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HYPERTENSION MANAGEMENT IN METABOLIC SYNDROME

Abstract:

Hypertension is one of the key risk factors for cardiovascular morbidity and mortality. Metabolic syndrome (synonyms: syndrome X, insulin resistance syndrome) is characterized by increased visceral fat mass, decreased sensitivity of peripheral tissues to insulin (insulin resistance) and hyperinsulinemia, which cause disorders of carbohydrate, lipid, and purine metabolism. Hypertension is an integral component of the metabolic syndrome. The severity of hypertension in patients with metabolic syndrome is higher in comparison with patients without metabolic disorders. In patients with metabolic syndrome, the probability of cardiac and brain damage increases fivefold, kidney damage threefold, and the vessels twofold. The presence of diabetes reduces the likelihood of achieving effective control of blood pressure by 1.4 times, hypercholesterolemia — by 1.5 times, obesity — by 1.7 times. In the presence of any three factors, the effectiveness of treatment is reduced twofold. In this article, approaches to the management of patients with hypertension and metabolic syndrome, aspects of non-drug therapy, target blood pressure levels, and the choice of drugs are presented in accordance with evidence-based medicine and current recommendations.

Key words: *hypertension, metabolic syndrome, syndrome X, combined treatment, risk of cardiovascular events, 24-hour blood pressure monitoring, home blood pressure monitoring, drugs of choice, comorbidity, hypertensive crisis*

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β-blockers — beta-blockers, BP — blood pressure, AO — abdominal obesity, ARBs — angiotensin receptor blockers, CCB — calcium channel blockers, LVH — left ventricular hypertrophy, home BPM — home BP measurement, ACE inhibitors — angiotensin converting enzyme inhibitors, CMS — cardiometabolic syndrome, MS — metabolic syndrome, DT — drug therapy, TOD –target organ damage, RAAS — renin-angiotensin-aldosterone system, DM — diabetes mellitus, 24-hour BPM — 24-hour blood pressure monitoring, SNS — sympathetic nervous system, CVR — cardiovascular risk, Tg — triglycerides, HDL cholesterol — high density lipoprotein cholesterol, LDL cholesterol — low-density lipoprotein cholesterol, CKD — chronic kidney disease, HR — heart rate

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Introduction

Hypertension is one of the key risk factors for cardiovascular morbidity and mortality. Currently, more than 1 billion people worldwide have hypertension [15]. Globally, the prevalence of hypertension among the adult population is 30–45%; and in Russia it amounts 40–47% [6]. As the population ages and the sedentary lifestyle becomes common, an enormous increase in the number of patients with hypertension to 1.5 billion people is expected by 2025 [15].

At the end of the last century, the concept of the metabolic syndrome (MS; its synonyms: syndrome X, insulin resistance syndrome) was proposed for people with several risk factors united by the same pathogenetic basis [1]. MS is characterized by an increase in visceral fat mass, a decrease in the sensitivity of peripheral tissues to insulin (insulin resistance) and hyperinsulinemia, which cause disorders of carbohydrate, lipid, purine metabolism and hypertension [1, 6]. Globally, the prevalence of MS among the adult population is 10–30%; in Russia it amounts 20–35%, and in women it is 2.5 times more common. The incidence increases with age [1].

Hypertension is an integral component of metabolic syndrome [1]. The combination of carbohydrate, lipid and purine metabolic disorders with hypertension increases mortality, therefore MS is also called the deadly quartet. Since MS increases the risk of cardiovascular diseases (CVD) by 3 to 6 times, its successor and one more synonym is cardiometabolic syndrome (CMS) [5]. The severity of hypertension in patients with MS is higher compared to patients without metabolic disorders. In patients with MS, the probability of cardiac and brain damage increased fivefold, kidney damage — threefold, and vascular damage — twofold [6]. Diabetes mellitus (DM) reduces the likelihood of effective control of blood pressure (BP) by 1.4 times, hypercholesterolemia by 1.5 times, and obesity by 1.7 times. If there are any three risk factors, the effectiveness of treatment decreases twofold [6]. In this regard, hypertension treatment in patients with MS is an urgent problem. The article is dedicated to this problem.

Diagnostic Criteria for Cardiometabolic Syndrome

Currently, there are at least 7 alternative guidelines on MS diagnosis: WHO — World Health Organization; EGIR — European Group for the Study of Insulin Resistance; NCEP-ATP III — National Cholesterol Education Program-Adult Treatment Panel III; AACE — American Association of Clinical Endocrinologists; IDF — International Diabetes Federation; International Institute of Metabolic Syndrome; and the Recommendations for the Diagnosis and Treatment of Metabolic Syndrome of the Russian Society of Cardiology. At the same time, there are not enough prognostic data concerning the advantages of different diagnostic criteria for MS [1].

In accordance with the Russian recommendations, the **main criterion for diagnosis of MS/CMS** is central (abdominal, AO) obesity with the waist circumference (WC) >80 cm in women and >94 cm in men [1].

Additional Diagnostic Criteria for MS:

1. BP level >140/90 mm Hg or antihypertensive drug use
2. Triglycerides level (Tg) >1.7 mmol/L
3. High density lipoprotein cholesterol (HDL cholesterol) <1.0 mmol/L in men, and <1.2 mmol/L in women
4. Low density lipoprotein cholesterol (LDL cholesterol) >3.0 mmol/L
5. Impaired fasting glycemia (IFG) — fasting blood plasma glucose >6.1 and <7.0 mmol/L, provided that plasma glucose after 2 hours via Oral Glucose Tolerance Test (OGTT) — the load with 75 g of anhydrous glucose — is less than 7.8 mmol/L

6. Impaired glucose tolerance (IGT) — blood plasma glucose 2 hours after OGTT is within the range of >7.8 and < 11.1 mmol/L, provided that fasting plasma glucose level is less than 7.0 mmol/L.
7. Combined IFG/IGT; fasting plasma glucose is ≥6.1 and <7.0 mmol/L, and plasma glucose level via OGTT in 2 hours is ≥7.8 and <11.1 mmol/L.

Abdominal obesity with any two additional criteria serves as the basis for diagnosis of CMS in a patient [1].

Hypertension in Patients with Metabolic Syndrome

Several pathogenetic mechanisms of insulin resistance lead to the development of hypertension. First, it promotes the activation of the sympathetic nervous system (SNS): with insulin blood concentration increase, a dose-dependent norepinephrine increase is revealed. This leads to vasoconstriction, increased systemic vascular resistance (SVR) and cardiac output. In addition, insulin increases sodium reabsorption in the kidneys by 30–40%, and therefore, hyperinsulinemia accompanying insulin resistance in MS has an antinatriuretic effect with an increase in water retention, blood volume (BV) and blood pressure [3].

Clinical Pattern of Hypertension in Patients with MS

Features of hypertension in MS are: frequent refractoriness to treatment, and early target organ damage — the development of left ventricular hypertrophy (LVH), which rapidly leads to myocardial dysfunction, renal hyperfiltration and albuminuria, and arterial stiffness [1]. The severity of hypertension in patients with CMS directly depends on its components. In patients with CMS, the probability of cardiac and brain damage increased fivefold, kidney damage — threefold, and vascular damage — twofold, compared to patients without metabolic disorders [6]. According to 24-hour BP monitoring, patients with hypertension and MS had more pronounced circadian rhythm disturbances, higher pressure load at night and increased variability compared to hypertensive patients without metabolic disorders [1].

Diagnosis of Hypertension

Diagnosis of hypertension in patients with MS is carried out in accordance with the procedure in all other conditions. The primary methods of detecting hypertension are office BP measurement by the Korotkov's method, measurement of BP at home (a synonym for self-monitoring of BP — self-BPM), and 24-hour BPM [1]. For timely and accurate diagnosis of hypertension, it is necessary to strictly follow the BP measurement rules.

BP measurement rules:

- BP is measured in the morning at the same time
- BP should be measured on the same arm using a precisely calibrated tonometer
- It is necessary to use a cuff of the appropriate size and to mark the use of a different size cuff and all other changes in the BP measurement procedure
- The patient should be seated while measuring BP, the patient's arm should lie on the armrest approximately at the level of the heart
- The patient should rest for at least 5 minutes before BP measurement
- Patients should not smoke or consume caffeine-containing beverages at least 30 minutes before BP measurement
- Repeated BP measurement is carried out after 3–5 minutes
- If the difference between BP in these two measurements is <5 mm Hg, the third BP measurement is performed, and the average value between the three measurements is recorded in the individual medical record

- If the difference between BP in the first two measurements is > 5 mm Hg, the measurement should be repeated after the patient has rested for at least 15 minutes
- At the first visit, BP is measured on both arms in a standing and sitting position
- The blood pressure cuff is placed on the arm with the highest value of BP if there are significant differences in this parameter at the arms [1].

According to the new American guidelines of 2017, hypertension should be diagnosed for BP >130/80 mm Hg. (Table 1) [14]. This criterion is based on the SPRINT study results, in which the achievement of target BP value below 120/80 mm Hg leads to a decrease in the risk of myocardial infarction, stroke and death in high-risk patients [11]. Hence, it was suggested to consider normal BP level <120/80, elevated level — 120–129 / 80 mm Hg, grade 1 hypertension at 130–139 / 80–89 mm Hg, and grade 2 hypertension at ≥140/90 mm Hg. [14].

Using the new American diagnostic criteria, the prevalence of hypertension in the USA increased from 32% to 46%; in absolute terms — from 72.2 to 103.3 million people, i. e. by 31.1 million people [13]. Since the criteria for initiating treatment in these recommendations were revised less radically, the need to prescribe drug therapy (DT) increased in only 4.2 million people [8]. In this regard, when developing the European recommendations in 2018, after long discussions it was decided that it would not be advisable to diagnose hypertension in a large number of patients without DT prescription. Thus, the classification of BP and the definition of hypertension in these recommendations did not change in comparison with the recommendations of 2013 [12, 14, 15].

According to European recommendations, normal BP is considered to be <130/85, high normal level is 130–139 / 85–89, grade 1 hypertension is 140–159 / 90–99, grade 2 hypertension is 160–179 / 100–109, and grade 3 hypertension is ≥180 / 110 mm Hg. Thus, hypertension is

Table 1. *Classification of office blood pressure and determining the degree of hypertension in accordance with the 2018 ESC/ESH and 2017 ACC/AHA recommendations [4, 14,15]*

Blood Pressure Classification	2018 ESC/ESH			Blood Pressure Classification	2017 ACC/AHA		
	SBP, mm Hg		DBP, mm Hg		SBP, mm Hg		DBP, mm Hg
Optimal	<120	and	<80				
Normal	120–129	and/or	80–84	Normal	<120	and	<80
High normal	130–139	and/or	85–89	High normal	120–129	and	<80
Grade 1 hypertension	140–159	and/or	90–99	Grade 1 hypertension	130–139	or	80–89
Grade 2 hypertension	160–179	and/or	100–109	Grade 2 hypertension	≥140	or	≥90
Grade 3 hypertension	≥180	and/or	≥110				
Isolated systolic hypertension	≥140	and	<90				

Note: BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension is graded as 1, 2, or 3 according to SBP values in the ranges indicated; BP — blood pressure; SBP — systolic blood pressure, DBP — diastolic BP, ACC — American College of Cardiology, AHA — American Heart Association, ESH — European Society of Hypertension, ESC — European Society of Cardiology

Table 2. *Hypertension diagnosis based on office BP, 24-hour BPM, home BPM in accordance with the 2018 ESC/ESH and 2017 ACC/AHA recommendations [4, 12, 14, 15]*

Category	2018 ESC/ESH			2017 ACC/AHA		
	SBP, mm Hg		DBP, mm Hg	SBP, mm Hg		DBP, mm Hg
Office BP	≥140	and/or	≥90	≥130	and/or	≥80
Home BPM, mean	≥135	and/or	≥85	≥130	and/or	≥80
24-hour BPM:						
Daytime (or awake), mean	≥135	and/or	≥85	≥130	and/or	≥80
Nigh (or asleep), mean	≥120	and/or	≥70	≥110	and/or	≥65
24-hour, mean	≥130	and/or	≥80	≥125	and/or	≥75

Note: BP — blood pressure; SBP — systolic BP, DBP — diastolic BP

an increase in office systolic BP (SBP) ≥140 and/or diastolic BP (DBP) ≥90 mm Hg [15].

In addition to office blood pressure measurement, home and 24-hour BP measurement can be used for primary diagnosis [12, 14]. Normal BP values and diagnostic criteria for home and 24-hour BP measurement somewhat differ from BP office figures. In accordance with the European recommendations, it is necessary to diagnose hypertension with mean daily BP values for 24-hour BPM ≥130/80 mm Hg and for home BPM ≥135/85 mm Hg (Table 2) [12, 15]. According to the American guidelines, it is necessary to diagnose hypertension with mean daily BP values for 24-hour BPM ≥125/75 mm Hg and for home BPM ≥130/80 mm Hg. When determining the degree of hypertension, office BP values should be used.

The advantage of home BPM is that it enables to monitor blood pressure for a long time in conditions that are familiar for the patient. It is very important that the patient or his/her relatives are trained in BP measurement rules, the tonometer is calibrated, and the cuff size is correctly selected. At present, it is not recommended to use wrist-cuff devices, except for patients with obesity, for whom it is difficult to choose a cuff for the arm.

Twenty-four-hour BPM allows to determine daily BP variability and the presence/absence of nocturnal BP decrease. Normally, BP decreases by 10–20 mm Hg at night. Patients with normal nocturnal BP decrease are called dippers. Patients without adequate BP decrease at night are called non-dippers. The main reasons for the absence of BP decrease are obstructive sleep apnea (OSA), obesity, diet high in salt, diabetic nephropathy, chronic kidney disease (CKD), old age, orthostatic hypotension, and autonomic dysregulation. However, the effect of BP decrease at night is not 100% reproducible. For example, sleep disorder can lead to the absence of BP decrease at night. According to studies, BP values obtained using 24-hour BPM are more correlated with the prognosis of patients (risk of death, stroke and other CVD) than with measurements at the doctor's office. Moreover, the measurement of BP at night has maximum correlation with the patients' prognosis.

Assessment of the Hypertension Risk

Over 20 years, the main international guidelines on hypertension have focused on the fact that treatment should be carried out taking into account individual CVR [10, 15]. In the European

Recommendations 2018, uric acid increase (which is often found in patients with MS), early menopause and heart rate >80 beats per minute are added to the risk factors (Table 3). In the new European and American recommendations, low-mobility and low socioeconomic status of a person are indicated as risk factors. In the American recommendations, unhealthy diet and OSA are also listed as risk factors [12, 14, 15].

In order to assess individual CV risk, ESC/ESH recommends to use the standard SCORE System (https://www.escardio.org/static_file/Escardio/Subspecialty/EACPR/Documents/score-charts.pdf), which allows to calculate the risk of a fatal CV event within 10 years based on 5 risk factors: gender, age, SBP, total cholesterol and smoking. Regardless of SCORE values, patients with diagnosed CVD, CKD, DM, LVH or a significant increase in any risk factor are considered to be patients of high or very high risk (e. g, total cholesterol ≥8 mmol/L, LDL cholesterol ≥6 mmol/L, or BP ≥180/110 mm Hg) (Table 4) [15].

In the American guidelines, a calculator is available to evaluate the individual 10-year risk of atherosclerotic CVD; the calculator is available at http://tools.acc.org/ASCVD-Risk-Estimator. The estimation is based on a large number of risk factors: gender, age, race, SBP, DBP, total cholesterol, HDL and LDL cholesterol, DM, smoking, antihypertensive treatment, statins, and aspirin [14].

Table 3. *Risk factors in patients with hypertension in accordance with 2018 ESC/ESH and 2017 ACC/AHA [4, 12, 14, 15]*

2017 ACC/AHA	2018 ESC/ESH
Male	Male
Age	Age (≥55 years in male, ≥65 years in female)
Smoking (current or past history)	Smoking (current or past history)
Dyslipidemia, hypercholesterolemia	Total cholesterol and HDL-C
	Blood uric acid
Diabetes mellitus	Diabetes mellitus
Overweight or obesity	Overweight or obesity
Family history of premature CVD	Family history of premature CVD (men aged <55 years and women aged <65 years), family or parental history of early-onset hypertension
	Early menopause
Sedentary lifestyle	Sedentary lifestyle
Psychological stress, low socioeconomic level	Psychosocial and socioeconomic factors
	Heart rate (resting values >80 beats/min)
Unhealthy diet	
Obstructive sleep apnea	

Note: CVD — cardiovascular diseases, HDL-C — high density lipoprotein cholesterol

Table 4. *Evaluation of cardiovascular risk in patients with hypertension by 2018 ESC/ESH [15]*

Risk category	People with any of the following
Very high risk	1. IHD: acute myocardial infarction, postinfarction cardiosclerosis, acute coronary syndrome, coronary or other arterial revascularization, stroke, and TIA 2. History of ischemic stroke, TIA 3. eGFR <30 mL/min / 1.73 m² (4–5 stage CKD) 4. Significant (≥50% stenosis) plaques in the coronary and/or carotid arteries 5. Aortic aneurysm 6. Diabetes mellitus with target organ damage, e. g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolemia 7. Peripheral artery disease 8. A calculated 10-year SCORE of ≥10%
High risk	1. Significantly pronounced one risk factor (for example, total cholesterol ≥8 mmol/L, LDL cholesterol ≥6 mmol/L or blood pressure ≥180/110 mm Hg) 2. Diabetes mellitus without target organ damage and without a major risk factor who may be at moderate-risk 3. LV hypertrophy 4. eGFR 30–59 mL/min / 1.73 m²(4–5 stage CKD) 5. A calculated 10-year SCORE of 5–10%
Moderate risk	1. A calculated 10-year SCORE of ≥1% to <5% 2. Grade 2 hypertension 3. Many middle-aged people belong to this category
Low risk	1. A calculated 10-year SCORE of <1%

Note: BP — blood pressure, LV — left ventricle; IHD –ischemic heart disease; LDL — low-density lipoproteins, eGFR — estimated glomerular filtration rate; TIA — transient ischemic attack

In most patients with MS, the risk is high and very high, which requires immediate initiation of the necessary treatment.

Treatment of Hypertension

Treatment of hypertension in patients with CMS is not an easy task. DM reduces the probability of achieving effective control of BP by 1.4 times, hypercholesterolemia — by 1.5 times, and obesity — by 1.7 times. If there are any three risk factors, the effectiveness of treatment decreases twofold [6].

Drug-Free Hypertension Treatment

The cornerstone in the treatment of MS, including in hypertension, are drug-free methods that involve lifestyle changes, including proper diet, avoidance of bad habits, increased physical activity, and weight loss until normal weight is achieved (Table 5) [15]. ACC/AHA recommends the DASH (Dietary Approaches to Stop Hypertension) diet and elevated potassium content for patients with hypertension, except patients with CKD and receiving medication that reduces potassium excretion [14].

The effect of garlic, dark chocolate, tea or coffee consumption for stress relief has not been sufficiently proven. Behavioral therapy, including controlled breathing, yoga, transcendental meditation, and biofeedback, do not have conclusive evidence of long-term BP decrease [14].

Drug-free hypertension treatment is recommended for all patients, regardless of BP value [14, 15]. It is of particular importance in patients with MS, because weight loss itself leads to BP decrease [3].

Table 5. *Non-drug therapy for hypertension with MS [15]*

Recommendation	Class	Level
Salt restriction to <5 g per day is recommended	I	A
It is recommended to restrict alcohol consumption to: • Less than 14 units per week for men • Less than 8 units per week for women (1 unit = 125 ml wine or 250 ml beer) *	I	A
Avoid binge drinking	III	C
Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products are recommended	I	A
Body-weight control is indicated to avoid obesity (BMI >30 kg/m^2 or waist circumference >102 cm in men and >88 cm in women), as is aiming at healthy BMI (about 20–25 kg/m^2) and waist circumference values (<94 cm in men and <80 cm in women) to reduce BP and CV risk	I	A
Regular aerobic exercise (e. g. at least 30 min of moderate dynamic exercise on 5–7)	I	A
Smoking cessation, supportive care, and referral to smoking cessation programs are recommended	I	B

*** Note:** ACC/AHA recommends less than 2 "drinks" (1 "drink" = 14 g of ethanol, which corresponds to 5 oz of wine (usually 12%), 12 oz of beer (usually 5%) and 1.5 oz of purified alcohol (usually 40%)) per day for men, less than 1 "drink" per day for women [14].

Drug Therapy of Hypertension

Principles of drug therapy in patients with hypertension and MS are the same as in all patients with hypertension [3]. The main practical issues of antihypertensive treatment are:

1. Initiation of drug therapy
2. Target BP values
3. Selection of drugs for BP control

Initiation of Drug Antihypertensive Treatment in Hypertension and MS

In accordance with the 2018 ESC/ESH recommendations, drug therapy (DT) can be considered at high normal BP level (130–139 / 85–89 mm Hg) at very high CVR due to diagnosed CVD, especially IHD (Table 6) [15]. DT (the optimal combination of two antihypertensive drugs) should be recommended for patients with high or very high risk or target organ damage (TOD) at BP ≥140/90 mm Hg. Consequently, most patients with MS require DT. For patients with BP level 140–159 / 90–99 mm Hg, without TOD and with low or moderate risk monotherapy is recommended in case of ineffectiveness of lifestyle changes (Fig. 1) [15].

In patients aged 65–80 years, according to the 2018 ESC/ESH guidelines, MT should be initiated at BP level >140/90 mm Hg; in patients older than 80 years — with BP level ≥160/90 mm Hg. The focus should be on biological, rather than chronological age. Frailty (fragility, poor health), patient's self-support and treatment tolerability should be considered. Treatment should not be unavailable or canceled based on age, provided that it is necessary and permitted [15].

According to the recommendations of ACC/AHA 2017, the choice of treatment depends on the severity of hypertension and does not

Table 6. *Drug therapy start in hypertension [4, 12, 14, 15]*

	2017 ACC/AHA	2018 ESC/ESH
BP 130–139/ 85–89	DT recommended at very high risk (≥10%)	DT can be assigned to patients with very high CVR, established in connection with the presence of CVD*, especially CHD
CVR	DT for primary prevention is recommended • Patients with very high ≥10%) risk with mean SBP ≥130 mm Hg and average DBP ≥80 mm Hg • Patients* at risk <10% are recommended with mean SBP =140 mm Hg and average DBP = 90 mm Hg	• At high / very high CV risk or TOD ** DT recommended for BP 140–159 / 90–99 • Low/moderate risk at BP 140–159 / 90–99 mm Hg without TOD it is recommended that monotherapy with inefficiency change of the LF. • MT* recommended for any with risk if BP =160/100 mm Hg
BP	• DT for secondary prevention of CV events is recommended for patients with CVD and mean SBP = 130 mm Hg and average DBP = 80 mm Hg • Rest — when SAD ≥140 mm Hg, DBP ≥90 mm Hg	• DT is recommended immediately at BP = 160/100 mm Hg at any risk and at BP 140–159 / 90–99 mm Hg at high / very high risk or TOD • With BP 140–159 / 90–99 mm Hg with low and moderate risk without TOD, monotherapy is recommended if inefficiency change of the LF
Elderly and senile age	DT in elderly and senile patients does not differ from therapy in the General population, even at the age of >80 years, but it is necessary to take into account the risk of orthostatic hypotension and falls	• For safe patients >65, for <80 years, DT is recommended for BP >140/90 mm Hg with its good tolerability • Safe patients over 80 years of age DT is recommended for SBP ≥160 mm Hg

Note: LF — lifestyle, DT — drug therapy, BP — blood pressure, SBP — systolic BP, DBP — diastolic BP, HNBP — high normal BP, 24-hour BPM — 24-hour BP monitoring, HBPM — home BP monitoring, TOD — target organ damage, CV — cardiovascular, CVD — CV disease, CVE — CV event

*CVD diagnosis — cerebrovascular disease: ischemic, hemorrhagic stroke, TIA; ischemic heart disease: myocardial infarction, angina, revascularization; atherosclerotic plaque imaging; heart failure, including HFpEF; peripheral arterial disease; atrial fibrillation

** TOD includes pulse BP (in the elderly) ≥60 mm Hg; carotid-femoral PWV >10 m/s; ankle-brachial index of <0.9; LVH in ECG: Sokolov-Lyon index >3.5 mV, RaVL >1.1 mV, Cornell index >244 mV×MS; LVH in Echocardiography: LVMMI: >115 g/m² in men and 95 g/m² in women; albuminuria (30–300 mg/day) or the ratio of albumin to creatinine (30–300 mg/g; 3.4–34 mg/mmol, preferably in the morning portion of urine), CKD with GFR >30–59 mL/min/1.73m² or severe CKD with GFR <30 mL/min /1.73m², progressive retinopathy: hemorrhages or exudates, optic disk swelling

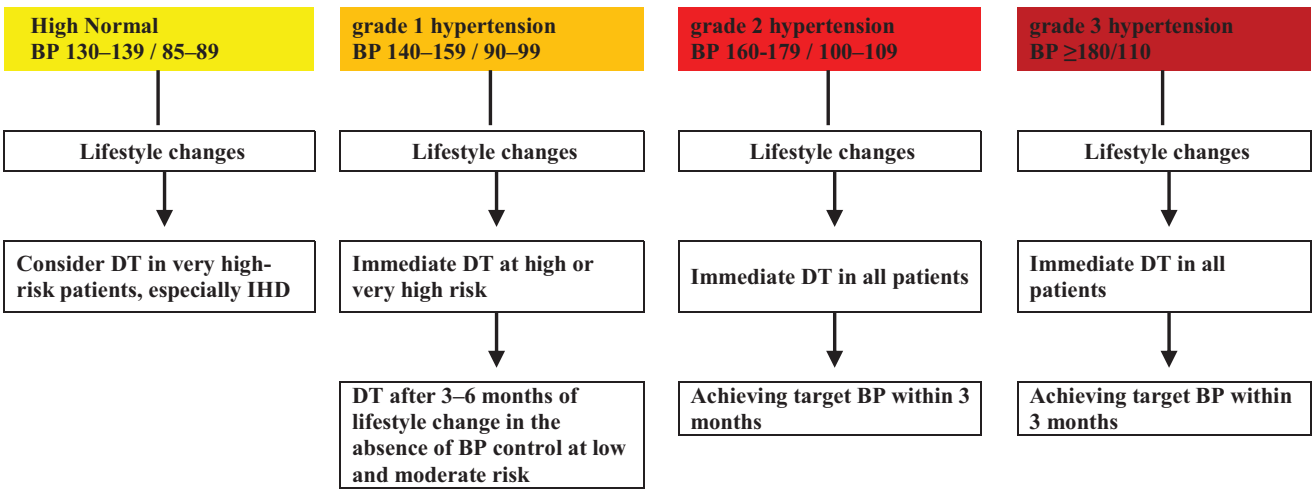

Figure 1. *Lifestyle changes and the onset of antihypertensive drug therapy in different degrees of hypertension according to 2018 ESC/ESH*

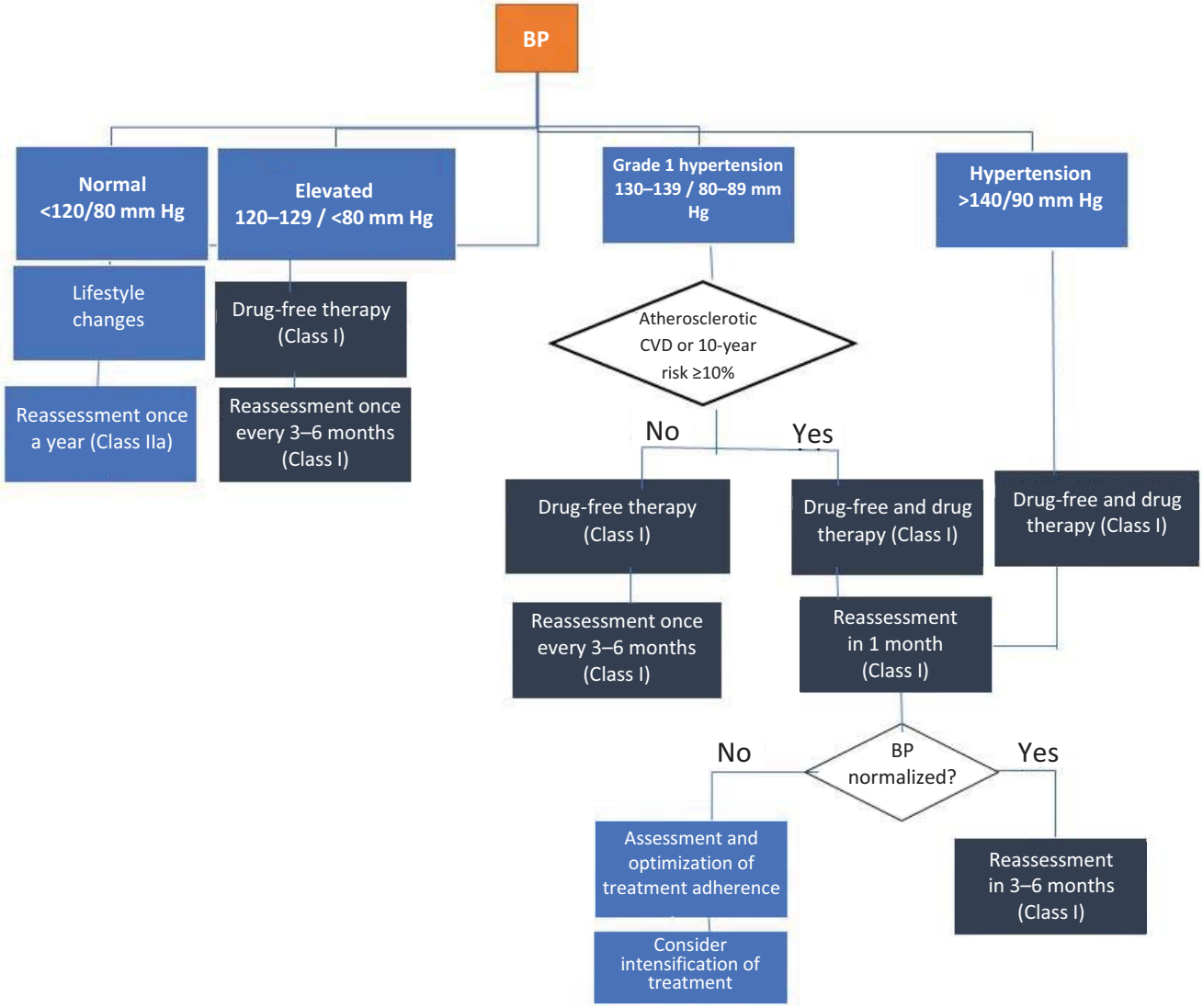

Figure 2. *Management of patients with hypertension according to 2017 ACC/AHA [12]*

depend on age (Figure 2) [14]. In the presence of elevated BP (SBP 120–129 mm Hg), drug-free therapy is recommended [14]. At BP level 130–139 /80–89 mm Hg drug-free therapy is recommended, mainly, lifestyle changes [14]. Drugs at BP of 130–139 / 80–89 mm Hg shall be prescribed to patients with CVD or in at least 10% of 10-year CVR. At BP ≥140/90 mm Hg, regardless of the 10-year risk or CVD [14].

Target BP Levels

According to the 2017 ACC/AHA recommendations, the target values of BP in all patients should be less than 130/80 mm Hg (Table 7) [14].

In the 2018 ESH/ESC guidelines in the general population of patients with hypertension, the target BP was <140/90 mm Hg, with good tolerability — <130/80 mm Hg. The target level of systolic BP in patients with DM, IHD, and with history of stroke/TIA is 120–130 mm Hg, in CKD and in patients ≥65 years — 130–140 mm Hg [15]. It is noteworthy that the BP level has been specified, below which decrease is impractical due to the risk of acute kidney injury. Previously, it was specified only in the guidelines on kidney disease (Table 8). The target DBP level for all patients is 70–80 mm Hg. According to 24-hour BPM, the target mean SBP is 125 mm Hg, and home BPM is 130 mm Hg [15].

Table 7. *Target levels of blood pressure [4, 12, 14, 15]*

Patient group	2017 ACC/AHA	2018 ESC/ESH
Population	<130/80 mm Hg	<140/90 mmHg (<130/80 if tolerated)
Diabetes mellitus	<130/80	120 — <130/70 — <80
IHD	<130/80	120 — <130/70 — <80
CKD	<130/80	130 — <140
Stroke/TIA	<130/80	120 — <130
Heart failure	<130/80	
Peripheral artery disease	<130/80	
Older patients (aged ≥65 years)	<130 in patients ≥65 years	SBP 120 — <130 in patients <65 years SBP 130 — <140 in patients ≥65 years

Table 8. *Age-dependent target level of office BP according to 2018 ESC/ESH [15]*

Age	SBP, mm Hg					DBP, mm Hg
	Hypertension	+Diabetes	+CKD	+IHD	+Stroke/TIA	
18–65 years	Target to 130 or lower, if tolerated, not <120		Target <140 to 130, if tolerated		Target to 130 or lower, if tolerated, not <120	<80 to 70
65–79 years	Target <140 to 130, if tolerated					<80 to 70
>80 years	Target to <140 to 130, if tolerated					<80 to 70
DBP, mm Hg	<80 to 70	<80 to 70	<80 to 70	<80 to 70	<80 to 70	<80 to 70

Selection of Drugs for BP Control

In accordance with the 2013 ESH/ESC recommendations, the benefits of antihypertensive treatment are caused by the result of a decrease in BP itself, and do not depend on the drugs prescribed for this purpose. The following drug groups are suitable for monotherapy and combined treatment of hypertension: diuretics (including thiazide and thiazide-like chlorthalidone, indapamide), β-blockers, calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs) and other antihypertensive agents (direct renin inhibitors — DRIs, central action drugs, α-blockers) [12]. Depending on the clinical situation, certain groups of antihypertensive agents should be preferred (Table 9) [12]. In patients with hypertension and MS, preference is given to the administration of ACEIs, ARBs and CCBs, in the presence of DM — ACEI and ARBs [15].

In accordance with the 2018 ESH/ESC guidelines, the basis of hypertension treatment should be drugs that in RCTs have proven able to reduce BP and the risk of CV events — ACE inhibitors, ARBs, CCBs and thiazide / thiazide-like diuretics [15]. There is no emphasis on patients with MS in this section of recommendations.

The 2017 ACC/AHA guidelines recommend to start treatment with first-line drugs, which include thiazide / thiazide-like diuretics, ACEIs, ARBs and CCBs (Table 10) [14]. The optimal DT in MS is not defined; there are concerns about thiazide diuretics and β-blockers due to their ability to increase insulin resistance and dyslipidemia. Study data on chlorthalidone showed improvement in cardiovascular and kidney outcomes. Newer vasodilating β-blockers (labetalol, carvedilol, and nebivolol) have a neutral or beneficial effect on metabolic profiles. In DM, first-line antihypertensive agents (diuretics, ACE inhibitors, ARBs, CCBs) are effective and useful [15].

Contraindications to certain groups and individual medicines must be considered in the decision-making process (Table 11).

Table 9. *Selection of antihypertensive drug groups in certain clinical situations [4, 12, 14, 15]*

Situation	2013 ESC/ESH	2017 ACC/AHA	2018 ESC/ESH
LVH	ACEI, CCB, ARB		
Asymptomatic atherosclerosis	CCB, ACEI		
CKD: albuminuria, decreased kidney function	ACEI, ARB	Hypotensive first-line agents; CKD ≥3 stage or CKD 1–2 stage with albuminuria ≥300 mg/day (mg/g) — ACEI, with their intolerance — ARB	ACEIs or ARB + CCB or ACEIs or ARB + loop diuretic
ESRD / kidney transplant	ACEI, ARB	CCB	
Stroke, history of TIA	Any drug that effectively reduces BP	Thiazide diuretics, ACEI, ARB or a combination of thiazide diuretic with ACEI	
History of myocardial infarction	β-blocker, ACEI, ARB	β-blocker is advisable to continue for 3 years after MI/ACS; β-blocker and/or CCB can be considered 3 years after MI/ACS	ACEI or ARB + β-blocker or CCB or CCB + diuretic or β-blocker + diuretic Monotherapy can be considered at low risk of 1-degree hypertension or in elder patients (≥80 y. o.)
Angina	β-blocker, CCB	β-blocker, ACEI / ARB; in failure of target BP achievement and preservation of pain — dihydropyridine CCB; in failure of target BP achievement and absence of pain — dihydropyridine CCB, thiazide diuretic, and/or ARB	

Table 9. (The ending)

Situation	2013 ESC/ESH	2017 ACC/AHA	2018 ESC/ESH
Heart failure with reduced LV EF	Diuretic, β-blocker, ACEI, ARB, mineralocorticoid receptor antagonists	Non-dihydropyridine CCB are not recommended	
Heart failure with preserved LV EF		In congestion — diuretics; in hypertension preservation after congestion elimination — ACEIs / ARB and β-blocker	
Aortic aneurysm	β-blocker	β-blocker	
Atrial fibrillation, prevention	ARB, ACEI, β-blocker or mineralocorticoid receptor antagonists	ARB	
Atrial fibrillation, ventricular rhythm control	β-blocker, non-dihydropyridine CCB		
Peripheral artery disease	ACEI, CCB	Treatment approach same as in absence of peripheral artery disease	
ISH (elderly and senile age)	Diuretic, CCB		
Metabolic syndrome	ACEI, ARB, CCB	Optimal DT has not been determined; there are concerns about thiazide diuretics and beta-blockers due to their ability to increase insulin resistance and dyslipidemia. However, chlorthalidone improved CV and renal outcomes. Newer vasodilating beta-blockers (labetalol, carvedilol and nebivolol) have neutral or beneficial effects on metabolic profiles	
Diabetes mellitus type 2	ACEI, ARB	Hypotensive first-line agents (diuretics, ACEI, ARB, CCB) are useful and effective	
Pregnancy	Methyldopa, β-blocker, CCB	Methyldopa, nifedipine and/or labetalol	
Negroid race	Diuretic, CCB	Initial therapy in patients without HF and CKD should include thiazide diuretics or CCB	
Aortic stenosis		There is no evidence that hypotensive therapy leads to excessive hypotension. Although there are no specific studies comparing different classes of antihypertensive drugs in this group, ACEIs and ARBs may have benefits due to regression of LV fibrosis, shortness of breath and improvement of exercise tolerance. Low initial dose, slow titration	
Aortic insufficiency		Avoid heart rate lowering drugs, including β-blocker	

Table 10. *2017 ACC/AHA first- and second-line antihypertensive agents [14]*

Drug group	Drug	Dosage (mg/day) *	Dosage Frequency	Comments
First-Line Treatment				
Thiazide or thiazide-like diuretics	Chlorthalidone Hydrochlorothiazide Indapamide Metolazone	12.5–25 25–50 1.25–2.5 2.5–10,0	1 1 1 1	Chlorthalidone is a drug of choice based on its prolonged half-life and proven reduction of CVE Hyponatremia, hypokalemia, uric acid and calcium monitoring Use with caution in patients with history of acute gout unless patient receives uric acid–lowering drugs
ACEI	Benazepril Captopril Enalapril Fosinopril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril	10–40 12.5–150 5–40 10–40 10–40 7.5–30 4–16 10–80 2.5–10 1–4	1 or 2 2 or 3 1 or 2 1 1 1 or 2 1 1 or 2 1 or 2 1	Do not use in combination with ARBs or direct renin inhibitor Risk of hyperkalemia, especially in patients with CKD or receiving potassium supplements or potassium-sparing drugs Risk of acute kidney injury in patients with severe bilateral renal artery stenosis Avoid in pregnancy
ARB	Azilsartan Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan	40–80 8–32 600–800 150–300 50–100 20–40 20–80 80–320	1 1 1 or 2 1 1 or 2 1 1 1	Do not use in combination with ACEIs or direct renin inhibitor Risk of hyperkalemia, especially in patients with CKD or receiving potassium supplements or potassium-sparing drugs Risk of acute kidney injury in patients with severe bilateral renal artery stenosis Do not use in patients with a history of ARB-induced angioedema. Patients with a history of ACEI-induced angioedema can receive ARB 6 weeks after ACEI withdrawal Avoid in pregnancy
CCB—dihydropyridines	Amlodipine Felodipine Isradipine Nicardipine SR Nifedipine SR Nisoldipine	2.5–10 5–10 5–10 5–20 60–120 30–90	1 1 2 1 1 1	Avoid in patients with CHF with reduced EF; amlodipine or felodipine may be used as required Dose-dependent lower extremity edema may occur, more common in women
CCB—non-dihydropyridines	Diltiazem SR Diltiazem ER Verapamil IR Verapamil SR Verapamil-delayed onset ER (various forms)	180–360 120–480 40–80 120–480 100–480	2 1 3 1 or 2 1 (in the evening)	Avoid use with beta blockers because of increased risk of bradycardia and heart block Do not use in patients with CHF with reduced EF Drug interactions with diltiazem and verapamil may occur (CYP3A-mediated)
Second-Line Treatment				
Loop diuretics	Bumetanide Furosemide Torasemide	0.5–4 20–80 5–10	2 2 1	Preferred in patients with symptomatic HF. Preferred over thiazides in patients with moderate-to-severe CKD (GFR <30 mL/min / 1.73 m^2)

Table 10. (Continued)

Drug group	Drug	Dosage (mg/day) *	Dosage Frequency	Comments
Potassium sparing diuretics	Amiloride Triamterene	5–10 50–100	1 or 2 1 or 2	Used as monotherapy; has minimal antihypertensive effect. Combination with thiazides can be considered in hypokalemia on thiazide monotherapy Avoid in severe CKD (GFR <45 mL/min / 1.73 m²)
Aldosterone antagonists	Eplerenone Spironolactone	50–100 25–100	1 or 2 1	Drug of choice in primary aldosteronism and resistant hypertension. Spironolactone is associated with higher risk of gynecomastia and impotence compared with eplerenone; use in resistant hypertension polytherapy. Avoid use with potassium supplements, potassium-sparing diuretics, or in severe kidney disease. Eplerenone often requires twice-daily dosing for adequate BP lowering
β-blocker—cardioselective	Atenolol Betaxolol Bisoprolol Metoprolol tartrate Metoprolol succinate	25–100 5–20 2,5–10 100–400 50–200	1 or 2 1 1 2 1	Not recommended as first-line treatment unless in IHD or HF. Preferred in patients with bronchospasm requiring a beta blocker Bisoprolol and metoprolol succinate are preferred in HF with reduced EF. Avoid abrupt discontinuation.
β-blocker—cardioselective and vasodilating	Nebivolol	5–40	1	Cause nitric oxide–induced vasodilation. Avoid abrupt discontinuation.
β-blocker—non-cardioselective	Nadolol Propranolol IR Propranolol SR	40–120 160–480 80–320	1 2 1	Avoid in airway obstruction. Avoid abrupt discontinuation.
β-blocker—intrinsic sympathomimetic activity	Acebutolol Carteolol Penbutolol Pindolol	200–800 2,5–10 10–40 10–60	2 1 1 2	Generally avoid, especially in IHD or HF. Avoid abrupt discontinuation.
αβ-blocker	Carvedilol Carvedilol phosphate Labetalol	12,5–50 20–80 200–800	2 1 2	Carvedilol is preferred in patients with HF with reduced EF. Avoid abrupt discontinuation.
Direct renin inhibitor	Aliskiren	150–300	1	Do not use in combination with ACEI or ARB. Very long acting drug. Increased risk of hyperkalemia in CKD or in patients on potassium supplements or potassium-sparing drugs. May cause acute kidney injury in severe bilateral renal artery stenosis. Avoid in pregnancy.
α_1-blocker	Doxazosin Prazosin Terazosin	1–8 2–20 1–20	1 2 or 3 1 or 2	Cause orthostatic hypotension, especially in older patients. May be used as a second-line agent in BPH.

Table 10. (The ending)

Drug group	Drug	Dosage (mg/day) *	Dosage Frequency	Comments
Central-acting agents	Clonidine oral Clonidine patch Methyldopa Guanfacine	0,1–0,8 0,1–0,3 250–1000 0,5–2	2 1 weekly 2 1	Last-line treatment because of significant CNS adverse effects, especially in older patients. Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis, especially in older patients; clonidine must be tapered to avoid rebound hypertension
Direct vasodilators	Hydralazine Minoxidil	250–200 5–100	2 or 3 1–3	Cause sodium and water retention and reflex tachycardia; use in combination with beta-blockers and diuretics. Hydralazine in high doses can cause drug-induced lupus. Minoxidil is associated with hirsutism; should be combined with loop diuretics. May induce pericardial effusion.

Table 11. *Absolute and relative contraindications to the use of specific antihypertensive drugs [15]*

Drug	Contraindications	
	Absolute	Relative
Diuretics (thiazides/ thiazide-like, e. g. chlorthalidone and indapamide)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcemia Hypokalemia
β-blocker	Asthma Any high-grade sinoatrial or atrioventricular block Bradycardia (heart rate <60 bpm)	Metabolic syndrome Glucose intolerance Athletes and physically active patients
Calcium antagonists: dihydropyridines		Tachyarrhythmia Heart failure (HF with reduced EF, NYHA class III or IV) Pre-existing severe leg edema
Calcium antagonists: verapamil, diltiazem	Severe LV dysfunction (LV ejection fraction <40%) Any high-grade sinoatrial or atrioventricular block Bradycardia (heart rate <60 bpm)	Constipation
ACE inhibitors	Pregnancy Previous angioedema Hyperkalemia (potassium >5.5 mmol/L) Bilateral renal artery stenosis	Women of reproductive age without reliable contraception
ARB	Pregnancy Hyperkalemia (potassium >5.5 mmol/L) Bilateral renal artery stenosis	Women of reproductive age without reliable contraception
MCA	eGFR <30 ml/min/1.73 m^2 Hyperkalemia (potassium >5.5 mmol/L)	

Justification of the Choice of Treatment in Hypertension and MS

Selection of antihypertensive agents in patients with hypertension and MS should be especially careful, since some of them can enhance metabolic disorders [3, 7]. It is advisable to use drugs that can improve or at least not worsen the sensitivity of tissues to insulin. These include blockers of the renin-angiotensin-aldosterone system (ACEI, ARBs) and CCBs (both dihydropyridine and non-dihydropyridine) [3].

Favorable metabolic effects accompany the RAAS block: an increase in tissue sensitivity to insulin, insulin secretion, glucose uptake by tissues due to decreased SNS activity and improved blood flow in skeletal muscles, an improvement in signal transduction via insulin receptors, an influence on the level of free fatty acids and on adipose tissue, and activation of PPARγ receptors. In this regard, in ACEIs and ARBs are key in the treatment of hypertension in patients with MS [6].

The undoubted advantage of these drugs is the absence of negative effect on carbohydrate, lipid and purine metabolism. These drugs have an organic protective effect: LVH reduction, myocardium remodeling and fibrosis delay, albuminuria and proteinuria reduction, nephroangiosclerosis and terminal CKD prevention [6]. In addition, they prevent cardiovascular complications in high and very high-risk patients, including patients with hypertension, MS and type 2 DM.

There are 3 groups of ACEIs, depending on their chemical structure: containing sulfhydryl (captopril, zofenopril), carboxyl (enalapril, quinapril, ramipril, perindopril, trandolapril, spirapril, cilazapril, lisinopril), and phosphoryl group (fosinopril). Since fatty tissue growth often occurs in hypertension and metabolic disorders, the choice of a particular ACEI should consider its lipophilicity, because a higher level of lipophilicity determines greater tissue affinity for the drug (i. e., the ability to influence ACE activity both in plasma and directly in tissues). The active metabolites of fosinopril, quinapril, trandolapril, ramipril and perindopril are highly lipophilic; enalapril, moexipril and captopril have moderate lipophilicity; and lisinopril belongs to hydrophilic compounds. The kidneys eliminate the majority of ACEIs; only 4 agents (zofenopril, fosinopril, trandolapril, spirapril) are eliminated via both liver and kidneys.

The effect of angiotensin II receptor blockers (ARBs), or sartans, is also associated with the suppression of RAAS activity, but they do not affect the kinin-kallikrein system. Antihypertensive efficacy of ACEIs and ARBs is equivalent, but the latter have a better tolerability profile: do not cause cough and angioedema. ARBs provide higher adherence to treatment among patients with hypertension due to better tolerability profile and absence of "escape" of hypotensive effect [6].

ARBs do not affect lipid and purine metabolism, except for losartan, which has been proven to reduce uric acid levels. In addition, lipophilic ARBs improve tissue sensitivity to insulin, carbohydrate and lipid metabolism due to interaction with PPARg- receptors.

CCBs, or calcium antagonists, have a significant vasodilating effect due to inactivation of potential-dependent calcium channels and blocking of the flow of calcium fluxes into vascular smooth muscle cells. Depending on the chemical structure, 3 groups of CCBs are distinguished: dihydropyridines (nifedipine, amlodipine, felodipine, etc.), phenylalkylamines (verapamil), and benzodiazepines (diltiazem). Non-dihydropyridine calcium blockers have negative ino- and dromotropic effects. Dihydropyridine CCBs have a significant vasodilating effect on peripheral arteries, do not affect the cardiac conduction system, and mostly do not reduce myocardial contractility.

To treat hypertension in patients with MS, as well as with type 2 DM, both non-dihydropyridine (verapamil, diltiazem) and long acting dihydropyridine CCBs are used. CCBs do not adversely affect lipid, carbohydrate, and purine metabolism. Reduction of new cases of type 2 DM in long-term treatment with CCBs in combination with ACEIs was established in the ASCOT (amlodipine + perindopril) and INVEST (verapamil + trandolapril) trials.

Nitrenedipine has the most significant preventive effect on cognitive disorders (by 55%) [3].

β-blockers (other than vasodilating ones) and diuretics should be considered only as additional agents in MS. However, in case of high SNS activity and the need in this drug group, it is advisable to use only cardioselective β-blockers (nebivolol, bisoprolol, extended release metoprolol succinate) or vasodilating agents (nebivolol, carvedilol — non-cardioselective αβ-blocker) in order to avoid a negative effect on carbohydrate and lipid metabolism. Carvedilol reduces SPR, improves glomerular filtration and reduces insulin resistance [3].

Thiazide diuretics can adversely affect carbohydrate and lipid metabolism. However, hypervolemia that develops in MS due to increased reabsorption of sodium and water often leads to the need for diuretics. Chlorthalidone and indapamide are the drugs of choice among thiazide-like diuretics. Loop diuretics are not recommended in the treatment of MS: they can cause IGT, glucosuria, and hyperosmolar conditions [3].

I_2-imidazoline receptors agonists (moxonidine, rilmenidine) can be used in MS due to the fact that they improve tissue sensitivity to insulin and promote weight loss [3].

α-antibodies also reduce insulin resistance, improve carbohydrate and lipid metabolism. But they can cause postural hypotension, and therefore they should be combined with β-blockers [3].

Mono- and Combined Hypertension Treatment

The 2018 ESC/ESH guidelines in the majority of cases suggest initiating treatment with a combination of two agents and not with monotherapy (Table 12). At the first treatment stage, a double combination of ACEI (or ARB) with CCB (or thiazide/thiazide-like or looped diuretic in CKD) should be prescribed. Monotherapy can be considered in low-risk patients with BP level 140–159 / 90–99 mm Hg, or in senile (>80 years) or frail patients. If the double combination is ineffective, the second treatment stage is switched to, and a triple combination is prescribed: ACEI (or ARB) with CCB and diuretic (thiazide / thiazide-like or looped in CKD). If the triple combination is ineffective, the third treatment stage is switched to, and 25–50 mg/day of spironolactone or other diuretics, alpha-blockers or β-blockers are added to the triple combination [15].

Monotherapy can be considered in case of low CVR at BP 140–159 / 90–99 mm Hg, or in senile (>80 years) or frail patients [15].

The 2018 ESH/ESC guidelines recommend the addition of β-blockers to the hypertension treatment at any stage in the presence of indications: HF, angina, history of MI, AF or in young women with a planned pregnancy [15]. The American recommendations specify that β-blockers are the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease [14]. In contrast, in patients with chronic aortic insufficiency systolic hypertension should be treated with agents that do not slow heart rate, and β-blockers should be avoided. This is due to the fact that when the heart rate decreases, the diastolic filling time increases and, consequently, aortic regurgitation increases [14].

The 2017 ACC/AHA guidelines also recommend to prescribe two agents of different first-line drug groups (fixed combination, or individual

Table 12. *Therapy choice in hypertension according to 2018 ESH/ESC [15]*

	Drug groups	Comments
Step 1 (initial therapy) — dual combination	ACEI or ARB + CCB or diuretic (loop in CKD)	Consider monotherapy in low risk grade 1 hypertension (systolic BP <150 mmHg), or in very old (80 years) or frail patients
Step 2 — triple combination	ACEI or ARB + CCB + diuretic	
Step 3 — triple combination + spironolactone or another drug	Resistant hypertension: add spironolactone (25–50 mg o. d.) or other diuretic, alpha-blocker or beta-blocker	Referral to a medical specialist as required

medications) as the onset of antihypertensive DT in adults with BP level ≥140/90 mm Hg and mean BP level ≥20/10 mm Hg above target [14]. Hypertension monotherapy is indicated in patients with BP of 130/80 mm Hg, followed by dose titration or addition of other drugs to achieve target BP [14].

The course of hypertension in patients with MS is characterized by refractoriness to treatment, therefore it is advisable to use combined therapy immediately after hypertension diagnosis in this group of patients. In this case, two-component treatment with diuretic and β-blocker should be avoided [3, 7]. When using diuretics, an additional potassium-sparing agent should be prescribed, because hypokalemia may impair glucose tolerance [15].

The 2018 ESH/ESC 2018 guidelines emphasize low adherence to treatment as the main reason for poor BP control [15]. In this regard, the use of the so-called "single pill combination" (SPC) and "polypill" was proposed. SPC is a fixed combination of two or more drugs that affect a particular risk factor (for example, fixed combinations of antihypertensive agents). SPCs are preferred for most patients. A simplified procedure for drug hypotensive treatment includes SPC (ACEI or ARB with CCB or/and thiazide / thiazide-like diuretic) as the main treatment strategy for most patients; in case of specific indications the addition of β-blockers should be considered [15]. Polypill is a combination of two or more agents that affect various risk factors. For example, a combination of antihypertensive agents with antiplatelets and statins [15].

In both the European and American guidelines, single administration of medicines is preferable, since in this case the adherence to treatment increases. In addition, adherence to treatment when taking fixed combinations is better than when taking drugs separately [14, 15].

Hypertension and MS Treatment in Order to Reduce CVR

Isolated antihypertensive treatment does not sufficiently reduce CVR in patients with moderate- or higher-risk hypertension, as well as in patients with established CVD. In these patients, treatment with statins leads to the decrease of MI risk by 1/3 and of stroke by 1/4 even with optimal control of BP [15].

In this regard, in the presence of dyslipidemia, patients with MS should be prescribed statins at the maximum or maximum tolerated doses. In case of intolerance to statins, ezetimibe or bile acid sequestrants, or their combination, should be prescribed [2, 9].

The main goal of dyslipidemia treatment in MS is the correction of LDL cholesterol level. Its target level for very high-risk patients is <1.8 mmol/L

or a decrease of 50% at the baseline level of 1.8–3.5 mmol/L; for high-risk patients it is <2.6 or decrease by ≥50% of the baseline [2, 9]. If the target LDL cholesterol is not achieved, a combination of statin and ezetimibe should be prescribed [2, 9].

Antiplatelet treatment, especially low doses of aspirin, is recommended for the purpose of secondary prevention in patients with hypertension, but is not recommended for primary prevention (in patients without CVD) [15]. This is specified in the 2018 ESH/ESC recommendations. In the American guidelines, almost no attention is paid to aspirin and statins [14]. The Russian recommendations for the management of comorbid patients indicate that prescribing antiplatelets as the primary prevention of CVD in MS has not yet been resolved. In very high-risk patients with hypertension and MS, administration of acetylsalicylic acid should be considered in case of good BP control [3]. In the presence of risk factors for erosive and ulcerative lesions of the gastrointestinal tract, acetylsalicylic acid can be administered under the "cover" of proton pump inhibitors and/or rebamipide, a universal gastroprotective agent. Clopidogrel is recommended as an alternative antiplatelet treatment in patients with ASA intolerance [3].

Conclusion

Hypertension in patients with MS is therefore an extremely urgent problem. In patients with MS, it is necessary to diagnose hypertension in a timely manner with an increase in office systolic BP ≥140 and/or diastolic BP ≥90 mm Hg; and/or at mean daily BP according to 24-hour BPM >130/80 mm Hg; and/or at mean BP values according to home BPM ≥135/85 mm Hg. Most patients with MS have a high or very high cardiovascular risk, which requires immediate initiation of drug antihypertensive treatment. The target BP level in the majority of patients with MS is 120–130 / 70–80 mm Hg. Treatment of most patients with hypertension should be started with a combination of two agents. At the first treatment stage, a double combination of ACEI (or ARB) with CCB (or thiazide / thiazide-like or looped diuretic in CKD) should be prescribed. Monotherapy can be considered in low-risk patients with BP level 140–159 / 90–99 mm Hg, or in senile (>80 years) or frail patients. If the double combination is ineffective, the second treatment stage is switched to, and a triple combination is prescribed: ACEI (or ARB) with CCB and diuretic (thiazide / thiazide-like or looped in CKD). If the triple combination is ineffective, the third treatment stage is switched to, and 25–50 mg/day of spironolactone or other diuretics, α-blockers or β-blockers are added to the triple combination. In patients with MS and dyslipidemia, statins should be prescribed to reduce CVR. In patients with MS, BP stabilization and dyslipidemia correction are extremely important for the prevention of life-threatening complications.

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