CHARLES UNIVERSITY IN PRAGUE
FACULTY OF PHARMACY IN HRADEC KRALOVE
Department of Social and Clinical Pharmacy

MASTER PHARMACY

***Diploma Thesis:***

# ANALYSIS OF PHARMACOTHERAPY AND DRUG RELATED PROBLEMS IN PATIENT WITH ARTERIAL HYPERTENSION IN GREECE

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Hradec Kralove, 15/05/2014 Zisis Papadopoulos

Abstract

Title: Analysis of pharmacotherapy and drug related problems in patients with arterial hypertension in Greece

Analýza farmakoterapie a lékových problémů u nemocných s arteriální hypertenzí v Řecku

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**Úvod:** Arteriální hypertenze je chronické onemocnění charakterizované vysokým krevním tlakem a je důležitým rizikovým faktorem pro budoucí vývoj kardiovaskulárních onemocnění. Často je řazeno k asymptomatickým onemocněním, protože dlouhou dobu nemusí být doprovázeno symptomy, dokud nejsou poškozeny vitální orgány. Přesto je jednou z největších příčin morbidity a mortality tím, že je spojena s některými vážnými onemocněními, jako je ischemická choroba srdeční, náhlá cévní příhoda mozková, ateroskleróza, selhávání ledvin, dyslipidémie, diabetes mellitus, obezita a metabolický syndrome. Arteriální hypertenze pro dospělé, kteří netrpí jinou chorobou, je definována zvýšením tlaku krve rovné nebo vyšší než 140/90mm Hg.

**Cíl**: Hlavním cílem teoretické části bylo analyzovat literární informace týkající se etiopatogeneze, diagnostických metod a strategie léčby arteriální hypertenze a také klasifikace a příčiny lékových problémů (DRP) především antihypertenzív. V experimentální části bylo cílem analyzovat farmakoterapii a DRP u 60 řeckých pacientů léčených pro arteriální hypertenzi.

**Metoda:** Literární informace byly sbírány z posledních 4 let především pomocí PubMed a z doporučení Evropské společnosti pro hypertenzi. Data 60 nemocných s arteriální hypertenzí byla získána od jednoho řeckého specialisty (kardiologa) a obsahovala věk, pohlaví, farmakoterapii včetně síly a dávkového schéma a potenciální nežádoucí účinky a využita k frekvenční analýze.

**Výsledky:** Současná retrospektivní studie zahrnovala 60 případů. Arteriální hypertenze byla zastoupena ve všech věkových skupinách dospělých, ale nejčastěji u starých nemocných. Nejčastějšími komorbiditami byla dyslipidémie a ischemická choroba srdeční (37 a 32% ze studované populace). Jako antihypertenzívum byly nejčastěji používané betablokátory a sartány (samy nebo v kombinaci s hydrochlorothiazidem) a doprovázeny

byly hypolipidemiky. Preferovaná léčiva bylata, která bylo možno podat jednou denně a také byla preferována kombinační terapie antihypertenzív (88 a 65% studované populace). Nejčastějšími DRP byla pozorována bradykardie, únava, periferní edémy a suchý kašel – hlavně jako důsledek užívání betablokátorů, amlodipinu a inhibitorů enzymu konvertujícího angiotensin. Navíc bylo pozorováno zvýšení kreatinkinázy a mylagie při užívání statinů, používaných k léčbě dyslipidémie jako součást maximalizace účinku léčby arteriální hypertenze.

**Závěr:** Byly získány data od 60 pacientů s arteriální hypertenzí z ambulance jednoho kardiologa v menším městě s 50000 obyvateli v severním Řecku. Výsledky nejsou reprezentativní pro celé Řecko a slouží jako signál pro další plánování observačních farmakoepidemiologických studií k analýze léčby hypertenze a výskytu DRP.

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**Background:** Arterial hypertension or high blood pressure is a chronic medical condition which is characterized by elevated blood pressure in the arteries and is an important risk factor for future development of cardiovascular disease. Also belongs to asymptomatic diseases because it usually does not cause symptoms for years until a vital organ is damaged. Moreover is a major cause of morbidity and mortality, due to its association with some other serious diseases like coronary heart disease, cerebrovascular disease, atherosclerosis, renal disease, dyslipidemia, diabetes, obesity and metabolic syndrome. Arterial hypertension for adults, who don't suffer from any other kind of diseases, is defined by an elevation of blood pressure to 140 / 90 mm Hg or to higher values.

**Aim:** In the theoretical part the main aim is to analyze information regarding etiopathogenesis, diagnostic methods and treatment strategies of arterial hypertension, as well as classification and causes of drug-related-problems to antihypertensive agents. In the experimental part the aim is to analyze the pharmacotherapy and drug-related-problems of 60 Greek hypertensive patients.

**Methods:** Literature research was made during a four month period, mainly from PubMed and guidelines of European society of hypertension. Additionally 60 patient cases were collected from one Greek health professional specialist (cardiologist) regarding age, gender, pharmacotherapy, dosage scheme, strength and adverse drug reaction which were used for statistical analysis.

**Results:** The present retrospective study included 60 patient cases. Hypertension can affects all ages with higher prevalence in men gender. Most common co-morbidities along with hypertension were dyslipidemia and coronary heart disease accounting 37% and 32% of the population, respectively. Most frequently used antihypertensive drug groups was β-blockers and angiotensin II receptor blockers (alone or in combination with hydroclorothiazide) along with antidyslipidemics as additive to antihypertensive therapy. Once daily regimens and combination therapy of antihypertensive agents appears to be more favorable accounting 88% and 68% of the population, respectively. The most common adverse drug reactions appear to be bradycardia, fatigue, peripheral edema and dry cough, mainly due to β-blockers, amlodipine and angiotensin-converting-enzyme-inhibitors. Additionally increased levels of creatine phosphokinase and myalgia were observed mainly due to statins, as additive to antihypertensive therapy for management of co-morbidities, like dyslipidemia.

**Conclusion:** On this study 60 hypertensive patient cases was collected from one cardiologist, in small city of 50.000 inhabitants in north Greece. Due to certain limitations these findings are not representative of a whole Greek population and it can be used only for observational purpose, to give us just an idea of the kind of pharmacotherapy used most frequently in Greek population, along with the drug related problems commonly faced. Further investigations it will be necessary in the future to produce more accurate and representative findings.

**CONTENTS**

# 1. INTRODUCTION

The present retrospective study consists of two parts: theoretical and experimental both regarding arterial hypertension. The main goal of the theoretical part is to give to give the etiopathogenesis, diagnostic methods and treatment strategies of arterial hypertension, as well as classification and causes of drug-related-problems (D.R.P) to antihypertensive agents. The methodology to accomplice this task is simply follow the way of literature research through the books, European hypertension guidelines, web encyclopedias and articles mainly from PubMed.

In experimental part the main goal is to analyze pharmacotherapy and A.D.Rs of 60 patients suffering mainly by arterial hypertension in Greece. In order to accomplice this task the methodology is to collect the patients' data (age, gender, diagnosis, pharmacotherapy, dosage scheme, strength, A.D.Rs) from one cardiologist in Greece, store all the data into the evaluation database (Microsoft Excel) and analyze rate of use of particular drugs that are the most frequently administered in hypertensive patients, their doses and the most frequently prescribed dosage schemes by statistical meaning and look for potential drug related problems of these particular patients. In addition discussion of therapy strategy and management of these particular patients regarding pharmacotherapy based evidence used in arterial hypertension will be also mentioned and in the end some conclusions will be given.

# 2. THEORETICAL PART –ARTERIAL HYPERTENSION

## 2.1) DEFINITION

Arterial hypertension or high blood pressure is a chronic medical condition which is characterized by elevated blood pressure in the arteries and is an important risk factor for future development of cardiovascular disease. Arterial hypertension belongs to asymptomatic diseases because it usually does not cause symptoms for years until a vital organ is damaged (Walker R. and Whittlesea C., 2012).

In order to understand this chronic condition we should first understand the role and the meaning of blood pressure. Blood pressure can be defined as the force against the walls of arteries when the heart pumps blood through the body. We can easily say that blood pressure is the product of cardiac output and total peripheral resistance. The main role is the maintenance of the systemic circulation. That means that the blood pressure has a vital significance (Dugdale D., 2012).

Blood pressure is represented by two values. The higher value called systolic is the highest pressure in the arteries when the heart contracts (systole). The lower value is the lowest pressure in the arteries when the heart relaxes between beats (diastole). Arterial hypertension for adults, who don't suffer from any other kind of diseases, is defined by an elevation of blood pressure to 140 / 90 mm Hg or to higher values (AHA, 2012).

On the table below there is a classification of arterial blood pressure according to European Society of Hypertension (ESH) (ESH-ESC, 2013):

| BLOOD PRESSURE CATEGORY | SYSTOLIC (mm Hg) | | DIASTOLIC (mm Hg) |
|---|---|---|---|
| **IDEAL** | less than 120 | and | less than 80 |
| **NORMAL** | 120-129 | or/and | 80-84 |
| **PREHYPERTENSION** | 130-139 | or/and | 85-89 |
| **HYPERTENSION – MILD-STAGE 1** | 140-159 | or/and | 90 - 99 |
| **HYPERTENSION – MODERATE-STAGE2** | 160-179 | or/and | 100-109 |
| **HYPERTENSION – SEVERE-STAGE3** | Higher or equal to 180 | or/and | Higher or equal to 110 |
| **ISOLATED SYSTOLIC HYPERTENSION** | Higher or equal to 140 | and | Less than 90 |

***Table 1: Blood pressure classification according to E.S.H (ESH-ESC, 2013).***

## 2.2) SIGNS–SYMPTOMS–COMPLICATIONS OF ARTERIAL HYPERTENSION

Hypertension as we mention above belongs to asymptomatic diseases. Rarely is accompanied by any symptoms and its identification is very often accidentally through routine physical examination or examination of unrelated problem. Many people can have high blood pressure for years without knowing it. This condition can damage vital organs and can cause serious health problems like coronary heart disease, stroke or kidney failure.

Some people with high blood pressure report that they had an experience of headaches especially during the morning at the back side of the head, vertigo, tinnitus, visual disturbances such as blurred vision, dizziness and fatigue. However, these symptoms might be related to anxiety or to another related disease rather than high blood pressure itself.

In addition in cases of severe high blood pressure, due to cerebral ischemia and edema some other symptoms can occur such as nausea, vomiting, worsening headache, confusion, nosebleeds, seizures and even coma. This condition is called hypertensive encephalopathy. Also in severe high blood pressure because the workload of the heart increases may cause chest pain and shortness of breath. In that case people who have an experience of this condition require emergency treatment.

In a case that high blood pressure is due to pheochromocytoma or due to other endocrine diseases, symptoms may include severe headache, anxiety, excessive perspiration, palpitations and tremor as well (Bakris G., 2013).

So we can summarize and say that high blood pressure in early stages causes no symptoms, so it is easy to ignore. However, if left untreated it can damage vital organs over the years and eventually it can lead to serious complications. The WHO classifies the hypertension into three clinical stages according to the organ damage and alteration of their function (WHO Expert Committee Report, 1978):

| CLINICAL STAGES | DAMAGE | SYMPTOMS |
|---|---|---|
| **I** | NO ORGAN DAMAGE | OFTEN SILENT |
| **II** | ORGAN DAMAGE WITHOUT CHANGE IN THE FUNCTION | HYPERTROPHY OF LEFT VENTRICLE, PROTEINURIA, ATHEROSCLEROSIS |
| **III** | ORGAN DAMAGE WITH FAILURE IN THE FUNCTION | CHRONIC HEART DISEASE, STROKE,RENAL FAILURE, RETINOPATHY |

***Table 2: Hypertension Clinical Stages (WHO Expert Committee Report, 1978).***

Knowledge of individual blood pressure values, monitoring and prevention of high blood pressure is very important for helping reduce the risk of developing health related problems such as:

1) **Damage in the heart in several ways:**
    - **Coronary artery disease:** Occurs when the arteries that supply blood to the heart become narrowed, blood can't flow through them easily. This condition can cause chest pain known as angina or arrhythmias and finally it may result in a heart attack if left untreated.
    - **Heart attack:** Occurs when one of the arteries that supply blood to the heart becomes blocked by blood clots or atherosclerosis. Eventually the part of the heart supplied by the artery due to lack of oxygen begins to die. Heart damage depends on the time that this condition left untreated. Higher time, worst the damage.
    - **Left ventricular hypertrophy:** Occurs when the narrow, harder and thicker arteries force the heart to work harder in order to pump blood through the body according to their needs. This condition causes enlargement of the heart muscle in the left ventricle. Eventually enlargement and stiffening makes hearts job more difficult and can lead to pulmonary edema.
    - **Heart failure:** Occurs when the heart becomes weaker and can't work efficiently due to the added strain trying to pump blood against the higher pressure in the vessels. Eventually heart fails to pump blood according to body's needs. This condition is known as heart failure (Health Line, 2010).
2) **Damage in blood vessels in several ways:**
    - **Atherosclerosis:** Occurs due to overstretching of arteries when the blood pressure is too high. As a result the inner wall of arteries which called endothelium is damaged, allowing the deposit of fatty acids like cholesterol and macrophages, resulting in formation of plague. Eventually fibrosis and calcification take place and over the years the arteries becomes narrow, thick and stiff disrupting the blood flow around the body.
    - **Aneurysm:** It's a blood-filled balloon-like abnormal bulge in the wall of an artery. Aneurysm can become unstable and finally can ruptures and

eventually can lead to life threatening condition (Nordqvist C., 2013, Nordqvist J., 2013).

3) **Kidney damage:**
   - **Kidney failure:** Occurs when the blood vessels due to high blood pressure become weakened and narrowed, decreasing the blood supply to the kidney. This condition can prevent the kidney from functioning normally and can lead to kidney failure. Loss of kidney function allows the buildup of fluid and waste in the body (Health Line, 2010).

4) **Brain damage in several ways:**
   - **Stroke:** Occurs when blood supply to the brain is disturbed due to ischemia, caused by blockage from thrombus or embolus or due to hemorrhage caused by rupture of aneurysm. Eventually the brain loses the function of the area that is affected.
   - **Dementia:** Occurs due to stroke or when the blood flow to the brain is reduced by narrowed arteries. Dementia is a brain disorder characterized by impairments in thinking, speaking, learning, memory and other mental skills.

5) **Eye damage:**
   - **Hypertensive retinopathy:** Occurs when due to high blood pressure the light sensitive tissue at the back of the eye – retina is damaged. Eventually can lead to vision disturbances or even blindness.

6) **Pregnancy complications:**
   - **Preeclampsia:** It's a serious medical condition which is characterized by increased protein amount in the urine and life threatening seizures during pregnancy. Also can cause heavy bleeding, liver and kidney problems. As well can increase the risk for slow growth of the fetus, low birth weight, premature birth and breathing problems.

7) **Male sexual complications:**
   - **Erectile dysfunction:** Might occur when high blood pressure left untreated and over the years can damage the arteries. So the arteries become narrowed and decrease the blood flow that riches penis and can cause erectile dysfunction (Health Line, 2010).

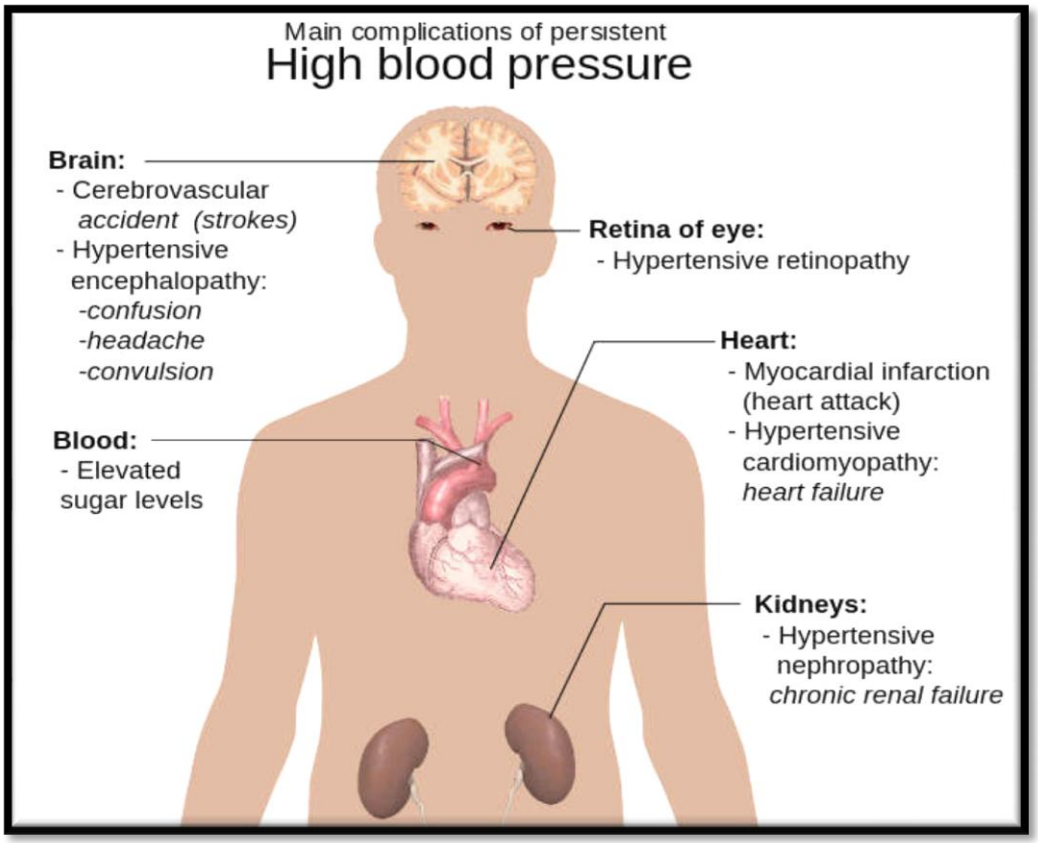



***Image 1: Main complications of Hypertension (Wikipedia, 2009).***

Fortunately dietary and lifestyle changes can improve blood pressure control and increase life expectancy. Although for people for whom the above changes are not effective drug treatment is necessary.

## 2.3) PATHOPHYSIOLOGY OF ARTERIAL HYPERTENSION

In real life, arterial hypertension is a major cause of morbidity and mortality, due to its association with some other serious diseases like coronary heart disease, cerebrovascular disease, atherosclerosis, renal disease, dyslipidemia, diabetes, obesity and metabolic syndrome (Walker R. and Whittlesea C., 2012).

So explanation of pathophysiology of arterial hypertension it's not as simple as it looks like. Before to analyze it, we should understand first the physiology. What is and why is so important the blood pressure. How the body controls the blood pressure, through which mechanisms and which factors play important role in maintenance of elevation in blood pressure.

Blood pressure is important for maintenance of systemic circulation by which transfers oxygen and nutrients to the muscles and vital organs. Blood pressure is the final result of cardiac output and total peripheral resistance. Is defined by the equation:

**BLOOD PRESSURE = (CARDIAC OUTPUT) X (TOTAL PERIFERAL RESISTANCE)**

Cardiac output depends on:

- Stroke volume which is the volume of the blood ejected per systole
- Heart rate which actually represent the heart beats per minute and
- Heart contractility which is equal to the force of contraction during systole

Total peripheral resistance which is represented by the arterioles, the main blood vessel resistance, is affected by their activity and structural – morphological changes like radius, length and smoothness of walls. Arterioles regulate resistance which called "afterload", against which the blood is ejected by the heart during systole. On the other hand veins regulate the venous blood return to the heart which called "preload".

So we can understand that if any change will happen to anyone of the above factors has directly effect on the blood pressure (Homoud M., 2008).

The endogenous regulation of arterial blood pressure is accomplished by the action of two main mechanisms:

1) Renin – Angiotensin – Aldosterone System
2) Autonomic Nervous System Response - Baroreceptor Reflex Mechanism

Renin–Angiotensin–Aldosterone system is one of the most important of the endocrine systems that affect control of blood pressure when it's too low and fluid balance. This system mainly allows the activation of endogenous vasoconstrictor known as angiotensin II and stimulates the secretion of aldosterone which is released from adrenal cortex and antidiuretic hormone from pituitary gland in response to angiotensin II increasing by this way fluid retention and indirectly arterial pressure (Beevers G.et al., 2001).

Full activation and action of the above system is showed schematically on the image below.

If however, there is abnormal overaction of this system, blood pressure will be too high. In that case drug treatment which interrupts in different steps the above system is necessary.

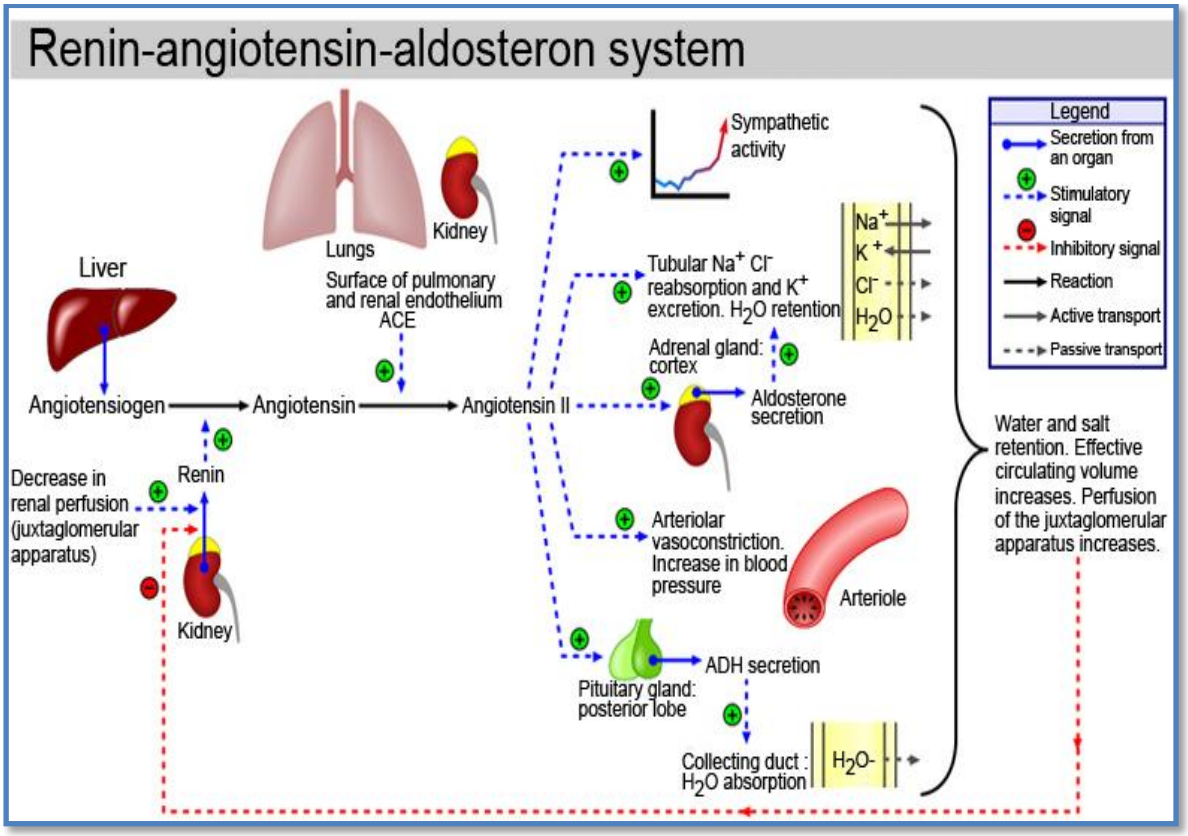



***Image2: Schematically Presentation of Renin-Angiotensin-Aldosterone System Action (Wikipedia, 2006).***

The baroreceptor reflex mechanisms according to stimulus could increase sympathetic activity resulting in contraction of arterioles increasing the total peripheral resistance, in stimulation of the heart increasing the force and speed of contraction increasing by this way the amount of the blood the heart pumps and also can trigger the secretion of renin which eventually can stimulate the renin-angiotensin-aldosterone system. The final result is elevation of blood pressure.

The above mechanisms are not independent of each other and can work conversely, to decrease also blood pressure according to body's needs. Moreover the heart can pump less forcefully or rapidly, arterioles and veins can dilate, and fluid can be removed from the bloodstream.

Normally, whenever a change causes alteration in blood pressure, the body's compensatory mechanisms is triggered in response to the change, trying to keep blood pressure in normal levels (Bakris G., 2013).

There is evidence that in young people high blood pressure is due to high cardiac output while the total peripheral resistance remains normal. This condition is related to sympathetic overactivity. Increased sensitivity to endogenous catecholamines or responsiveness to stressful stimulus also can be found.

The opposite condition could be seen in older people. Cardiac output falls and peripheral resistance rises with age. Also pulse pressure which is defined as the difference between systolic and diastolic blood pressure is frequently increased in older people. Arterial stiffness, reduction in the number or density of capillaries and increased cardiac preload plays a role on increased peripheral resistance (Foex P. and Sear J., 2004).

Some other factors that may also contribute to increase peripheral resistance, vascular damage and establishing eventually hypertension could be:

1) **Renin – Angiotensin – Aldosterone System abnormalities:** Implicates overproduction of sodium retaining hormones and vasoconstrictors causing disturbances in renal salt and water balance. However, elderly and black patients tend to have low renin levels. In that case may be there is genetically inherited abnormality of sodium handling. For others individuals who have high renin levels are more likely in higher risk to develop cardiovascular complications (Foex P. and Sear J., 2004)
2) **Autonomic Nervous System abnormalities:** Increased activity of sympathetic nervous system which accompanied by stimulation of heart, kidneys and peripheral vasculature causes increased cardiac output, increased peripheral resistance and fluid retention. This condition is accompanied by decreased parasympathetic tone and several metabolic, trophic, hemodynamic and rheological abnormalities. Also alterations in baroreflex and chemoreflex pathways can occur. Chronic increased sympathetic tone may lead to increased diastolic blood pressure causing smooth muscle cell proliferation, vascular remodeling, left ventricular and vascular hypertrophy (Oparil S. et al., 2003).
3) **Genetic factors:** Is very difficult to determine accurately dependence of having hypertension in the future due to genetic factors. However many epidemiological studies suggest that separate genes and genetic factors are associated with 30% to 60% of the variation in blood pressure in various populations. Examples of genetic mutations causing hypertension could be: Liddle's, Conn's, Gordon's and Cushing's syndrome. Also experimental studies in animals and humans with transplanted kidneys have shown that the inherited tendency to hypertension it may be due to kidneys (Beevers G. et al., 2001).

4) **Insulin Resistance:** Genetic studies have established a clear association between hypertension, dyslipidemia and diabetes type 2. These diseases have the tend to coexist. Hypertension, dyslipidemia, insulin resistance, central obesity and glucose intolerance are associated with abnormalities like microalbuminuria, high uric acid levels, hypercoagulability and accelerated atherosclerosis. This condition it is known as metabolic syndrome and can lead to serious cardiovascular complications.
5) **Endothelial Dysfunction, Vascular Remodeling and Stiffness:** Deficiencies of vasodilators such as prostacyclin, nitric oxide and natriuretic peptide, alterations in kallikrein-kinin system that affect vascular tone and renal salt handling, increased activity of vascular growth factors such as endothelins, prolonged vascular smooth muscle constriction by increasing cytosolic calcium mediated by over activity of sympathetic nervous system or due to angiotensin or other reason can induce structural changes like thickening of the arteriolar walls causing vascular remodeling, stiffness and endothelial dysfunction (Beevers G. et al., 2001, Foex P. and Sear J., 2004, Oparil S. et al., 2003).
6) **Intrauterine Influence:** According to **''Barker Hypothesis''** there is association between the low birth weight and development of hypertension and other metabolic abnormalities during adolescence. However it is possible, that genetic factors influence the above hypothesis (Beevers G. et al., 2001).
7) **Increased homocysteine levels:** There are studies that shown hyperhomocysteinemia causes vascular dysfunction by increasing blood pressure and impairing the vasorelaxation activity of endothelial derived nitric oxide. Also causes imbalances of elastin/collagen ratio and metabolites of hyperhomocysteinemic endothelium may contribute to vascular dysfunction and hypertension (Sen U. et al., 2010).
8) **Endogenous Ouabain:** There is evidence that in response to high salt intake, endogenous Ouabain which is cardiac glycoside is secreted by brain and adrenal glands. Endogenous Ouabain through the complex double action (binding and inhibition of sodium pump, and secondary effect on handling of calcium ions by sodium calcium exchanger) has cardiotonic and vasotonic effect. The final action of Ouabain is synergistic and causes vasoconstriction and that's why increases total peripheral resistance and maintain elevated the

blood pressure. These structural changes can lead to vascular remodeling (Blaustein P. et al., 2012).

## 2.4) CAUSES-RISK FACTORS-CLASSIFICATION OF ARTERIAL HYPERTENSION

According to the causes, we can classify arterial hypertension into two main groups: primary or essential and secondary hypertension.

Primary or essential hypertension is the most common type of hypertension and accounts 90-95% of all cases. The reasons that can cause this type of hypertension are not fully understood but appear to involve a complex interaction of genes, behavioral and environmental factors. Many hypotheses have been suggested. Moreover genetic predisposition, family history, age, race, gender, socioeconomically status, stress, inappropriate diet, excessive salt and alcohol intake, physical inactivity, obesity, dyslipidemia and insulin resistance are seems to be some of the factors that contribute for development of essential hypertension. Furthermore interaction between these factors can influence sympathetic nerve activity, renin-angiotensin-aldosterone system, kallikrein-kinin system and endothelial factors which in turn can influence sodium excretion, cardiac contractility, vascular reactivity and eventually blood pressure.

In addition from pharmacodynamic point of you, all the above factors that contribute to increase blood pressure called hypertensinogenic factors and their interaction and final effect is additive for population who already have established inherited hypertension. On the other hand for population who is unaffected by inherited hypertension the action of hypertensinogenic factors to blood pressure will follow normal distribution (Carretero O. and Oparil S., 2000).

Also according to a recent study which is a summary and analysis of the main hypotheses for etiology of primary hypertension led to conclusion that renal involvement, through three different pathways plays important role in pathogenesis of primary hypertension through which can alter the physiological balance between sodium retention and sodium excretion.

Summarizing we can say that primary hypertension is caused by complex interaction between genetic, behavioral and environmental factors to which renal involvement, circulating factors and arteriosclerosis play critical role (Johnson R. et al, 2008).

Secondary hypertension accounts 5-10% of all cases, and is a direct result of underlying problem. Renal disease seems to be the most common cause of this type of hypertension because kidneys regulate the amount of the body fluid. Higher the blood volume higher the force that is needed to pump blood through the vessels. Also could be caused by endocrine diseases, obesity, sleep apnea which can damage the lining of vessels walls due to insufficient amount of oxygen, pregnancy, excessive consumption of certain drugs, herbal remedies, illegal drugs and alcohol abuse (Bakris G., 2013).

Classification, causes and examples of arterial hypertension are presented on the table below (Madhur M. et al, 2014).

| TYPES OF ARTERIAL HYPERTENSION | CAUSES |
|---|---|
| • **PRIMARY OR ESSENTIAL (90-95%)** | • Not clear identifiable causes – probably through genetic, behavioral and environmental interaction |
| • **SECONDARY (5-10%)** | • **Renal Diseases:**<br>-Due to Inflammation<br>-Due to renal artery stenosis due to atherosclerosis<br>-Diabetic Nephropathy<br>-Glomerular Disease or other Disorder<br>• **Endocrine Diseases:**<br>-Cushing Syndrome (hyperglucocorticoidism)<br>-Conn's Syndrome (hyperaldosteronism)<br>-Hyperthyroidism (excess of thyroid hormone)<br>-Hyperaldosteronism (excess of aldosterone)<br>-Pheochromocytoma ( excess of catecholamine)<br>-Acromegaly (excess of growth hormone)<br>- Pre-eclampsia (during pregnancy)<br>• **Vascular cause:**<br>- Arteriosclerosis.<br>- Coarctation of aorta (narrowed aorta)<br>• **Herbal Remedies and Drugs:**<br>-Saint John's Wort<br>-Licorice in excessive amounts<br>-Cyclosporine<br>-Erythropoietin<br>-NSAIDS<br>-Steroids<br>-Estrogens ( e.g. hormonal replacement therapy, combined oral contraceptive pills)<br>-Alcohol, cocaine, amphetamines, Ecstasy (NMDA derivatives)<br>-Pseudoephedrine<br>• **Other:**<br>-Cold and Asthma relief medicines, Antidepressants |

***Table 3: Classification of Arterial Hypertension (Madhur M. et al, 2014).***

Moreover there are some other risk factors that mentioned above, which contribute to development or worsening of already existence hypertension. Management of those factors, when it's possible is very important especially in patient of high risk like patients with cardiovascular or renal diseases, or diabetes.

We can divide the above risk factors into two groups, modifiable and non modifiable. On the table below there is a summary of hypertension risk factor (AHA, 2012, ESH-ESC, 2013, Kienreich K. et al, 2013).

| **Non Modifiable Risk Factors** |
|---|
| 1) **Age**: Vessels losses their flexibility by aging. |
| 2) **Ethnicity**: Hypertension is more severe and develops earlier in life in African-American. |
| 3) **Gender**: Men ≥ 55, Women ≥ 65 after menopause are in higher risk. |
| 4) **Family History**. |
| **Modifiable Risk Factors** |
| 1) **Obesity**: B.M.I.≥ 30 $Kg/m^2$ |
| 2) **Physical Inactivity**: Increases the chance of high blood pressure, heart and vessels disease, stroke and also makes easier to become obese. |
| 3) **Smoking**: Can damage blood vessels. |
| 4) **Too much salt on the diet**: Causes retention of fluid. |
| 5) **Too little vitamin D on the diet**: Has to do with suppression of renin-angiotensin-aldosterone system and improvements of endothelial dysfunction. |
| 6) **Too much alcohol**. |
| 7) **Stress**. |
| 8) **Unhealthy diet and lifestyle general**. |
| **Higher Risk Patient to Appear Cardiovascular Complications** |
| 1) **Central Obesity**: Men abdominal perimeter ≥ 102 cm, Women abdominal perimeter ≥ 88 cm. |
| 2) **Dyslipidemia**: TC> 4.9 mmol/L, LDL> 3.0 mmol/L, TG> 1.7 mmol/L, HDL: men< 1.0 mmol/L, women< 1.2 mmol/L. |
| 3) **Diabetes Mellitus**: Fasten Glucose≥ 7.0 mmol/L, Postprandial Glucose> 11.0 mmol/L. |
| 4) **Chronic kidney Disease**: eGFR< 30mL/min/1.73$m^2$**,** proteinuria> 300mg/24h |

***Table 4: Hypertension Risk Factors (AHA, 2012, ESH-ESC, 2013, Kienreich K. et al, 2013).***

## 2.5) DIAGNOSIS OF ARTERIAL HYPERTENSION

As we have mention, hypertension is an important risk factor for cardiovascular morbidity and mortality, especially in the elderly. So on time diagnosis and prevention is of great importance. The main aim of diagnosis and treatment of arterial hypertension is to increase quality of life of patients and also lower the risk of cardiovascular, cerebrovascular and renal complications (Lionakis N. et al., 2012).

To achieve the above goal there are some rules for correct measurement of blood pressure (ESH-ESC, 2013):

**1) Blood pressure should be measured in both arms using sphygmomanometer and stethoscope and the arm with the highest value used for readings.**

**2) Two separate sphygmomanometer measurement are required at least, at one – two minutes intervals. If it's necessary we can take the average of the measurements.**

**3) The Patient should be relaxed for 3-5 min before first measurement. Feet should be on the floor and the arm at heart level.**

**4) Blood pressure should be measured in both standing and sitting position for identification of orthostatic hypotension especially in elderly and diabetic patients.**

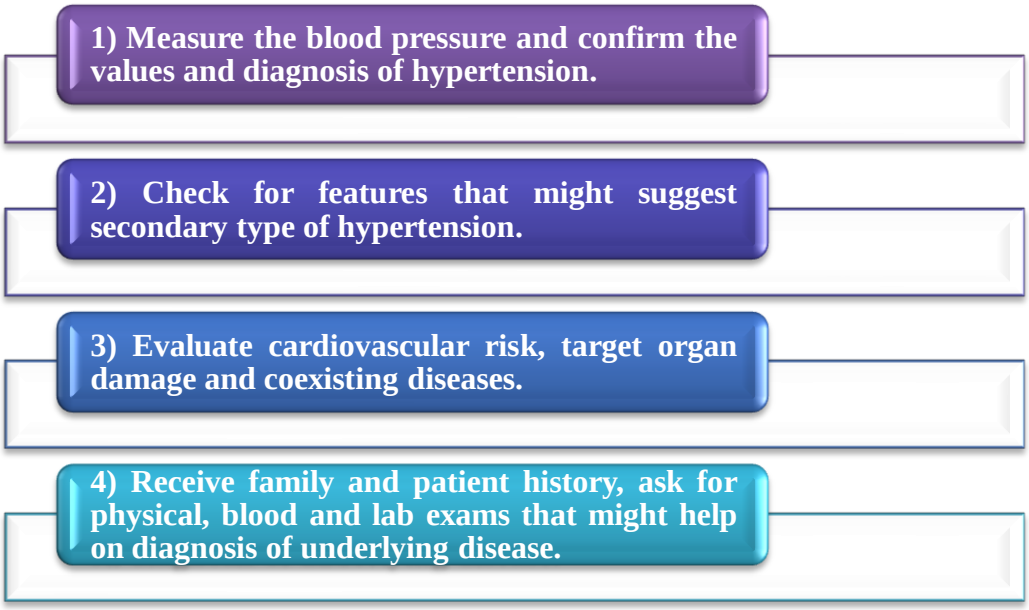
**5) An appropriate sized cuff should be used to ensure accuracy of measurements.**

**6) Caffeine, exercise and smoking should be avoided at least 30 minutes prior the measurement.**

**7) Blood pressure is measured using Korotkoff sounds. First sound is equal to systolic blood pressure and the last one is equal to diastolic blood pressure.**

**8) The diagnosis of hypertension should be based on at least 3 different measurements taken on 2 or more separate office visits depends on a case.**

For correct diagnosis, except of the above rules we should take in account some other parameters. For correct evaluation of patient condition we should (ESH-ESC, 2013):




***Schema 1: Steps for patient diagnostic evaluation (ESH-ESC, 2013).***

Also here, we should mention that there are some patients that can show specific types of hypertension known as: white coat hypertension and masked hypertension. Patients with white coat hypertension have elevated office blood pressure and normal out of office blood pressure, whereas those with masked hypertension show normal office blood pressure and elevated out of office blood pressure. Diagnosis is very important because it can help in prevention of target organ damage. These types of hypertension are more common in elderly than in children (Lionakis N. et al., 2012).

Nowadays, there is a possibility to use different types of blood pressure measurement like 24h-ambulatory and self monitoring blood pressure, which gives the opportunity for easier identification of patients with different subtypes of hypertension status. Moreover are useful for patients with diabetes mellitus, kidney diseases or suspected non-adherence. The prognostic value of these two types of measurements is equal for all ages and gender and we can say that is supplementary to office measurement (ESH-ESC, 2013, Hwang E. et al., 2007, Ogedegbe G. et al., 2010, McKay D. et al., 2007).

In addition some other patients may not respond to lifestyle modifications and antihypertensive treatment. This condition is known as resistant hypertension. Many factors may contribute and make blood pressure resistant to treatment such as: improper blood pressure measurement, excess sodium intake, inadequate diuretic therapy,

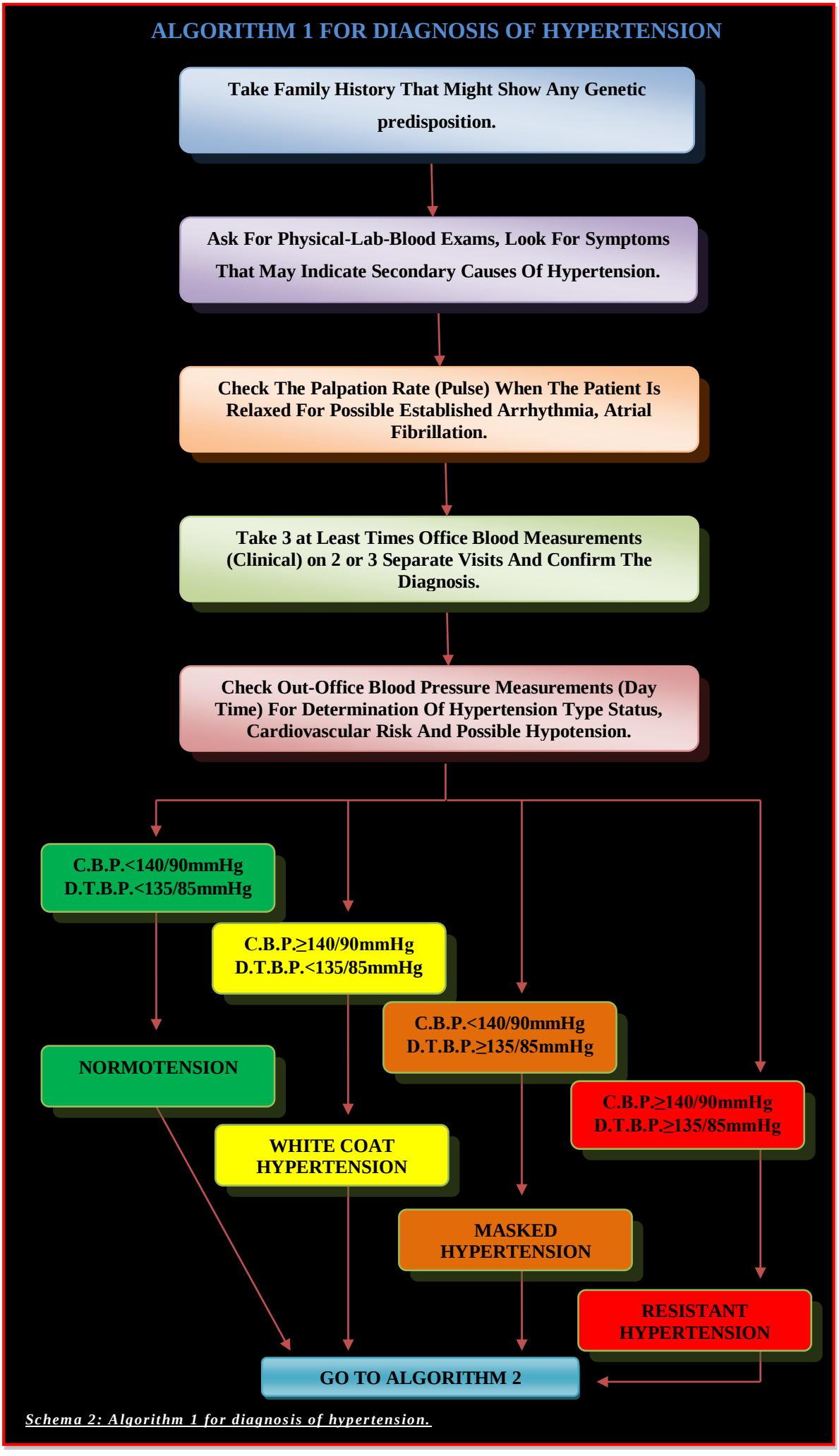
inadequate drug therapy (e.g. doses, actions and interactions), target organ damage, excess alcohol intake and other primary and secondary causes (Lionakis N. et al., 2012).

Family history can show any genetic predisposition and plays important role in diagnosis. In addition patients' clinical image and symptoms such polyuria, haematuria, polydipsia, chest pain, dyspnea, headache, etc, can also help in diagnosis. Moreover physical, blood and lab examination can help to identify secondary causes of hypertension and assess the presence of other diseases and the possibility of target organ damage. Some of the typical blood – lab exams that could be performed are presented on the table below (ESH-ESC, 2013, Noohi F. et al., 2012).

| TESTS | REASON OF PERFORMING |
|---|---|
| **1) Blood urea nitrogen, creatinine, urinalysis, electrolytes, uric acid, eGFR, proteinuria, ratio albumin/creatinine, kidney ultrasonography.** | Evaluation of Kidney Function – Impairment. |
| **2) Special tests for hormones of adrenal and thyroid glands, serum calcium, potassium, sodium.** | Evaluation of Endocrine System Function – Correlation with Endocrine Diseases. |
| **3) Hematocrit, Hemoglobin, Homocysteine and hs-CRP.** | Provide improved cardiovascular risk assessment. |
| **4) Fasting blood glucose, HDL, LDL, Triglycerides, Total cholesterol.** | Correlation with Diabetes, Dyslipidemia, Arteriosclerosis for evaluation of risk. |
| **5) Electocardiogram, Echocardiogram, Chest X-Ray, Magnetic Resonance Imaging** | Look for signs of heart enlargement or damage such as heart attack, arrhythmia, hypertrophy of heart walls, ischemia and atrial fibrillation. |
| **6) Doppler Ultrasound, Magnetic Resonance Angiography** | Check blood flow through the arteries – Detection of peripheral vascular disease and renal stenosis. |
| **7) Eye examination.** | Look for ocular damage like detection of hemorrhage and edema. |
| **8) Brain Computed Tomography, Magnetic Resonance Imaging.** | Performed in patients with neurologic symptoms, mental dysfunction. |

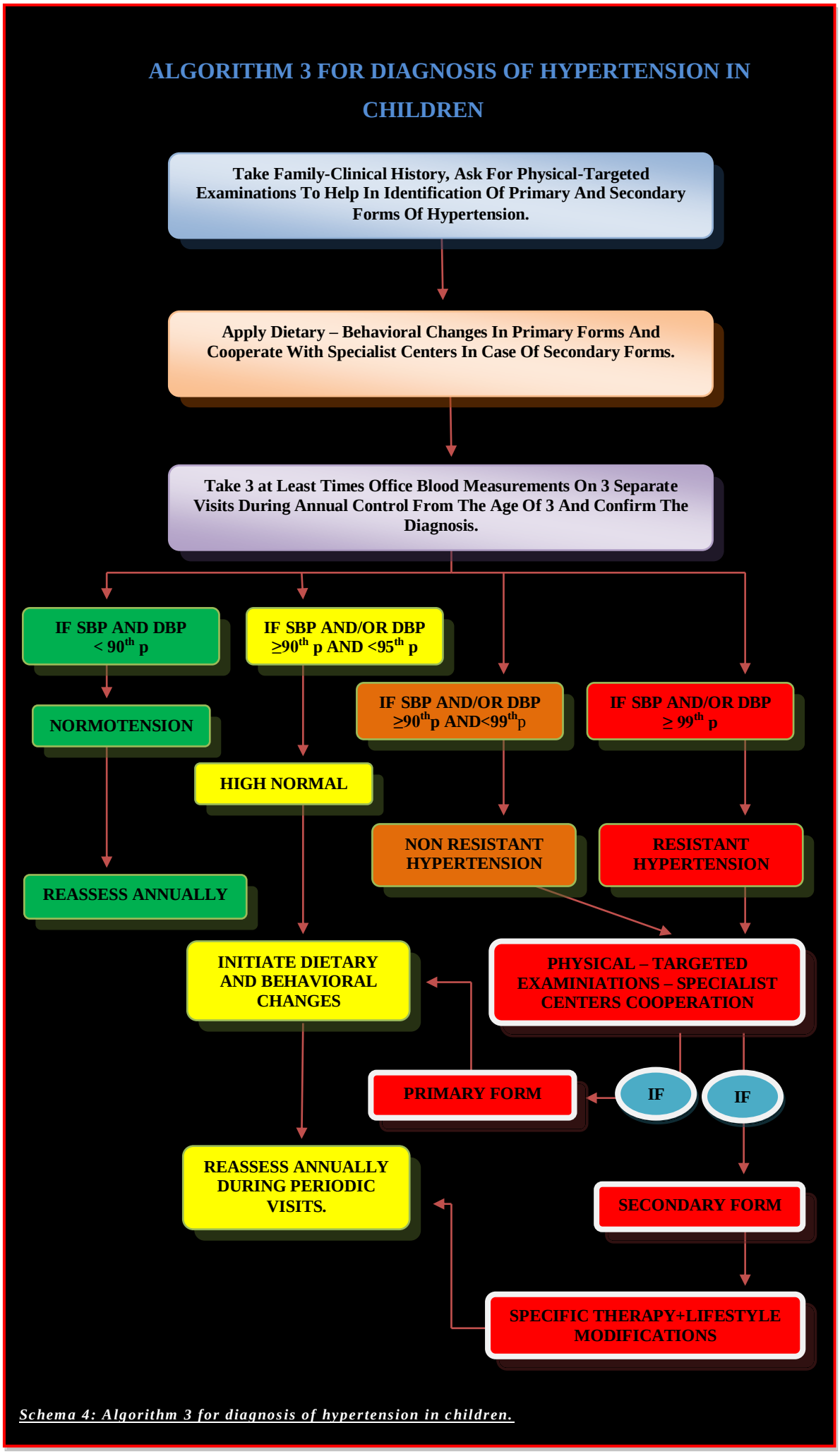
***Table 5: Typical Lab Tests (ESH-ESC, 2013, Noohi F. et al., 2012).***

Also below are presented three algorithms for diagnosis of hypertension in adults and children. For diagnosis in children we can follow the same methodology as in adults with the main difference in blood pressure values, which are based on statistical observations according to sex, age, height and body mass and are counted in percentiles. In addition obesity and heritability represents a strong risk factor for development of child hypertension (Spagnolo A. et al., 2013, ESH-ESC, 2013, Noohi F. et al., 2012, Walker R. and Whittlesea C., 2012, Ogedegbe G. et al., 2010).




***Schema 2: Algorithm 1 for diagnosis of hypertension.***


*Schema 3: Algorithm 2 for diagnosis of hypertension.*




*Schema 4: Algorithm 3 for diagnosis of hypertension in children.*

## 2.6) AIM OFARTERIAL HYPERTENSION TREATMENT

The major aim of treatment of arterial hypertension is to decrease cardio-cerebrovascular and renal morbidity and mortality. So becomes obvious that the aim should be to lower elevated arterial pressure to normotensive levels due to its association with the above risks. Moreover the attention that has to be given in finding secondary causes of hypertension should be inversely proportional to age and directly proportional to the severity of the hypertension. In addition special efforts should be given in management of coexistence diseases because may make the patient's more prone to side effects of the medication. Also the assessment of hypertension should consider blood pressure values, age, gender, clinical signs, family history, primary and secondary cause (Spagnolo A. et al., 2013).

Arterial hypertension treatment goals depend on a patient's blood pressure stage and coexistence of other medical conditions. Treatment goals for adults and children are presented on the tables below (Noohi F. et al., 2012):

| MEDICAL CONDITION | TREATMENT GOAL IN ADULTS |
|---|---|
| **1)** Hypertension with no target organ damage or other medical condition. | Blood pressure **< 140/90 mmHg**. |
| **2)** Patients with diabetes. | Blood pressure **< 130/80 mmHg**. |
| **3)** Patients with chronic kidney disease. | Blood pressure **< 130/80 mmHg**. |
| **4)** Hypertensive emergency. | Reduction of blood pressure by **25%** in first **30-60 minutes**. Reaching a goal of **160/100-110 mmHg** within **2-6 hours**. If clinically stable condition **further gradual reductions** within **24-48 hours**. |
| **5)** Patients with acute ischemic stroke. | Rapid reduction in blood pressure should be avoided and should control lowered. |
| **6)** Patients with aortic dissection. | Systolic blood pressure **< 100-110 mmHg** within 10-20min. |
| **7)** Patients who need thrombolytic therapy. | Blood pressure < 160/110mmHg before starting thrombolytic therapy. |
| **8)** Pregnant patients. | In case that blood pressure ≥**180/110 mmHg** should be treated immediately with intravenous drugs and is considered as hypertensive crisis. In all other cases **diastolic blood pressure should be >90mmHg** in order to protect fetus from distress, asphyxia and even death. |

***Table 6: Hypertension treatment goals in adults (Noohi F. et al., 2012).***

| MEDICAL CONDITION | TREATMENT GOAL IN CHILDREN |
|---|---|
| **1)** Children with no target organ damage or other medical condition. | Blood pressure<**90$^{th}$ percentile. (according to age, sex, height and body mass)** |
| **2)** Children without proteinuria. | Blood pressure<**75$^{th}$ percentile.** |
| **3)** Children with proteinuria. | Blood pressure<**50$^{th}$ percentile.** |

***Table 7: Hypertension treatment goals in children (Noohi F. et al., 2012).***

In order to achieve the above goals there is one key factor that plays an important role in successfully meeting and maintaining of hypertension treatment goals and it's the patient's compliance and good adherence to therapy. That's why single pill antihypertensive combinations started at low doses and increased gradually are recommended. However, in reality due to more complicated medical conditions multiple drug combinations are needed to reach the appropriate blood pressure target goals. Moreover good collaboration and patients' trustfulness to their self and to their health care provider play an important role in goal achievement. It's very important to treat the patients and not the number and as the Hippocrates said **'first, do no harm '(**Lionakis N. et al., 2012).

Moreover another important factor in patients that have start antihypertensive therapy is the follow-up. Generally for patients that they just start drug therapy they should see a doctor at least once or twice a month until the blood pressure goal is reached to ensure that blood pressure is improving. More frequent visits will be necessary for patients with stage 2 hypertension or with other complicated conditions. Once or twice a year the patients should do laboratory tests (electrolytes, lipids, glucose, creatinine, hormones) in order to check the general medical condition such as health of kidney-endocrine system, dyslipidemia, etc and to ensure that there are no further complications due to untreated hypertension or due to pharmacotherapy interactions. After the blood pressure is reached the patient should see the doctor every three to six months depending on coexistence of other diseases.

The blood pressure target goal should be achieved within 6 months otherwise patient care needs different approach with different pharmacotherapy combinations which should not exclude in any condition lifestyle changes (ESH-ESC, 2013).

## 2.7) MANAGEMENT OF ARTERIAL HYPERTENSION

### 2.7.1) Lifestyle Modifications

Management of arterial hypertension could be achieved by lifestyle modifications or pharmacotherapy or combination of both. Also another important factor for prevention and treatment of hypertension is the patient compliance. Lifestyle modifications play an important role in hypertension therapy but should not delay the onset of pharmacotherapy in high risk patients. Lifestyle modifications could help to (ESH-ESC, 2013, Ziv A. et al, 2013):

| BENEFITS FROM LIFESTYLE MODIFICATIONS | |
|---|---|
| 1) | **Reduce the blood pressure in patients who are under antihypertensive medication therapy.** |
| 2) | **Allow dose reduction of antihypertensive therapy.** |
| 3) | **Control and more effective prevention of other cardio-vascular risks.** |
| 4) | **Enhance antihypertensive drug efficacy.** |
| 5) | **Delay or prevent the appearance of hypertension in non-hypertensive patients.** |
| 6) | **Delay or prevent the onset of pharmacotherapy in hypertensive patient's stage 1.** |
| 7) | **Reduce the cost of pharmacotherapy.** |
| 8) | **Improvement of lipid and blood glucose profile.** |
| 9) | **Provide general better therapeutic control.** |

***Table 8: Benefits From Lifestyle Modifications (ESH-ESC, 2013, Ziv A. et al, 2013).***

Effects of lifestyle modifications are similar to single drug therapy. Combinations of two or more lifestyle modifications can achieve even better results.

Lifestyle modifications and DASH (Dietary Approaches to Stop Hypertension) dietary plan combination that have shown their effectiveness on lowering the blood pressure include (Hinderliter A. et al, 2011, ESH-ESC, 2013, Hedayati S. et al, 2011).

| LIFESTYLE MODIFICATIONS | |
|---|---|
| 1) | **Reduction of dietary sodium intake up to 5-6g/day.** |
| 2) | **Reduction of alcohol consumption to 20-30g of ethanol/day for men and to 10-20g ethanol/day for women.** |
| 3) | **High consumption of fruits, vegetables and products with low fat content.** |
| 4) | **Reduction of overweight whenever is present to B.M.I $\leq$ 25Kg/m$^2$ and size of abdominal perimeter in men <102cm and in women <88cm.** |
| 5) | **Increase in physical activity at least 30min of aerobic exercise 5 to 7 days/week.** |
| 6) | **Quit smoking.** |
| 7) | **Stress management through relaxation techniques in patients to whom stress could be a contributing factor for their hypertension.** |

***Table 9: Lifestyle Modifications (Hinderliter A. et al, 2011, ESH-ESC, 2013, Hedayati S. et al, 2011).***

Long – term lifestyle modifications are difficult to maintain and may decrease the patient compliance. Moreover pharmacotherapy treatment will be needed in specific cases. The above lifestyle modifications are recommended as prevention in non hypertensive patients and as initial therapy in patients with stage 1 hypertension for the first 3 – 6 months or up to 12 months if no other risk factors are present. Other patients with stage 2 hypertension, or stage 1 and organ damage or other cardiovascular risks or in case of diabetes and chronic kidney disease and when the patient don't respond to lifestyle changes and they don't reach the target blood pressure goal should be treated by pharmacological therapy and lifestyle modification is recommended as adjunctive to this therapy (Frisoli T.et al., 2011, University of Maryland, 2012)

Major attention should be paid to heart, arteries, kidney, nervous system and retina of the patients especially in elderly.

### 2.7.2) Pharmacotherapy Treatment

Lifestyle modifications can be very effective but in real life patients usually need a combination of them with pharmacological therapy. Very often they need more than one type of anti-hypertensive medication or combination of more in order to achieve their blood pressure target goal.

Combination of lifestyle modifications and pharmacological medication may allow reduction of drugs doses, better therapeutic control, more effective treatment and prevention of other cardiovascular risks factors (Wald D. et al, 2009).

Classifications and characteristics of drugs that currently used for treatment of hypertension are presented on the tables below (ESH-ESC, 2013, Walker R. and Whittlesea C., 2012):

| FIRST LINE ANTIHYPERTENSIVE AGENTS |
|---|
| **1) Antagonists of β-adrenoreceptors (Beta-blockers).** |
| **2) Diuretics (mainly thiazide, loop and potassium sparing).** |
| **3) Calcium channel blockers (dihydropyridines – non dihydropyridines).** |
| **4) Angiotensin cconverting enzyme inhibitors (ACEis).** |
| **5) Angiotensin II receptors blockers (Sartans).** |
| **6) Direct inhibitors of renin (Aliskiren-New in therapy, lack of experience).** |
| **OTHER ANTIHYPERTENSIVE AGENTS** |
| **1) $\alpha_1$-adrenoreceptors-blockers, centrally acting vasodilators and direct acting vasodilators.** |

***Table 10: Classification of Antihypertensive Agents (ESH-ESC, 2013, Walker R. and Whittlesea C., 2012).***

| ANTIHYPERTENSIVE AGENTS - GROUPS | INDICATIONS | MAJOR SIDE EFFECTS | CONTRA-INDICATIONS |
|---|---|---|---|
| β-Blockers. | Post-myocardial infarction, angina, heart failure, atrial fibrillation, pregnancy. | Bradycardia, hypotension, fatigue, drowsiness, weight gain, glucose metabolism disturbances, arrhythmia, coldness of extremities. | COPD, asthma, atrioventricular block, combinations with non-dihydropyridines due to risk of bradycardia, heart failure, AV block. |
| Thiazide Diuretics. | Systolic hypertension in elderly, black patients, heart failure. | Hypokalemia, hyperuricemia, hyperglycemia, Hypercalcemia, orthostatic hypotension. | Pregnancy, gout, hypercalcαemia, Renal impairment, caution with b-blocker use due to metabolic effects. |
| Loop Diuretics. | Renal impairment, heart failure, hypertensive crisis, edematous states. | Hypokalemia, hyperuricemia, hyperglycemia, hyperlipidaemia, ototoxicity. | Pregnancy, gout. |
| Aldosterone antagonists. | Heart failure, post-myocardial infarction, primary-secondary hyperaldosteronism, resistant hypertension. | Hyperkalemia, gynecomastia. | Hyperkalemia, caution with use with ACEis, Sartans and other potassium sparing diuretics. |
| ACEis. | Heart failure, left ventricular dysfunction, post-myocardial infarction, left ventricular hypertrophy, proteinuria, diabetic nephropathy. | Dry cough, hyperkalaemia, angioedema, renal failure, rash. | Pregnancy, combination with sartans and direct renin inhibitors in renal impairment and diabetes. |
| $AT_1$-Receptor Antagonists (Sartans). | Same as ACEis, In case of ACEis intolerance. | Same as ACEis except dry cough. | Same as ACEis. |
| Direct Renin Inhibitors (Aliskiren). | Hypertension, new in therapy, lack of experience. | Same as ACEis, diarrhea. | Same as ACEis. |
| CCBs (dihydropyridines). | Systolic hypertension in elderly, black patients, angina, pregnancy, metabolic syndrome. | Postural hypotension, edema around ankles, headache, flushing. | |
| CCBs (Non Dihydropyridines). | Angina, atrial fibrillation, pregnancy, ischemic disease of lower limb, ischemic heart disease. | Edema around ankles, hypotension, headache, dizziness, constipation, bradycardia. | Heart failure, AV block and bradycardia due to negative inotropic – chronotropic effect, combination with β-blockers. |
| α-Blockers. | Benign prostatic hyperthrophy, pheochromocytoma. | Tachycardia, edema around ankles, sexual dysfunction, orthostatic hypotension, vertigo, diarrhea. | Syncope in elderly – start with low doses, urinary incontinence. |
| Centrally Acting. | Pregnancy (only methyldopa), resistant hypertension. | Bradycardia, depression, postural hypotension, rebound phenomenon. | |

*Table 11: Characteristics of Antihypertensive Agents (ESH-ESC, 2013, Walker R. and Whittlesea C., 2012).*

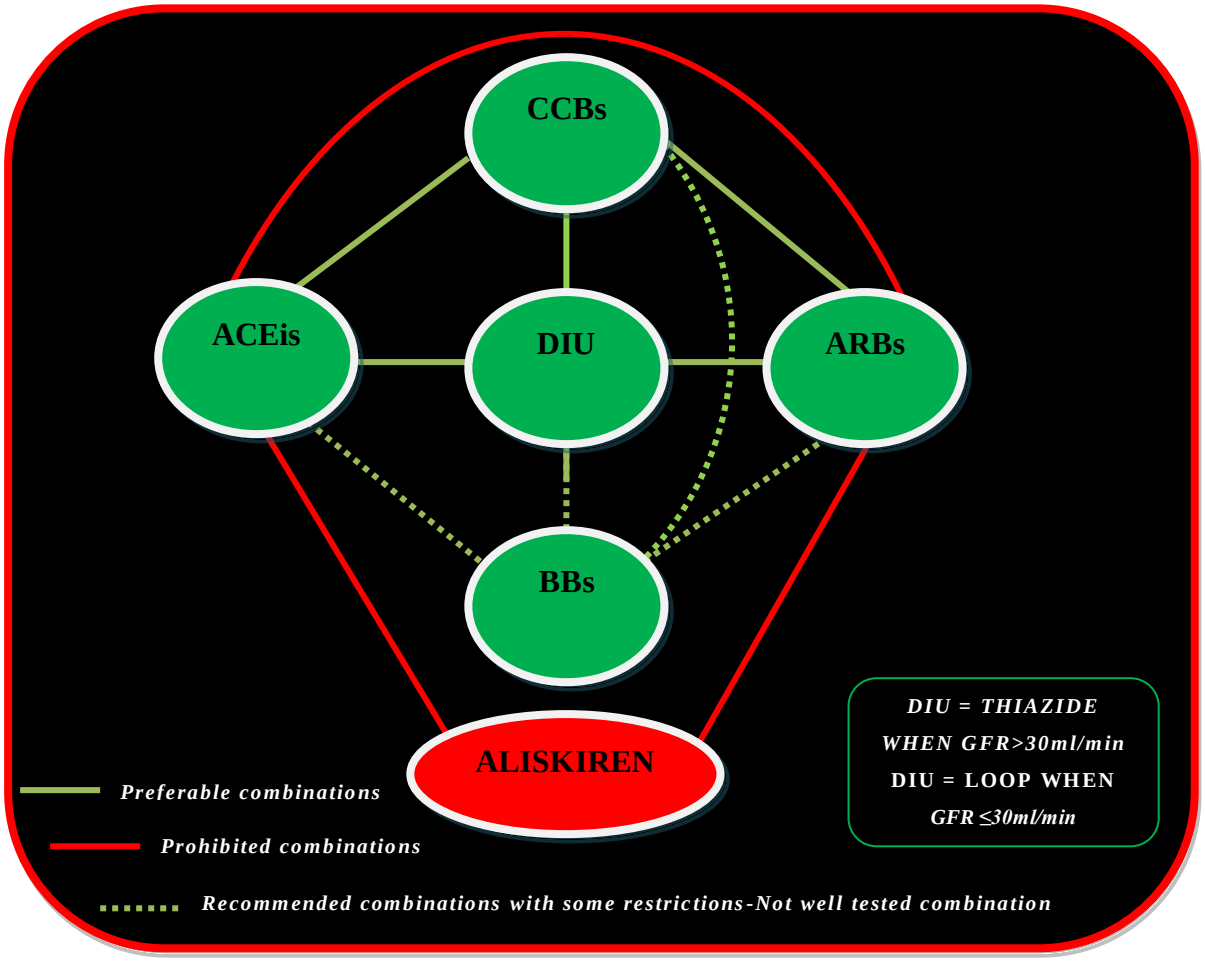
For better pharmacological treatment outcomes, drugs should be chosen on the basis of efficacy, safety, convenience to the patient and cost. For assessment of efficacy evidence from large scale clinical trials should be used. Moreover recognition of adverse effects is another important factor because is associated with patient adherence and effectiveness of treatment. In addition the use of regimens (FDC) that is more convenient to the patient like once-daily regimens and also cost of treatment are other important factors because could help to improve the patient compliance (Gupta A. et al, 2010).

There are some meta-analyses that have shown that there are no important clinical differences between different antihypertensive groups. The β-blockers (**BBs**), calcium channel blockers (**CCBs**), angiotensin converting enzyme inhibitors (**ACEis**), angiotensin II receptor blockers (**ARBs**) and diuretics mainly thiazide (**DIU**) are all appropriate for starting and maintenance of antihypertensive therapy as monotherapy or in combination despite the age and gender. In addition one meta-analysis suggests that low dose diuretics are the best choice treatment on the beginning, in patients with uncomplicated hypertension. Also another study has shown that combination therapy is more effective than monotherapy (Psaty B. et al., 2003, ESH-ESC, 2013, BPLT Trialist's Collaboration, 2008).

There is no clear evidence to support recommendations for usage of particular antihypertensive drug classes. However there are some preferable combinations of drugs that are recommended according to clinical trials (e.g. **ADVANCE, HYVET, CAPPP, SCOPE, LIFE, FEVER, ELSA, ASCOT, ACCOMPLISH, SHEP, STOP, ALLHAT, ONTARGET, ALTITUDE** etc) that have studied the health outcomes from combination of two drugs to another combination or to placebo on specific groups of patients. In addition some important outcomes were that combination of **ACEis/CCBs** was superior to **ACEis/DIU** and both were superior to **BBs/DIU** combination from the point of reduction in cardiovascular events. Moreover there was association with the last combination **BBs/DIU** of thiazide type, with the new onset of diabetes. Also the combination of drugs that act on renin-angiotensin-aldosterone system should be avoided because the total benefit of drugs action is not additive and there is also incensed risk of renal impairment (ESH-ESC, 2013, Jong G-P. et al, 2009, The ONTARGET Investigators, 2008).

Summarizing the recommended and prohibited combinations is presented below (schema 5). However combinations of other antihypertensive agents like β-blockers and other groups could be possible in case that patients' condition indicates the use of these drugs like β-blockers in coronary heart disease. Below are presented two algorithms for

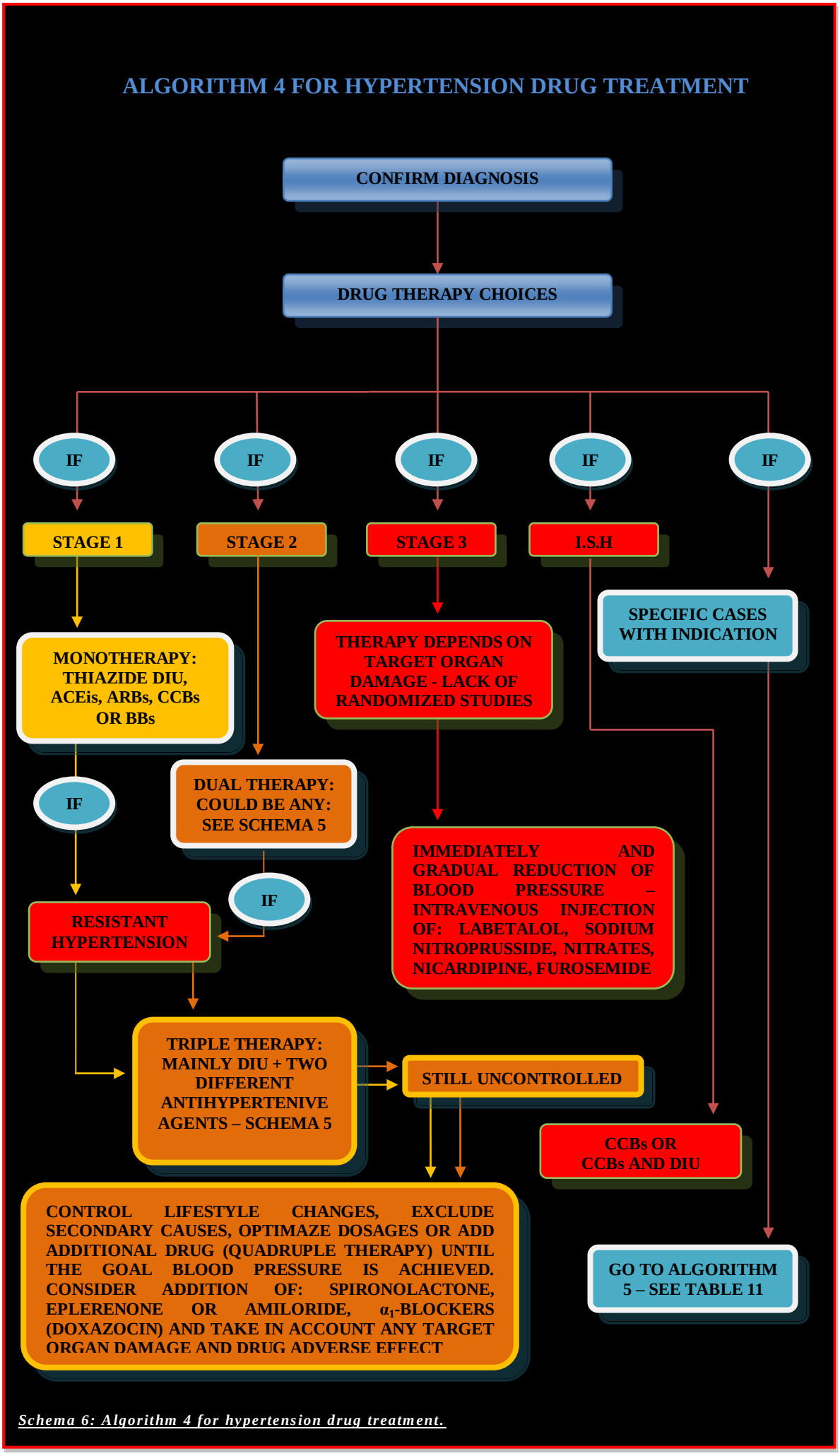
hypertension drug treatment (ESH-ESC, 2013, Noohi F. et al., 2012, Tashko G. and Gabbay R., 2010, Levin A et al, 2008, Varon J. and Marik P., 2003, Pimenta E. and Oparil S., 2008, Parving H-H. et al, 2012).



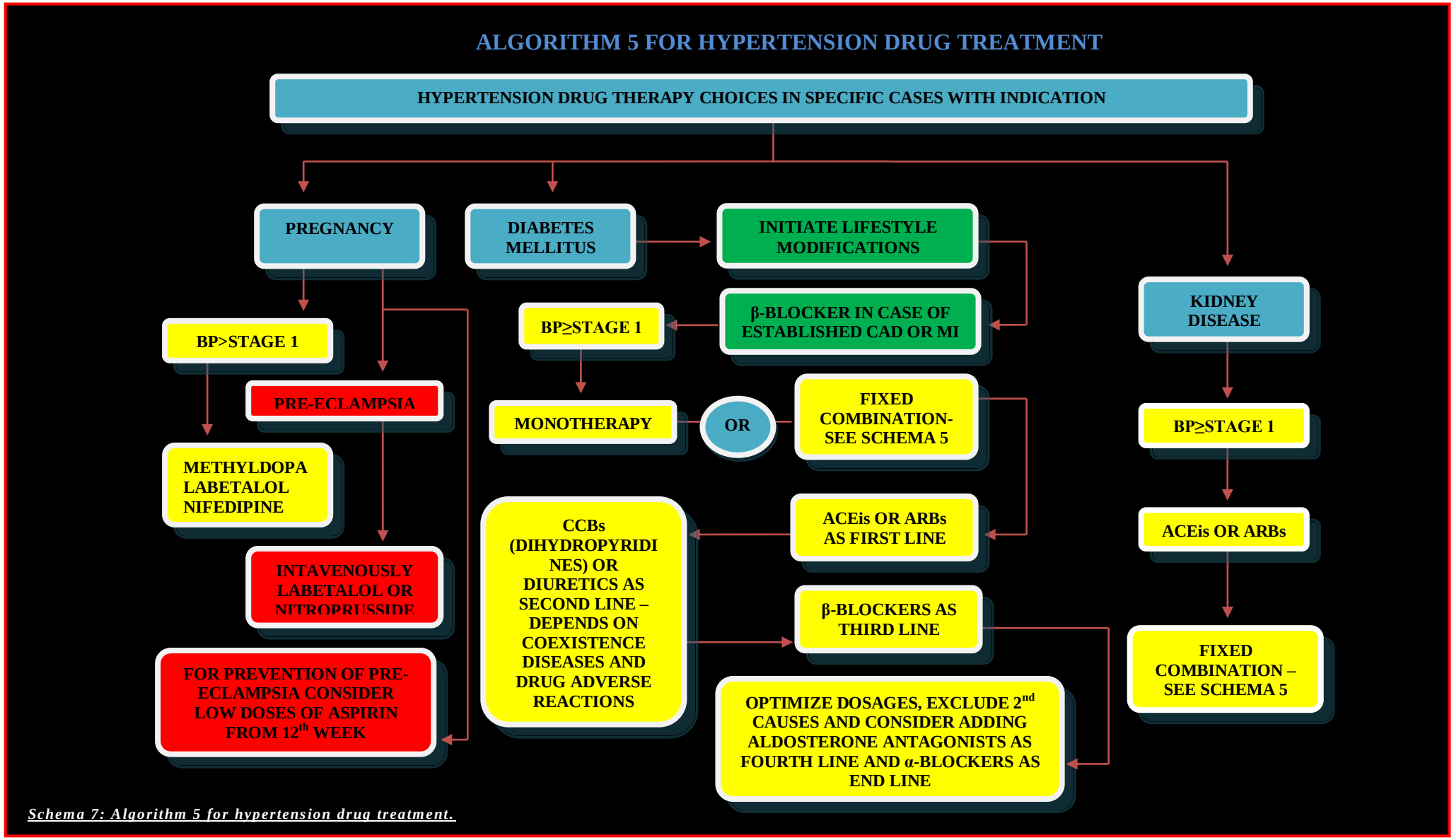

***Schema5: Recommended and Prohibited Combinations of Antihypertensive Agents.***

Another important factor that we should mention is that treatment of dyslipidemia, and therapy of hyperglycemia could be beneficial in hypertensive patients and particularly in those with diabetes and metabolic syndrome. The **ASCOT-LLA** study has shown that addition of statins in antihypertensive therapy reduces the cardiovascular events and combination of statins with amlodipine is more beneficial than statins with atenolol.

Summarizing, hypertensive patients in high cardiovascular risk (goal: LDL<3.0 mmol/L) and patients with coronary heart disease (goal: LDL<1.8mmol/L) should take statins in order to control dyslipidemia and reduce the cardiovascular events. Moreover the goal in therapy of hyperglycemia should be: Glycated hemoglobin HbA1c<7.0% for young hypertensive – diabetic patients and HbA1c<7.5-8.0 % for elderly hypertensive-diabetic patients (ESH-ESC, 2013, Sever P. et al., 2011).




*Schema 6: Algorithm 4 for hypertension drug treatment.*




***Schema 7: Algorithm 5 for hypertension drug treatment.***

# 3. THEORETICAL PART – DRUG RELATED PROBLEMS

## 3.1) DEFINITIONS

Drugs are therapeutic tool that are used to treat, prevent and diagnose diseases, signs or symptoms. But improper use of drugs could have opposite undesired results, like can lead to serious adverse events, decreasing by this way the compliance of the patients and be the cause of patients' morbidity and mortality (Egberts and Van Den Bermt, 2007).

A drug related problem according to Pharmaceutical Care Network Europe (PCNE) "is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" (PCNE, 2010).

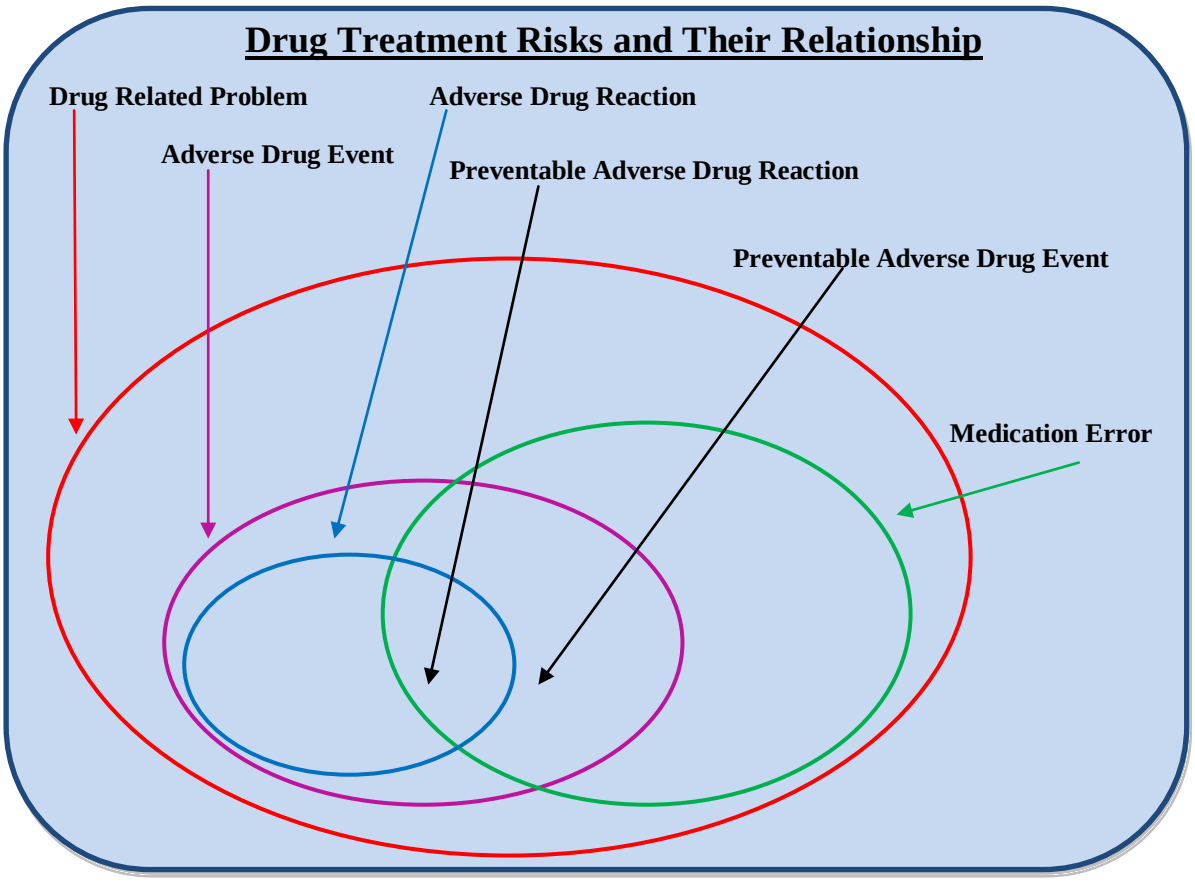
Drug related problems include medications errors and adverse drug reactions. Medication errors include mistakes that occurs in the process of prescribing, transcribing, dispensing or administering of a drug, whether adverse drug reactions according to World Health Organization (WHO) include any response to a drug which is 'noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, therapy of disease or for the modification of physiological function'. Furthermore, adverse drug reactions can be defined as an injury or as a harmful-unpleasant reaction occurring at therapeutic doses by the interaction of the drug itself with the human biosystem and needs specific treatment or alteration of dosage regimen or withdrawal of the product (Bemt V. et al, 2000, Egberts and Bemt V., 2007).

The terms "adverse reaction" and "adverse effect" are synonyms, with the main difference that the first one is seen from the point of view of the patient, whereas the second one is seen form the point of view of the drug. In addition the term "adverse effect" includes all unwanted effects such as "toxic effect" or "side effect". A "toxic effect" is always dose-related, not common at normal doses (unless if there is target organ damage especially on eliminating organs liver-kidney) and occurs through the same mechanism as an exaggeration of the desired therapeutic effect. On the other hand "side effect" can be dose-related or not and occurs through different mechanism which is not associated with the desired therapeutic effect and pharmacological action of the drug for which the drug is being used. According to American Society of Health-System Pharmacists (ASHP) a side effect is defined as an expected well-known reaction with a predictable frequency, resulting in little or no change in patient management. These effects could be beneficial rather than harmful in specific cases like anticholinergic side effect of tricyclic

antidepressant could be beneficial in depressed patients with irritable bowel syndrome. Also an allergic reaction (an immunologic hypersensitivity, occurring as the result of unusual sensitivity to a drug) and an idiosyncratic reaction (an abnormal susceptibility to a drug that is peculiar to the individual) are also considered as adverse drug reactions which are caused by the action of the drug.

Moreover an "adverse drug event (ADE)" is defined as any harmful event occurring during drug therapy from the use of drug and resulting either from appropriate care (non preventable ADEs) or from medication errors (preventable ADEs). In addition according to Food and drug Administration adverse event is that in which "the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage" (ASHP, 1995, Nebeker J. et al, 2004).

Identifying risk factors that contribute to the development of adverse drug reactions, it would be helpful in the prevention of these reactions. The relationship of the above key terms is presented schematically below.




***Schema8: Schematically Relationship of Key Terms.***

## 3.2) ADVERSE DRUG REACTION AND DRUG RELATED PROBLEMS CLASSIFICATION

Adverse drug reactions are classified into six types. Classification of adverse drug reactions, types, features and examples are presented on the tables below (Edwards R. and Aronson J., 2000).

| ADVERSE DRUG REACTION CLASSIFICATION |
|---|
| **1) Dose-depended – Type A (Augmented)** |
| **2) Non-dose- depended – Type B (Bizarre)** |
| **3) Dose and Time - depended – Type C (Chronic)** |
| **4) Time- depended – Type D (Delayed)** |
| **5) Withdrawal Reactions – Type E (End of use) and** |
| **6) Failure of therapy – Type F (Failure)** |

***Table 12: Adverse Drug Reaction Classification (Edwards R. and Aronson J., 2000).***

| TYPE OF REACTION | FEATURES | EXAMPLES |
|---|---|---|
| **1) Type A** | Commonest type, 80% of all adverse effects, predictable, related to pharmacological action of the drug, low mortality. | Toxic and side effects like digoxin toxicity, hemorrhage due to oral anticoagulants, hypoglycemia of oral hypoglycemic drugs, bone marrow depression due to cytotoxic agents, anticholinergic effects of tricyclic antidepressant, etc. |
| **2) Type B** | Uncommon, unpredictable, no relation with the dose-response and pharmacological action of the drug, high mortality. | 1) Immunological reactions:<br>Type I: Anaphylactic or immediate hypersensitivity.<br>Type II: Cytotoxic reactions.<br>Type III: Reaction of immune complexes.<br>Type IV: Lymphocyte mediated.<br>2) Idiosyncratic reactions: usually genetically determined. |
| **3) Type C** | Uncommon, relate to the cumulative dose, tolerance development. | Hypothalamic - pituitary adrenal axis suppression by corticosteroids. |
| **4) Type D** | Uncommon, occurs some time after the use of the drug. | Teratogenesis, carcinogenesis. |
| **5) Type E** | Uncommon, occurs soon after withdrawal of the drug. | Withdrawal syndrome from opiates and β-blockers. |
| **6) Type F** | Common, dose related, often caused by drug interactions. | Inadequate dosage of an oral contraceptive particularly when used with specific enzyme inducers. |

***Table 13: Adverse Drug Reaction Features and Examples (Edwards R. and Aronson J., 2000).***

On the above classification we should add some explanations on the terms tolerance and withdrawal syndrome (Anand K. et al., 2010).

Type C (chronic) reaction is related to the long length therapy and to totally administered dose which can lead to tolerance of organism to drug effects and to chronic damage of organism like chronic treatment with antipsychotic drugs can lead to neurological complications like Parkinson's syndrome or corticosteroids can lead to osteoporosis etc. The term tolerance means a gradual decrease of drug effect and in order to achieve the desired response it's necessary to increase the dose of the drug. There are two types of tolerance:

a) Pharmacokinetic tolerance which is related to enzyme induction.

b) Pharmacodynamic tolerance which is related to adaptive changes in tissues.

Moreover type E (end of use) reaction is characterized by withdrawal syndrome as a result of adaptive changes in the organism. Symptoms of this syndrome have generally the opposite character as comparing to the effects of the drug. There are two types of withdrawal syndrome:

a) Abstinence syndrome which is characterized by occurrence of new symptoms.
b) Rebound phenomenon which is characterized by recurrence of symptoms in more serious form for which the drug was administered.

A mechanism that could explain the above changes can be the increase ("up regulation") or decrease ("down regulation") in number of receptors following the administration of antagonists and agonists agents (Anand K. et al., 2010).

The above classification of adverse drug reaction is based on properties of the drug (its known pharmacology and dose dependence of its effects). However another three dimensional classification system (DoTS) was proposed which takes in account the properties of the reaction (time of its appearance and its severity), dose relatedness, timing and patient susceptibility (genetic, pathological, biological differences).

In preliminary study in hospitalized patients the DoTS classification system allowed the evaluation of the types of ADRs and this system would improve drug development and patient care (Aronson J-K. and Ferner R-E., 2003).

On the other hand drug related problems according to Pharmaceutical Care Network Europe (PCNE) classification (V6.2)are classified into three groups from the point of problems, causes (often referred as medication errors) and interventions separating by this

way the real problem that affects or is going to affect the outcome from its cause. Causes and problems together will lead to one or more interventions to correct the cause of the problem. In addition for evaluation purposes a last group (outcome) has been added in order to indicate if the problem has been solved. Classification of drug related problems is presented on the table below (Mill F., 2005, PCNE, 2010).

| **DRUG RELATED RPOBLEM CLASSIFICATION** | | | |
|---|---|---|---|
| **1) CAUSES** | **2) PROBLEMS** | **3) INTERVENTION** | **4) OUTCOME** |
| **Definition:** The action or lack of action that leads to occurrence of a problem. Maybe more than one cause responsible for a problem. | **Definition:** Expected or unexpected event or circumstance that is or might be wrong in therapy with drugs. | **Definition:** The actions that can lead to correction of the problem cause/s. One problem can lead to more interventions. | **Definition:** The interventions final result which is used only for evaluation/indication purposes. |
| **EXAMPLES** | | | |
| **a) Drug selection:** Inappropriate drug, combination of drugs, or drugs and foods, polypharmacy.<br>**b) Drug form.**<br>**c) Dosage schedule selection:** drug dose too low, too high, dosage regimen too or not frequent at all, pharmacokinetic problem or disease improvement requires dose adjustment.<br>**d) Treatment duration:** too long, too short.<br>**e) Drug use or administration process:** timing, dosing intervals, over or underused, wrong or drug not taken at all, drug abused.<br>**f) Logistics errors of the prescribing and dispensing process.**<br>**g) Patient behavior and personality:** forgets to take drug, uses unnecessary drug, takes food that interacts, inappropriately drug storage.<br>**h) Other.** | **a) Treatment effectiveness:** lack of effect, not optimal effect, wrong effect, untreated indication.<br>**b) Adverse Reactions:** non allergic, allergic, toxic adverse drug events.<br>**c) Treatment costs:** unnecessary expensive, unnecessary pharmacotherapy.<br>**d) Other:** patient dissatisfaction despite optimal clinical and economical outcome, unclear complaint. | **a) No intervention.**<br>**b) At prescriber level:** Prescriber asked for information and proposed an intervention.<br>**c) At patient level:** Provided written information, medication counseling to the patient or to relatives/caregivers.<br>**d) At drug level:** directly changing drug, dosage, formulation, drug use instructions.<br>**e) Other.** | **a) Unknown outcome.**<br>**b) Problem totally solved.**<br>**c) Problem partially solved.**<br>**d) Problem not solved:** lack of cooperation of patient or/and prescriber, not effective intervention, no need or possibility to solve the problem. |

***Table 14: Drug Related Problem Classification (Mill F., 2005, PCNE, 2010).***

## 3.3) ANTIHYPERTENSIVE DRUG-DRUG INTERACTIONS

An antihypertensive drug-drug interaction is showed on the table below (Helms R. et al., 2006):

| ANTIHYPERTENSIVE DRUG INTERACTIONS | | | |
|---|---|---|---|
| **Group of Drug** | **↑ Antihypertensive Effect** | **↓ Antihypertensive Effect** | **Other Drug Interactions** |
| **Loop Diuretics** | ACEIs, ethanol, antipsychotics, β-blockers, CCBs, antiadrenergic agents. | Aspirin/NSAIDs, bile acid resins, sympathomimetics, anticonvulsants. | ACEis ↑ renal insufficiency<br>Carbenoxolone ↓ K<br>Corticosteroids ↓ K<br>↑ Digoxin toxicity from hypokalemia<br>Fibric acids ↓ albumin binding<br>↑ Lithium toxicity<br>SSRIs: severe hyponatremia. |
| **Thiazide Diuretics** | | Aspirin/NSAIDs, bile acid resins, sympathomimetics. | Calcium: milk alkali syndrome<br>Carbenoxolone ↓ K<br>↑ Digoxin toxicity from hypokalemia<br>↑ Lithium toxicity<br>↓ Hypoglycemic agent effects from antagonism. |
| **K - Sparing Diuretics** | Antipsychotics, ethanol, nitrates. | Aspirin/NSAIDs, sympathomimetics. | ↑ Amantadine levels with triamterene<br>↑ Digoxin levels with spironolactone<br>Acute renal failure with indomethacin and triamterene<br>↑ Hyperkalemia with ACEis/ARBs<br>↑ Quinidine toxicity with amiloride. |
| **β-Blockers** | α-blockers, antipsychotics, CCBs, ethanol, antiadrenergic agents, $H_2$ blockers, SSRIs, antiarrhythmics, quinolones (↑ β-blocker). | Aspirin/NSAIDs, antacids, sympathomimetics<br>↓ β-blocker levels: Barbiturate, Carbamazepine, Rifampin, Rifabutin, Sulfasalazine. | $\alpha_1$-blockers and $\alpha_2$-agonists ↑ rebound hypertension,<br>Amiodarone: bradycardia cardiac arrest<br>Contrast media (intravenous): ↑ anaphylaxis<br>↓ Diazepam metabolism<br>Digoxin: bradycardia, ↓digoxin levels with carvedilol<br>Ergot alkaloids: ↑ vasoconstriction<br>Hypoglycemic agents: mask hypoglycemic symptoms<br>↓ Quinidine effect with hepatic metabolized β-blockers<br>Sympathomimetics: ↑ blood pressure, ↑ terbutaline levels, ↑ theophylline levels. |
| **ACEis / ARBs** | Antipsychotics, β-blockers, diuretics, ergot alkaloids. | Aspirin/NSAIDs, sympathomimetics, antacids (captopril). | Azathioprine toxicity<br>↑ Lithium levels, hyperkalemia with K-sparing diuretics, antacids ↓absorption. |
| **Vasodialators** | Antipsychotics, β-blockers, diuretics, ethanol. | Aspirin/NSAIDs, sympathomimetics. | |

| | | | |
|---|---|---|---|
| **Peripheral Adrenergic Blockers** | Diuretics, ethanol. | Aspirin/NSAIDs, antipsychotics, MAOIs, sympathomimetics. | |
| **Ca - Channel Blockers** | Antipsychotics, β-blockers, diuretics, ethanol (postural hypotension)<br>↑ Calcium blocker levels:<br>$\alpha_1$-blockers, Cimetidine, Erythromycin, Grapefruit juice (↑ Dihydropyridines), Proton pump inhibitors, Quinidine, Valproic acid. | Aspirin/NSAIDs, sympathomimetics ↓ Calcium blocker levels:<br>Carbamazepine, Barbiturates, Rifampin, Rifabutin. | β-blockers: cardiac depression<br>↑ Carbamazepine levels with diltiazem or verapamil<br>↑ Cyclosporine levels<br>↑ Digoxin levels except Dihydropirydines<br>↑ Ethanol<br>↑ Lithium neurotoxicity<br>↑ Phenytoin levels with nifedipine<br>↑ Quinidine levels with nifedipine<br>↑ Quinidine bradycardia and hypotension with verapamil<br>↑ TCA levels<br>↑ Theophylline levels with verapamil<br>↑ HMG Co-A reductase inhibitor levels with diltiazem and verapamil. |
| **$\alpha_1$-Blockers** | ACE inhibitors, antipsychotics, β-blockers, calcium blockers, diuretics, ethanol. | Aspirin/NSAIDs, sympathomimetics. | ↑ Orthostatic hypotension with diuretics. |
| **$\alpha_2$- Agonists** | Antipsychotics, diuretics, ethanol, nitrates. | Aspirin/NSAIDs, MAOIs, TCAs, trazodone, phenothiazines, sympathomimetics. | ↑ Cyclosporine levels with clonidine transdermal patches<br>↓ Symptoms of hypoglycemia with clonidine<br>↑ Rebound hypertension with β-blockers<br>↑ Bradycardia with β-blockers<br>↑ CNS depression with all CNS depressants<br>↑ Lithium levels with methyldopa. |

***Table 15: Antihypertensive Drug Interactions (Helms R. et al., 2006).***

## 3.4) DRUG RELATED PROBLEMS TO ANTIHYPERTENSIVES AGENTS

Hypertension is one of the most common and most important risk factor for cardiovascular and kidney disease. Hypertension rarely occurs in isolation and insulin resistance (diabetes) and hyperlipidemia are common accompanying medical conditions. Despite the number of available pharmacological groups for treatment of hypertension and accompanying conditions many times fails to achieve the goal due to drug related problems.

Recommendations for hypertension treatment are based on evidence form clinical trials from the point of efficacy (proper drug, dose and dosage schedule), safety (control of side effects and contraindications) and cost. Moreover in real life another important factor should be taken into account and it's the patient treatment adherence. Persistence (duration over which a patient had not ceased their medication) and adherence (the degree of prescription filling in a defined period of time) to antihypertensive treatment is essential for treatment success (Lachaine J.et al., 2008, Bramalge P. and Hasford J., 2009).

Studies have shown that the persistence and adherence of antihypertensive medication that is observed in clinical trials often is not observed in clinical practice which shows lower level of adherence. In addition patients who were taking diuretics appeared less compliant (adherent and persistent) comparing to patients who were using any other antihypertensive agents.

Another factor that contributes to non adherence is polypharmacy. In fact many hypertensive patients need multiple antihypertensive medications in order to achieve the blood pressure treatment goals. Multiple antihypertensive medications can be the reason of increasing adverse drug events and be the cause of poor patients' compliance.

Also undertreatment of hypertension, cost of therapy including medications and physician's visits for management of blood pressure contribute to increased health care expenditure and worsening by this way the patients' compliance (Lachaine J. et al., 2008, Bramalge P. and Hasford J., 2009).

Patients' non compliance it's a major health problem in the treatment of hypertension. Reasons of non compliance that studies have shown are presented on the table below (Gascon J. et al., 2004).

| REASONS OF NON COMPLIANCE | | |
|---|---|---|
| **1)Patients Beliefs, Attitudes, Thoughts About Antihypertensive Medication** | **2)Patients Beliefs, Attitudes, Thoughts About Hypertension** | **3)Patients Beliefs, Attitudes, Thoughts About Interaction With Physicians** |
| **EXAMPLES** | | |
| **a)**Fear and Negative Feelings of Antihypertensive drugs<br><br>**b)**Medications will Damage Rather Cure the Body<br><br>**c)**Fears About Long-Term Use of Antihypertensive<br><br>**d)**Side Effects Of Drugs<br><br>**e)**Leaflets Syndrome<br><br>**f)**Difficulty to Understand The Leaflets<br><br>**g)**Herbal or Natural remedies are Effective for Control of Hypertension<br><br>**h)**High Cost of Therapy<br><br>**i)**Forget to Take Medications due to Polypharmacy or to Regular Intervals Throughout the Day | **a)**Lack of Basic Knowledge About Hypertension, Risks, Complications and Treatment<br><br>**b)**Disease is Cured When Hypertension is Controlled<br><br>**c)**No symptoms and Well – Being Felling → Time to Cut Out Medication or to Experimenting in Doses, Dosage Schedule etc<br><br>**d)**Most Knowledge About Hypertension and Treatment From Sources Other Than Physicians | **a)**Very Short Consultation<br><br>**b)**Unsatisfactory – Few Explanations<br><br>**c)**Information is Provided After a Patients' Request<br><br>**d)**Difficult to Understand Physicians' Language or Writing<br><br>**e)**Physicians Created Nervousness to The Patients<br><br>**f)**Information Provided From Physicians It Was General and Simple and Not Specific For Each Case<br><br>**g)**Physicians Didn't Encourage Interaction |

***Table 16: Reasons of Patients' non Compliance (Gascon J. et al., 2004).***

Patients with hypertension are at an increased rate for abnormalities in vascular structure and elasticity, stroke, changes in renal function, end-stage renal disease, and heart failure. Also hypertension contributes in worsening of insulin resistance, lipid abnormalities, endocrine abnormalities, left ventricular hypertrophy and diastolic dysfunction (Munger M. et al., 2007).

Studies have shown that the first several months of hypertension therapy is characterized by high discontinuation rate. Only 59% of patients with hypertension are receiving drug therapy, but only 34% of those achieve adequate control of blood pressure.

The main reason is the effect of contributory factors to the medication adherence such as age, race and ethnicity, gender, drug class, type of adverse effects, polypharmacy, and drug costs. Moreover the adherence is decreasing by age and presence of co morbidities and is found that is lower between 60-79 years of age and is higher over 80 years of age. Also patients who receiving ARBs, ACEis or CCBs showed better adherence and significantly lower incidence of adverse effects in patients receiving losartan. In addition use of long-acting drugs to decrease the frequency of doses (e.g. amlodipine, nadolol, olmesartan, ramipril), simplify the dosing regimen and adequate patient education helps to improve compliance with antihypertensive regimens and control blood pressure over time (Munger M. et al., 2007).

Another problem that could reduce the patients' adherence and cause problems is switching between drugs. Any existence of co-morbidities especially in a case of heart failure, diabetes mellitus or diabetic nephropathy, drug adverse effect and patients' negative beliefs about the new drug can lead to negative outcomes and decrease by this way patient's compliance. Also could be a reason of medication discontinuation. Patients with existence of above co-morbidities should not be switched from an ARBs pharmacotherapy. In addition dry cough and angioedema are common side effects with ACEis and reason of medication discontinuation. In that case switching with ARBs is necessary (Johnston A. et al., 2010).

Moreover generic versions of drugs, formulation differences among antihypertensive agents can alter medication properties and patients beliefs about the drug and introduce unexpected effects that affect drug efficacy and safety. Packaging too can influence a drug formulation's stability. Changing of product packaging and tablet appearance can cause confusion especially in elderly people and reduce compliance. In addition poorer adherence and persistence can increase the total treatment cost by increasing the follow-up visits, laboratory tests, drug wastage and hospitalization (Johnston A. et al., 2010).

## 3.5) DRUG RELATED PROBLEMS TO ANTIHYPERTENSIVE AGENTS IN HYPERTENSIVE PATIENTS WITH DIABETES TYPE 2

Patients with diabetes type 2 and hypertension are at increased risk for experiencing drug related problems (DRPs) due to multiple medications (polypharmacy), aged related changes in pharmacokinetics and pharmacodynamics of drugs and accompany co morbidities like renal impairment. These DRPs can contribute to significant morbidity and mortality, prolonged hospitalization and increased health care expenditure. That's why the optimal choice and use of appropriate medication plays a key role on achieving target blood glucose, blood pressure and lipids levels.

DRPs to antihypertensive agents in patients with diabetes type 2 are presented on the table below (Roozendaal B. and Krass L., 2009).

| DRUG RELATED PROBLEMS TO ANTIHYPERTENSIVE AGENTS IN HYPERTENSIVE PATIENTS WITH DIABETES TYPE 2 | |
|---|---|
| **DRPs** | **EXAMPLES** |
| **1) Drug Interactions** | 1) Hypoglycemia – ACEis may enhance the hypoglycemic effect of insulin, sulphonylureas and metformin.<br>2) 'Triple Whammy Effect' - Combinations of ACEis or ARBs with Thiazide Diuretics and NSAID increases the risk of renal failure. |
| **2) Drug Choice Problem** | Missing of Antihypertensive Agent or inappropriate or contraindicated drug was prescribed as monotherapy like CCBs or non-Selective β-Blockers or drugs that were categorized at high risk in the modified Beers criteria for elderly. |
| **3) Dosing problem** | 1) Overused or Underused of ACEis due to inappropriately infrequent Dosing Regimen.<br>2) Inappropriate dosing particularly in patients with renal or liver impairments.<br>3) Too short or too long duration of treatment. |
| **4) Drug Use Problem** | Due to Patient Non – Adherence (see chapter 2.4) or because patient is unable to understand instructions-Inappropriate administration or dosing intervals, underused of drug or patient is unable to use the drug. |

| | |
|---|---|
| **5) Therapy Failure** | Failure to achieve the target blood pressure, blood glucose and lipids levels despite the pharmacotherapy treatment due to missing drug agents, incorrect administration or patient non-adherence. |
| **6) Insufficient Awareness of Health and Diseases** | Lack of knowledge for hypertension and diabetes type 2 and their complications. |
| **7) Logistics** | 1) Prescribed drug is not available.<br>2) Prescribing error. |
| **8) Patient Psychology** | See table 16. |

***Table 17: Drug Related Problems to Antihypertensive Agents In Hypertensive Patients With Diabetes Type 2 (Roozendaal B. and Krass L., 2009).***

However hypertensive patients with diabetes type 2 also had shown poor glycemic control, as well as suboptimal lipid control and suboptimal blood pressure control due to missing or contraindicated anti-platelet (not taking aspirin), lipid lowering, blood glucose lowering and blood control medications. Moreover non-adherence was another factor which contributes to poor control and to significantly higher glycated hemoglobin ($HbA_{1c}$).

Also studies have shown that there is statistically association between DRPs and renal impairment, polypharmacy, cardiovascular disease, elderly status, and duration of hospital stay. More specific the relation between DRPs and above factors is presented on the table below (Huri H-Z. and Wee H-F., 2013).

| RELATION BETWEEN DRPs AND CONTRIBUTORY FACTORS | |
|---|---|
| **FACTORS** | DRPs |
| **1) Renal Impairment** | Drug choice problems or dosing problems |
| **2) Polypharmacy** | Drug interactions |
| **3) Cardiovascular Disease** | Drug interactions |
| **4) Elderly Status** | Drug choice problems |
| **5) Duration of Hospital Stay** | Drug choice problems |

***Table 18: Association Between DRPs and Contributory Factors (Huri H-Z. and Wee H-F., 2013).***

In addition it was reported that in hypertensive patients with type 2 diabetes the most frequently antihypertensive drug classes that caused ADRs was:

1) CCBs (amlodipine) - Increased heart rate and bilateral leg swelling
2) ACEis (perindopril) - Electrolyte imbalances (hyperkalemia) and
3) Diuretics (indapamide) - Electrolyte imbalances (hyponatremia).

## 3.6) DRUG RELATED PROBLEMS TO ANTIHYPERTENSIVE AGENTS IN HYPERTENSIVE PATIENTS WITH CHRONIC KIDNEY DISEASE

Patients with CKD are considered as high risk population for experiencing ADEs due to aged-related structural and functional renal changes which causes alteration in drug phramacokinetic and phramacodynamic profile. In addition existence of co-morbidities including diabetes, hypertension and heart failure and multiple medication regimens increases the risk for potential medication errors, drug–drug interactions, and ADEs.

DRBs to antihypertensive agents and some contributory factors for presence of ADEs are presented on the tables below (Marcum Z. and Fried L., 2011).

| DRUG RELATED PROBLEMS TO ANTIHYPERTENSIVE AGENTS IN HYPERTENSIVE PATIENTS WITH CHONIC KIDNEY DISEASE | |
|---|---|
| **DRPs** | **EXAMPLES** |
| **1) Drug Interactions** | 1) 'Triple Whammy Effect' - Combinations of ACEis or ARBs with Thiazide Diuretics and NSAID increases the risk of renal failure.<br>2) Hyperkalemia by use of an ACEis compared with an ARBs, β-blocker, CCBs, or potassium sparing diuretics or concomitant use of potassium-sparing diuretics and NSAIDs.<br>3) Hypokalemia (serum potassium <3.5 mEq/l) – Occurs more frequently to patients receiving chlorthalidone compared with those receiving amlodipine or lisinopril after 4 years follow – up therapy.<br>4) Acute Kidney Injury (AKI) – Increased risk by combination of ACEis/ARBs.<br>5) Orthostatic hypotension in those taking ACEis/ARBs, β-blocker with α-blocking activity e.g. carvedilol, or CCBs.<br>6) Diastolic hypotension from CCBs because of increased pulse pressure. |
| **2) Drug Choice Problem** | Inappropriate or contraindicated drug like ACEis in patients with ESRD or short-acting nifedipine in those with a history of CAD as this agent has been shown to increase mortality in such patients. |

| | |
|---|---|
| **3) Dosing problem** | 1) Overused or Underused of ACEis due to inappropriately infrequent Dosing Regimen.<br>2) Inappropriate dosing particularly in patients with renal or liver impairments.<br>3) Too short or too long duration of treatment. |
| **4) Therapy cost** | Drug cost can reduce the patient compliance. However ACEis and ARBs are available in generic forms which are more cost-effective but caution should be given in patient tolerability. |

***Table 19: Drug Related Problems to Antihypertensive Agents In Hypertensive Patients Chronic Kidney Disease (Marcum Z. and Fried L., 2011).***

| RELATION BETWEEN ADEs AND CONTRIBUTORY FACTORS | |
|---|---|
| **ADEs** | Contributory Factors |
| **1. Hyperkalemia** | Older age, higher protein excretion, decreased GFR≤45 ml/min, higher baseline potassium levels>4.5 mEq/l, presence of diabetes mellitus or heart failure, use of potassium supplements or potassium-sparing diuretics and a high dose of ACEis. |
| **2. Acute Kidney injury** | Preexisting renal impairment decreased renal perfusion, prerenal azotemia. |
| **3. Increased Blood Pressure and Peripheral Vascular Resistance, Postural Hypotension** | Age-Related impaired baroreceptor sensitivity, increased sympathetic nervous system activity, and increased vascular stiffness. |
| **4. Hypotension, Volume Retention, Syncope** | Use of non-first line agents like $\alpha_1$-blockers, central α-agonists or direct vasodilators. |
| **5. Atrioventricular Block** | Use of non dihydropyridines (e.g. diltiazem and verapamil) due to prolongation of atrioventricular conduction time in old population. Also should be avoided in patients with heart failure because of their ability to cause a heart failure exacerbation |
| **6. Constipation** | Use of verapamil. |
| **7. Peripheral Edema** | Use of amlodipine but also other CCBs. |
| **8. Cough** | Use of ACEis. |
| **9. Drug Accumulation and Exacerbation of Drug Action and ADEs** | Age-related decreased hepatic metabolism due to reduced liver mass and hepatic blood flow, reduced albumin synthesis, reduced glomerular filtration rate (GFR) and tubular function. |

***Table 20: Association Between ADEs and Contributory Factors (Marcum Z. and Fried L., 2011).***

In general, assessing route of metabolism and elimination (hepatic/renal) plays important role for prevention of potential ADEs.

# 4. EXPERIMENTAL PART

## 4.1) METHODOLOGY – DATA EXTRACTION

The main aim of the experimental part of this particular retrospective study is to analyze the pharmacotherapy and drug-related-problems of 60 Greek hypertensive patients. To accomplice these task 60 patient cases obtained from one cardiologist electronic medical records in Greece, regarding age, gender, diagnosis, pharmacotherapy, dosage scheme, strength and adverse drug reactions which were used for statistical analysis.

The data collection was achieved from July 2013 to September 2013.

## 4.2) METHODOLOGY – STUDY POPULATION

The study population consisted from adults patients aged 40 and over. The criteria for selection of patients which included in this study it was an established diagnosis of arterial hypertension and the patients who had during the last visit BP higher than 140/90 mmHg.

## 4.3) METHODOLOGY – EVALUATION

In this project 60 patient cases were collected from one cardiologist in Greece regarding age, gender, diagnosis, pharmacotherapy (active substances), strength, dosage scheme, adverse drug reactions and way of dealing with them. The city from which the patients' data was collected is located in north Greece and account approximately 50.000 inhabitants.

In order to analyze the selected patients' data, we stored all the collected information into the evaluation database (Microsoft Excel) and analyzed the antihypertensive agents, as well as some additive agents like antidyslipidemics. More specific, frequency of used active substances and pharmacological groups, as well as D.R.P to particular pharmacological groups was preliminary analyzed.

Results are presented below on corresponding graphs. Additionally discussion of therapy strategy and management of these particular patients, regarding pharmacotherapy based evidence used in arterial hypertension, will also be mentioned and in the end some conclusions will be given.

# 5. RESULTS

The examined data have shown the patients' characteristics regarding age, gender, diagnosis, pharmacotherapy and adverse drug reactions.

Firstly the comparison of hypertensive patients' gender showed that 57% of the total examined population which suffered with hypertension was male and 43% was female (figure 1). The age of study population was determined from 41 and above. In order to simplify the analysis procedure, the age of study population was divided into four age groups: 41-50, 51-60, 61-70 and 71 and above. The age group 61-70 appears to have higher percentage of hypertensive patients, accounting 32% of the total number of study population with the age group 51-60 followed by 28% (figure 2). Also, was determined that the average age of people suffering with hypertension was 63 years old.

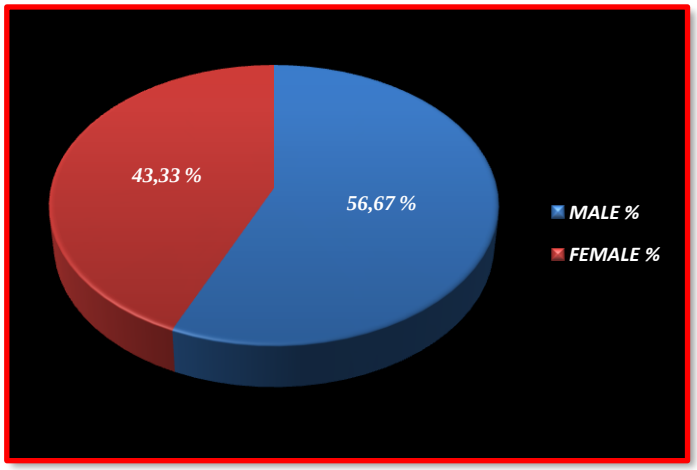



***Figure 1: The pie graph shows the comparison of hypertensive patients' gender, where 100% is the total number of patients' population (N=60).***

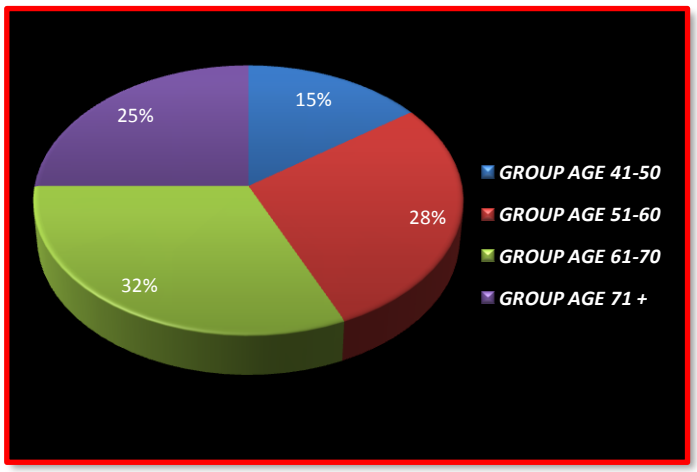



***Figure 2: The pie graph shows the distribution of hypertensive patients' age, where 100% is the total number of patients' population (N=60).***

Secondary, it is known that hypertension is accompanied many times by other co-morbidities. In this study 35% of the study population was suffering from hypertension (mainly stage 1 and stage 2) accompanying one more disease mainly C.H.D or obesity or dyslipidemia, followed by 27% of the population suffering from hypertension accompanied by two other co-morbidities mainly dyslipidemia and C.H.D or dyslipidemia and D.M type 2 (figure 3).

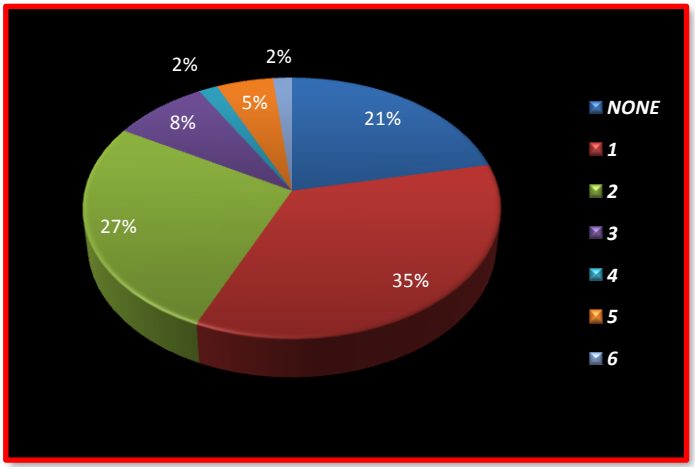



***Figure 3: The pie graph shows the number of co-morbidities per hypertensive patient, where 100% is the total number of patients' population (N=60).***

In addition dyslipidemia and C.H.D appear to be the most frequent coexisting diseases that accompany hypertension in our study population, despite age and gender, accounting for 37% and 32% of the population respectively (figures 4, 5, 6, 7, 8).

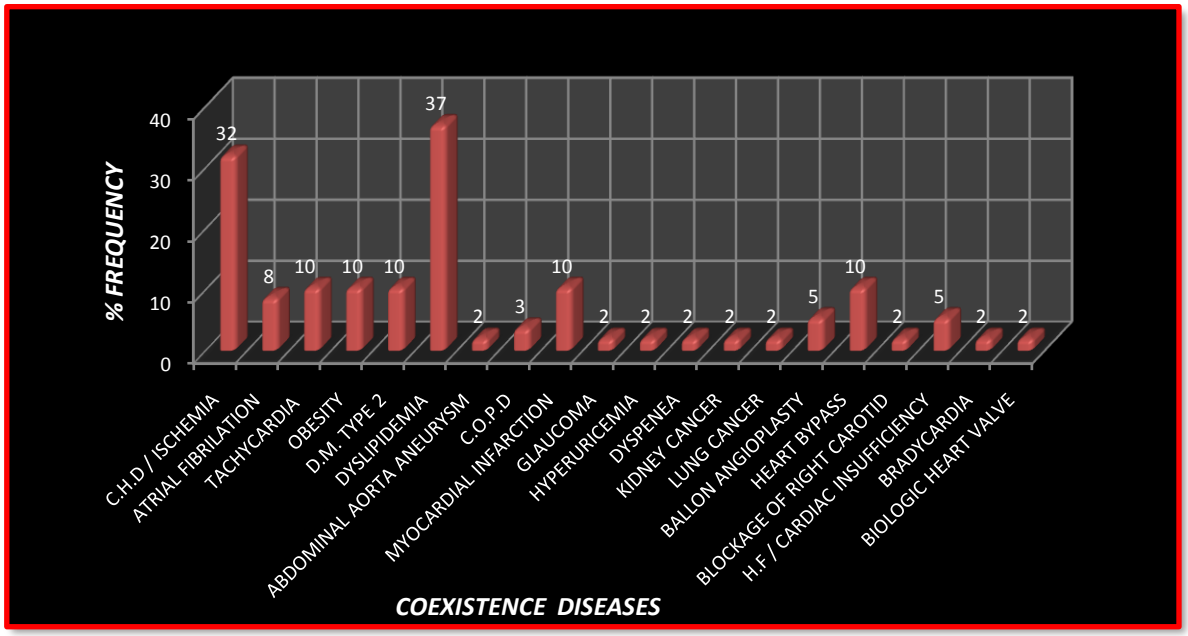



***Figure 4: The bar graph shows the % frequency of coexistence diseases in hypertensive patients where 100% is the total number of patients' population (N=60).***

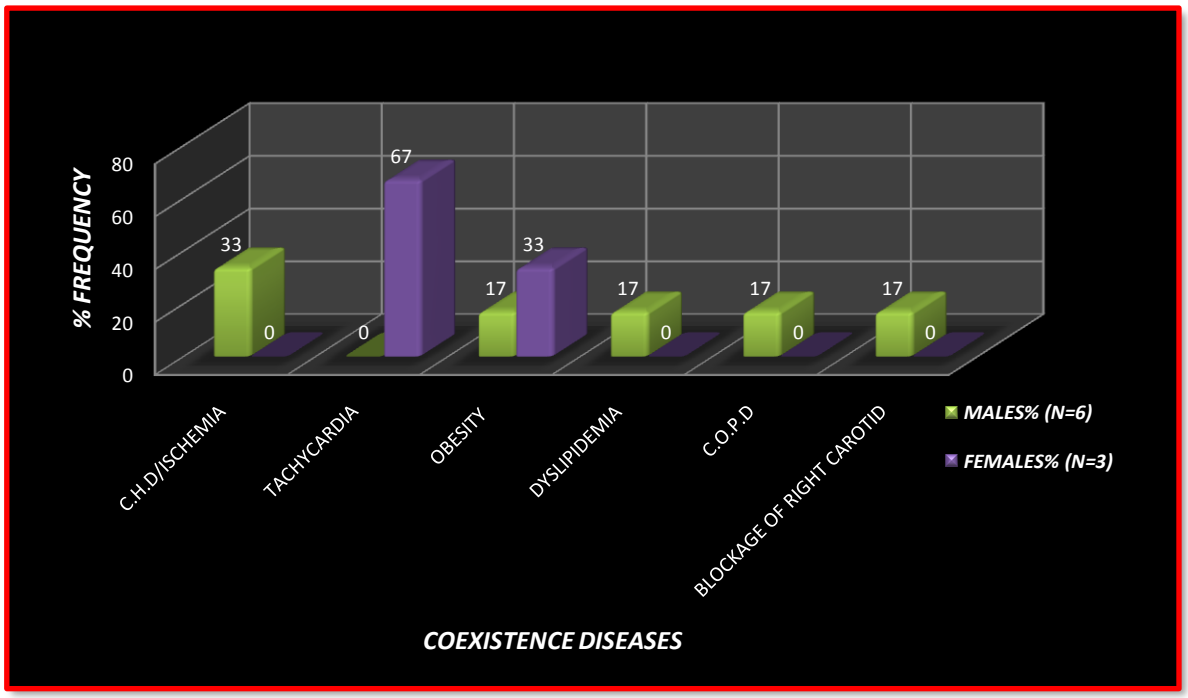



*Figure 5: The bar graph shows the % frequency of coexistence diseases in hypertensive patients according to group age (41-50) and gender, where 100% is the total number of patients' population to corresponding age group and gender.*

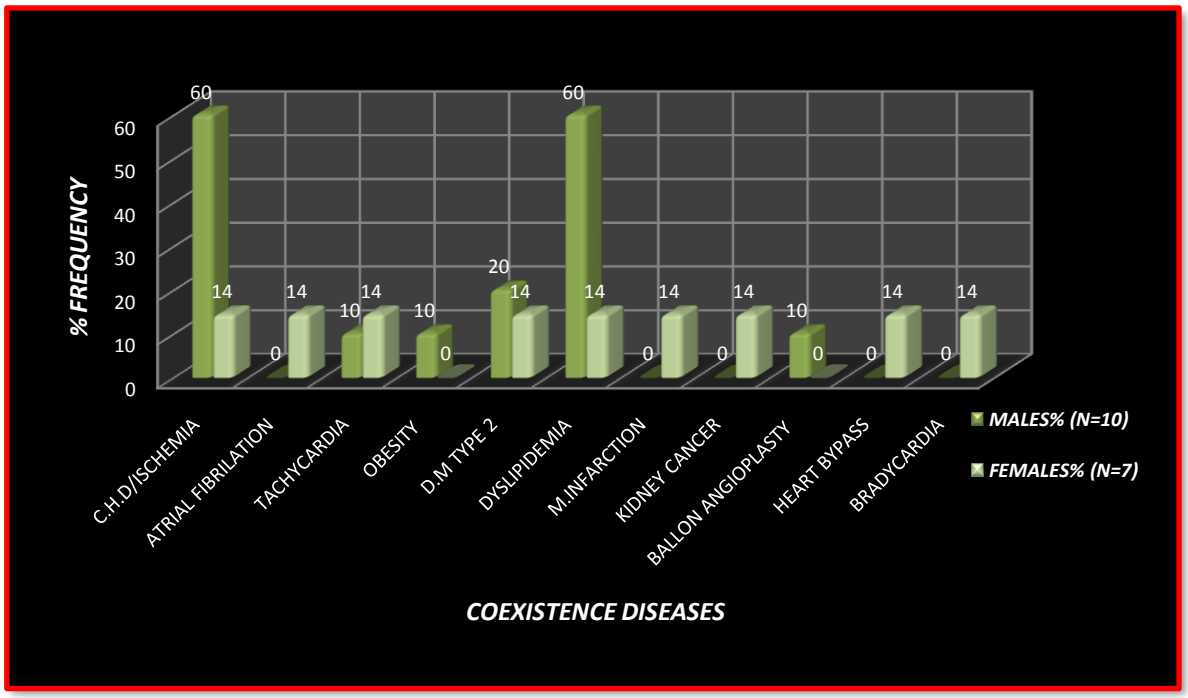



*Figure 6: The bar graph shows the % frequency of coexistence diseases in hypertensive patients according to group age (51-60) and gender, where 100% is the total number of patients' population to corresponding age group and gender.*

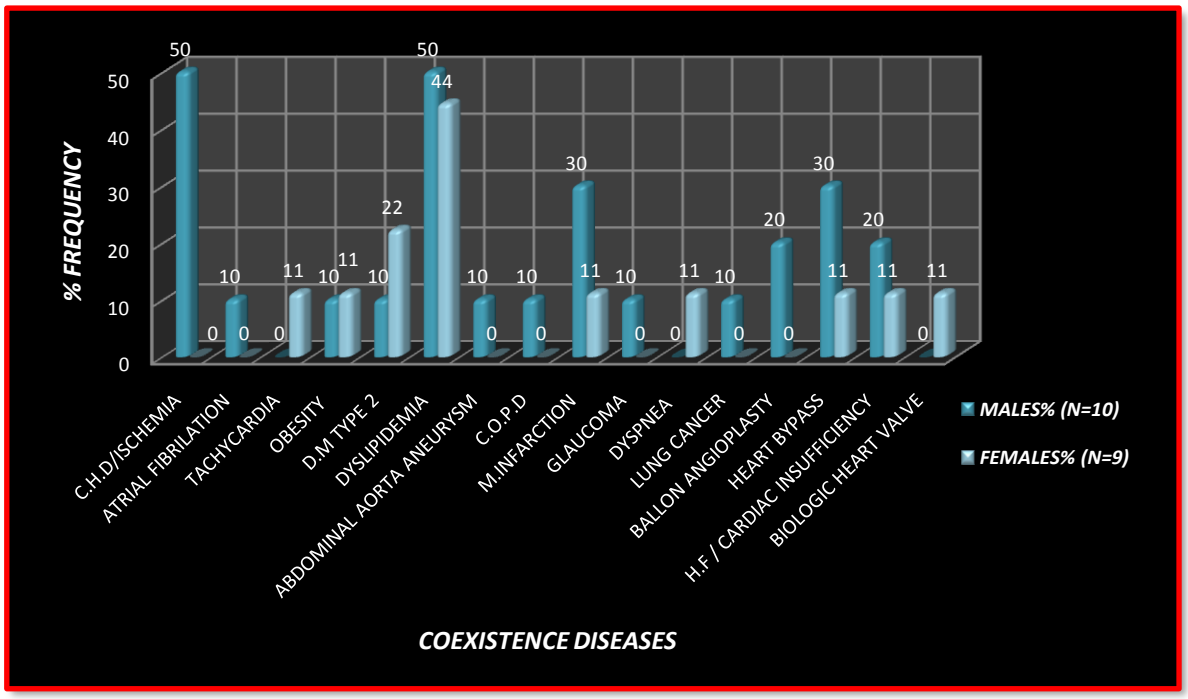



*Figure 7: The bar graph shows the % frequency of coexistence diseases in hypertensive patients according to group age (61-70) and gender, where 100% is the total number of patients' population to corresponding age group and gender.*

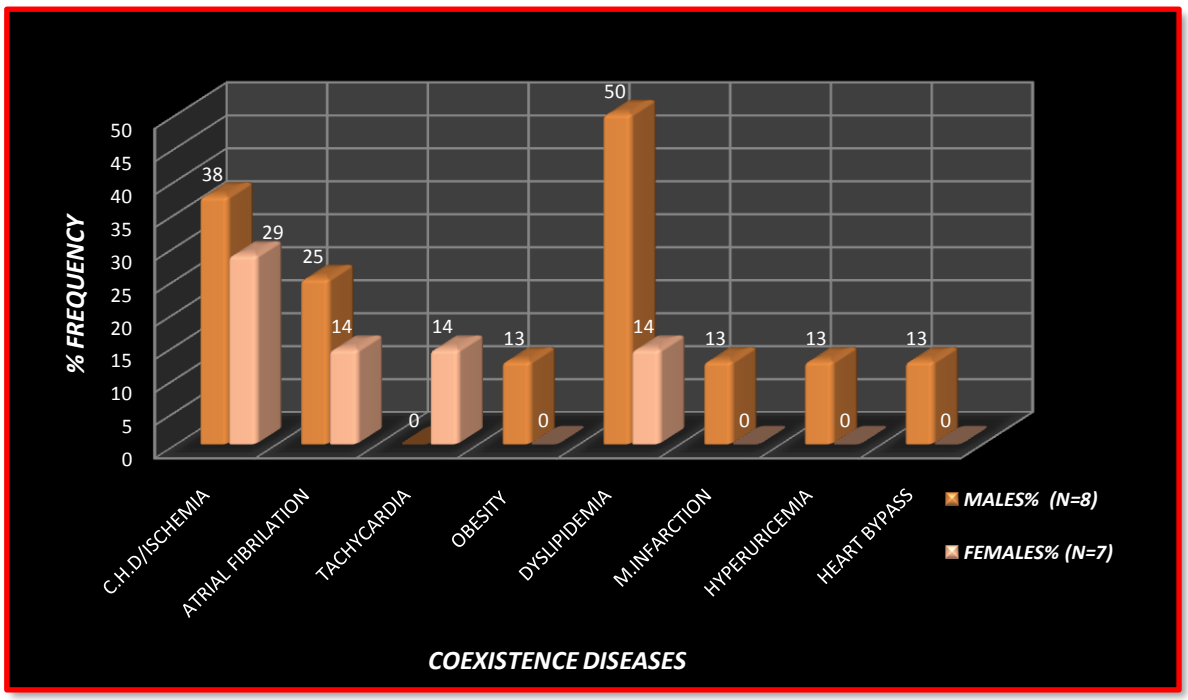



*Figure 8: The bar graph shows the % frequency of coexistence diseases in hypertensive patients according to group age (71+) and gender, where 100% is the total number of patients' population to corresponding age group and gender.*

The above findings could explain that the most frequently used drug formulations were antihyperlipidemics, BBs, anticoagulant/antiplatelet and ARBs accounting 70%, 68%, 48% and 38% of the population respectively (figures 9, 10).

Also drug formulations like ACEis, CCBs, ARBs+CCBs, Thiazide Diuretics+ARBs/ACEis, Loop Diuretics and some Other Agents like Digoxine, Amiodarone and Trimetazidine seems to be less favorable accounting 15%, 17%, 17%, 13%, 12% and 17% (figures 9, 10) of the population respectively.

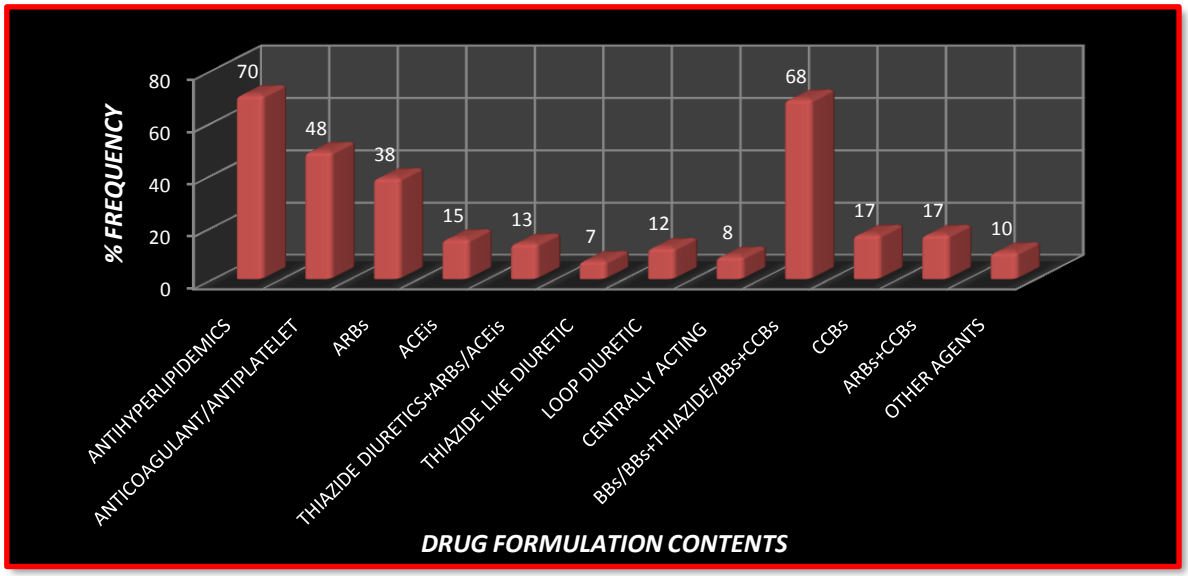



***Figure 9: The bar graph shows % frequency of different drug formulation contents use among patients' population, where 100% is the total number of patients' population (N=60).***

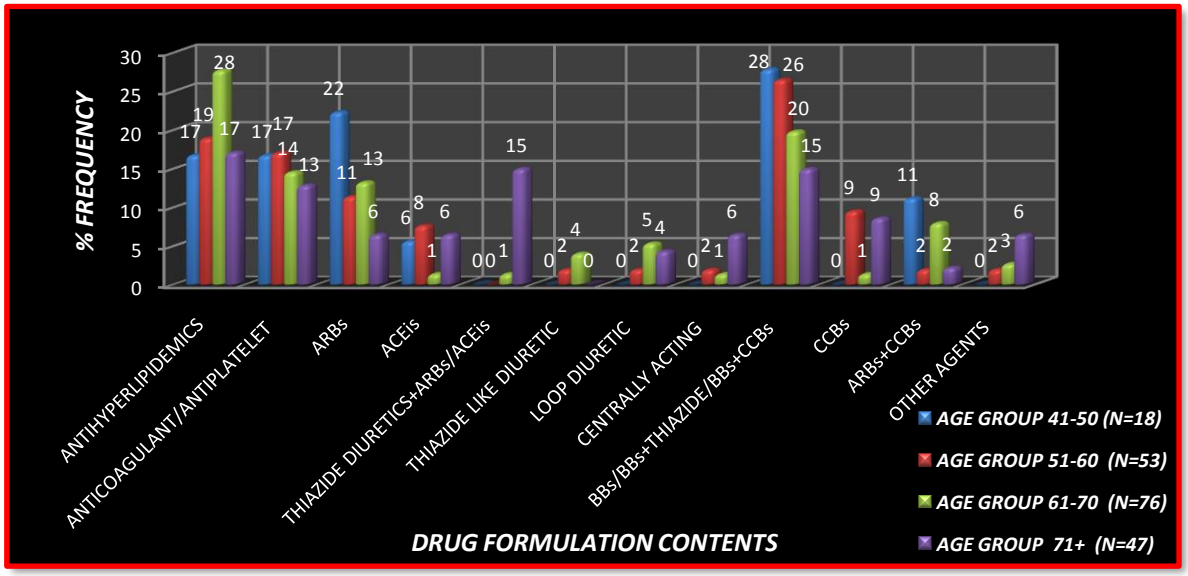



***Figure 10: The bar graph shows % frequency of different drug formulation contents among patients' age group, where 100% is the total number of drug formulation contents per patient that have been used on each age group.***

Additionally the ACEis is less favorable comparing to ARBs due to their side effects like dry cough. The effect of the rest of the drugs is additive to pharmacotherapy, that's why account less percentage of use in study population.

Furthermore from the point of the active substances despite of the strength, dosage scheme and formulation contents, the most frequent prescribed (figure 11) it can be seen on the table below. The rest of the prescribed active substances account 7% or less.

| *DRUG GROUP* | *ACTIVE SUBSTANCES* | *%* |
|---|---|---|
| ***1) Antihyperlipidemics*** | *Atorvastatin* | *38%* |
| | *Simvastatin* | *30%* |
| | *Fenofibrate* | *11%* |
| ***2) BBs*** | *Atenolol* | *13%* |
| | *Carvedilol* | *29%* |
| | *Metoprolol* | *34%* |
| | *Nebivolol* | *13%* |
| ***3) Anticoagulant-Antiplatelet*** | *Acenocoumarol* | *11%* |
| | *Aspirin* | *39%* |
| | *Clopidogrel* | *13%* |
| ***4) CCBs*** | *Amlodipine* | *11%* |
| ***5) ARBs*** | *Olmesartan* | *16%* |
| | *Telmisartan* | *28%* |
| | *Valsartan* | *19%* |
| ***6) ACEis*** | *Quinapril* | *16%* |
| | *Ramipril* | *11%* |
| ***7) DIU*** | *Furosemide* | *15%* |
| | *Indapamide* | *9%* |
| | *HCTZ (only in combinations with other agents)* | *21%* |

***Table 21: The most frequent prescribed active substances from the total number of prescribed active substances according to drug group.***

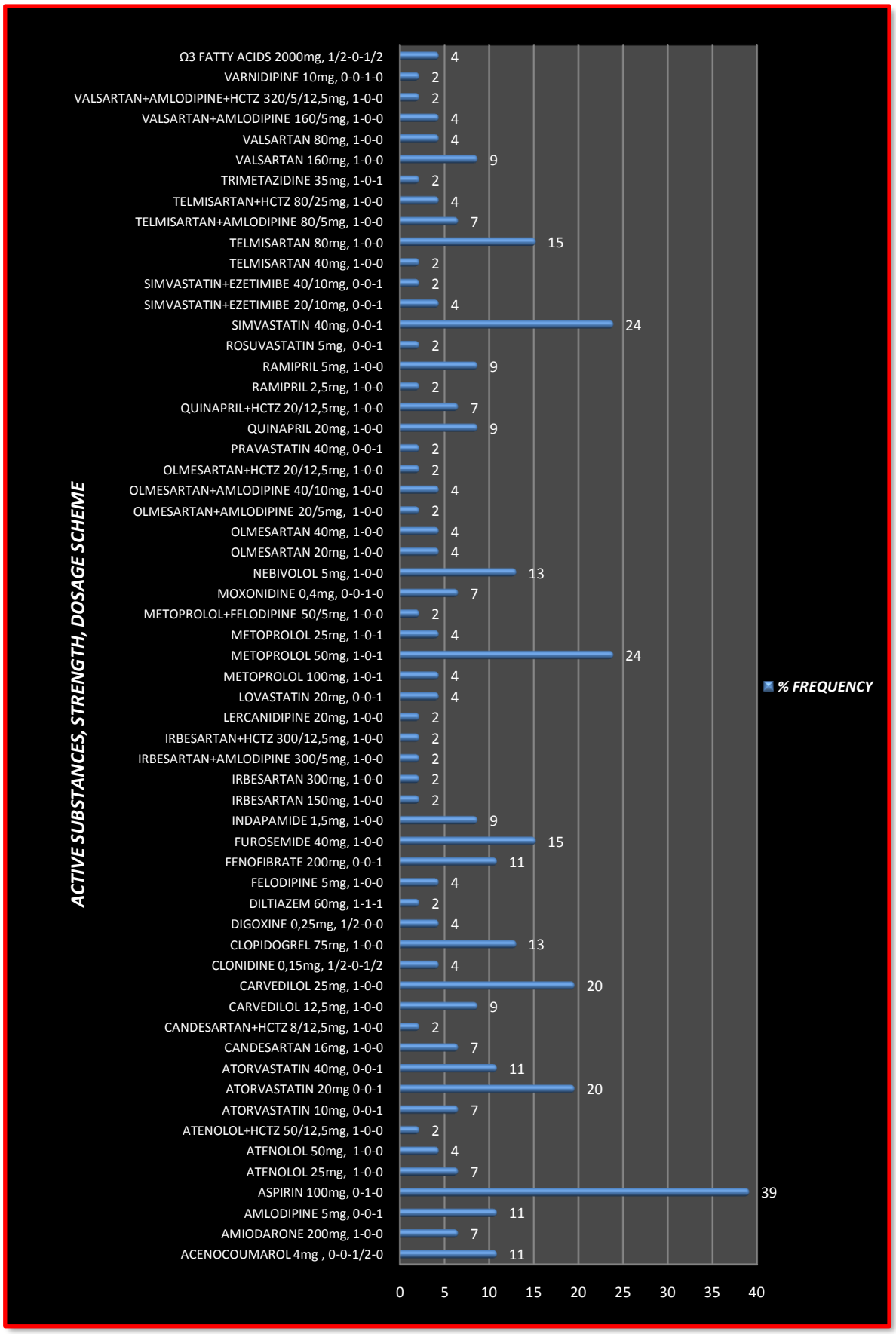



***Figure 11: The bar graph shows the % frequency of active substances in hypertensive patients, where 100% is the total number of active substances, including the additive substances to antihypertensive therapy (N=46).***

Moreover the 88% of the total number of antihypertensive active substances was prescribed once daily (figure 12) and only 32% of the total population it was treated by monotherapy and the rest by combination of two or more active substances (figure 13).

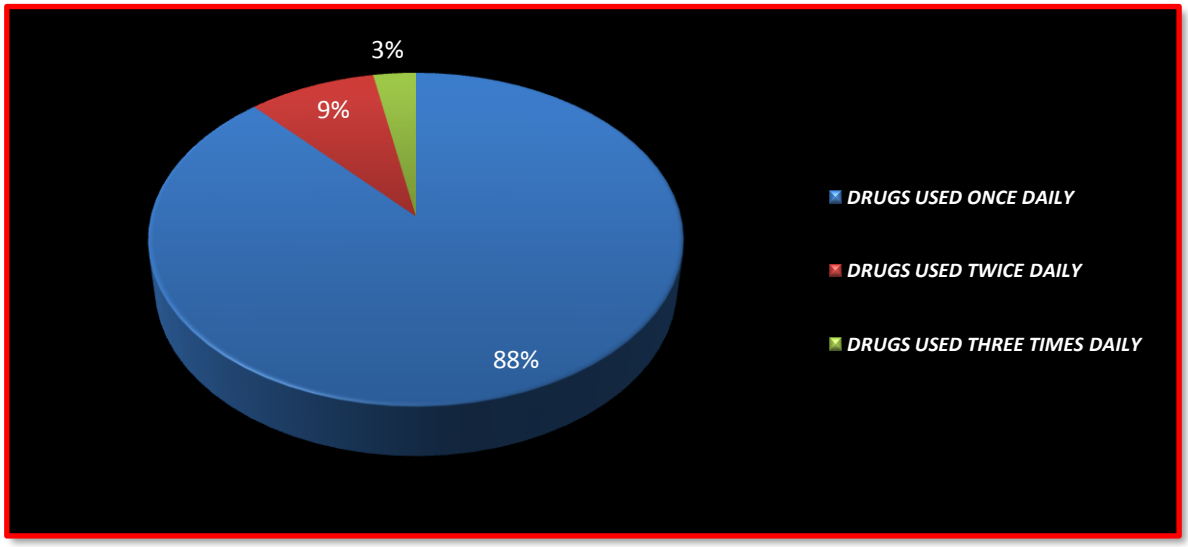



***Figure 12: The pie graph shows % frequency of dosage scheme, where 100% is the total number of antihypertensive active substances (N=34).***

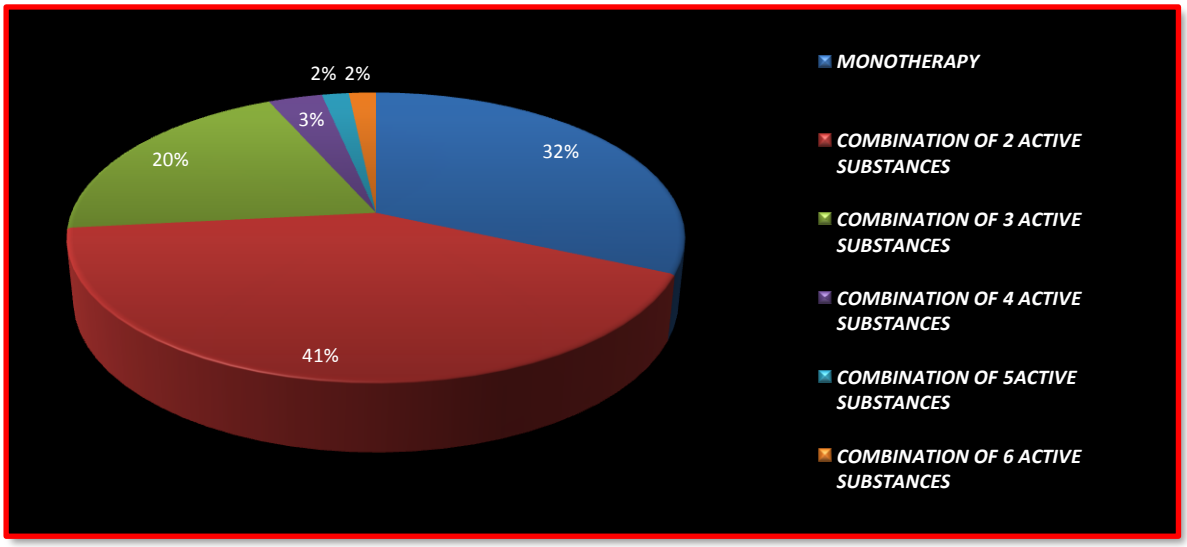



***Figure 13: The pie graph shows total number of antihypertensive active substances per patient, where 100% is the total number of patients' population (N=60).***

Furthermore most patients had an experience of adverse drug reactions due to pharmacotherapy. More specific 62% of study population had an experience of one A.D.R, 13% had an experience of two A.D.Rs and only 15% had no experience of A.D.R (figure 14).

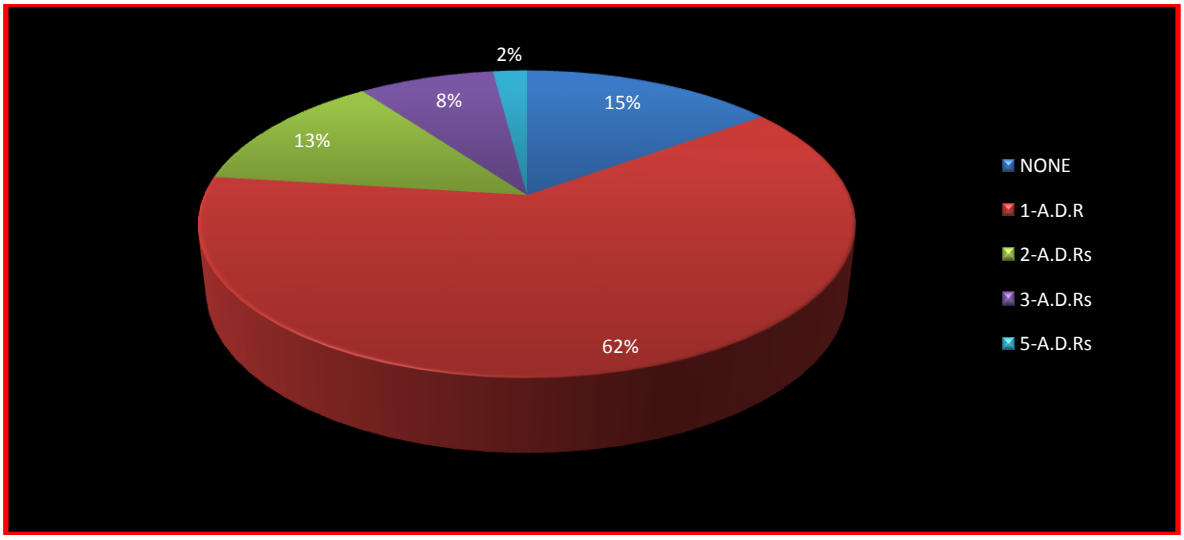



***Figure 14: The pie graph shows number of A.D.R. per patient, where 100% is the total number of patient population (N=60).***

In more details 30% of the study population they experienced fatigue, dizziness, weakness, bradycardia mainly due to BBs, 22% they experienced peripheral edema mainly due to amlodipine and 13% they suffered from dry cough due to ACEis. Also 13% they showed myalgia and increased CPK levels due to statins which was an additive to antihypertensive therapy, and the rest of A.D.Rs, each of them accounts 5% or less of the total study population (figure 15).

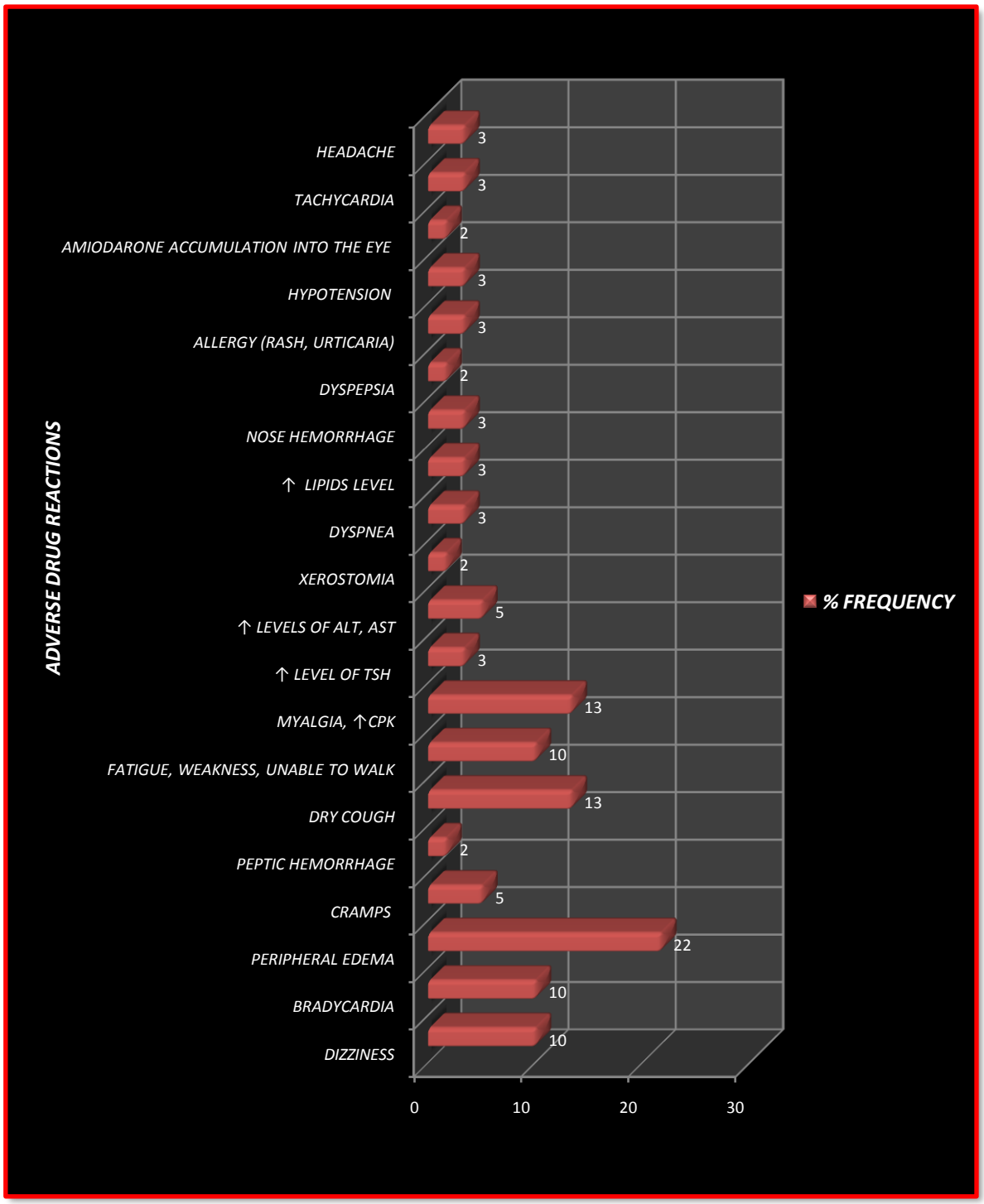



***Figure 15: The bar graph shows % frequency of adverse drug reactions among patients' population, where 100% is the total number of patients' population (N=60).***

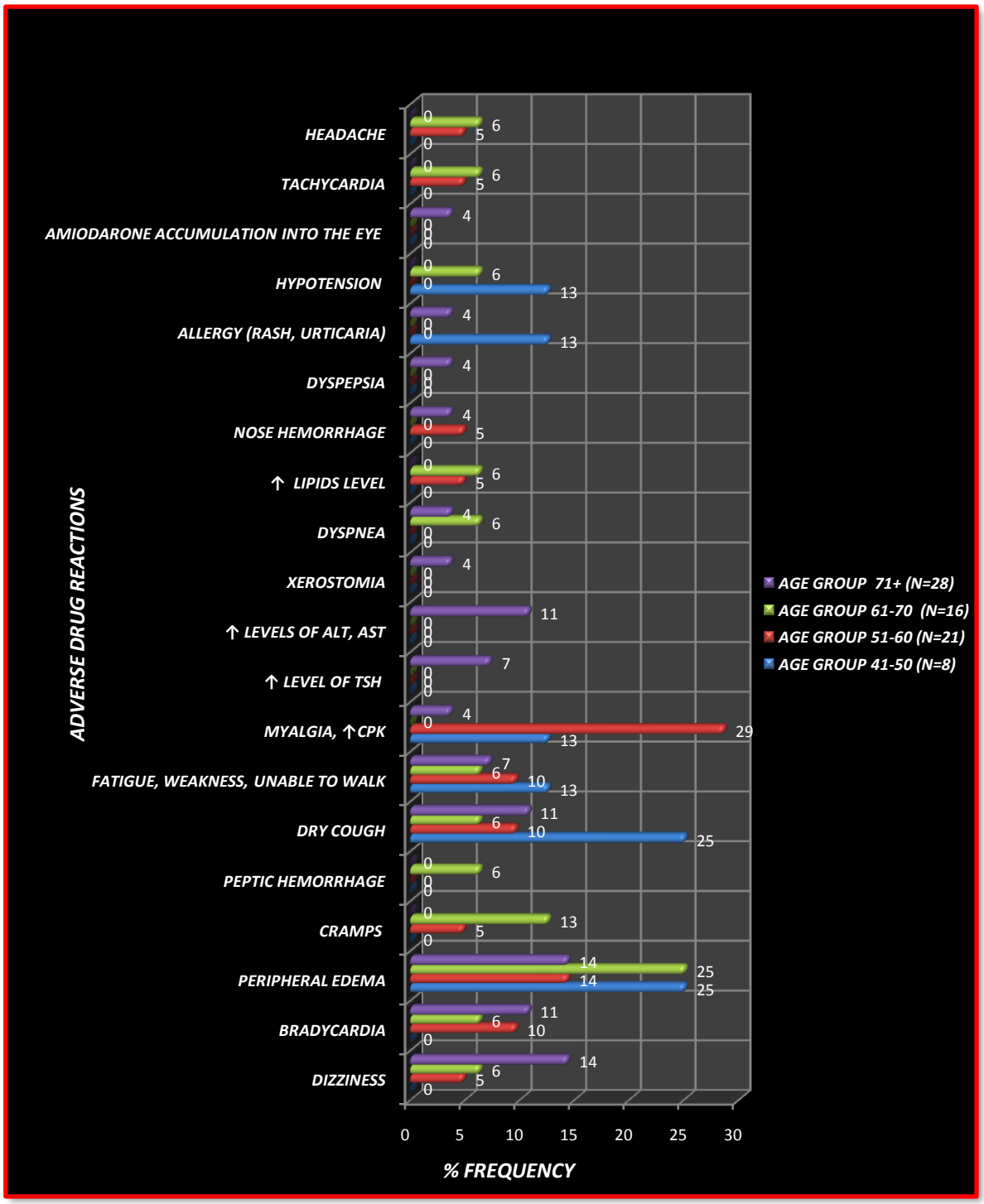



***Figure 16: The bar graph shows % frequency of adverse drug reactions among patients' age group, where 100% is the total number of adverse drug reactions appearance to corresponding age group.***

In addition, the table below represents the causes and types of A.D.Rs. Here we should mention that due to missing patients' information like blood-biochemical test results, for evaluation of A.D.Rs we based on the information from personal doctor's experience, based mainly on the symptomatic origin of A.D.Rs.

| *A.D.Rs CAUSES* | *A.D.Rs TYPES* |
|---|---|
| *1)AMIODARONE* | *1) ↑TSH LEVEL, AMIODARONE ACCUMULATION INTO THE EYE* |
| *2)AMLODIPINE* | *2) PERIPHERAL EDEMA* |
| *3)AMLODIPINE+ARBS* | *3) PERIPHERAL EDEMA, TACHYCARDIA, HYPOTENSION* |
| *4)ASPIRIN* | *4) NOSE HEMORRHAGE* |
| *5) ATORVASTATIN* | *5) DIZZINESS, FATIGUE, WEAKNESS, UNABLE TO WALK, MYALGIA, ↑ CPK, ↑ ALT - AST LEVEL* |
| *6) QUINAPRIL / QUINAPRIL +HCTZ* | *6) DRY COUGH* |
| *7) DIGOXINE DUE TO LOW K LEVEL* | *7) DIZZINESS, BRADYCARDIA, PERIPHERAL EDEMA, FATIGUE, WEAKNESS, UNABLE TO WALK, DYSPNEA* |
| *8) BAD B.P CONTROL-NON COMPLIANCE* | *8) ↑B.P, ↑ LIPIDS LEVEL, TACHYCARDIA* |
| *9) NEBIVOLOL* | *9) BRADYCARDIA, FATIGUE, WEAKNESS, UNABLE TO WALK* |
| *10) ATENOLOL* | *10) DIZZINESS, BRADYCARDIA* |
| *11) METOPROLOL* | *11) FATIGUE, WEAKNESS, UNABLE TO WALK, DIZZINESS, BRADYCARDIA, ↑ LIPIDS LEVEL* |
| *12) SIMVASTATIN* | *12) MYALGIA, ↑ CPK, DYSPNEA* |
| *13) VALSARTAN* | *13) ALLERGY (RASH, URTICARIA), HYPOTENSION, HEADACHE, DRY COUGH* |
| *14) INDAPAMIDE* | *14) CRAMPS, ↓ K LEVEL* |
| *15) MOXONIDINE* | *15) XEROSTOMIA* |
| *16) CLOPIDOGREL* | *16) PEPTIC-NOSE HEMORRHAGE* |
| *17) DILTIAZEM* | *17) PERIPHERAL EDEMA* |
| *18) FELODIPINE* | *18) PERIPHERAL EDEMA* |
| *19) IRBESARTAN* | *19) HEADACHE* |
| *20) DIURETICS (HCTZ, FUROSEMIDE)* | *20) ALLERGY (RASH, URTICARIA), CRAMPS, ↓ K LEVEL* |

***Table 22: A.D.R. Causes and Types.***

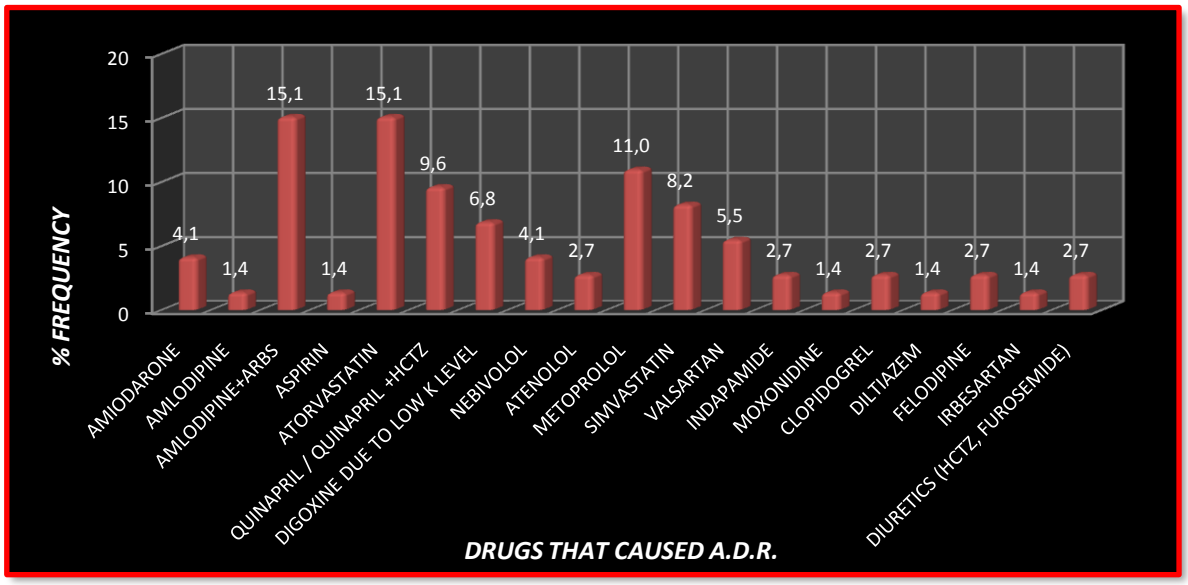



***Figure 17: The bar graph shows % frequency of A.D.R. per drug, where 100% is the total number of A.D.R. that was appeared for each drug (N=73).***

# 6. DISCUSSION

In this project, 60 patient cases with diagnosis of arterial hypertension were collected from one cardiologist in Greece. That cardiologist is located in the center of a small city Giannitsa, which accounts 50.000 inhabitants and its 50km away from Thessaloniki. For this study, hypertension was defined as SBP ≥140 mmHg and DBP ≥90 mmHg, or previous diagnosis of hypertension or current use of antihypertensive medication or any combination of the above. Furthermore control of hypertension was defined as SBP <140 mmHg and DBP <90 mmHg. For diagnosis and treatment of high blood pressure the doctor was following the guidelines of European society of hypertension.

Despite the study limitations, all the results was given in the form of graphs (figure 1 to figure 17) on the previous chapter 5 and on this chapter it will be discussion about the findings and limitations.

Firstly regarding findings , the comparison of hypertensive patients' gender and age showed that prevalence of hypertension was higher in men than in female aged 61 and above. According to Hypertenshell National Study in Greek population, hypertension prevalence was higher in men, which is increased by age especially after 65 (Efstratopoulos A. et al, 2005). Besides that, in relation to the Greek EPIC Study, the prevalence of hypertension is increased by age, accounting higher ratios in women after the age of 65 (Psaltopoulou T. et al, 2004). These differences on the hypertension prevalence between genders could be explained by the different definitions and methodologies that the investigators were following regarding measurements and diagnosis of hypertension, as well as in the different criteria in which the study population was chosen.

Secondly, age, hypertension, dyslipidemia and diabetes mellitus are the major atherosclerotic risk factors. On the other hand, atherosclerosis is the underlying condition which causes C.H.D. In our study population, dyslipidemia and C.H.D seems to be the most frequently coexisting diseases that accompany hypertension, accounting for 37% and 32% of the population respectively. These findings can be supported by the results of ATTICA study which have shown that hypertension, dyslipidemia, diabetes mellitus and obesity have been increased in alarming rates in Greek population, increasing the risk for C.H.D (Panagiotakos D. et al, 2009).

Moreover the 88% of the total number of antihypertensive active substances was prescribed once daily and only 32% of the total study population it was treated by

monotherapy and the rest by combination of two or more active substances. Concerning some other studies, have also showed that combination of two or more active substances in lower doses could be more effective comparing to monotherapy. In addition regimens that used once daily could be more effective by increasing patients' compliance (Gupta A. et al, 2010, Psaty B. et al, 2003).

In addition, the choices of drugs for treatment and management of arterial hypertension should be based on patient age, severity stage and existence co-morbidities, as well as should be in agreement with hypertension treatment guidelines. According to European society of hypertension in stage 1 hypertension, all first choice antihypertensive agents are appropriate for starting and maintenance of antihypertensive therapy, as monotherapy or in combination despite the age and gender. Also low dose diuretics are the best choice treatment on the beginning, in patients with uncomplicated hypertension stage 1.In case of stage 2 hypertension, combination of active substances should be preferred (ESH-ESC, 2013, Noohi F. et al., 2012).

In addition in relation to European society of hypertension but also to one Greek study about prevalence, treatment and control of hypertension on a Greek population (Triantafyllou A. et al, 2010) have shown that the most favorable choices for hypertension treatment in elderly is combination of ACEis/DIU (42,9%) followed by combination of ARBs/ DIU (22,2%).

In our retrospective study regarding the above results, the use of ACEis/DIU and ARBs/DIU combinations, accounts only 13%. The most favorable antihypertensive choices in case of monotherapy, appears to be BBs followed by ARBs accounting 68% and 38% respectively. Despite that the BBs, especially their combination with thiazide diuretics should be avoided in those who are at risk of developing diabetes, one possible reason that could explain the above choice is that BBs remain favorable to those who have another indication like C.H.D (Walker R. and Whittlesea C., 2012). In our study population, dyslipidemia and C.H.D are the most frequently co-morbidities along with hypertension, something that can explain also the high frequency usage of antidyslipidemics which is additive to antihypertensive therapy. According to Devabhaktuni M. and Bangalore S. study, combination of CCBs with statins especially of amlodipine with atorvastatin shows excellent efficacy and safety profiles for the treatment of hypertension and dyslipidemia (Devabhaktuni M. and Bangalore S., 2009). Additionally in case of combination therapy, the most favorable antihypertensive choices in our study

population seem to be combination of BBs with ARBs and addition of CCBs mainly amlodipine and DIU when it was needed.

On the other hand CCBs, as well as diuretics mainly thiazide and loop, appears to be more favorable in elderly population. This finding complies with paper of Walkerand Whittlesea (2012), according to which CCBs and low dose thiazide diuretics are safe and effective choice for elderly hypertensive population. Furthermore diuretics could be used in combination with the other antihypertensive agents in order to achieve better results in lowering the blood pressure. Here it should be mentioned that the thiazide diuretics is not effective and should be switched to loop diuretics for patients with kidney problems, especially when GFR is 30ml/min or less. In our study only one patient was suffering from kidney cancer, in which one kidney has been removed by surgery and that patient wasn't under diuretic treatment. However because there is no evidence about patients' kidney function, we cannot say if the use of diuretics was rational or not.

In our study HCTZ which belongs to thiazide diuretics, was used only as a combination therapy, mainly with BBs, ACEis and ARBs. Combination of thiazides with newer antihypertensive agents is recommended by many guidelines in response to realization that most patients require multiple antihypertensive agents to reach B.P treatments goal. One explanation for that could be that one pill regimen can increase patients' compliance by decreasing A.D.Rs and also two active substances in lower doses in one pill are more effective in lowering the blood pressure comparing to monotherapy (Pimenta E. and Oparil S., 2008).

Moreover as seems in our study group, that ACEis have used much less comparing to ARBs (figure 12), accounting only 15% of the total population. The main reason is some side effects, like dry cough or because couldn't be tolerated by the patients (table 22).

A.D.Rs of particular drugs can influence compliance of antihypertensive agents, because they frequently decrease QoL, which is important by asymptomatic disease. Therefore we were looking for physicians notice in health documentation regarding A.D.Rs. It will be better if we define what data is necessary to collect from individual patients regarding pharmacotherapy before our observation and in this way increase the chance that will focus on all A.D.Rs and not only to these with symptomatic origin.

Moreover, after discussion with a doctor, any appearance of A.D.Rs due to side effects of the drugs or due to bad control and patients' non compliance (refuse to follow doctors' instructions or forgetting to take the medicine), it was treated mainly by decreasing the doses of the drugs, switching them to another active substances from the same

pharmacological group (depends on patients' tolerability) or by adding more active substances from different pharmacological groups in lower dosages and combined pills, in order to achieve the B.P goals. Also in case of patients' non-compliance, the use of combined slow release regimens it was preferred.

Regarding study limitations, the obtained results are not representative of a whole population due to a small sample size used for the research. The results were gathered from just one health care professional, as a result, this does not correspond to a larger population. The information obtained gives us a representation of the kind of pharmacotherapy used most frequently in Greece. Moreover, the drug related problems commonly faced in a Greek population and a means of dealing with them.

In addition to the use of small population size and no variation in health care professional, there was also lack of patient information in the physician's records. For example, laboratory results of blood analysis, biochemical tests, and pharmacotherapy of co-existing diseases, were absent in most of the cases. This information would aid in better understanding of rational medication use and adverse drug reactions, as well as in better care management of patients.

Also, information about pharmacotherapy was focused mainly in the use of active substances, strength and dosage scheme, missing the trade names of drugs. That could be helpful in better understanding of patients and doctors preference, regarding level of reimbursement, drug prices and market trends. Additionally correlation evaluation of specific adverse drug reactions between generic and prototype drugs could be more clearly established.

Moreover another contributory factor to study limitations was the short period of time during which the collection and analysis of the information was achieved. Missing information about treatment duration could be helpful in evaluation of treatment effectiveness. Therefore we are not able to analyze if we reached the aim. The patients which are under antihypertensive treatment should be measure the blood pressure every 3-6 months in order to know if they reach the B.P treatment goal.

Furthermore knowledge of patient's beliefs about their disease and pharmacotherapy regarding price and effectiveness would be helpful in better management of patient adherence and would aid in better evaluation of the results.

As a result, in future studies, larger population size and the involvement of numerous health care professionals will be necessary to produce more accurate and representative findings.

# 7. CONCLUSION

In conclusion arterial hypertension is an important risk factor for cardiovascular diseases and also contributes to increased morbidity and mortality. Many pharmacological agents are available for treatment; however, the choice depends on the patients' age, diagnosis, co-morbidities, appropriate strength-dosage scheme and patients' tolerability.

Hypertension can affect all ages despite gender and ethnicity. In our study it was proved that hypertension appears more often in men than in women. Also the combination of drug treatment was more beneficial in order to achieve the blood pressure treatment goals and could be helpful to increase patients' compliance comparing to monotherapy.

Also the most common co-morbidities along with hypertension were dyslipidemia and C.H.D, as well as the most frequently used drug groups were antihyperlipidemics, BBs, anticoagulant-antiplatelet and ARBs. More specific from the point of active substances atorvastatin, metoprolol, aspirin and telmisartan in different combinations, doses and dosage schemes seems to be the most favorable prescribed drugs.

Furthermore any appearance of A.D.Rs due to side effects of the drugs or due to bad control and patients' non compliance, it was treated mainly by decreasing the doses of the drugs, switching them to another active substances from the same pharmacological group or by adding more active substances from different pharmacological groups in lower dosages in order to achieve the B.P goals.

However due to certain study limitations like small sample size, no variation in health care professional, lack of patient information on when it was the first diagnosis and treatment, duration of treatment etc the obtained results are not representative of a whole Greek population and further investigations it will be necessary in the future to produce more accurate and representative findings.

# 8. ABBREVIATIONS

A.D.Es = Adverse Drug Events

A.D.Rs = Adverse Drug Reactions

ACEis = Angiotensin - Converting Enzyme Inhibitors

AKI = Acute Kidney Injury

ALT = Alanine Aminotransferase (SGPT)

ARBs = Angiotensin II Receptor Blockers

ASHP = American Society of Health-System Pharmacists

AST = Aspartate Aminotransferase (SGOT)

AV Block = Atrioventricular Block

BBs = Beta-Blockers

BMI = Body Mass Index

BP = Blood Pressure

C.H.D = Coronary Heart Disease

CAD = Coronary Artery Disease

CBP = Clinical Blood Pressure (Office Measurements)

CCBs = Calcium Channel Blockers

CKD = Chronic Kidney Disease

CNS = Central Nervous System

COPD = Chronic Obstructive Pulmonary Disease

CPK = Creatine Phosphokinase

D.M. TYPE 2 = Diabetes Mellitus Type 2

D.R.P = Drug Related problem

DASH = Dietary Approaches to Stop Hypertension

DBP = Diastolic Blood Pressure

DIU = Diuretics

DTBP = Day Time Blood Pressure (Out of Office Measurements)

eGFR = estimated Glomerular Filtration Rate

ESH = European Society of Hypertension

ESRD = End Stage Renal Disease

FDC = Fixed-Dose Combination

H.F = Heart Failure

HbA1c = Glycated Hemoglobin

HDL = High Density Lipoprotein

HMG-CoA = 3-Hydroxy-3-Methyl-Glutaryl-CoA Reductase

hs-CRP = High Sensitivity C-Reactive Protein

ISH = Isolated Systolic Hypertension

LDL = Low Density Lipoprotein

M.I = Myocardial Infarction

MAOIs = Monoamine Oxidase Inhibitors

NMDA = N-Methyl-D-Aspartate

NSAIDs = Non Steroidal Anti-inflammatory Drugs

P.EDEMA = Peripheral Edema

PCNE = Pharmaceutical Care Network Europe

QoL = Quality of Life

SBP = Systolic Blood Pressure

SSRIs = Selective Serotonin Reuptake Inhibitors

T.S.H = Thyroid Stimulating Hormone

TC = Total Cholesterol Level

TCA = Tricyclic Antidepressants

TG = Triglycerides Level

WHO = World Health Organization

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