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Arterial Hypertension and its relation to atherosclerosis

(Diploma Thesis)

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ABSTRAKT

Tato práce se zabývá arteriální hypertenzí ve vztahu s aterosklerózou, kde lidé s vysokým krevním tlakem mají větší pravděpodobnost vzniku ischemické choroby srdeční. Obě nemoci jsou pro život nebezpečné. Podstatou této práce je posoudit a analyzovat, v první části arteriální hypertenzi, poté budeme zkoumat vše o ateroskleróze a v poslední fázi budeme analyzovat vztah mezi nimi. Závěrem posuzování hypertenze a aterosklerózy je způsob jejich léčby, zahrnuje užívání léků, dávkování a vše co se týká lékové terapie. Do této diplomové práce lze také zahrnout prevenci a řízení hypertenze a aterosklerózy.

ABSTRACT

This thesis is about arterial Hypertension in relationship with Atherosclerosis, where people with high blood pressure are more likely to develop coronary artery disease. Both health diseases are serious for continuing of life.

The rationale of this thesis is to examine and analyze at the first part of this thesis, the arterial hypertension, then we will examine all about atherosclerosis and at the last stage we are going to analyze the relationship between the two of them.

In the examination of hypertension and atherosclerosis is concluded the treatment methods in both, the drugs including use, dosage and everything concerns drugs therapy.

Prevention and management of hypertension and atherosclerosis will also include in this thesis diploma.

Contents

1 Introduction

Over the past century, we have recognized that blood pressure (BP) is a reason of an increase the risk for cardiovascular disease. Blood pressure divided into low and high blood pressure where in this diploma thesis we are going to examine the high blood pressure (hypertension).

Ventricles force blood into large, thick- walled elastic arteries close to the heart that expand as the blood to continuously into them. High blood pressure in these arteries forces the blood to continuously move into areas where the pressure is lower. [1]

Hypertension is the major risk factor for cardiovascular disease, which may lead to dead, but also it can be control by treatment to reduce risk for cardiovascular disease and extend life.

Hypertension from its own is a serious health problem and in relation with atherosclerosis the problem comes more seriousness. Several risk factors may contribute to coronary artery disease and hypertension including diabetes, smoking, stress, age, genetics and family history, obesity and physical inactivity.

Hypertension is usually one of the major causes of atherosclerosis, despite the fact that there is not enough empirical research to justify it. Nevertheless, the cellular and molecular mechanisms of the pathogenesis of atherosclerosis and the effects of hypertension have been clearly defined and researchers have come to suggest that the two processes have certain common mechanisms. [2]

During the past few years, however, a large amount of information has been collected on the vascular inflammation, indicating that inflammation may involve in the initiation as well as development of hypertension and coronary artery disease and allowing us to reconsidering the pathogenic mechanisms of those diseases.

2 Aims of Work

Hypertension is a health condition with a high percentage in worldwide. It is usually creating by reasons such lifestyle, diet or genetics. Hypertensive people have the risk of other diseases that causes by high blood pressure such atherosclerosis.

The objectives of this study are:

1. To examine the hypertension as alone health condition in all ages; with concentration symptoms, causes, treatment and other.
2. To analyze the medicines that should help the hypertensive patients.
3. Atherosclerosis will examine as well in all aspects by alone and also in relation with hypertension.

3 Hypertension

3.1 Definition

In order to understand the meaning of hypertension, we need to have a general view of blood pressure. Marieb suggest that blood pressure is the pressure the blood exerts against the inner walls of the blood vessels, and it is the force that keeps blood circulating continuously even between heartbeats**.** [1]

There are many definitions about hypertension and felt appropriate to mention several definitions to have an open opinion by formulating definitions of experienced scientists. Hypertension is a cardiovascular disease where is usual chronic and it causes when blood pressure excess the normal grade. It is a disease, which has different names such high blood pressure and in sometimes when has unknown cause it called essential hypertension where doctors are not able to know a single cause. [3] There are also more names, when someone has only high systolic blood pressure this is called isolated systolic hypertension (ISH). This condition is more likely in older people. [4]

Another definition holds that hypertension is likely to be due to one single cause and it is typically the result of a complex interaction between the individual's genes and his environment. Environmental factors, high salt intake and psychological stress can lead to hypertension because nervous system is influenced to increase the blood pressure. Being overweight, diabetic or alcoholic person or have a genetic problem then it is more likely to have a predisposed to hypertension. [5]

Hypertension, or high blood pressure, also, is a silent killer because it may progress for years without symptoms, slowly chipping away at the blood vessels, heart and kidneys. It is classified as a cardiovascular disease (CVD) as a result the major underlying cause of heart attacks and strokes.

Secondary hypertension is a type of hypertension resulting from underlying or condition. Secondary hypertension can be caused by conditions that affect kidneys, arteries, heart or endocrine system. [5]

Hypertension is estimated to cause 4.5% of current global disease burden and is as prevalent in many developing countries. [6]

4 Symptoms

Like all the diseases thus the hypertension has symptoms but also in many times hits insidiously the human organism. Symptoms will not alert you every time you get high blood pressure. Therefore, having our blood pressure constantly checked is highly important as we prevent it from increasing. If we do not, then we take a dangerous risk of our life including stroke and heart disease.

In some rare case of people with high blood pressure experiencing symptoms such headache, dizziness, chest pains, [7] blurred or double vision, nosebleeds, facial flushing or shortness of breath, blood spots in the eyes are more common in people with diabetes or high blood pressure. [8]

However, those symptoms may not lead to the diagnosis of hypertension because each symptom of the above can be a cause of other causes. As an example, blood spots in the eyes may be is damage to the optic nerve or facial flushing is response to certain triggers such as sun exposure, cold weather, spicy foods, wind, hot drinks and skin-care products and can also occur with emotional stress, exposure to heat or hot water, alcohol consumption and exercise, all of which can raise blood pressure temporarily. [9]

5 Causes

Some major causes of high blood pressure are very simple that can be easily understood by humans, but some other causes are flow without seeking by individuals. There are literally dozens of situations that can cause problems in either of the primary determinants of blood pressure. [5]

The most common root causes high pressure are divided into eight categories which are salt overdose, kidney disease, stress, aging, overweight, excess alcohol, genetics and certain medications.

5.1 Salt intake

Blood volume has the trend to increase blood pressure when sodium excesses the normal intake. High proportion of salt intake in blood volume makes you feel thirsty but the extra fluid expanding into your blood volume, which increases the blood pressure.[5] No matter if

you're taking too much salt and your blood pressure is in normal stage because the coronary heart disease does not start when you have high blood pressure. A research shows that blood pressure increases by 15 mmHg between the ages of twenty- five and fifty- five. Another study taken place between two villages' shows that the village with low salt intake has huge difference in results of blood pressure, nevertheless the other village had high blood pressure .[10]

Drs Rose and Jeremiah Stamler shown that eating less salt can prevent the development of hypertension (over 140/90 mmHg) in a person with high normal blood pressure (130- 139/85-89 mmHg).[5] By all those researches we can conclude that salt intake is the most important and seriousness cause of increase blood pressure. Also there is a proof coming from epidemiological, migration and intervention studies, treatment trials, genetic studies and from animal models. [10]

5.2 Kidney disease

Kidneys have a significant role in blood pressure because they have the responsibility of regulating the arterial blood pressure by modify blood volume. But how are actually high blood pressure and kidney disease related? The answer is twofold: a) High blood pressure is a leading cause of CKD (Chronic kidney disease). With time, blood vessels are destroyed by high blood pressure. This in effect, reduces the blood supply to important organs like the kidneys. High blood pressure also damages the tint filtering units in kidneys. As a consequence, the kidneys may well stop removing wastes and extra fluid from blood, b) High blood pressure can also be o complication of CKD. Thus, it follows that in the case of CKD, high blood pressure makes it more likely that your kidney disease will get worse causing you further heart problems.[11] Moreover, when arterial blood pressure is low, certain kidney cells release the enzyme renin into the blood. Renin triggers a series of chemical reactions that result in the formation of angiotensin II. Angiotensin excites the adrenal cortex to liberate aldosterone, a hormone that boosts ion absorption sodium by the kidneys. Sodium moves through the blood and the blood volume and blood pressure, both rises. [1]

5.3 Stress

" Stress was the most frequently reported problem by all categories of the population, with the exception of the elementary education group of pupils aged from 10 to 14 years old; within which stress, although still at high levels, ranked below hypertension and cardiovascular disease".[12] In addition, stress can cause hypertension through repeated blood pressure elevations as well as by stimulation of the nervous system to produce large amounts of vasoconstriction hormones that increase blood pressure. Factors affecting blood force exerted per unit area through stress include white coat high blood pressure, job strain, race, social environment, and emotional distress. [13] Studies show that stress does not directly cause high blood pressure but can effect on its development. Also, a non- pharmacologic treatment are found to manage stress to reduce high blood pressure. Therefore the consequence of stress on blood force per unit area is of increasing relevance and importance. Although stress may not directly cause high blood pressure, it can lead to ingeminated blood force per unit area elevations, which eventually may lead to high blood pressure.

5.4 Aging

AGE (YEARS)	SYSTOLIC PRESSURE (MM HG)	DIASTOLIC PRESSURE (MM HG)
NEWBORN	80	45
10	105	70
20	120	80
40	125	85
60	135	88

Figure 1. Blood pressure by aging. **Source:** McGowan and McGowan-Chopra 2001.

The risk of developing hypertension is increases as you get older because the valves inside the heart, which control the direction of blood flow, thicken and become stiffer. A heart murmur caused by valve stiffness is fairly common in the elderly. [5]

5.5 Overweight

High blood pressure is more common among the obese than among the no obese and, conversely, a significant proportion of hypertensive persons in the population are overweight. The mortality rates for obese hypertensive persons are higher than those with obesity alone or hypertensive alone.

It has been shown that blood-pressure control is more difficult to be achieved in obese than lean hypertensive patients. Several lines of evidence indicate a graded positive correlation between body mass index and blood pressure levels, while weight loss results in blood pressure reduction. [14]

5.6 Excess alcohol

MacGregor and Kaplan suggest that heavy alcohol consumption causes distinguished elevations in blood force per unit area and surreptitious alcoholism can be a cause of resistant high blood pressure until the underlying problem is bring revealed. Health professionals said over times that alcohol in daily use is good for the heart, but people misunderstand this phrase and in sometimes they consume large amounts of alcohol on a daily basis. [10]

5.7 Genetics

The genetic interaction ascertains the high blood pressure since children who have hypertensive parents are more prone. Twin studies document greater concordance of blood pressures of monozygotic than dizygotic twins, [15] and population studies demonstrate greater similarity of blood pressure within families than between families. [15] Single genes can impact large effects on blood pressure is demonstrated by rare Mendelian forms of high and low blood pressure. High blood pressure is about twice as common in subjects who have one or two hypertensive parents, and many epidemiological studies propose that genetic factors account for approximately 30% of the variation in blood force per unit area in various populations. [16]

Regarding the seventh report of the Joint National Committee genetic abnormalities associated with several rare forms of hypertension, including mineralocorticoid-remediable aldosteronism, 11beta-hydroxylase and 17alpha-hydroxylase deficiencies, Liddle's syndrome, the syndrome of apparent mineralocorticoid excess, and pseudohypoaldosteronism type II .[17]

6 Pathophysiology

Physiological mechanisms are involved to conservation the normal blood pressure and the disorder is playing an important role in the development of hypertension. In some cases the contributing factors of increasing the blood pressure in hypertensive patients may vary among individuals.

Genetics, endothelial dysfunction, low birth, weight and intrauterine nutrition and neurovascular anomalies have been evaluated as factors of hypertension. Cardiac output, Peripheral resistance, Renin- aldosterone system, and Autonomic nervous system are some of the physiological mechanisms involved in development of hypertension. [18]

Pathophysiologic mechanisms that lead to blood pressure elevation are very complicated and as an effect mechanistically based antihypertensive treatment is rarely possible in any hypertensive patient.[19] Researchers tend to highly recommend a generic approach to treating hypertension with little emphasis on selecting therapy on the basis of the underlying pathophysiology of the elevated blood pressure .[20]

6.1 Cardiac output and peripheral resistance

Maintaining a normal blood pressure depends on the balance between cardiac output and peripheral vascular resistance. Results shows that most hypertensive patients have a normal cardiac output but they have a raised peripheral resistance. Peripheral resistance is determined by small arterioles, where their walls contain smooth muscle cells. “Contraction of smooth muscle cells is thought to be related to a rise in intracellular calcium concentration, which may explain the vasodilatatory effect of drugs that block the calcium channels”.[16]

Clancy and McVicar suggest that peripheral resistance is regulated by the activity of the sympathetic nervous system, which promotes constriction and dilation of arterioles, or by the release of vasoconstrictor hormones. According to some commentators and researchers on the pathogenesis of hypertension, cardiovascular risk factors, tend to occur more frequently. [21] Approximately 40% of people with hypertension also have hypercholesterolemia. [22] Furthermore, genetic studies have established a clear association between hypertension and dyslipidemia. Moreover, hypertension tends to be apparent in type 2 diabetes patients. It is also important to note that hypertension is approximately twice as common in persons with

diabetes as in persons without diabetes, and this association is even stronger in African Americans and Mexican Americans. [23]

6.2 Renin- aldosterone system

The renin–angiotensin system (RAS) or the renin–angiotensin–aldosterone system (RAAS) is a hormone system that regulates blood pressure and fluid balance. The renin- angiotensin system is perhaps the most important of the endocrine systems that affect the control of blood pressure. Renin is also responsible for converting rennin substrate (angiotensinogen) to angiotensin I, a physiologically inactive substance which is rapidly converted to angiotensin II in the lungs by angiotensin converting enzyme (ACE). Worth mentioning is that angiotensin II is a potent vasoconstrictor and thus causes a rise in blood pressure. Moreover, it stimulates the release of aldosterone from the zona glomerulosa of the adrenal gland which as in effect increases blood pressure related to sodium and water retention. [16]

7 Diagnosis of hypertension and measurement

Initial management of hypertension conventionally requires a diagnosis based on several clinic or office blood pressure measurements. “Ambulatory blood pressure monitoring, however, estimates “true” mean blood pressure more accurately than clinic measurement because multiple readings are taken; it has also been shown to have better correlation with a range of cardiovascular outcomes and end organ damage”.[24] It is typically used when there is uncertainness in diagnosing, opposition to treatment, irregular or diurnal variation, or concerns about variability and the "white coat" consequence ambulatory blood pressure monitoring.

Home blood pressure monitoring has become very popular and also widely debated in terms of ambulatory versus home blood pressure. It is consider one of the best prognostic indicators regarding to stroke and cardiovascular mortality and can determine white coat and hidden hypertension. [24]

However, a study conducted by Eguchi et al yielded to quite different results. When home and one of the ambulatory blood pressure values were simultaneously included in the same regression model, each of the ambulatory blood pressure values remained a significant predictor of silent cerebrovascular lesions, whereas home blood pressure lost its predictive value. Of the ambulatory blood pressure values, night-time blood pressure was the strongest

predictor of silent cerebrovascular lesions. The home blood pressure value was more closely associated with the risk of carotid atherosclerosis than any of the ambulatory blood pressure values when home and one of the ambulatory blood pressure values were simultaneously included in the same regression model. The casual/clinic blood pressure value had no significant association with the risk of subclinical cerebrovascular diseases. Although the clinical indications for ambulatory blood pressure monitoring and home blood pressure measurements may overlap, the clinical significance of each method for predicting target organ damage may differ for different target organs. [25]

Notwithstanding the differences between home blood pressure monitoring and ambulatory or clinic patients should conform to some standards and prerequisites. Before and during blood pressure measurement patients should have not smoked in the last 30 minutes and also must be relaxed since anxiety can function negative as a result of an increase blood pressure. Patients should be seated comfortable or lying in a bed with the arm supported on a pillow at a level of the heart.

Blood pressure is measured in millimetres of mercury (mm Hg) and recorded with the systolic number first, followed by the diastolic number. For example, a normal blood pressure would be recorded as something under 120/80 mm Hg. [25]

7.1 Manual measurement

This method is used to measure blood pressure with a stethoscope placed in the brachial artery of the arm.

Auscultator methods have three stages to measure blood pressure where at first the blood pressure cuff is wrapped snugly around the arm just above the elbow and inflated until the cuff pressure exceeds the systolic blood pressure. At this point blood flow into the arm is stopped, and a brachial pulse cannot be felt or heard. At next stage the pressure in the cuff is gradually reduced while the examiner listens for sounds in the brachial artery with a stethoscope. The pressure read as the first soft tapping sounds are heard is recorded as the systolic pressure. Then, as the pressure is reduced still further, the sounds become louder and more distinct; when the artery is no longer constricted and blood flows freely, the sounds can no longer be heard. The pressure at which the sounds disappear is recorded as the diastolic pressure. [24]

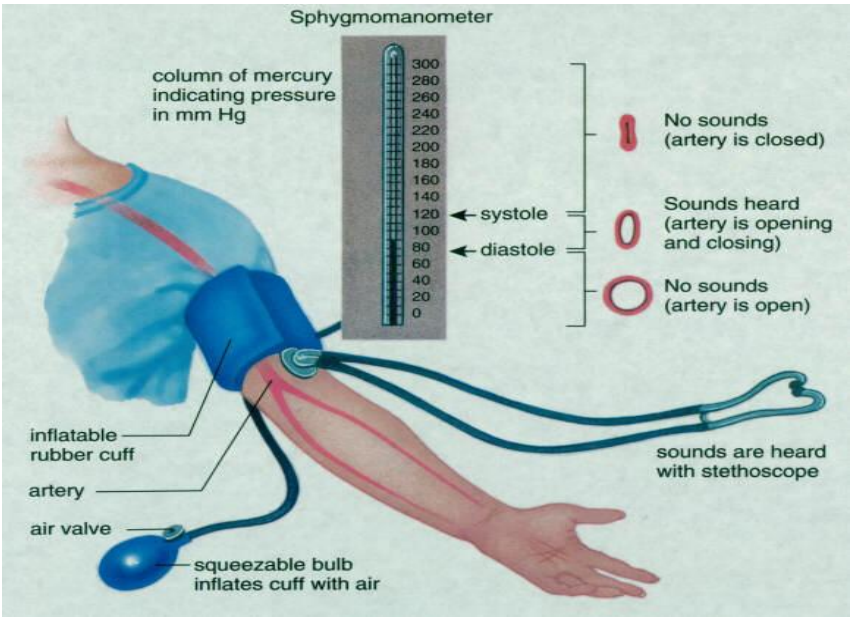

Figure 2: Manual measurement with stethoscope

Source: How to measure blood pressure and what it all means, *http://homepage.smc.edu/wissmann_paul/anatomy1/1bloodpressure.html* Retrieved 2 February 2014

7.2 Electronic measurement

In nowadays electronic equipment is the most preferable way to measure blood pressure and also clinicians used it much more than mercury sphygmomanometer. But when a patient has irregular heartbeats the manual method is using. [26]

8 Management

8.1 Non pharmacological management:

Lifestyle management is playing a significant role in life even you are not a hypertensive person. It can help individuals to prevent hypertension and can reduce the risk of blood pressure related clinical complication. Gupta and Guptha suggested that "in hypertensive individuals, lifestyle modifications can serve as initial treatment before the start of drug therapy and as an adjunct to drug therapy in persons already on medication. [27]

Although some lifestyle modifications may seem to offer only minimal blood pressure–lowering effects, they should not be discounted. A reduction in systolic blood pressure of 5

mm Hg has been associated in observational studies with reductions of 14 percent in mortality caused by stroke, 9 percent in mortality caused by heart disease, and 7 percent in all-cause mortality. In addition, a weight loss of 10 lb (4.5 kg), a realistic goal for most individuals who are overweight, can reduce or prevent hypertension. [28]

Generally, five lifestyle modifications are recommended by the literature for reducing blood pressure: (1) reducing sodium intake, (2) increasing exercise, (3) moderating alcohol consumption, (4) following the Dietary Approaches to Stop Hypertension (DASH) eating plan and losing weight. The DASH eating plan outlines a diet rich in fruits and vegetables; high in low-fat dairy products, potassium, magnesium, and calcium; and low in total saturated fats These modifications have been proven to reduce blood pressure, although their direct impact on morbidity and mortality is not yet known. [29]

Treatment is successful when multiple factors in the patient's life are addressed, since essential hypertension is considered as a result of interactions between genes and environment. The environmental effects are powerful and explain most of the BP differences between individuals and populations and their control in management of high BP is crucial. [30]

8.2 Pharmacological management

Pharmacological solution to control hypertension is coming after non-pharmacological management. In cases where the blood pressure occurs at a very high level and the life of individual is on danger pharmacological management enters to regulate blood pressure. Under these circumstances pharmacological approaches must be considered. The questions are (i) when to treat and (ii) with which drug? [27]

9 Prevention and treatment

Barriers to prevention include cultural norms; inadequate attention to health education by health care professionals; lack of compensation for health education services ; lack of access to places to engage in physical activity; larger portions of food in restaurants; lack of availability of healthy food options in many schools, worksites and restaurants; lack of exercise programs in schools ; large amounts of sodium added to foods by the food industry and restaurants; and higher food costs that are lower in sodium and calories. Prevention

programs such culturally sensitive; education and lifestyle support should promoted by communities to prevent hypertension. [4]

Therefore, communities, schools, worksites and food industry should contribute to face all mentioned above barriers.

As mentioned, above the treatment for high blood pressure can be non-pharmacological or pharmacological or both together. Non- pharmacological treatments may change significantly our life style by reducing salt, consuming food that is low in fat and eating healthy foods like fruits and vegetables, reducing the alcohol or sweet beverages, which contain sugar. Also, non-pharmacological treatment is to be more active person such to walk more or be active person in any sport. Before starting a drug therapy all those daily habits should involve the life of a hypertensive person. It is the effort of being healthy before the heavy treatment. [27]

Moreover, another prevention technique is the biofeedback therapy, which is very beneficial for reducing blood pressure. Almost all researchers agree that biofeedback therapy promotes relaxation, which can help relieve a number of conditions that are related to stress. [21]

During a biofeedback session, electrodes are attached to your skin. Finger sensors can also be used. These electrodes/sensors send signals to a monitor, which displays a sound, flash of light, or image that represents your heart and breathing rate, blood pressure, skin temperature, sweating, or muscle activity. When you're under stress, these functions change. Your heart rate speeds up, your muscles tighten, your blood pressure rises, you start to sweat, and your breathing quickens. You can see these stress responses as they happen on the monitor, and then get immediate feedback as you try to stop them. Biofeedback sessions are typically done in a therapist's office, but there are computer programs that connect the biofeedback sensor to your own computer. [31]

10 Treatment strategies

Treatment of hypertension is consequently largely empiric, with physicians selecting from approximately 70 different antihypertensive medications until adequate blood pressure reduction is achieved. The category of medication depends on blood pressure measurements and also from other medical problems.

The treatment in hypertensive patients is to be reducing the risk of cardiovascular morbidity and mortality by lowering BP and treating other modifiable risk factors. These goals are achieved through lifestyle modification or drug therapy. [32]

11 Analysis of the drugs, adverse reaction, contraindications, mechanism of action.

11.1 Diuretic Drugs

For high blood pressure, diuretics, commonly known as "water pills," help your body get rid of unneeded water and salt through the urine. Getting rid of excess salt and fluid helps lower blood pressure and can make it easier for your heart to pump.[33] Diuretics are divided into three main categories where each of them is playing a significant role in management of hypertensive patients. Their job is to decrease blood pressure by increasing urine output.[21]Diuretic drugs aid the body acquire disembarrass of excess Na (salt) and H_2O (water) and aid control blood pressure. They are often used in combination with additional prescription therapies.

There are several types of diuretics, also called water pills:

- Loop diuretics, such as bumetanide (Bumex) and furosemide (Lasix), get their name from the loop shaped part of the kidneys where they have their effect.
- Thiazide diuretics include such commonly used diuretics as hydrochlorothiazide (HydroDIURIL, Esidrix), chlorothiazide (Diuril), and chlorthalidone (Hygroton).
- Potassium-sparing diuretics prevent the loss of potassium, which is a problem with other types of diuretics. Examples of potassium-sparing diuretics are amiloride (Midamor) and Triamterene (Dyrenium).

In addition, some medicines contain combinations of two diuretics. The brands Dyazide and Maxzide, for example, contain the thiazide diuretic hydrochlorothiazide with the potassium-sparing diuretic Triamterene. [21]

More details about the aforementioned types are as follows:

11.1.1 Thiazide-type

Thiazide-type diuretics are among the best-tolerated antihypertensive agents in terms of symptomatic adverse effects, diuretic-related adverse side effects include those with established mechanisms (eg, such as electrolyte changes and/or metabolic abnormalities) and other side effects, which are less well understood mechanistically (eg, impotence), although the latter is not universally accepted as a diuretic-related side effect . According to a study conducted by James et al (2005) and which aimed at investigating the diabetogenic potential of thiazide-type diuretic and beta-blocker combinations in patients with hypertension showed that patients exposed to treatment regimens combining thiazides and beta-blockers are at greater risk of developing diabetes than regimens avoiding this combination of drugs (risk ratio for alternative therapy 0.81, 95% confidence interval 0.77–0.86). Current data cannot inform reliably about the risks associated with individual older drugs because of similar overall exposures in patients starting on newer and older drugs. Therefore, the implications of this study are vital because the results suggest that the routine combined use of a thiazide with a beta-blocker should be questioned in the early management of hypertension, particularly in patients who are at increased risk of developing new-onset diabetes. Consequently, in such patients the increased risk of developing diabetes may exceed the benefit of blood pressure lowering. **[34]**

11.1.1.1 Chlorothiazide:

Chlorothiazide (Diuril) has been widely found to be a potent orally effective diuretic and saluretic agent. Because it's pronounced saluretic action a clinical trial of this agent was undertaken in hypertensive patients. **[35]** Their study was conducted with a total of 73 patients under prior treatment with various anti-hypertensive agents. The findings revealed that the reduction in blood pressure after these various treatment regimes varied from good to poor in individual cases and for the group as a whole. After the addition of Chlorothiazide there was a prompt further reduction in blood pressure in 68 patients. Worth noting is the fact that the average control blood pressure for the whole group before any therapy was 211 systolic and 126 diastolic, but after Chlorothiazide this had gone 153 systolic and 98 diastolic. **[35]**

The use of Chlorothiazide is highly important because it helps to prevent strokes, heart attacks and kidney problems. It increases the amount of urine to get rid of extra salt and water.

When administered the Diuril through the mouth with or without food. The daily dose is once or twice daily as your doctor suggest. It is recommended to take the pill 4 hours before bedtime because of urinate. If you are taking the suspension, shake the bottle well before each dose and measure the dose using a medication spoon/ cup. [36]

The appropriate prescription dose is based on your medical condition. In children the dose is based on age and weight. Children under 2 years old should not take more than375 milligrams per day, and children between 2 – 12 years old should take up to 1,000 milligrams per day. [36]

Some researchers warn us against increased dose and suggest we should skip doses or stop taking the medication without your doctor's advice even you feel well because in high blood pressure treatment the drug needs several weeks before the full benefit of it. [37]

The adverse effects of Diuril vary and could be as follows: dizziness, light-headedness, headache, and blurred vision, loss of appetite, stomach upset, diarrhea or constipation. Also, it may cause dehydration and loss of salt/ minerals. Symptoms of dehydration or mineral loss include dry mouth, thirst, muscle cramps, weakness, fast heartbeat, nausea, vomiting, dizziness, unusual drowsiness, fainting and others. [36]

It is strongly recommended that if you are allergic to chlorothiazide or if you have any other allergies tell it to your doctor because the drugs contains ingredients where can cause allergic reaction or other problems. Tell your doctor if you have kidney disease, liver disease and diabetes because duiril have effects in those health conditions. [36]

11.1.1.2 Hydrochlorothiazide

HCTZ (hydrochlorothiazide) is a thiazide diuretic (water pill) that helps prevent your body from absorbing too much salt, which can cause fluid retention. HCTZ treats fluid retention (edema) in people with congestive heart failure, cirrhosis of the liver, or kidney disorders, or edema caused by taking steroids or estrogen. This medication is also used to treat high blood pressure (hypertension). [38]

A study conducted by Jamerson et al which aimed at identifying the optimal combination drug therapy for hypertension found that the benazepril–amlodipine combination was superior to the benazepril–hydrochlorothiazide combination in reducing cardiovascular

events in patients with hypertension who were at high risk for such events.[39] Furthermore, another study conducted by Frishman et al (1994) had come to an extremely important finding as it showed that the effects of bisoprolol and hydrochlorothiazide were additive with respect to reductions in diastolic and systolic blood pressures over the dosage ranges studied. The sample and the inclusive criteria of the study were as follows: a total of 512 patients with mild to moderate essential hypertension were randomized to once-daily treatment with bisoprolol (0, 2.5, 10, or 40 mg), hydrochlorothiazide (0, 6.25, or 25 mg), and all possible combinations. Diastolic and systolic blood pressures were monitored during this 12-week trial. The addition of hydrochlorothiazide (or bisoprolol) to therapy with bisoprolol (or hydrochlorothiazide) produced an incremental reduction in blood pressure .Dosages of hydrochlorothiazide as low as 6.25 mg/d contributed a significant antihypertensive effect. A hydrochlorothiazide dosage of 6.25 mg/d produced significantly less hypokalemia and less of an increase in uric acid levels than a dosage of 25 mg/d. The low-dose combination of bisoprolol, 2.5 mg/d, and hydrochlorothiazide, 6.25 mg/d, reduced diastolic blood pressure to lower than 90 mm Hg in 61% of patients and demonstrated a safety profile that compared favorably with that of placebo. Worth mentioning is that the importance of the study largely rests on its methodological design which uses a factorial design the utility of which, is basically, according to the researchers, to characterize dose-response relationships and to test the potential interactions between various antihypertensive agents has been demonstrated. The combination of low dosages of bisoprolol and hydrochlorothiazide may be a rational alternative to conventional stepped-care therapy for the initial treatment of patients with mild to moderate hypertension. [40]

11.1.1.3 Indapamide:

Because hypertension is an important risk factor of cardiovascular morbidity and mortality that can be at least in part decreased by pharmacological reduction in elevated blood pressure, it is necessary, according to the views and findings of some research, that an antihypertensive agent be effective, but at the same time well tolerated and, according to some recent hypotheses, have no deleterious effect on serum electrolyte levels, as well as lipoprotein and glucose tolerance. [41]

However, due to different cultural and social backgrounds, lifestyles, and so on, the tolerability may differ from one population to another and the conclusions drawn from a

population cannot be extrapolated to people of other countries.[41] For these reasons, the well-being of patients, as well as the tolerability of indapamide, a non-thiazide diuretic, has been in vestigated in patients with hypertension of mild and moderate degree from different parts of Italy with a satisfactory blood-pressure response to this drug (−22.8 ± 0.6 /−17.1 ± 0.5 mm Hg). Simultaneous to the significant blood-pressure reduction, the only significant change among the metabolic effects was a slight reduction in plasma potassium levels (−0.37 ± 0.03 meq/liter). Therefore, the study that was conducted by Leonetti et al (1988) it is very important because it reports that the tolerability was, on the whole, very good with a tendency toward an improvement of well-being in patients, the majority of whom were already asymptomatic before they had started the treatment.Therefore, according to the findings of the aforementioned research we may well come to the conclusion that Indapamide is used to treat hypertension. The substance of indapamine is used to reduce extra salt and fluid in the body caused by congestive heart failure. [41] As all other diuretics pills this also increases the amount of urine as a result the rid of extra water and salt that helps the blood to flow more easily in vessels.[42] Nevertheless, like all agents for hypertension, Indapamide has also some effects such as follows: dizziness or headaches are the possible effects. Indapamine also may cause to dehydration (too much body water and salts may lost). Diarrhea, vomiting or sweating can increase the risk. It is essential to drink plenty of fluids. [42]

The blood sugar level may rise which can cause diabetes. However if you have diabetes you have to check your blood sugar daily, take medication, exercising or follow a diet program [42] There is not a specific and serious allergic reaction to this drug but if you may notice any symptoms such rash, itching/ swelling, dizziness or trouble breathing.

11.1.1.4 Metolazone

Zaroxolyn and Mykrox:

Metolazone is a diuretic ("water pill") used in the treatment of high blood pressure and fluid accumulation. It works by blocking salt and fluid retention by the kidneys, thereby increasing urinary output of salt and water (diuresis). Although it is not a true thiazide, metolazone is chemically related to the thiazide class of diuretics (for example, chlorthalidone [Hygroton], hydrochlorothiazide), and works in a similar manner. Zaroxolyn is the original formulation of metolazone, and Diulo is similar. The absorption of these two drugs is relatively incomplete. Mykrox has more complete absorption. Therefore, less

Mykrox needs to be given to have the same effects as a larger dose of Zaroxolyn or Diulo. The FDA approved Metolazone in 1973. [43]

As all drugs, metolazone is not without effects. Therefore, side effects of this drug are dizziness, light-headedness, headache, and blurred vision, loss of appetite, stomach upset, diarrhea or constipation. Also, it may cause dehydration and loss of salt/ minerals. Symptoms of dehydration or mineral loss include dry mouth, thirst, muscle cramps, weakness, fast heartbeat, nausea, vomiting, dizziness, unusual drowsiness, fainting and others. [44]

Some other effects may occurs numbness/ tingling of the arms/ legs, decreased sexual ability, persistent sore throat or fever, bleeding or bruising, stomach/ abdominal pain, nausea/ vomiting, yellowing of eyes or skin. [44]

Allergic reactions are unlikely but there is a possibility to change existing data. The symptoms that may cause serious allergic reaction are rash, itching/ swelling of the face tongue or throat, dizziness or trouble breathing. [44]

Some precautions to be taken into consideration may well require awareness of the fact that inactive ingredients in the Zaroxolyn may cause allergic reaction or other problems. Therapy with this drug must be controlled if there is a kidney disease, liver disease, untreated mineral imbalance, gout and lupus. [44]

Zaroxolyn may well affect blood sugar lever therefore it is recommend in diabetic patient to check blood sugar level. Another precaution is that taking this drug there is a possibility to reduce potassium level in the blood. If that happens doctor must add potassium in a patient's diet. [44]

Sensitiveness to the sun, dizziness, vision problems, limit alcohol, do not drive or use machinery are also some of the precautions. [44]

As far as interaction is concerned, Zaroxolyn should not be used in combination with cisapride because of serious interactions that may generate. Cholestyramine, colestipol, diazoxide, digoxin and lithium are some drugs which must watch out during the treatment with Zaroxolyn. [44]

In the case of an overdose, contact a poison control centre or emergency room immediately. Symptoms of overdose may include fainting, severe weakness, a severe decrease in amount of urine, or slow or shallow breathing. [44]

11.1.1.5 Chlorthalidone :

Chlorthalidone is a diuretic (water pill). It works by reducing the kidneys' ability to hold on to salt and water and increasing the kidneys' production of urine (diuresis). It is used to eliminate excess salt and water from the body and to treat high blood pressure. Chlorthalidone is closely related chemically to hydrochlorothiazide. [45] It also helps to prevent strokes, heart attacks, and kidney problems. It also reduces extra salt and water in the body caused by conditions such as heart failure, liver disease and kidney disease. In that way it helps to decrease swelling and breathing problem caused by fluid in the lugs. Also increases the amount of urine as a result the rid of extra water and salt that helps the blood to flow more easily in vessels. [46]

Unlike loop diuretics, Chlortalidone efficacy is diminished in patients with certain renal diseases (eg chronic renal disease). A clinical trial (ALLHAT) in 2002 compared chlortalidone to doxazosin in the treatment of high-risk hypertensive patients. In this study, only chlortalidone significantly reduced the risk of combined cardiovascular disease events, especially heart failure, when compared with drugs such as doxazosin.[47] Hence, what is interesting about the ALLAT study is the fact that findings yielded no significant difference in all-cause mortality, fatal heart disease, or non-fatal myocardial infarction when chlortalidone was compared with lisinopril or amlodipine but did show decrease rates of heart failure after 6 years when compared with amlodipine and decreased rates of cerebrovascular disease after 6 years when compared with lisinopril leading the study conclusions to say that thiazide-type diuretics are preferred first-step in antihypertensive therapy.[47]

This medication may also be used to treat a certain disease (diabetes insipidus) and to help prevent calcium kidney stones in people with increased calcium in their urine (hypercalciuria). [46]

Hygroton is a trademark of Novartis Pharmaceuticals for Chlorthalidone, an antihypertensive diuretic based on Thiamine. In other words, Hygroton tablets contain the active ingredient chlortalidone, which is a type of medicine known as a thiazide-related

diuretic.[48]

A study conducted by Vaughan et al with 71 patients with essential hypertension exhibiting either low or normal plasma renin activity showed that the patients with low renin activity were more responsive to both of these diuretic agents, but neither drug was uniquely or uniformly effective in this group. Blood pressure became normal in only 57 percent of patients with reduced renin activity receiving spironolactone therapy, whereas 24 percent maintained a diastolic pressure greater than 105 mm Hg; 44 percent of them responded to chlorthalidone, but 31 percent did not. In patients with normal renin values the blood pressure was normalized in 36 percent by spironolactone and in 37.5 percent by chlorthalidone. [49]

The effects of chlorthalidone vary and these manifest as upset stomach, dizziness and light-headedness are the main symptoms. To help you avoid dizziness get up slowly when rising from sitting or lying position. It may cause dehydration and loss of salt/ minerals. A symptom of dehydration or mineral loss includes dry mouth, thirst, muscle cramps, weakness, fast heartbeat and confusion. [46]

Other serious effects are fainting, toe/ joint pain and change the urine amount. Rash, itching/ swelling, dizziness and trouble breathing are some other symptom you may have if you have a serious allergic reaction to this drug. [46]

11.1.1.6 Furosemide

Furosemide was previously known as frusemide (former BAN), is a loop diuretic used in the treatment of congestive heart failure and edema. It is most commonly marketed by Sanofi under the brand name Lasix, and also under the brand names Fusid and Frumex. [96] It has also been used to prevent Thoroughbred and Standardbred race horses from races. Along with some other diuretics, furosemide is also included on the World Anti-Doping Agency's banned drug list due to its alleged use as a masking agent for other drugs. [50]

Lasix, its generic name being furosemide (fur OH se mide), usually known as ‘‘furosemide’’ is a loop diuretic (water pill) that prevents your body from absorbing too much salt, allowing the salt to instead be passed in urine.

Lasix treats fluid retention (edema) in people with congestive heart failure, liver disease, or a kidney disorder such as nephrotic syndrome. This medication is also used to treat high blood pressure. [51]

A study conducted by Olshan et al (1981) yielded to some significant results. More precisely the study was carried out with twelve white men with essential hypertension and they were treated for 1 month in randomized order with either placebo or low-dose furosemide (40 mg/day) and compared to 22 race, age-, and diet-matched normal controls. The findings revealed that furosemide therapy significantly reduced mean arterial pressure (108.6 +/- 2.4 vs. 101.0 +/- 2.7 mm Hg. $p < 0.02$) in association with a significant increase in 24 hr urinary kallikrein activity (7.9 +/- 1.8 vs. 13.4 +/- 2.8 esterase units/24 hr. $p < 0.02$). Normal controls on no therapy excreted 19.4 +/- 2.6 esterase units/24hr of urinary kallikrein activity, significantly greater than hypertensives on placebo ($p < 0.01$) but not hypertensives on furosemide ($p < 0.01$). The decrease in mean arterial pressure and the increase in urinary kallikrein activity induced by furosemide were not associated with a demonstrable change in renal hemodynamics. Plasma renin activity, or plasma aldosterone concentration, but they were associated with a significant increase in intravascular volume (5.876 +/- 339 vs. 6.808 +/- 346 ml. $p < 0.01$). A significant ($p < 0.05$) inverse correlation between mean arterial pressure and urinary kallikrein activity suggests a possible role for the kallikrein-kinin system in the antihypertensive mechanism of furosemide. [52]

The adverse side effects of lasix manifest as follows: dizziness, light-headedness, headache, and blurred vision. To help you avoid dizziness get up slowly when rising from sitting or lying position. [53]

Lasix can cause serious loss of body water and salt/ mineral, which causes muscle cramps, weakness, tiredness, confusion, dizziness, fainting drowsiness, dry mouth/ thirst, nausea, vomiting, fast/ irregular heartbeat, and unusual decrease in the amount of urine. [53]

There is a possibility to arise serious side effects such numbness/ tingling/ pain/ redness/ swelling of the arms/ legs, hearing changes (ringing in the ears, temporary or permanent deafness), stomach/ abdominal pain, yellowing eyes/ skin .[53]

Allergic reactions are unlikely but there is a possibility to change existing data. The symptoms that may cause serious allergic reaction are rash, itching/ swelling of the face tongue or throat, dizziness or trouble breathing. [53]

Worthnoting is that inactive ingredients in the Lasix may cause allergic reaction or other problems. Therapy with this drug must be controlled if there is a kidney disease, liver disease, untreated mineral imbalance, gout and lupus. [53]

Lasix affect blood sugar lever therefore it is recommended in diabetic patient to check blood sugar level. Another precaution is that taking this drug there is a possibility to reduce potassium level in the blood. If that happens doctor must add potassium in a patient's diet. [53]

Sensitiveness to the sun, dizziness, vision problems, limit alcohol, does not drive or use machinery is also some of the precautions. [53]

11.1.2 Loop-active agents

Loop diuretics should not be used as first-line therapy in hypertension since there are no outcome data with them. They should be reserved for conditions of clinically significant fluid overload (eg, heart failure and significant fluid retention with vasodilator drugs, such as minoxidil) or with advanced renal failure and can be combined with thiazide-type diuretics. [54]

11.1.2.1 Bumetanide

It is used to reduce extra fluid in the body (edema) caused by conditions such as heart failure, liver disease, and kidney disease. This can lessen symptoms such as shortness of breath and swelling in your arms, legs, and abdomen. Bumetanide is a "water pill" (diuretic) that causes you to make more urine. This helps your body get rid of extra water and salt. [55]

A study conducted by Pedrinelli et al (1980) which aimed at investigating the influence of indomethacin on the natriuretic and renin-stimulating effect of bumetanide in essential hypertension, the data analysis yielded to some interesting findings and conclusions. More precisely the study examined the effect of bumetanide on absolute and fractional sodium excretion, creatinine clearance, and plasma renin activity (PRA) which was studied in eight patients with essential hypertension before and after indomethacin. The interesting findings

with which the study came up have been that after bumetanide, urinary sodium excretion increased only in the first 4 hr, creatinine clearance only in the first 2 hr, and PRA rose progressively. After indomethacin, bumetanide caused a smaller increase in urinary sodium excretion, decreased creatinine clearance, and caused a small early and late PRA rise. Prostaglandin inhibition and indomethacin did not, per se, affect the tubular natriuretic mechanism but they abolished both early vascular and sustained PRA-stimulating effects of bumetanide. [56]

The effects of Bumetanide are as follows: Dizziness may occur as your body adjusts to the medication. To reduce the risk of dizziness and light-headedness, get up slowly when rising from a sitting or lying position. [57]

This medication may cause a serious loss of body water (dehydration) and salt/minerals. You may have any of these unlikely but serious side effects: muscle cramps, weakness, unusual tiredness, confusion, severe dizziness, fainting, drowsiness, unusual dry mouth/thirst, nausea, vomiting, fast/irregular heartbeat, unusual decrease in the amount of urine. [57]

Serious side effects occur: numbness/tingling/pain/redness/swelling of the arms/legs, hearing changes (such as ringing in the ears, temporary or permanent decreased hearing/deafness), easy bruising/bleeding. [57]

A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing. [57] It should be also noted that inactive ingredients in the Bumetanide may cause allergic reaction or other problems. Therapy with this drug must be controlled if there is a kidney problem, liver problem, inability to make urine, gout. [57]

Bumetanide affect blood sugar lever therefore it is recommended in diabetic patient to check blood sugar level. Another precaution is that taking this drug there is a possibility to reduce potassium level in the blood. If that happens doctor must add potassium in a patient's diet. [57]

11.1.2.2 Ethacrynic acid:

This medication decreases swelling/ fluid retention caused by conditions such as cancer, congestive heart failure, liver disease and kidney disease. [58]

Ethacrynic acid is an unsaturated ketone derivative of an aryloxyacetic acid. It is designated chemically as [2,3-dichloro-4-(2-methylene-1-oxobutyl) phenoxy] acetic acid, and has a molecular weight of 303.14. Ethacrynic acid is a white, or practically white, crystalline powder, very slightly soluble in water, but soluble in most organic solvents such as alcohols, chloroform, and benzene. Its empirical formula is $C_{13}H_{12}C_{l2}O_4$. [59]

This drug is a strong "water pill" (diuretic). Serious symptoms of dehydration if you use too much Ethacrynic acid. Symptoms usually are loss of appetite, confusion, severe dizziness/fainting, unusual dry mouth/thirst, severe headache, fast/irregular heartbeat, muscle cramps/spasms, nausea/vomiting, numbness/tingling, seizure, decrease in amount of urine, unusual weakness/tiredness. [58]

Very serious side effects occur: easy bleeding/bruising, black/bloody stools, severe watery diarrhea, signs of infection (eg, fever, persistent sore throat), ringing in the ear, feeling of spinning (vertigo), hearing loss, mental/mood changes (eg, extreme sleepiness), pain/redness/new swelling of arms/legs, stomach/abdominal pain, large change in the amount of urine, dark urine, vomit that looks like coffee grounds, yellowing eyes/skin .[58]

A very serious allergic reaction to this drug is rare. However, seek immediate medical attention if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing. [58] This drug can lower potassium/sodium levels in your blood. Your doctor may order you to increase your salt intake or eat foods high in potassium. Carefully follow the diet prescribed by your doctor. Do not change your salt intake without talking with your doctor first. A potassium supplement may be prescribed by your doctor. [58]

This drug should not be used with the following medications because a very serious interaction may occur such as cisapride, furosemide. [58]

11.1.3 Potassium-sparing agents

11.1.3.1 Amiloride

Amiloride HCl, an antikaliuretic-diuretic agent, is a pyrazine-carbonyl-guanidine that is unrelated chemically to other known antikaliuretic or diuretic agents. It is the salt of a moderately strong base (pKa 8.7). It is designated chemically as 3, 5-diamino-6-chloro-N-(diaminomethylene) pyrazinecarboxamide monohydrochloride, dihydrate and has a molecular weight of 302.12. Its empirical formula is $C_6H_8ClN_7O$ † HCl † $2H_2O$. [60]

It is an oral drug and you can use it once daily. As all drugs, amiloride have effects in patient such headache, dizziness, nausea, vomiting, loss of appetite, stomach/ abdominal pain, gas or diarrhea. [60]

Dehydration of this medication causes very dry mouth, thirst, muscle cramps, weakness, fast heartbeat, dizziness, confusion, and decrease in the amount of urine, fainting and seizures. [60]

Allergic reaction such rash, itching/ swelling, dizziness and trouble breathing may occur by the drug. [60]

11.1.3.2 Triamterene

1 Dyrenium

Triamterene, its trade name known as Dyrenium is a potassium-sparing diuretic used in combination with thiazide diuretics for the treatment of hypertension and edema. In combination with hydrochlorothiazide, it is marketed under the names Maxzide and Dyazide. According to Bush et al Triamterene directly blocks the epithelial sodium channel (ENaC) on the lumen side of the kidney collecting tubule. Other diuretics cause a decrease in the sodium concentration of the forming urine due to the entry of sodium into the cell via the ENaC, and the concomitant exit of potassium from the principal cell into the forming urine. Blocking ENaC prevents this from happening. [61]

11.2 Beta- blockers

B-blockers not be considered as first-line therapy in uncomplicated hypertension, especially in older patients. “Concerns about the use of β- blockers as first- line agents for hypertension have been raised because of a 2005 meta- analysis that found β- blockers do not significantly reduce cardiovascular events, especially stroke, compared with other antihypertensive drug classes” .[62]

11.2.1 Atenolol

Atenolol is a selective β_1 receptor antagonist, a drug belonging to the group of beta blockers (sometimes written β-blockers), a class of drugs used primarily in cardiovascular diseases. Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension. It works by slowing down the heart and reducing its workload. Unlike propranolol, atenolol does not pass through the blood–brain barrier thus avoiding various central nervous systems. [63]

11.2.2 Metoprolol:

Metoprolol “is a relatively β1- adrenergic receptor selective agent, but loses this selectivity at higher plasma concentrations. [62]This agent has two formulations; an immediate release (tartrate) and an extended- release (succinate)”. [62]

Metoprolol (tartale) dosage is usually between 1 – 3 times a day and it takes several weeks before the full benefit of this medication.

11.2.3 Labetalol

Labetalol is a mixed alpha/beta adrenergic antagonist that is used to treat high blood pressure. Labetalol has two chiral carbons and consequently exists as four stereoisomers. Two of these isomers, the (*S, S*) - and (*R, S*) - forms are inactive. The third, the (*S, R*)-isomer, is a powerful α_1 blocker. The fourth isomer, the (*R, R*)-isomer which is also known as dilevalol, is a mixed nonselective β blocker and selective α_1 blocker. [64]

Labetalol acts by blocking alpha and beta adrenergic receptors, resulting in decreased peripheral vascular resistance without significant alteration of heart rate or cardiac output. The β:α antagonism of labetalol is approximately 3:1. [64]

The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily with or without food. Patients with severe hypertension may require from 1,200 to 2,400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered twice daily, the same total daily dose administered three times daily may improve tolerability and facilitate further titration? Titration increments should not exceed 200 mg twice daily. [65]

The effects of Labetalol are largely reported as dizziness and tiredness are the most usual effects of this drug. Labetalol can decrease sexual ability. This drug also may reduce the blood flow to the hands and feet. [65]In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor, as compared to 0.7% reported to occur with labetalol HCl alone. [65]

11.3 ACE inhibitors

Angiotensin converting enzyme (ACE) inhibitors are high blood pressure drugs that widen or dilate the blood vessels to improve the amount of blood the heart pumps and to lower blood pressure. [66]

11.3.1 Captopril

1.Capoten

Captropril, its trade neam known as Capoten, is an angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension and some types of congestive heart failure. Captopril was the first ACE inhibitor developed and was considered a breakthrough both because of its novel mechanism of action and also because of the revolutionary development process. [67] The initial dose of CAPOTEN (captopril tablets, USP) is 25 mg build. Or t.i.d. If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg. [68]

11.4 Angiotensin II receptor blockers

11.4.1 Atacand

1. Candesartan

ATACAND (candesartan cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist. Candesartan cilexetil, a no peptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[p-(o-1H-tetrazol-5ylphenyl) benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester). Its empirical formula is $C_{33}H_{34}N_6O_6$. **[69]**

It is also indicated for the treatment of hypertension in adults and children 1 to < 17 years of age. Blood pressure response is dose related over the range of 2 to 32 mg. The usual recommended starting dose of ATACAND is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. ATACAND can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. **[69]** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%). **[69]**

11.5 Calcium channel blocker

11.5.1 Norvasc

1.Amlodipine

Norvasc, its trade name knows as Amlodipine, is the besylate salt of amlodipine, a long-acting calcium channel blocker. Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl] - 4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$. **[70]**

The recommended starting dose is 5 mg once a day. Depending on the patient's response, the dosage can be decreased to 2.5 mg or increased to 10 mg once a day. These adjustments should occur generally at intervals of not less than 2 weeks. The recommended dosage range is 2.5–10 mg once daily. In clinical trials, doses above 10 mg daily showed an increased

blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events. [70]

Adverse events that occurred in 0.5 up to 1.5% of patients who received PLENDIL in all controlled clinical trials at the recommended dosage range of 2.5 mg to 10 mg once a day, and serious adverse events that occurred at a lower rate, or events reported during marketing experience. Myocardial infarction, abdominal pain, diarrhea, vomiting are some of the effects. [70]

11.6 Central agonists

11.6.1 Clonidine

Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2, 6-dichlorophenylamino)-2-imidazoline hydrochloride. Clonidine hydrochloride is an odorless, bitter, white, crystalline substance soluble in water and alcohol. The dose of Catapres (clonidine hydrochloride, USP) tablets must be adjusted according to the patient's individual blood pressure response.0.1 mg tablet twice daily (morning and bedtime). Elderly patients may benefit from a lower initial dose. [71]

Most adverse effects are mild and tend to diminish with continued therapy. The most frequent (which appear to be dose-related) are dry mouth, occurring in about 40 of 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100.[71]

New drug treatment for hypertension

It is obviously that science is evolving rapidly with a revise follow studies that originated much difficulty.

"New drug classes, eg, inhibitors of vasopeptidases, aldosterone synthase and soluble epoxide hydrolase, agonists of natriuretic peptide A and vasoactive intestinal peptide receptor 2, and a novel mineralocorticoid receptor antagonist are in phase II/III of development, while inhibitors of aminopeptidase A, dopamine β-hydroxylase, and the intestinal Na^+/H^+ exchanger 3, agonists of components of the angiotensin-converting enzyme 2/angiotensin (1-7)/ Mas receptor axis and vaccines directed toward angiotensin II and its type 1 receptor are in phase I or preclinical development" [72]

12 Combination treatment of antihypertensive drugs

Combination treatment means another class of blood pressure medication is added to the first drug to increase effectiveness. In most case hypertensive patients are responding to one medication and it takes many tries until to find the most effective drug. Practical strategies for the optimal use of combination therapy continue to evolve from the older stepped-care approach to the use of low-dose combinations, and to initiation of combination therapy in a broader range of hypertensive patients. [73]

Thiazide diuretics may be used alone to treat hypertension. Yet, low-dose diuretics are also used with medications such as beta-blockers.

A beta-blocker is combined with an alpha-blocker. This may be useful for men who have hypertension and an enlarged prostate. The alpha-blocker may help both problems at the same time.

Other combinations may include an ACE inhibitor with a thiazide diuretic. Sometimes, an angiotensin II receptor antagonist is combined with a diuretic. Or an ACE inhibitor may be combined with a calcium channel blocker. [73]

13 Atherosclerosis

13.1 Definition of atherosclerosis

An explanation given by Clancy and McVicar stated that "atherosclerosis is a type of arteriosclerosis characterized by the deposition of lipids, cholesterol compounds, excessive smooth muscle and fibroblastic cells in the form of atheromatous plaques in the blood vessel wall" [p323] [21]. Plaques grow and spread longitudinal the arterial wall, forming a swelling protruding into the lumen, thereby limiting blood flow to the organs that are affected. Plaque is a sticky substance made up of fat, cholesterol, calcium, and other substances found in the blood. [74]

Atherosclerosis can lead to serious problems such coronary artery disease, carotid artery disease and peripheral arterial disease. Its causes are unknown, but studies show that atherosclerosis may start in childhood and passing years is developing very fast.

Atherosclerosis also does not have signs and symptoms until of totally blocks an artery. In many cases people do not know that they have atherosclerosis until they have a heart attack or stroke. On the other hand, some other people have signs and symptoms of atherosclerosis where it is based on which arteries are affected.

According to some researchers, atherosclerosis is neither a degenerative disease, nor an inevitable one. [75] However, atherosclerosis seems to be a chronic inflammatory condition that is converted to an acute clinical event by the induction of plaque rupture, which in turn leads to thrombosis. [75]

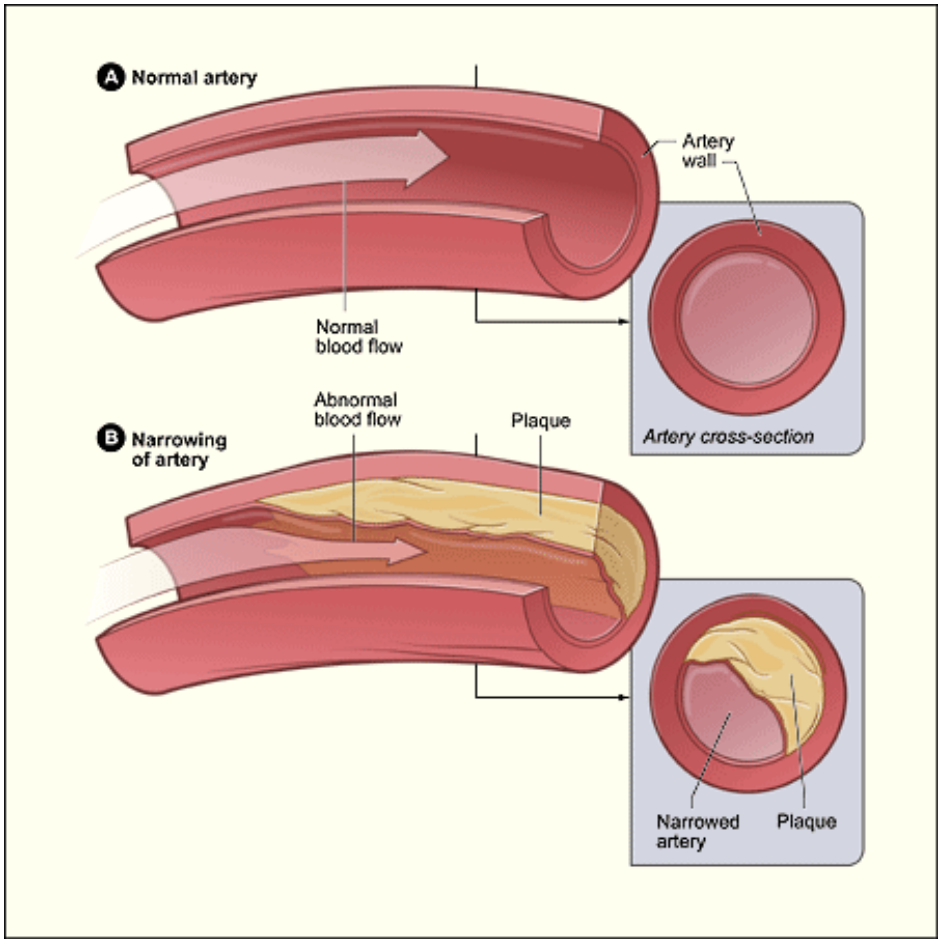

Figure3. A show a normal artery with normal blood flow. **B** show an artery with plaque build-up [76]

Source: National Heart Lung and Blood Institute, *http://www.nhlbi.nih.gov/health/health-topics/topics/atherosclerosis/*Retrieved 2 February 2014

14 Diagnosis

The diagnosis of atherosclerosis is come out based on the medical and family histories, a physical exam and test results of the individual. The specialized doctor for this health condition is the cardiologist, a vascular specialist, a neurologist and a nephrologist. Each one has a specific job to do in the human being. The cardiologist can diagnose and treat heart diseases and conditions (coronary heart disease, coronary microvascular disease), the vascular specialist is an expert to diagnose and treat blood vessels problems (peripheral arterial disease), the neurologist is specialized in diagnosing and treating nervous system disorders (carotid artery disease) and finally the nephrologist can diagnose and treat kidney disease and conditions (chronic kidney disease). [77]

According to a recent study conducted by Teramodo et al which aimed at examining the diagnostic mechanisms of atherosclerosis, the findings of the study showed that diagnostic techniques other than morphological tests include physiological tests such as the brachialankle pulse wave velocity and cardio-ankle vascular index. The same authors denote that although these parameters are easily determined by measuring the pulse wave in the extremities by using a dedicated device, it should be noted that the values function as indices of artery stiffness do not always reflect the presence of atherosclerosis. [78]

Moreover, the same authors state that the techniques used to measure the vascular endothelial function impaired in the early stage of atherosclerosis include flow-mediated vasodilation , which measures and calculates changes in the vascular diameter following ischemic reactive hyperemia of the extremities using ultra sound as well as strain gauge plethysmography which electrically observes and measures changes in the volume of the arterial blood flow in the extremities as changes in the circumference using a strain gauge. Nevertheless, and as the authors note, the use of these techniques is quite limited in general practice. [78]

However, The doctor has the ability to diagnose atherosclerosis with a physical exam, from blood test, EKG (Electrocardiogram), chest X-ray, ankle/ brachial index, echocardiography, computed tomography scan, stress test, angiography and others.

Physical exam

During the physical exam the arteries do an abnormal whooshing sound called a bruit. Stethoscope is helping doctor to hear the bruits which indicate poor flow due to plaque build-up. [77]

Blood test

With blood test doctor can check the levels of certain fats, cholesterol, sugar and proteins in the blood. Atherosclerosis sign will be seen with abnormal levels in the blood. [77]

EKG (Electrocardiogram)

This diagnostic way is simple and painless test which identify and records the heart's electrical activity. Electrocardiogram shows how fast the heart is beating and its rhythm. An EKG also records the strength and timing of electrical signals as they pass through the heart. [77]

Chest X Ray

Organs and structures inside the chest can be seen by a chest X-ray such heart, lungs and blood vessels. [77]

Ankle/ Brachial Index

This test compares the blood pressure in your ankle with the blood pressure in your arm to see how well your blood is flowing. [77]

Echocardiography

Known as echo uses sound waves to create a moving picture of the heart. In this way, doctor can collect information about the size and shape of the heart. Also, the test provides information of how well your heart chambers and valves are working. [77]

Computed Tomography Scan

It is generally accepted that "CT scan creates computer-generated pictures of the heart, brain, or other areas of the body. The test can show hardening and narrowing of large arteries". [77]

Stress testing

The purpose of this test is to make heart work hard and beat fast. If a person cannot do that, he or she will take a medicine to make heart work hard and beat fast. With this, heart needs more blood and oxygen. "Plaque narrowed arteries cannot supply enough oxygen- rich blood to meet heart's needs". [77]

The stress test can see signs and symptoms of CHD such as:

- Abnormal changes in your heart rate or blood pressure
- Shortness of breath or chest pain
- Abnormal changes in your heart rhythm or your heart's electrical activity

Angiography

The test that uses dye and x rays to show the inside of arteries. This test can show whether plaque is blocking arteries and how severe the blockage is.

A thin, flexible tube called a catheter is put into a blood vessel in arm, groin (upper thigh), or neck. A liquid dye is injected into the arteries of heart through the catheter that's fed through an artery. As the dye fills arteries, the arteries become visible on X-ray, revealing areas of blockage. [77]

15 Treatment

The major treatment of atherosclerosis includes lifestyle changes, medicines and medical procedures or surgery. The goals of treatment includes exempt symptoms, decrease risk factors in an effort to slow or stop the build- up of plaque, drooping the risk of blood clots forming, widening or bypassing plaque-clogged arteries and to prevent atherosclerosis related diseases.

Lifestyle changes

It is obvious that lifestyle is the most significant factor of prevention or to treat a number of serious health diseases. Healthy diet belongs in lifestyle because it can prevent or decrease high blood pressure, high blood cholesterol and maintain a healthy weight.

Fruit proportions and vegetables, fish and limited alcohol can contribute to achieving the healthy lifestyle.

Physical activity is also the other important factor to maintain you healthy. It can protect individuals from atherosclerosis.

Diet and physical activity can help you to keep a healthy weight with a body mass index of less than 25. A BMI between 25 and 29.9 is considered overweight. A BMI of 30 or more is considered obese. A BMI of less than 25 is the goal for preventing and treating atherosclerosis. The doctor or health care provider can help to set an appropriate BMI goal. **[79]**

Quit smoking

Smoking can damage and tighten blood vessels and raise the risk for atherosclerosis. With smoking nicotine increases platelet adhesion and carbon monoxide may increase the permeability of the arterial endothelium, therefore increasing plaque formation. **[21]** Also second-hand smoke can also contribute affecting your health by atherosclerosis.

Manage stress

Studies show that emotionally upsetting events can harm heart as a result of risk of heart attack. Physical activity, medicine, and relaxation therapy can help relieve stress. **[79]**

Medicine

To slow the progress of plaque buildup, doctor may prescribe medicines to help lower your cholesterol level or blood pressure. Doctor also may prescribe medicines to prevent blood clots from forming. For successful treatment, take all medicines as doctor prescribesnes. **[79]**

Medical procedures and Surgery

1. **Angioplasty**

"This procedure is used to open blocked or narrowed coronary arteries. Angioplasty can also improve blood flow to the heart and relieve chest pain. In some cases a small mesh tube name stent which is placed in the artery to keep it open". **[79]**

2. Coronary artery bypass grafting

"CABG is a surgery where arteries or veins from other areas in the body are used to bypass the narrowed coronary arteries. It can get better blood flow to your heart, relieve chest pain, and possibly prevent heart". [79]

3. Carotid endarterectomy

"It is a surgery to remove plaque build-up from the carotid in the neck". [79] By this, restores blood is flowing into the brain.

16 Risk factors of atherosclerosis

Smoking, high amounts of certain fats and cholesterol in the blood, high blood pressure and high amounts of sugar in the blood due to insulin resistance or diabetes are the factors which damage the inner layers of the arteries.

Much of the clinical interest as well as most of research available on the risk factors of atherosclerosis has largely focused on emerging lipid parameters such as lipoprotein (a), apolipoprotein (apo) A-I, and apo B-100; on inflammatory biomarkers such as C-reactive protein (CRP) and fibrinogen; and on nutritional markers associated with premature atherothrombosis, such as total plasma homocysteine.[80] However, direct comparisons of the magnitude of predictive value associated with each of these parameters have been have been scarcely examined. Moreover, researchers conclude that it has been uncertain whether screening for any of these novel biomarkers substantially improves risk prediction over that associated with standard lipid screening alone.[80] Therefore, the data analysis of the study conducted by Ridker et al, which used a nested case-control methodological design with plasma samples collected at baseline from a prospective cohort of 14 916 initially healthy US male physicians aged 40 to 84 years, suggests that evaluation of 11 plasma atherothrombotic biomarkers associated with the development of PAD (peripheral arterial disease), the TC/HDL-C (high-density lipoprotein cholesterol) ratio proved to be the single strongest lipid predictor of risk. And so, the researchers conclude that once this ratio was taken into account they found little evidence that additional screening for other lipid parameters including LDL-C (low-density lipoprotein cholesterol), apo A-I, apo B-100, or lipoprotein (a) had significant clinical usefulness. Eventually, they end up with the conclusion that the addition of either CRP or fibrinogen to standard lipid screening significantly had improved the predictive value

of computed risk prediction models. They also come to denote that of these two intercorrelated inflammatory variables; CRP proved to be the strongest univariate predictor of risk and had the greater additive value when combined with either TC or the TC/HDL-C ratio, although the magnitude of these latter differences was small. Nevertheless, they found little efficacy for homocysteine evaluation in these data, either alone or in combination with standard lipid screening. **[80]**

A more recent study on the strong association between high levels of LDL cholesterol as well as low levels of HDL cholesterol and coronary heart disease (CHD) is the one conducted by Fruchart et al and is a review of the literature on the studies focusing on the risk factors of hypertension. Therefore, the researchers have come up with the conclusion that hypertension is a multifactorial disease, and as such, none could deny the great impact that age, sex, elevated blood pressure, smoking, high levels of LDL cholesterol, and low levels of HDL cholesterol have on CHD. Therefore, their analysis show that increased triglyceride levels are also associated with increased CHD risk. In particular, they have come to suggest that triglyceride-rich lipoprotein remnants associated with apo C-III appear to have a major impact on risk. Moreover, they add to the already known risk factors the value of homocysteine and hs-CRP for assessment of CHD risk and they stress the need for future prospective research that will seek to examine these factors. In addition, they reassure us that the combination of traditional risk factors and emerging risk factors is expected to facilitate the assessment of patients' global risk, thereby allowing optimal use of diagnostic and therapeutic efforts in high-risk subjects .**[81]**

An enlightening study about the risk factors of atherosclerosis which are abundant is the ethnicity based research conducted by Anand et al with 985 participants from Canada which confirms previous studies findings that rates of cardiovascular disease vary between ethnic groups. Therefore the study based on a sample from three different cities (Hamilton, Toronto, and Edmonton), yields to the following interesting results. Surprisingly, within each ethnic group and overall, the researchers found that the degree of carotid atherosclerosis was associated with a higher prevalence of cardiovascular disease. More particular, South Asians had the highest prevalence of this condition compared with Europeans and Chinese. Notwithstanding this finding, the research revealed that Europeans had more atherosclerosis than South Asians and Chinese. Moreover, the same researchers have brought into the fore that South Asians had an increased prevalence of glucose intolerance, higher total and LDL

cholesterol, higher triglycerides, and lower HDL cholesterol, and much greater abnormalities in novel risk factors including higher concentrations of fibrinogen, homocysteine, lipoprotein (a), and plasminogen activator inhibitor-1.[82] The most important thing about this research is how the researchers have come to interpret those findings by concluding that despite the differences in conventional and novel risk factors between ethnic groups, the variation in their study as well as the degree of atherosclerosis only partly explains the higher rates of cardiovascular disease among South Asians compared with Europeans and Chinese. Moreover, they denote that the increased risk of cardiovascular events could be due to factors affecting plaque rupture, the interaction between prothrombotic factors and atherosclerosis, or as yet undiscovered risk factors. [82]

17 Hypertension and the pathogenesis of atherosclerosis

A general view held by many researchers on the pathogenesis of atherosclerosis and hypertension is that the pathogenesis of the latter is a multifactorial process that involves the interaction of genetic and environmental factors. In varying degrees, abnormalities of volume regulation, enhanced vasoconstriction, and remodeling of the arterial wall (decreasing lumen diameter and increasing resistance) contribute to the development of hypertension. [2][83]

According to some recent views, hypertension is a highly prevalent cardiovascular risk factor that causes significant morbidity and mortality, and is becoming an increasingly common health problem because of the increasing longevity and prevalence of predisposing factors such as sedentary lifestyle, obesity and nutritional habits. Further complicating the impact of this disease, mild and moderate hypertension is usually asymptomatic, and their presence (and the subsequent increase in cardiovascular risk) is often unrecognized. It has been widely asserted and documented that the pathophysiology of hypertension involves a complex interaction of multiple vascular effectors including the activation of the sympathetic nervous system, of the renin–angiotensin–aldosterone system and of the inflammatory mediators. Subsequent vasoconstriction and inflammation ensue, leading to vessel wall remodelling and, finally, to the formation of atherosclerotic lesions as the hallmark of advanced disease. [83]

High blood pressure can be the risk factor of atherosclerotic cardiovascular disease, although the mechanisms have not been well elucidated. [2] The incidence of atherosclerosis

increases with advancing years. However, it is more usual in men than women until the time of menopause. After that time both males are equal to atherosclerosis. [21]

Sowers et al (1993) stated that "one of the most serious health problems related to untreated high blood pressure is atherosclerosis, or plaque build-up in the arteries. When those blockages occur in the arteries that supply blood to the heart muscle, the end result is called coronary artery disease". [84]

It is widely accepted that retinal microvascular abnormalities, such as generalized and focal arteriolar narrowing, arteriovenous nicking and retinopathy, reflect cumulative vascular damage from hypertension, aging, and other processes. These wideheld views steam from the notion that these abnormalities are strongly and consistently associated with elevated blood pressure. [85]

Important to the pathogenesis of atherosclerosis is the role of renin- angiotensin system. According to a recent study, the renin-angiotensin system (RAS) has been demonstrated to play a critical role in the initiation and progression of atherosclerosis, thereby contributing to development of cardiovascular diseases. [86] The same authors have generated the following results and conclusions. More particularly, Angiotensin II (Ang II), a major substrate in RAS, has been found to stimulate atherosclerosis through various deleterious effects such as endothelial dysfunction, cellular proliferation and inflammation. The same authors denote that local RAS in vasculature is reported to play an important role. Many of these atherogenic actions of Ang II are mediated by reactive oxygen species (ROS). Investigation of the role of ROS and inflammation induced by RAS may provide a clue to understanding the pathophysiology of atherosclerotic diseases, and may lead to a new therapeutic strategy. [86] In general, the findings of the aforementioned study are important in that they have shown that AT1aR expressed not only on vascular cells but also on bone marrow derived cells plays a role in the pathogenesis of atherosclerosis, at least in part, by accelerating infiltration of bone marrow-derived inflammatory cells in the vessel wall. Therefore, the researchers conclude that blockade of AT1R may well be an important strategy to prevent progression and destabilization of atherosclerotic. [86]

As far as the role of renin- angiotensin system, another recent study has generated similar findings. More precisely, the study suggests that activation of the renin-angiotensin system with subsequent stimulation of angiotensin receptors is a major stimulus for NAD(P)H oxidase and production of ROS in both animal models and in hypertensive

patients. [87] In addition, the same authors inform us that preventing ROS generation by deleting a subunit of NAD(P)H oxidase, it may well cause resistance to angiotensin II–induced hypertension, and, as an effect, it may well reduce the associated endothelial generation of superoxide anions. Likewise, in rat models of hypertension, ACE (angiotensin-converting enzyme) inhibitors and ARBs decrease the generation of superoxide anions, diminish the amplitude of endothelium-dependent contractions, and restore the amplitude of both NO-mediated and EDHF-mediated endothelium-dependent relaxations. In addition to lowering lipids, statins also decrease the expression of NAD(P)H subunits and increase eNOS (endothelial NO synthase)expression, improving the balance between NO and ROS. The same authors warn us of the danger that these endothelial effects may contribute to the pleiotropic effects of these compounds. [87]

The molecular mechanisms of the pathogenesis of atherosclerosis and the effects of hypertension have certain common mechanisms. The most likely central focus for the effect of the two diseases is the endothelium. The loss of proper endothelial function, is a hallmark for vascular diseases, and is often regarded as a key early event in the development of atherosclerosis. Impaired endothelial function, causing hypertension and thrombosis, is often seen in patients with coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, as well as in smokers. [88]

As far as diabetes mellitus is concerned, atherosclerosis is often developed and accelerated by it. Subtle abnormalities of carbohydrate metabolism and overt diabetes mellitus are not only associated with the development of atherosclerosis, but they are also related to a substantial increase in the prevalence of hypertension. According to some researchers' views, hypertension is also a presumed independent risk factor for atherosclerosis, although some of the atherogenic properties of hypertension may be related to the recently recognized subtle metabolic abnormalities commonly found in persons with essential hypertension. [89]

More recent perspectives suggests that patients with diabetes mellitus have an over tenfold risk for cardiovascular disease during their lifespan, therefore they conclude that a key feature of diabetes is the development of an accelerated atherosclerosis. [90] Some epidemiologic studies hold that the enhanced fasting and postprandial insulin levels that often occur in patients with essential hypertension, as well as in patients with type II diabetes mellitus, are an independent risk factor for atherosclerotic cardiovascular disease. [85][91]. Moreover, a few similar other studies suggests that elevated glucose levels in patients with diabetes and

hypertension appear to contribute to the acceleration of atherosclerosis, perhaps through toxic effects on the vascular endothelium. At the same time these studies denote that there are other cardiovascular risk factors at play that are accentuated in persons with carbohydrate intolerance and hypertension, and these include abnormalities in platelet function, clotting factors, the fibrinolytic system, and dyslipidemia. Worth noting is that these studies have come to confirm that the goals of both non-pharmacologic and pharmacologic therapy for patients with abnormal carbohydrate metabolism and hypertension are to decrease cardiovascular risk as well as lower blood pressure. [92][89]

As already mentioned, hypertension is also a presumed independent risk factor for atherosclerosis, although some of the atherogenic properties of hypertension may be related to the recently recognized subtle metabolic abnormalities commonly found in persons with essential hypertension. A cross sectional study with 849 Japanese men aged 50.3 ± 8.5 years with obesity, aimed at testing the hypothesis that intra-abdominal fat (IAF) plays a primary role over general adiposity for metabolic abnormalities and atherosclerosis. The results were astonishing as they revealed that Intimal-medial thickness (IMT) of the carotid artery was measured by ultrasound. [92] Worth noting is that general adiposity was assessed by BMI. Additionally, waist circumference and waist-to-hip ratio (WHR) were used as a surrogate measure for abdominal fat. Moreover, abdominal subcutaneous fat area (ASF) and intra-abdominal fat area (IAF) were measured by computed tomography. Correlations between these measures and carotid IMT were analysed. [92] It is also worth to note that the interaction of generalized adiposity (BMI) and IAF in relation to metabolic variables, such as glucose tolerance, insulin resistance, and serum lipids, was also evaluated. Succinctly, results have lead to the conclusion that the primary importance of IAF over general adiposity for carotid atherosclerosis was not confirmed. Caution is recommended when using WHR as a measure of abdominal fat. The roles of IAF for metabolic abnormalities may be more limited than conventionally thought. BMI and WHR are simple and better clinical predictors for carotid atherosclerosis versus IAF. [92]

In addition to the metabolic abnormalities explained above we come to the conclusion that obesity, which is described by some commentators as the accumulation of excess body fat, is not only a major risk factor for diabetes mellitus and hyperlipidemia, but also for hypertension and atherosclerotic diseases in industrialized countries. Recent advances in obesity research have revealed that body fat distribution rather than the total amount of fat is

related to obesity-linked disorders. A study has demonstrated that visceral fat accumulation is a feasible condition for the development of various human diseases. [93] Visceral fat tissue produces and secretes various biologically active molecules. In addition, FFAs (free fatty acids) secreted from visceral fat upregulates hepatic genes for lipoprotein synthesis and are possibly related to hyperlipidemia. Moreover, PAI-1 (plasminogen activator-) is related to thrombotic disorders commonly found in visceral fat obesity. Overall, the importance on the studies rests on the finding that a new adipose-specific protein, adiponectin, having a collagen-like motif may be related to human disorders. Adipocytokines produced by the accumulated in visceral fat may be a causative factor in the development of various features in visceral fat syndrome. [93]

As previously noted, epidemiological studies show that two other independent factors for atherosclerosis are increased fasting and postprandial levels of insulin which often occur in patients with primary hypertension and in patients with diabetes type II. More particularly, diabetic patients are more likely to exhibit an overall coronary plaque burden as well as a higher rate of multivessel disease. [90] This is due to the fact that the amount of stenotic segments is directly proportional to the duration of disease. Therefore, when these factors are combined, diabetic patients are placed under a great risk for myocardial infarction. Added to these effects, are the effects of diabetes on the vasculature which become quite extensive as diabetes affects not only the endothelium and smooth muscle cells, but also platelets, lipoproteins, local vasoactive substance production and function, clotting factors, triglycerides, as well as local arterial response to hypoxia and new collateral vessel formation [90]. The reason that reference to diabetes is made here, is mainly because the development of diabetes which is related to atherosclerosis follows exactly the same histologic course as atherosclerosis in non diabetic patients.

In regard with the endothelium, this has been intensely studied for the last 15 to 20 years. Abnormalities of the endothelium underlie a number of human diseases and appear to be central to the pathogenesis of atherosclerosis. Changes in endothelial function and morphology are also cardinal features of hypertension. The importance of the endothelium in the development of atherosclerosis was first appreciated when it was observed that its removal facilitated atherosclerotic lesion development in hypercholesterolemic animal models. [2]

More recent views tend to associate endothelial dysfunction with hypertension and oxidant stress. More particular, oxidative stress and endothelial dysfunction are consistently observed in hypertensive subjects, but emerging evidence suggests that they also have a causal role in the molecular processes leading to hypertension. [83] Researchers denote that reactive oxygen species (ROS) may directly alter vascular function or cause changes in vascular tone by several mechanisms including altered nitric oxide (NO) bioavailability or signalling. ROS-producing enzymes involved in the increased vascular oxidative stress observed during hypertension include the NADPH oxidase, xanthine oxidase, the mitochondrial respiratory chain and an uncoupled endothelial NO synthase. In the current review, we will summarize our current understanding of the molecular mechanisms in the development of hypertension with an emphasis on oxidative stress and endothelial dysfunction. [83]

Another study which aimed to examine the possibility that small increments in angiotensin II are responsible for an increase in blood pressure and maintenance of hypertension through the stimulation of oxidative stress came up with the following interesting results: Superoxide radicals and nitric oxide can combine chemically to form peroxynitrite, which can then oxidize arachidonic acid to form F_2-isoprostanes. F_2-isoprostanes exert potent vasoconstrictor and antinatriuretic effects. Moreover, angiotensin II can stimulate endothelin production, which also has been shown to stimulate oxidative stress. Therefore the researchers of the aforementioned study have sought to suggest theta a reduction in the concentration of nitric oxide (which is quenched by superoxide) along with the formation of F_2-isoprostanes and endothelin could potentiate the vasoconstrictor effects of angiotensin II. The researchers also assume that these mechanisms, which underlie the development of the slow pressor response to angiotensin II, also participate in the production of hypertension when circulating angiotensin II levels appear normal, as occurs in many cases of essential and renovascular hypertension. [94]

As far as the endothelium is concerned, endothelial dysfunction has been reported to have a significant effect on hypertension and some clinical studies have generated important insights on the pathophysiology of the disease. More particularly, it has been reported that endothelial dysfunction, which is a reduced vascular availability of endothelium-derived nitric oxide, has been analyzed in numerous experimental and clinical studies as a potential mechanism mediating the adverse vascular effects of hypertension. Moreover, the understanding of mechanisms underlying endothelial dysfunction in hypertension has been

substantially advanced recently. A significant direction endothelial dysfunction mechanism is the marvelous finding that increased oxidant stress is thought to represent a major mechanism leading to reduced vascular availability of endothelium-derived nitric oxide. [95] As Landmesser and Drexler put it "Vascular nicotinamide adenine dinucleotide phosphate oxidases, uncoupled nitric oxide synthase and xanthine oxidase have been identified as major sources of reactive oxygen species in hypertension. Endothelial dysfunction has been implicated in the macrovascular complications of hypertension, such as stroke or myocardial infarction, coronary microvascular dysfunction and increased arterial stiffness, probably at least partly resulting from loss of the antiatherogenic and vasculoprotective effects of endothelium-derived nitric oxide".[95, p.316]

Similarly, other researchers on the endothelial dysfunction have come to confirm that the endothelium exerts a number of vasoprotective effects, such as vasodilation, suppression of smooth muscle cell growth, and inhibition of inflammatory responses. Davignon and Ganz assert that "many of these effects are largely mediated by nitric oxide, the most potent endogenous vasodilator. Nitric oxide opposes the effects of endothelium-derived vasoconstrictors and inhibits oxidation of low-density lipoprotein. A defect in the production or activity of nitric oxide leads to endothelial dysfunction, signalled by impaired endothelium-dependent vasodilation."[97, p. 27] Overall, research suggests that endothelial dysfunction is an early marker for atherosclerosis and can be detected before structural changes to the vessel wall are apparent on angiography or ultrasound. A view expressed by the aforementioned researchers holds that "many of the risk factors that predispose to atherosclerosis can also cause endothelial dysfunction, and the presence of multiple risk factors has been found to predict endothelial dysfunction" [97] They support this view by adding that a number of clinical trials have shown that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) improve endothelial dysfunction in patients with coronary risk factors beyond what could be attributed to their impact on plasma lipids. Studies have elucidated several possible mechanisms by which statin therapy may improve endothelial dysfunction, including upregulation of nitric oxide production or activity and reduction of oxidative stress. [97]

A more recent study conducted by Sitia et al, has yielded to quite similar findings about endothelial dysfunction and its association to nitric oxide. More particularly the same authors acknowledge the causes of endothelial dysfunction and its association to atherosclerosis.

They point out that "endothelial dysfunction is an early step in the development of atherosclerosis and is mainly characterised by a reduction in the bioavailability of nitric oxide. All of the traditional cardiovascular (CV) risk factors (dyslipidemia, arterial hypertension, hyperglycemia and diabetes) are associated with endothelial dysfunction, and oxidised low-density lipoproteins, the renin-angiotensin axis and insulin resistance play important roles in the pathogenesis of impaired endothelial function. The increased expression of adhesion molecules and pro-inflammatory cytokines leads to abnormal endothelium-dependent vasodilation which could be investigated using vasoreactivity tests such as flow-mediated dilation in the brachial artery" **[98,p.830]** Nevertheless, with their study they add valuable knowledge to our understanding of in the pathogenesis of endothelial dysfunction and atherosclerosis. More particularly, they have shown that the immune system plays an important role in the pathogenesis of endothelial dysfunction and atherosclerosis with a particular regard towards autoimmunity. Relying on this assumption, the same authors confirm their initial hypothesis, which holds that immune pathogenesis is largely caused by the high prevalence of the atherosclerotic process in systemic autoimmune diseases. Moreover, they denote that "evaluating coronary microvascular dysfunction by means of transthoracic echocardiography with non-invasive coronary flow reserve assessment is particularly interesting as it could detect preclinical impairment of coronary microvascular function". **[98,p.830]** Therefore, their views and approach are a major contribution to the understanding to the pathogenesis of endothelial dysfunction and its association to atherosclerosis because they acknowledge that the mechanisms responsible for endothelial damage have a genetic basis could improve the approach to CV diseases.

Succinctly, hypertension is a risk factor for the development of atherosclerosis, despite the fact the mechanisms have not been well elucidated by the literature. According to some views, as the cellular and molecular mechanisms of the pathogenesis of atherosclerosis and the effects of hypertension are being more clearly defined, it becomes apparent that the two processes have certain common mechanisms. **[2]** A study conducted in order to review evidence that leads to the postulate that hypertension predisposes to and accelerates atherosclerosis at least in part because of synergy between elevated blood pressure and other atherogenic stimuli to induce oxidative stress on the arterial wall, has generated the following results: The endothelium is a likely central focus for the effect of both atherosclerosis and hypertension. The same author also stresses the need to view atherosclerosis mainly as an inflammatory disease. the same author also acknowledges that atherogenic stimuli such as

hyperlipidemia appear to activate the inflammatory response by causing expression of mononuclear leukocyte recruiting mechanisms, for as he further denotes "the gene for one of these, the vascular cell adhesion molecule-1, is controlled at least in part by transcriptional factors regulated by oxidative stress, which modifies the redox state of the endothelial cell".[2 p155] The same author suggests that alterations in the redox state of the arterial wall may well contribute to vascular smooth muscle cell growth. In a somewhat parallel fashion, there is evidence that hypertension may also exert oxidative stress on the arterial wall.

18 Conclusion

As we have examined and analyzed in the whole thesis, we understand that individuals have the responsibility of suffering from hypertension by its own or in relation with atherosclerosis, except from genetics.

Hypertension is a cause that can appear usually in any age with the highest percentage of older people. Lifestyle, salt intake, exercise, genetics, causes, treatment and drug treatment analyzed above. Drug divided in many categories, which can cure high blood pressure and prevent hypertensive people from having an extra health condition such atherosclerosis which is most common in hypertensive people.

Atherosclerosis is caused by high blood pressure and is an important health cause that may lead to strokes and others. Blood should have regular circulation to avoid any of these health problems.

According to a US survey, it was found that blood pressure higher than 140/90 caused the 69% of people diagnosed with their first heart attack, 77% of people have their first stroke, and 74% of people have heart failure. [99] Those are statistical percentages of high blood pressure in relation with atherosclerosis which is cause all the above; heart attack, stroke, peripheral arterial disease and others.

The main secret is to treat high blood pressure to prevent atherosclerosis. As an example, 10 points down of systolic blood pressure leads to 50% - 60% lower risk of dying from stroke and 40% - 50% lower risk of death from heart attack. [99]

To achieve that people should have a healthy diet, exercise, low salt intake and others, but, in some cases healthy lifestyle does not have the appropriate results and there is coming

the need of medicines. In some cases two or three medicines must combine to have the desirability result.

To conclude, the risk of death in the situation of having high blood pressure and atherosclerosis together is very high. Each people from the youngest to oldest should have the appropriate knowledge to protect his or her selves. Parents, schools and community are responsible to inform people about them. Professionals and doctors who experienced every single day situation of people with those cause are must do their best to reduce the percentage of people diagnosed with high blood pressure or in combination with atherosclerosis.

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