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**Diploma Thesis:**  
**ANALYSIS OF PHARMACOTHERAPY BY PATIENTS WITH DIAGNOSIS OF**  
**ARTERIAL HYPERTENSION**

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Hradec Kralove, 2013

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## **Abstract**

Title: Analysis of Pharmacotherapy by patients with diagnosis of arterial hypertension

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**Introduction:** Arterial Hypertension (AH) is characterized by elevated blood pressure, which often leads to increased morbidity and mortality. AH divided into primary and secondary.

**Aim:** In the theoretical part the aim is to analyse the etiopathogenesis, methods of diagnosis and the treatment strategies of arterial hypertension in the recent literature. In the experimental part the aim is to analyse the provisions of the above diagnosis of arterial hypertension.

**Method:** During a six month period were collected 58 prescriptions with the diagnosis of arterial hypertension from a pharmacy that provided pharmaceutical care in the Greek village, Mytikas. Only one prescription for one patient was analysed. In the prescriptions were collected data on drugs, patients and physicians.

**Results:** The pilot study included 58 prescriptions. Most patients were elderly, over 65 years old and 30% were in age 71 – 80 years. General practitioners prescribed 65% of the medical prescriptions. Most frequently prescribed ARBs with hydrochlorothiazide drugs (27%) and ARBs as monotherapy (25%). Most frequent prescribed ARB, irbesartan (10%). Most of the drugs were prescribed once daily (62%). The treatment of 50% of the patients was based on combination of two active substances and 32.7% of the patients have monotherapy as their treatment. 54% of the prescribed medicines covered their monthly medication with one package.

**Conclusion:** In this Greek village the most commonly used antihypertensive was the sartan, irbesartan and the combination of sartan with thiazide. Certain limitations are mainly the population (physicians, patients) is not representative of the whole Greece, lack of information about the clinical state of the patients and the marketing activities of the pharmaceutical companies. The results will stimulate border observation study analyzing the

how the treatment of arterial hypertension in Greece.

## **Souhrn**

Název: Analýza farmakoterapie u nemocných s diagnózou arteriální hypertenze

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**Úvod:** Arteriální hypertenze (AH) je charakterizována zvýšeným krevním tlakem, který častěji vede k vyšší morbiditě a mortalitě. AH rozdělujeme na primární a sekundární.

**Cíl:** Cílem teoretické části bylo analyzovat etiopatogenezi, metody diagnostiky a strategie léčby arteriální hypertenze v současné literatuře. Cílem experimentální části byla analýza předpisů s uvedenou diagnózou arteriální hypertenze.

**Metoda:** V průběhu 6 měsíců probíhal sběr receptů s Dg arteriální hypertenze v lékárně, která poskytuje farmaceutickou péči v řecké vesnici Mytikas. Pouze jeden recept od konkrétního pacienta byl analyzován. Z receptů byla shromažďována data o léčivech, pacientech a lékařích.

**Výsledky:** Do pilotní studie bylo zařazeno 58 receptů. Většina pacientů byla starších než 65let a 30% pacientů bylo ve věku 71 – 80 let. Praktický lékař předepsal 65% předpisů. Nejčastěji byly předepsány sartany a hydrochlorothiazid (27%) a sartany v monoterapii (25%). Nejvíce předepisovaným sartanem byl irbesartan (10%). Nejčastěji byly léky předepisovány jednou denně (62%). Léčba 50% pacientů byla založena na dvojkombinaci antihypertenziv a 32.7% pacientů užívalo monoterapii. 54% předepsaných léčivých přípravků pokrylo měsíční terapii jedním balením.

**Závěr:** V této řecké vesnici nejčastěji používání antihypertenzivem byl Sartani, irbersartan a kombinace santonů s hydrochlorothiazidem. Určitými limitacemi jsou hlavně, že populace (pacientů a lékařů) není reprezentativní pro celé Řecko, nedostatek informací o klinickém stavu pacienta a marketingových aktivitách farmaceutických firem. Výsledky budou inspirovat pro vytvoření širší observační studie analyzující léčbu arteriální hypertenze v Řecku.

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## **1. Introduction**

Elevated arterial blood pressure is a major cause of severe and dangerous vascular disease which is promoting the cerebrovascular events, the ischemic heart disease such as stroke and the peripheral vascular disease via the action of specific hormones. The levels of blood pressure belonging to the characteristics of each individual with several marked individual variations even if during the same day. The levels of blood pressure depend on the characteristics of the population which is selected for study in particular the age and the ethnic group of each patients examination. Blood pressure in industrialized countries rises with the age certainly up to the seventh decade. This rise is more connected with the systolic pressure especially in men. Referring to the diagnostic criteria, hypertension is present in 20-30% of the adult population and the blood pressure rise much higher in black Africans (40-45% of the adults) (Joffres et al 2005, Khan et al 2005).

The risk of the mortality or morbidity seems to be rises with the elevation of the systolic (mainly) and diastolic pressures, with each measure having an independent prognostic values and importance to other factors (Beckett et al 2008, Mann et al 2008).

All adults should have been measured the blood pressure routinely after the age of 50 years old. Seated blood pressure when measured after 5 minutes resting, but the standing (and your side) blood pressure should be measured in diabetic and elderly in order to avoid the case of orthostatic hypotension. The cuff should be deflated at 2 min/s and the blood pressure to nearest 2mmHg. Two consistent blood pressure measurements are necessary to measure the blood pressure and more are recommended if there are large differences in the pressure for each individual. When assessing the cardiovascular risk, the average blood pressure at separate visits is more accurate than measure at a unique visit (Beckett et al 2008).

This project is divided in two parts, the first part is called the theoretical and the other one is the experimental part. The theoretical part is represented by the factors that are causing the arterial hypertension, who is measured the arterial hypertension. The aim of this part is the examination of the arterial hypertension, its diagnosis and when a patient starts to use antihypertensive treatment. At last in the theoretical part is represented all the antihypertensive agents groups that are used in the treatment of the arterial hypertension.

On the experimental part, it was selected 60 medical prescriptions from one pharmacy in Greece over a six month period, in these prescriptions patients have been diagnosed with arterial hypertension. The aim of this part is to analyse from the collected prescriptions first of all what kinds of physicians are prescribed these prescriptions, the physicians' gender and their age. It is going to be analysed the patients' age and gender. After that the aim is to be analysed the frequency of the used antihypertensive agents, the dosage scheme that was used by the patients.

## **2. Literature review**

Literature search was conducted via Internet, electronic databases Medline, Embase, the Association of Greek Academic Libraries (HEAL-Link) and through the search engine Google Scholar for the period 2002-2011 with the following keywords: "hypertension ", "drug therapy of hypertension", " symptoms and causes of hypertension", "Pathophysiology of hypertension".

Of the large number of studies initially rejected the earlier studies focused as mentioned in modern literature data reported on surveys reliable scientific organizations and research groups from Europe and the U.S., into the goal to capture international practice in the administration of an appropriate therapeutic approach in patients' hypertension and the diseases causes from this.

The studies were considered acceptable for the literature review were primary articles, in English, which focused on the pathophysiology of heart disease, changes, risk factors, the treatment in hard function and clinical nursing and management patients who develop hypertension symptoms.

The criteria for selecting articles from other screening studies of retrospectively, was the choice of primary research with key findings and results in the management of patients with obstructive lung disease.

From the initial studies were selected about 65 investigations and has been evaluated critically on the contribution of each drug treatment of hypertension.

The results and conclusions of the studies were compared with those of questionnaires collected from our primary research and were receiving drug therapy in Greek patients with hypertension.

## **2.1 Causes of hypertension**

The majority of patients, 80 – 90%, with hypertension have a primary elevated of blood pressure which can be controlled with a long time results only by using pharmacological therapies. Both systolic and diastolic blood pressures increased levels are strong and very important prognostic factors for cardiovascular disease and stroke. Since blood pressure 115/75 mmHg (systolic / diastolic) is becoming higher of the natural levels, the increase of 10 mmHg diastolic and the increase of the systolic 20 mmHg doubles the risk for both fatal stroke and for coronary episode. In people over 50 years the systolic pressure is much stronger prognostic factor of cardiovascular disease than the diastolic pressure (Adrogué et al 2007).

The antihypertensive therapy reduces the risk of stroke at about 30% more than of cardiovascular disease by 25% and for heart failure in 50%. The benefit of each high blood pressure treatment depends mainly on reduce of stress, the nutrients choices of the patients and less and secondly to the type of the drug therapy, because the higher cardiac risk is connecting to the necessity of the greater benefit of treatment. In people with high cardiovascular risk or with multiple cardiovascular risk factors, the benefit of treatment is higher than that in people with little risk (Adrogué et al 2007).

## **2.2 Essential hypertension**

The essential individual hypertension has a multifactor etiology.

### **2.2.1 Genetic factors**

Blood pressure tends to run in families and children of hypertension parents tend to have higher blood pressure than age-matched children of people with normal blood pressure. This familial concordance of blood pressure may be explained, at least in the part of shared environmental influences. However it still remains a large, still largely unidentified genetic component (Kaplan et al 2007).

### 2.2.2 Fetal factors

Low birth-weight in some cases is associated with subsequent high blood pressure especially in neonatal with other genetic factors. This relationship may be due to the adaptation of the uterine nutrition with long term changes in blood vessel structure or in the function of crucial hormonal system (Kaplan et al 2007).

### 2.2.3 Environmental factors

Among the several environmental factors that have been proposed, the smoking and stress conditions seems to be the most significant (Kaplan et al 2007).

### 2.2.4 Obesity

People with high body mass index have higher blood pressure than people low body mass index. But in these cases it is a problem about the overestimation of the blood pressure because of technical measurement technique with a small cuff. Sleep disordered breathing had often seen with obesity may be an additional risk factor (Magnussen et al 2007).

### 2.2.5 Alcohol intake

Most studies have shown a close relationship between the consumption of alcohol and elevated blood pressure level because even if higher amounts of alcohol seem to have higher blood pressure even if it compared with no alcohol intake patients (Beulens et al 2007).

### 2.2.6 Sodium intake

A high sodium intake has been suggested to be a major factor of blood pressure increase and there are differences within populations around the world. Patients with higher sodium intake have higher average blood pressures than those with the lower sodium in-take. The increased migration from a natural to an urban environment is always associated with an increase in blood pressure and this condition is related with the amount of salt concentrations in the diet. There is some evidence that a high potassium diet can protect against the effects of high sodium intake (Calhoun et al 2008).

### 2.2.7 Stress

Stress can raise blood pressure the relationship between chronic stress and blood pressure is uncertain (Calhoun et al 2008).

### 2.2.8 Humoral mechanisms

The autonomic nervous system as well as the renin angiotensin, the natriuretic peptide and the kallikrein-kinin system plays a important role in the physiological regulation of several changes of blood pressure and have been implicated in the pathogenesis of essential hypertension. In a low renin essential hypertension, patients have renal sodium and water retention higher than natural levels (Kaplan et al 2007, Matchar et al 2008).

### 2.2.9 Insulin resistance

An association between diabetes and hypertension has long been recognized and a syndrome has been recognized for several blood evidences such as hyperinsulinaemia, glucose intolerance, reduced levels of HDL cholesterol, hypertriglyceridaemia and central obesity which all are associated with hypertension. This association with the factors referred above (also called metabolic syndrome) is a major risk factor for cardiovascular disease (Barzilay et al 2006).

## 2.3 Secondary hypertension

In adults the prevalence of secondary hypertension does not exceed 5%. The more often causes of secondary hypertension include chronic renal disease, sleep apnea, renovascular hypertension due to stenosis of renal AP- arteries (atherosclerotic usually cause) and less often the primary aldosteronism. Other causes such as syndrome Cushing, the coarctation of the aorta and pheochromocytoma are rare (Schrader et al 2005).

Drugs (NSAIDs, erythropoietin, cyclosporine, decongestants, nose, corticosteroids) and substances (cocaine) can cause increase in blood pressure.

The history, says that clinical examination and simple laboratory exams may

pose suspected secondary hypertension. Very high blood pressure, sudden occurrence of hypertension and resistant hypertension may also disclose a secondary hypertension. This control can be complex and costly and involve discomfort for the patient. For this reason must be performed only by specialists.

So secondary hypertension is where blood pressure elevation is the result of the specific and potential treatable cause. Secondary forms of hypertension include the following (Schrader et al 2005).

### 2.3.1 Renal diseases

These account for over 80% of the cases of the secondary hypertension. The common cause is the diabetic neuropathy, chronic glomerulonephritis, adult polycystin disease, chronic tubulointerstitial nephritis and renovascular disease. The Hypertension can cause itself because of the higher pressure at the renal vascular complexes cause exacerbations of the renal disease. The mechanism of this fact is due to sodium and water retention although there can be inappropriate elevation of plasma rennin levels.

### 2.3.2 Endocrine causes

These includes

- ✓ Conn's Syndrome
- ✓ Adrenal hyperplasia
- ✓ phaeochromocytoma
- ✓ Cushing Syndrome
- ✓ acromegaly

### 2.3.3 Congenital Anatomical Cardiovascular causes

The major cause is the coarctation of the aorta which alters the anatomical evaluations of blood circulation.

### 2.3.4 Drugs

There are many drugs that have been shown to cause an increased hypertension or these are such as NSAID's, oral contraceptive, steroids, carbenoxolone, liquorice, sympathomimetics and vasopressin. Patients taking monoamine oxidase inhibitors, who consume tyramine foods, may develop paroxysms of severe hypertension (Halperin et al 2008).

### 2.3.5 Pregnancy

The individual cardiac output rises in pregnancy connecting with a severe relative greater reduction in the peripheral blood pressure in pregnant women comparing with this of not pregnant. Hypertension is noted in 8-10% of pregnancies.

The Hypertension presenting in the second half of pregnancy usually resolves after delivery and is characterized as transient individual hypertension. When the blood pressure increases to 160/110 mmHg may be dangerous for the baby the is necessary to be setted a antihypertensive treatment for the protection of the mother and secondary the baby.

Pre-eclampsia is a serious but not common syndrome for the pregnant women induced hypertension with proteinuria. The primary pathophysiology is unknown but is likely to involve and connected to the abnormalities in cellular and physiological levels of the uteroplacental circulation, which may result the intrauterine growth restriction. Hypertension in pregnancy together with pulmonary embolus, are the most common causes of maternal death and the most severe pregnant diseases with the rate of 10 million pregnancies.

Furthermore the critical condition of eclampsia, which is associated with severe hypertension, may lead to severe clinical pathologies such convulsions, cerebral and pulmonary oedema with targeted symptoms and high risk of fatal results, clotting abnormalities especially in feet and lung tissues and death (Lip et al 1997, Higgins et al 2001).

## **2.4 Pathophysiology of systemic hypertension**

The pathogenesis and the pathophysiology of the mechanism of development essential hypertension remain to be clear and determined. Most of the patients with hypertension are also responsible of early increase in cardiac output, in connection with increased pulse rate and circulating level of the blood hormones like catecholamines. This could result in alterative changes in the operation of the molecular receptors sensitivity and function which could lead to a higher blood pressure degree.

We have already characterized that the cause of the chronic hypertension is

the increased peripheral resistance and not the cardiac output because the vessels with high resistance (arteries and arterioles) show structural, operational and functional changes in hypertension. These are characterized by increase in wall thickness with a reduction in the vessel diameter.

The hypertension also causes changes in the large arteries especially these which are crucial for the circulation of the upper and lower parts of the body such as carotids and aorta. In molecular level at these cases the vessels are becoming thinner with entire collagen and deposition of calcium. These functional and anatomical changes results in loss of arterial compliance, affecting the blood circulation, the arterial function via reducing the vessels diameter (which inhibits the flow) and increasing the blood pressure. Furthermore the endothelial dysfunction with alterations in agents such as nitric oxide and endothelins appear to be involved and are crucial for the mechanism of hypertension appearance.

Left ventricular hypertrophy which results from increased peripheral vascular resistance, and increased left ventricular load, is a significant prognosis indicator of future cardiovascular events (Mc Phee et al 2007).

As we have already referred above the cerebrovascular disease and the coronary artery disease are the most common causes of death at the developing countries, because there is another option the fact that the hypertensive patients has also renal failure and peripheral vascular disease. The hypertensives patients have six times higher possibility of developing stroke (hemorrhagic and atherothrombotic). Additionally these patients have increase incidence of cardiac failure, due to the coronary events and stroke development factors.

The characteristic histological changes of the vessels walls are the fibrinoid necrosis, istological condition which may lead to death from the progressive renal failure, heart failure or stroke. The changes in the renal circulation could develop the renal failure, proteinuria and haematuria. We already know that there is also an increased risk of cerebral oedema and haemorrhage in patients with hypertension because of the higher function of the vessels walls which can also lead to pappilodema with a survival rate of less than 20% if this condition remains untreated (Kaplan et al 2007, Mc Phee et al 2007).



## 2.5 Classification of arterial hypertension

The classification of blood pressure for adults has already referred previously. This classification and characterization of the essential and severe blood pressure characterized and determined by the measurements at least in 2 visits at the doctor in practice, with at least 2 measurements in a sitting position after getting rest for a small time of period without having smoke at least 30 min ago. In U.S. National Guidelines on Hypertension (JNC-7, 2003), blood pressure values 120-139/80-89 mmHg characterized as "pre-hypertension" (without be necessary a drug therapy) condition which is connected with greater cardiovascular and higher cases of possible increase after few years.

### 2.5.1 Measurement of blood pressure

Increased blood pressure rarely causes several symptoms. The Symptoms, presented due lesions in target organs that usually occurs, after many years. Therefore, the diagnosis of hypertension solely on the measurement is of border pressure and the diagnosis of hypertension should be determined the blood pressure of the individual, which requires specific rules and way of selection for each patient.

The measurement of blood pressure with a stethoscopic technique and Mercury sphygmomanometer produce a estimation of blood pressure which must be checked as soon as it has been estimated. The dimensions of the tube cuff should be adapted at the size of the test arm.

Two cuffs, one tube with  $23 \times 13$  cm (for perime-terrorist arm 23-29 cm) and a second tube with  $28 \times 15$  cm (for arm 28-35 cm) are sufficient for most cases. In arm  $<23$  cm we may use a Zeta lower cuff with diameter of  $> 35$  cm higher.

The patient has to sit quiet for a few minutes supported and the arm cuff-mounted, at heart level and then made 2-3 measurements in order to estimate the blood pressure at the most close condition and level. The recorded systolic pressure maybe be estimated by hearing the cardiac sound S1 and S2 and the diastolic sound of point extinction (sound V) (Sega et al 1998).

Although the mercury sphygmomanometer is easy to be used and the most

useful, on the other hand the certification of its use and estimation is being gradually restricted for several reasons. Moreover, the measurement technique of stethoscopic blood pressure is usually not estimated in worthy way because of the individual depended way of estimation (Sega et al 1998).

For the diagnosis of hypertension are usually required repeated measurements of the blood pressure as we have already refer in order to estimate the correct pressure without other factors influencing them. The best measure assessment is recommended to estimate the blood pressure levels in both arms in order to avoid a possible difference which could be caused by an aneurysm of a technical default (systolic > 20 mmHg and / or diastolic > 10 mmHg), condition which needs further investigation.

In cases of the identified increased blood pressure especially at the first visit to the doctor, the identification of the situation should be determined after 1-2 visits at intervals in one week between the visits. The diagnostic criteria and the possible decision of starting the antihypertensive therapy should not be based on measurements made in a unique visit because the unique event could be a multifactorial symptom. Even if in cases with the higher blood pressure levels (systolic / diastolic > 180/110 mmHg), should be a typical period of several days of reassessment blood pressure case in order to set the definitely diagnosis and the appropriate therapy. Even at the borders of the clinical pro-hypertension (140/90) mmHg of different number of doctors' diagnosis needed again to confirm the hypertension (Modesti et al 2006).

The individual calculation of cardiovascular risk for heart disease is not only connected with the level of blood pressure, but has a range of vascular and operational cases to target organs installed cardiovascular disease. Depending on the stage of hypertension, the existence risk factors of hypertensive individuals classify then to small, medium or high cardiovascular risk. People with stage 1 of hypertension, may be at very different risk depends on the other clinical factors affecting the hypertension development (Modesti et al 2006).

## **2.6 White Blouse Hypertension (single hypertension) and covert hypertension**

The white coat hypertension is defined as this because of the white coat of

the doctor, it is defined as the elevated blood pressure in the office of the doctor at least for three visits, which is not increased at the home when the patients are estimating it, which while the pressure is normal. The phenomenon is frequent and is becoming more frequent at the past years because the situation of the blood pressure is recognized better nowadays (Fagard et al 2007).

People with white coat hypertension do not need specific medical treatment but the diagnosis of this type of hypertension provided when (1) the doctor is sure about the confirmation, (2) there are no other factors for the increased blood pressure especially from the attack target organs and (3) the total cardiovascular risk is small.

The finally confirmation of the diagnosis of the white coat hypertension should be done in a few weeks or months by estimating with the same technique (recording the blood measurements at home). The white coat hypertension is treated with non-pharmaceutical means and monitoring 1-2 times time by measuring the pressure in the doctor's office. But most of the cases should be developed to systemic hypertension after several years situation which needs antihypertensive drug treatment because the increasing of blood pressure (Fagard et al 2007).

On the other hand the last years we already have recognized and the phenomenon of "co-covered" hypertension (masked hypertension) which is recognized as normal in the clinic or the doctor's office but increased outside the clinic or the office, which is equally order like the common hypertension of white coat. This type of hypertension is associated with severe damage of the organs and increased cardiovascular risk. Also the finally confirmation of the diagnosis of the covered hypertension should be done in a few weeks or months by estimating with the same technique (recording the blood measurements at home) (Fagard et al 2007).

## **2.7 Measurement of blood pressure at home**

The diagnosis of the white coat hypertension and the covert hypertension recruit long term monitoring patients on therapy. Reliable measurements at home may be by the usage of a mercurial sphygmomanometer or metal and a classical stethoscopic technique, even if nowadays by the electronic machine of the pressure

measurement. For the easier technique the electronic pressure machine is more recommended, but the automatic electronic pressure could be measured and the machine can hold in the memory the pressure levels each time recorded. For the correct use of pressure gauges of those which are having less education, the measurements are easier to be compared. On the other hand there are some disadvantages of these type of pressure estimation, because the electronic pressure gauges on the market should be checked in order to be appropriate and worth for the methodology. (Mengden et al 2003).

About the faithfulness of pressure gauges are available online sources ([www.dableducational.org](http://www.dableducational.org) or [www.hypertension.gr](http://www.hypertension.gr)). For long-term monitoring of blood pressure of patients, 1-2 measurements of the blood pressure per week is usually enough for the checking the levels of blood pressure. Measurements of the first day is usually higher and unstable and is not used in calculating the blood pressure which is comparing with the measurements after several days because these period could be useful for the standardization of the technique and the measurement in order to estimate a pressure average per day (Mengden et al 2003).

Average pressure at home  $\geq 135/85$  mmHg could indicate hypertension, and  $<130/85$  mmHg normal blood pressure (Intermediate values). The daily measurement of pressure and the technical changes which affecting the resulting individual levels of blood pressure should be avoided (O' Brien et al 2001).

The main indication of the 24 hour record is the unknown hypertension (isolated clinical hypertension). Other indications are: covert hypertension, borderline hypertension in people with small heart-vessel risk, resistant hypertension, and abnormal variability of blood pressure and symptoms of hypotension in individuals on antihypertensive therapy.

The most reliable parameter of the diagnostic threshold of the diagnostic 24h estimation is the unknown blood pressure and its etiology.

The pressure load (percentage of measurements with values  $> 135/85$  mmHg for the day and  $>120/70$  mmHg for night), although it is estimated by most programs automatically recording devices 24h, usually is not used (O' Brien et al 2001).

## **2.8 Clinical approaches of measurement the blood pressure**

The normal medical procedure of taking family history and personal clinical examination is necessary to all people with increased blood pressure in order to recognize and to evaluate all the responsible factors of the hypertension. These factors which are increasing the cardiovascular risk, and are helping the careful detection of the disease with no symptoms, injuries such as heart disease, stroke, peripheral arterial disease, renal failure and for the severe and carefully diagnosis of the unique secondary hypertension. The family history is also needed to be used as most informative as it can include elements about the lifestyle, such as smoking, alcohol and salt intake, physical activity and maybe drug use, or even of the working and family condition, which are strongly related factors to hypertension and stress (Mansia et al 1995, Mansia et al 2001).

In most cases according to most well characterized the situation of the patient is required to be informed and to do several other testes and examinations by whom it may estimate the sugar level, the total HDL and LDL cholesterol level, triglycerides, creatinine, uric acid, potassium, sodium, blood count, urinalysis and general electrocardiogram.

Tests to detect asymptomatic lesion or the target (echocardiography and carotid arteries, measurement of microalbuminuria) is useful, especially in cases of doubt about the necessity of treatment (e.g. limits pressure or hypertension white blouse). Other more specific tests are needed for patients with possible cardiovascular disease or when there are suspected secondary hypertension (Mansia et al 2001, Mansia et al 2007).

## **2.9 Examination of hypertension**

The high blood pressure level is usually the only not normal and more well recognized sing and symptom of the hypertension which recognized by the patients. The main symptoms could be recognized and the most recognized and these are severe for the additional treatment and the decision for the drug therapy.

The heart examination could show and reveal the features of possible anatomical disconfirmation of the heart function such as the left ventricular hypertrophy and the aortic operation.

In cases such the cardiac failure, should be appeared by the clinical unvestgarion the symptom of tachycardia and a third heart sound. The Fundoscopy is an essential part of the examination of any hypertensive patient. The abnormalities are graded according to the Keith-Wagener classifications.

**Grade 1** - Tortuosity of the retinal arteries with increased reflectiveness (Silver wringing)

**Grade 2** - The same as grade 1 plus the appearance of arteriovenous nipping produced when thickened retinal arteries pass over the retinal veins.

**Grade 3** - grade 2 plus flame shaped-haemorrhages and soft “cotton wool” exudates actually due to small infracts

**Grade 4** - grade 3 plus papilloedema (Blurring of the margins of the optic disc).

Grades 3 and 4 are diagnostic of malignant hypertension.

## **2.10 Decision to start drug therapy**

The medical option to start the drug therapy is taken by the comparison of the level and the high total risk to each patient. Thus, for each stage of hypertension the decision intervention is determined by whether the total cardiovascular-terrestrial risk is small, medium or large (Cuspidi et al 2001).

In hypertensive subjects with low or medium cardiovascular risk, proposed monitoring effort with food habits of life for 3-12 months (depending on level of risk) before the start drug therapy. The lower the cardiovascular risk and lower blood pressure, the greater should to be the follow-up before initiation of treatment. In people with high cardiovascular risk proposed to start antihypertensive therapy at levels of blood pressure are  $> 130/85$  mmHg, confirmed after increasing blood pressure at least 2 visits in a few weeks (Cuspidi et al 2001).

## **2.11 Ambulatory blood pressure monitoring**

Indirectly automatic blood pressure measurements can be made over an 24 hour period using a measuring device worn by the patients. The clinical role of such devices remains uncertain, although they are used to confirm the diagnosis in those patients with white coat hypertension, in those subjects with blood pressure is completely normal at all stages except during a clinical consultation. These patients do not have any evidence of the target organs damage and unnecessary treatment can be avoided. These devices may also be used to determine the adequacy of 24 hour control with once daily medication.

An ambulatory blood pressure recording seems to be better predictor of cardiovascular risk than the clinic measurements. Analysis of the diurnal variation in blood pressure suggests that those hypertensives with loss of the usual nocturnal fall in blood pressure (“non-deeper”) have a worse prognosis than those who retain this pattern.

## **2.12 Routine clinical investigations**

Routine investigation of hypertensive therapy should include:

- ✓ ECG
- ✓ urine sticks test for protein an blood
- ✓ fasting blood for lipids (total and high density lipoproteins cholesterol)
- ✓ Serum urea, creatinine, and electrolytes.

If the urine or creatinine is elevated more specific indicated by renal investigations, which are indicated as creatinine clearance, renal ultrasound (in case of polycystic kidney disease, or parenchymal renal artery disease) and a renal isotope scan or renal angiography if renovascular disease (either atheromatous or fibromuscular dysplasia) is suspected. A low serum potassium level may indicate an endocrine disorder (either primary hyperaldosteronism or glycocorticoid excess) and aldosterone, cortizol, and renin measurements then must be made, preferable

prior to initiating pharmacological therapy. Clinical suspicion of pheochromocytoma should be investigated further with measurements of urinary metanephrines and plasma or urinary catecholamines.

If the ECG shows evidence of coronary artery disease, the coronary vascular status should be assessed. If left ventricular hypertrophy is suspected echocardiography or MRI should be undertaken. A chest X-ray is indicated if cardiac involvement or aortic coarctation is likely (Mansia et al 2001, Mansia et al 2007).

### **2.13 The goals of the therapy of hypertension**

- To protect the patient from complications, such as cardiovascular risks and renal morbidity and mortality.
- To reduce the raised blood pressure, the target blood pressure is <140/90mmHg or <130/80mmHg in patients with diabetes or with chronic kidney disease.
- Do not harm the patient

### **2.14 The strategy of hypertension treatment**

✓ To achieve these goals, in most cases, it is more likely to use a combination of drugs and often require 3 or more drugs (mainly in patients with renal failure, diabetes, systolic hyper- voltage, etc.).

✓ Along with hypertension treatment should be treated effectively and other risks factors of cardiovascular disease (smoking, hypercholesterolemia, diabetes, etc.).

✓ The appropriate drug therapy. These tools are beneficial impact, because they do not only reduce the stress, but also in treatment of other risk factors (diabetes, dyslipidemia, obesity). However, there is difficulty in long-term implementation, because the anti-hypertensive treatment lowers the effort after some time. RIS- reminded of the importance of non-pharmacological means should



be done at each visit, a ranking of emphasis each of them, as appropriate.

✓ Although cigarette smoking affects shortly the blood pressure, stopping is the first target for hypertensive smokers, since it is equally important, and in some cases more important, factor risk of hypertension.

✓ To reduce the blood pressure, is the most effective non-pharmaceutical means, by the reduction of body weight in overweight or obese hypertensives.

✓ Even a small reduction in weight (5 kg) can help to reduce stress and improve other risk factors.

✓ Other effective means to reduce pressure are: a diet rich in fruits, vegetables, lean dairy milk foods, potassium and calcium and low fat, a reduced salt intake in the diet, a reduced consumption of alcohol (2-3 drinks a lot day for men and 1-2 for women) and a regular physical exercise.

✓ Attitudes like that it is not anti-hypertensive food the oranges or coffee, or that it is useful to eat garlic or garlic preparations, are a popular myth without scientific documentation (Benetos et al 2003, Liu et al 2005).

## **2.15 Antihypertensive Drug Therapy**

### **2.15.1 First line drug therapy**

If there are no specific treatment indications, the choice the first antihypertensive drug is not so important because (a) to achieve optimal regulation is more important than to reduce the risk (b) in most cases need a combination 2-3 drugs.

Based on positive results of large studies survival, initiating therapy in people with hypertension with no major complications can be done with thiazide diuretics, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists or angiotensin receptor antagonists.

Beta-blockers are not considered first choice drugs from all the categories of drugs that used in hypertension, except where a specific indication for administration (e.g. myocardial infarction, heart failure, angina pectoris, tachyarrhythmia). In people with post-convenient syndrome or an increased risk of

diabetes, beta-blockers especially in combination with thiazide diuretics should be avoided, unless of course no absolute indication. Also, in the elderly people, the Beta-blockers are less effective than other first-line antihypertensive drugs for reducing both blood pressure and cardiovascular protection (Nakao et al 2003).

Other drugs such as alpha-blockers, the centrally anti-adrenergic factors and acting immediately angioedema-broadly used when first line drugs are insufficient or not well tolerated.

## **2.16 Indications of first choice therapy**

### **2.16.1 Antihypertensive Medicines**

All the hypertensive individuals often have other coexisting diseases which could be treated with the choice of specific category of antihypertensive drugs. The choice of each drug should be used based on the results of large studies, which have shown that used in order to improve the prognosis and the treatment result.

#### *2.16.1.1 Heart Failure*

ACE inhibitors, beta-blockers and compactor receptor blockers are drugs of first choice. The aldosterone antagonists are useful as additional therapy. The use of diuretics should only be in the presence of oedema.

#### *2.16.1.2 After Myocardial infraction*

Beta-blockers, ACE inhibitors and competition facturers receptor blockers are first choice drugs in the treatment of Myocardial Infraction.

#### *2.16.1.3 Angina pectoris*

Beta-blockers and long acting calcium antagonists are drugs of first choice in the treatment of Angina Pectoris.

#### *2.16.1.4 Diabetes - Metabolic Syndrome*

The effectiveness of each intervention usually evaluated after one month of stable treatment. If the blood pressure response is observed little or without an

effect; actions proposed replacement with drug other category. In most cases there is a good response but the blood pressure remains above the goal and proposes the addition of other drugs to reach the therapeutic goal. If it is preferred the long-acting medications with such provision, medication shall be made only once a day. Medications administered a) daily, and in rule b) in the morning and c) for life.

Unless the patient has severe or malignant hypertension there should be a period of assessment with repeated blood pressure measurements, which combined with advice and non pharmacological measures prior to the initiation of drug therapy. The guidelines of the British Hypertension Society suggest the followings:

Use of non-pharmacological therapy in all hypertensive and borderline hypertensive people:

- ✓ weight reduction BMI should be  $< 25\text{Kg/m}^2$
- ✓ low fat and saturated fat diet
- ✓ low salt diet should be  $< 6\text{g}$  sodium chloride per day
- ✓ limited alcohol consumption  $< 21$  units/week for men and  $< 14$  units / week for women
- ✓ increased fruit and vegetable consumption
- ✓ reduce cardiovascular risk by stopping smoking and increasing oily fish consumption

Additionally the pharmacological therapy should be based on the followings:

- ✓ The initiation of anti hypertensive therapy in subjects with sustained systolic blood pressure should be  $> 160$  mmHg or sustained diastolic  $> 100$  mmHg.
- ✓ Decide on treatment in subjects with sustained systolic blood pressure between 140 and 159 mmHg or sustained diastolic blood pressure between 90 and 99 mmHg according to the presence or absence of target organ damage or a 10 year cardiovascular disease risk  $> 20\%$ .
- ✓ In patients with diabetes mellitus the initiation of anti hypertensive drug therapy if systolic blood pressure is sustained  $> 140$  mmHg or diastolic blood pressure sustained  $> 90$  mmHg.
- ✓ In non diabetic hypertensive subjects treatment goals  $< 140/85$  mmHg. In some hypertensive subjects these levels may be difficult to achieve.

✓ The main determinant outcome following treatment is the level of blood pressure reduction that is achieved rather than the specific drug used to lower blood pressure.

✓ Most hypertensive patients will require a combination of anti hypertensive drugs to achieve the recommended targets.

✓ In most hypertensive patients therapy with statins and aspirin to reduce the overall cardiovascular risk burden. Glycemic control (or in Diabetes Mellitus management should be taught HbA1c<7) should be optimized in diabetics (HbA1c<7%) (McPhee et al 2007).

### **2.16.2 Diuretics**

Thiazide diuretics such as bendroflumethiazide at a dose of 2,5 -5 mg daily and cyclopethiazide 0,25-0,5mg at a daily dose are well recognized and used agents which have been shown that they reduce the risk of stroke, heart failure, lung oedema and improve mortality in patients with hypertension.

The lower doses of these drugs seem to be equally effective as the same higher doses in the reduction of blood pressure and the most of them have duration of up to 24 hours. The major concern with these agents is their adverse metabolic effect particularly increased uricaemia (which may precipitate gout) and hypokalemia. This tends to occur with higher doses of thiazide diuretics (Hoes et al 1985, Lancet et al 2005).

Loop diuretics such as furosemide (40mg per day) do have hypotensive effects but are not routinely used in the treatment of hypertension. Potassium sparing diuretics such as amiloride 5-10mg per day and spironolactone 50-200mg are not effective agents when used alone with the exception of spironolactone in the treatment of hypertension and hypokalemia associated with primary hyperaldosteronism (Lancet et al 2005).

### **2.16.3 Beta – adrenoreceptor blockers**

The beta blockers have also been shown to improve the prognosis of anti-

hypertensives subjects. They have been suggested to exert their effects of the sympathetic nervous system and the renin angiotensin systems. They reduce the force of the cardiac contraction as well as resting and exercise induced increase in heart rate. But there are differences between these hypertensive drugs (Pepine et al 2003).

✓ **Cardioselectivity:** Some have less effect on the beta-2 non cardiac receptors and are therefore said to relatively cardioselective. These include atenolol, metoprolol and bisoprolol.

✓ **Intrinsic sympathicomimetic activity.** Some agents have partial agonist activity and cause less bradycardia. These include oxeprenol, acebutol and pindolol.

✓ **Lipid solubility.** The agents that are less lipid soluble are less likely to cause central nervous system side effects. These include atenolol (Table 1).

The major side effects of this class of agents is bradycardia

	Cardiac Selectivity	ISA	Plasma half-life (hours)	Usual dosage
Acebutatol	+	+	5	400 mg once or twice daily
Atenolol	+	-	6	50 mg once daily
Bisoprolol	++	-	10-12	10-20 mg once daily
Celiprolol	-	+	5	200 mg once daily
Oxprenolol	-	++	1.5	20-80 three times daily
Metoprolol	+	-	3-10	100-200 mg daily
Propranolol	-	-	5	80-160 mg twice daily
Timolol	-	-	5	5-20 mg twice daily

Table 1. Main properties of the beta blockers commonly used for hypertension (McPhee et al, 2007).

#### **2.16.4 Angiotensin-converting enzyme (ACE) inhibitors**

These which are characterized as inhibitor of the axis of the aldosterone inhibits the conversion of angiotensin I to angiotensin II, which is a unique and a very important vasoconstrictor influencing the blood pressure. They also block the degradation of bradykinin, which is also a potent vasolidator. There is evidence that black African patients respond less well to ACE inhibitors unless combined with nephropathy where they have been shown to slow disease progression and in those patients with symptomatic or asymptomatic left ventricular dysfunction where they have been shown to improve survival.

The major potential side effects are profound hypotension following the first dose, which is usually seen in sodium depleted patients or in those on treatment with large dose of diuretics and deterioration of renal function in those with severe bilateral renovascular disease (in whom the production of angiotensin II is playing a major role in maintaining renal perfusion by causing efferent arteriolar constriction at the glomerulus).

They may also cause mild dry cough in a number of patients especially if prescribed at high doses, due to their effect on bradykinin (Wing et al 2003). There are several ACE inhibitors available and there are no significant differences between them in terms of blood pressure effect other than the half-life and therefore the frequency at which they have to be prescribed for 24h blood pressure control. Those with the longest duration of action may be taken once daily which is clearly a benefit in terms of compliance. The drugs include captopril (50-150mg daily in divided doses), ramipril (2.5-10 mg daily), enalapril or lisinopril (10-20mg daily) andtrandolapril (1-4mg daily) (Dahlof et al 2002).

#### **2.16.5 Angiotensin II receptors antagonists**

This group of agents selectively blocks the receptors for angiotensin II. They share many of the actions of ACE inhibitors but since they do not have any effect on bradykinin and do not cause cough. Angioneurotic oedema and renal dysfunction are encountered less with these drugs than with the ACE inhibitors. The agents include losartan (50-100 mg per day), candesartan (16 mg daily), valsartan (80-

160mg daily), irbesartan (75-300mg daily) and telmisartan (20-80mg/daily) (Pepine et al 2003).

#### **2.16.6 Calcium Channel blockers**

These agents effectively reduce blood pressure by causing arteriolar dilatation and some also reduce the force of cardiac contraction. Like the beta blockers they are especially useful in patients with concomitant ischaemic heart disease. The major side effects are particularly seen with the short acting agents and include headache, sweating, swelling of the ankles, palpitations and flushing. Many of these side effects can be lessened by the co-administration of the beta blocker. The short acting agents such as nifedipine (10-20mg three times daily), are being replaced by once daily agents that are very well tolerated included amlodipine, (5-10mg daily), felodipine (5-20mg daily), (20-90mg daily) (Wing et al 2003) (Table 2).

#### **2.16.7 Alpha blockers**

These agents cause postsynaptic  $\alpha_1$  receptor blockade with resulting vasodilation and blood pressure reduction. Earlier short acting agents caused serious first dose hypotension, but the newer longer acting agents are far better tolerated. These included doxazosin (1-4mg daily), labetalol is an agent that has combined alpha and beta blocking properties but is not commonly used except in pregnancy-induced hypertension.

#### **2.16.8 Other vasodilators**

These drug categories include the very useful drug hydralazine (up to 100mg daily) and monoxidil (up to 50 mg daily). Both drugs are extremely potent

vasolidators that are reserved for patients resistant to other forms of treatment.

	Diuretics	Beta-blockers	ACE inhibitors/angiotensin II receptors	Calcium channels	Alpha Blocker
Diabetes	Care	Care	Yes	Yes	Yes
Gout	No	Yes	Yes	Yes	Yes
Dylipidaemia	Care	Care	Yes	Yes	Yes
Ischaemic heart disease	Yes	Yes	Yes	Yes	Yes
Heart failure	Yes	Yes	Yes	Care	Yes
Asthma	Yes	No	Yes	Yes	Yes
Peripheral vascular disease	Yes	Care	Care	Yes	Yes
Renal artery stenosis	Yes	Care	No	Yes	Yes

\*Care – It means that patients should be checked often for this medication by their physicians.

Table 2. Advantages and disadvantages of drug used in hypertension with respect to associated conditions ( McPhee, et al 2007).

The hydralazine drug may be associated with some several side effects such as tachycardia, fluid retention and a systemic lupus erythematosus like syndrome. On the other hand the minoxidil can cause severe oedema and excessive hair growth and coarse fasial features.

As we emphasize about the precautions of hypertension drug therapy, the main diuretics drug in some not usual cases may aggregate diabetes, comparing with the beta blockers which may worsen the glucose intolerance and mask symptoms of hypoglycaemia.

Both diuretics and beta blockers disturb the lipid profile. Verapamil and diltiazem may exacerbate heart failure, although amlodipine appears to be safe. Finally patients with peripheral vascular disease may also have renal artery stenosis and therefore ACE inhibitors should be used cautiously.



## **2.17 Centrally acting drugs**

Reserpine is used in a low dose 0.5 mg per day which provides almost all its hypertensive action with fewer side effects than higher doses. It has a slow onset of action measured in some weeks. Methyldopa is still widely used despite central and potentially serious hepatic and blood side effects. It acted on central receptors usually without slowing the heart rhythm.

## **2.18 Difficulties of the antihypertensive therapy**

Resistant hypertension is defined as hypertension when the target is achieved despite the concomitant full dose of three different categories drugs of which is a diuretic (Kaplan et al 2007, McPhee et al 2007).

- Reduced cooperation between doctor and patient and about the drugs they are taking (irregular or occasional medication)
- Diet aberrations (increased physical exertion, alcohol abuse, diet high in salt)
- Inadequate doses of medication
- Inappropriate use of diuretics (e.g. thiazides day after day or in patients with creatinine > 3 mg / dl)
- Co-administration of drugs that increase blood pressure (non-steroidal anti-inflammatory, corticosteroids, etc.)
- Sleep apnea syndrome and other rarer parameters may cause secondary hypertension.

## 2.19 Urgent hypertension

The cases that need urgent intervention basis for lowering blood pressure is rare. This is where a large increase in blood pressure in combination with acute target organ damage that requiring immediate hospitalization and urgent medication.

In normal cases rise in blood pressure can not be combined with acute organ failure target ("spikes" hypertension), urgent intervention reducing the pressure has no benefit. In contrast, is potentially dangerous, especially in elderly and people with vascular disease, because the sharp and sudden reduction in pressure can cause ischemic-approved or heart attack due to a sharp decrease perfusion of the respective institutions (Kaplan et al 2007, McPhee et al 2007).

In this sense that the term "hypertensive crisis" should be repealed it refers to the need for direct intervention which, except for the few cases mentioned above, no.

The Indications for urgent treatment of hypertension are:

- ✓ Myocardial infarction
- ✓ Pulmonary edema
- ✓ Stroke
- ✓ ruptured aortic dissection
- ✓ traumatic brain injury
- ✓ Eclampsia
- ✓ Malignant hypertension
- ✓ Hypertensive encephalopathy

The popular practice of sublingual administration tablets of nifedipine, captopril, or nitrites in people with "spikes" hypertension should immediately be abolished and replaced by cool-long effort chronic regulation of arterial pressure. The sublingual medication has absolutely no evidence in the treatment of hypertension.

## **2.20 Long term monitoring of drug therapy**

Objectives of long-term monitoring:

- Confirmation of maintaining good regulation pressure
- Check for undesirable appearance of further energy- crops of treatment
- Check for display of target organ damage
- Control of other cardiovascular risk factors- mind

The set up treatment of people with hypertension is usually done every 3-6 months especially in people with high cardiovascular risk (multiple risk factors- mind, target organ damage or cardiovascular disease) or monitoring every 2 or 4 months.

In general, the antihypertensive medication granted for life. Stopping of the medication often follow -Tai recurrence of hypertension, often after period of months. Reduce the number or dose of drugs may be attempted in a few cases, when it has achieved very good control of blood pressure (less than 10 mmHg under stress target) at least 2-3 visits at least 1 year.

The cooperation of hypertensive individuals is parser to achieve long-term objectives treatment. Reduced cooperation is more common because interruption of treatment and monitoring that the side effects of medications.

In the first visits the doctor needs to spend some time to explain the hypertensive person in danger runs and benefits, objectives and rules of long-term monitoring and treatment (Kaplan et al 2007, McPhee et al 2007).

## **2.21 Measures to improve long-term cooperation to the drug therapy**

- ✓ Good information to the patient with verbal instructions and printed educational materials (see [www.hypertension.gr](http://www.hypertension.gr) “About public”)
- ✓ Involvement of family members to update and goals of therapy

- ✓ Simplify treatment by reducing the number of doses
- ✓ Regular and timely search-finding adverse mitten treatment effects
- ✓ Monitor blood pressure by patients at home

The education of the hypertensive individual aims: a) the acceptance of the need lifelong treatment and el-radical eradication therapy, b) the perception of hypertension as one of the cardiovascular risk factors and not as a direct threat, c) the need to continue therapy after achieving a reduction in pressure d) removing the fear of drugs and combat myths about the risk of Long-term use and e) the discharge beliefs.

Patients with severe hypertension (diastolic pressure > 140 mmHg malignant hypertension grades 3 or 4 retinopathy, hypertensive encephalopathy or with the severe hypertensive complications such as cardiac failure, should be admitted to hospital for immediate initiation of treatment. However, it is unwise to reduce the blood pressure too rapidly since this may lead to cerebral, renal, retinal or myocardial infraction and the blood pressure response to therapy must be carefully monitored, preferably in a high-dependency unit. In most cases the aim is to reduce the diastolic blood pressure to 100-110 mmHg over 24-28 hours. This is usually achieved with oral medication e.g. atenolol or amlodipine. The blood pressure can then be normalized over the next 2-3 days.

When rapid control of blood pressure is required (e.g. in an aortic dissection) the agent of choice is intravenous sodium nitroprusside. Alternatively, an infusion against the blood pressure may response. Fenoldopam a selective peripheral dopamine receptor agonist is as effective as nitroprusside (Kaplan et al 2007, McPhee et al 2007).

Beta – blockers such as atenolol, Calcium – channel blockers, labetalol and hydralazine can be used in the treatment of hypertension in pregnancy. Mild hypertension (150-160/100-110mmHg) in pregnancy can be treated with methyldopa, which has been established with a long-term safety record. However ACEIs and ARBs are contraindicated in the pregnancy due to renal failure and intrauterine death. (Walker et al 2012).

The prognosis from hypertension depends on a number of features:

- ✓ level of blood pressure
- ✓ presence of target-organ changes (retinal, renal, cardiac or vascular)
- ✓ Coexisting risk factors for cardiovascular disease such as hyperlipidaemia, diabetes, smoking, obesity, male sex.
- ✓ age at presentation

Several studies have already confirmed that the treatment of hypertension even mild hypertension will reduce the risk not only of stroke but of coronary artery disease as well (Kaplan et al 2007, McPhee et al 2007).

### **3. Methodology**

#### **3.1 Collection of medical therapies**

In this project, it was collected 60 medical prescriptions from one pharmacy in Greece. The dispensed prescriptions that were selected were from the period of 02/2012 until 06/2012. From the sixty (60) prescriptions, the fifty-eight were found that patients were diagnosed with Arterial Hypertension.

In order to analyze the selected prescriptions were set up some limits such as it was analysed only the antihypertensive agents that each patient was receiving. According the antihypertensive agents was analysed the strength that used, the drug formulation, the dosage scheme of the antihypertensive agents and at last the number of packages that was prescribed.

In the selected prescriptions were also analysed the patients' age, the patients' gender, in order to understand better what kind of patients were treated.

From the medical prescriptions were evaluated data also for the prescribers such as their medical specialization, their age and their gender. The physicians are following the Greek guidelines, which are corresponded according the World Health Organization's guidelines.

The medical orders received and recorded according the corresponding pharmaceutical guidelines. The most frequently administered drugs discussed and analyzed in the results section of the table with the detailed individual patient and the corresponding medication. The results were represented in corresponding graphs, bar charts and pie charts using conventional statistical packages and analysis programs with a view of better understanding of display sizes.

### **3.2. Evaluation**

In this project, it was collected the medical prescriptions from one pharmacy in Greece, which is located in a village, therefore there is not big total number of patients visiting this pharmacy. The total number of patients, who are visiting this pharmacy, is approximately 450 per month. As it is located in a village, it is the only one in the village and most of the population is visiting this pharmacy, but it has some extra visitors.

From the total visiting number of 450 per month, 55 are patients which are suffering with Arterial Hypertension and they have been diagnosed about that.

The medical orders that were collected for this study were prescribed by four

physicians. Their medical specialization was evaluated such as if there are cardiologists, pathologists or general practitioners or nurses and the gender of the physicians was evaluated.

It was calculated in percentage which group of antihypertensive agents is most frequent used by the patients. According the antihypertensive group that was used, it was analysed the dosage scheme and the number of packages that was given in the patients. Some patients buy some antihypertensive agents but they do not have prescriptions for it, these patients were not analysed in this project.

The evaluation of medical prescriptions arranged by the recommended medical treatment for patients with hypertension in the effort to see the frequency of commonly used medications associated with treatment of hypertension disease and whether the frequency of administration of treatments is consistent with our literature review on the effectiveness of therapeutic regimens.

### **3.3. Results**





<b>Trade Name</b>	<b>Strength</b>	<b>Active Substances</b>
Co – Diovan	160 + 12.5mg	Valsartan & Hydrochlorothiazide
Co – Diovan	320 + 12.5mg	Valsartan & Hydrochlorothiazide
Co – Dalzad	160 + 12.5mg	Valsartan & Hydrochlorothiazide
Triatec Plus	5 + 12.5mg	Ramipril & Hydrochlorothiazide
Micardis Plus	80 + 12.5mg	Telmisartan & Hydrochlorothiazide
Pritor Plus	80 + 12.5mg	Telmisartan & Hydrochlorothiazide
Accuretic	10 + 12.5mg	Quinapril & Hydrochlorothiazide
Copalia	5 + 160mg	Valsartan & Hydrochlorothiazide
Copalia	10 + 160mg	Valsartan & Hydrochlorothiazide
Moduretic	5 + 50mg	Amiloride & Hydrochlorothiazide
Co – Renitec	20 + 12.5mg	Enalapril & Hydrochlorothiazide

Table 3. The combination medicines which are used as monotherapy and their active substances.

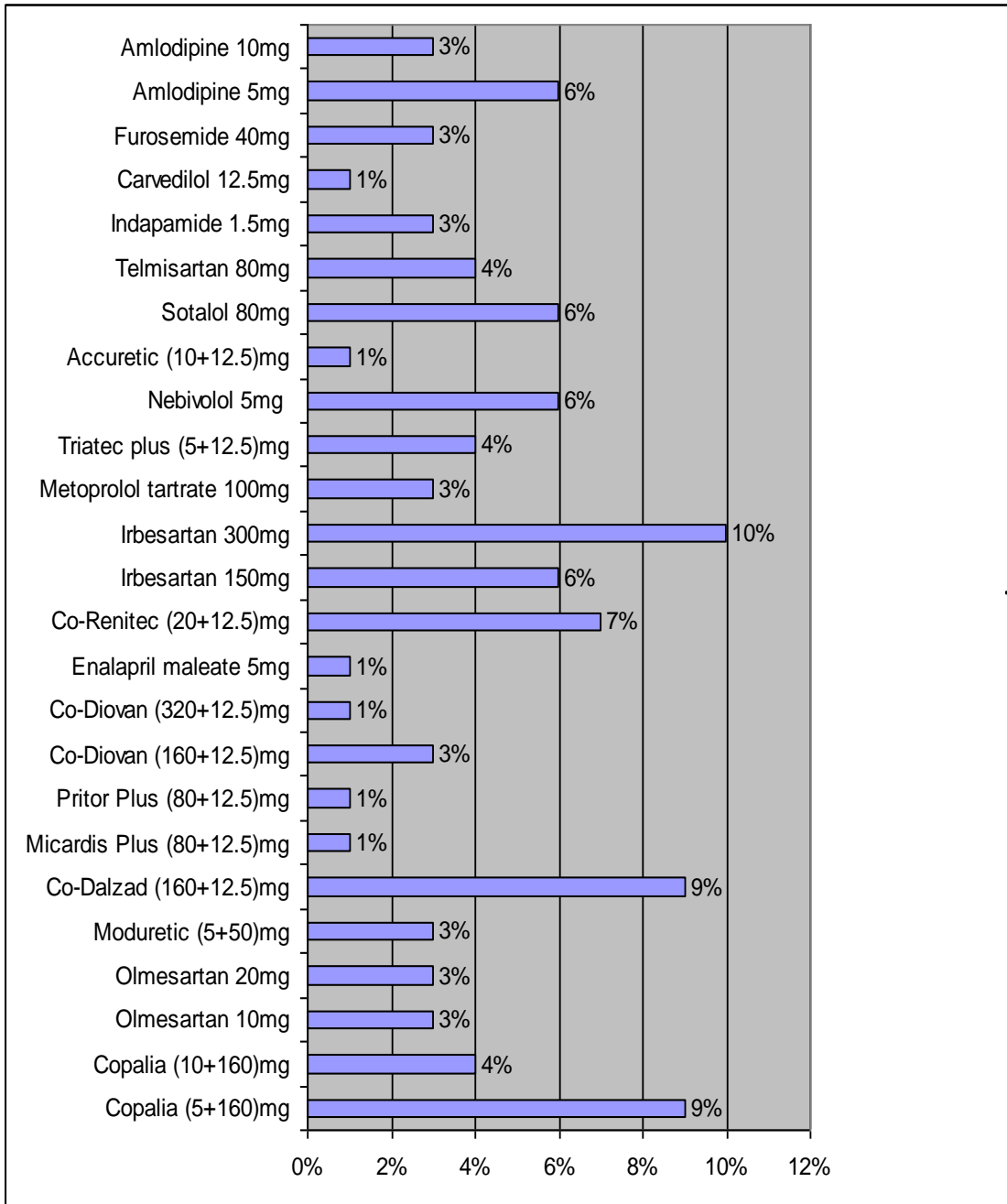


Figure 1. The graph shows the strength of the used drugs in the medical prescriptions compared with their frequency.

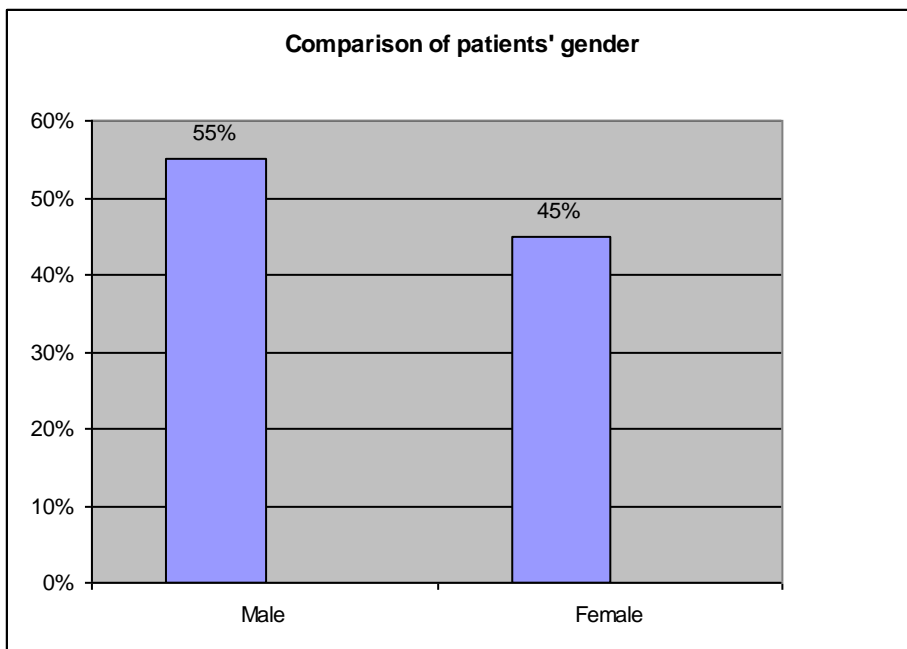


Figure 2. The gender distribution (in %) at the prescriptions where the 100% = the total number of prescriptions.

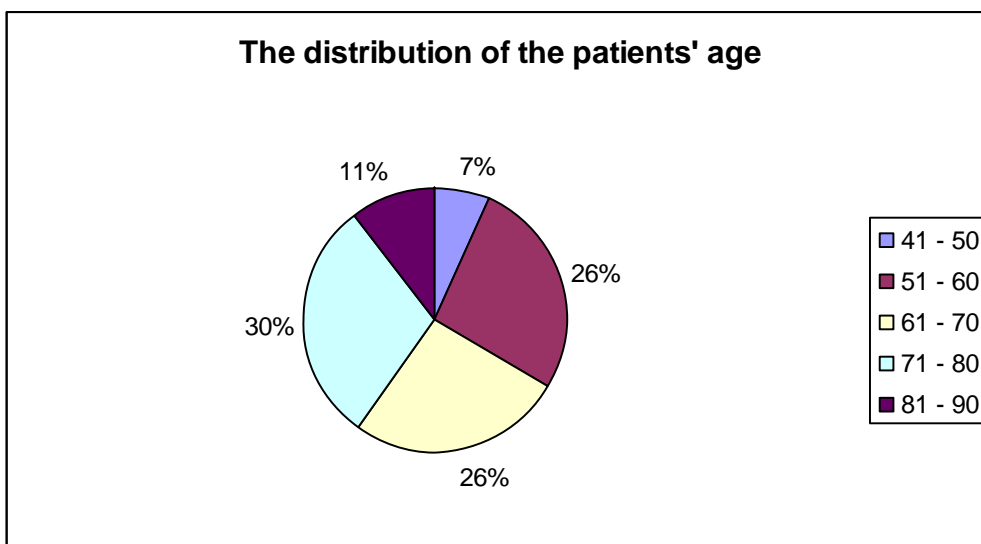


Figure 3. The distribution of patients' age (in %) into decades of age (100% = the total number of prescriptions).

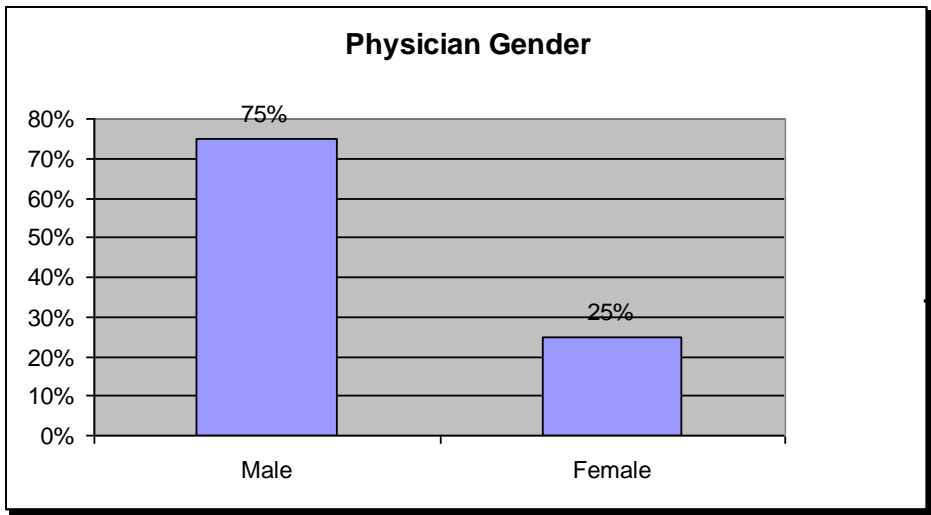


Figure 4. The difference between the physicians' gender (in %) where the 100% = total number of physicians that prescribed these prescriptions.

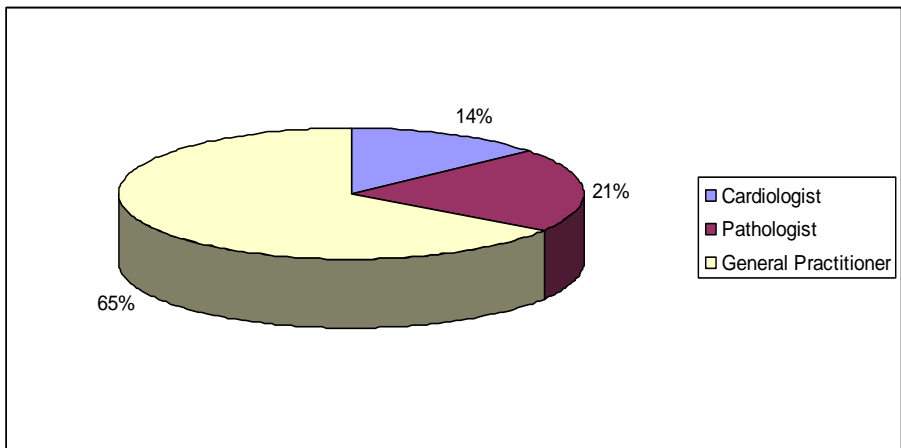


Figure 5. The rate of prescription (in %) in particular specialization of physicians' (100% = total number of prescriptions).

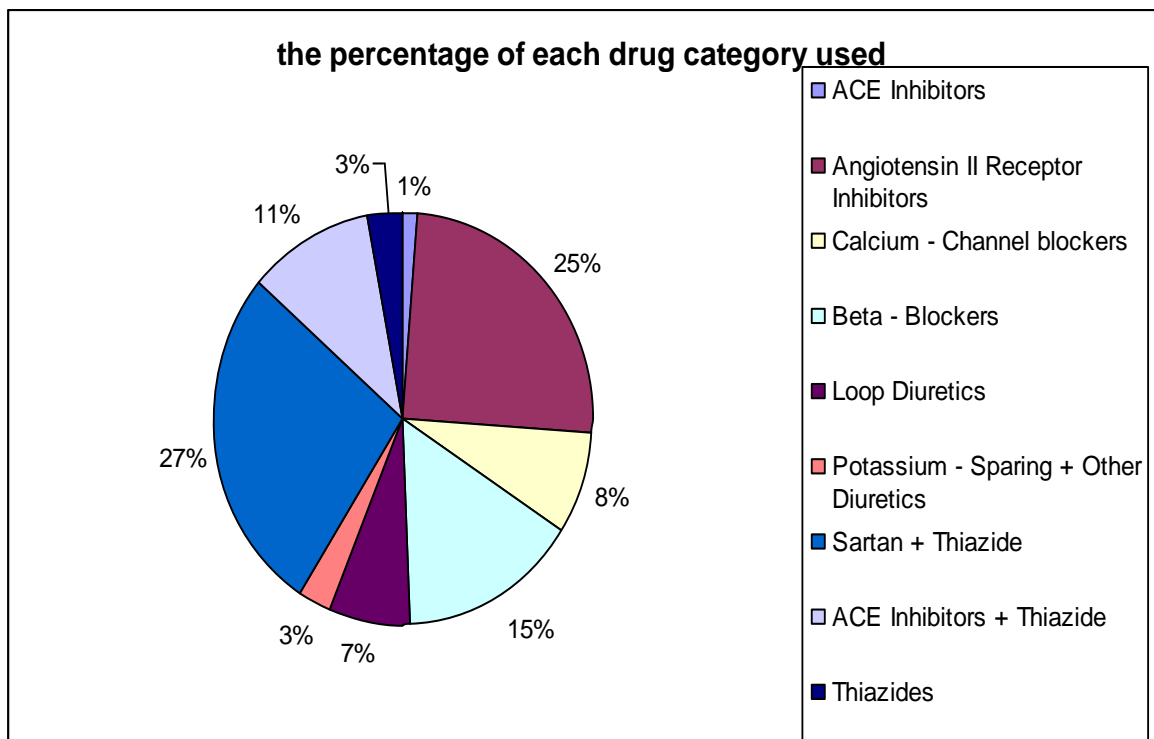


Figure 6. Frequency analysis (in %) of different groups of antihypertensive agents where the 100% = total number of active substances.

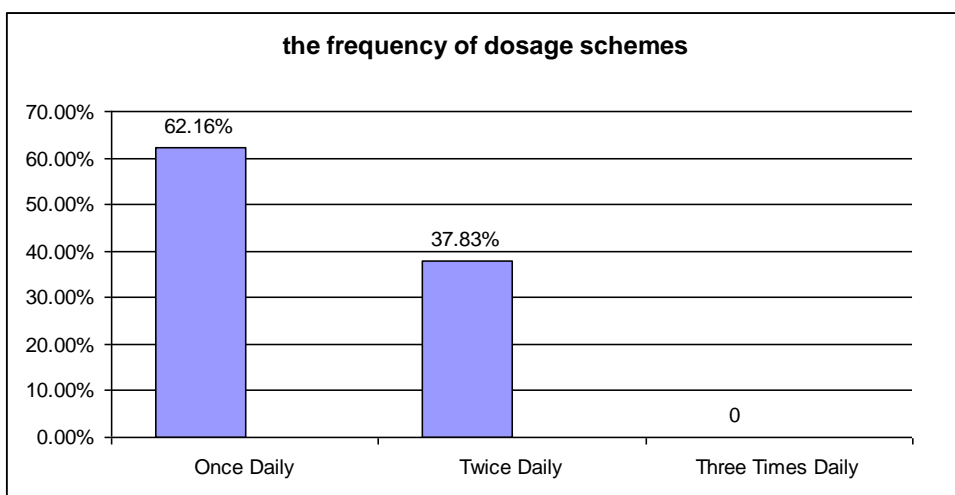


Figure 7. The distribution of the dosage schemes (in %) used daily by the patients where the 100% = the total number of active substances.

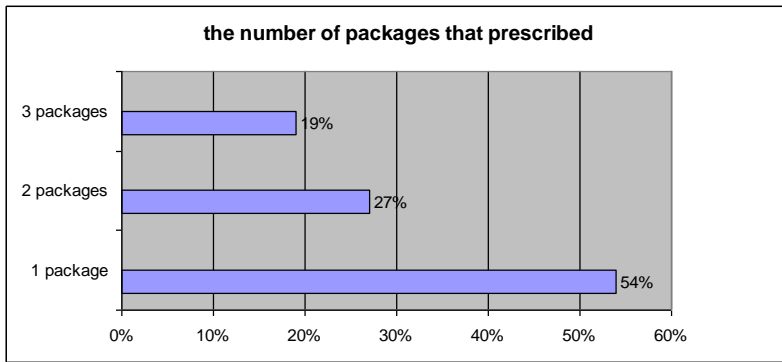


Figure 8. The distribution of the number of packages per patient (in %) that were prescribed by particular substances (100% = total number of trade names).

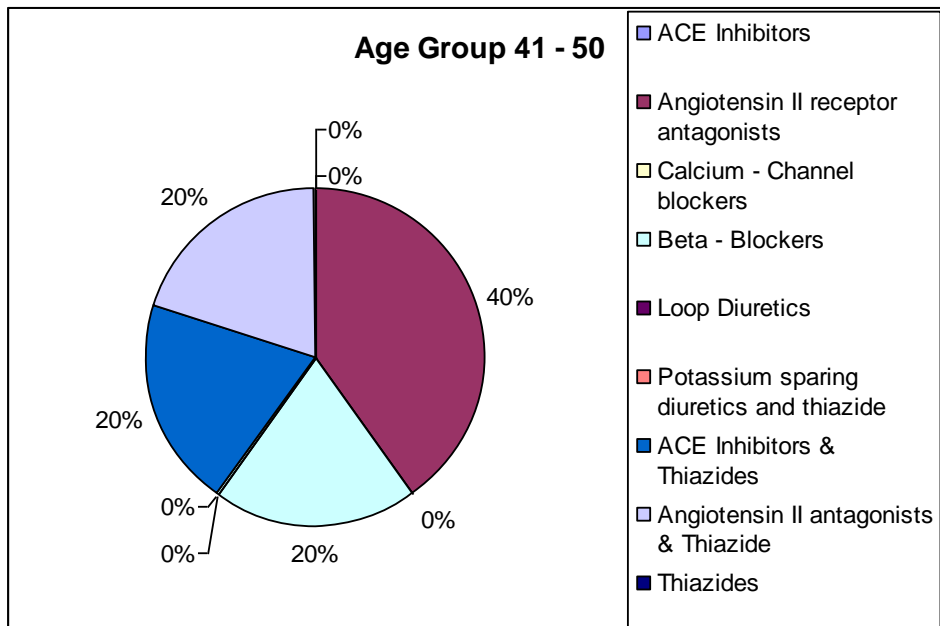


Figure 9. Frequency analysis (in %) of the antihypertensive agents used in the age group 41 – 50 (100% is equal to the total number of the active substances).

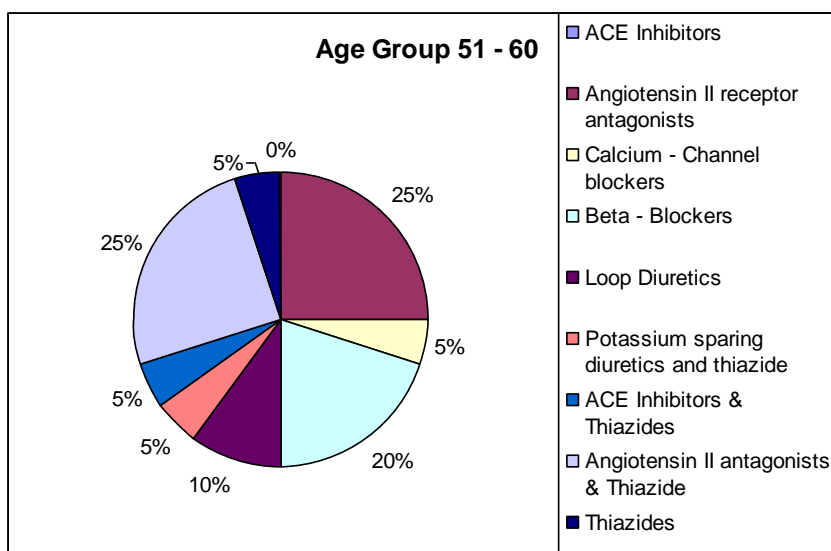


Figure 10. The distribution of the antihypertensive agents (in %) used in the age group of 51 – 60, where the 100% = the total number of the active substances.

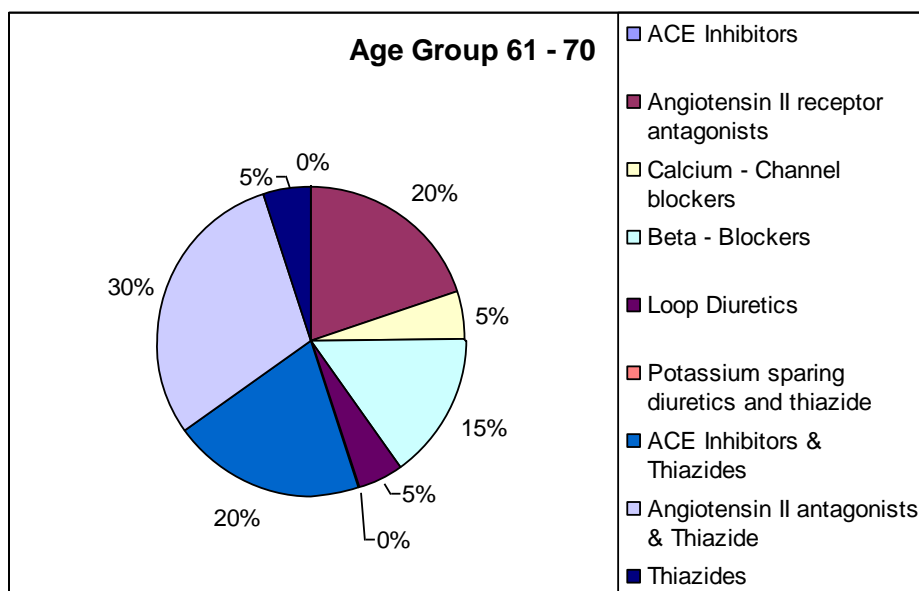


Figure 11. Frequency analysis (in %) of the antihypertensive agents used in the age group 61 – 70, where the 100% is equal to the total number of the active substances.

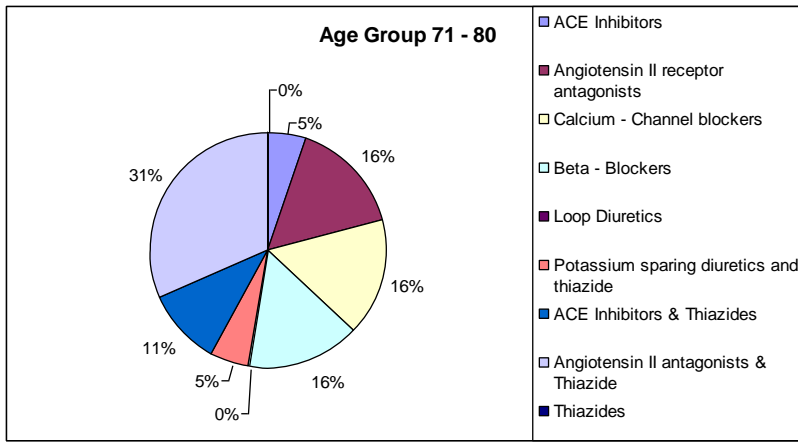


Figure 12. Frequency analysis (in %) of the antihypertensive agents used in the age group of 71 – 80, where the 100% = the total number of active substances.

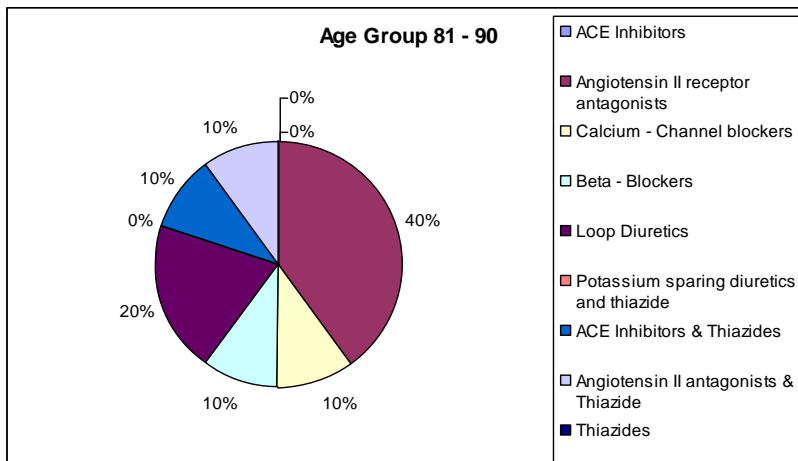


Figure 13. The distribution (in %) of the antihypertensive agents used in the age group of 81 – 90, where the 100% is equal to the total number of the active substances.

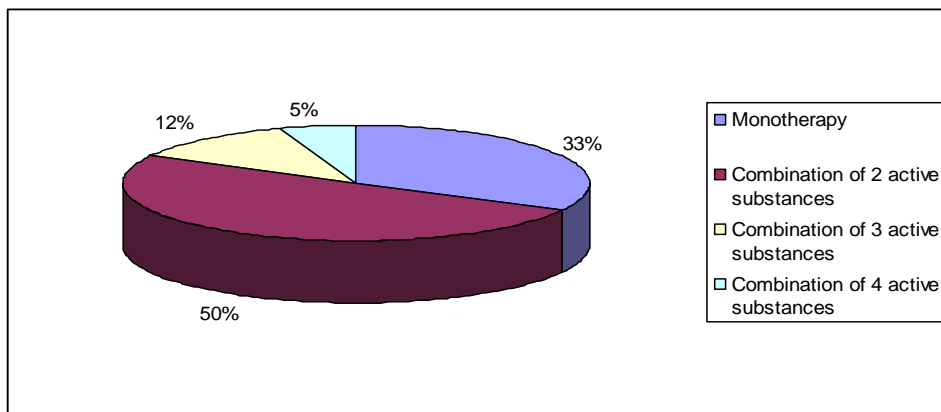


Figure 14. The distribution of people (in %) which are taking one medication, or two or three (100% is equal to the total number of patients).



Prevalence of arterial hypertension	Number of people	Percentage
Citizens	700	100%
Total patients visiting pharmacy	450	64.2%
Kids	160	22.85%
arterial hypertension	55	10.18%

Figure 15. The prevalence of arterial hypertension in Greek village.

In this project, it was collected 58 prescriptions for people who are diagnosed with arterial hypertension and they were all adults.

Firstly, the prescribers, in this study were four in number and they had three kinds of specialization. It was seen that 65% of the prescribers were general practitioners, 21% Pathologists and 14% Cardiologist (Figure 5). In the Figure 4, it was determined that 75% of the prescribers are male and only 25% are female. It was also calculated the average of the physician's age, which was 49.75 years, where only one physician were the youngest, 40 years old. The oldest physician was 58 years old.

Secondly, the patients' characteristics, the gender, it was determined that 55% of the patients are male patients and 45% are female (Figure 2). The age, for better estimation the age was divided into 5 decades, from 41 years old to 90 years old. The higher percentage of people with arterial hypertension was determined among the decade 71 – 80 years old and it was 30% (Figure 3). The decades 51 – 60 years old and 61 – 70 years old have the same percentage 26% of patients. The decade with the least percentage of patients with hypertension is 41 – 50 years old with 7%. While the average age of people are suffering with arterial hypertension is approximately 67 years old.

An important part of this study is the results of the drugs that patients with arterial hypertension according in which class anti-hypertensive agent they belong. Therefore the most favorable category of antihypertensive treatment is a combination of sartans and thiazides and the percentage of this group is 27% (figure 6). However the combination of ACE Inhibitors with the thiazides has 11%

of patients, which make them not as favorable as the combination of the sartans with the thiazides. In the second position are the sartans with 25%. Another group of antihypertensive agents is the beta – blockers which they have a 15% of people which are using them as antihypertensive drugs. The Calcium – channel blockers contain 8% while the loop diuretics contain 7%. The groups of Potassium – sparing diuretics with thiazide and thiazides have each 3%. But the ACE – Inhibitors have only 1%.

In more details, it can be determined which specific agents of these antihypertensive groups used more often. The higher percentage belongs to irbesartan 300mg and is 10% (Figure 1), which means that was used by seven (7) patients. The percentage 9% contains respectively Co – Dalzad (160+12.5) mg (valsartan & hydrochlorothiazide) and Copalia (5+160)mg (valsartan & hydrochlorothiazide – table 4). The Co – Renitec (20+12.5)mg (enalapril & hydrochlorothiazide) has 7%.

The beta – blockers, sotalol 80mg and nebivolol 5mg have taken 6% each and the sartan irbesartan 150mg has also 6%. Each of the following drugs contains the percentage 4%, these drugs are Triatec Plus (5+12.5)mg (ramipril & hydrochlorothiazide), telmisartan 80mg and the Copalia (10+160)mg (valsartan & hydrochlorothiazide). amlodipine 5mg which belongs in the group of Calcium – channel blocker has also obtained 6%.

There are eight drugs that have determined 3%, and these are metoprolol tartrate 100mg, indapamide 1.5mg, furosemide 40mg, amlodipine 10mg, Co – Diovan (160+12.5)mg (valsartan & hydrochlorothiazide), olmesartan 10mg and olmesartan 20mg and Moduretic (5+50)mg (amiloride & hydrochlorothiazide) respectively. However there are a lot of antihypertensive drugs which have obtained only 1% and there are from different class antihypertensive agents. Co – Diovan (320+12.5)mg (valsartan & hydrochlorothiazide), Micardis – Plus (80+12.5)mg (telmisartan & hydrochlorothiazide), Pritor – Plus (80+12.5) mg contain 1% each of them and they are all combination medicines. This 1% also contained by Accuretic (10+12.5)mg (quinapril & hydrochlorothiazide), enalapril maleate and carvedilol respectively.

Furthermore in this experiment was also evaluated the dosage scheme of the medicine. In this study were not used the dosage scheme three times daily (tid – 0%) (figure 7). The 62% of patients are taken their medication once a day. Whereas the 38% of patients are receiving their medicines twice a day (bid).

It was also analysed the number of packages that 54% have taken one package per month which is medication for one month. Two packages obtained the 27% and the three packages obtained 19% (figure 8) again medication covers one month.

The majority of the patients are taken a combination of two active substances which contains a 50% of the total patients (figure 14), whereas the patients using a single antihypertensive agent as monotherapy were 32.7%. The combination of three active ingredients has received 12.1% and 5.2% has received the combination of four active ingredients.

It was analysed the frequency of the antihypertensive agents according the age groups. In the age group of 41 – 50, it was determined that 40% of this age group are taking some angiotensin II receptor inhibitors, while 20% have obtained three groups the beta – blockers, the angiotensin II receptor inhibitors with thiazides and the ACE Inhibitors with the thiazides respectively (figure 9). But the other groups are not used in this age group.

Another age group is the 51 – 60, in which the most favorable antihypertensive agents are the angiotensin II receptor inhibitors with thiazides and the angiotensin II receptor inhibitors alone, with 25% each one (figure 10). Beta – blockers obtained 20% and loop diuretics obtained 10%.

In the age group of 61 – 70, a 30% was obtained by the angiotensin II receptor inhibitors with the thiazides (figure 11), whereas thiazides obtained only 5%. Loop diuretics and Calcium – channel blockers have 5% each one. The combination of ACE inhibitors with thiazides obtained the 20% and the angiotensin II receptor Inhibitors obtained the same percentage, while beta – blocker have 15%.

The age group of 71 – 80 again was determined that the combination of sartans with thiazides have the highest percentage, 31% (figure 12). In this age group the 16% have equally obtained three groups of antihypertensive agents the Calcium – channel blockers, the beta – blockers respectively and the sartans whereas the combination of ACE inhibitors with thiazides obtained 11% and the ACE inhibitors 5%.

In the age group 81 – 90 sartans have taken the biggest percent 40%, loop diuretics have 20%. But the beta – blockers, the Calcium – channel blockers, ACE inhibitors with thiazide and the sartans with thiazides have 10%, when the other groups do not have anyone.

#### 4. Discussion

In this project, it was collected 58 prescriptions for people who are diagnosed with arterial hypertension from one pharmacy in Greece. That pharmacy is localized in a small village Mytikas in Evia island. The number of citizens of the village are 700 (Figure 15), from this population the 160 are children, indicates that 540 are the adults of this village. The population that visits the pharmacy per month is 450 and from them the 55 people are diagnosed with arterial hypertension, which is a 10.2% of the population of the village. As it was referred earlier the pharmacy from which these prescriptions were collected it is a pharmacy in a village and there is not any other pharmacies in this village. The prevalence of arterial hypertension in our study seems to be 10.2% and if you compare it with the data from the published study (telephone survey for the hypertension rate in larger population in Greece was 17%) our result is a bit lower (Maniadakis, et al 2011). It seems that the size of the tested population plays an important role for the arterial hypertension prevalence as well as that some patients can visit another pharmacy.

This pilot study can be compared with the prevalence of people with arterial hypertension in the Efstratopoulos cross-sectional study where the prevalence of hypertension is 31.1% and the prevalence in the elderly were higher, 65% (Efstratopoulos et al 2005). In the Efstratopoulos study the prevalence of the disease is much higher than our study, this maybe is due to the larger population that used in Efstratopoulos study, because they collaborate with physicians from 98 Health Centers and physicians have better view of the hypertension patients in whole Greece. The Efstratopoulos study can be compared with Mandialakis survey, which is a telephone survey in the patients. In this telephone survey, people may not know the exact state of their hypertension, or may not know if they suffer with arterial hypertension. The people that they do not be aware that they suffer from hypertension are 39% in the Efstratopoulos et al. whereas in our study there was no evidence in the prevalence of awareness. In this Efstratopoulos study was determined that the 32.8% of the treated population was well controlled and the 18.4% was not well controlled by their treatment. As it was referred before there are not evidence in our study if the patients controlled well their blood pressure by their treatment.

In Greece, in the prescription medicines were written with their trade names and their dosage forms were predominantly tablets or capsules for the treatment of

arterial hypertension. An important information is that medications prescribed by the physician are valid for one week but the medication is for one month. So the same patients are approximately visiting the pharmacy every month. Some patients would not like to visit the doctor every month because they think that it is a waste of time, however these are the regulations of the validity of the prescriptions, so they have accepted it. In the regulations, it has also be written that the patient has to visit the pharmacy with the medical prescription within one week from the day of the doctor's prescribed the medical prescription, if the patient visit the pharmacy the eighth day, the prescription is not valid and the patients has to refer again to the doctor for another prescription.

In the prescriptions, it was also written the information about the physicians' age and gender and the patients' age and gender. The age of the physicians and patients was determined by a specific number that each Greek citizen has, and is called AMKA. From that number the six first digits are indicating the date of birth.

In the medical prescriptions, there is information about the prescriber's specialization, in this selection were three kinds of physicians, prescriptions were written by cardiologists, pathologists and the most of them were written by general practitioners. In this pilot study it was determined that the most the prescriptions were written by the general practitioner, because in this village there are not any specialists. If the patients want to visit a specialist has to travel about 10Km. In Greece, the majority of people visit a specialist even for prescribing the same medication each month. In order to first diagnosis of any disease they usually visit a specialist. However in this project, it is like an exception, because the pharmacy is localized in a village, which means that the patients visiting more often the general practitioner. Although there are some patients that they refer to their specialist to have their medical prescriptions. The physicians are following the Greek guidelines, which are corresponded according the WHO's guidelines. As it was said earlier 65% medical prescriptions were written by the general practitioners (figure 5), which is significant high amount corresponding that most of the prescriptions in Greece were written by a specialist, while the rest 35% were written by specialized physicians such as cardiologists and pathologists.

In the treatment of arterial hypertension, as it was referred previously, it can be used a combination of two, three or four active substances, most of them were combined two actives in one pill and some different in order to achieve the goal of the treatment, which is to reduce the blood pressure. According to Neal et al the

combination of two active substances in the beginning of the therapy is more effective for the control of the arterial blood pressure in compare with the monotherapy (Neal et al 2000).

In this paper it was analyzed the frequency and nature of the content of medical prescriptions issued to patients with arterial hypertension disease during the period of this study. The most frequent category of antihypertensive agents that was used is the combination of angiotensin II receptor inhibitors or sartans with thiazide diuretic which have obtained 25% (figure 6). It has to be emphasizes that the combination of the drug treatment as it has been made an extremely reference to the worthy use of these drugs mixtures for the hypertension treatment. It has been also noticed that the patients feel that they have better compliance with a combination of two drugs in one pill. It has also determined by studies that the combination drugs with thiazides are more effective in the controlling of the raised blood pressure even in patients with hyperuricemia (Hosoya et al 2012). This is may be due to small doses of thiazide and for the patients in order to improve compliance.

The combination of sartans with the thiazides has shown that it favorable also among the age groups such as in the age group of 51 – 60 has a 25% (figure 10), in the 61 – 70 a 30% (figure 11) and in the 71 – 80 a 31% (figure 12) . Due to studies, it was shown that the combination has achieved its goal in the treatment of arterial hypertension in the people over 65, which it complies the figure of this project (Germino et al 2012).

It was noticed in this study that there were a lot of combination of two drugs such as Copalia, Co-Dalзад, Co-Diovan, Micardis Plus and Pritor – Plus which is a combination of a sartan and a thiazide diuretic such as Hydrochlorothiazide. Copalia, Co – Dalзад, Co – Diovan contain the same active ingredients (table 3), some with the same strength and some with different. It has been noticed that the one brand name, Co –Dalзад, has obtain 9% (figure 1), while the other only 3%, this can be explained by the physicians, if for example a physician may has better business relationship with one company but there are not available data for the physicians in this pilot study. It can be as well the good drug marketing, the experience of the physicians with these drugs or the good tolerance by the patients.

The usual dose of Co-Diovan is (80+12.5) mg, (160+12.5) mg or (320+12.5) mg once a day. If the blood pressure is still too high after 4 weeks, the doctor may increase the dose to 160/25 mg or 320/25 mg once a day, which complies with

Greek National Medicine Organisation ΕΟΦ (ΕΟΦ et al 2012).

The Copalia is a medicine containing two active substances and in this study there are used two different strength of this drug but the one strength (5+160mg) has 9% frequency (figure 1) while the other (10+160mg) has 4%, this is another trend which may be the factor that the (10+160) were high dose for the patient and has to change to lower dose. It has been determined by the health care professionals and the scientists that combination drugs used as in one pill has to be in lower doses, because if the patient takes the higher doses might suffer from some side effects (BNF, 2007). The Copalia is used to treat patients with the increased hypertension (high blood pressure) which is not controlled by amlodipine or valsartan as monotherapy, that is why it was used two drugs in the same formulation. In this experiment it has also been shown that doctors have prescribed the Copalia with the 10mg of hydrochlorothiazide but its frequency is not as high as the Copalia with the 5mg.

The use of Copalia in our study was in caution in patients with liver or biliary obstructive disorders (disorders elimination of bile). The percentage of the patients who used hydrochlorothiazide as monotherapy is 12.5% and all the other may use Hydrochlorothiazide as a combination with another drug such as sartans (Table 1, Table 2).

Angiotensin II Receptor Inhibitors is another category of antihypertensive agents, which plays an important role, in this project, because obtained 25% (figure 6). There are three different drugs from this group that used in this study, the irbesartan, the telmisartan and the olmesartan. Irbesartan used more often from this group (figure1). Sartans were used by all the age groups and with significant percentage in all groups (figure 9 - 13).

The irbesartan is indicated for use in adults for the treatment of essential hypertension acting by the same way such as valsartan. It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of treatment of comparative antihypertensive medicine and safe treatment. The dosage scheme of this drug is once daily, which is within the limits because most of the patients are elderly. The ratio age of the participants was the 67 years old and most of the patients refer smoking history.

Valsartan is an 'angiotensin II receptor antagonist', which inhibits the action of a hormone in the body especially, not arresting the action and the transformation of angiotensin II. The angiotensin II is a potent vasoconstrictor (a substance that

affecting the blood vessels), valsartan inhibits the unions action, contributing in this way to the dilation of blood vessels.

The usual recommended according to the British National Formulary (BNF, 2007) starting dose and maintenance dose is 150 mg once daily, with or without food. As it is known by several studies in high hypertension patients a dose at 150 mg once daily provides a better 24 hour blood pressure than the dose of 75 mg. In the cases of controlling the higher levels of hypertension, the appropriate dose is also 300mg daily. The limit of our study is that we do not know the duration of the treatment of arterial hypertension and we do not know the incidence of arterial hypertension, such as if there were new patients in our study.

In hypertensive patients with type 2 diabetes which is very sensitive group of therapy, the treatment should be adjusted at 150 mg irbesartan once a day and to 300 mg adjusted up once daily and the treatment of kidney disease by checking always the kidneys operation.

Olmesartan is another sartan which has been found here in two strengths both equally represented in percentage. The antihypertensive effect of olmesartan medoxomil is appearing within 2 weeks and reaches the maximum at about 8 weeks after initiation of therapy. This should be taken into account when considering changing the regimen for each patient. For the best response of the patient, Olmesartan should be taken approximately the same time each day, with or without food.

Based on five main clinical studies involving nearly 5,200 patients, we emphasize our clinical data about the influence on the hypertension therapy after drug treatment. In two studies (involving almost 3,200 patients) compared the effectiveness of amlodipine, valsartan or combination of two compounds with that of placebo it was shown an effective result which is involved (Lacourciere et al 2003, McPhee et al 2007).

In another study (involving 1,029 patients) compared the effects of combination in patients whose hypertension is not adequately controlled with either amlodipine or valsartan shows that combination therapy is more affecting than the monotherapy (Cheng et al 2012, McPhee et al 2007 ).

In order to investigate the drug effectiveness of comparison of olmesartan medoxomil and hydrochlorothiazide, the Kereiakes et al. (Kereiakes et al 2007) made an extensive clinical study. Patients were randomized following a 3- to 4-week with a treatment with placebo drug comparing the results with the drug



intake. The differences measured on two separate visits during the run-in period and show a very useful and positive result.

The maximum dose in elderly patients is 20 mg once daily, due to limited experience with higher doses in this group of patients and in renal failure, the maximum dose in patients with mild to moderate renal insufficiency (creatinine clearance 20-60 mL / min) is 20 mg olmesartan medoxomil once daily, due to limited experience with higher doses in this group of patients. The use of olmesartan medoxomil in patients with severe renal impairment (creatinine clearance less than  $\leq$  20 mL / min) is not recommended, because there is very limited experience in this group of patients complies with ΕΟΦ (ΕΟΦ, 2012).

At the OLMEBEST study, patients who participated had a diastolic blood pressure 90 mmHg after 8 weeks of open a treatment as monotherapy with olmesartan 20 mg and some of them received olmesartan 40 mg or olmesartan 20 mg/hydrochlorothiazide 12.5 mg for more 4 weeks. Each randomized treatment resulted in a further reduction in blood pressure beyond (Barrios et al 2007, Dahlof et al 2002).

At the end of the randomized treatment phase, patients who had received olmesartan 20 mg/hydrochlorothiazide 12.5 mg showed a larger change in systolic blood pressure and diastolic blood pressure (10.8 and 7.9 mmHg, respectively) than the olmesartan 40 mg group (5.3 and 5.1 mmHg), and larger comparing with group of olmesartan 20 mg/hydrochlorothiazide 12.5 mg (Dahlof et al 2002, Barrios et al 2007). Additionally the clinical effects on blood pressure were assessed after 3 months on irbesartan therapy and the systolic blood pressure and diastolic blood pressure were reduced by 22.5 mmHg and 10.7 mmHg, respectively, while systolic blood pressure and diastolic blood pressure reduction (DBP 90 mmHg) was achieved in 43% and 74% of patients.

The results of these observational studies confirm the beneficial results of irbesartan/hydrochlorothiazide in patients with hypertension suggesting that irbesartan and irbesartan/hydrochlorothiazide can help achieve blood pressure control. In order to analyze the effects of the drug on hypertension we may say that ACEIs and Sartans have similar effects on blood pressure reduction in patients with essential hypertension. This conclusion was based on 77 studies with a total number of patients 26,170 participants which the duration of patient follow-up investigation ranged from 12 weeks to 5 years (Kintscher 2007).

At the protection of the cardiac pressure at this study, it was used four beta –

blockers agents carvedilol, nebivolol, sotalol and metoprolol. The doses of them are between 5mg-15mg per day, preferably at the same time each day according EOP (EOP, 2012). The decrease in blood pressure has been shown 1 to 2 weeks after starting the treatment and the best result is achieved only after 4 weeks of treatment. With 15% the beta – blockers are represented in the frequency of the antihypertensive agents (figure 6).

Nebivolol belongs to cardioselective, lipid soluble and without intrinsic sympathomimetic activity. The recommended dose according BNF is 5mg daily, but in elderly the starting dose is 2.5mg daily and increased to 5mg if it is necessary. It was determined that all these five people are taking 5mg daily so the daily dose complies with BNF, and as it is already known the beta-adrenergic antagonists should not be use for treatment of patients with decompensated congestive heart failure unless the condition of health is being stable.

Metoprolol and carvedilol are cardioselective, lipid soluble and without Intrinsic Sympathomimetic Activity. Nebivolol and carvedilol have an addition property they have an arteriolar vasodilating action by diverse mechanism and thus lower peripheral resistance. Their used doses comply with EOP.

Beta-blockers can be used alone or with other drugs. To date, an additional antihypertensive effect was observed only when the Nebivolol 5mg combined with hydrochlorothiazide 12.5 - 25mg. In patients with renal insufficiency, the recommended starting dose is 2.5 mg a day according to BNF (BNF, 2007).

On this side it has referred that the treated patients should be checked carefully about what medicines they received. Additionally doctors and pharmacists have to be extremely careful in patients with peripheral circulatory disorders (disease syndrome or Raynaud, intermittent claudication), because it can occur acceleration of these disorders with block of AV and in patients with Prinzmetal angina due to competition with alpha-receptors could also be negative and not with good result but they can also cause bradycardia.

A significant feature of beta – blockers is that among the age groups, it has been analysed that the elderly used more often the beta – blockers for example in the age group of 61 – 70 have obtained 15%, in 71 – 80 have obtained 16% and in 81 – 90 have obtained 10%, while in the 41 – 50 have obtained 20%. In these percentages it has to be reminded that there are different the number of patients in each group, for example in the age group of 41 – 50 there only 5 active substances and only one is a beta – blocker. On the other hand in the age group of 61 – 70

there are 20 active substances and three are beta –blockers.

From other studies was determined that it is more favorable by the physicians and patients to take their medication once daily, because the patients do not forget them, and the physicians have found that the dosage scheme once daily, morning or evening has better results in the achievement of the goal of the hypertension treatment (Konstas et al 2002). In this study, the most of the patients are using the dosage scheme of once daily 62%, while the 38% is using the twice daily. It is believed that chronic diseases, it is good that the patient disrupted with medication once or twice daily.

In this study, it was determined that it was used another combination of two drugs the ACE inhibitors with thiazide diuretics, but it was not used as frequent as the sartans with the thiazides, they received an 11%. There were three different brand names which contain three different ACE inhibitors, the Co – Renitec, the Triatec Plus and Accuretic (table 4).

Co-Renitec (20+12.5) mg contains enalapril and hydrochlorothiazide, which is a combination ACE inhibitor and a thiazide and received the higher percentage of the other combinations of this group the 7% (figure 1). The recommended initially daily dose of enalapril is 5mg for hypertension and the usual maintenance daily dose is 20mg and in combination with a diuretic (EOF, 2012). In this case, there is no evidence why the physicians prescribed Co – Renitec more often and there is no evidence if there is another brand with the same active ingredients in this study so it can not be compared.

As it is concerned this combination is found in every age group but with different percentage. In the age groups 41 – 50 and 61 – 70 has achieved their highest percentage, 20% and their lower in the age 5% group 51 – 60.

In this study, it was also determined that Calcium - channel blockers were used in the control of high blood pressure and they received an 8% in the frequency of the antihypertensive agents. Amlodipine as an inhibitor of calcium – channel blockers was used with two different strengths the one is 10mg and the other is 5mg. Blocks special channels on the surface of cells, called calcium channels through which ions calcium normally enters cells. The entry of calcium ions in muscle cells fibers of the blood vessel wall causes contraction. On this molecular base the drug is reducing the flow of calcium into the cells.

It had been determined that there is a difference in how many people use different strengths of amlodipine, 6% are taking amlodipine 5mg and 3% for

amlodipine 10mg. This difference might have to do with the fact that patients feel more compliant with the lower dose or that they take double the lower dose which is again 10mg. Both doses are complied with the EOP (EOP, 2012). Sometimes patients tolerate if they started with the lower doses, or with the lower doses themselves, but there are not evidence about the history of the patients, so it cannot be judged the different dosages if they reached the particular aim.

It has been determined that the higher percentage of the usage of Calcium – channel blockers is in the age group of 71 – 80, with a 16%, which is the highest percentage that this antihypertensive agents achieved. It has been found that the Calcium – channel blockers are used more often by the elderly, which is a safe choice of antihypertensive agents as it complies with the Walker (Walker et al, 2012).

The group of diuretics contains the sub groups of thiazides, loop diuretics and Potassium - sparing and aldosterone agonists are used in the project. Loop diuretics have only one active substance furosemide, but they are used by 7%. Furosemide is used in the treatment of hypertension with strength 40mg. It is more often used by the elderly in order to have better control of the blood pressure (BNF, 2007). Some of these subjects, they are taking in combination with other antihypertensive agents such as beta-blocker or Calcium-channel blocker in order to achieve better result in lowering the blood pressure which complies with BNF (BNF, 2007). In this study, it was more often used in the elderly as it was referred earlier, although in the middle aged patients was not used.

Thiazides used in combined drugs or as combination of two or three drugs. On failing a satisfactory result is added diuretic (thiazide, chlorothalidone, indapamide or loop diuretics if there is influence of renal function). In the treatment with diuretics added one after the other drugs. In this study has used only by the 3% as monotherapy (figure 6), but used more frequently in the combined drugs.

Thiazides may not be appropriate diuretics for use in patients with renal function weary and are not effective if values of creatinine clearance is 30ml/min or less (eg, moderate or severe renal failure). In this study, there is not evidence about the kidney function of the patients, therefore it cannot be judged if the use of thiazides or loop diuretics is rational or not. The majority of patients, at a rate of 80-90% with hypertension have primary elevation of blood pressure with systolic (high) and diastolic (low) blood pressure to be strong and independent risk factors

for cardiovascular disease. It is therefore clear that the average blood pressure should be 115/75 mmHg (systolic/diastolic) and that more than 20 mmHg increase in systolic blood pressure or 10 mmHg respectively diastolic lead to a doubling of risk for both fatal stroke and for coronary artery disease. It also seems that people over 50 years the systolic pressure is much stronger indicator of cardiovascular risk than diastolic pressure.

Hydrochlorothiazide belongs to diuretics and in this study it does not appear to be prescribed as monotherapy but only in combination with other drugs. In this study it is also appeared that it is prescribed in combination with other drugs in the same medicine. When the doctors' were asked why it is prescribed like that it was said that it seems that two drugs in the same medicine is better result in lowering the blood pressure, as well as the patients thought that were easier for them. Patients also said that it is only one pill and they do not forget it.

At last the ACE inhibitors have used by only 1% of the antihypertensive agents maybe due to some side effects of them, such as cough, or they cannot be tolerated. This study is retrospective and therefore we are not able to see these details from the personal history of the patients. They can be replaced by angiotensin II receptor inhibitors that can explain the higher percentage in the use of the sartans. There is a study in USA about the ACE inhibitors and the sartans that middle aged Americans with hypertension have a risk of appendicitis (Mukamal et al 2012). The active substance that used here is enalapril malaete.

This project has determined that most of the patients in our study have taken a combination of two drugs, 50%, while the people who are using the monotherapy are 32.7%. In this percentage of the combination of two active substances is included the combined drugs such as Copalia, as it was expected. There are studies that determined that two active substances combined together achieve the goal of the treatment but they have lower cardiovascular prognosis than the monotherapy (Weber et al 2012). Although the combination of three active substances has also a significant percentage of 12.1% which again complies with the literature the combination of four drugs have the lowest percentage 5.2%, which is significant because there are cases that cannot be managed with two or three actives and it has to be added and a forth substance. This can be explained by the means that it is complicated for the elderly patients to have taken three drugs daily therefore the physicians' might also prefer the combined medicines for better tolerance.

Study reference	Design	Entry criteria	Primary efficacy endpoint	Treatment arms/drug dosages
Pooled factorial design studies (Chrysant et al 2004; Daiichi-Sankyo, Integrated Summary of Efficacy, data on file)	Randomized, db, pc, pg, mc, factorial design	Mean seDBP 100–115 mmHg at weeks 3 and 4 of placebo run-in	Change from baseline in mean trough seDBP at week 8 or 12	Placebo OLM (10, 20 or 40 mg/day) HCTZ (12.5 or 25 mg/day) OLM plus HCTZ (all combinations)
HCTZ add-on cohort (Sellin et al 2005)	Partially randomized, db, pc, pg, mc	Mean seDBP 100–115 mmHg and mean 24-hour DBP (by ABPM) $\geq$ 84 mmHg; $\geq$ 30% daytime DBP $>$ 90 mmHg; seDBP $\geq$ 90 mmHg after olmesartan run-in	Change from baseline to end of study (week 12) in mean daytime DBP (by ABPM)	OLM (20 mg/day) OLM plus HCTZ (20 mg/day plus 12.5 or 25 mg/day)
Severe hypertensive cohort (Ball et al 2001)	Randomized, db, pg, mc, double-dummy, dose-titration, comparison study	Moderate–severe essential I (seDBP 100–120 mmHg) at end of HCTZ run-in.	Change from baseline in mean trough seDBP at week 12	OLM plus HCTZ (10 or 20 mg/day plus 25 mg/day) Atenolol plus HCTZ (50 or 100 mg plus 25 mg/day)
Treat-to-target cohort (Neutel et al 2004, 2006)	Open-label, non-comparative, mc, treat-to-target, with 6-step treatment algorithm	Mean seDBP 90–109 mmHg	Change from study baseline/treatment baseline to the end of each 4-week period using the LOCF in seDBP and seSBP and number of responders (SBP $\leq$ 130 mmHg, DBP $\leq$ 85 mmHg).	OLM (20 or 40 mg/day) OLM plus HCTZ (40 mg/day plus 12.5 or 25 mg/day) OLM plus HCTZ plus amlodipine (40 mg/day plus 25 mg/day plus 5 or 10 mg/day)

Abbreviations: ABPM, ambulatory blood pressure monitoring; db, double-blind; HCTZ, hydrochlorothiazide; LOCF, last observation carried forward; mc, multicenter; OLM, olmesartan medoxomil; pc, placebo-controlled; pg, parallel-group; seDBP seated diastolic blood pressure; seSBP, seated systolic blood pressure.

Figure 2. Comparison of the recommended drug therapy of hypertension (Kereiakes et al 2007).

Another important feature of this study was the number of packages of the prescribed drugs. It was determined that 19% have taken three packages, for example in Co – Renitec package there only 10 tablets (EOΦ, 2012), therefore the patient need three packages in order to have medicines for one month. The two packages have a 27%, which in most of the cases it means that the package contains fourteen tablets or capsules, or that the patient may take double dose that is why it was prescribed two packages.

In the studies comparing ACEIs with ARBs, only 38 deaths and 13 strokes were reported. A study conducted by Barnett (Barnett et al. 2004) evaluated cardiovascular outcomes in 250 patients with type 2 diabetes treated with enalapril 20 mg daily or telmisartan 80 mg daily over a 5-year period (Galzerano et al 2010).

The higher-risk sample included individuals with comorbidities such diabetes and early nephropathy which has a higher cardiovascular risk than the others. Among patients treated with enalapril against telmisartan, there were similar results of deaths (6 in each group), strokes (6 in each group) and nonfatal Myocardial Infractions (6 in the enalapril group and 9 in the telmisartan group) (Galzerano et al 2010).

The levels of blood pressure observed, depend on the characteristics of the population, especially by age and ethnicity. Blood pressure in developed countries

increases with age until the seventh decade, with the increase being more pronounced for systolic pressure (i.e. known as "big"), particularly in men. Depending on the diagnostic criteria, hypertension is present in 20-30% of the adult population and the rate of hypertension appears to be much higher in individuals originating from Africa at a rate of 40-45% of adults.

The risk of mortality or morbidity increases progressively with the increase in systolic and diastolic pressure, with each measure to have independent prognostic value. For example the isolated systolic pressure is two to three times the increase in cardiac mortality. All adults should be regulated their blood pressure by measuring it usually every 6 months even those without history of hypertension. Our limitation is that we have no access to blood pressure data and therefore we are not able to analyse if we reached the aim.

The majority of patients, at a rate of 80-90% with hypertension have primary elevation of blood pressure with systolic (high) and diastolic (low) blood pressure to be strong and independent risk factors for cardiovascular disease. It is therefore clear that the average blood pressure should be 115/75 mmHg (systolic / diastolic) and that more than 20 mmHg increase in systolic blood pressure or 10 mmHg respectively diastolic lead to a doubling of risk for both fatal stroke and for coronary artery disease. It also seems that people over 50 years the systolic pressure is much stronger indicator of cardiovascular risk than diastolic pressure.

In cases of increased pressure, the final confirmation of the diagnosis requires repetitive measurements at even 1-2 doctor visits, at intervals of at least one week from the primary diagnosis to rule out the possibility of a temporary change. Usually, the diagnosis of hypertension and the decision to start antihypertensive treatment should not be based on measurements made with a single estimate. Even in patients with a large increase in blood pressure (systolic/diastolic >180/110 mmHg), there is usually room for a few days to reassess the levels of blood pressure and finalization of drug or no treatment.

The collected data always had been a part of many studies supporting the view that antihypertensive treatment with diuretics and beta – blockers has a major positive impact on a wide range of cardiovascular diseases. Generally there are results are based on studies with control groups receiving except a lowering of stroke that if the administration of calcium channel blockers in the study systolic hypertension in Europe (Systolic Hypertension in Europe trial) (Gasowski et al 1999).

This study is a pilot study, and therefore the patients' sample is quite small in order to determine more specific results about the pharmacotherapy in Greece. It was analysed only a small village not the whole country. If it has been used a larger period of time, it might have shown better more specific results in the analysis of the pharmacotherapy. Another disadvantage of this study is that there are not available data about the patients' history, when they are diagnosed with arterial hypertension, which was the first treatment, how long do they take this medication. There were not available data about any co-morbidities or mortalities. It was only used the information from the prescriptions, so it has no evidence if the patients suffer from another disease.

Additionally there were not data about the physicians if they cooperate better some companies so they can prescribe their medicines or with what criteria do they choose which treatment is better for each patient.

## **5. Conclusion**

In conclusion, arterial hypertension is a disease with particular pathologies, risk factors and outcomes which seems to depending on the choice of the appropriate drug therapy which could be effectively for the patients.

In this pilot study was determined that hypertension was appeared more often to the elderly and also in men than women. In the treatment, the combination of two active substances (50%) plays better role in the goal of the treatment than the monotherapy (32.7%). The most commonly used class of antihypertensive agents was the combination sartans with thiazides (27%), while the most frequent used medicine was the sartan, irbesartan (10%). Once daily was the usual dose with 62% of the patients using it and 54% are taking one package per month.

In this study, they have been determined some results about the pharmacotherapy that used in this particular pharmacy. However it cannot be done assumptions about the pharmacotherapy in Greece, because the sample is too small and there are missing some important information about the patients, such as the current clinical state of the patients or when they started the treatment, or if they experience some side effects. Some other limitations that we had, was about the physicians, there are not available data about them, if they collaborate with some pharmaceutical companies, or why do they prescribe those medicines, or if they



have experience some morbidity and mortality about some medicines, therefore they do not prescribe them. To conclude further investigation should be done in order to summarize the results for the whole Greece.

## **6. List of Abbreviations**

ACEIs – angiotensin converting enzyme inhibitors

AH – arterial hypertension

AMKA – Greek social security number

ARBs – angiotensin II receptors blockers

Bid – twice daily

BMI – body mass index

DBP – diastolic blood pressure

ECG – electronic cardiogram

HDL – high density lipoproteins

ISA – intrinsic sympathomimetic activity

LDL – low density lipoproteins

MRI – magnetic resonance imaging

NSAIDs – non-steroidal anti-inflammatory drugs

SBP – systolic blood pressure

Tid – three times daily

## 7. References

Adroge HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med.* 2007; 356(19): 1966-78.

Amery A, Birkenhager W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial *Lancet* 1985; 1: 1349 – 1354.

Barrios V, Boccanelli A, Ewald S, et al. Efficacy and tolerability of olmesartan medoxomil in patients with mild to moderate essential hypertension: the OLMEBEST Study. *Clin Drug Investig,* 2007; 27: 545–8.

Barzilay JI, Davis BR, Cutler JA, et al. Fasting glucose levels and incident diabetes mellitus in older non-diabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med.* 2006 13; 166(20): 2191-201.

Beckett NS, Peters R, Fletcher AE, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med,* 2008; 358: 1887-98.

Benetos A, Thomas F, Bean KE, Guize L. Why cardiovascular mortality is higher in treated hypertensives versus subjects of the same age, in the general population *J Hypertens* 2003; 21: 1635 –1640.

Beulens JW, Rimm EB, Ascherio A, et al. Alcohol consumption and risk for coronary heart disease among men with hypertension. *Ann Intern Med.* 2007 2; 146(1): 10-9.

Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus. Results of prospectively designed overviews of randomized trials. *Arch Intern Med,* 2005; 165: 1410 – 1419.

Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed over views of randomized trials. *Lancet* 2003; 362: 1527 – 1535.

BNF 53, British National Formulary, British Medical Association, Royal Pharmaceutical Society of Great Britain, March 2007, 70-116

Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*, 2008 24; 117(25): e510-26

Campbell M, Sonkodi S, Soucek M et al. A candesartan cilexetil/hydrochlorothiazide combination tablet provides effective blood pressure control in hypertensive patients inadequately controlled on monotherapy. *Clin Exp Hypertens*. 2001; 23: 345–55

Cheng SM, Mar GY, Huang SC et al. Post-marketing surveillance study valsartan/amlodipine combination in Taiwanese hypertensive patients, *Blood Press*, 2012 Jul; 21 Suppl 1:11-9

Connolly HM, Oh JK. Echocardiography. In: Libby P, Bonow RO, Mann DL, Zipes DP, eds. *Libby: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 8th ed. Saunders 2007; 14-21.

Cuspidi C, Macca G, Salerno M, et al. Evaluation of target organ damage in arterial hypertension: which role for qualitative funduscopic examination? *Ital Heart J* 2001; 2: 702 – 706.

Dahlof B, Devereux RB, Kjeldsen SE, et al. LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002; 359: 995 – 1003.

Dahlof B, Lindholm LH, Hansson L, et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991; 338: 1281 – 1285.

Efstratopoulos AD, Voyaki SM, Baltas AA, et al. Prevalence, awareness, treatment and control of hypertension in Hellas (Greece). The Hypertension National Study (hypertension study in general practice in Hellas), *AMER J HYPERTENS*, 2006; 19: 53-60

EOF, Greek National Organization of Medicines, [www.eof.gr](http://www.eof.gr), 2012

Fabia MJ, Abdilla N, Oltra R, et al. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring. *J Hypertens*. 2007; 25: 1327–36.

Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. *J Hypertens*. 2007 Nov; 25(11):2193-8.

Galzerano D, Capogrosso C, Michele SD, et al. New standards in hypertension and cardiovascular risk management: focus on telmisartan. *Vasc. Health Risk Manag.* 2010; 6: 113–133.

Gasowski J, Staessen JA, Celis H et al. Systolic Hypertension in Europe (Syst-Eur) trial phase 2: objectives, protocol, and initial progress. Systolic Hypertension in Europe Investigators. *J Hum Hypertens*, 1999 Feb; 13(2): 135-45.

Germino FW, Neuter JM, Dubiel R et al. Efficacy of olmesartan medoxomil and hydrochlorothiazide fixed-dose combination therapy in patients aged 65 years and older with stage 1 and 2 hypertension or isolated systolic hypertension, *AM J Cardiovasc Drugs.* 2012 Oct 1; 12(5): 325-33

Halperin RO, Gaziano JM, Sesso HD. Smoking and the risk of incident hypertension in middle - aged and older men. *Am J Hypertens* 2008; 21: 148-52.

Hergens MP, Lambe M, Pershagen G, Ye W. Risk of hypertension amongst Swedish male snuff users: A prospective study. *J Intern Med* 2008; 264: 187-94.

Higgins JR, de Swiet M. Blood pressure measurement and classification in pregnancy. *Lancet* 2001; 357 : 131 – 13.

Hoes AW, Grobbee DE, Lubsen J, et al. Diuretics, beta-blockers, and the risk for sudden cardiac death in hypertensive patients. *Ann Intern Med* 1995; 123 : 481– 487.

Hosoya T, Kurivama S, Yoshizawa T, et al. Effects of combined antihypertensive therapy with losartan/hydrochlorothiazide on uric acid metabolism, *Intern Med.* 2012; 51(18): 2509-14

Joffres MR, Hamet P, Rabkin SW, et al. Prevalence, control and awareness of high blood pressure among Canadian adults. Canadian Heart Health Surveys Research Group *CMAJ* 1992; 146: 1997-2005.

Kaplan NM. Systemic hypertension: therapy. In: Libby P, Bonow RO, Mann DL, Zipes DP, eds. *Libby: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 8th ed. Saunders; 2007.

Kereiakes DJ, Neutel JM, Punzi HA, et al. Efficacy and safety of olmesartan medoxomil and hydrochlorothiazide compared with benazepril and amlodipine besylate, *Am J Cardiovasc*, 2007; 7(5): 361-72

Khan NA, Wardman D, Campbell NR. Differences in need for antihypertensive drugs among those aware and unaware of their hypertensive status: A cross sectional survey. *BMC Cardiovasc Disord*, 2005 ;5: 4.

Kintscher U, Bramlage P, Paar WD, et al. Irbesartan for the treatment of

hypertension in patients with the metabolic syndrome: a sub analysis of the Treat to Target post authorization survey. Prospective observational, two armed study in 14,200 patients. *Cardiovasc Diabetol*. 2007; 6: 12.

Konstas AG, Nakos E, Tersis I, et al. A Comparison of Once – Daily morning vs evening dosing of concomitant lataloprost/timolol, *Am J Ophthalmol* 2002 Jun; 133(6): 753-7

Lacourciere Y, Gil-Extremera B, Mueller O, et al. Efficacy and tolerability of fixed-dose combinations of telmisartan plus HCTZ compared with losartan plus HCTZ in patients with essential hypertension. *Int J Clin Pract*, 2003; 57: 273–9.

Lacourciere Y, Poirier L. Antihypertensive effects of two fixed-dose combinations of losartan and hydrochlorothiazide versus hydrochlorothiazide monotherapy in subjects with ambulatory systolic hypertension. *Am J Hypertens*. 2003; 16: 1036–42.

Lacourciere Y, Tytus R, O’Keefe D, et al. Efficacy and tolerability of a fixed-dose combination of telmisartan plus hydrochlorothiazide in patients uncontrolled with telmisartan monotherapy. *J Hum Hypertens*. 2001; 15: 763–70.

Liu L, Zhang Y, Liu G, Li W et al. FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo - controlled trial in Chinese hypertensive patients. *J Hypertens* 2005; 23: 2157 – 2172.

Mc Phee J, Papadakis M, Tierney L. *Current Medical Diagnosis and Treatment*, 46<sup>th</sup> Edition, 2007

Magnussen EB, Vatten LJ, Lund-Nilsen TI et al. Pre-pregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. *BMJ*, 2007 10; 335(7627): 978.

Mancia G, Ferrari A, Gregorini L et al. Blood pressure and heart rate variability’s in normotensive and hypertensive human beings. *Circ Res* 1983; 53: 96 – 104.

Mancia G, Omboni S, Parati G et al. Twenty-four hour ambulatory blood pressure in the Hypertension Optimal Treatment (HOT) study. *J Hyper tens* 2001; 19: 1755 – 1763.

Mancia G, Omboni S, Ravogli A, et al. Ambulatory blood pressure monitoring in the evaluation of antihypertensive treatment: additional information from a large data base. *Blood Press* 1995; 4: 148 – 156.

Mancia G, Parati G, Bilo G. et al. Assessment of long-term antihypertensive

treatment by clinic an ambulatory blood pressure. Data from the ELSA Study. *J Hypertens* 2007; 25: 1087 – 1094.

Maniadakis N, Kourlaba G, Fragoulakis V, Self-reported prevalence of atherothrombosis in general population sample of adults in Greece; A telephone survey, *BMC Cardiovascular Disorders* 2011, 11:16, <http://www.biomedcentral.com/1471-2261/11/16>

Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; 372: 547-53.

Matchar DB, McCrory DC, Orlando LA et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med.* 2008 Jan 1; 148(1): 16-29.

Mengden T, Myers M, Padfield P, et al. Europe an Society of Hypertension Recommendations for Conventional, Ambulatory and Home Blood Pressure Measurement. *J Hypertens* 2003; 21: 821 – 848.

Modesti PA, Morabito M, Bertolozzi I et al. Weather related changes in 24-hour blood pressure profile: effects of age and implications for hypertension management. *Hypertension* 2006; 47: 155 – 161.

Mukamal KJ, Ghimire S, Pandey R, et al. Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and risk of appendicitis. *Ann Epidemiol.* 2012 Oct; 22(10): 747-50

Nakao N, Yoshimura A, Morita H et al. Combination treatment of angiotensin - II receptor blocker and angiotensin - converting - enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial. *Lancet* 2003; 361: 117 – 124.

Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. *Lancet* 2000; 356: 1955-64.

Neutel JM, Littlejohn TW, Chrysant SG, et al. Telmisartan/hydrochlorothiazide in comparison with losartan/hydrochlorothiazide in managing patients with mild-to-moderate hypertension. *Hypertens Res.* 2005; 28: 555–63.

Neutel JM, Smith DH, Silfani TN, et al. Effects of a structured treatment

algorithm on blood pressure goal rates in both stage 1 and stage 2 hypertension. *J Hum Hypertens*. 2006; 20: 255–62.

Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. *Lancet* 2007; 370: 829-40.

Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist versus a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003; 290: 2805 – 2816.

Salerno CM, Demopoulos L, Mukherjee R, et al. Combination angiotensin receptor blocker/hydrochlorothiazide as initial therapy in the treatment of patients with severe hypertension. *J Clin Hypertens (Greenwich)* 2004; 6: 614–20.

Schrader J, Bramlage P, Luders S, et al. BP goal achievement in patients with uncontrolled hypertension: results of the treat-to-target post-marketing survey with irbesartan. *Clin Drug Investig*. 2007; 27(11): 783–796.

Schrader J, Luders S, Kulschewski A, et al. MOSES Study Group. Morbidity and Mortality after Stroke. Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005; 36: 1218 – 1226.

Sega R, Cesana G, Bombelli M, Grassi G, et al. Seasonal variations in home and ambulatory blood pressure in the PAME LA population. *Pressione Arteriale Monitorate e Loro Associazioni*. *J Hypertens* 1998; 16: 1585 – 1592.

Waeber B, Aschwanden R, Sadecky L, et al. Combination of hydrochlorothiazide or benazepril with valsartan in hypertensive patients unresponsive to valsartan alone. *J Hypertens*. 2001; 19: 2097–104.

Walker R, Whittlesea C, *Clinical Pharmacy and Therapeutics*, Fifth Edition, Churchill Livingstone Elsevier, 2012; 295-311 Watanabe LA, Wei M, Sun N, et al. Effect on blood pressure control of switching from valsartan monotherapy to losartan/hydrochlorothiazide in Asian patients with hypertension: results of a multicentre open-label trial. *Curr Med Res Opin*. 2006; 22: 1955–64.

O'Brien, Weber B, Parati G et al. Blood pressure measuring devices: recommendations of the European Society of Hypertension. *Br Med J* 2001; 322: 531 – 536.

Weber MA, Julius S, Kjeldsen SE, et al. Cardiovascular outcomes in hypertensive patients: comparing single-agent therapy with combination therapy, *J Hypertens*. 2012 Nov;



30(11): 2213-22

Wen CP, Tsai MK, Chan HT, et al. Making hypertensive smokers motivated in quitting: Developing 'blood pressure equivalence of smoking'. *J Hypertens*, 2008; 26: 672-7.

White WB, Giles T, Bakris GL, et al. Measuring the efficacy of antihypertensive therapy by ambulatory blood pressure monitoring in the primary care setting. *Am Heart J*. 2006; 151: 176–84.

Wing LM, Reid CM, Ryan P, et al. Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*, 2003; 348: 583 – 592.

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