# CHAPTER 3

# PRIMARY HYPERTENSION

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## INTRODUCTION

Hypertension (HT) is one of the most common chronic diseases in the world. More than 150 million people in Europe have HT and its prevalence is expected to increase by about 15% to 20% by 2025(1). HT is a preventable and treatable disease, with a strong association with cardiovascular disease, stroke, kidney failure, and premature death. However, despite all treatment possibilities, only 53% of people with HT could lower their blood pressure (BP) below 140/90mmHg. The main reasons for this were determined as not making the necessary life style changes, low patient compliance, wrong prescribing and isolated systolic HT seen in the geriatric population(2).

### DiagnosticPrinciples of Hypertension

The definitions of HT in The International Society of Hypertension (ISH) 2020 and EuropeanSociety of Cardiology (ESC) and EuropeanSociety of Hypertension (ESH) 2018 guidelines are similar[3-5].In the 2017 guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA), HT is defined with lower values[6] The 2018 ESC/ESH guidelines added the presence of retinal exudate or hemorrhage, left ventricular hypertrophy, hypertensive retinopathy with vascular or kidney damage to the definition of high blood pressure (≥ 180/110mmHg) (4). (Table1-Table2)

In addition to these guidelines, "Turkish Hypertension Consensus Report has been published first in 2015 [7]and was updated in 2019. In the current report, two separate classifications were made for the diagnosis of HT according to clinical BP levels and according to the measurement method (Table3 and Table4). In general, HT is defined as with systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg with repeated clinical measurements in adults over 18 years of age. The main thing in the diagnosis is SBP[8].(Table2-3)

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| Table 1-Definition of hypertension (P. Verdecchia, et al) | | | |
|---|---|---|---|
| Definition of HT | ISH Practice Guidelines 2020 (mmHg) | ESC/ESH 2018 (mmHg) | ACH/AHA 2018 (mmHg) |
| Clinic BP | SBP ≥ 140 and/or DBP ≥ 90 | SBP ≥ 140 and/or DBP ≥ 90 | SBP≥ 130or DBP≥ 80 |
| Self-measured home BP | SBP ≥ 135 and/orDBP ≥ 85 | SBP ≥ 135 and/or DBP ≥ 85 | SBP≥ 130 or DBP ≥ 80 |
| Average 24-h ABP | SBP ≥ 130and/or ≥ DBP 80 | SBP ≥ 130 and/or DBP ≥ 80 | SBP≥ 125 or DBP ≥ 75 |
| Average day time ABP | SBP ≥ 135 and/or DBP ≥ 85 | SBP ≥ 135 and/or DBP ≥ 85 | SBP ≥ 130 or DBP ≥ 80 |
| Average night time ABP | SBP ≥ 120 and/or DBP ≥ 70 | SBP ≥ 120 and/or DBP ≥ 70 | SBP ≥ 110 or DBP ≥ 75 |

| Table 2-Blood pressure grading (P. Verdecchia, et al) | | | |
|---|---|---|---|
| Hypertension grade | ISH Practice Guidelines 2020 (mmHg) | ESC/ESH 2018 (mmHg) | ACH/AHA 2018 (mmHg) |
| Optimal | Not defined | SBP < 120 and DBP < 80 | Not defined |
| Normal | SBP<130 DBP<85 | SBP 120–129 and/or DBP 80–84 | SBP < 120and DBP < 80 |
| Elevated | Not defined | Not defined | SBP 120–129 and DBP < 80 |
| High-normal | SBP 130–139 and/or DBP 85–89 | SBP 130–139 and/or DBP 85–89 | Not Defined |
| Grade 1 | SBP 140–159 and/or DBP 90–99 | SBP 140–149 and/or DBP 90–99 | SBP 130–139 or DBP 80–89 |
| Grade 2 | SBP ≥ 160 and/or DBP ≥ 100 | SBP 170–179 and/or DBP 100–109 | SBP ≥ 140 or DBP ≥ 90 |
| Grade 3 | Not Defined | SBP ≥ 180 and/or DBP ≥ 110 | Not Defined |
| Isolated systolic hypertension | SBP ≥ 140 and DBP < 90 | SBP ≥ 140 and DBP < 90 | Not Defined |

| Table3-Blood pressure classification according to clinical blood pressure levels (Turkish Hypertension Consensus Report-2019) | | | |
|---|---|---|---|
| category | SBP (mmHg) | | DBP (mmHg) |
| normal | <120 | and | <80 |
| elevated | 120-139 | and/or | 80-89 |
| hypertensıon | ≥140 | and/or | ≥90 |
| – Stage 1 | 140-159 | and/or | 90-99 |
| – Stage 2 | ≥160 | and/or | ≥100 |

| Table 4-Diagnosis of hypertension by measurement method (Turkish Hypertension Consensus Report-2019) | | | |
|---|---|---|---|
| CATEGORY | SBP **(mmHg)** | | DBP **(mmHg)** |
| CLINIC | ≥140 | and/or | ≥90 |
| HOME | ≥135 | and/or | ≥85 |
| Ambulatory blood pressure | | | |
| 24-hour average | ≥130 | and/or | ≥80 |
| Day time average | ≥135 | and/or | ≥85 |

**SBP:systolic blood pressure – DPB:diastolic blood pressure**

## White Coat Hypertension

Determined as when the patient's BP measurement is higher than home measurements in the office or hospital. It is detected in approximately 20% of patients, mostly in the elderly (9,10). Life style changes and frequent BP monitoring are important for this group.

## Masked Hypertension

It is the case where home measurements are higher than clinical measurements (>135/85mmHg). It is especially detected in people working under high stress. Its prevalence is between 10-25%. The risk of developing HT and cardiovascular events in the future is higher than normotensive people(6,11).Life style changes and if needed, a short-acting antihypertensive therapy are recommended for this group.

## Blood Pressure Measurement

For the diagnosis BP, it is very important to make the measurement with the appropriate technique and to interpret it correctly.

- The patient should be sitting comfortably for at least 5 minutes in a comfortable position and at least 30 minutes before the measurement, caffeine/alcohol / cigarette should not be used, exercise should not be done and patient's bladder must be empty
- Clothes in the cuffarea should be removed
- Periodically calibrated sphygmomanometer should be used.
- The middle of the cuff should be placed on the patient's upper arm at the level of the right atrium (middle of the sternum) and must overlap the central brachial artery.
- The size of the cuff used should cover 80% of the patient's arm.
- If the patient has arrhythmia, BP should be measured using a stethoscope with the classical method.
- Two measurements should be made on both arms, and if the difference is over 15mmHg, the measurement should be repeated on the higher arm. In this case, possible subclavian stenosis and peripheral vascular disease should be kept in mind.

## Ambulatory Blood Pressure Monitorization (ABPM)

ABPM is a method in which blood pressure is recorded during the patient's 24-hour routine activities –15-20 minutes per day, every 30-60 minutes at night – and it has a higher correlation with target organ damage[12] and cardiovascular events(13,14).Although there is no clear consensus on the minimum number of readings that should be included in the assessment, in some guidelines, it is stated that it is sufficient to successfully record 70% of 24 hours, and it would be appropriate for at least 20 of them to be day time and 7 of them to be at night(4). ABPM is used to detect white coat HT, masked HT, suspected BP attacks (phechromocytoma), treatment response, hypotension attacks developed under treatment, to confirm resistant HT, autonomic dysfunction and normal BP follow-ups at home. Studies have shown that there is an increased risk of cardiovascular mortality in patients with abnormalities in ABPM, especially those with nocturnal non-dipper BP. Most experts agree that a 24-hour BP of <115/75 mmHg is normal and ≥125/≥75 mmHg should be considered abnormal(6).

**Nocturnal Dipping** – Dipping is the proportional reduction of BP measured at night compared to day time BP. Mean night time systolic and diastolic BP is approximately %15 lower than the day time value in both normotensive and hy-

pertensive patients (15).When the BP does not drop by at least 10 percent during sleep, it is called "non-dipping". Although not fully known, this condition is thought to be associated with intrinsic kidney defects (16).And it has been found to contribute to the development of heart failure (HF) and other cardiovascular events (17).In one large cohort, the risk of HF among nondippers were more than twice that of dippers, although day time office BP checks were good (18). In addition, non-dipping is associated with progression of nephropathy and rapid deterioration in renal function in diabetic patients(19).

**Etiology and Pathogenesis**

While the salt load that develops with an increase in sodium intake in a normotensive individual is rapidly eliminated, this "pressure-natriuresis" relationship is abnormal in a hypertensive patient. The salt load threshold is higher, especially in HT patients under the age of 40, which are defined as salt-resistant HT. On the contrary, BP increases more at a similar salt load, generally in the elderly group. This group of patients is defined as salt-sensitive HT. Oxidative stress, endothelial dysfunction, hyperuricemia, high fructose diets are some of the causes of this local inflammatory effect. Diets with high salt content have a direct immune system activating effect through hyperosmolarity-related mechanism. Experimental studies have reported that high uric acid may mediate hypertension associated with the development of mild kidney damage (20).

In the case of tubulointerstitial injury and intrarenal ischemia, the salt load triggers an intense renal afferent sympathetic nervous system (SNS) activity that stimulates the sympathetic outflow of the central nervous system (CNS). Some studies have suggested that a hyperactive SNS is responsible for early HT, especially in young or borderline hypertensive patients. Defects in baroreceptor sensitivity and increased SNS response to emotional or work-related stres have been shown to be the reason for this. Also,hypertonicity activates the CNS, increasing vasopressin release and thus volume expansion leads to the release of cardiotonic steroids that act as Na+,K+-ATPase inhibitors. It also blocks Na+,K+-ATPase in vascular smooth muscle, causing vascular smooth muscle contraction. Sodium retention can lead to HT, either as a result of volume expansion or as a response to hypertonicity. However, there are publications suggesting that hypertonicity plays a larger role (21).Plasma aldosterone was elevated, particularly in patients whose renin angiotensin system (RAS) was inhibited by angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). This is known as aldosterone breakthrough(22).These patients are generally obese and have hyperinsulinemia or endothelial dysfunction.

More than 20 genes with mutations or polymorphisms associated with HT have been identified. Many of these affect sodium transport in the distal tubule or collecting duct. Lifton and colleagues suggest that genetic polymorphisms that promote sodium retention by the kidney, combined with excessive salt intake (>10g/day), may play an important role in triggering primary HT. (23).The higher risk of developing HT in the future in low birth weight(LBW) infants has been attributed to a lower than normal nephron number due to inadequate kidney development (24,25)It would be more accurate to consider LBW as a risk factor for HT. Experimental studies have shown that the immune system can cause HT by inducing persistent renal vasoconstriction and disrupting pressure natriuresis (26). Studies have shown that the effect is mediated by both macrophages and T cells (particularly CD8 cells) and is counter-regulated by CD4 T regulatory cell populations and T cells become sensitized to neonatigens (heatshock protein 70 – HSP70) and oxidized (isoketal-containing) proteins and leads to autoimmune mediated HT(27).

## Diagnosis of Hypertension and Clinical Manifestations

First of all, in order to determine the risk factors (table5) of the patient and to question the causes of secondary hypertension, a detailed medical history should be taken, systemic physical examination and necessary laboratory examinations should be performed

**Table5: Risk factors for hypertension**

- Male gender
- Advancing age (man>55 andwoman>65)
- Obesity (body mass index>30)
- Elevated uric acid level
- Dyslipidemia
- Family history – the risk is almost double for individuals with at least one parent with HT.
- Genetic
- Race – HT is more aggressive and seen at earlier ages in black race
- Diabetes Mellitus
- Physical inactivity
- Reduced nephron number
- High-sodium diet – >3 g/day
- Excessive alcohol consumption and smoking

In the physical examination, target organ damage and complications (Table6) should be screened first. Fundoscopic examination is needed to evaluate hypertensive retinopathy to determine the severity of involvement in the microvascular

circulation. In the first stage, as laboratory tests in patients, electrolytes, serum creatinine, estimated glomerular filtration rate (GFR), fasting blood glucose, urinalysis, complete blood count, thyroid-stimulating hormone (TSH), lipid profile, uric>100mmol/l K+ in 24 hours ) should be requested. A chest x-ray film and electrocardiogram should be performed to assess cardiac size and look for aortic dilatation. Although echocardiography is more sensitive to detect left ventricular hypertrophy,it is not recommended for routine use. Since high albuminuria is an independent risk factor for cardiovascular disease, it should be investigated in all renal patients and diabetic patients

**Table6:Complications of Hypertension**

- Intra cerebral hemorrhage
- Left ventricular hypertrophy (LVH)
- Heart failure (systolic and diastolic)
- Ischemic stroke
- Ischemic heart disease
- Chronic kidney disease
- Aortic dissection (rare)
- Cerebral and aortic aneurysms (rare)

HT is usually asymptomatic, but especially in stage 2, the patient describes a pulsatile occipital headache. If it is a hypertensive emergency, encephalopathy may occur, with mental deterioration and seizures. Rare, patients may experience vision loss due to papill edema. Persons with stage 2 HT are at acute risk for myocardial infarction (MI), congestive heart failure (CHF) with pulmonary edema, aortic dissection, cerebrovascular accident (stroke) and kidney failure. Studies have suggested that childhood-onset HT may be associated with impaired memory and mental performance, and HT remains a major risk factor for vascular dementia(28). The prognostic significance of systolic and diastolic BP as cardiovascular risk factors appear to be age dependent. Systolic pressurea nd pulse pressure are greater risk predictors in patients aged 50 to 60 years (29). Under 50 years of age, DPB is a beter predictor of mortality than systolic measurements (30). The most common cause of stroke and CHF is HT, and the risk increases linearly with an increase in BP (31) If HT is due to a known etiological cause, it is considered as secondary HT and constitutes approximately 10% of patients. Since excluding secondary causes of HT in each hypertension patient increases the cost, further investigation may be requested only in suspected patient groups

Suspected patient group for secondary HT:

- Detection of unusual HT (new onset, especially in a young or especially old age, presentation with stage 2 HT),

- HT
- BP control suddenly deteriorates while on antihypertensive therapy
- severe target organ damage than expected based on BP level
- with HT before the age of 30
- elevation (>30%) in creatinine levels after use of ACE inhibitors or ARBs
- Abdominal pain (renovascular HT)
- Low serum potassium (primary hyperaldosteronism)
- history of kidney disease

## TREATMENT

When differences in outcomes were noted in studies comparing different antihypertensive drugs, the treatment strategy that yielded beter results also resulted in beter BP control. Antihypertensive drugs are almost equally effective at lowering BP and show a good antihypertensive effect in 30 to 50 percent of patients(6). For example, in the ASCOT study, cardiovascular disease and mortality were lower with a calcium channel blocker (amlodipine) compared to a beta-blocker (atenolol). Also, patients in the amlodipine arm had lower mean BP at the end of the study (32). In the HOPE and EUROPA studies, ramipril and perindopril performed better than placebo in patients at highc ardiovascular risk, and BP was significantly lower in treated patients (33) In the VALUE study of more than 15,000 patients with preexisting atherosclerotic cardiovascular disease or at least one cardiovascular risk factor, amlodipine produced better results than valsartan, but also resulted in greater blood pressure reduction (34). When exactly matched 5000 pairs of systolic for BP and other risk factors, the two groups had nearly identical cardiovascular event rates (35). In the ALLHAT study, more than 41,000 hypertensive patients (mean BP 146/84 mmHg) with at least one other coronary risk factor were randomly assigned to one of four baseline regimens (chlorthalidone, amlodipine, lisinopril, ordoxazosin). The doxazosin arm was terminated prematurely due to an increased risk of heart failure (HF). At a mean follow-up of 4-9 years, the primary out come (fatal coronary heart disease or non-fatal myocardial infarction) was similar in all three arms. However, the chlorthalidone arm had a significantly lower HF than amlodipine and lisinopril. In addition, the rate of cardiovascular disease outcomes was significantly lower than with lisinopril. The benefits seen with chlortalidone appear to be at least partly due to earlier and greater BP reduction, similar to the findings with amlodipine in the VALUE study described in the previous section(36).Recently, the SystolicbloodPREssureINtervention (SPRINT) study documented a significant reduction in cardiovascular events and mortality in non diabetic hypertensive

subjects in the group targeting SP of 120 mm Hg with standard therapy compared to the group with SB of 140 mm Hg(37).In young and elderly patients with HT, the main determinant of cardiovascular risk reduction is the amount of BP reduction, not the choice of antihypertensive drug, unless there is a specific indication for the use of diltiazem, verapamil, or a beta-blocker such as atrial fibrillation(38)

**MajorAntihypertension Drug Groups**

**ACE Inhibitors and Angiotensin II Receptor Blockers** — It is the first choice for the treatment of hypertension in all patients with HF or a history of asymptomatic left ventricular hypertrophy , ST-elevation MI or non-ST-elevation anterior MI, diabetic, systolic dysfunction, and proteinuric chronic kidney disease. It is suggested that these drugs also have cardioprotective effects independent of their blood pressure lowering effects.

**ThiazideDiuretics** — Chlorthalidone has been the choice in patients with primary hypertension, as its benefit has been proven in large studies such as ALLHAT(36). Another thiazide-like diuretic, indapamide, can also be used instead of chlortalidone. There is little evidence that hydrochlorothiazide improves cardiovascular outcomes, and it has fewer and shorter-lasting effects than others(39).The disadvantage of chlorthalidone is that there is no combination drug preparation with ACE inhibitors or ARBs and it is available in high doses on the market. Thiazides may be more effective when combined with drugs, such as ACE inhibitors or ARBs, especially in patients with resistant HT. Since these drugs stimulate distal tubular calcium reabsorption and reduce urinary calcium excretion, they may be the first choice in hypertensive patients with osteoporosis. However, thiazide and thiazide-like diuretics loose their effectiveness in patients with a GFR below 30 ml/min.

**Potassium-Retaining Diuretics**

In this group, there are spironolactone, eplerone and amiloride. Spironolactone is a relatively weak diuretic that is an aldosterone receptor antagonist. Experiences for eplerenone are limited for the routine treatment. Also amiloride has been used less recently, however, spironolactone and amiloride are highly effective as adjunctive diuretic therapy in multidrug strategies for the treatment of resistant hypertension.

**Calcium Channel Blockers**—There are two main groups of calcium channel blockers (CCB), dihydropyridines (eg, amlodipine, nifedipine) and non-dihydropyridines (eg, diltiazem, verapamil). Verapamil has an additional antiarrhythmic effect on atrioventricular node. CCBs effectively reduce blood pressure and have extensive evidence to support their use in the treatment of HT(40).

**Beta Blockers**— Beta-blockers should be given to stable patients after acute MI with HF or asymptomatic left ventricular dysfunction. Beta-blockers are preferred for rate control in patients with atrial fibrillation and for angina control. In the absence of such indications, beta-blockers are not recommended to be used as first-line therapy, especially in patients over 60 years of age(41,42). Compared with other antihypertensive drugs in the primary treatment of HT, beta-blockers may be associated with lower protection against stroke risk and all-cause death (43) There is evidence that β-blockers-apart from vasodilator beta-blockers such as carvedilol and nebivolol – increase the likelihood of new onset diabetes, especially in combination with thiazide-type diuretics(44).In conclusion, both UK guidelines and recent US guidelines state that β-blockers are not preferred as initial therapy for routine HT and are only suitable for use in patients with angina or CHF combined with HT(6,39).

**Alpha Blockers**—An alpha-blocker is not recommended for initial monotherapy, except in elderly men with symptoms of prostatism and not at high cardiovascular risk. In the ALLHAT trial, the doxazosin arm was terminated prematurely due to a significantl yincreased risk of HF compared to chlorthalidone (36).

## Initial Monotherapy

Although initial single drug therapy is mostly successful in mild HT, it is generally not sufficient in patients with BP above 20/10 mmHg above the target. Combination therapy is more effective in these patients (41). Three main drug groups are used in monotherapy and each has been equally effective in monotherapy trials. These are thiazidediuretics, long-acting calcium channel blockers (most often a dihydropyridine), and ACE inhibitors or ARBs. Elderly patients (ie, age ≥60 years) respond better to thiazide diuretics or calcium channel blockers in monotherapy, but less to ACE inhibitors /ARBs or beta-blocker therapy. Beta blockers, ACE inhibitors /ARBs are not the first choice for elderly people in monotherapy unless there are specific indications such as CHF, previous MI or proteinuria. Young patients (eg, <50 years) respond better to ACE inhibitors or ARBs and beta-blockers. However, beta-blockers are not the first choice fo rmonotherapy in this group of patients, as they have less protection against stroke risk (45) It has been determined that both drug toxicity was reduced and might produce better patient outcomes in treatments where two or even three drugs are given together, given at half the dose of the standard treatment (46).With most antihypertensive drugs, as the dose is increased, the antihypertensive response decreases and the side effects become more pronounced. Therefore, in patients with little or no reduction in blood pressure with monotherapy, continuing treatment

with another group of drugs rather than adding a second drug to the treatment provides control in 60-80% in patients with grade 1 HT (47) Response to monotherapy should be evaluated with a follow-up of 4-6 weeks. If the response is insufficient, the patient should be followed up for 4 to 6 weeks, even in case of drug change or dose increase. Although a once-daily antihypertensive drug produces a high peak response, BP tends to rise again at night or in the early morning hours. Cardiovascular disease risk increases with increased daily BP load, nocturnal HT and increases in BP in the early morning. Therefore, long-acting drugs should be preferred (48).

**Combination Therapy**

The EuropeanSociety of Hypertension/ European Society of Cardiology (ESH/ESC) and the 2017 AmericanCollege of Cardiology/American Heart Association (ACC/AHA) Guidelines recommended combination therapy for patients whose BP were 20/10 mmHg above the target (4,6). The International Society of Hypertension (ISH) guidelines recommend that every patient with BP >140/90 mmHg receive combination therapy(3).A long-acting dihydropyridine calcium channel blocker plus a long-acting ACE inhibitor/ARBs (such as amlodipine plus benazepril used in ACCOMPLISH) is recommended as first choice in combination therapy.In addition, in patients currently being treated with a combination of a thiazide diuretic and a long-acting ACE inhibitor /ARBs and whose BP is controlled by this combination, it is recommended that the thiazide diuretic be replaced with a long-acting dihydropyridine calcium channel blocker. In obese patients, a combination of a thiazide diuretic and a long-acting ACE inhibitor / ARBs can be used (49).If the patient has a recent history of MI, the combination can be changed to a long-acting ACE inhibitor /ARBs and beta-blocker. In the case of CHF, a long-acting ACE inhibitor /ARBs can be given with a loop diuretic for edema. The second drugs of choice in patients treated with a beta-blocker are a thiazide diuretic or a dihydropyridine calcium channel blocker (46).An alpha-blocker may be added to treatment only if there is another indication, such as symptomatic benign prostatic hyperplasia.Beta blockers reduce renin secretion and thus angiotensin II formation. Therefore, in patients treated with a beta-blocker, an ACE inhibitor or ARB will be less effective (50).In addition, the combination of beta-blockers with verapamil or diltiazem potentiates the cardiac depressant effect, increasing bradycardia and may even cause cardiac block. Average night time BP is about 15% lower than day time values. Less than 10% drop in blood pressure during sleep is called “dipping” and is a stronger predictor of adverse cardiovascular outcomes than day time BP. Some studies have found

that shifting at least one antihypertensive medication from morning to evening improves night time BP reduction and 24-hour mean BP (51).

Only the ACCOMPLISH study directly compared different combination regimens in hypertensive patients (52).The ACCOMPLISH study included 11,506 patients with HT who were at high risk for a cardiovascular event and 97 percent had a mean baseline BP of 145/80 mmHg despite prior antihypertensive therapy (many requiring two or more medications) (53). Patients were randomly assigned to initial combination therapy with benazepril (20 mg/day) plus amlodipine (5 mg/day) or hydrochlorothiazide (12.5 mg/day) (49). The primary end point was measured as time to first event, which was a combination of death from cardiovascular causes, non-fatal MI, non-fatal stroke, hospitalization for angina, sudden cardiac death, or resuscitation after coronary revascularization. The primary endpoint was reached significantly less frequently in the benazepril-amlodipine group. However, the superiority of amlodipine-based therapy was most pronounced in non-obese subjects; In obese patients, the results were similar between both combinations (49). The development of CKD (often defined as a doubling of serum creatinine) was lower with benazepril-amlodipine, while reductions in secondary end points such as cardiovascular death or non-fatal MI or stroke were similar in both combinations (55). In contrast to all other larger and randomized studies, ACCOMPLISH included 24-hour BP monitoring in a subgroup of 573 patients. While mean office BP was significantly lower in the benazepril-amlodipine group, mean 24-hour BP was not statistically significant, although was higher in the group. Similar trends were also noted in day time and night time mean BP (55).Therefore, the clinical benefits observed with the benazepril-amlodipine combination can not be explained by beter BP control. The difference in outcome can be explained by a beneficial effect of benazepril-amlodipine or by the side-effects of benazepril-hydrochlorothiazide combination.

What needs to be followed carefully; it is the group whose BP value is around 130–139 mmHg, which is normal-high in the 2018 ESC/ESH guidelines, and stage 1 HT in the American College of Cardiology (ACC) and American Heart Association (AHA) 2017 guidelines. This group constitutes 14% of adult patients not receiving treatment in the United States (USA). Overt cardiovascular disease developed in 4%, diabetes mellitus in 9%, and chronic renal failure (CRF) in 3% of these individuals, while 16% had an expected cardiovascular disease probability within 10 years (56). Life style change is recommended for this group. Drug therapy should be initiated only in those at risk of cardiovascular disease. In the 2019 "Turkish Consensus Report on Hypertension", it was recommended to start HT treatment primarily with combination therapy in patients with BP level ≥150/90

mmHg. It was suggested that drug therapy can be started with a risk-based approach in the increased BP group with SBP, 120–139 mmHg, and DBP, 80–89 mmHg. The threshold clinical SBP level was lowered from 160 mmHgto ≥150 mmHg for initiation of drug therapy in persons aged 80 years and older.

In conclusion, although this report provides evidence-based recommendations for most patients,, it should be noted that there may be differences from patient to patient, and in such cases, the physician should adopt an individualized approach to patients based on a good clinical assessment. Effectively controlled HT prevents all possible complications. The patient's life style changes and compliance with the treatment are as important as the treatment.

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