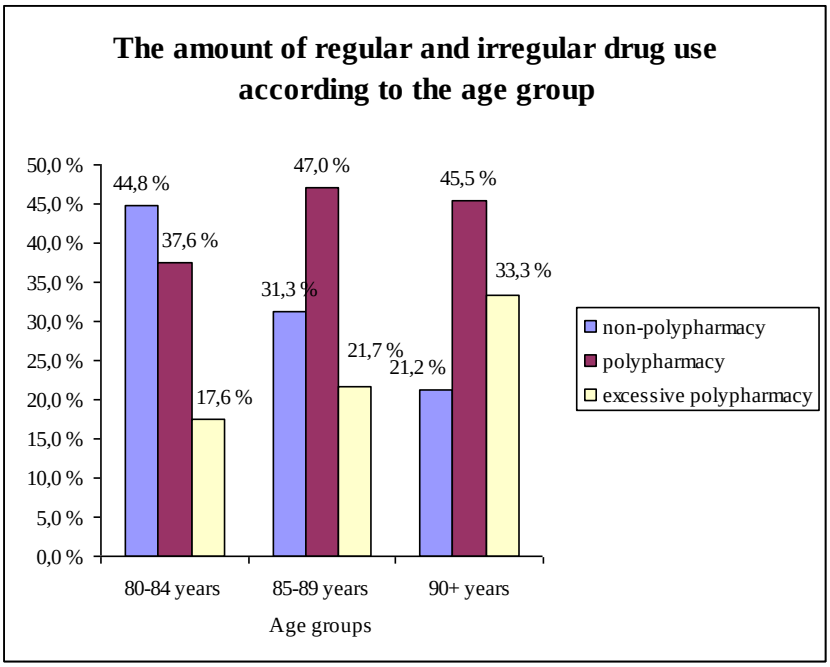
8.3 Polypharmacy according to the age and gender, levels of blood pressure and orthostatic hypotension

We stated 3 categories of medicine intake. Non-polypharmacy means intake of 0-5 medicines, polypharmacy means intake of 6-9 medicines and excessive polypharmacy means 10 and more medicine intake.

8.3.1 Polypharmacy according to the age and gender

The most of persons are occurring in the category of non-polypharmacy (80-84 years) or polypharmacy (85-89 years and 90+ years). There is step-by-step decrease of % in non-polypharmacy and increase of % in excessive polypharmacy according to the increase of age (figure 2). The average regular use of drug was 4, 9 medicines in group 80-84; 5, 6 medicines in group 85-89 and 6, 2 medicines in group 90+. The average irregular use of drug was 1, 3 medicines in group of aged 80-84, 1, 7 medicines in group of aged 85-89 and 2, 1 medicines in group aged 90 and more.

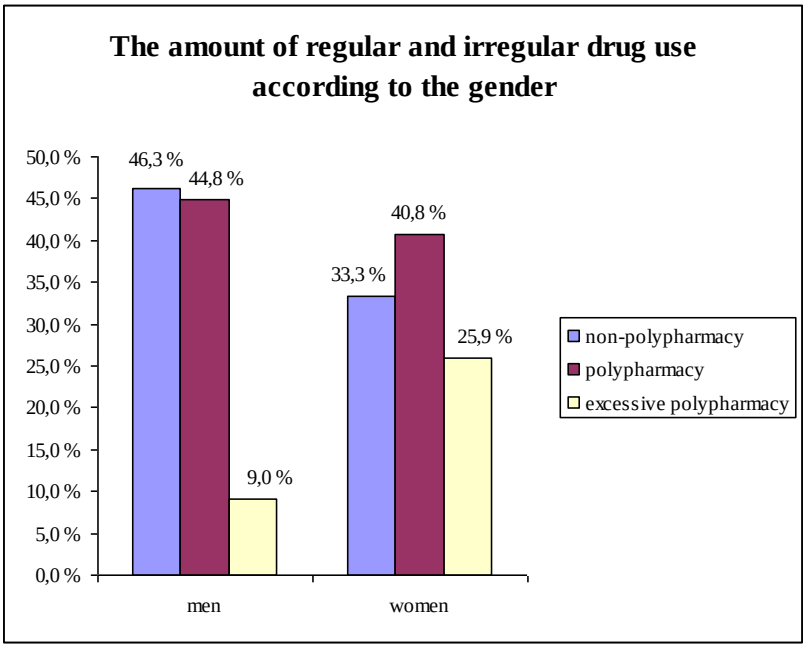
Figure 2: Distribution of participants in categories of drug use according to the age



Notes: Age group 80-84 years contains 125 persons, age group 85-89 years contains 83 persons and the group of 90 and more years contains 33 persons.

Women are more exposed to use of medicines in our study (figure 3). The average regular use of drugs differs, 4, 3 medicines in men and 5, 5 medicines in women. The average irregular use of drugs doesn't differ highly 1, 2 medicines in men and 1, 3 medicines in women.

Figure 3: The drug use according to the gender



8.3.2 Polypharmacy and level of blood pressure

We compared the medicine intake among categories of blood pressure. 241 participants were divided into 3 group, low BP group (BP less than 120mmHg), normotonics (BP=120-139mmHg) and hypertonics (BP=140+mmHg). BP values were obtained in sitting position. The largest group was hypertonics (155 participants), then normotonics (60 participants) and the smallest was group of low BP (26 participants).

We found tendency of increase use of drugs and the decrease of systolic blood pressure. According to the results, more than 50 % hypotonic fall within the category of excessive polypharmacy and less than 15% of hypertonic fall within excessive polypharmacy (table 27). It is obvious; they are probably using combination of different drugs for lowering blood pressure with success. We considered both use of drug, regular and irregular.
The average regular use was 7, 6 medicines in hypotensive, 6, 0 medicines in normotensive and 4, 6 medicines in hypertensive group. The average irregular use was 1, 5 medicines in hypotensive, 1, 6 medicines in normotensive and 1, 7 medicines in hypertensive.

Table 27: The whole medicine intake among systolic BP in sitting position (n=241)

Drug use	HYPOTENSIVE % (n)	NORMOTENSIVE % (n)	HYPERTENSIVE % (n)
Non-polypharmacy	19,2 (5)	28,3 (17)	43,2 (67)
Polypharmacy	26,9 (7)	48,3 (29)	41,9 (65)
Excessive polypharmacy	53,8 (14)	23,3 (14)	14,8 (23)
Total	100 (26)	100 (60)	100 (155)

Table 28: The regular medicine intake among systolic BP in sitting position (n=241)

Drug use	HYPOTENSIVE % (n)	NORMOTENSIVE % (n)	HYPERTENSIVE % (n)
Non-polypharmacy	23,1 (6)	46,7 (28)	63,2 (98)
Polypharmacy	50,0 (13)	36,7 (22)	32,9 (51)
Excessive polypharmacy	26,9 (7)	16,7 (10)	3,9 (6)
Total	100 (26)	100 (60)	100 (155)

8.3.3 Polypharmacy and orthostatic hypotension

We found no difference in regular intake of medicine in OH positive and OH negative participants (table 29). Distribution in all categories is almost equal. The average regular drug use was 5, 4 medicines in OH– and 4, 9 medicines in OH+, the average irregular drug use was 1, 5 medicines in OH- and 2, 2 medicines in OH+.

Table 29: Amount of medicine taken regularly and irregularly OH- x OH+

	OH- **% (n)**	**OH+** **% (n)**
Non-polypharmacy	38,0 (70)	33,3 (19)
Polypharmacy	41,3 (76)	43,9 (25)
Excessive polypharmacy	20,7 (38)	22,8(13)
Total	100 (184)	100 (57)

Table 30: The drop out in measurements according to polypharmacy

	Measurement 1 min **% (n)**	**Measurement 1 + 3 min** **% (n)**
Non-polypharmacy	34,8 (31)	65,2 (58)
Polypharmacy	33,7 (34)	66,3 (67)
Excessive polypharmacy	47,1 (24)	52,9 (27)
Total	100 (89)	100 (52)

8.4 Comparison of medicine use between OH+ and OH- in BP categories

The hypertonic group consists of the most of participants (155), in comparison to the smallest group of "hypotonic", where are only 26 participants together, results obtained in this group can be caused just by accident. Especially the group of OH + is small in every category of BP and when we compare percentages of medicine taken regular (table 31) versus medicine taken regular and irregular in OH+ (table 32), there are big differences. This makes results less reliable. We found no participant OH+ of "hypotonics" in category excessive polypharmacy in regularly taken medicine for instance (table 31) and 3 of them in the same category in regularly and irregularly taken medicine (table 32). It set up 50% difference suddenly.

Table 31: Regularly taken medicine among sys BP groups and OH presence

	HYPOTENSIVE		NORMOTENSIVE		HYPERTENSIVE	
	OH-	OH+	OH-	OH+	OH-	OH+
Drug use	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Non-polypharmacy	20,0 (4)	33,3 (2)	51,1 (23)	33,3 (5)	61,3 (73)	69,4 (25)
Polypharmacy	45,0 (9)	66,7 (4)	31,1 (14)	53,3 (8)	35,3 (42)	25,0 (9)
Excessive polypharmacy	35,0 (7)	0,0	17,8 (8)	13,3 (2)	3,4 (4)	5,6 (2)
Total	100,0 (20)	100,0 (6)	100,0 (45)	100,0 (15)	100,0(119)	100,0 (36)

Table 32: Regularly and irregularly taken medicine among BP groups and OH presence

	HYPOTENSIVE		NORMOTENSIVE		HYPERTENSIVE	
	OH-	OH+	OH-	OH+	OH-	OH+
Drug use	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Non-polypharmacy	15,0 (3)	33,3 (2)	35,6 (16)	6,7 (1)	42,9 (51)	44,4 (16)
Polypharmacy	30,0 (6)	16,7 (1)	44,4 (20)	60,0 (9)	42,0 (50)	41,7 (15)
Excessive polypharmacy	55,0 (11)	50,0 (3)	20,0 (9)	33,3 (5)	15,1 (18)	13,9 (5)
Total	100,0 (20)	100,0 (6)	100,0 (45)	100,0 (15)	100,0 (119)	100,0 (36)

8.5 OH presence and medicine intake according to the ATC groups

We considered specific medicine categories, which were taken in higher amount, trying to find any difference. OH+ and OH- participants don't differ significantly in taking medicines in specific categories. P- values are higher than the threshold for significance (table 33).

Table 33: Comparison of using medicine among OH+ (n=57) and OH- (n=184)

ATC		OH + %(n)	OH - %(n)	P
C01	Cardiac therapy	42,1(77)	41,8(24)	1,00
C03	Diuretics	35,1(74)	40,2(20)	0,54
C07	Beta blocking agents	45,6(102)	55,4(26)	0,23
C08	Kalcium channel blockers	26,3(45)	24,5(15)	0,86
C09	ACE inhibitors	29,8(61)	33,2(17)	0,75
N05	Antipsychotics	22,8(52)	28,3(13)	0,50
N06	Psychoanaleptics	8,8(33)	17,9(5)	0,14

We studied the use of medicine and prevalence of OH and its possible effect on developing orthostatic hypotension. We present % of participants who are taking specific category of medicine and are positive or negative for OH presence (table 34).

Table 34: OH according to different drug categories OH+ (n=57) and OH- (n=184)

ATC		OH- % (n)	OH+ % (n)
C01	Cardiac therapy	76,2 (77)	23,8 (24)
C03	Diuretics	78,7 (74)	21,3 (20)
C07	Beta blocking agents	79,7 (102)	20,3 (26)
C08	Kalcium channel blockers	75,0 (45)	25,0 (15)
C09	ACE inhibitors	78,2 (61)	21,8 (17)
N05	Antipsychotics	80,0 (52)	20,0 (13)
N06	Psychoanaleptics	86,8 (33)	13,2 (5)

The use of specific class of drugs was compared between OH positive and negative (table 35). The number of persons is small in every class, especially antiparkinsonian drugs for instance, 1 person occurs in OH- and 3 persons using antiparkinsonian drugs occur in OH+. In every class, there are drugs, which differ in their ability to produce orthostatic hypotension. The spectrum of drugs which were used by study participants was reviewed (Appendix 8).

Table 35: Use of specific drug group according to OH presence

ATC		**OH - % (n=184)**	**OH + % (n=57)**
C01D	Vasodilatators used in cardiac diseases	35,3	36,8
C03C	High ceiling diuretics	22,3	14,0
C03E	Diuretics and potassium sparing agents	16,3	19,3
C07A	Beta blocking agents	54,3	40,4
C08C	Selective Ca channel blockers with mainly vascular effects	21,7	19,3
C08D	Selective Ca channel blockers with cardiac effect	2,7	7,0
C09A	ACE inhibitors alone	19,6	14,0
C09B	ACEI + combinations	6,5	3,5
C09C	Angiotensin II inhibitors	6,0	10,5
C09D	Angiotensin II inh + combinations	1,6	1,8
N04	Antiparkinsonian drugs	0,5	3,5
N05C	Hypnotics and sedatives	21,2	22,8
N06A	Antidepressants	13,6	7,0

9 DISCUSSION

Blood pressure overview

Blood pressure was obtained in four different positions. The main feature of BP was fall in systolic BP from lying position to standing position after 1 min and increase of BP from standing position after 1 minute to standing position after 3 min. Diastolic blood pressure didn't differ almost during changing position. The mean of BP was always higher in women but we didn't find any significant difference between genders. We found decreasing tendency of systolic and diastolic BP in age groups according to the increase of age in all positions. The goal of hypertension therapy is blood pressure below value 140/90 mmHg (Bhattacharyya and Das 1999;Chobanian et al 2003). The most of participants, exactly 49% of men and 52% of women, obtained values of systolic blood pressure more than 140 mmHg and diastolic blood pressure less than 90 mmHg in sitting position. The result is lower than published in article (Plouin, Rossignol and Bobrie 2006), there is suggested prevalence of hypertension exceeding 70 % in the elderly aged 70 and more.

Orthostatic hypotension

We stated prevalence of orthostatic hypotension to be 23, 7 % in home-dwelling persons of our study, the percentage includes all considered types of OH (systolic/diastolic, 1/3 min). Reported prevalence was higher than reported in review done by Hajjar 2005 where the range of OH prevalence is supposed to be 5%-15% in home-dwelling persons. As we mentioned, it is difficult to compare results from different studies, they differ in design, in methods of measurements and also by definition of OH finally. We have to admit, the study sample of population was very old in comparison population in another studies, where the range of age was wider.

There was 37 % decrease of participants between OH 1 min assessment and OH 3 min assessment. The reason is understandable. We observed frail and very old people in advanced age who suffer from different disorders. They differ in physical condition as they have different lifestyle including activities during day. Some of them are taking high amount of medicine for lowering BP which can influence their ability of standing for longer time. We counted separately OH 1 and OH 3 min in systolic and diastolic BP. Study done by Luukinen

et al. 1999 showed diastolic OH 1 min and systolic OH 3 min to predict vascular death in older persons. Systolic OH was more prevalent than diastolic OH in study population. The highest prevalence was OHS after 1 minute standing (**16, 2 %)**, followed by prevalence of OHS after 3 min (**12, 5%).** We noticed an increase of percentage in OHD 3 min (**8, 6%**) in comparison to OHD 1 min (**6, 2%**).

No difference was reported between genders in prevalence of OH. The distribution of genders wasn't equal in study. Only 27, 8% of participants were men. This has been regarded as one limitation. Some studies reported women are supposed to have lower orthostatic tolerance and are more prone to develop OH. We cannot support this conclusion as our study sample was predominantly female and although this feature there was no significant difference in OH between men and women. There was also no significant difference in certain OH (systolic/diastolic, 1/3 min) between genders. To observe orthostatic hypotension from another point of view, three age groups were defined in our sample and we were looking for differences. The first difference was distribution in group, naturally the youngest group contained the most of persons and the oldest group had the fewest amount of participants. OH prevalence was stated, age group 80-84 and 85-89 didn't differ and there was a decrease in OH prevalence in the oldest group which could have been caused by small number of participants. There was observed high drop out of persons between OH 1 min and 3 min assessment. The decrease of participants, who attended the BP measurement after 3 minutes, was obvious, especially in the oldest group. We were interested in drop of OH + 1 min participants according to the age groups, which could have influenced the results of OH 3 min prevalence. The result is there were 6 from 30 OH positive participants (age group 1), 9 from 21 OH positive (age group 2) and 5 from 6 OH positive (age group 3) haven't been measured for OH after 3 min. Especially drop out in the oldest group was very high and it is possible causation, why there is no participants aged 90 and more who suffered from OH 3 min (table 21).

We defined three groups according to the systolic blood pressure values obtained in sitting position (6.2.4.BP categories and OH prevalence). The most of participants was ranged to hypertonic group, the smallest group was hypotensive. Participants from a different category could have had different potential for decreasing blood pressure during orthostatism (James and Potter 1999). We cannot sustain it. OH prevalence didn't differ among BP groups. The highest OH prevalence was reported in normotensive group, which was also the oldest group.

We took into consideration defined intermediate drop (ID) in systolic BP 10-19 mmHg and diastolic BP 5-9 mmHg (Weiss et al 2004). We found many cases occurring in ID, more cases was found in assessment OH 1 min than OH 3 min and in systolic than diastolic. The highest percentage of participants in systolic ID had normotensive group in both OH after 1 and 3 minutes of standing. On the other hand, the most of participants in ID had hypotensive group in diastolic OH assessment after 1 and 3 minutes of standing. We observed drop out of participants in every group separately. Follow-up in measurements was significantly different among BP groups but not significantly different between OH + and OH –. There was high drop out of 53, 8% of participants in the group with low BP, 50, 0% in the group normotensive and smaller drop out of 29, 0% in the group hypertensive. This high result can be connected to the smaller size of hypotensive and normotensive.

Polypharmacy

Polypharmacy is problem related to elderly population. We observed regular and irregular use of medicine separately in age groups and gender. The mean of used drugs was increasing according to the increase of age in regular and irregular use. Participants aged 90 years and more almost in 80 % of cases, participants aged from 85 to 89 almost in 70 % and participants aged from 80 to 84 years in 54 % of cases were ranked to polypharmacy or excessive polypharmacy category (graph 2). Women are using higher amount of drugs than men in study sample. Regular drug use is higher in women, irregular use don't differ in gender. Women occur in 77% of cases in polypharmacy or excessive polypharmacy (26%) category in comparison to men, who 54 % of cases there (9% in excessive polypharmacy). Polypharmacy in blood pressure categories is increasing according to the decrease of systolic blood pressure. The average regular use was the highest in hypotensive and lowest in hypertensive. The average irregular use doesn't differ highly. Almost 54% of hypotensive group belonged to excessive polypharmacy group. On the opposite, the most of normotensive (48%) belonged to polypharmacy group and the most of hypertensive belonged either to non-polypharmacy (42%) or polypharmacy (43%) group. The small number of persons in hypotensive and normotesive group can make results less reliable.

Polypharmacy and orthostatic hypotension

Orthostatic hypotension positive and negative participants didn't differ in polypharmacy. The regular drug use was higher in OH negative and irregular drug use was higher in OH positive persons. We were interested in drop out in measurement after 3 minutes of standing according to polypharmacy categories. The highest drop out was in category of excessive polypharmacy (47%), in polypharmacy and non-polypharmacy categories there were drop out around 34 %. If we consider specific ATC group, which are suspected from developing orthostatic hypotension, we will find no significant difference between OH negative and positive in study sample. The possible effect of medicine on orthostatic hypotension was difficult to assess. Participants are taking different combinations of drugs and evaluation of individual drug's effect couldn't have been proceeding. Every drug in specific ATC group doesn't posses the same effect on cardiovascular and other systems which are included in blood homeostasis. They are not equal in characteristics. The participants were using many different drugs.

Limitations of study

In general, there were limitations in our measurements and our observations. At first, they were carried out just once in all participants. The possibility to compare more obtained values from one position could make our results more precise and we would have a chance to observe intraindividual changes in blood pressure. We had to rely on the results concluded from one measurement. On the second, we don’t know conditions during examination of participants, if the blood pressure was assessed during the same daytime, before or after meal in all of them. The orthostatic hypotension is unstable phenomena and the mechanism of developing is complex that means different conditions can have effect on its developing or disappearing. Repeated measurements are one of the recommendations for further studies in this area, another recommendation is recording conditions and time, when observation are done. In the end, orthostatic hypotension can be accompanied with specific symptoms. We unfortunately obtained no information about any of them. We couldn’t assess prevalence of asymptomatic or symptomatic OH separately.

10 SUMMARY (WRITTEN IN ENGLISH AND CZECH)

English version

1. Orthostatic hypotension was stated to be 23, 7 % in 241 study participants. The percentage includes all defined types of OH .Systolic OH and OH after 1 minute was more prevalent than diastolic OH and OH after 3 minutes. We observed high drop out (37%) of participants in BP measuring in position D (standing 3 min). This could have decreased the prevalence of OH 3 min.

2. No significant difference was found nor in genders nor in three defined age groups. Higher blood pressure and higher level of polypharmacy was not associated with the presence of OH. There was no difference between OH positive and negative participants in drug use according to specific ATC. It is understandable, because every participant is using combinations of drugs and the effect of one drug is hard to define.

3. Higher values of systolic and low diastolic blood pressure values were obtained. 49 % of men and 52 % of women belonged to isolated systolic hypertension (according to the 7th JNC). Diastolic BP didn´t differ during changing positions, but systolic BP decreased from position A (lying) to position C (standing 1 min) and increased from position C to position D (standing 3 min). Blood pressure systolic and also diastolic decreased in all positions according to increase of age. Values of BP did not differ significantly in genders.

4. Women were exposed to the drug use more than men in study sample. They occur in cathegory polypharmacy and excessice polypharmacy in high percentage. There was increase of drug use exposition according to the increase of age and decrease of systolic blood pressure values (sitting position).

Czech version

1. Ortostatická hypotenze se stanovila u 241 členů studie. Prevalence byla 23, 7 % (procento zahrnuje všechny zmíněné typy OH), což je vyšší výsledek než zaznamenaný v předchozích studiích. Systolická OH a OH zaznamenaná po 1. minutě byly frekventovanější než diastolická OH a OH zaznamenaná po 3.minutě. Zaznamenali jsme 37 % pokles v účasti na měření krevního tlaku při stání po 3. minutě, což není opomenutelné a mohlo to uměle snížit prevalenci OH po 3. minutě.

2. Nebyl nalezen rozdíl v OH prevalenci mezi muži a ženami, ani mezi určenými třemi věkovými skupinami. Zvýšený krevní tlak a taktéž vyšší stupeň polyfarmacie nebyl asociován s přítomností OH. Nenašli jsme signifikantní rozdíl v užívání léčiv mezi OH pozitivními a negativními v jednotlivých kategoriích ATC. Na druhou stranu se tento výsledek dal očekávat, protože každý jedinec užívá různé kombinace léků a vliv jednoho léčiva na vyvolání OH je těžké určit.

3. Byly nalezeny vyšší hodnoty systolického a zároveň nízké hodnoty diastolického tlaku. 49 % mužů a 52 % žen patří svými hodnotami do kategorie izolované systolické hypertenze (určeno podle 7th JNC). Diastolický tlak se při změnách poloh téměř neměnil, naopak systolický klesal z polohy A (ležení) do C (stání 1 minutu) a stoupal z polohy C do D (stání 3 minuty). Krevní tlak systolický i diastolický klesal s vzrůstajícím věkem ve všech polohách. Nebyl nalezen rozdíl v hodnotách mezi pohlavími ani v jedné poloze.

4. V naší studii ženy užívaly více léků oproti mužům. Větší procento žen se vyskytovalo v kategorii polyfarmacie a excesivní polyfarmacie. Expozice lékům se zvyšovala všeobecně s vzrůstajícím věkem a klesajícími hodnotami systolického krevního tlaku (hodnoty z polohy vsedě).

11 CONCLUSION (WRITTEN IN CZECH)

Podle výsledků studie se ortostatická hypotenze vyskytovala u téměř každého 4. člověka, což není zanedbatelný údaj. Tento jev se prozatím v každodenní praxi spíše opomíjí a stanovení OH nepatří mezi standardní vyšetření. Vzhledem k tomu, jaké zdravotní komplikace přináší, obzvláště u starších lidí, by se mohla ortostatické hypotenzi věnovat větší pozornost. Některé informace týkajících se metod studie nebyly plně dostačující (viz diskuse/discussion), přesto se domnívám, že naše výsledky mohou sloužit jako podkladový materiál k dalšímu výzkumu. Pro příští design studie týkající se této tématiky bych především doporučila opakované měření krevního tlaku za pevně stanovených podmínek pro všechny členy a sledování symptomů doprovázející tento jev.

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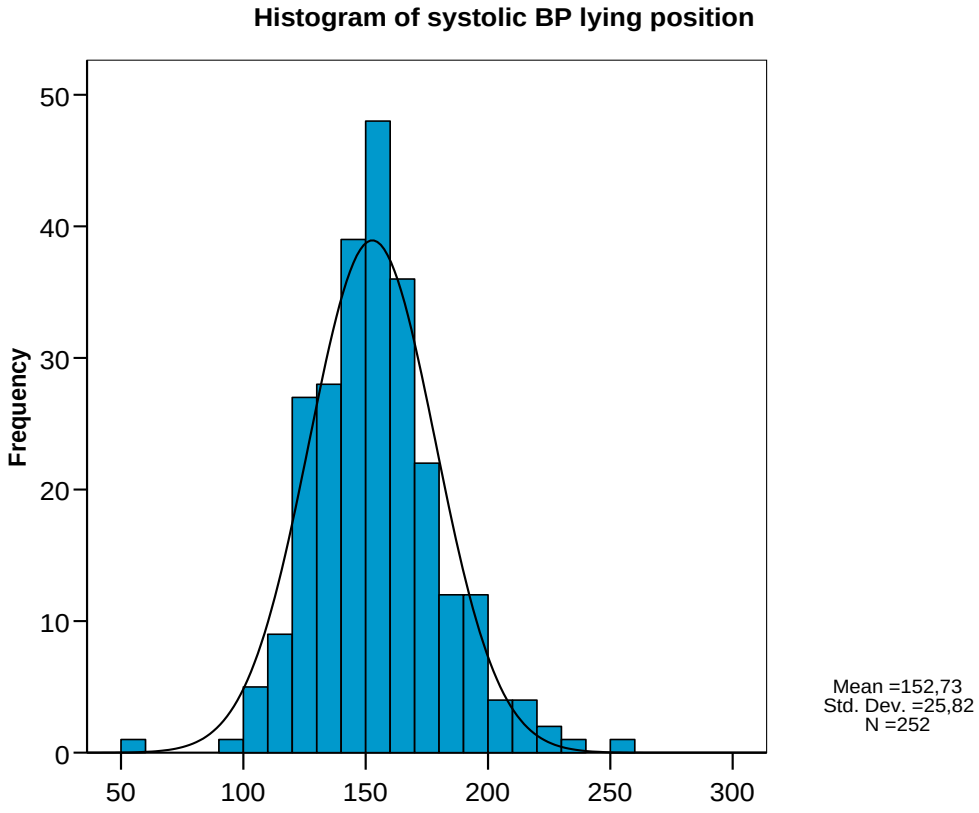
13 APPENDICES

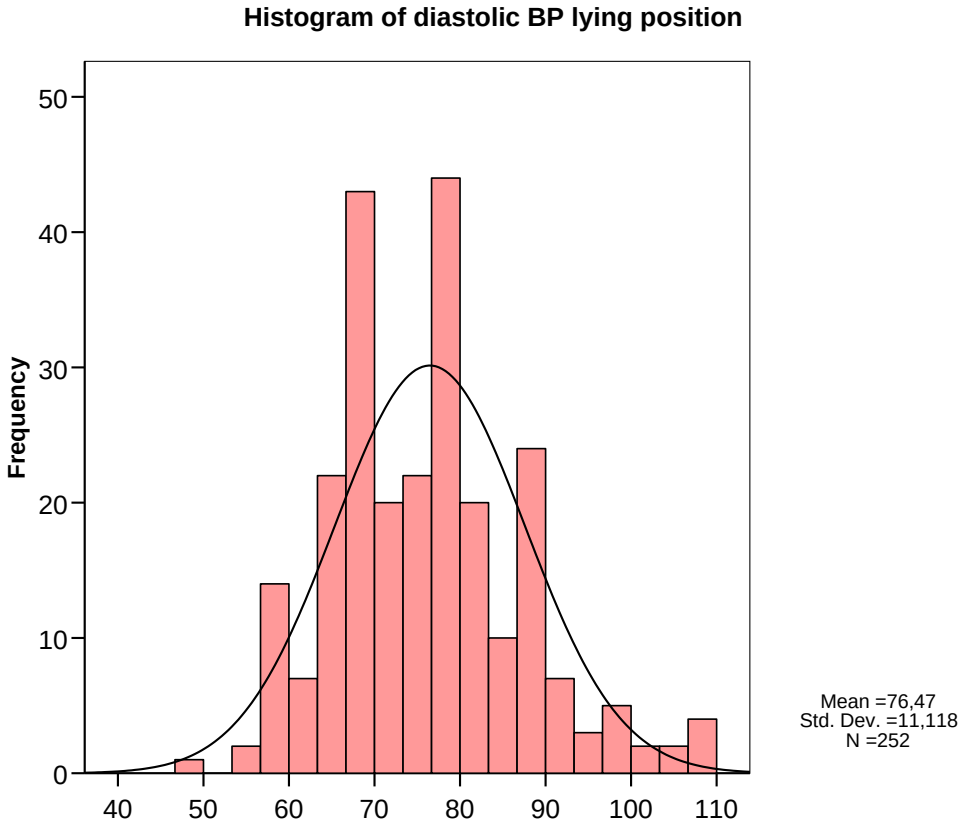
Appendix 1: Blood pressure overview in different position according to BP categories

Systolic BP sitting position categories (mmHg)		OHS 1 min standing	OHS 3 min standing	OHD 1 min standing	OHD 3 min standing
<119	Mean ± SD (mmHg)	**8,0** ± 10,9	**-3,1** ± 16,3	**0,2** ± 10,8	**-1,5** ± 11,7
	Min-Max (mmHg)	(-16) - 34	(-42) - 23	(-33) – 27	(-27) – 14
	Total number	26	12	26	12
120-139	Mean ± SD (mmHg)	**9,9** ± 11,0	**7,1** ± 9,9	**-0,3** ± 6,1	**-2,6** ± 8,9
	Min-Max (mmHg)	(-21) - 40	(-11) - 24	(-19) – 12	(-37) – 10
	Total number	60	30	60	30
140-149	Mean ± SD (mmHg)	**11,2** ± 16,0	**7,5** ± 17,9	**-0,2** ± 6,9	**-1,7** ± 10,2
	Min-Max (mmHg)	(-12) - 60	(-24) - 55	(-22) – 15	(-27) – 22
	Total number	39	28	39	28
150-159	Mean ± SD(mmHg)	**2,5** ± 12,8	**-2,0** ± 12,5	**-1,0** ± 6,9	**-1,1** ± 8,6
	Min-Max (mmHg)	(-28) - 32	(-35) - 16	(-20) – 11	(-20) – 16
	Total number	40	25	40	25
160-169	Mean ± SD (mmHg)	**4,0** ± 13,3	**-0,3** ± 14,4	**-2,0** ± 6,9	**-2,4** ± 8,5
	Min-Max (mmHg)	(-22) - 40	(-32) - 23	(-16) – 9	(-25) – 11
	Total number	29	24	29	24
170-179	Mean ± SD (mmHg)	**-5,2** ± 34,9	**0,4** ± 19,1	**-1,2** ± 6,0	**-2,9** ± 5,8
	Min-Max (mmHg)	(-132) - 26	(-18) - 37	(-16) – 14	(-12) – 4
	Total number	17	7	17	7
>180	Mean ± SD (mmHg)	**2,6** ± 20,8	**2,4** ± 22,0	**-1,8** ± 9,6	**-2,2** ± 11,2
	Min-Max (mmHg)	(-39) - 46	(-44) - 46	(-23) – 27	(-25) – 28
	Total number	30	26	30	26

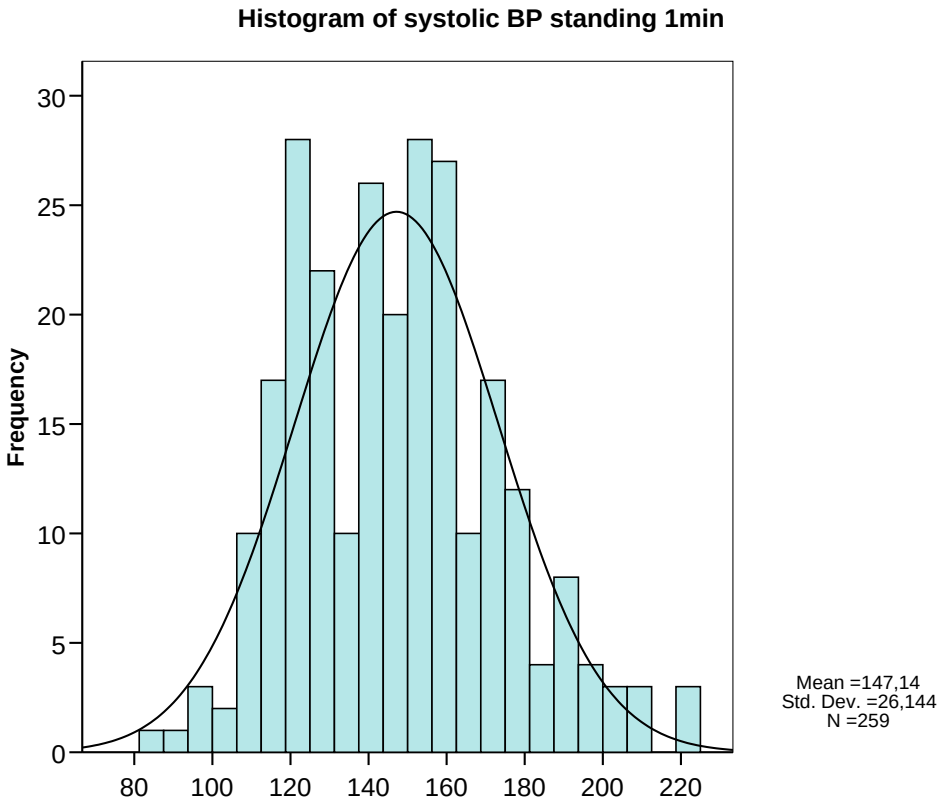
Appendix 2: Systolic blood pressure in lying position



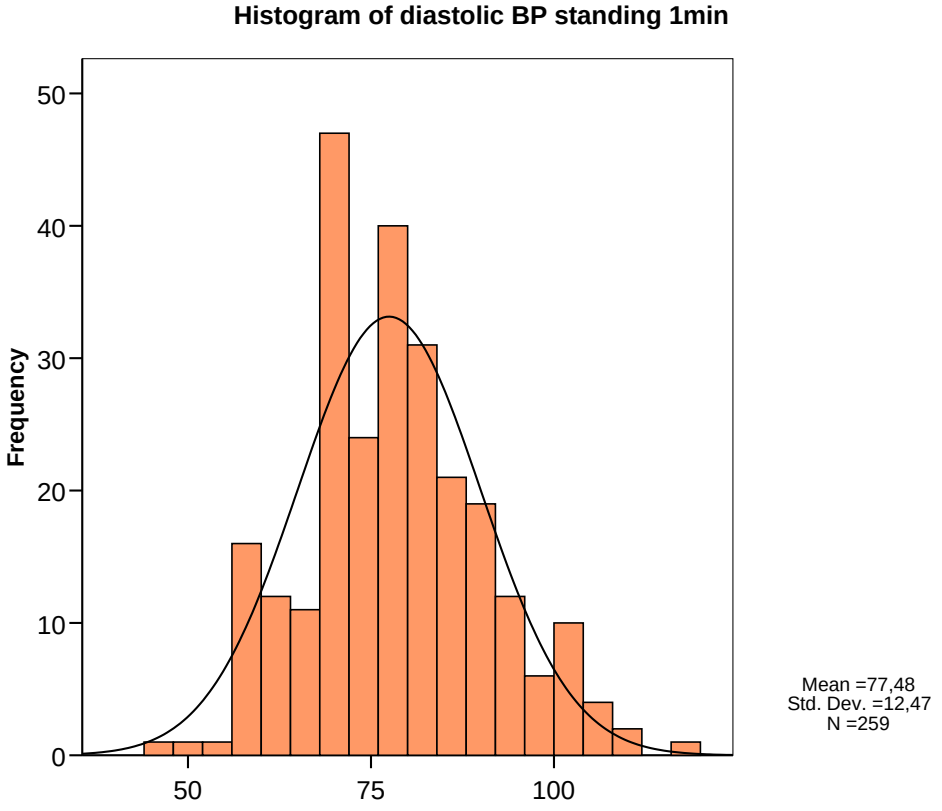
Appendix 3: Diastolic blood pressure in lying position



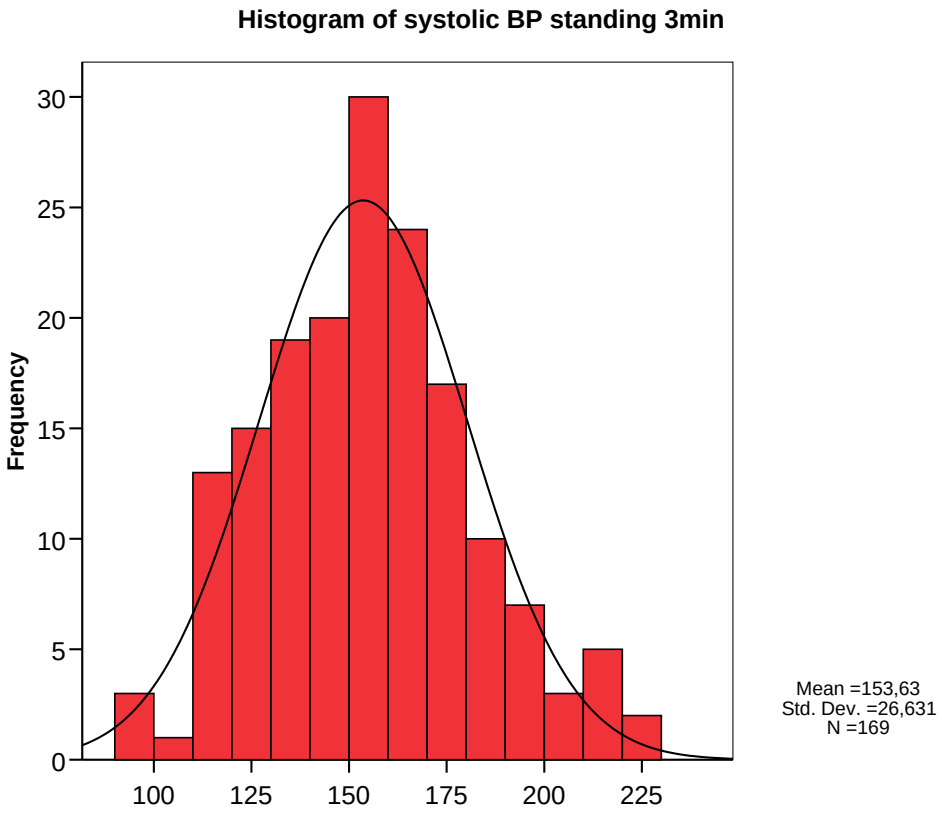
Appendix 4: Systolic blood pressure in standing position after 1 minute



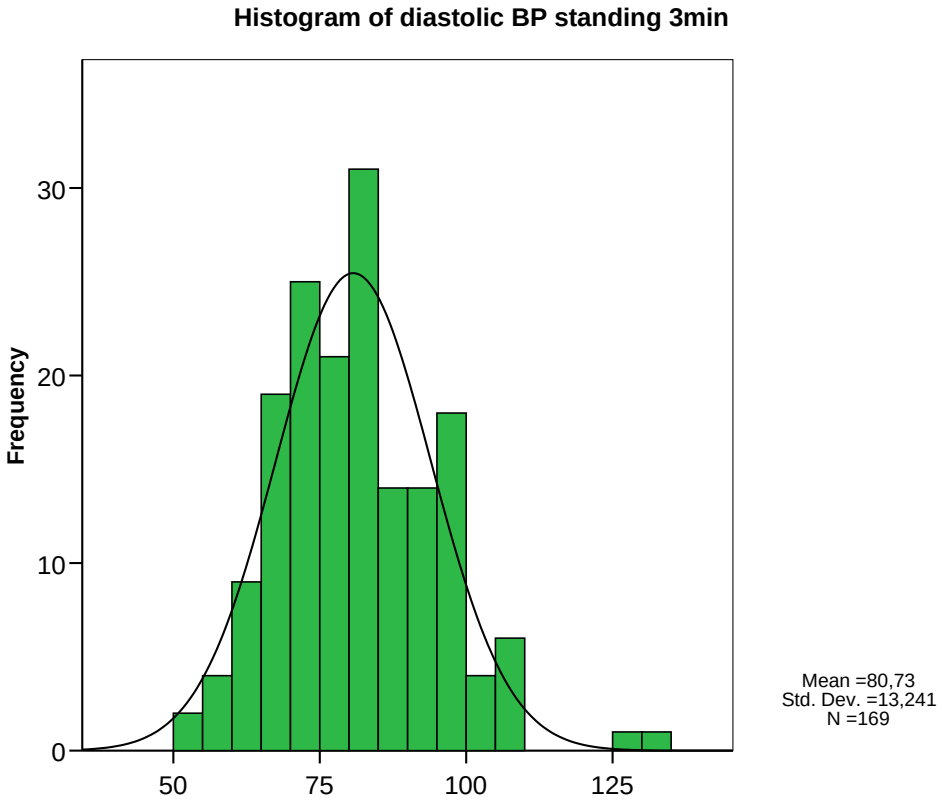
Appendix 5: Diastolic blood pressure in standing position after 1 minute



Appendix 6: Systolic blood pressure in standing position after 3 minutes



Appendix 7 Diastolic blood pressure in standing position after 3 minutes



Appendix 8: Drug use in study sample according to OH presence

Drug use		
C01	Cardiac therapy	
C01D	Vasodilators used in cardiac diseases	
	OH+	**OH-**
	C01DA08 isosorbid dinitrate	C01DA08 isosorbid dinitrate
	C01DA14 isosorbid mononitrate	C01DA14 isosorbid mononitrate
		C01DA02 glyceryltrinitrate
C03	Diuretics	
C03C	High-ceiling diuretics	
	C03CA01 furosemide	C03CA01 furosemide
C03E	Diuretics and potassium-sparing agents in combination	
	C03EA01 hydrochlorothiazide + K sparing agents	C03EA01 hydrochlorothiazide + K sparing agents
	C03EB01 furosemide+ K sparing agents	C03EB01 furosemide+ K sparing agents
		C03EA02 trichlormethiazide + K sparing agents
C07	Beta blocking agents	
C07A	Beta blocking agents	
	C07AA03 pindolol (non-selective)	C07AA03 pindolol (non-selective)
	C07AB02 metoprolol (selective)	C07AA05 propranolol
	C07AB03 atenolol	C07AA06 timolol
	C07AB04 acebutolol	C07AA07 sotalol
	C07AB07 bisoprolol	C07AB02 metoprolol (selective)
	C07AB08 celiprolol	C07AB03 atenolol
	C07AG02 carvedilol	C07AB04 acebutolol
		C07AB07 bisoprolol
		C07AB08 celiprolol
		C07AG02 carvedilol
C08	Calcium channel blockers	
C08C	Selective calcium channel blockers with mainly vascular effects	
	C08CA01 amlodipine	C08CA01 amlodipine
	C08CA02 felodipine	C08CA02 felodipine
	C08CA05 nifedipine	C08CA05 nifedipine
	C08CA13 lercanidipine	C08CA13 lercanidipine
		C08CA03 isradipine
		C08CA07 nisoldipine
C08D	Selective calcium channel blockers with direct cardiac effect	
	C08DB01 diltiazem	C08DB01 diltiazem
C09	Agents acting on the rennin-angiotensin system	
C09A	ACE inhibitors, plains	

	C09AA01 captopril	C09AA01 captopril
	C09AA02 enalapril	C09AA02 enalapril
	C09AA03 lisinopril	C09AA03 lisinopril
	C09AA06 quinapril	C09AA06 quinapril
		C09AA04 perindopril
C09B	ACE inhibitors, combinations	
	C09BA02 enalapril+diuretics	C09BA02 enalapril+diuretics
		C09BA03 lisinopril+diuretics
		C09BA06 quinapril + diuretics
C09C	Angiotensin II antagonists, plain	
	C09CA01 losartan	C09CA01 losartan
	C09CA06 candesartan	C09CA06 candesartan
C09D	Angiotensin II antagonists, combination	
	C09DA03 valsartan + diuretics	C09DA01 losartan + diuretics
		C09DA06 candesartan + diuretics
N05	Psycholeptics	
N05C	Hypnotics and sedatives	
	N05CF01 zopiclon	N05CF01 zopiclon
	N05CF02 zolpidem	N05CF02 zolpidem
	N05CD07 temazepam	N05CD07 temazepam
	N05CD02 nitrazepam	N05CD02 nitrazepam
N06	Psychoanaleptics	
N06A	Antidepressants	
	N06AB04 citalopram	N06AB04 citalopram
	N06AX03 mianserin	N06AB06 sertralin
	N06AX11 mirtazipine	N06AX03 mianserin
		N06AX11 mirtazipine
		N06AX16 venlafaxine
		N06AA09 amitryptilline
		N06AA12 doxepine
		N06AG02 moclobemid

Appendix 9: Distribution in systolic BP categories according to different position

		LYING POSITION		SITTING POSITION		STANDING 1 MIN		STANDING 3MIN	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Valid	<119	16	5,5	28	9,7	34	11,8	17	5,9
	120-139	55	19,0	64	22,1	70	24,2	34	11,8
	140-149	39	13,5	47	16,3	36	12,5	20	6,9
	150-159	48	16,6	41	14,2	39	13,5	30	10,4
	160-169	36	12,5	34	11,8	26	9,0	24	8,3
	170-179	22	7,6	23	8,0	25	8,7	17	5,9
	>180	36	12,5	33	11,4	29	10,0	27	9,3
	Total	252	87,2	270	93,4	259	89,6	169	58,5
Missing	System	37	12,8	19	6,6	30	10,4	120	41,5

Appendix 10: Distribution in diastolic BP categories according to different position

		LYING POSITION		SITTING POSITION		STANDING 1 MIN		STANDING 3MIN	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Valid	<59	5	1,7	11	3,8	19	6,6	6	2,1
	60-69	61	21,1	64	22,1	47	16,3	28	9,7
	70-79	93	32,2	83	28,7	87	30,1	46	15,9
	80-89	60	20,8	66	22,8	61	21,1	45	15,6
	90-99	21	7,3	33	11,4	28	9,7	32	11,1
	>100	12	4,2	13	4,5	17	5,9	12	4,2
	Total	252	87,2	270	93,4	259	89,6	169	58,5
Missing	System	37	12,8	19	6,6	30	10,4	120	41,5