Evaluation of blood pressure, treatment parameters and cardiovascular risk stratification of patients with arterial hypertension in primary health care

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UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

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Diploma thesis

Academic Year:
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Assist. Prof. Marion Tomičić, MD, GP, PhD

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AKNOWLEDGMENT

I would like to express gratitude to my mentor Prof. Marion Tomicic, MD, PhD for her guidance and help throughout the process of writing this thesis.

To my family, particularly my parents who always supported me in any way possible.

Lastly, I wish to thank my closest friends in Split who have made these six years unforgettable and a special mention to my soon to be married dear friend Baudouin and his master skills at Microsoft Excel.

LIST OF ABBREVIATIONS

HTN – Hypertension

BP – Blood pressure

CV – Cardiovascular

CVD – Cardiovascular disease

OSA – Obstructive sleep apnea

HBPM – Home blood pressure monitoring

ABPM – Ambulatory blood pressure monitoring

SBP – Systolic blood pressure

DBP – Diastolic blood pressure

LVH – Left ventricular hypertrophy

ICH – Intra cerebral hemorrhage

HMOD – Hypertension mediated organ damage

CKD – Chronic kidney disease

ESDR – End stage renal disease

ACE – Angiotensin converting enzyme inhibitor

BB – Beta blocker

ARB – Angiotensin receptor blocker

DIU – Diuretics

CCB – Calcium channel blocker

WHR – Waist hip ratio

GGT – Gamma-glutamyl transferase

AST – Aspartate aminotransferase

LDL – Low density lipoprotein

1.INTRODUCTION

1.1. Definition and classification

Hypertension or high blood pressure is a long-term medical condition characterized by a sustained elevated blood pressure (BP) in the vascular system. BP is divided into systolic BP and diastolic BP, systolic BP measures the pressure in your blood vessels when your heart pumps the blood out into the vessels, and diastolic BP measures the pressure in your blood vessels when your heart rests in between beats (1).

Definitions for HTN are based upon the relationship between BP and cardiovascular (CV) risk which have a strong correlation from lower levels of BP as low as >115mmHg for systolic blood pressure (SBP) (2). However, HTN is described as the level of BP at which benefits of treatment outweighs its risks.

European guidance defines HTN using office-based blood pressure as systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg. HTN is also subdivided into three grades, according to its severity, as depicted in Table 1 (3).

Table 1. Classification of office blood pressure and definitions of hypertension grade

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

Source: 2018 ESC/ESH Guidelines for the management of arterial hypertension.

1.2. Epidemiology

Hypertension is an essential global health issue, it is the most common CV disease and remains one of the main risk factors for stroke, heart disease and end-stage kidney disease which

are significant considering their very high prevalence. High BP also stands as the most significant preventable risk factor for premature death and disability in the world (4).
According to office BP, the worldwide prevalence of HTN approximated 1.13 billion in 2015 (in contrast to 594 million in 1975), with an overall prevalence in adults averaging 30-45%, including over 150 million people in Central and Eastern Europe. HTN becomes increasingly more common with advancing age, with a prevalence of >60% in populations over 60 years old. During the past few decades, we can observe a shift in the world highest BP from high-income countries to low-income countries in south Asia and sub-Saharan Africa, while blood pressure has been a constant health issue in central and eastern Europe (5).

1.3. Types and subtypes of HTN

1.3.1. Primary (essential) HTN

1.3.1.1 Definition

Arterial blood pressure is characterized by the intricate interactions of CV hemodynamics, kidney function as well as endocrine, paracrine and neural activity. The role of the kidneys in adjusting the fluid and electrolyte balance has been proven to be the most crucial long-term factor of blood pressure control. Thus, essential HTN represents the imbalance of one or more of these determinants of arterial pressure (6).
Primary HTN accounts for 85-95% of cases and has no detectable etiology.

1.3.1.2. Pathogenesis

Maintenance of arterial BP is essential to preserve organ blood perfusion. In general, the arterial BP is determined by the following equation:
Blood Pressure (BP) = Cardiac Output (CO) x Systemic Vascular Resistance (SVR)
BP continuously adapts to diverse environmental changes. The primary components determining the BP are the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the plasma volume (largely mediated by the kidneys).

The pathogenesis of primary HTN is poorly understood but most occurs from the influence of various genetic and environmental factors affecting the CV and renal structures and functions (7).

1.3.1.3. Risk factors and genetics

Although the actual etiology behind essential HTN remains uncertain, multiple risk factors are evidently and independently associated with its development. Among these, the most relevant ones include: advanced age, obesity and weight gain, positive family history (about two times more common in patients that have at least one parent hypertensive), race (black population tends to get HTN more commonly, earlier in life and are subject to more extensive organ damage), high sodium intake (>3g/day), alcohol consumption, smoking, physical inactivity, and reduced nephron number (8-15).

As previously mentioned, a positive family history is a rather common feature in hypertensive patients, revealing genetics as a strong component. However, HTN is a highly heterogeneous disorder and multiple genome-wide researches have established about 120 loci that are responsible for BP variations. Yet, these biological insights only justify approximately 3,5% of trait variance (16).

1.3.2. Secondary HTN

Secondary HTN accounts for 5-15% of cases of HTN in adults and are due to specific organic condition. Secondary HTN most frequently results from renal diseases such as renovascular HTN, endocrine illnesses or from other distinct conditions.

Among renal etiologies, renovascular stenosis, polycystic kidney disease, acute and chronic renal failures and glomerulonephritis should be investigated.

Endocrine dysfunctions include primary hyperaldosteronism, primary hyperparathyroidism, hyperthyroidism, hypercortisolism, and pheochromocytoma.

Other specific causes such as aortic coarctation, medication and illicit drug use or obstructive sleep apnea (OSA) should be considered (17).

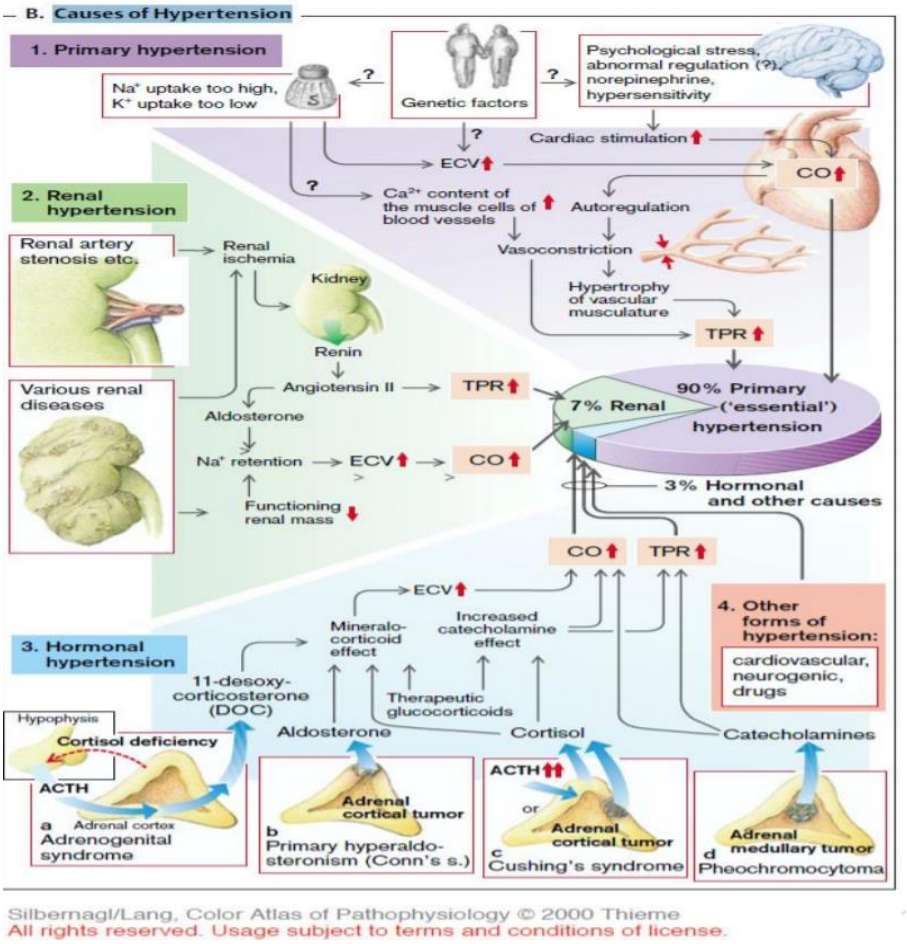

Figure 1. Causes of Hypertension
Source: Silberngl/Lang, Color of Atlas of Pathophysiology

Etiologies in children are most often different from those in adults. Among adults, renovascular hypertension, renal disease, aldosteronism, and OSA make up for most cases of secondary HTN. Whether in children and adolescents, renal parenchymal diseases and coarctation of the aorta predominate largely. Therefore, an age-based diagnosis approach should be initiated (18).

Secondary HTN should be considered in the existence of suspicious symptoms and signs. For instance, an early age of onset of HTN, severe or resistant HTN, malignant HTN or an acute elevation of the BP compared to previous measurements. Moreover, all newly diagnosed cases of HTN should undergo basic laboratory tests such as measurements of hematocrit, electrolyte, creatinine and calcium levels, along with a lipid profile, urinalysis and an electrocardiography. It is also essential to revise the patient's diet and use of medication (17).

Table 2. Diagnosis of secondary hypertension; an age-based approach

Table 3. Most Common Causes of Secondary Hypertension by Age*

Age groups	*Percentage of hypertension with an underlying cause*	*Most common etiologies†*
Children (birth to 12 years)	70 to 85	Renal parenchymal disease Coarctation of the aorta
Adolescents (12 to 18 years)	10 to 15	Renal parenchymal disease Coarctation of the aorta
Young adults (19 to 39 years)	5	Thyroid dysfunction Fibromuscular dysplasia Renal parenchymal disease
Middle-aged adults (40 to 64 years)	8 to 12	Aldosteronism Thyroid dysfunction Obstructive sleep apnea Cushing syndrome Pheochromocytoma
Older adults (65 years and older)	17	Atherosclerotic renal artery stenosis Renal failure Hypothyroidism

*—Excluding dietary and drug causes and the risk factor of obesity.
†—Listed in approximate order of frequency within groups.

Information from references 2, 3, and 30 through 34.

Source : Viera AJ, Neutze DM. Diagnosis of secondary hypertension: an age-based approach. American family physician. 2010;82(12):1471-8.

1.3.3. Masked hypertension

Masked HTN refers to the untreated patients in whom the BP is normal in the office but is increased when measured by Home blood pressure monitoring (HBPM) or Ambulatory blood pressure monitoring (ABPM) (19).

This phenomenon has been observed in as many as 15% of the general population (20), and may be considerably higher in those with chronic kidney disease (30-70%).

Masked HTN has been linked to increased all-cause mortality as well as CV morbidity. Therefore, ABPM should be considered in patients that are suspected to have HTN but demonstrate repeated normal values when measured at the office (21).

1.3.4. White coat hypertension

White coat HTN describes the condition in which BP is elevated in the office but within normal range when measured by HBPM or ABPM.
This white-coat effect has a prevalence of about 20-40% of the general population and its associated risks still remain unclear (22).

1.4. Blood pressure measurements

Appropriate standardized technique for BP measurement is of paramount importance as accurate readings are essential in the diagnosis and management of HTN.

1.4.1. Office-based blood pressure measurement

Proper methods and interpretation of the BP is essential, especially because office BP is often performed improperly. Therefore, the European guidelines for hypertension recommend several steps to follow in order to achieve the highest accuracy when measuring BP as described in Figure 4 (3).

In elderly, those with diabetes, or patients with other cause of orthostatic hypotension, BP should also be taken 1 and 3 min after standing. Orthostatic hypotension refers to the reduction in SBP of >20 mmHg or in DBP of >10 mmHg within 3 min of standing, it is associated with an increased risk of mortality and CV event (23).

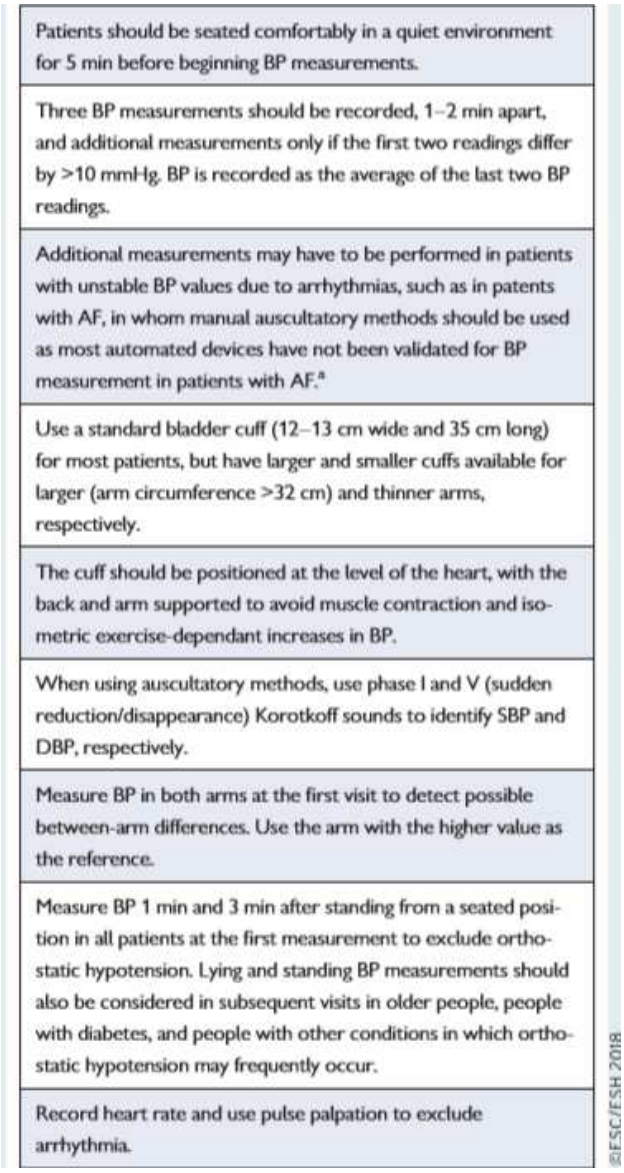

Figure 2. Recommended procedure for routine office BP measurement
Sources: 2018 ESC/ESH Guidelines for the management of arterial hypertension.

1.4.2. Ambulatory BP monitoring

ABPM records blood pressure at regular intervals over a defined time period, providing high quality data about daytime, night-time. Most commonly the BP is monitored for 24 hours with recordings every 15-20 mins during daytime and every 30-60 mins at night, at least 70% usable recording are required to interpret the findings.

ABPM is the preferred technique to confirm the diagnosis of HTN and identify masked HTN and white coat HTN and is the only definite way to obtain nocturnal BP values. Also, it is more reliable when predicting target-organ damage and CV events than office BP readings (24).

Blood pressure naturally declines during sleep, this phenomenon is called “dipping” and is defined as a fall in BP by 10% compared to the BP daytime average, however dipping is highly variable from night to night, thus is poorly reproducible (25).

When using ABPM, the diagnostic threshold for hypertension is defined as ≥ 130/80 mmHg over 24 h, ≥ 135/85 mmHg for the daytime average, and ≥ 120/70 for the night-time average (3).

1.4.3. Home blood pressure monitoring

Home BP refers to the average of all BP readings using a validated, automated oscillometric device, for a minimum of 3 days and ideally for a week before each clinic visit, with readings done in the morning and the evening. When measuring their BP, the patients should be seated with their back and arm supported, in a quiet environment after 5 mins of rest. Also, BP should be measured twice and 1 to 2 min apart from each other (26). HBPM can also identify white coat HTN and masked HTN and shows to predict CDV morbidity and mortality better than office BP (27).

In comparison with office BP, HBPM readings tend to be lower, therefore the diagnostic threshold for HTN is ≥135/85 mmHg. (3)

1.5. Making the diagnosis of HTN

1.5.1. Screening

All individuals above 18 years old should have their BP taken and documented in their medical record. Further screening should be performed at regular intervals with the frequency depending on one’s BP readings. For adults within optimal BP range (BP<120/80), BP should be remeasured at least every 5 years and more frequently as opportunistic screening. Patients with normal BP (120–129/80–84), BP should be monitored at least every 3 years. Patients with high–

normal BP (130–139/85–89 mmHg) are recommended to measure their BP annually as well as patients diagnosed with masked HTN. (3)

1.5.2. Diagnosis

A diagnosis can be established without confirmation under two conditions, when a patient presents with hypertensive urgency or emergency (BP >180/>120) or if a patient presents with an initial BP reading of >160/100 mmHg with concomitant known target end-organ damage.

In all other patients with only elevated BP, the diagnosis must be confirmed and should not be solely based on a single set of measurements. BP pressure measurements should be repeated during office visits, the frequency of visits should correlate to the HTN status and severity of the condition.

European guidance also supports the use of ABPM and HBPM as another method to confirm the diagnosis of HTN as it provides a more comprehensive and larger number of BP readings, unfortunately these devices aren't always available and may not be economically feasible for some patients. (28)

In comparison to office BP, out of the office BP diagnostic threshold for HTN are lower than office BP measurements as shown in Table 3.

Table 3. Definitions of HTN according to office, ABPM and HBPM levels

Category	SBP (mmHg)		DBP (mmHg)
Office BP[a]	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

Sources: 2018 ESC/ESH Guidelines for the management of arterial hypertension.

1.6. Risk associated to HTN

HTN is linked to a serious increase in risk of adverse CDV and renal outcomes, it is now evident that there is a continuous relationship between high BP and risk of events at any age and among all races.

1.6.1. HTN and CV risk

HTN represents the most significant risk factor for CV disease along with others including smoking, dyslipidemia, obesity and diabetes, resulting in a cumulative effect on the CV system (29). The likelihood of acquiring a CV event increases as BP augment, two essential CV events, coronary heart disease and stroke mortalities all of which is displayed below (Figure 3 & 4). CV event risks has been shown to begin to rise from BP levels as little as 115/75 mmHg (2).

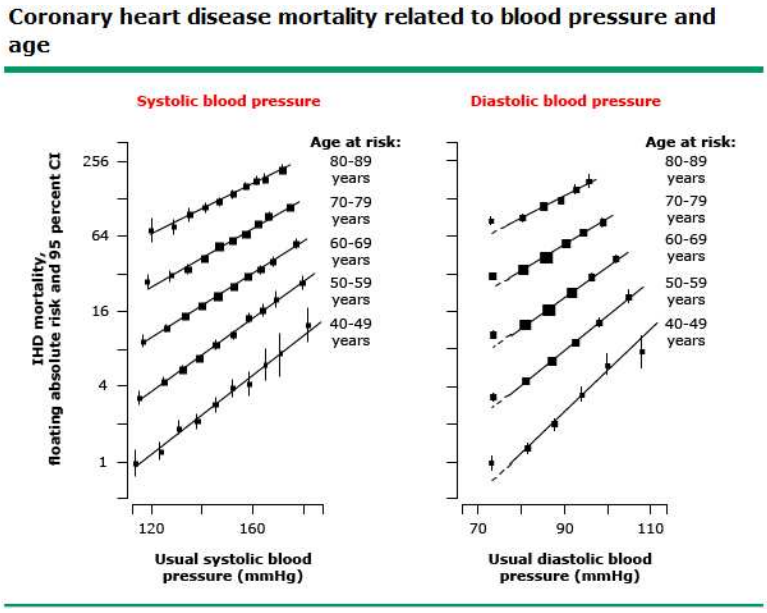

Figure 3. Coronary heart disease mortality related to blood pressure and age.
Sources: Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360:1903.

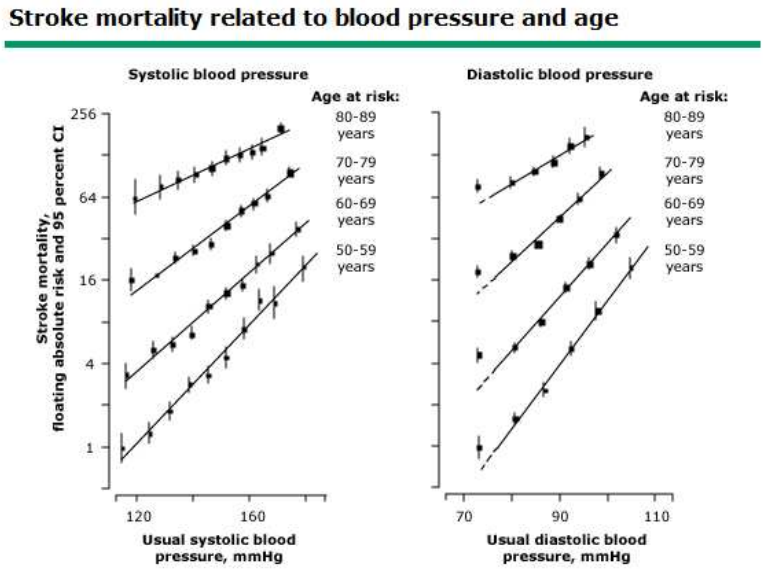

Figure 4. Stroke mortality related to blood pressure and age
Sources: Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360:1903.

Among those CV risk associated with HTN, left ventricular hypertrophy (LVH) is a common finding and is important to consider as the degree of growth in left ventricular mass directly relates to the increase of CV risks, including heart failure, ventricular arrhythmias and myocardial infarction. (30)

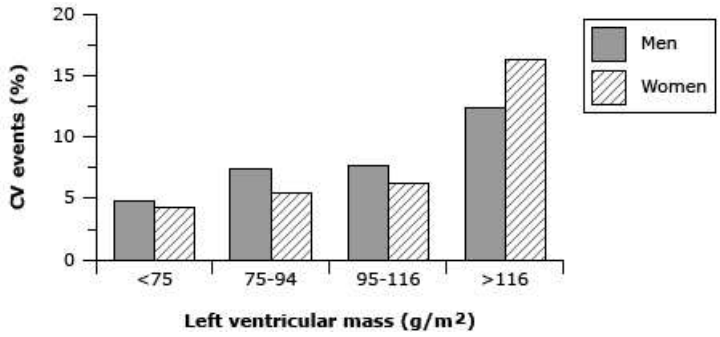

Figure 5. CDV risk with LVH by echocardiography
Sources : Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990; 322:1561.

HTN may also result in the development of intracerebral hemorrhage (ICH), studies have shown that HTN approximately doubles the risk of ICH to take place, making it the most important single risk factor. (31) In addition, HTN also presents as the most impactful component for development of congestive heart failure. (32)

1.6.1.1. CDV risk assessment

Multiple 10 years-CV risk assessment systems are accessible, European guidelines suggests using the Systematic Coronary Risk Evaluation (SCORE) system. The model is applicable for patients aged 45-65 with no previous history of CV condition. The SCORE system predicts the 10-year risk of CV mortality in an individual according to their gender, age, smoking status, lipid panel and SBP as demonstrated by Figure 9. (33)

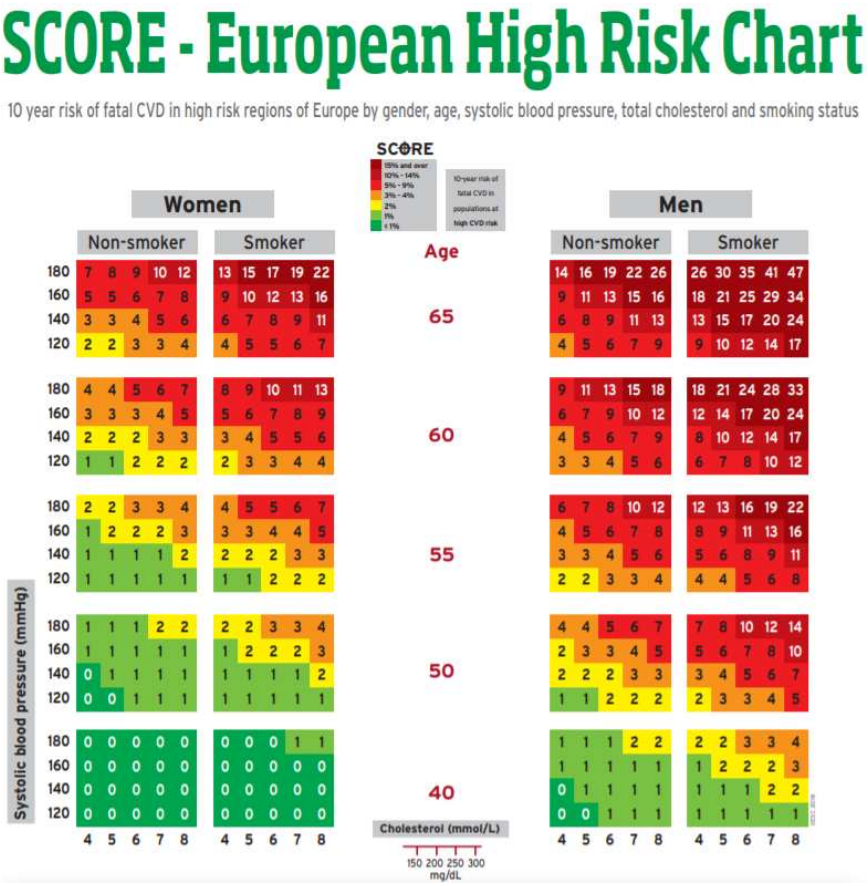

Figure 6. Systematic Coronary Risk Evaluation (SCORE) system
Sources: European Society of Cardiology, www.escardio.org

1.6.1.2. Importance of hypertension mediated organ damage (HMOD) in assessing CV risk

HMOD is defined as organ damage due to hypertension. This in turn induces structural and/or functional remodeling of main organs such as the brain, retina, kidney and vasculature. HMOD is a common finding in hypertensive patients and should be carefully reviewed when establishing the CV risk assessment. HMOD may already be present in asymptomatic patients and has been proven to significantly increase CV risks. Unfortunately, HMOD frequently goes unnoticed and is not implemented into one's CV risk assessment, for instance in the SCORE system (34).

Therefore, by inserting HMOD into the CV risk assessment, it allows the identification of actual high-risk hypertensive individuals who would otherwise be categorized as low risk patients. (35) Consequently, other risk stratification systems including additional risk factors may be appropriate. Table 4. depicts a CV risk assessment comprising extra criteria such as comorbidities and HMOD (3).

Table 4. Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities.

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Sources: 2018 ESC/ESH Guidelines for the management of arterial hypertension.

1.6.2. HTN and chronic kidney disease association

Chronic kidney disease (CKD) is defined as persistent kidney damage or decreased kidney function for at least three or more months, regardless of the etiology.

CKD and HTN are related because HTN is a common cause for CKD and vice versa. The decline in renal function enhances the rise in arterial BP and the resultant high BP results in faster progression of the renal condition (36). Uncontrolled HTN is an important risk factor for developing CKD, it is present in about 80-85% of patients with CKD and stands as the second leading cause of end stage renal disease (ESDR) (37).

Patients with CKD and HTN should modify their lifestyle and take special care of their sodium intake, they usually also require a combination of antihypertensive drugs in order to achieve their BP target (36).

1.7. Clinical evaluation of the hypertensive patient

When hypertension is suspected or diagnosed in a patient, a detailed clinical examination should be undertaken to find out the extent of HMOD, to establish the presence of CDV or renal condition as well as their risk factors, and to identify factors that might have played a role in the development of HTN such as lifestyle, family history or interfering substances.

1.7.1. History

The important aspects of the medical history of a hypertensive patient that should be documented include: duration and course of HTN, medication record, intake of substance (estrogens, NSAIDs, excessive sodium, cocaine), family history, presenting symptoms, dietary habits, psychosocial factors (family situation, work status, educational level), sexual function and sleep (features of sleep apnea) (38).

1.7.2. Physical examination

Physical examination provides essential indications about the patient' state and the accompanying disease. Once the general appearance of the patient and BP measurement are reviewed, the focus should shift to evaluating the signs of end-organ damage. This means thorough examination of the heart (size, rhythm, sounds), neck (carotid palpation and auscultation), peripheral arteries, neurological examination (visual disturbances, focal weakness) and fundoscopy (papilledema, hemorrhage, cotton wool spots) should be performed. Potential causes of secondary HTN should be excluded by inspecting the patient' skin (café-au-lait patches), palpating kidneys for signs enlargement (PCKD), and look for signs of endocrine condition (thyroid or Cushing's disease) (39).

1.7.3. Laboratory analysis

Routine workup for evaluation of hypertensive patients should be performed in all newly diagnosed patients with HTN. Suggested tests are the following: electrolytes, serum creatinine, fasting glucose and glycated HbA1c level, urinalysis, lipid panel, complete blood count, liver profile, ECG (40).

1.7.4. Assessment of HMOD

HMOD assessment is crucial, HMOD causes multiple organ damage and is a marker of pre-clinical or asymptomatic CV disease that may be reversed by antihypertensive treatment if prescribed on time. Basic screening tests for HMOD consist of ECG (for detection of LVH or and other cardiac abnormalities), urine albumin:creatinine ratio, blood creatinine and eGFR (renal profile), fundoscopy (hypertensive retinopathy finding).

If the basic tests are not enough to determine the HMOD, further detailed screening tests may be undertaken: echocardiography, carotid and abdominal ultrasound, pulse wave velocity (index for aortic stiffness), ankle-brachial index, cognitive function testing and brain imaging (3).

1.8. Treatment

1.8.1. Non-pharmacological treatment

Treatment of HTN should always include lifestyle modifications alone or along with an antihypertensive therapy.

1.8.1.1. Dietary salt restriction

Elevated dietary intake of salt (>5g of sodium/day) is associated with high BP and development of HTN. Dietary sodium restriction proves to be efficient at any stage of the disease as it prevents HTN, it lowers the BP in both hypertensive and normotensive patients and also reinforces the BP response to most antihypertensive drugs.

Many studies have showed that a moderate reduction in salt intake results in a fall in systolic and diastolic pressures of 4.8/2.5 and 1.9/1.1 mmHg, respectively (41).

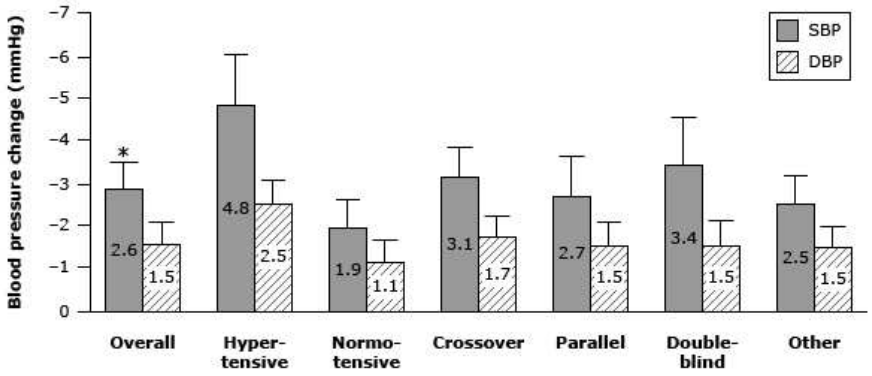

Figure 7. Blood pressure change and sodium restriction
Source: Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. The American journal of clinical nutrition. 1997;65(2 Suppl):643s-51s.

The current sodium intake per day is about 3,3-5,5g but varies among regions of the world, and between countries. In both hypertensive and normotensive populations, guidelines recommend diminishing salt intake to <2,3g per day. Salt reduction is most efficiently achieved by eliminating high-salt foods (processed food) and avoid adding salt (42).

1.8.1.2. Weight loss

Overweight and obesity are associated with HTN. Reducing body weight in overweight individuals results in a fall in BP. The weight loss-induced reduction in BP averages from 0.5 to 2 mmHg for every 1 kg lost. The optimal BMI should ideally be maintained at 20-25 kg/m^2 in patients younger than 60 years old, and a waist circumference <94 cm for men and <80 cm for women. Although weight loss is recommended in overweight and obese patients, often weight stabilization is a reasonable objective for many patients. The decline in BP usually occurs along with sodium restriction, dietary counselling and regular physical exercises as a multidisciplinary approach (43).

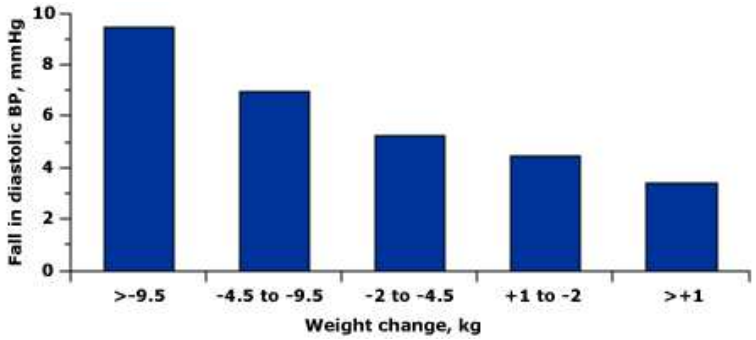

Figure 8. Weight loss and diastolic BP relationship
Source : Stevens VJ, Corrigan SA, Obarzanek E, et al. Weight loss intervention in phase 1 of the Trials of Hypertension Prevention. The TOHP Collaborative Research Group. Arch Intern Med 1993; 153:849.

1.8.1.3. Other dietary approaches

Hypertensive patients are advised to change their dietary pattern to a nutrition high in vegetables and fruits, whole grains, poultry, fish, nuts and low-fat dairy products and low sweets, sugar-sweetened beverages and red meats. This translates to having a diet rich in potassium, magnesium, calcium, protein and fiber with low amounts of saturated fat, total fat, and cholesterol. (44) The Mediterranean diet contains many of these foods and nutrients and is associated with a fall in CV events and all-cause mortality (45).

1.8.1.4. Alcohol consumption

The relationship between alcohol consumption and incidence of HTN and CDV risk has been long-established. During the week, alcohol use and binge drinking avoidance should be advised to all patients. Hypertensive adult men and women that consume alcohol should have, respectively, no more than 14 units and 8 units per week (1 unit = 125mL of wine or 250mL of beer) (46).

1.8.1.5. Regular physical activity

Aerobic physical exercises, resistance and isometric training decrease systolic and diastolic pressure and are also lowering overall CV risk and mortality. Therefore, all hypertensive individuals should be recommended to practice aerobic exercise such as walking, jogging or swimming 5 to 7 times a week for at least 30 mins (47).

1.8.2. Pharmacological treatment

1.8.2.1. When to initiate blood pressure-lowering drug treatment

The decision to begin drug therapy should be a shared decision-making between the patient and his/her physician. According to the latest European guidance, antihypertensive treatment should be initiated in patients with grade 1 HTN at high risk of CVD or with HMOD. In patients with low-risk grade 1 HTN, BP-lowering medications should commence only after 3-6 months if the BP could not be controlled by lifestyle changes alone. The table below defines when to initiate blood pressure-lowering drugs according to its initial office blood pressure measurements (3).

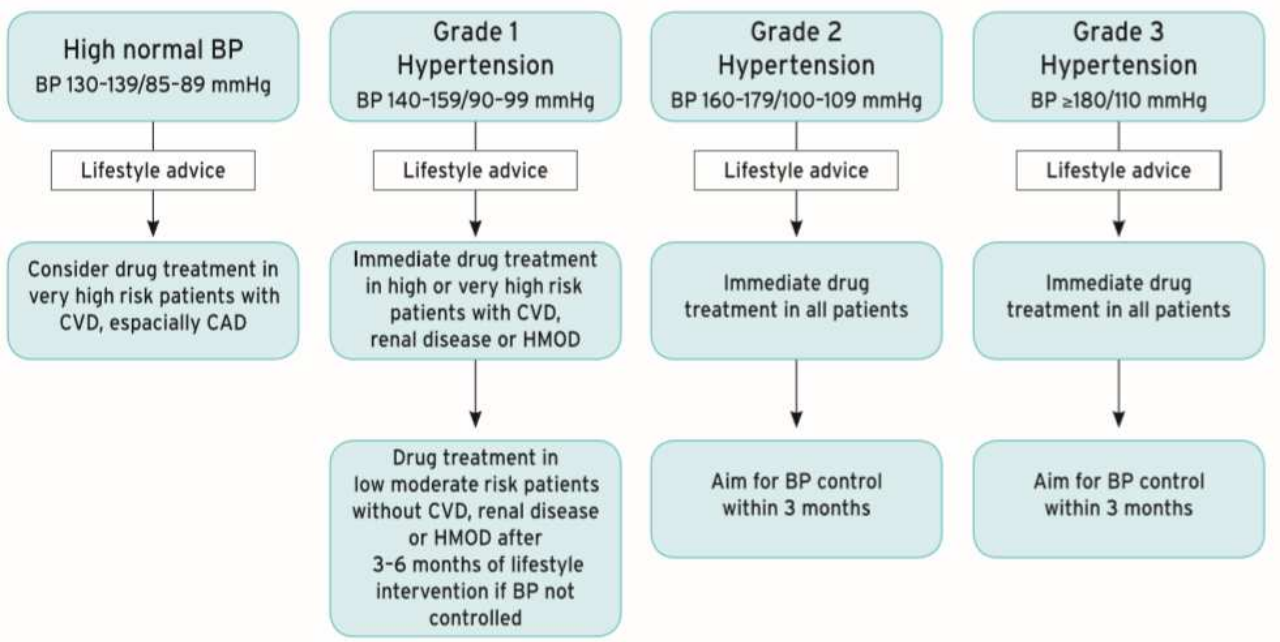

Figure 9. Initiation of blood pressure-lowering treatment (lifestyle changes and medication) at different initial office blood pressure levels
Source: 2018 ESC/ESH Guidelines for the management of arterial hypertension

1.8.2.2. Blood pressure treatment targets

When antihypertensive drugs are prescribed, the first goal should be to lower BP to <140/90 mmHg in all patients. Once established that the treatment is well tolerated, the second BP value target should aim to 130/80 mmHg or lower in most patients. In hypertensive individuals over 65 years of age, SBP should be targeted to between 130-140 mmHg and DBP to <80 mmHg (see Table 15). (3) Under no circumstance SPB should aim to 120 mmHg or less, lowering SBP to <130 mmHg is associated with no further benefit on the CV system and studies have shown that reducing SPB to <120 mmHg may increase the incidence of CV events and death in higher-risk patients (48).

Table 5. Office blood pressure treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
18 - 65 years	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	**Target to <140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	70–79
65 - 79 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
≥80 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

Source: 2018 ESC/ESH Guidelines for the management of arterial hypertension

1.8.2.3. Initial antihypertensive drug choice

In addition to lifestyle modifications, most patients require drug therapy to achieve their BP target. Five main drug classes are usually prescribed for HTN treatment, these include angiotensin-converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), beta-blockers (BB), calcium channel inhibitors (CCB) and diuretics (DIU). Overall, major CV and mortality determinants are similar with treatment based on initial therapy with all five classes. Thus, the use of antihypertensive drugs is based on the degree of BP reduction rather than the choice of antihypertensive medications. This allows the physician to individualize the therapy based on the patient's characteristics and preferences although some patients have possible or compelling indications or contraindications to certain drug class according to their comorbidities (49). Table 6. here below summarizes considerations for individualizing antihypertensive therapy (40).

Table 6. Considerations for individualizing hypertensive therapy

Indication	Antihypertensive drugs
Compelling indications (major improvement in outcome independent of blood pressure)	
Systolic heart failure	ACE inhibitor or ARB, beta blocker, diuretic, aldosterone antagonist*
Postmyocardial infarction	ACE inhibitor or ARB, beta blocker, aldosterone antagonist
Proteinuric chronic kidney disease	ACE inhibitor or ARB
Angina pectoris	Beta blocker, calcium channel blocker
Atrial fibrillation rate control	Beta blocker, nondihydropyridine calcium channel blocker
Atrial flutter rate control	Beta blocker, nondihydropyridine calcium channel blocker
Likely to have a favorable effect on symptoms in comorbid conditions	
Benign prostatic hyperplasia	Alpha blocker
Essential tremor	Beta blocker (noncardioselective)
Hyperthyroidism	Beta blocker
Migraine	Beta blocker, calcium channel blocker
Osteoporosis	Thiazide diuretic
Raynaud phenomenon	Dihydropyridine calcium channel blocker
Contraindications	
Angioedema	Do not use an ACE inhibitor
Bronchospastic disease	Do not use a non-selective beta blocker
Liver disease	Do not use methyldopa
Pregnancy (or at risk for)	Do not use an ACE inhibitor, ARB, or renin inhibitor (eg, aliskiren)
Second- or third-degree heart block	Do not use a beta blocker, nondihydropyridine calcium channel blocker unless a functioning ventricular pacemaker
Drug classes that may have adverse effects on comorbid conditions	
Depression	Beta blocker, central alpha-2 agonist
Gout	Loop or thiazide diuretic
Hyperkalemia	Aldosterone antagonist, ACE inhibitor, ARB, renin inhibitor
Hyponatremia	Thiazide diuretic
Renovascular disease	ACE inhibitor, ARB, or renin inhibitor

Source: The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA 2003; 289:2560.

1.8.2.4. Initial monotherapy

Initial monotherapy with one of the five major BP lowering drugs is frequently successful in those with mild HTN. The past guidelines generated different approaches to improve BP using monotherapy. One way is to increase the initial dose until achieving the goal BP, however higher doses result in little BP reduction at the price of greater adverse effects. The other strategy, so called “sequential monotherapy” consists of switching from one antihypertensive to another every 4-6 weeks using minimal doses and titrating upwards only to moderate doses in order to find out the lowest recommended dose, however, proceeding in this manner is often ineffective as well as frustrating and time-consuming for the patient. In patients whose BP is more than 20/10

mmHg above goal, single drug therapy is unlikely to reach the desired BP level and combination therapy is recommended (50).

1.8.2.5. Combination therapy

In order to attain their BP target, most patients will require combination therapy. Using a combination of low-dose agents has better BP-lowering effect than raising the dose of a single agent as it targets different physiological BP control mechanisms. Also, it has been shown to be well tolerated, safe and presents very little risk of hypotensive episodes (51).

Latest guidelines for initial dual combination therapy recommend using one ACE or ARB with a CCB or diuretic, ACE and ARB should never be used concomitantly as they act through a similar mechanism. Such treatment has showed to control BP of about two thirds of patients.

For those whose BP target cannot be achieved, three drugs combination is indicated, it includes an ACE or ARB plus CCB and a diuretic, BP control is achieved in over 80% of patients. Initial three drug combination is not recommended (3).

Assuming that secondary HTN causes and poor adherence of the patient have been excluded, individuals not controlled on a combination of three antihypertensives which were taken at moderate doses and included a diuretic are classified to have drug resistant HTN. Such patients are required to be evaluated by a specialist that usually manages the further treatment with the addition of a low dose of spironolactone or another diuretic therapy, or beta-blockers, alpha-blockers (52). Figure 10. below illustrates the core treatment strategy recommended in an uncomplicated patient with HTN.

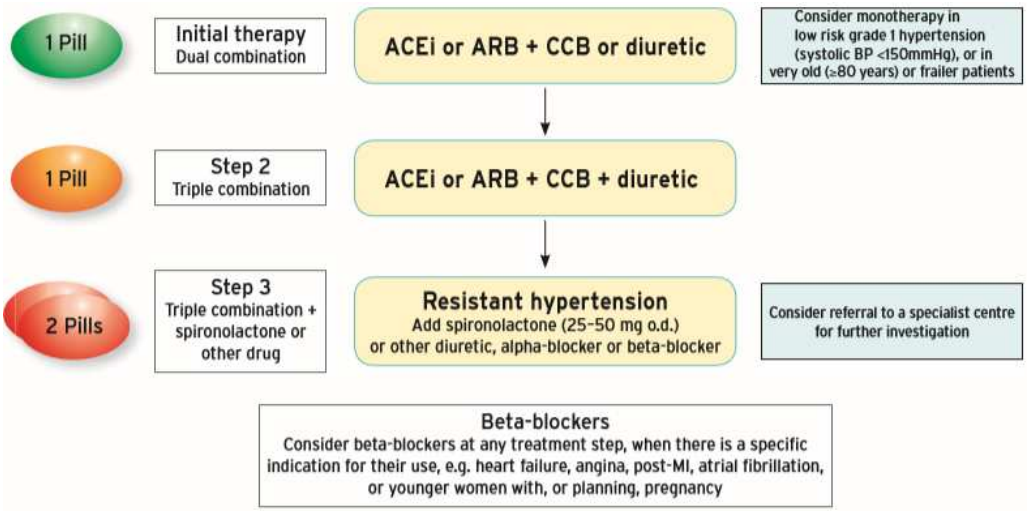

Figure 10. Treatment strategy in an uncomplicated patient with hypertension
Source: 2018 ESC/ESH Guidelines for the management of arterial hypertension

Fixed-dose combination preparations are now widely available and are encouraged to be employed as a direct inverse relationship between the number of pills and the likelihood of adherence has been demonstrated. Also, single pill combination showed an improvement in BP control and offers a comprehensive therapeutic approach for the patient when progressing from 1, 2 or 3 drugs treatment whilst preserving their single pill regimen (53).

1.8.2.6. Discontinuing therapy

Majority of patients with HTN will require lifelong antihypertensive drug therapy to manage their BP. However, reducing or discontinuing antihypertensive medication may be an option in some patients with HTN that is well controlled for at least a year. Among those, cessation of antihypertensive therapy is more likely to be successful in younger individuals, those who had lower pretreatment BP and those who initiate and adhere to lifestyle modifications. A study showed that 40% remained free from treatment one year after discontinuing and 25% were off therapy at two years.

Another option is to lighten the therapy by decreasing the number and/or dose of medications taken. This method is simpler, presents less risks and it is more accessible towards the patients. Economically, reducing the treatment is preferable as the overall cost of frequent

follow-up that is required after stopping may be greater than the cost of continuing the treatment with generic pills.

All in all, the value of discontinuing antihypertensive drugs still remains uncertain and should be a shared decision between the patient and his/her medical caretaker (54-56).

2.OBJECTIVES

2.1. HYPOTHESES

1. Our hypertensive sample is at higher risk for CV disease occurrence
2. Most of our examinees are at a relatively low BP grade and stage of the disease
3. Hypertensive individuals over 65 years old are less likely to achieve their BP treatment target than younger patients
4. Dual antihypertensive therapy is the most commonly prescribed treatment

2.2. AIMS

The aims of this study are:

- To determine the age, gender, BMI and BP of the sampled population
- To analyze parameters related to the patient's ABPM and BP cutoff in individuals under antihypertensive therapy
- To evaluate the stage and grade of the disease
- To determine the BP treatment target range using ABPM
- To establish CV risk stratification according to BP, risk factors & comorbidities
- To analyze the therapy regimens and their relationship to BP

3.MATERIALS AND METHODS

3.1. Study design

The study was conducted as a retrospective cross-sectional study.

3.2. Study sample

168 patients were included between the period of 1st of September 2018 and 1st of April 2019, the patients were treated across eight offices of family medicine specialists in Spit, all of them belonging to the Split Community health center.

3.3. Method of collecting and analyzing data

The study material was collected from eight different offices of family medicine specialists in Split. Following the gathering of materials from the specialist's databases and archives, the patients' medical records were then reviewed and inserted in Microsoft Excel program.

A questionnaire for data collection was designed, the first part was dedicated to basic information such as gender, age, personal and family medical history including the occurrence of CV disease and CV incidents, kidney disease, diabetes and atrial fibrillation, and other known chronic disease. The following section was allocated to smoking history, height, weight, waist-hip ratio, BMI, as well as a complete biochemical laboratory test. The last part retrieved the data about the 24-hours ABPM and the last office-BP measurement.

The criteria of inclusion were as follows: all patients from 1st September 2018 to 1st of April 2019 who undertook ABPM measurements and are being followed by one of the eight family medicine doctor taking part in the study.

4.4.Statistical analysis

By using the medical records, the needed parameters were analyzed and shown in figures and tables. Microsoft Excel and Microsoft Word were used to design the tables and figures.

The data was analyzed using STATISTICA 12 software. Data distribution was assessed by the Kolmogorov-Smirnov test. To test for correlation, Pearson's correlation coefficient was employed. Throughout the statistical analysis we displayed the average and standard deviation for normal distributed and median and interquartile range (IQR) for non-normal distributed variables. The differences in BP were analyzed using t-test. T Chi-Square test was used to assess the homogeneity by categorical variables. Statistical significance was set to $P < 0.05$.

4.RESULTS

PART 1. ALL EXAMINEES (n=168)

Out of 168 examinees, arterial HTN occurred in 68 male (40.48%) and in 100 females (59.52%) showing that we significantly had more women with HTN than men (χ^2=6.10; p=0.014).

The median of age of the examinees was 64 years (IQR=55-70) and most patients were in the age group 61-80 years. We had a significant difference in number of patients showing its heterogeneity (χ^2=102.29; p<0.001).

The average BMI was 27.19 kg/m^2 (SD=3.6), which indicated that most patients are overweight (BMI= 25-30). In our sample, male examinees had a significantly higher BMI than women (28.41 and 26,40 kg/m2, respectively) (t=3.03; p=0.003). There was no correlation found between age and BMI index (r=-0.01; p=0.941).

When evaluating the BP levels, we noted that the average value of office systolic BP is 138,93 mmHg (SD=22,37), showing that most patients are under the HTN cutoff (systolic BP <140 mmHg). The average office systolic BP exceeds the average ABPM systolic BP for 4,01 mmHg. The average value of office diastolic BP is 82,14 mmHg (SD=13,07), indicating that most patients are well under the cutoff for diastolic HTN (diastolic BP <90 mmHg). The average value for office BP is higher of 5,22 mmHg compared to the average 24h diastolic BP.

The relationship between gender and BP was then assessed, the average 24h-diastolic BP is lower of 3,91 mmHg in female patients than male patients, the difference is significant (t=2,81; p=0,006). The difference in daily diastolic BP is of 3,22 mmHg and is also significant where male patients have a higher BP value (t=2,18; p=0,031). Lower values can be seen for mean office systolic BP, office diastolic BP and average 24h systolic BP between male and female patients but the difference is not significant (p value more than 0,050).

PART 2. PATIENTS UNDER ANTIHYPERTENSIVE THERAPY USING 24-H AVERAGE - MEASURED BY ABPM (n=126)

This part was conducted on 126 examinees that are using antihypertensive medications. When considering the relationship between gender and BP cutoff, we observed a difference of

11,53% between gender, having more female patients under cutoff BP values (140/90 mmHg) than male, although the difference was not significant (X^2=1,88; p=0,171).

The correlation between age and BP cutoff was then established, we noted that examinees under cutoff values tend to be older of 2,61 years than patients with HTN. The difference was not significant (t=1,13; p=0,261).

Also, the comparison between BMI and BP cutoff showed that patients under cutoff values have a BMI mean 0,67 kg/m2 lower than those with HTN. The difference is not significant (t=0,78; p=0,435).

Table 7. compares multiple laboratory parameters measured and compared to the examinees with BP cutoff over and under 140/90 mmHg.

Table 7. Comparison of laboratory parameters between patients over and under the BP cutoff

	hypertension (average)							
	Over cutoff			**Under cutoff**				
	N	**Mean**	**Std.Dev.**	**N**	**Mean**	**Std.Dev.**	**t**	**p***
WHr	86	0,45	0,46	39	0,62	0,45	1,93	**0,028**
Cholesterol	76	5,62	1,25	36	5,28	1,01	1,44	0,076
HDL	75	1,22	0,37	35	1,20	0,37	0,31	0,380
LDL	72	3,66	1,06	34	3,38	1,00	1,27	0,103
Triglycerides	76	1,68	0,84	36	1,55	0,78	0,77	0,221
Uric acid	61	330,54	91,00	23	319,26	61,19	0,55	0,292
GLU	78	6,27	1,82	37	5,97	1,60	0,85	0,199
AST	75	22,97	10,90	35	22,00	6,44	0,49	0,313
GGT	74	33,97	31,91	35	27,71	21,27	1,05	0,147
ALT	75	29,12	22,62	35	29,80	27,17	-0,14	0,445
Sodium	53	137,39	18,66	27	139,41	2,45	-0,56	0,290
Potassium	56	4,64	1,86	26	4,43	0,33	0,56	0,290
Urea	68	6,15	1,57	34	6,06	1,75	0,28	0,391
Creatinine	76	71,27	18,25	35	69,11	15,64	0,60	0,274
Pulse	87	71,63	9,63	39	67,90	7,43	2,15	**0,017**

WHr – Waist hip ratio; HDL – High density lipoprotein; LDL – Low density lipoprotein; GLU – Glucose; AST – Aspartate aminotransferase; GGT – Gamma-glutamyl transferase; ALT – Alanine aminotransferase

Patients with BP under cutoff values have a higher waist hip ratio (WHr) of 0,17 units more than hypertensive patients. The difference was significant (t=1,93; p=0,028). Patients under the BP

cutoff had a lower pulse by 3,73bpm than patients with HTN. The difference was significant (t=2,15; p=0,017). We also noticed higher levels of cholesterol, low density lipoproteins (LDL), triglycerides, uric acid, glucose, aspartate aminotranferase (AST), gamma-glutamyl tranferase (GGT), urea and creatinine but these were not significant between the two groups.

PART 3. RISK STRATIFICATION, BP GRADING AND DISEASE STAGING

The following part is dedicated to evaluating the risk of our examinees for CV diseases according to BP level grades and comorbidities (previous CV incident (CVI), diabetes mellitus (DM) and chronic kidney disease (CKD)). From there, eight CV risk factors based on the European guidelines were selected to design the table below:

1. Gender: Male
2. Age: >65 years old
3. Smoker: Yes, or used to
4. Overweight or obesity: WHr>1 in males and >0.85 in females
5. Total cholesterol level: >5mmol/L
6. Creatinine level: >104mmol/L in males and >90mmol/L in females
7. Uric acid level: >400mmol/L in males and >340mmol/L in females
8. Pulse: >80 beats per minute

Table 8. Classification of hypertension disease staging according to BP level grades, presence of CV risk factors (gender, age, total cholesterol, creatinine level, smoking, overweight, pulse & uric acid level) and comorbidities (previous CVI, DM and CKD).

Hypertension disease staging	Other risk factors	BP (mmHg) grading				
		Normal SBP<130 DBP<85	High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP>180 DBP>110
Total n=166		n=59 35%	n=51 30.3%	n=48 28.5%	n=8 5.3%	n=0 0%
Stage 1 (uncomplicated)	No risk factor	6 (3.6%)	2 (1.2%)	2 (1.2%)	1 (0.6%)	0
	1 or 2 risk factors	23 (13.7%)	28 (16.7%)	21 (12.5%)	2 (1.2%)	0
	≥ 3 risk factors	21 (12.5%)	16 (9.5%)	15 (8.9%)	5 (2.9%)	0
Stage 2 (asymptomatic disease)	CKD stage 3 or DM without organ damage	4 (2.3%)	5 (2.9%)	7 (4.2%)	1 (0.6%)	0
Stage 3 (established disease)	Established CDV, CKD≥4 or DM with organ damage	5 (2.9%)	0	3 (1.7%)	0	0

The CV risk distribution is as follows, the green color represents Low CV risk which had 49.0% of our examinees. Low to moderate risk translates to the yellow color and makes up 25.0% of patients. 13.2% of patients have moderate risk for CV disease occurrence defined as orange here. The remaining examinees are categorized as high risk (red) and very high risk (blue) with CV risk rate of 10.3% and 2.5%, respectively.

According to our outcome, BP grading is distributed as followed: Examinees with normal BP represent 35% of our sample, closely followed by high-normal BP and 30.3% Grade 1 HTN

which signifies 30.3% and 28.5%, respectively. We noted 5.3% of examinees with grade 2 HTN and none exhibiting grade 3 HTN.

Lastly, the HTN disease staging of the examinees was evaluated and showed that the vast majority 84.5% were at stage 1 (uncomplicated disease), 10.0% at stage 2 (asymptomatic disease), and the remaining 4.6% at stage 3 (established disease).

PART 4. DETERMINATION OF BP CONTROL OF HYPERTENSIVE SUBGROUPS

In table 9 here below, we described the proportion of examinees under hypertensive therapy reaching their BP treatment target range across five subpopulations.

Table 9. BP treatment target range among subgroups of patients

BP target	**>65yo**	**<65yo**	**DM**	**CVI**	**CKD**
Sys BP target	**130-139**	**≤130**	**130-139**	**130-139**	**130-139**
Syst BP	18 (22.5%)	35 (39.8%)	11 (52.4%)	5 (62.5%)	5 (71.4%)
Dia BP target	**70-79**	**70-79**	**70-79**	**70-79**	**70-79**
Dia BP	36 (40.0%)	39 (48.75%)	16 (76.2%)	7 (87.5%)	6 (85.7%)
Sys/dia BP	7 (8.7%)	22 (25%)	8 (38%)	4 (50%)	4 (57.1%)

We can note that patients <65 years of age tend to achieve their BP target more than those above 65 years old, 17,3% more for systolic BP and 8,75% more for diastolic BP.

PART 5. TREATMENT PARAMETERS

In the following four tables, the type of therapy, proportion of patients taking a specific medication (within each treatment group and across the whole sample n=122) and its according rate of success to lower BP below 140/90 mmHg was determined for examinees prescribed single, dual and triple or four or more drug therapies.

Table 10. Patients on monotherapy and its BP relationship

Monotherapy	Patients (n=48)	% (n=48)	% (n=122)	BP <140/90
CCB	17	35.4	13.9	58.8%
BB	9	18.75	7.4	77.8%
ACE	19	39.9	15.6	42.1%
DIU	3	6.2	2.5	33.3%
ARB	0	-	-	-
	48		39,4	

Patients under antihypertensive monotherapy represent 39.4% of our sample. They are most commonly prescribed CCB (35%) and ACE (nearly 40%) and respectively have a success rate of 58.8% and 42.1% to control BP.

Table 11. Patients on dual therapy and its BP relationship

Dual therapy	Patients (n=48)	% (n=48)	% (n=122)	BP <140/90
ACE + CCB (1 pill)	16	33.33	13.1	31.3%
ARB + DIU (1 pill)	5	10.4	6.6	60.0%
ACE + DIU (1 pill)	7	14.6	9.2	85.7%
CCB + ACE (2 pills)	5	10.4	4.1	80.0%
ACE + BB (2 pills)	9	18.75	7.4	66.7%
alpha2 + BB (2 pills)	1	2.0	0.8	0.0%
CCB + BB(2 pills)	3	6.25	2.5	66.7%
ACE + DIU (2 pills)	1	2.0	0.8	0.0%
CCB + DIU (2 pills)	1	2.0	0.8	100.0%
	48		39,4	

Individuals on dual therapy make up 39.4% and are mostly prescribed ACE + CCB (33.3% of patients) with a BP control rate of 31.3%. ACE + BB is often given and regulated the BP in 66.7% of cases. ACE + DIU was ordered to nearly 15% of patients and decreased the BP under the cutoff in 85.7% of them.

Table 3. Patients on triple therapy and its BP relationship

Triple therapy	Patients (n=21)	% (n=21)	% (n=122)	BP <140/90
CCB + BB +ACE (3 pills)	2	9.5	1.6	50.0%
CCB + a2 + BB (3 pills)	1	4.8	0.8	0.0%
ACE + DIU + BB (2 pills)	3	14.3	2.5	66.7%
ARB + DIU + BB (2 pills)	2	9.5	1.6	0.0%
ACE+ CCB + DIU (2 pills)	2	9.5	1.6	100.0%
CCB + ACE + DIU (2 pills)	2	9.5	1.6	50.0%
ACE + CCB + BB (2 pills)	6	28.6	4.9	0.0%
CCB + BB + DIU (3 pills)	2	9.5	1.6	100.0%
ARB + DIU + CCB (2 pills)	1	4.8	0.8	0.0%
	21			

Triple therapy is given to 17.2% of our patients. It is composed of various combinations of drugs, ACE + CCB + BB is the most frequently used (28.6% of patients) but did not adjust the BP under 140/90 in any patient.

Table 12. Patients using 4 or more antihypertensive and its BP relationship

≥ 4 medications	Patients (n=5)	% (n=5)	% (n=122)	BP<140/90
ACE + CCB + BB + DIU (3 pills)	3	60.0	2.5	66.7%
ARB + DIU + BB + CCB (3 pills)	1	20.0	0.8	0.0%
CCB + ACE + DIU + BB (4 pills)	1	20.0	0.8	0.0%
	5			

The most common combination of 4 drugs is ACE + CCB + DIU + BB (60%) and maintained the BP under cutoff in 60%. Only 4.0% of our examinees receive 4 or more drugs.

Table 13 describes the relationship between number of pills prescribed to the examinees and the proportion of patients under the BP cutoff.

Table 13. Relationship between the number of pills prescribed and BP

Number of pills	Patients	%	<140/90
1	76	62.3	52.6%
2	36	29.5	52.8%
3	9	7.4	55.6%
4	1	0.8	0.0%

Majority of patients are administered a single pill (76%), and about 30% take two medications for BP control. We can state that the BP control rate is fairly similar upon number of medications taken.

5. DISCUSSION

In this study, we establish a general evaluation over many parameters in a hypertensive population. In the discussion, we present the analogy between our results and those of four other comparative studies from hypertensive populations that were mostly conducted across Europe. The results are described and interpreted here below.

The first step was to assess and compare multiple demographic parameters, we noted that our population was mostly composed of elderly with a median age of 64 years old and that 60% of our patients were females. The average BMI shows that most of our hypertensive patients are overweight, it especially applies to males who tend to have BMI higher than females. We then described the comparison of BP measuring methods and figured that the average ABPM values tend to be lower than the average office BP measurements (134.9/76.9 mmHg vs. 138.3/82.14 mmHg). These BP values were then distributed across gender, we noticed that females showed slightly lower values for both ABPM and office BP measurements compared to males with a significant difference for the ABPM average diastolic BP (75.3 mmHg vs. 79.2 mmHg, respectively).

When comparing our demographic data to the findings of Afsar et al., Corbaton et al., and Menendez et al., our population obtained fairly similar outcomes. Two studies have an average age a bit younger around 50 years old. Overall BMI was nearly the same for all studies (27 kg/m^2 in our research vs. 28 kg/m2). The average office-BP levels of hypertensive patients ranged from 159/96 mmHg to 137/79 mmHg to 127-78 mmHg across three studies vs. 138/82 mmHg in our sample. The difference between office BP and ABPM BP values were also observed in these articles (57-59).

The second part was dedicated to the differences in parameters between patients above and below the HTN BP cutoff (140/90 mmHg) who are using antihypertensive therapy. We observed that women proportionally achieved a better BP control than men (35.5% vs. 24.0%). Patients that were regulated under the BP cutoff were younger (mean of 2.6 years less) than those with BP over 140/90. Additionally, the relationship between BP cutoff and BMI showed that patients under the BP cutoff have a slightly lower BMI (27.6 kg/m2 vs. 27.0 kg/m2). Lastly, laboratory parameters differences were tested across the two cutoff groups, the results showed elevated levels of cholesterol, LDL, triglycerides, uric acid, glucose, AST, GGT, urea, and creatinine but only WHr and pulse showed a considerable increase in those above the BP cutoff.

We set side by side our results with these of two other Spanish studies only targeting the age group 61-75 years old. The prevalence of controlled BP across hypertensive examinees was 16% & 33% for men, and 26% & 33% for women in their findings while our outcome was 24% and 35% for males and females, respectively. We can note the same association between a better controlled BP with female gender and younger age. Their study also showed that there was merely no difference in BP level management between patients with BMI ranging from 25-30 kg/m2 and >30 kg/m2 (58, 59).

The following section was focused on CV risk stratification. Our data about CV risk were compared to a study from Penuela et al. which stratified hypertensive patients' CV risk according to the European guidelines, their outcome demonstrated that 28% are at low-risk (vs.49%), 35% at medium risk (vs.28%), 19% at high risk (vs. 10%) and the remaining 15% at very-high risk (vs. 2.5%) for CV disease occurrence. It was also reported that there was 57% of their sample exhibiting 1 or 2 risk factors and 39% with 3 or more risk factors, in our population we obtained 44.1% and 33.8%, respectively (60).

The upcoming part addresses the classification of our sample for BP treatment target range according to the last European guidelines. It was demonstrated that patients <65 years old achieve their systolic BP target (≤130 mmHg) more consistently than those over 65 years of age (39.8% vs. 22.5%). A similar trend is seen for diastolic BP but to a lesser degree (48,.5% vs. 40.0%). Patients that reached both systolic and diastolic treatment BP target represent 25% of patients under 65 and only 8.7% of individuals over 65.

Similar data were addressed and interpreted in the second part of this discussion.

This last paragraph is advocated to the analysis of treatment parameters, more particularly to the therapy regimen and its relationship to BP. The data about monotherapy revealed that it is as equally prescribed as dual therapy, they nearly reach 40% each. CCB and ACE are the two most commonly single drug prescribed (13.9% and 15.6% respectively), CCB having a 58.8% success rate over BP control. Combination dual therapy follows a somewhat similar pattern as the most frequently prescribed medications are CCB + ACE (ordered to 13.1% of all patients), its control rate over BP reaches 31.3%. Other combinations, such as ACE + DIU or ACE + BB obtain higher BP control rate, 85.7% and 66.7%, respectively. Triple therapy is used in 17% of our patients, it most often consists of ACE + CCB + BB, representing only 4.9% of all prescriptions. Patients needing 4 or more medications are very few (4.0%) and usually receive ACE + CCB + BB + DIU.

We also calculated the frequency of patients taking specific number of pills and its relationship to BP control, the findings were that 62.3% of patients are taking a single pill (that does not mean that they are on monotherapy), 29.5% of individuals are administered 2 pills and the remaining 8.2% get 3 or 4 pills. The efficient control of BP is best achieved in patients under triple therapy with 55.6%, patients taking 1 or 3 pills both attain a BP success rate of about 52.7%.

Upon comparison with Corbaton et al. study about pharmacologic hypertensive drug prescriptions, we can discern similarities and differences with our therapy parameters. First, 70% of their patients receive monotherapy, our sample using single-drug therapy is about 40%. The drug class used the most often in monotherapy is ACE inhibitor in both their results and our findings with 30% and 15.6%. Our second most frequently prescribed single-drug therapy is CCBs (14%) versus DIU used in 32% of cases in the other study. Dual therapy is given to 50% of their examinees vs. 40% in our results, the most frequent combinations used are DIU + ACE or DIU + ARBs (both 30%) while our patients were prescribed more commonly ACE + CCB (13%) but also DIU + ACE (10%). Finally, triple therapy is given to 24% of their patients compared to 17% of our population sample. We can observe that their study and ours are quite similar but contrast on the use of diuretics being prescribed more widely on their end (58).

This study has limitations that deserve mention. Firstly, since the design of the study is cross-sectional retrospective, cause and effect relationships cannot be suggested. Secondly, measurements were made only once for office BP, the question of reproducibility and protocol should be raised as the office BP measurements were taken by 8 different doctors with different equipment in different offices. The sample size is also worth commenting on, some parameter results should not be interpreted literally (DM patients, patients with history of CVI or triple therapy combination BP control rate) as only a few patients in these categories can result in a false outcome. Another issue is the number of sources for data collection. Patients' information came from 8 different specialists and information from medical records were frequently missing for some variables depending on which office it originated from, this in turn affected the statistical accuracy of some parameters. Lastly, an additional form of bias was the transcription from the medical records to a questionnaire which was then converted into an excel table, this process was completed by three medical students separately. Therefore, improving the quality of the study may be feasible by: increasing the sample pool, establishing a systematic reproducible BP assessment by a well-trained team with a rigorous protocol and carrying out serial measurements, adding inclusion

criteria (such as age, known or newly diagnosed patients), completing our questionnaire with for instance: education, socioeconomic status, marital status, professional status, detailed personal and family history, alcohol consumption, exercise, dietary habits, awareness and comprehension of the disease by the patient.

HTN is one of the most significant public health challenges and the biggest contributor to the global burden of disease. Improving health outcomes worldwide will require concerted global action to address the burden of hypertension. The field of hypertension needs transformation and its future will depend on the successful convergence of digital data and biotechnological and biomedical sciences coupled with their implementation in healthcare delivery with new models of delivery and the effective strategy for population health (61).

6.CONCLUSIONS

1. Hypertension grading: 35% of patients are normotensive, 30.3% have high-normal BP, grade 1 HTN population makes up 28.5% and grade 2 HTN comprises the remaining 5.3%, no patient belongs in grade 3 HTN in our sample.
2. Staging of the disease: 84.5% of patients are at stage 1 with an uncomplicated disease, 10% remain asymptomatic and are classified at stage 2 of the disease, stage 3 constitute 4.6% and defines patients with an established disease.
3. CV risk stratification: 49% at low-risk for CV disease, 28% at medium risk, 10% at high risk and the remaining 2.5% at very-high risk for CV event occurrence.
4. Women proportionally achieved a better BP control than men (35.5% vs. 24.0%).
5. Patients that are regulated under the BP cutoff have an age mean that is 2.6 years more than those with BP over 140/90 mmHg.
6. Patients under the BP cutoff have a slightly lower BMI than hypertensive individuals (27.6 kg/m2 vs. 27.0 kg/m2).
7. Elevated levels of cholesterol, LDL, triglycerides, uric acid, glucose, AST, GGT, urea, and creatinine were observed in those above 140/90 mmHg but only WHr and pulse showed a statistically significant increase.
8. Patients <65 years old achieved their systolic BP target (≤130/70-79 mmHg) more consistently than those over 65 years of age (39.8% vs. 22.5%)
9. Patients <65 years old achieved their diastolic BP target (≤70-79 mmHg) more consistently than those over 65 years of age (48,.5% vs. 40.0%).
10. Antihypertensive monotherapy and dual therapy are prescribed equally in our study sample, reaching nearly 40% each.
11. CCB and ACE are the two most commonly single drug prescribed (13.9% and 15.6% respectively), CCB exert a 58.8% success rate over BP control.
12. The most common dual therapy combination prescribed is CCB + ACE, it is prescribed to 13,1% of all patients and its control rate over BP reaches 31.3%.
13. Other less frequently prescribed combinations, such as ACE + DIU or ACE + BB obtained a higher BP control rate, 85.7% and 66.7%, respectively.
14. Triple therapy was used in 17% of our patients, it most often consists of ACE + CCB + BB, representing only 4.9% of all prescriptions.

15. 62.3% of patients are taking a single pill, 29.5% of individuals are administered 2 pills and the remaining 8.2% get 3 or 4 pills.
16. Efficacy in controlling BP was best achieved in patients under triple therapy with 55.6%, patients taking 1 or 3 pills both attained a BP success rate of 52.7%.

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8.SUMMARY

OBJECTIVES: The aims of the paper were to establish the patients' BP grading and disease staging, stratify the CV risk of the hypertensive population, determine if the BP treatment target ranges are achieved and assess their treatment parameters.

MATERIALS AND METHODS: The study is a cross-sectional retrospective study including 168 patients with HTN from the 1st of September 2018 to the 1st of April 2019. The data was collected from eight different offices of family medicine specialists in Split. Following the gathering of materials from the specialist's databases and archives, the patients' medical records were then reviewed and inserted into Microsoft Excel program.

RESULTS: Hypertension grading demonstrated that 35% of patients are normotensive, 30.3% have high-normal BP, grade 1 HTN population makes up 28.5% and grade 2 HTN comprises the remaining 5.3%, no patient belongs in grade 3 HTN. Staging of the disease was then evaluated, the results showed that 84.5% of patients are at stage 1 with an uncomplicated disease, 10% remain asymptomatic and are classified at stage 2 of the disease and stage 3 constitute 4.6% and defines patients with an established disease. CV risk was stratified, the outcome displayed that 49% of patients are at low-risk for CV disease, 28% at medium risk, 10% at high risk and the remaining 2.5% at very-high risk for CV event occurrence. Women (35.5% vs. 24.0%) and patients <65 years old achieve both their systolic and diastolic BP target (≤130/70-79 mmHg) more consistently (39.8% vs. 22.5% and 48.75% vs. 40.0%, respectively). Antihypertensive monotherapy and dual therapy are prescribed equally in our study sample, nearly reaching 40% each. CCB and ACE are the two most commonly single drug prescribed (13.9% and 15.6% respectively) with a BP control rate of 58.8%. The most common combination dual therapy prescribed medications are CCB + ACE, prescribed to 13.1% of all patients and its control rate over BP reaches 31.3%. Triple therapy is used in 17% of our patients, it most often consists of ACE + CCB + BB, representing only 4.9% of all prescriptions. 62.3% of patients are taking a single pill, 29.5% of individuals are administered 2 pills and the remaining 8.2% get 3 or 4 pills. Efficacy in controlling BP was best achieved in patients under triple therapy with 55.6%, patients taking 1 or 3 pills both attain a BP success rate of about 52.7.

CONCLUSIONS: Most patient of our study are normotensive, high-normal or exert grade 1 HTN. Majority of hypertensive individuals are at stage 1 of the disease and are at low to moderate risk for occurrence of CV disease. Demographically, women and younger individuals tend to achieve their treatment BP target more efficiently. Mono- and dual therapy represent 80% of all prescription, the most common drugs used are ACE and CCB taken in the form of one or two pills.

9.CROATIAN SUMMARY

CILJ: Ciljevi ovog istraživanja bili su odrediti stupanj i stadij bolesti, potom stratificirati hipertenzivne bolesnike prema ukupnom stupnju kardiovaskularnog rizika, te utvrditi da li su postignute ciljne vrijednosti arterijskog tlaka uz procjenu terapijskog pristupa.

ISPITANICI I METODE: Provedeno je presječno, retrospektivno istraživanje u koje je uključeno 168 ispitanika sa dijagnozom arterijske hipertenzije kojima je u periodu od 01. rujna 2018. do 01. travnja 2019. urađeno 24 h monitoriranje arterijskog tlaka. Podatci su prikupljeni u osam specijalističkih ordinacija obiteljske medicine u Splitu. Za istraživanje je osmišljen upitnik temeljem kojeg su prikupljeni podatci iz elektronskih zdravstvenih kartona. Po prikupljanju podataka za sve ispitanike kreiran je skupni zapis u Microsoft Excel programu.

REZULTATI: Temeljem izmjerenih vrijednosti arterijskog tlaka 35% ispitanika bilo je normotenzivno a 30,3% imalo je visoko normalan arterijski tlak. Prvi stupanj arterijske hipertenzije zabilježen je kod 28,5% a drugi stupanj kod 5,3% ispitanika.
U prvom stadiju bolesti bez komplikacija bila je većina ispitanika, njih 84,5%,
u stadiju dva sa asimptomatskom bolesti 10%, dok je u stadiju 3 bilo 4,6% ispitanika.
Nakon stratifikacije prema ukupnom kardiovaskularnom riziku 49% ispitanika imalo je nizak, 28% umjeren, 10% visok i 2,5% vrlo visok rizik. Žene i ispitanici mlađi od 65 godina bolje su postizali ciljne vrijednosti arterijskog tlaka. Više od 80% ispitanika liječeno je s jednim ili dva lijeka a najčešće propisani lijekovi bili su ACEI i blokatori kalcijevih kanala.

ZAKLJUČAK: Većina ispitanika je postigla ciljne vrijednosti tlaka (>60%) a kod trećine (28,5%) je zabilježen prvi stupanj arterijske hipertenzije. Većina ispitanika (84,5%) je u prvom stadiju bolesti bez komplikacija, sa niskim i umjerenim ukupnim kardiovaskularnim rizikom. Žene i mlađi ispitanici su najčešće postizali ciljne vrijednosti arterijskog tlak. Više od 80% ispitanika liječeno je s jednim ili dva lijeka a najčešće propisani lijekovi bili su ACEI i blokatori kalcijevih kanala.

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