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Treatment of diseases with comorbidity

Chapter 1. Hypertension

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Treatment of common diseases with comorbid conditions is presented in the reference book. It deals of original classification of drug preferences in comorbidities. The information may help to select more effective and safe treatment. The content of the book is based on modern guidelines and randomized studies. This book is intended for internists and other physicians whose knowledge is not limited by bounds in their speciality.

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Preface

The most patients have more than one disease, and therefore the assessment of comorbidity is important for patient care, for quality assurance, and for the evaluation of therapy. Comorbid diseases may affect multiple clinical outcomes, including mortality, functional capacity, quality of life, and cost.

Patients with comorbid diseases are in a new clinical state. There are significant peculiarities in the selection and interpretation of diagnostic tests. Selection of drugs needs to take into account the comorbidities. A drug may help for one disease and be contraindicated for others. On the contrary, a drug can be very effective for both diseases.

While making clinical decision physicians should consider drugs investigated in prospective, large, randomized and placebo-controlled trials. But patients with severe comorbid diseases are usually excluded from these trials. So there are insufficient trials of diseases with comorbidities and the most of associated conditions are poorly investigated.

In connection with poor investigation of a number of comorbidities the book presents data from less reliable studies. In addition modern recommendations worked out by authoritative medical societies are widely used.

Unfortunately, references used are numerous and are not included in this manual. The most important investigations are mentioned in the text.

The influence of drugs on comorbid diseases is classified according original classification (table).

Table. Classification of drug effect on associated disease (Belyalov F., 1998).

Effect	Description of the effect on comorbid disease
FAVOURABLE	drug is very effective
POSSIBLE	moderate effect
NEUTRAL	no substantial influence or data are not adequate for an effect evaluation
UNDESIRABLE	rare hazard events
UNFAVOURABLE	high frequency of hazard events

The scientific conferences on management of diseases with comorbid conditions are organized in Irkutsk, Russia annually. The reference book was published for Russian physicians in 1998 and updated in 2000, 2007, 2008, 2009 and 2007. I hope this book would be useful for foreign medics also.

The work over the improvement of the book is continuing and author will be thankful for advices and remarks. All proposals may be sent on email fbelyalov@yandex.ru.

ABBREVIATION

ACE	– angiotensin-converting enzyme
AED	– automated external defibrillator
ARB	– angiotensin II type 1 receptor blocker
AV	– atrioventricular
BMI	– body mass index
BP	– blood pressure
bpm	– beats per minute
CAD	– coronary artery disease
CDV	– circulating blood volume
CHD	– coronary heart disease
CK	– creatine kinase
CVD	– cardiovascular disease
DBP	– diastolic blood pressure
ECG	– electrocardiogram
EF	– ejection fraction
GFR	– glomerular filtration rate
HDL-C	– high density lipoprotein-cholesterol
HF	– heart failure
HR	– heart rate
IPP	– proton pump inhibitor
ISA	– intrinsic sympathomimetic activity
LDL-C	– low density lipoprotein-cholesterol
LMWH	– low-molecular-weight heparin
LV	– left ventricle
LVEF	– left ventricular ejection fraction
MAO	– monoamine oxidase
MI	– myocardial infarction
NSAID	– non-steroid anti-inflammatory drug
PTCA	– percutaneous transluminal coronary angioplasty
SBP	– systolic blood pressure
SSRI	– selective serotonin reuptake inhibitors
TCA	– tricyclic, tetracyclic antidepressant

Chronic cardiovascular diseases

Chapter 1 Hypertension

The main aims of hypertension treatment are reduction of cardiovascular risk (myocardial infarction, stroke, death) and hypertensive symptoms. These aims are achieved by lowering blood pressure (BP) with different antihypertensive drugs (CAPPP, JNC-7, ESH/ESC, 2007). The selection of drugs is determined in a great deal of comorbid diseases.

Table 1-1. Antihypertensive drugs.

Class	Drug name
alfa₁- blockers	prazosin, doxazosin
alfa₂- adrenoreceptor agonists	guanfacine, clonidine, methyldopa
calcium antagonists	<i>nondihydropyridines</i> : verapamil, diltiazem
	<i>dihydropyridines</i> : amlodipine, nifedipine long-acting
angiotensin receptor blockers	valsartan, irbesartan, losartan
beta-blockers	<i>selective (beta₁-blockers)</i> : atenolol, metoprolol
	<i>highselective</i> : bisoprolol, nebivolol
	<i>nonselective</i> : nadolol, propranolol
	<i>alfa-beta-blockers</i> : labetalol, carvedilol
thiazide diuretics	hydrochlorothiazide, indapamide, chlorthalidone
ACE inhibitors	captopril, enalapril, lisinopril, perindopril, ramipril
other drugs	moxonidine, reserpine

Gastrointestinal diseases

Constipation

The estimated prevalence of persistent constipation is near 10% and 25% in persons aged 60 and above. Discomfort from constipation and intraabdominal pressure promotes the elevation of BP. Hypothyroidism and diabetes may declare themselves by hypertension and constipation.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, alfa₂-agonists, ARBs, dihydropyridines, diuretics, reserpine, peripheral vasodilators, reserpine.

UNDESIRABLE EFFECT

beta-blockers, beta-alfa-blockers, clonidine, nondihydropyridines.

Calcium antagonists reduce bowel motility and may induce atonic constipation. Beta-blockers enforce tonus of smooth muscles and result in spastic constipation sometimes. Clonidine elevates water absorption in intestines and promotes constipation.

Gastroesophageal reflux

Gastroesophageal reflux occurs in 20–40% population, but severe forms are found in 2% only. Dangerous complications (esophagitis, ulcer, stenosis, bleeding, malignant transformation) demand active treatment. The critical factor is the lower esophageal sphincter incompetence: the most refluxes occur during the transient relaxation of the lower esophageal sphincter. The influence of antihypertensive drugs on lower esophageal sphincter is discussed below.

POSSIBLE EFFECT

beta-blockers.

Beta-blockers increase tone of smooth muscles of esophageal sphincter and may reduce gastroesophageal refluxes.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, alfa₂-agonists, ARBs, beta-alfa-blockers, diuretics, peripheral vasodilators, reserpine.

UNDESIRABLE EFFECT

calcium antagonists.

Calcium antagonists reduce tone of esophageal sphincter and may increase the gastric juice regurgitation into esophagus.

Liver diseases

Hepatitis

Hypertension and hepatitis are widespread diseases. This association of diseases may be revealed in a patient sometimes. A damage of hepatocytes does not increase BP, but hypertension does not injure the liver.

At the same time it is necessary to take into account the risk of hepatotoxic effects of antihypertensive drugs. Usually the hepatotoxic reactions occur without warning, they are unrelated to dosage and have variable latency periods, ranging from a few days to 12 months. Drug-related hepatotoxicity is supported by the decreasing of serum alanine aminotransferase levels more 50% during 8 days after the treatment was ceased. But sometimes, the high level of alanine aminotransferase may stay for few months.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, alfa₂-agonists, beta-blockers, calcium antagonists, diuretics, labetalol, reserpine.

Rare hepatotoxic reactions with an elevation of aminotransferase level are described as to many antihypertensive drugs (alfa₁-blockers, alfa₂-agonists, calcium antagonists, beta-blockers, ACE inhibitors, labetalol, hydralazine).

UNDESIRABLE EFFECT

methyldopa.

Methyldopa causes drug-related hepatitis more frequently than other antihypertensive drugs and is contraindicated to patients with liver lesion. Drug-related hepatitis develops during 1–20 weeks (until 4 weeks in 50% cases) after the onset of treatment. Improvement occurs in the most cases, although progress of the disease, cirrosis or death can occur. Slight elevation of serum aminotransferase level may vanish during continuous treatment.

Combination treatment

Treatment of viral hepatitis with ACE inhibitors and interferon is accompanied with an elevation of neutropenia risk. Autoimmune hepatitis is preferably treated with corticosteroids with less mineralocorticoid effects (triamcinolone, methylprednisolone) and less hypertensive effect.

Portal hypertension

Portal hypertension in cirrhotic patients is caused by intrahepatic obstruction and decrease of outflow through hepatic veins. Besides, the increase of cardiac output results in portal hypertension without an elevation of systemic BP.

FAVOURABLE EFFECT

beta-blockers (nadolol, propranolol, carvedilol), diuretics.

Beta-blockers and diuretics are used for treatment of portal hypertension. Non-selective beta-blockers are basic drugs for primary and secondary prevention of bleeding from esophageal varices.

Selective drugs decrease portal BP less than propranolol or carvedilol. But these drugs have not substantial antihypertensive effect.

Treatment of ascites consists of aldosterone receptor antagonists and furosemide. Thiazide diuretics increase risk of hypokalemia more than furosemide and are recommended as additional drugs in refractory edema. Diurnal diuresis may be 2–3 liters until edema conserves.

POSSIBLE EFFECT

alfa₁-blockers, alfa₂-agonists, verapamil.

Alfa₁-blockers, alfa₂-agonists and verapamil may decrease portal BP.

NEUTRAL EFFECT

ACE inhibitors, calcium antagonists, peripheral vasodilators, reserpine.

UNDESIRABLE EFFECT

ARBs.

Losartan lowers portal pressure insignificantly, but decreases GFR and systemic BP. Irbesartan decreases portal BP 12%, but in 22% patients develop hypotension with considerable impairment of renal function that demands the ceasing of the offending medication.

Particular treatment of portal hypertension

Pituitrine is not indicated for the reduction of portal BP in patients with hypertension.

Liver failure

Useful information about dosage of antihypertensive drugs in liver failure is presented in the table 1-2.

Table 1-2. Dose adjustment for liver failure.

Same dose	Decreased dose
beta-blockers (atenolol, nadolol)	beta-blockers (carvedilol propranolol, metoprolol)
ACE inhibitors (captopril, lisinopril, ramipril, fosinopril)	ACE inhibitors (zofenopril, enalapril)
thiazide diuretics	calcium antagonists
clonidine	guanfacine, hydralazine, indapamide, labetalol
valsartan	alfa ₁ -blockers (prazosin, doxazosin)

Enalapril is converted in active enalaprilat in the liver. Therefore effect of enalapril is reduced significantly in patients with liver failure. Valsartan is removed in unchanged form through biliary tract mostly and lower doses are needed in cholestasis or heavy liver failure.

Lipophilic beta-blockers may be accumulated in patients with low hepatic circulation (cirrhosis, old, heart failure).

Dose adjustment for drugs metabolized by the liver may be indicated in the liver failure (table 1-3).

Table 1-3. Dosage of antihypertensive drugs in patients with liver failure.

Drug	Class Child-Pugh		
	A	B	C
Dose of the drug metabolized in a liver	100%	75%	25–50%
Dose of the drug excreted by kidneys	100%	100%	100%

Peptic ulcer

Antihypertensive drugs may damage mucosa of gastrointestinal tract.

NEUTRAL EFFECT

ACE inhibitors, ARBs, alfa₁-blockers, alfa₂-agonists, beta-blockers, calcium antagonists, diuretics, peripheral vasodilators.

Calcium antagonists (verapamil, nifedipine), beta-blockers and clonidine decrease gastric acid secretion, but this effect is significantly lower than H₂-blockers or IPP. Calcium antagonists may improve gastroduodenal circulation.

Calcium channel blockers usage may be associated with an elevated risk of gastrointestinal bleeding. Higher risk of gastrointestinal bleeding is revealed in few small studies. But the risk of gastrointestinal bleeding was higher on lisinopril than amlodipine in the large Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT).

UNFAVOURABLE EFFECT

reserpine, spironolactone.

Reserpine elevates parasympathetic activity, gastric acid production and increases risk of exacerbation of ulcer disease. High dose of reserpine provokes acute gastroduodenal ulcerations in experimental conditions.

Use of spironolactone is associated with increased relative risk (2.7) of gastroduodenal ulcer and upper gastrointestinal tract bleeding.

Particular treatment of ulcer

Prokinetic metoclopramide contraindicated for patients with pheochromocytoma.

Combination treatment

Antacids decrease absorption of drugs and the latter are recommended to intake in 4 hours later or 1 hour before antacids.

Pancreatitis

Association of hypertension and chronic biliary or alcoholic pancreatitis is frequent in clinical practice. At the same time severe pancreatitis may be accompanied with hypotension.

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, calcium antagonists, beta-blockers, ACE inhibitors, peripheral vasodilators.

Nifedipine is useful in sphincter Oddi dysfunction. The latter may appear in recurrent “idiopathic” pancreatitis or biliary colic after cholecystectomy. Beta-blockers reduce function of pancreas slightly. But there is actually no evidence that therapy for reducing of pancreatic secretion is effective. ACE inhibitors seldom provoke pancreatitis.

UNDESIRABLE EFFECT

diuretics, methyldopa.

Thiazide diuretics and methyldopa cause drug-related pancreatitis more frequently than other antihypertensive drugs. Diuretics are undesirable in hypovolemia.

Neurologic disorders

Migraine

The majority of headaches in patients with hypertension is not associated with BP according ambulatory BP monitoring. Tension-type headache and migraine are the most common causes of headache in the general population. Prevalence of migraine is 4–30% in the population.

FAVOURABLE EFFECT

beta-blockers.

First-line migraine prophylaxis in adults includes beta-blockers (propranolol, timolol). There is limited evidence to support the use of atenolol, metoprolol or nadolol for migraine prevention.

POSSIBLE EFFECT

candesartan, clonidine, ergot alkaloids, lisinopril, verapamil.

For prophylaxis of migraine other antihypertensive drugs may be effective: clonidine 50-150 mcg/day, verapamil. There are single small trials to support the use of lisinopril or candesartan for migraine prevention.

NEUTRAL EFFECT

alfa₁-blockers, reserpine.

UNDESIRABLE EFFECT

nifedipine, peripheral vasodilators.

Nifedipine and peripheral vasodilators may increase frequency of migraine.

Particular treatment of migraine

Some drugs for acute migraine (ergotamine, dihydroergotamine, triptans) and prophylaxis (naproxen) elevate BP.

Combination treatment

Combined use of beta-blockers and ergot alkaloids may induce severe vasoconstriction. Interaction of amitriptyline and antihypertensive drugs are described below in the section of depressive and anxiety disorders.

Stroke

Hypertension considerably increases ischemic and hemorrhagic stroke risk. Stroke risk grows as BP raises and doubles each 7.5 mmHg independently from a gender.

Antihypertensive therapy reduces stroke rate by 34–73% (Syst–Eur, INDANA, SCOPE). In particular, DBP reducing on 5–6 mmHg results 40% decrease of stroke nearest 2–3 years. Stroke risk is reduced more than coronary events.

A goal BP of <130/80 mmHg has been proposed for individuals after ischemic or hemorrhagic stroke (PROGRESS; ESC, 2007). In patients with intracranial stenosis higher blood pressure is associated with increased risk of ischemic stroke and stroke in the territory of the stenotic vessel. It seems the danger of brain hypoperfusion is exaggerated. Moreover, antihypertensive treatment (candesartan) may be initiated on the first day of ischemic stroke (ACCESS).

Ischemic stroke

Hypertension promotes atherosclerosis of cerebral vessels and thrombosis on damaged arteries. Thrombus may occlude a lumen of artery or lose touch with plaque and obturate distal cerebral arteries that results in brain infarction. Also hypertension is risk factor for atrial fibrillation, sometimes complicated by embolic stroke. Note, that most ischemic strokes occurs at BP below 160/100 mmHg.

Patients after stroke or with transient ischemic attacks have risk of stroke more than 4% per year. Risk of cerebrovascular events has straight relationship with BP. Meta-analysis of 9 randomized controlled trials showed 28% reduction of stroke recurrence after antihypertensive treatment. Optimal DBP for secondary prevention of ischemic stroke is 80–84 mmHg (HOT).

Patients after stroke or with transient ischemic attacks are treated with perindopril and indapamide had lower risk of stroke on 28%, including reductions in the risk of hemorrhagic stroke on 50%, ischemic stroke on 24%, fatal or disabling stroke on 33%, though mortality was reduced (–16%) insignificantly. The main preventive effect is attributed to combined drug use only. It may be suggested that the main preventive role belongs to indapamide, as shown in PATS trial. It should be noted, that preventive effect was revealed in patents with normal BP.

There are greater benefits from larger BP reductions, and initiating and maintaining BP reduction for stroke prevention are a more important issue than choice of initial agent according meta-analysis. At the same time, there was demonstrated a higher risk of stroke in the atenolol group compared with losartan and in the lisinopril group compared with amlodipine or chlorthalidone in LIFE and ALLHAT studies.

Calcium antagonists (lacidipine, isradipine, verapamil) slow down the intima-media thickness and advance of an atherosclerotic plaque carotids in larger degree than atenolol or diuretics (ELSA, VHAS, MIDAS). It is necessary to avoid orthostatic reactions and to control night-time BP after an elevation of drug dose.

Nephrourological disorders

Benign prostatic hyperplasia

When the urinary bladder extends approximately to 300 ml, sympathetic activation can cause substantial increase of BP. In patients even without hypertension the severe obstruction of urinary tract caused by benign prostatic hyperplasia, promotes high BP (up to 200/120 mmHg) and serum creatinine, which are quickly normalized after obstruction elimination. In the case of hypertension substantial BP increase or hypertensive crisis, refractory to usual treatment can develop.

The benign prostatic hyperplasia causes mechanical and dynamic obstruction of urinary tract. Growth of prostate stroma causes intravesicular mechanical obstruction shown by a weak stream of urine, sensation of incomplete voiding and retardation of urination. High tone of smooth muscles of bladder and back urethra leads to dynamic obstruction, which are characterized by day and night pollakiuria, urgency.

FAVOURABLE EFFECT

alfa₁-blockers.

The dynamic obstruction of urinary tract is mediated by sympathetic nervous system. Besides, in benign prostatic hyperplasia 5-alfa-androstandiol (the biological blocker of alfa₁-adrenoreceptors) is coordinating work of detrusor and neck of the bladder. Therefore in case of prevalence of dynamic intravesicular obstructions alfa₁-blockers (doxazosin, alfuzosin) are effective.

Now for treatment of benign prostatic hyperplasia apply tamsulozine, which blocks mainly alfa_{1A}- adrenoreceptors and little influences on BP. Alfa_{1a}- adrenoreceptors are in smooth muscles of neck of bladder, prostate and the prostatic part of urethra, and alfa_{1B}- adrenoreceptors are in smooth muscles of vessels.

POSSIBLE EFFECT

beta-alfa-blockers.

Beta-alfa-blockers (carvedilol) have the relatively weak alfa-blocking effect.

NEUTRAL EFFECT

ACE inhibitors, alfa₂-agonists, ARBs, beta-blockers, calcium antagonists, peripheral vasodilators, reserpine.

UNFAVOURABLE EFFECT

diuretics.

Diuretics can strengthen obstruction of urinary tract up to acute renal failure.

Nephrolithiasis

High frequency of combination of hypertension and kidney stones is explained by high prevalence of the given diseases. Disturbance of urination in the presence of stones in urinary tract often leads to pyelonephritis and hypertension.

In this case influence of antihypertensive drugs on risk of urinary stones and their passage through urinary ways is should be taken into account.

Calcium stones

Calcium stones are the most frequent urinary stones (approximately 80% in the form of oxalatus, more rare phosphatus). The calcium composition of stones may be identified by X-ray examination.

POSSIBLE EFFECT

Thiazide diuretics decrease calcium excretion and are used for prevention of calcium stones. It is recommended to intake hydrochlorothiazide 25 to 50 mg once a day. Then the dose may be elevated to 50 mg twice a day according to urine analysis. Amilorid is used for correction of hypokalemia and it also reduces calciuria.

Calcium antagonists reduce development of calcium phosphate stones and relieve passage of small stones without influence on the frequency of acute renal colic. Also beta-blockers can improve passage of stones at the lower part of ureter. The relieving of stones passage has significance for small (<5 mm) stones, which exit spontaneously in 80% during 1–2 weeks.

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, ACE inhibitors, ARBs, peripheral vasodilators.

UNDESIRABLE EFFECT

triamteren.

Triamteren is badly dissolved and raises risk of kidney stones.

Uric acid stones

Near 10% urinary stones consist of urate or mixture of urate and calcium salts. Formation of uric acid stones is caused by disorders of purine metabolism and raises of uric acid level in a blood. Major risk factors for stone formation are hyperuricuria and urine pH lower than 5.5–6.0. Uric acid stones are not visible in X-ray images.

POSSIBLE EFFECT

calcium antagonists, beta-blockers.

Calcium antagonists and beta-blockers may relieve passage of small stones (<5 mm) at low part of ureter.

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, ACE inhibitors, ARBs, peripheral vasodilators, reserpine.

UNFAVOURABLE EFFECT

diuretics.

Thiazide diuretics elevate level of uric acid in the blood and are not indicated for patients with uric acid urolithiasis. Tienil acid strengthens urates excretion and raises risk for stone formation.

Particular treatment of urolithiasis

The daily reception of 2.5-3 litres of liquid for excretion of fine stones and prevention of stones formation can be undesirable. NSAIDs relieve pain but reduce effect of antihypertensive drugs, except calcium antagonists, and raise BP.

Nephropathies

Hypertension may be course and consequence of kidney lesion. Irrespective of cause hypertension is the important risk factor for progression of chronic renal disease and terminal renal insufficiency.

Primary renal diseases cause 3–4% of cases of hypertension and 1% of cases is caused by disease of renal arteries.

POSSIBLE EFFECT

ACE inhibitors, ARBs.

ACE inhibitors and ARBs reduce proteinuria, decrease or delay progression of chronic diabetic and nondiabetic nephropathy even in patients without hypertension, however the all-cause mortality does not change (GISEN, REIN).

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, beta-blockers, beta-alfa-blockers, diuretics, peripheral vasodilators, reserpine.

UNDESIRABLE EFFECT

dihydropyridines.

There are enhancement of proteinuria after appointment of dihydropyridines in patients with nondiabetic nephropathy in the GISEN study. This effect is explained by renal hyperfiltration, which promotes glomerulosclerosis development.

Renal insufficiency

Long and substantial increase of BP can lead to damage of kidneys. In debut of hypertension it is revealed the narrowing of renal arteries, reversible under the influence of ACE inhibitors or calcium antagonists. In later stages of disease the persistent narrowing of renal vessels is formed and the sodium and water retention promotes high BP.

There are registered hypertension with elevated level of the serum creatinine in 2.1% of US population (NHANES III). Hypertension is the cause of end-stage renal disease in 25% of all cases and take the second place after diabetes.

Antihypertensive therapy retards the development of chronic kidney disease and reduces risk of kidney failure. For example, DBP reduction on 5 mmHg leads to decrease terminal renal insufficiency risk for 25%. Besides, BP decreasing reduces an over-all mortality and mortality from cardiovascular diseases in patients with terminal renal insufficiency.

It is recommended to lower BP until 130/80 mmHg and probably until 120 mmHg for reduction of intraglomerular pressure and adequate protection of renal function. In case of a proteinuria >1 g/day target BP should not exceed 125/75 mmHg (MDRD). It should be noted, that achievement of DBP <80 mmHg was required combined antihypertensive therapy at 74% of patients in HOT trial.

It is recommended to reduce BP by 15–20% in the start of treatment and then gradually to lower until desirable level. The start of antihypertensive treatment in patients with renal insufficiency is quite often accompanied by rising of serum creatinine owing to intracapillary pressure decrease. However after stable normalization of BP serum creatinine goes down within one or several weeks until pretreatment level.

For correction of night hypertension, frequent in patients with renal insufficiency, it is reasonable to transfer reception of antihypertensive drugs from the morning to the evening.

POSSIBLE EFFECT

ARBs, ACE inhibitors.

ACE inhibitors slow down deterioration of kidney function of any causes at the expense of relaxation of glomerular efferent arterioles and reduction of intracapillary BP. ACE inhibitors are effective even in the severe renal insufficiency (GFR 10–30 ml/min and serum creatinine 265–442 μmol/l) (BACRI, REIN).

ACE inhibitors, especially in the first 7–14 days, reduce hydrostatic pressure in glomerular capillaries and GFR. Treatment in this situation is insufficiently developed. On the one hand, it is recommended to cancel ACE inhibitors if the serum creatinine remains raised on ≥30% from initial level within 2 months. On the other hand, researches testify, that stable creatinine elevation not only is acceptable, but even desirable. Intake of ACE inhibitors even in case of creatinine elevation to 440–530 μmol/l is possible. At normal liver function and the severe renal insufficiency it is preferable fosinopril or spirapril which are inactivated by a liver.

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, calcium antagonists, hydrophilic beta-blockers, loop diuretics, metolazone, hydralazine.

Hypertension in renal insufficiency is promoted by hypervolemia, therefore diuretics are indicated. Loop diuretics, unlike thiazides, are effective even in low GFR. Furosemide preferably looks

as ethacrynic acid has more ototoxic action. It is recommended to prescribe diuretics more often within a day because of restricted filtration of sodium in renal insufficiency.

Alfa₂-agonists have little influence on kidney function, it is necessary to consider undesirable sedation in uremic encephalopathy. In comparison with lipophilic beta-blockers, hydrophilic ones (nadolol, atenolol) reduce GFR less. At the same time the dose of these drugs needs to be reduced, because they are eliminated by kidneys slowly.

Dihydropyridines influence on proteinuria inconsistently. These drugs, along with BP reduction, relax afferent glomerular arterioles, raise intraglomerular BP, slowe the rate of GFR decline and amplify proteinuria (REIN).

UNDESIRABLE EFFECT

beta-blockers lipophilic/nonselective, minoxidil, reserpine, thiazides.

Thiazides, except metolazone, are ineffective in serum creatinine >220 mcmmol/l.

Lipophilic beta-blockers (propranolol, metoprolol) can lower GFR and consequently are not recommended at serum creatinine >220 mcmmol/l. Nonselective beta-blockers raise serum potassium. For example, nadolol in a dose of 80 mg/day elevates the serum potassium by 1.2 mmol/l on the average.

The antipsychotic effect of reserpine is undesirable in patients with uremic encephalopathy. Minoxidil can temporarily raise serum creatinine.

UNFAVOURABLE EFFECT

potassium-sparing diuretics.

High serum potassium may cause heart asystole. Because the exact estimation of serum potassium is difficult, the potassium-sparing diuretics are not applied even at mild renal insufficiency. Drugs suppressing sinus node and AV conduction (beta-blockers, alfa₂-agonists, verapamil, diltiazem, reserpin), and also ACE inhibitors are dangerous in high serum potassium.

Table 1–4. Dosage of antihypertensive drugs in renal insufficiency

Drug	Adjustment for renal insufficiency	
	GFR=10–50 ml/min	GFR <10 ml/min
Atenolol	50%	25%
Verapamil	=	50–75%
Hydralazine	8 ч	q8–16h, 75%
Hydrochlorothiazide	=, no effect	X
Zofenopril	50%	25%
Captopril	=	50%
Lisinopril	50%	25%
Methyldopa	0.25–0.5 g q8–12h	0.25–0.5 g q12–24h
Nadolol	50%	25%
Ramipril	50%	25%
Reserpine	=	50%
Spironolacton	q12–24h	X
Enalapril	=	50%

Note: X – to avoid appointment, = – no change. GFR=10–50 ml/min approximately corresponds to serum creatinine of 170–880 mcmmol/l or 2–10 mg/dl or urea of 25–40 mmol/l.

Particular diagnostics of kidney diseases

Severe hypertension (DBP >110 mmHg) is relative contraindications for kidney biopsy. In this case it is recommended infusion of antihypertensive drug (nitroprusside sodium, trimethaphan) during a puncture and 2–3 days after it.

Particular treatment of renal insufficiency

Anemia treatment with erythropoietin accompanies with BP rising in 18–45% of cases, owing to vasoconstriction and hematocrit growth. Treatment of erythropoietin-induced hypertension includes

the control of CDV, augmentation of a dose of antihypertensive drugs and, in some cases, a decline of erythropoietin dosage or change way from intravenous to subcutaneous.

In 20–25% of patients on hemodialysis severe lowering of BP (SBP on 30 mmHg and more) develops.

Let's notice, that treatment with lisinopril increases the risk of an anaphylactic shock in patients on dialysis with a polyakril-sodium membrane.

In late stages of renal insufficiency hypertension becomes refractory and the hemodialysis or renal transplantation is required for adequate control of BP. Ultrafiltration regimen of hemodialysis is applied in refractory hypertension.

It is recommended low doses of aspirin and statin in patients of 50 years and more with hypertension and moderate renal insufficiency (serum creatinine >115 $\mu\text{mol/l}$) even in the absence of CAD (HOT; ESC, 2007). The good control of BP is necessary for lowering risk of intracranial hemorrhages.

Sexual Dysfunction

Frequency of all sexual dysfunctions reaches 43% of women, and 31% of men in the USA (NHSLs, 1992). Frequency of erectile dysfunction is raised with the years: from 4% in 50 years, 26% in 50–59 years and 40% in 60–69 years old (Health Professional Follow-Up Study).

Among the population with a normal BP frequency of erectile dysfunction is about 7%, in not treated hypertension – 17%, and in treated hypertension – 25%. These results reflect to influence of cardiovascular disease and drugs on erectile function.

NEUTRAL EFFECT

alfa₁-blockers, beta₁-blockers (bisoprolol, metoprolol), calcium antagonists, ARBs, ACE inhibitors, peripheral vasodilators.

In TOMHS study in patients with soft hypertension after 4 years of treatment with acebutolol (400 mg/day), amlodipine (5 mg/day), doxazosin (2 mg/day) and enalapril (5 mg/day) frequency erectile dysfunction was not above, than in placebo group.

UNDESIRABLE EFFECT

beta₁-blockers (atenolol, nadolol), labetalol, lisinopril.

Nadolol and atenolol cause sexual dysfunction in 2–3% of cases. Lisinopril can cause temporal sexual dysfunction which passes without stop of treatment within 4 months. Sometimes in long intake of labetalol the ejaculation is disturbed.

UNFAVOURABLE EFFECT

alfa₂-agonists, nonselective beta-blockers, thiazides, reserpine, spironolactone.

Thiazides in high doses (for example, hydrochlorothiazide of 50–100 mg/day) cause erectile dysfunction in 4–32% of cases. It should be noted, that now thiazides are applied in small doses, which not influence on erectile dysfunction rate. For example, in TOMHS study in patients with soft hypertension after 2 years of chlorthalidone intake in a small dose (15 mg/day) frequency of erectile dysfunction was above, than in treatment with amlodipine, acebutolol, enalapril and placebo. However after 2 years results in all groups did not differ.

Spironolactone blocks link of dihydrotestosterone with androgenic receptors and causes erectile dysfunction in 30% of cases.

Nonselective blockade of beta-adrenoreceptors can lead to reduction vasodilating effect mediated by beta₂-adrenoreceptors. Vasoconstriction is developed because of activation of alfa₁-adrenoreceptors, that reduces blood filling of corpora cavernosa and erection. Erectile dysfunction is registered in 10–15% of patients treated with nonselective beta-blockers. Especially high frequency of erectile dysfunction is observed in use of high doses of drugs.

Methyldopa and clonidine cause erectile dysfunction in 20–30% patients. Methyldopa reduces libido in 17% of cases. Reserpine not only reduces libido and erection, but also can break spermatogenesis.

Table 1–5. Influence of antihypertensive drugs on sex function(Kochar M.S. et al, 1999).

Drug	disorders of erection	reduction of libido	disorders of ejaculation	priapism
thiazides	+	+	+	–
spironolactone	+	+	–	–
beta-blockers	+	+	–	–
alfa ₁ -blockers	+	+	–	–
alfa ₂ -agonists	+	+	+	–
peripheral vasodilatators	+	–	–	+
ACE inhibitors	–	–	–	–
calcium antagonists	–	–	–	–

Particular treatment of erectile dysfunction

For erection improvement sildenafil, which dilates arterioles and amplifies blood filling of corpora cavernosa, now is widely used. In 1 hour after drug intake BP is usually decreased on 8–10/5–6 mmHg, and in 4 hours return to pretreatment level. In patients with poor control of hypertension (BP >170/110 mmHg) risk of side effects of sildenafil is raised significantly.

Iohimbin is effective in psychogenic erectile dysfunctions, but elevates BP and contraindicated in severe hypertension.

Combination treatment

The combination of sildenafil and amlodipine is safe. The data about combination of sildenafil with other antihypertensive drugs are insufficient. It should be noted, that sildenafil is not indicated during treatment by nitroprusside sodium in view of dangerous hypotension risk.

Local injections of alprostadil causes prolonged erection in patients treated with and beta-blockers. Iohimbin is selective antagonist of alfa₂-adrenoreceptors and it is not applied together with alfa₂-agonists.

Sexual intercourse

Let's notice, that during orgasm BP may raises to 200/130 mmHg at persons without hypertension, therefore for patients with hypertension preventive antihypertensive drugs (calcium antagonists, ACE inhibitors) are useful.

Mental disorders

Alcohol use disorders

Alcohol abuse

Regular long reception more than 30 ml of ethanol (2 drinks, 60 ml of whisky, 300 ml of wine, 720 ml of beer) a day can cause secondary hypertension. The hypertensive effect of ethanol is dose-dependant and SBP is raised in larger degree. In these cases the refusal from alcohol can lead to normal BP after 1–14 days. Besides, alcohol promotes BP elevation in patients with hypertension.

At the same time, moderate drinking, reduction of alcohol use on 20 ml/day has not lowered significantly BP in patients with hypertension according to PATHS trial.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, calcium antagonists (amlodopine, diltiazem, verapamil), labetalol.

UNDESIRABLE EFFECT

ACE inhibitors (enalapril, lisinopril), beta-blockers, calcium antagonists (nifedipine, felodipine), diuretics, peripheral vasodilatators.

Intake of diuretics quite often causes an orthostatic hypotension and a syncope if man has drunk before. Besides, diuretics can aggravate electrolytic disorders (hypokalemia, hypomagnesemia).

Ethanol unpredictably strengthens hypotensive effect of beta-blockers, hydralazine, enalapril, nifedipine and felodipine. Besides, irregular intake of beta-blockers raises the risk of withdrawal syndrome. Lizinopril can strengthen alcohol effects.

UNFAVOURABLE EFFECT

alfa₂-agonists, reserpine.

Intake of alcohol together with clonidine can cause dangerous hypotension. The risk of clonidine withdrawal is raised in irregular drug intake. Joint intake of antipsychotic reserpine and alcohol is dangerous.

Particular treatment of alcohol abuse

In the presence of severe hypertension sensitising treatment by disulfirame is contraindicative.

Alcohol withdrawal

It is known, that sympathetic activity and BP are raised in alcohol withdrawal, sometimes considerably. It is prescribed antihypertensive drugs if hypertension leads to headaches, dizziness and other symptoms.

FAVOURABLE EFFECT

clonidine, beta-blockers.

Clonidine and beta-blockers normalize BP and weaken autonomic symptoms of alcohol withdrawal which remain after benzodiazepine detoxication. During detoxication clonidine and beta-blockers are not recommend to apply with benzodiazepines. Autonomic blockers mask changes of heart rate and BP, which are indicators of titrated sedation. These drugs do not prevent cramp and delirium. Moreover, beta-blockers may induce psychoses during the early withdrawal syndrome.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, ARBs, calcium antagonists.

UNDESIRABLE EFFECT

diuretics.

Diuretics can aggravate electrolytic disorders (hypokalemia, hypomagnesemia), often occurring in the alcohol abuse, and consequently are undesirable.

Activity with high attention

In many situations high attention and fast reaction are necessary for patients. For drivers it is important to exclude intake of drugs which can reduce attention and psychomotor skills.

NEUTRAL EFFECT

ARBs, ACE inhibitors, alfa₁-blockers, beta-blockers hydrophilic, beta-alfa-blockers, calcium antagonists, diuretics, peripheral vasodilators.

Dizziness is required certain care with ACE inhibitors intake, especially when the treatment begins. Diuretics, especially in the first week of treatment, raise diuresis frequency. At the start of nifedipine treatment transport driving is not recommended.

UNDESIRABLE EFFECT

alfa₂-agonists, lipophilic beta-blockers, reserpine.

Lipophilic beta-blockers (metoprolol, oxprenolol, propranolol) reduce rate of psychomotor skills. Drugs with sedative effect (clonidine, reserpine) in the given situation are not indicated.

Anxiety disorders

Anxiety disorders occur in 10–14% of outpatients and in 11–30% of inpatients. The anxiety is usually accompanied by high sympathetic activity and elevation of BP. On the other hand, poorly controlled hypertension promotes anxiety.

In patients with benign adrenal or extra-adrenal tumor of chromaffin tissues (pheochromocytoma) fits resembling panic attacks develop. Hypertensive crises are quite often accompanied by symptoms reminding panic attacks.

FAVOURABLE EFFECT

beta-blockers, clonidine.

Beta-blockers and clonidine may reduce frequency of panic attacks and attenuate anxiety symptoms.

POSSIBLE EFFECT

reserpine.

Reserpine is neuroleptic agent and may diminish anxiety.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, ARBs, calcium antagonists, diuretics, peripheral vasodilators.

Combination treatment

Extrapyramidal effect of reserpine and methyldopa sharply amplifies in combination with phenothiazines and butyrophenones derivatives.

Interaction of antidepressants and tranquilizers with antihypertensive drugs is surveyed in section of mental disorders.

Depressive disorders

Depression is three times more often in patients with hypertension than without it. Mood disorders in patients with hypertension or cerebrovascular diseases are considered in the concept of vascular depression.

Depression in patients with hypertension is associated with elevation of stroke risk twice, and heart failure risk more than twice (SHEP).

In patients with raised production of corticosteroids (hypophysis adenoma or adrenal tumor) are quite often observed symptoms of severe depression. Suicidal thoughts or intentions are revealed in 10% of patients with hypercorticism.

NEUTRAL EFFECT

alfa₁-blockers, ARBs, ACE inhibitors, hydrophilic beta-blockers, beta-alfa-blockers, calcium antagonists, diuretics, hydralazine, methyldopa.

Hydrophilic beta-blockers (atenolol, nadolol) transfer through lipid layer of hematoencephalic barrier badly and have a small influence on affective state. Labetalol and carvedilol induce depression very rarely. Antidepressive properties of verapamil and ACE inhibitors are confirmed insufficiently.

UNDESIRABLE EFFECT

lipophilic beta-blockers, clonidine.

There are inconsistent data about relationship of lipophilic beta-blockers (metoprolol, propranolol, timolol) and depression. Higher frequency of depression after propranolol intake is not revealed.

During beta-blockers treatment (selective or nonselective) can develop fatigue or weakness which usually pass within several weeks without special treatment. Only in rare instances it is required to lower dose or to cancel drug.

The analysis of 44 studies of clonidine treatment has revealed depression in 1.5% of patients with hypertension. It should be noted, that clonidine can be used for treatment of refractory manic episodes.

UNFAVOURABLE EFFECT

reserpine.

Reserpine and reserpine-containing drugs cause depression in 5–20% of patients. Reserpine depression is caused by reduction of monoamines in brain, while both TCA and MAO inhibitors raise

norepinephrine concentration in synapses. Depression depends of reserpine dose and is more when patients intake >0.5 mg of reserpine a day.

Combination treatment

Pindolol accelerates the SSRIs action which is usually developed on 2–4 week. ACE inhibitors slow down lithium excretion.

In more details combination treatment with antidepressants is discussed below.

Sleep disorders

Sleep disorders occur in 20–30% of population and can induce hypertension. On the other hand, the night rising of BP leads to sleep disorder.

BP monitoring reveals nondipper status in 15–20% of patients with hypertension. Nondipper status includes persons in whom there is an absence of the normal nocturnal fall in BP (<10% from day levels). Besides, nondipper status includes nightpeaker status with increasing of nocturnal BP. The such profile of BP is an independent risk factor of MI and stroke, its frequency increases in 1.5–2 times. In cases of nondipper the malignant hypertension, severe hypertension with organs damages, heavy diabetes, secondary hypertension, renal insufficiency, preeclampsia or night apnoea are often met.

Quite often the BP decreases is superfluous («extreme-dipper») at night, that can lead to a angina, myocardial infarction, transient ischemic attack and a stroke. The risk of latent and symptomatic cardiovascular complications at elderly age is especially high at night.

POSSIBLE EFFECT

clonidine, reserpine.

Drugs with sedative effect can improve sleeping and increase duration of sleep.

NEUTRAL EFFECT

ARBs, ACE inhibitors, alfa₁-blockers, beta-blockers hydrophilic, calcium antagonists, diuretics, peripheral vasodilators.

It is necessary to order diuretics so, that their maximal effect do not develop night. Probably, calcium antagonists and ACE inhibitors decrease night BP better, than other antihypertensive drugs.

UNDESIRABLE EFFECT

lipophilic beta-blockers, methyldopa.

Lipophilic beta-blockers (propranolol, metoprolol, oxprenolol) and methyldopa can provoke sleep disorder.

Rheumatic diseases

Gout

Hyperuricemia and raised BP are often combined. For example, patients with hypertension in 22–38% have hyperuricemia, and patients with gout in 25–50% have hypertension. At the same time, it is not revealed correlation between serum uric acid and BP.

POSSIBLE EFFECT

ACE inhibitors, ARBs, tienil acid.

Losartan raises uric acid excretion 2 times and reduces concentration of uric acid in blood on 8–16%. At the same time, such effect has not been shown for other ARBs (candesartan, eposartan).

ACE inhibitors can lower serum uric acid in patients with hyperuricemia. Besides, captopril is structurally similar to penicillamine and has mild antiinflammatory effect.

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, beta-blockers, calcium antagonists, peripheral vasodilators, reserpine.

Clonidine has analgetic property in dose of 200 mcg and can be used for pain control in patients with chronic arthritis.

UNDESIRABLE EFFECT

thiazides.

Thiazides are not indicated in gout as they cause hyperuricemia. However, gout is not developed in patients without other risk factors of gout, even in case of long-term intake of thiazides. For example, gout has developed only in 0.4% of patients who were receiving thiazides during 5 years (HDFP).

It is necessary to consider presence thiazides in many combined antihypertensive drugs. Aspirin in small doses can cause gout exacerbation and is contraindicated in severe gout.

Psoriasis

Osteoporosis

It is revealed more frequent disturbances of calcium metabolism in hypertension. For instance, elderly women with hypertension have lost calcium more and have lower femoral neck bone mineral density.

Thiazides reduce calcium excretion by 25–40% and decrease on the third frequency of hip fractures in postmenopausal women. In elderly patients the antihypertensive drugs causing orthostatic reactions (alfa₁-blockers, alfa₂-agonists, dihydropyridines, peripheral vasodilators), raise risk of fractures.

Combination treatment

Preparations of calcium and vitamin D used for osteoporosis prevention, do not reduce risk of fractures but can weaken antihypertensive effect of calcium antagonists.

Psoriasis occurs in 1–2% of population. In patients with psoriasis an appointment of beta-blockers can induce exacerbation of skin disease. Smoking associates with rising of psoriasis risk on 78%.

Systemic lupus erythematosus

Approximately in half of cases the lupus nephritis associates with hypertension. Quite often systemic lupus erythematosus combined with secondary hypertension. According to the Swedish case-control trial a history of hypertension (odds ratio 3.7), drug allergy (odds ratio 3.6) were significantly associated with an increased risk of systemic lupus erythematosus.

In the given situation it is necessary to know, that some antihypertensive agents are capable to cause systemic lupus erythematosus (to 3–4% of all cases of disease) and to worsen autoimmune reactions.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, alfa₂-agonists, ARBs, beta-blockers, calcium antagonists, diuretics, reserpine.

Calcium antagonists are drugs, whose antihypertensive effect is not lowering in joint intake with NSAID.

Rather rare cases of drug-induced systemic lupus erythematosus are described for methyl dopa, beta-blockers, indapamide, chlorthalidone and reserpine.

Methyl dopa intake in 20% induces positive Coombs' test, and in 1% causes an autoimmune hemolytic anaemia.

Long beta-blockers intake can induce lupus erythematosus-like syndrome with positive test on antinuclear antibodies, myalgia, arthralgia and arthritis. Lupus erythematosus-like syndrome may be

caused by reserpine, indapamide and chlortalidone rarely. Labetalol can cause occurrence of antinuclear antibodies in the blood.

UNDESIRABLE EFFECT

ACE inhibitors, hydralazine.

Hydralazine and the combined preparations in long application can cause lupus erythematosus-like syndrome on 6-24 months of treatments in 10–20% of patients. Given complication is promoted in presence of heart failure, renal insufficiency and slow acetylation in the liver.

ACE inhibitors increase (to 7%) the risk of neutropenia in patients with systemic lupus erythematosus. Besides, ACE inhibitors (captopril, lisinopril) can cause lupus erythematosus-like syndrome. For example, elevated level of antinuclear antibodies in the blood, ESR acceleration and joint pains are described in patients treated with lisinopril.

Cardiovascular disorders

Arrhythmias

Sinus node dysfunction

Sinus node dysfunction may be caused by structural changes of atrial myocardium in hypertension. It is shown by severe bradycardia or sinus pauses.

Bradyarrhythmia may induce systolic hypertension, caused by accumulation of blood in the left ventricle during long diastole and augmentation of systolic stroke volume.

POSSIBLE EFFECT

dihydropyridines, peripheral vasodilators.

Drugs with vasodilating effect cause a reflex rising of sympathetic activity and can be used in secondary sinus node dysfunction. At the same time nifedipine influences transmembrane potential of sinus node to similarly verapamil and though this effect is masked by reflex sympathicotonia, it is necessary to observe certain care.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, diuretics.

Diuretics can raise the heart rate only in severe hypokalemia or hypovolemia. Alpha-blockers, despite vasodilating action, seldom raise the heart rate significantly.

ACE inhibitors detain potassium and increase serum potassium. Therefore at the start of ACE inhibitors intake monthly test of serum potassium is recommended. In order to avoid undesirable effects of ACE inhibitors it is better to combine ones with thiazides.

UNFAVOURABLE EFFECT

alfa₂-agonists, beta-blockers, beta-alfa-blockers, diuretics, moxonidine, nondihydropyridines, reserpine.

Beta-blockers with intrinsic sympathetic activity have smaller negative chronotropic effect. Diltiazem suppresses sinus node weaker, than verapamil. Though labetalol does not cause sinus bradycardia in patients with sinus node dysfunction its prevailing beta-blocking activity can be dangerous. Reserpine has parasympathetic activity.

Atrioventricular block

A damage of the cardiac conduction system may be in patients with hypertension. In this case it is necessary to consider drugs influence on the cardiac conduction system. It should be noted, that reduction of HR can cause systolic BP elevation.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, ARBs, dihydropyridines, diuretics, methyldopa, moxonidine, reserpine.

ACE inhibitors are capable to raise serum potassium that can worsen AV conduction. Therefore at the start of treatment monthly test of serum potassium is recommended. It is desirable to combine the ACE inhibitors with thiazides.

In patients with severe hypertensive heart dihydropyridines may strengthen AV conduction.

UNDESIRABLE EFFECT

nifedipine, peripheral vasodilators.

At distal AB block reflex rising of sympathetic activity and frequency of impulses in sinus node can lead to paradoxical intensifying of bradycardia.

UNFAVOURABLE EFFECT

alfa₂-agonists, beta-blockers, nondihydropyridines, moxonidine.

Verapamil, diltiazem and beta-blockers suppress AV conduction. There are described AB block of 1-2 degrees during reception of alfa₂-agonists (clonidine, guanfacine).

Tachyarrhythmias

Long-term and severe hypertension may cause structural changes of heart, for example, myocardial hypertrophy and dilatation of the left auricle. The risk of arrhythmias increases in these cases.

In the given situation antiarrhythmic effect of antihypertensive drugs can be important as well as the reducing of left ventricular hypertrophy.

FAVOURABLE EFFECT

beta-blockers, nondihydropyridines.

Calcium antagonists (verapamil, diltiazem) and beta-blockers are applied to treatment of supraventricular tachyarrhythmias and rare ventricular tachyarrhythmias. Atenolol controls the heart rate in atrial tachycardias better, than other beta-blockers.

POSSIBLE EFFECT

ACE inhibitors, alfa₁-blockers, alfa₂-agonists, ARBs.

The antiarrhythmic effect of alfa₁-blockers is shown in some studies. Clonidine can be used for the heart rate control in supraventricular tachycardias.

ACE inhibitors and ARBs can lower frequency of first-detected and recurrent atrial fibrillation in patients with HF (SOLVD, CHARM, Val-HeFT).

NEUTRAL EFFECT

moxonidine, reserpine.

Reserpine is contraindicated in AED.

UNDESIRABLE EFFECT

beta-blockers with ISA, calcium antagonists, diuretics, peripheral vasodilators, reserpine.

Thiazides in high doses (hydrochlorothiazide ≥ 50 mg/day) are capable to cause potassium deficiency and to raise risk of tachyarrhythmias. For antihypertensive aim it is recommended small doses of drugs (hydrochlorothiazide 12.5 mg/day) with low risk of potassium deficiency.

Treatment with indapamide demands control of QT interval because the augmentation of the latter can be associated with higher risk of life-threatening ventricular arrhythmia "torsade de pointes".

Beta-blockers with ISA (oxprenolol, pindolol, acebotolol) can rise frequency of ectopic ventricular arrhythmias.

Peripheral vasodilators and dihydropyridines activate sympathetic nervous system and may increase heart rate during a tachycardia.

Combination treatment

Nifedipine reduces quinidine level in the blood, but verapamil and diltiazem raise it. Effects of anaesthetics used before AED are potentiated by clonidine. The indapamide enlarges QT interval that may be dangerous necessary in cases of intake of class 1A or 3 antiarrhythmic drugs. Even the small hypokalemia is caused by diuretics, can be dangerous in patients with long QT interval.

Coronary artery disease

It is known, that the hypertension is the major risk factor for CAD, and the decreasing of BP reduces this risk (MRC, IPPPSH, HAPPY, SHEP). For example, in SHEP trial frequency of CAD in effective antihypertensive therapy has decreased on 27% (4.4% against 5.9%). At the same time, the lowering of DBP less than 55-60 mmHg is accompanied by rising of risk of cardiovascular events, including MI.

In patients with CAD the risk of coronary events is increasing according to BP rising (MRFIT). On the other hand, in patients with CAD depression of BP has led to reduction of risk of cardiovascular events in 3 trials (EUROPA, ACTION, CAMELOT), excluding PEACE. Antihypertensive treatment in patients after MI has considerably lowered cardiovascular morbidity and mortality (OPTIMAAL, VAMI). Positive effects of BP reduction did not depend of treatment type (ICVEST, ALLHAT).

It is recommended to achieve target BP $\leq 130/80$ mmHg in patients with CAD (ESC, 2007). Secondary hypertension less raises risk of atherosclerosis in comparison with essential hypertension.

Stable angina pectoris

The combination of hypertension and angina pectoris often occurs in clinical practice. On the one hand, hypertension increases myocardial requirement for oxygen, on the other hand, the myocardial ischemia promotes BP elevation that allows to enlarge myocardium blood supply.

In patients with stable angina pectoris BP depression by different drugs, for example ACE inhibitors or calcium antagonists, leads to reduction of coronary events frequency (EUROPA, CAMELOT, ACTION, but not PEACE).

In the given situation it is necessary to prefer antihypertensive drugs, effective in CAD. It is needed to lower BP cautiously, because of risk of coronary blood flow deterioration. In some patients fast lowering BP leads to the decrease of exercise tolerance. It should be noted, that «J-curve hypothesis» with increasing mortality in DBP $< 85-80$ mmHg, is not confirmed in HOT trial. However the analysis of patients with CAD was not made.

FAVOURABLE EFFECT

beta-blockers without ISA, calcium antagonists.

Beta-blockers without ISA and calcium antagonists are basic anti-anginal drugs, therefore their combination in patients with angina pectoris and hypertension is especially justified.

Beta-blockers are drugs of choice because they prevent sudden death and reduce mortality in patients after MI or with HF.

Calcium antagonists are prescribed in cases when beta-blockers are contraindicated. Calcium antagonists are useful in variability of exercise tolerance or severe sensitivity to cold. It is shown, that the slow-releasing nifedipine and verapamil are effective for stable angina pectoris as beta-blockers (APSYS, TIBET). The treatment with beta-blockers (\pm diuretic) or verapamil (\pm ACE inhibitors) leads to equal frequency of new coronary events in patients with CAD (INVEST).

Committee FDA admits for the treatment of stable angina pectoris amlodipine, slow-releasing nifedipine, nisoldipine and felodipine.

POSSIBLE EFFECT

beta-blockers with ISA, beta-alfa-blockers.

Beta-blockers with ISA do not increase survival rate of patients with CAD and are less effective in angina pectoris of small loads. Labetalol and carvedilol raise exercise tolerance in patients with exercise-induced angina pectoris.

NEUTRAL EFFECT

ACE inhibitors, alfa₂-agonists, ARBs, diuretics.

Clonidine can raise frequency of smoking cessation and reduce withdrawal symptoms. In EUROPA trial in patients with stable CAD without obvious HF treatment with perindopril during 4 years was associated with depression of complications risk (cardiovascular mortality, MI, sudden death) on 20%. Other researches had shown inconsistent conclusions. For example, in HOPE trial treatment with ramipril of patients with CAD was associated with lowering of mortality, risk of MI, worsening and new angina and coronary revascularization rate. At the same time according to QUIET study quinapril did not improve clinical and angiographic indicators within 3 years of observation. Efficiency of trandolopril and enalapril is not shown in PEACE and CAMELOT studies. ACE inhibitors did not reduce restenosis rate after stent implantation, but have even strengthened restenosis in the PARIS study.

UNDESIRABLE EFFECT

alfa₁-blockers, moxonidine, peripheral vasodilators, reserpine, short-acting dihydropyridines (nifedipine, nisoldipine, nicardipine, isradipine).

In some cases vasodilators lead to worsening of angina owing to tachycardia, fast drop of BP and «steal syndrome». For example, such negative effect is noted in 12% of patients treated with short-acting nifedipine.

The treatment for unstable angina with short-acting nifedipine in a dose >40 mg/day increases risk a MI and mortality in patients with unstable angina (HINT; Furberg C.D. et al, 1995). At the same time in combination with beta-blockers nifedipine improved the forecast (HINT). Long anti-hypertensive treatment with isradipine raised frequency of cardiovascular events (MI, angina pectoris and sudden death) in MIDAS study.

In 90% of cases of minoxidile intake the depression of ST segment and negative T wave in leads V₄₋₆ develops in the first 2 weeks. It is necessary to apply reserpine with care in patients with severe angina pectoris. Moxonidine is not indicated in unstable angina.

Combination treatment

It is undesirable to combine alfa₂-agonists, reserpine, labetalol with beta-blockers or nondihydropyridines in view of bradycardia risk. In the case of discontinuing of combined therapy with beta-blockers and clonidine the first should be canceled a beta-blocker, thereafter step-by-step reduce dosage of clonidine. Dihydroergotamine (component of combined antihypertensives) intake can lower antianginal action of nitroglycerine.

The ACE inhibitors with or without SH-groups, potentiate antiischemic action of nitrates and calcium antagonists in patients with CAD. Besides, ACE inhibitors and ARBs may reduce nitrates resistance.

Variant angina

The variant angina is caused by epicardial coronary artery spasm. In some cases there is arterial tonus influences on stress-induced angina. It is shown in lability of myocardial ischemia threshold and «pass through a pain».

FAVOURABLE EFFECT

calcium antagonists.

Calcium antagonists are drugs of choice in variant angina and are effective in 80% of patients.

POSSIBLE EFFECT

alfa₁-blockers.

Alfa₁-blockers (prazosin) may reduce variant angina. These drugs can be used in refractory variant angina in addition to calcium antagonists and nitrates if such combination does not cause severe hypotension.

NEUTRAL EFFECT

alfa₂-agonists, diuretics, ARBs, ACE inhibitors, peripheral vasodilators.

ACE inhibitors can strengthen anti-ischemic effect of nitrates and calcium antagonists in patients with CAD. Moreover ACE inhibitors reduce nitrate tolerance.

UNDESIRABLE EFFECT

beta-blockers, beta-alfa-blockers, peripheral vasodilators, reserpine.

In some cases beta-blockers amplify variant angina. Beta-blockers with ISA and labetalol have less vasospastic reactions. In patients with severe angina pectoris it is necessary to apply reserpine with care.

UNFAVOURABLE EFFECT

ergot alkaloids.

Ergot alkaloids entering into combined drugs, can provoke vasospasm and even are recommended as test for variant angina.

Secondary prevention of CAD

The primary goal of treatment after MI consists in the prevention of reinfarcts and sudden death which frequency is especially high within the first year. Target BP in patients with previous MI must be <130/80 mmHg (ESC, 2007).

FAVOURABLE EFFECT

beta-blockers without ISA.

Beta-blockers without ISA is the basic agents for secondary prevention, especially after Q-wave MI. Long-term treatment with beta-blockers decreases mortality on 20–25%.

POSSIBLE EFFECT

ACE inhibitors, nondihydropyridines.

ACE inhibitors raise survival in patients with heart failure or systolic dysfunction of left ventricle. The positive effect of treatment with ramipril remained within 5 years in AIREX study.

The diltiazem and verapamil significantly reduced frequency of death and reinfarction in patients with concomitant hypertension in DAVIT II and MDPIT studies.

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, beta-blockers with ISA, beta-alfa-blockers, diuretics, dihydropyridines, reserpine.

UNDESIRABLE EFFECT

nifedipine, peripheral vasodilators.

Short-acting nifedipine is dangerous during first 1–2 weeks after MI (SPRINT II). Beside, short-acting nifedipine in dose >40 mg/day increases mortality in patients after MI with hypertension (Furberg C.D. et al, 1995; INTACT).

Intake of the powerful vasodilators causes nonoptimal redistribution of coronary blood flow and is undesirable.

Dyslipidemia

Hypertension and dyslipidemia are often combined. For example, according to research NHANES II about 40% of patients with hypertension have serum cholesterol of 6.2 mmol/l and more. On the other hand, 4% of patients with hypercholesterinemia ≥ 6.2 mmol/l have increased BP.

The combination of dyslipidemia and hypertension considerably enlarges risk of CAD. Below it is surveyed the influence of antihypertensive drugs on lipid metabolism.

POSSIBLE EFFECT

alfa₁-blockers, peripheral vasodilators.

Alfa₁-blockers reduce blood LDL cholesterol, triglycerides and HDL cholesterol (HALT). Apparently, similar action of peripheral vasodilators possess also.

NEUTRAL EFFECT

ACE inhibitors, alfa₂-agonists, ARBs, beta-blockers with ISA, beta-alfa-blockers, calcium antagonists, diuretics (clopamide, indapamide), reserpine.

The treatment with lacidipine, the antagonist of calcium with expressed membranostabilising effect, has led to reduction of 40% in carotids thickness at ultrasonic visualization, in comparison with atenolol.

In the research ASCOT-LLA treatment with atorvastatin has lowered risk of cardiovascular events and CAD on 53% in patients, accepting amlodipine, and only on 16%, accepting atenolol.

UNDESIRABLE EFFECT

beta-blockers without ISA, diuretics, methyldopa.

High doses of thiazides are capable to cause the rising of LDL cholesterol on 0.13–0.26 mmol/l. According to LRC-CPPT trial in thiazide-treated patients the level of LDL cholesterol was more low, than in patients who do not received thiazides.

Beta-blockers without ISA can lower HDL cholesterol and raise triglycerides slightly, variably influencing on total cholesterol. The diet with low content of saturated fat and cholesterol allows to prevent or weaken adverse effects of thiazides and beta-blockers.

Drug-induced dyslipidemias usually pass in treatment by these drugs within a year. At the same time beta-blockers and diuretics have lowered risk of stroke and CAD in elderly patients in SHEP trial. Meta-analysis of 4 studies has shown, that beta-blockers authentically reduced volume of plaques according to intravascular investigation. According to recommendations of the National Cholesterol Education Program it is not necessary to avoid administration of beta-blockers and thiazides even in the presence of dyslipidemia, especially in cases when these drugs are especially indicated (for example, after a MI).

Methyldopa reduces level HDL cholesterol and raises level of triglycerides.

Combination treatment

Nicotinic acid can strengthen antihypertensive effect of vasodilating drugs. In case of intake of bile acid sequestrants it is recommended to accept other drugs 1 hour prior to or in 4 hours after lipid lowering drugs.

Heart failure

High systolic or diastolic BP elevates risk of HF 2–3 times. The risk of HF is especially high in elderly and Afro-Americans with hypertension. HF was registered in 40% of men and 60% of women with hypertension according to Framingham Heart Study.

Long-term antihypertensive treatment with diuretics and beta-blockers reduces risk of HF almost half in SHEP study. The same result was shown in five large trials (SHEP, Syst-Eur, EWPHE, STOP, UKPDS) in which long-term antihypertensive treatment lowered HF risk on 45%.

In patients with severe chronic HF and low cardiac output hypertension is registered infrequently.

It is recommended to reduce BP to 130/80 mmHg and lower to patients with HF (ESC, 2005).

Dyastolic heart failure

Quite often hypertension leads to left ventricular hypertrophy that allows to output sufficient volume of blood against increased BP in the aorta. However the severe left ventricular hypertrophy

may impair relaxation, decrease ventricular compliance and elevate end-diastolic pressure of left ventricle and pulmonary congestion.

Left ventricular diastolic dysfunction occurs in 84% of patients with hypertension, and among patients with HF and normal ejection fraction in 65% of cases the hypertension is revealed.

POSSIBLE EFFECT

ACE inhibitors, ARBs, beta-blockers, diuretics.

Diuretics reduce leg edemas and other symptoms of congestive HF though do not influence on myocardial relaxation. Reducing preload, diuretics diminish BP in the right ventricle and strain of an interventricular septum that can indirectly improve the left ventricular relaxation.

Beta-blockers can improve heart function at the expense of prolongation of diastole and augmentation of left ventricular filling.

ACE inhibitors did not reduce mortality and hospitalization rate, but enlarged term of repeated hospitalization from 47 till 70 days in patients with preserved systolic function (MISCHF). ACE inhibitors do not have essential influence on myocardial relaxation. It should be noted, that the ACE inhibitors-induced cough is observed more often at night and sometimes relieved by orthopnea.

ARBs in high doses can lower frequency of hospitalization of patients with HF (CHARM).

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, beta-alfa-blockers, calcium antagonists.

Calcium antagonists improve myocardial relaxation, however efficiency of drugs in diastolic HF is not proved. The lowering of BP improves diastolic function, irrespective of antihypertensive drug type (VALIDD).

UNDESIRABLE EFFECT

peripheral vasodilators.

Arterial vasodilators can lead to the severe arterial hypotension in patients with diastolic dysfunction. At the same time in V-HeFT-I study combination of hydralazine and isosorbit dinitrate raised survival in patients with the preserved systolic function.

Systolic heart failure

The main cause of systolic dysfunction in patients with hypertension is CAD. At the same time long-term BP elevation can lead to overload of the left ventricle, damage of cardiomyocytes, replacement of the latter by connective tissue and depression of myocardial contractility.

FAVOURABLE EFFECT

ACE inhibitors, ARBs, beta-blockers, carvedilol, diuretics, peripheral vasodilators.

Drugs of choice for the treatment of systolic dysfunction are ACE inhibitors and diuretics which are used even in the absence of hypertension (CONSENSUS I, SOLVD). Thiazides have the greatest antihypertensive effect among diuretics. In ELITE and RESOLVD studies ARBs were as effective, safe, and tolerable as ACE inhibitors in patients with HF, though the antihypertensive effect develops rather slowly.

Beta-blockers reduce mortality in patients with systolic dysfunction of the ischemic and non-ischemic origin (CIBIS-II, MERIT-HF). For the prevention of initial HF worsening is prescribed low dose of beta-blockers with slow titration. It is necessary to expect clinical effect of beta-blockers to 3 months. Beta-blockers reduce myocardial oxygen demand that leads to the awakening of "sleeping" cardiomyocytes and increase of myocardial contractility. Beta-blockers also prevent ventricular fibrillation and sudden cardiac death.

Carvedilol decreases mortality and frequency of hospitalization of patients with ischemic and nonischemic HF (ANZHFS, US Carvedilol). The effect of carvedilol has been shown in class 3-4 HF in COPERNICUS trial. According to SOLVD study combined treatment with beta-blockers and enalapril gives additional lowering of mortality.

In patients with hypertension chlorthalidone reduced risk of HF in comparison with amlodipine and lisinopril (ALLHAT).

The combination hydralazine and isosorbide dinitrate reduces mortality in patients with HF (VHeFT I, VHeFT II) and is recommended in contraindications to ACE inhibitors.

NEUTRAL EFFECT

alfa₂-agonists, amlodipine, felodipine, moxonidine.

Blockade of central imidazole I₁-receptors with moxonidine may decrease of pulmonary capillary wedge pressure in patients with NYHA class 3–4 HF. These data demand confirmation in randomized, placebo-controlled trial.

Amlodipine is quite safe in long-term treatment of patients with severe left ventricular dysfunction. Addition of amlodipine to standard treatment of NYHA class 3–4 congestive HF with EF <30% has not changed mortality in patients with ischemic and nonischemic cardiomyopathy (PRAISE–II). Felodipine also did not influence on mortality and frequency of hospitalization of patients with HF (V–HeFT III).

UNDESIRABLE EFFECT

alfa₁-blockers, dihydropyridines, diltiazem, reserpine.

Alfa₁-blockers reduce preload, however do not rise survival of patients with LV systolic dysfunction. In comparison with chlortalidone, doxazosin had raised risk of HF approximately 2 times and this branch of ALLHAT trial was stopped prematurely.

Nifedipine weakly suppresses myocardial contractility and this negative effect is usually overlapped by afterload reduction. However in severe HF nifedipine can strengthen the left ventricular dysfunction and is undesirable. Second generation dihydropyridines (nicardipine, isradipine, but not amlodipine) can worsen systolic HF also.

The diltiazem diminish LV contractility and is not recommended in systolic HF. For example, the drug raised risk of HF in the patients after MI in MDPIT study. At the same time in DiDi trial diltiazem prescribed in addition to usual treatment of dilated cardiomyopathy, improved left ventricle function, exercise tolerance and did not worsen the forecast. Reserpine is not indicated in severe HF.

UNFAVOURABLE EFFECT

verapamil.

Verapamil diminish LV contractility and is dangerous in the severe systolic dysfunction of LV (EF <40%, pulmonary congestion).

Table 1–6. Combination treatment.

drug	Drug	effect
beta-blockers, verapamil, reserpine, alfa ₂ -agonists	digoxin	suppression of sinus node and AV conduction
clonidine	digoxin	clonidine reduces digoxin excretion and increases serum digoxin
nitrendipine	digoxin	elevation of serum digoxin on 100%
verapamil	digoxin	elevation of serum digoxin on 60–90%
diltiazem	digoxin	elevation of serum digoxin on 20–60%
nifedipine, nisoldipine	digoxin	elevation of serum digoxin on 20%
carvedilol	digoxin	elevation of serum digoxin on 16%
hydralazine	digoxin	decrease of serum digoxin at the expense elevated renal secretion

Drug-related edema

Dihydropyridines (in 5–70%) and more rare beta-blockers, alfa₂-agonist and alpha-blockers cause edemas of low extremities and simulate worsening of HF, especially in the high doses. In this cases it is necessary to pay attention to absence of pulmonary congestion (dyspnea, wet rales in the lung fields), liver enlargement and cervical veins swelling. For the treatment of the dihydropyridines-

induced edemas it is recommended to replace calcium antagonists for nondihydropyridines, prescribe diuretics and venodilating drugs (ARBs, ACE inhibitors, nitrates).

Left ventricular hypertrophy

The left ventricular hypertrophy is quite often combined with hypertension and is a risk factor for MI, diastolic dysfunction of the heart, arrhythmias, sudden death and stroke. For example, according to Framingham study at the left ventricular mass $>140 \text{ g/m}^2$ frequency of cardiovascular events has increased in 2–4 times.

The assumption, that BP normalization should lead to elimination of the left ventricular hypertrophy, appeared not absolutely exact as for an origin of the left ventricular hypertrophy metabolic factors have great value.

The advantage of reduction of the left ventricular mass has been shown in several large studies. For example, in LIFE study the greater reduction of the left ventricular hypertrophy with losartan associated with reduction of cardiovascular risk. In HOPE trial ramipril reduced the left ventricular mass irrespective of hypotensive effect, but this effect was not correlated with the risk of death, MI, stroke or HF. Similar results were shown in Framingham study.

POSSIBLE EFFECT

ACE inhibitors, ARBs, beta-blockers without ISA, calcium antagonists, diuretics (chlorthalidone, hydrochlorothiazide, indapamide), methyldopa.

The first echocardiographic signs of an involution of the left ventricular hypertrophy can already appear through 4 weeks, and the definitive effect of the drug should be estimated not earlier than 6 months of treatment. Ability to reduce the left ventricular mass is shown for atenolol (ELSA), indapamide (LIVE), ACE inhibitors, calcium antagonists (ELVERA, PRESERVE, FOAM, ELSA) and candesartan (CATCH).

On the comparative analysis the larger hypotrophic effect, including and fibrotic component, is shown in ARBs, ACE inhibitors and, probably, calcium antagonists.

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, beta-blockers with ISA, nisoldipine, reserpine.

Data about influence of clonidine on the left ventricular hypertrophy are inconsistent. There is no information about hypotrophic effect of reserpine.

UNDESIRABLE EFFECT

peripheral vasodilators.

Monotherapy by peripheral vasodilators may increase the left ventricular hypertrophy.

Orthostatic hypotension

In patients with hypertension the orthostatic hypotension is caused as baroreflex dysfunction so venodilating effect of antihypertensive drugs.

The orthostatic hypotension associates with the increased risk of premature death, falling and fractures. Orthostatic hypotension sometimes leads to hypertensive crisis or cerebral circulation disorders in the elderly with polyneuropathy and vascular regulation disorder.

It is recommended to all patients after 50 years and with diabetes periodically to estimate BP at supine and upright position. Orthostatic hypotension is systolic BP decrease of at least 20 mmHg or diastolic BP decrease of at least 10 mmHg within three minutes of standing.

FAVOURABLE EFFECT

ergot alkaloids, beta-blockers.

Ergot alkaloids (dihydroergotoxin) with venoconstricting action and beta-blockers with arterioconstricting action are used for orthostatic hypotension treatment. Combined agents containing a diuretic with venoconstricting effect clopamid and a dihydroergotoxin or beta-blocker are effective too.

POSSIBLE EFFECT

clopamid.

Clopamid is preferable diuretic with unique venoconstricting effect.

NEUTRAL EFFECT

ACE inhibitors, ARBs.

ACE inhibitors have small vasodilating action and orthostatic reactions develop rarely.

UNDESIRABLE EFFECT

alfa₂-agonists, beta-alfa-blockers, calcium antagonists, diuretics, reserpine.

Reserpine, diuretics and calcium antagonists can cause orthostatic reactions. Among calcium antagonists nondihydropyridines have smaller orthostatic effect. Labetalol with alpha-blocking action is capable to cause orthostatic hypotension, however after 1 months of regular intake this effect weakens considerably.

Though alfa₂-agonists cause an orthostatic hypotension, in patients with autonomic insufficiency and the broken reflective vasoconstriction clonidine raises BP at upright position.

UNFAVOURABLE EFFECT

alfa₁-blockers, peripheral vasodilators.

Treatment with peripheral vasodilators and alfa₁-blockers cause orthostatic hypotension. The first dose phenomenon with severe orthostatic hypotension occurs in 16% after prazosin intake. For the prevention this side effect it is recommended to start treatment with 0.5–1 mg in the night. Continuation of treatment weakens severity of orthostatic reactions considerably.

Particular treatment of orthostatic hypotension

For treatment orthostatic hypotension apply the agents raising BP: sodium chloridum (4–16 g/day), midodrine, NSAIDs, mineralocorticoids.

Peripheral artery disease

Claudication occurs in 5% of men and 2.5% of women after 60 years. Sensitive non-invasive tests (duplex ultrasonography, ankle-brachial BP index [<0.8 – intermittent claudication, <0.5 – severe disease], exercise stress-test) peripheral revealed arterial disease, at least, in 3 times more often.

In 80% peripheral arterial disease is caused by the atherosclerosis the development of which is promoted by hypertension. According to Framingham Heart Research in patients with hypertension the risk of claudication increased 4 times more often among men, and 3 times – among women. Claudication associates with the raised risk of CAD and renovascular hypertension.

More often the atherosclerosis damages superficial femoral and popliteal arteries, the distal aorta and its bifurcation. BP lowering may reduce poststenotic blood flow and worsen claudication. Therefore at the beginning BP is reduced no more than 15–20%, and then cautiously is lowered to desirable level (130–140/80–90 mmHg). Now there are not convincing proofs of antihypertensive treatment influence on the degree of arterial obstruction.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, ARBs, calcium antagonists, diuretics, peripheral vasodilators, reserpine.

Peripheral vasodilators does not enhance blood flow substantially in the low extremities and does not facilitate claudication. The drug inefficiency is caused by the fixed stenosis, “steal syndrome” and reduction of pressure gradient in stenosis region.

Before appointment of ACE inhibitors and ARBs it is necessary to exclude bilateral stenosis of renal arteries firstly.

UNDESIRABLE EFFECT

alfa₂-agonists, beta-alfa-blockers, selective beta-blockers.

Beta-blockers raise tonus of peripheral vessels and can strengthen arterial insufficiency of low extremities. At the same time the meta-analysis of treatment with beta-blockers reveals small influ-

ence on walking distance and blood flow in ankle arteries. In patients with CAD and HF administration of beta-blockers reduces mortality and can be used despite the risk of ischemia worsening.

Beta-blockers ISA have less vasoconstrictive effect, but are insufficiently effective in CAD. Treatment with clonidine and beta-alpha-blockers may increase ischemia of soft tissues.

UNFAVOURABLE EFFECT

nonspecific beta-blockers.

Combination treatment

Alprostadil (prostaglandin E₁) can temporarily relieve pain in rest in nondiabetic patients with the severe arterial insufficiency and accelerate the healing of ulcers. This drug strengthens action of antihypertensive drugs and can cause heavy arterial hypotension.

Pentoxifylline and cilostazol (a phosphodiesterase inhibitors with vasodilator and mild antiplatelet properties) approved FDA for claudication treatment and strengthen action of antihypertensive drugs.

Endocrine disorders

Diabetes

Hypertension is revealed in 80% of patients with type 2 diabetes. Approximately in one third of cases hypertension is registered before the diagnosis type 2 diabetes, therefore test for diabetes in patients with hypertension begins earlier and more often, than the usual glycemia control every 3 years above the age of 45 (ADA, 2009).

Elevated BP in patients with type 2 diabetes is caused by essential hypertension and diabetic nephropathy mainly. In patients with type 1 diabetes hypertension is caused by diabetic nephropathy usually. Besides, the long-term any type diabetes can lead to isolated systolic hypertension owing to aorta atherosclerosis.

The combination of hypertension and 1 or 2 type diabetes considerably raises risk macrovascular (stroke, CAD, HF, peripheral arterial disease) and microvascular (nephropathy, retinopathy) complications, and also the total mortality. It is important to notice, that BP decreasing much larger reduces risk of cardiovascular events than strict glycemia control.

According to modern guidelines it is recommended to reduce BP to <130/80 mmHg (JNC-7, EHS/ESC, 2007). Antihypertensive drug treatment is indicated even in high normal BP (130–139/85–89 mmHg).

In patients with diabetes it is necessary to measure BP in upright position because high frequency of orthostatic hypotension.

POSSIBLE EFFECT

ACE inhibitors, ARBs.

Equal reduction of complications risk between amlodipine, chlortalidone and lisinopril in type 2 diabetes group is shown in ALLHAT trial. Similar results are received in comparison of irbesartan and amlodipine (IDNT). Thus for patients with hypertension and diabetes the main effect belongs to lowering BP, instead of drug selection.

The ARBs and ACE inhibitors are prescribed in diabetes in case of first signs of kidneys damage for prevention and treatment of diabetic nephropathy.

ACE inhibitors raise insulin sensitivity that promotes to decline insulin or oral antidiabetic drugs dosages.

NEUTRAL EFFECT

alpha₁-blockers, beta-blockers, diuretics, nondihydropyridines, peripheral vasodilators, reserpine.

Data concerning beta-blockers effect are inconsistent enough. In UKPDS 39 study atenolol and captopril equally reduced risk of macro- and microvascular complications, and also there were no differences in hypoglycemia frequency. Despite elevation of glycemia and diabetes risk the beta-

blockers and thiazides prevented cardiovascular complications in type 2 diabetes even better, than without this disease (UKPDS, SHEP).

At the same time captopril prevented cardiovascular complications (fatal and nonfatal MI, stroke, sudden death) better than beta-blockers and/or diuretics (CAPPP). In LIFE trial losartan lowered total and cardiovascular mortality, stroke risk in larger degree than atenolol.

In carvedilol-treated patients in comparison with metoprolol-treated ones there are lower HbA_{1c} and frequency of microalbuminuria, above insulin sensitivity (GEMINI).

Nonselective beta-blockers reduce insulin production in hyperglycemia reply, reduce insulin sensitivity and increase ketoacidosis risk. Beta₁-blockers are less dangerous, than nonselective drugs, but if the dose of beta-blockers is rising, the selectivity of beta-blockers is decreasing. Beta-blockers can mask hypoglycemic sympathetic signs (except sweating). In diabetic autonomic neuropathy the effect of beta-blockers can be absent.

UNDESIRABLE EFFECT

alfa₂-agonists, dihydropyridines, moxonidine.

Alfa₂-agonists quite often cause mouth dryness which is hyperglycaemic sign. Similar property is taped in moxonidine which causes mouth dryness in 25–30% of patients through 1 month, and 4–10% after 6 months.

There are conflicting data concerning efficiency dihydropyridines in patients with diabetes. According to Syst-Eur trial nitrendipine in patients with systolic hypertension and type 2 diabetes has lowered total mortality (–55%), cardiovascular mortality (–76%), all cardiovascular events (–69%), fatal and nonfatal strokes (–73%), and this effect was more, than in patients without diabetes. Especially favorable effects of nitrendipine were revealed in elderly. In HOT study felodipine also reduced the risk of cardiovascular events in patients with DBP <80 mmHg.

On the other hand, in ABCD and FACET studies in patients with hypertension and type 2 diabetes treated with nisoldipine and amlodipine risk of cardiovascular events (fatal and nonfatal MI, stroke) is higher then in patients treated with ACE inhibitors. Believe, that such results are caused more likely by cardioprotective effects of ACE inhibitors, than side effects of calcium antagonists. According to MIDAS study in patients with glucose metabolism disorder (HbA_{1c} >6.6%) treatment with isradipine leads to triple rising of cardiovascular risk in comparison with those receiving hydrochlorothiazide.

CAD prevention

Patients with types 2 diabetes above 40 years with other risk factors, including hypertension, are recommended aspirin 75-162 mg/day for primary prevention of CAD (ADA, 2008).

Prevention of type 2 diabetes

Type 2 diabetes develops less in patients treated by ACE inhibitors or ARBs, than by beta-blockers, thiazides (INSIGHT, CAPPP, LIFE, SCOPE, ALLHAT) and calcium antagonists (ALLHAT, VALUE). At the same time these drugs are not recommended for primary prevention of type 2 diabetes along with exercise, metformin, rosiglitazone, acarbose and orlistat (ADA, 2008). Vasodilating beta-blockers (carvedilol, nebivolol) do not increase risk of types 2 diabetes.

Diabetic nephropathy

Hypertension promotes kidneys damage and the good BP control is obligatory for patients with early signs of diabetic nephropathy. BP lowering to ≤130/80 mmHg effectively prevent nephropathy and slows down its development (UKPDS).

FAVOURABLE EFFECT

ACE inhibitors, ARBs.

In patients with diabetes ACE inhibitors (types 1–2) and ARBs (type 2) retard nephropathy advance in larger degree, than other antihypertensive drugs. It is evidence of nephroprotective effect of ACE inhibitors and ARBs independent from BP lowering (GISEN, HOPE, RENAAL). Treatment with ACE inhibitors/ARBs is recommended in microalbuminuria occurrence.

The combination of ACE inhibitors and ARBs, apparently, at larger degree reduces proteinuria, than each drug separately. ARBs have more renoprotective effect than amlodipine (IDNT) and atenolol (LIFE) in patients with type 2 diabetes .

POSSIBLE EFFECT

calcium antagonists (diltiazem, verapamil, nicardipine).

Several calcium antagonists (verapamil, diltiazem, nicardipine) reduce proteinuria in diabetic nephropathy, but do not reduce the rate of nephropathy development. The combination of ACE inhibitors and calcium antagonists is not more effective than monotherapy (BENEDICT).

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists, beta-blockers, beta-alfa-blockers, diuretics, dihydropyridines, peripheral vasodilators, reserpine.

In case of satisfactory glycemic control it is not necessary to be afraid of beta-blockers, as shown in research of patients with type 2 diabetes and hypertension where atenolol is compared to captopril (UKPDS).

Diabetes with hypoglycemic reactions

The intensive glucose control (fasting plasma glucose <6 mmol/l) by insulin and oral antidiabetic agents reduces frequency of diabetic microangiopathy, but increases the rate of hypoglycemia (<2 mmol/l).

In this cases agents raising hypoglycemia risk or/and masking hypoglycemic symptoms (weakness, hunger, palpitation, anxiety) may be dangerous. If the patient does not accept carbohydrates in time, neurologic symptoms (disturbance of consciousness, cramp) develop in hypoglycemia.

The basic prevention of hypoglycemia is careful antidiabetic treatment, a timely food and elimination of provoking factors (for instance, alcohol).

NEUTRAL EFFECT

calcium antagonists, diuretics, peripheral vasodilators.

UNDESIRABLE EFFECT

ACE inhibitors, alfa₁-blockers, alfa₂-agonists, beta₁-blockers, beta-alfa-blockers, moxonidine, reserpine.

The alfa₁-blocker, ACE inhibitors and moxonidine raise insulin sensitivity and can increase hypoglycemia risk. Moxonidine enlarges capture of glucose by cells (on 15% for the insulin unit). ACE inhibitors raise risk of hospitalization with serious hypoglycemia.

Alfa₂-agonist (clonidine, methyldopa) can strengthen hypoglycemia at the expense of reduction of glycogenolysis, augmentation gluconeogenesis and mask of hypoglycemic symptoms.

Reserpine has sympatholytic effect and weakens hypoglycemic symptoms. Selective beta₁-blockers do not raise frequency of severe hypoglycemia, but hide hypoglycemic symptoms.

UNFAVOURABLE EFFECT

nonspecific beta-blockers.

Nonspecific beta-blockers reduce hyperglycemic effect of catecholamines and raise frequency of clinically substantial hypoglycemia more than 2 times in patients receiving insulin. In patients taking oral antidiabetic drugs, frequency of substantial hypoglycemia doubles. Besides, beta-blockers hide sympathetic symptoms of hypoglycemia, except sweating.

Combination treatment

Reserpine potentiates sulphonylureas action, that can increase risk to hypoglycemia. Nifedipine and furosemide can strengthen hypoglycemic action of metformin.

Decompensated diabetes

In decompensated diabetes it is necessary to consider the influence of antihypertensive drugs on glycemia that can change a dosage of oral antidiabetic drugs and insulin.

POSSIBLE EFFECT

ACE inhibitors, alfa₁-blockers, moxonidine.

ACE inhibitors are especially effective in diabetic nephropathy as they reduce proteinuria and slow down development of renal insufficiency. Besides, ACE inhibitors raise sensitivity to insulin and promote reduction of a dose of insulin or oral antidiabetic drugs.

Let us notice, that drugs with sulfhydryl group (captopril, zofenopril) can give false positive reaction to acetone if reagent with nitroprusside sodium is used. Some cases of glucosuria after 2–16 weeks of treatment with ACE inhibitors were described.

The alfa₁-blockers and moxonidine raise insulin sensitivity that is useful in insulin resistance.

In case of diabetic neuropathy there can be no effect of alfa₁-blockers and even is paradoxical BP raise.

NEUTRAL EFFECT

ARBs, calcium antagonists, peripheral vasodilators, reserpine.

UNDESIRABLE EFFECT

alfa₂-agonists, beta-blockers, beta-alfa-blockers, diuretics, thiazides, triamteren.

Alfa₂-agonists quite often cause dryness of mouth which is hyperglycemic sign.

Nonselective beta-blockers reduce insulin production in reply to hyperglycemia and enlarge ketoacidosis risk. Selective beta₁-blockers and drugs with ISA are less dangerous, than nonselective beta-blockers without ISA.

Clonidine and beta-blockers may be ineffective in diabetic neuropathy or even BP may raise.

Thiazides promote insulin resistance and can cause impaired glucose tolerance or secondary diabetes in 0.5–1% of patients. The adverse events usually develop on 4 weeks of treatment. After cancel of thiazides these changes pass.

In patients with type 1 diabetes antihypertensive treatment with thiazides have associated higher mortality in comparison with nontreated hypertension. It should be noted, that these results have been received in trials of 70–80 years when high doses of diuretics were prescribed (for example, 50–100 mg/day of hydrochlorthiazide).

Diuretics in small doses (hydrochlorthiazide 12.5 mg/day) are effective and safe agents in type 2 diabetes and, apparently, 1 type. Triamterene can increase the level of blood glucose.

It should be noted, that hyperglycemia caused by antihypertensive drugs, is usually easily eliminated by augmentation of a dose of antidiabetic drugs or insulin.

Hyperthyroidism

The increase of thyroid hormones synthesis (hyperthyroidism) is quite often accompanied by BP increase, mainly systolic, at the expense of rising of heart rate and cardiac output. It should be noted, that the term "thyrotoxicosis" is not synonym of "hyperthyroidism" and means biochemical and physiological manifestation of raised thyroid hormones in blood.

Smoking is a risk factor not only for CAD, but also for hyperthyroidism.

It is necessary to consider influence of antihypertensive drugs on thyroid gland function and hyperkinetic hemodynamic.

POSSIBLE EFFECT

beta-blockers (propranolol).

Beta-blockers are drugs of choice as many manifestations of thyrotoxicosis (palpitation, tremor, alarm) are caused by high sympathetic activity. The last is the result of potentiation of catecholamines action by high level of thyroid hormones. Propranolol in high doses (>120–160 mg/days) retards secretion of thyroid hormones and peripheral transformation of thyroxine into more active triiodothyronine.

Beta-blockers are used for preoperative preparation, after treatment with radioiodine, elimination of thyrotoxicosis symptoms in subacute thyroiditis when thyreostatic drugs are contraindicated. Beta-blockers have replaced reserpine, widely used in these cases earlier.

NEUTRAL EFFECT

alfa₂-agonists, nondihydropyridines, reserpine.

Nondihydropyridines and alfa₂-agonist lower the heart rate. The reserpine with neuroleptic action reduces alarm, but can strengthen depression.

UNDESIRABLE EFFECT

ACE inhibitors, alfa₁-blockers, dihydropyridines, diuretics, peripheral vasodilators, reserpine.

Diuretics and vasodilating drugs are undesirable in hyperkinetic type of hypertension.

Particular treatment of hyperthyroidism

Certainly, the basis of symptomatic hypertension treatment is the suppression of thyroid function by antithyroid drugs or by surgery or radioactive iodine treatment.

Combination treatment

Joint intake of methimazole and ACE inhibitors essentially raises the risk of neutropenia.

Hypothyroidism

The thyroid gland hypofunction is accompanied by BP elevation approximately in half of the cases. In a case of hypothyroidism it is necessary to consider influence of antihypertensive drugs on thyroid function.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, ARBs, diuretics, dihydropyridines, peripheral vasodilators.

UNDESIRABLE EFFECT

alfa₂-agonists, beta-blockers, nondihydropyridines, reserpine.

It is necessary to avoid drugs suppressing sinus node (reserpine, alfa₂-agonist, verapamil, diltiazem, beta-blockers) as the dangerous bradycardia is possible.

Severe depression develops in 10% of patients with hypothyroidism and reserpine and alfa₂-agonists can strengthen mood disorder.

Menopause

In women, as well as in men, the risk of hypertension raises together with years. Raised BP, especially systolic, one can be attributed partly to menopause (JNC-7, EHS/ESC, 2007).

POSSIBLE EFFECT

alfa₂-agonists, beta-blockers, reserpine.

Clonidine in dose of 0.1–0.2 mg/day orally can lower frequency of hot flashes though essentially less, than hormone replacement therapy. Similar effect is described for methyldopa, beta-blockers and reserpine.

NEUTRAL EFFECT

ACE inhibitors, ARBs, diuretics.

UNDESIRABLE EFFECT

alfa₁-blockers, calcium antagonists, peripheral vasodilators.

Vasodilating drugs (the alfa₁-blocker, nifedipine, peripheral vasodilators) can strengthen hot flashes.

Particular treatment of menopausal symptoms

Estrogens or combination of estrogens with progestines do not raise BP considerably in the majority of women (PEPI). Nevertheless, hypertension is observed after administration of estrogens in some women. Therefore more careful BP control is recommended in women after the start of hormone replacement therapy and further every 6 month.

In case of hypertension transdermal forms estrogens are preferable, because they have no the first passage through liver associated with raise of angiotensinogen synthesis. Influence of progestines on BP is studied insufficiently.

Hormone replacement therapy is unreasonable in patients with CAD or multiple cardiovascular risk factors because of thrombosis risk (WHI; ICSI, 2006).

In long hormone replacement therapy and reception of contraceptives the risk of microalbuminuria which, in turn, associates with ascending of cardiovascular risk and chronic kidney disease raises.

Drugs containing ergot alkaloids are not indicated for the treatment of women with hypertension and hot flashes.

Obesity

The overweight is defined in body mass index (BMI) of 25-29.9 kg/m², and obesity – in 30 kg/m² and more. Obesity is a risk factor for hypertension development. Besides, the combination of obesity and hypertension enlarges risk of cardiovascular events.

In obesity CBV raises, so diuretics use is justified. Beta-blockers and minoxidil can raise body mass.

Particular obesity treatment

The basic treatment of obesity are the diet, physical activity and behavioural therapy. It is proved, that weight reduction by lifestyle or drugs lowers BP (TONE). On each 10 kg of weight reduction the SBP decreases for 5–20 mmHg.

The drugs reducing body weight, can be applied in patients with BMI >30 kg/m² without comorbid diseases, and with BMI >27 kg/m² at presence of comorbid diseases.

Antiobesity drug sibutramine little raises DBP (on the average 2 mmHg) and heart rate (on the average 5 beats/min) in patients with controlled hypertension. At the same time 40% of patients treated with sibutramine achieved weight loss >5%, elevation of serum HDL and cholesterol, decreasing of serum triglycerides, glucose and urinary acid.

Orlistat treatment associates with depression of BP, glycemia, frequency of diabetes, level of the total and LDL cholesterol.

Patients treated with rimonabant (endocannabinoid receptor antagonists) have higher level of HDL cholesterol and lower level of serum triglycerides, glucoses and BP.

Pheochromocytoma

The tumor of chromaffin cells produces excess of catecholamines and causes secondary hypertension. In these cases it is necessary to select antisympathetic agents and to avoid possible stimulation catecholamines production.

POSSIBLE EFFECT

alfa₁-blockers.

For treatment of pheochromocytoma-induced hypertension alfa₁-blockers are preferable. After alfa₁-blockers it is possible to appoint beta-blockers.

NEUTRAL EFFECT

ACE inhibitors, ARBs, calcium antagonists, clonidine.

UNDESIRABLE EFFECT

beta-blockers, beta-alfa-blockers, diuretics.

Monotherapy with beta-blockers is undesirable, because hyperactivity of alpha-adrenoreceptors may cause severe hypertensive crisis.

In reply to augmentation of diuresis after thiazides the sympathetic activity is raising and substantial BP increase is possible.

UNFAVOURABLE EFFECT

methyldopa, peripheral vasodilators, reserpine.

In patients with pheochromocytoma the methyldopa, containing precursors of catecholamines, is contraindicated. Besides, this drug and its metabolites can give false-positive test results for catecholamines.

Peripheral vasodilators raise sympathetic activity and may provoke hypertensive crisis. Reserpine also can stimulate additional release of catecholamines.

Other conditions and disorders

Airflow limitation

The airflow limitation occurs in 17–20% of patients with hypertension because of high prevalence of asthma and chronic obstructive pulmonary disease. Now there are no convincing proofs for recognition of respiratory hypertension. At the same time, increase of bronchial obstruction frequently leads to BP rising up to development of hypertensive crises.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, alfa₂-agonists, ARBs, calcium antagonists, celiprolol, diuretics, peripheral vasodilators.

ACE inhibitors at the first months of treatment in 5–10% of cases cause the dry cough, more often at night and sometimes facilitated at upright position. It should be noted, that drug-induced cough frequency does not raise in patients with asthma or chronic obstructive pulmonary disease. This cough is not caused by bronchospasm, but may provoke asthma. ACE inhibitor replacement with other ACE inhibitor eliminates cough very seldom. In some cases patients can have allergy on sulfhydryl group of some ACE inhibitors (captopril, zofenopril). In patients with allergic diseases the risk of ACE inhibitors-induced angioneurotic oedema is raised. Probably sodium cromoglycate reduces drug-induced cough.

ARBs cause cough much rarely than ACE inhibitors (In 0.6–0.8% of cases). The lowering of airway hyperreactivity is revealed after ARBs treatment in small studies.

Calcium antagonists have small bronchodilating effect, weakly reduce bronchial hypersensitivity, hyperreactivity and pulmonary artery pressure. Calcium antagonists may be effective in exercise-induced asthma.

In chronic obstructive pulmonary disease irregularity of ventilation and perfusion can partially be compensated by hypoxic vasoconstriction of pulmonary vessels. In this case calcium antagonists, reducing tonus of vessels, can worsen gas exchange.

Celiprolol owing alfa₁- and beta₁-blocking properties, is capable to stimulate beta₂-adrenoreceptors and very seldom causes bronchial obstruction.

Methyldopa can cause nasal congestion, unpleasant in comorbid rhinitis.

UNDESIRABLE EFFECT

beta₁-blockers, beta-blockers with ISA, beta-alfa-blockers reserpine.

Selective beta₁-blockers, especially high selective (nebivolol), induce airway obstruction less often than nonselective. Nonselective beta-blockers with ISA influence on airway weakly, however, unlike beta₁-blockers, they block beta₂-agonists action.

The labetalol has beta-blocking properties (beta- to alpha-blocking activity ratio is 3:1), but influences on airway much weaker, than usual beta-blockers.

It should be noted, that beta₁-blockers lose the selectivity with dose rising, therefore these drugs in high doses are contraindicated in asthma. At the same time in chronic obstructive pulmonary disease airflow limitation is not fully reversible and beta-blockers can be prescribed if necessary, for example after MI (ACC/AHA, 2001).

Beta-blockers can strengthen allergic reactions in reply to specific immunotherapy or even percutaneous skin testing with diluted allergens.

Reserpine has parasymphetic activity and can increase airflow limitation and nasal congestion.

UNFAVOURABLE EFFECT

nonselective beta-blockers without ISA.

Nonselective beta-blockers increase airflow limitation and also prevent beta₂-agonists effect. In case of beta-blockers-induced bronchospasm theophylline or cholinolytic is more preferable.

Glaucoma

Raised intraocular pressure (glaucoma) is the second cause of blindness after diabetes, and the commonest cause of irreversible blindness. Primary open angle glaucoma is the most common form of glaucoma. In the given situation it is useful to know influence of some drugs on intraocular pressure.

POSSIBLE EFFECT

beta-blockers, clonidine, diuretics.

Clonidine and beta-blockers decrease intraocular liquid production. They are used for the lowering of intraocular pressure in open angle glaucoma, usually in the form of eye drops. However after oral intake these drugs get into eye tissues and have favourable effect. Diuretics also reduce intraocular pressure and are used for glaucoma treatment. Diuretic acetazolamide reduces secretion of intraocular liquid though it has not antihypertensive effect.

NEUTRAL EFFECT

ACE inhibitors, alfa₁-blockers, alfa₂-agonists, ARBs, beta-alfa-blockers, calcium antagonists, diuretics, peripheral vasodilators, reserpine.

Combination treatment

Beta-blockers in eye drops well pass through mucosa of nose and gastrointestinal tract and can strengthen side-effects of oral beta-blockers, nondihydropyridines and alfa₂-agonists.

Elderly

Hypertension occurs in 60–90% of persons older than 60 years. Essential hypertension dominates but if hypertension has appeared after 60 years the share of renovascular hypertension and primary aldosteronism increases. It is necessary to take into account pseudohypertension in elderly caused by increased large artery stiffness.

In elderly the SBP is the best predictor of complications (CAD, stroke, terminal renal insufficiency, total mortality), than DBP (MRFIT).

Many studies show obvious advantage and safety of antihypertensive treatment in elderly (Syst-Eur, STOP). Efficiency of treatment in older patients even above, than in younger ones, as they have a higher risk of cardiovascular events.

The treatment of hypertension in people of 80 years or above reduced fatal and non-fatal cardiovascular events (MI, stroke, HF), but not all cause mortality in INDIANA trial. The HYVET trial active treatment by indapamide±perindopril (target BP is 150/80 mmHg) was associated with reduction in the rate of fatal or nonfatal stroke (–30%), death from stroke (–39%), death from any cause (–21%), death from cardiovascular causes (–23%), and HF (–64%).

The treatment of elderly needs caution because of elevated risk of orthostatic hypotension, mental disorders and impairment of comorbid diseases. Excessive lowering BP may cause latent and symptomatic cardiovascular events, including stroke and MI. Initial doses of drugs must be a half of those recommended for younger patients.

Nevertheless, the aim of antihypertensive treatment of elderly is BP level 140/90 mmHg or below, if tolerated.

NEUTRAL EFFECT

ACE inhibitors, ARBs, beta-blockers, calcium antagonists, diuretics.

Efficiency of calcium antagonists, diuretics and ACE inhibitors in elderly is similar (STOP–2, ALLHAT). In patients with isolated systolic hypertension diuretics and prolonged calcium antago-

nists are effective (SHEP, Syst–Eur). Probably, thiazides and ARBs are more effective than beta-blockers (LIFE, Messerli F.H. et al, 1998).

UNDESIRABLE EFFECT

alfa₁-blockers, alfa₂-agonists, peripheral vasodilators, reserpine.

The elderly have high risk of orthostatic hypotension caused by vasodilators (alfa₁-blockers, peripheral vasodilators) and high doses of diuretics.

Care is required for drugs which can disorder mental functions (reserpine, alfa₂-agonist).

Noncardiac surgery

Mild or moderate hypertension is not an independent risk factor for perioperative cardiovascular complications. At the same time the hypertension is a major risk factor for development of CAD which should be revealed before operation. Last intake of oral drugs is usually given in the morning of operation day.

Before operation it is necessary to achieve stable BP lowering, avoiding orthostatic hypotension. The operation can be performed, if DBP <110 mmHg (ACC/AHA, 2007). It is recommended to choose antihypertensive drug for intravenous BP control in perioperative time (esmolol, sodium nitroprusside, nitroglycerin).

POSSIBLE EFFECT

beta-blockers.

BP increase during the operation is accompanied by high level of serum catecholamines. Therefore beta-blockers are drugs of choice in perioperative time (ACC/AHA, 2006). Moreover, in patients with cardiovascular risk factors who intake beta-blockers the risk of cardiovascular events and mortality decreases.

NEUTRAL EFFECT

alfa₁-blockers, alfa₂-agonists.

The meta-analysis randomized trials shown that alfa₂-agonists reduce mortality and risk of MI after vascular operations, and also risk of myocardial ischemia during operation. The termination of clonidine intake can lead to withdrawal syndrome, therefore it is recommended to replace oral drug with plaster for maintenance of serum drug.

UNDESIRABLE EFFECT

ARBs, ACE inhibitors, calcium antagonists, diuretics, peripheral vasodilators.

Patients with hypertension have higher risk of intraoperative hypotension than patients without hypertension. This is particularly true for patients who take ACE inhibitors or ARBs which decrease vascular volume.

Diuretics can cause hypovolemia, therefore it is better to replace these drugs early and to carry out orthostatic test before operation. Peripheral vasodilators hydralazine and minoxidil raise the strain of vascular wall and the risk of bleedings from vascular stitches, and also reduce the sensitivity to vasopressors. In two trials rising risk of surgical bleedings is registered in patients taking calcium antagonists.

Postoperative treatment

After operation 25% of patients with hypertension and 5% of patients with normal BP have SBP more than 210 mmHg or rise of SBP on 50 mmHg and more. Hypertension can lead to bleeding, myocardial ischemia and HF. Perioperative hypertension is caused by sympathetic hyperactivity, pain, insufficient anaesthesia, hypoxia, fluid overload, stomach stretching, NSAIDs.

For hypertension treatment the effective anaesthesia (epidural) and good oxygenation are required. It is necessary to consider also a possibility of severe hypotension after pain elimination in case of intensive antihypertensive treatment.

Diuretics are not indicated during the first 24–48 hours after operation in view of hypovolemia risk. The severe hypotension can be observed after administration of venous vasodilators (nitroglycerin, sodium nitroprusside).

Pregnancy and breastfeeding

Pregnancy

Hypertension (BP >140/90 mmHg) is registered in 8–10% of pregnancies. It is classified pre-existing (chronic) hypertension and pregnancy induced (gestational hypertension and the syndrome of preeclampsia) hypertension. The term «unclassified hypertension» is used as the preliminary diagnosis before its refinement. Hypertension, especially gestational, can be dangerous for mother and child. Complications of hypertension are the third leading cause of pregnancy-related deaths, superseded only by hemorrhage and embolism.

There is an agreement between experts, that women with BP \geq 170/110 mmHg have risk of hemorrhagic stroke or eclampsia and demand hospitalization and urgent drug treatment. At the same time, it is necessary to avoid of excessive BP lowering which can reduce placental and fetal blood flow.

Meta-analysis has shown an absence of obvious advantages of any antihypertensive drug (Cochrane Reviews, 2007).

Gestational hypertension

Gestational hypertension (BP >140/90 mmHg) appears after 20 weeks of pregnancy and disappears during 12 weeks after (ESH/ESC, 2007). Such complication occurs in 5–10% of pregnant women. Combination of hypertension and proteinuria >300 mg/l (or >500 mg/day) is designated as preeclampsia.

In patients with BP 140–149/90–95 mmHg usually it is recommended nondrug treatment and also to stop work or to enlarge rest time. Strict restriction of salt in view of hypovolemia risk and lowering of placental circulation is undesirable.

It is recommended to begin drug treatment if BP \geq 150/95 mmHg, and if BP \geq 170/110 mmHg urgent hospitalization is required (ESH/ESC, 2007). In cases of combination of gestational and chronic hypertension, symptomatic manifestations or organ damage the drug treatment begins in BP >140/90 mmHg.

NEUTRAL EFFECT

alfa₂-agonists, beta-blockers, calcium antagonists (verapamil, nifedipine), labetalol, prazosin.

Among antihypertensives applied during pregnancy, methyldopa remains the most studied and safe drug. The drug is usually prescribed in higher dose (0.5–4 g/day q6-8h), in connection with high liver activity. At the same time beta-blockers prevent severe hypertension better than methyldopa (Cochrane Reviews, 2007). It is possible to use clonidine.

Many beta-blockers (atenolol, metoprolol, labetalol) are widely used for a long time in pregnancy. Fetal growth retardation (birth weight lower 10th percentile) in long-term atenolol intake are not proved. It is more preferable to prescribe selective beta-blockers with small influence on uterus contractility. Nifedipine is more often applied for treatment of acute hypertension.

UNDESIRABLE EFFECT

beta-blockers (carvedilol, nebivolol), calcium antagonists (diltiazem, felodipine, isradipine, nisoldipine, nicardipine), diuretics, doxazosin.

Diuretics may reduce uteroplacental circulation, birthweight and are not recommended.

Doxazosin, some calcium antagonists (diltiazem, felodipine, isradipine, nisoldipine, nicardipine) and beta-blockers (carvedilol, nebivolol) are insufficiently studied in pregnancy.

UNFAVOURABLE EFFECT

ACE inhibitors, ARBs, reserpine.

ACE inhibitors during 2–3 trimester of pregnancy may cause serious complications: neonatal renal insufficiency, fetal hypotensive syndrome, oligohydroamnion and fetal growth retardation.

Reserpine get through placenta and may cause mental suppression and mucous hypersecretion in airways that increases risk of asphyxia.

Chronic hypertension

Chronic hypertension occurs in 1-5% of pregnancies. In this case hypertension preceded pregnancy, is registered during first 20 weeks of pregnancy and remain more 6-12 weeks after delivery. In women with chronic hypertension BP decreases to norm in 40% at 2 trimester, and at 3 trimester BP rises again.

In pregnant women with mild to moderate hypertension (140–179/90–109 mmHg) and an absence of subclinical organ damage the cardiovascular risk during pregnancy remains low. In these women influence of antihypertensive treatment on maternal and neonatal morbidity and mortality is not proved (Cochrane Reviews, 2007). Therefore careful observation and lifestyle changes (activity restriction, the rest on left side, diet with salt and caloric restriction) are recommended, and drugs add in BP $\geq 150/95$ mmHg (ESH/ESC, 2007). In presence of symptoms or organ damages drug treatment is recommended in BP $\geq 140/90$ mmHg.

Physician's restraint concerning antihypertensive treatment in women with mild BP is supported by meta-analysis of 45 studies which have shown linear relationship between BP lowering and fetal growth retardation.

At the end of second and the start of third trimesters in women with chronic hypertension in 25% of cases develop proteinuria. In these cases chronic hypertension combined with gestational hypertension and preeclampsia is diagnosed. Diagnosis of preeclampsia in women with chronic hypertension is based on sudden BP raise ($>160/110$ mmHg) against initially good control and severe proteinuria (more than 3 g/day). The fetal growth retardation in preeclampsia occurs in 30–40% of cases, and the risk of prematurity increases to 20–30%. The perinatal mortality does not differ from that with high risk of obstetric complications.

In this section the choice of antihypertensive drugs in first trimester in women with chronic hypertension is described. The drugs choice in 2–3 trimesters is similar to those, described in section of gestational hypertension.

NEUTRAL EFFECT

alfa₂-agonists, beta-blockers (atenolol, metoprolol, propranolol, labetalol), calcium antagonists (nifedipine, verapamil).

There are not essential differences between various antihypertensive drugs. More often methyl-dopa and labetalol are used because of long experience. In children who were born from mothers, using during pregnancy clonidine, sleep disorders are revealed.

Earlier it was informed about extremities defects after appointment of ultrahigh doses of calcium antagonists in animals. However the subsequent studies have proved relation teratogenic effect of any antihypertensive drugs with substantial lowering of uteroplacental blood flow. Recent prospective studies have not confirmed teratogenic risk of calcium antagonists.

UNDESIRABLE EFFECT

beta-blockers (carvedilol, nebivolol), calcium antagonists (diltiazem, nisoldipine, nicardipine, isradipine, felodipine), doxazosin, diuretics, peripheral vasodilators, reserpine.

Effects of many calcium antagonists (diltiazem, nisoldipine, nicardipine, isradipine, felodipine), beta-blockers (carvedilol, nebivolol) and doxazosin on fetus are studied insufficiently. Spironolactone is contraindicated in first trimester.

UNFAVOURABLE EFFECT

ACE inhibitors, ARBs.

ACE inhibitors in 2–3 trimester may cause serious complications (acute renal insufficiency in newborns, fetal hypotensive syndrome, oligohydroamnion, fetal growth retardation) and even death of fetus. It is recommended to cancel ACE inhibitors as soon as possible after pregnancy detection. These negative effects are not correlated with endometrial drug content in 1 trimester.

ARBs in pregnancy are studied insufficiently, but they have similar action with ACE inhibitors and are contraindicated in 2–3 trimesters too.

Table 1–7. Pregnancy risk categories (FDA).

Category	Drug
B	hydrochlorothiazide, indapamide, pindolol
C	ARB (1 trimester), calcium antagonists (verapamil, diltiazem, isradipine, nifedipine, felodipine), beta-blockers (atenolol, metoprolol, nadolol, propranolol), hydralazine, doxazasin, ACE inhibitors (1 trimester), clonidine, labetalol, minoxidile, prazosin, reserpine
D	ACE inhibitors (2–3 trimester), ARB (2–3 trimester)

Features of conducting pregnancy and delivery

According to the meta-analysis aspirin in small doses (60–75 mg/day) reduces risk of pre-eclampsia by 17%, risk of baby dying by 14% and does not enlarge hemorrhages risk (Cochrane Reviews, 2007).

Oxytocin and pituitrin are used for labor induction, but they raise BP and are undesirable for women with hypertension. In the last cases it is preferable nonselective beta-blockers which are effective even when oxytocin is not working. For example, propranolol successfully stimulated labor in 87% of cases after the first intake and in 95% after the second intake. On the other hand, if women receive beta-blockers beta₂-agonists using for lowering of preterm labor risk will be ineffective. The calcium antagonists (nifedipine) have tocolytic action. A disadvantage of calcium antagonists is the impossibility of simultaneous magnesium appointment.

Usually in chronic hypertension, the necessity for urgent delivery is not present. In women with high BP efforts during uterine contractions are dangerous. Pregnancy is contraindicated at uncontrolled severe or malignant hypertension.

Breastfeeding

All antihypertensive drugs excrete into breast milk, that demands cautious use. Now there are no reliable clinical trials of drugs influence on fetal cardiovascular system. In mild hypertension it is possible to refrain from drugs during breastfeeding, carefully supervising BP.

Even low doses of antihypertensive drugs demand careful observation of newborn. If for BP lowering is required more than one drug, it is better to refuse breastfeeding.

NEUTRAL EFFECT

alfa₂-agonists (clonidine, methyldopa), beta-blockers (propranolol, labetalol, nadolol), calcium antagonists (verapamil, diltiazem, nifedipine), hydralazine, prazosin.

Methyldopa excretes into breast milk in very low dose and is capable to enlarge breast milk secretion. There are inconsistent estimations of propranolol and nifedipine concentration in breast milk.

UNDESIRABLE EFFECT

ACE inhibitors, ARBs, beta-blockers (atenolol, metoprolol), diuretics.

Atenolol, metoprolol and nadolol are long-acting drugs, moderately excreted in breast milk and consequently can cause hypotension, bradycardia and tachypnoe in fetus.

ACE inhibitors (captopril, enalapril) can be used. But newborns are very sensitive to ACE inhibitors action and intake its in the first month of life is undesirable. ARBs are little investigated. Diuretics may decrease of breast milk volume and suppress lactation.

UNFAVOURABLE EFFECT

reserpine.

Reserpine passes into breast milk and may cause unfavourable effects (difficult breathing, low temperature, loss of appetite) in infants.

Table 1–8. The antihypertensives in breastfeeding (UK drugs in lactation advisory service, 2008; Gardiner S., Begg E., 2001).

Group	Drug name	% maternal dose	Suitability for use in lactation
Beta-blockers	Atenolol	5.7–19.2	avoid
	Metoprolol	1.7–3.3	probably safe
	Nadolol	5.1	probably safe
	Propranolol	0.2–0.9	safe
ACE inhibitors	Captopril	0.014	safe
	Enalapril	< 0.1	safe
	Quinapril	1.6	safe
Calcium antagonists	Verapamil	0.14–0.84	safe
	Diltiazem	0.9	probably safe

Drug selection in lactation

It is important to know, that drugs safe in pregnancy are not always safe in breastfeeding.

Careful observation is needed for prematurely born infants, infants with health problems, and during the first weeks of the newborn.

For lowering of adverse effects it is recommended to choose drugs with short half-life, high drug-protein binding, low fat solution. One-time drugs are prescribed before the longest sleep time and infants are recommended to be fed before short-term drugs intake.