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# ЭПИДЕМИОЛОГИЯ, КЛИНИЧЕСКИЕ ОСОБЕННОСТИ И ТАКТИКА ЛЕЧЕНИЯ АРТЕРИАЛЬНОЙ ГИПЕРТОНИИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА. ОБЗОР ЛИТЕРАТУРЫ

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# Epidemiology and Clinical Features of Arterial Hypertension in Patients with Type 2 Diabetes Mellitus. Literature Review

**Резюме**

Артериальная гипертония и сахарный диабет 2 типа часто сочетаются и взаимно усиливают неблагоприятное влияние на сосудистый и почечный прогноз. Артериальная гипертония представлена примерно у 50 % больных с сахарным диабетом 2 типа, а диабет в свою очередь выявляется приблизительно у 20 % лиц с артериальной гипертонией. Риск развития артериальной гипертонии у больных с сахарным диабетом 2 типа в 2-2,5 раза выше, чем у лиц без диабета; во столько же раз наличие артериальной гипертонии увеличивает риск формирования сахарного диабета 2 типа. Артериальная гипертония и диабет взаимно отягощают течение друг друга: с одной стороны, наличие артериальной гипертонии существенно увеличивает вероятность развития диабетических макро- и микрососудистых осложнений (включая диабетические нефропатию и ретинопатию); с другой стороны, сахарный диабет 2 типа, как классический независимый фактор сердечно-сосудистого риска, примерно в 2 раза повышает риск осложнений, присущих артериальной гипертонии. Тщательное лечение диабета с поддержанием целевых значений гликемии в течение длительного времени может быть ассоциировано со снижением вероятности развития артериальной гипертонии на 24 % в сравнении с менее адекватным контролем гликемии. Артериальная гипертония при сахарном диабете 2 типа может иметь ряд особенностей, которые отличают таких больных от общей популяции лиц с артериальной гипертонией. К таким особенностям относятся: более высокий удельный вес изолированной систолической артериальной гипертонии и резистентной артериальной гипертонии, определенных типов нарушений циркадного ритма артериального давления (категорий «non-dipper» и «night-peaker»); частое сочетание с альбуминурией; нередкие высокая солечувствительность и объем-зависимый характер артериальной гипертонии и другие.

***Ключевые слова:*** *сахарный диабет 2 типа, артериальная гипертония, изолированная систолическая артериальная гипертония, резистентная артериальная гипертония*

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**Abstract**

Hypertension and type 2 diabetes mellitus are often combined and mutually enhance the adverse effect on vascular and renal prognosis. Hypertension is present in about 50 % of patients with type 2 diabetes, and diabetes, in turn, is detected in about 20 % of people with hypertension. The risk of developing hypertension in patients with type 2 diabetes is 2-2.5 times higher than in people without diabetes; the presence of hypertension increases the risk of type 2 diabetes by the same number of times. Hypertension and diabetes mutually burden each other: on the one hand, the presence of hypertension significantly increases the likelihood of developing diabetic macro- and microvascular complications (including diabetic nephropathy and retinopathy); on the other hand, type 2 diabetes, as a classic independent cardiovascular risk factor, increases the risk of complications inherent in hypertension by about 2 times Careful treatment of diabetes with maintenance of target values of glycemia for a long time may be associated with a decrease in the likelihood of developing hypertension by 24 % compared with less adequate control of glycemia. Hypertension in type 2 diabetes may have a number of features that distinguish such patients from the general population of people with hypertension. Such features include a higher proportion of isolated systolic hypertension and resistant hypertension, certain types of circadian rhythm disorders of blood pressure (categories "non-dipper" and "night-peaker"), frequent combination with albuminuria, frequent high salt sensitivity and volume-dependent nature of hypertension, and others.

***Key words:*** *type 2 diabetes mellitus, arterial hypertension, isolated systolic arterial hypertension, resistant arterial hypertension*

**Conflict of interests**

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α-AB — alpha-adrenoblocker, β-AB — beta-adrenoblocker, AH — arterial hypertension, BP — blood pressure, CAN — cardiovascular autonomic neuropathy, MRA — mineralocorticoid receptor antagonist, GLP1ra — glucagon-like peptide-1-receptor agonist, ASA — acetylsalicylic acid, CCB — calcium channel blocker, DBP — diastolic blood pressure, DNP — diabetic nephropathy, ACE inhibitors — angiotensin-converting enzyme inhibitors, IHD — ischemic heart disease, iSGLT2 — sodium glucose linked co-transporter-2 inhibitors, ISAT — isolated systolic arterial hypertension, LV — left ventricle, RATS — renin-angiotensin system, RCT — randomised controlled study, SBP — systolic blood pressure, DM — diabetes mellitus, GFR — glomerular filtration rate, CVR — cardiovascular risk, CKD — chronic kidney disease, LDL-C — low density lipoprotein cholesterol, CCF — chronic cardiac failure

## Relevance

Cardiovascular disorders are a leading cause of deaths in patients with type 2 diabetes mellitus (DM) [1]. One of the most common and significant cardiovascular diabetes-associated risk factors is arterial hypertension (AH) [2]. In type 2 DM, cardiovascular risk factors are often observed in various combinations; usually, AH is combined with abdominal obesity, dyslipidemia, albuminuria, blood-clotting disorders [3]. Such risk factor associations in type 2 DM patients and also in individuals with metabolic syndrome significantly and mutually boost adverse effects, promoting development and progression of a number of macro- and microvascular complications [4].

AH is a serious open problem in the current clinical picture of internal diseases, because of its high incidence and significant adverse effect on the prognosis. AH is recorded in 30–45 % of the general adult population. Its incidence grows with the age, and at least 60 % of individuals of over 60–65 years of age have high blood pressure (BP) or take antihypertensives. According to epidemiological studies, the probability of AH developing at a later stage in life in young adults of 20–40 years old can be as high as 90–95 % [2, 5].

AH is associated with a high incidence of cardiovascular death and a higher risk of cardiovascular complications in all age groups. There is also independent correlation between AH and a risk of cardiac failure, peripheral artery involvement and impaired renal function [3, 6, 7].

Systolic BP (SBP) values demonstrate the closest correlation with an increase in cardiovascular risk. This is particularly true for individuals over 50 years of age. SBP values tend to increase throughout life; at the same time, diastolic BP (DPB) starts decreasing at the age of 50–60 years [8, 9]. The process of SBP increase and DBP decrease (with an increase in pulse pressure) shows a progressive increase in vessel wall stiffness in the arterial bed. The exact mechanisms of this process are still understudied. It is worth mentioning that higher SBP values in elderly people are the most significant independent risk factor of cardiovascular and cerebrovascular complications, as well as renal disorder progression.

In individuals below 50 years old, DBP values demonstrate the most clear correlation with the degree of cardiovascular risk [2, 4, 9].

Despite modern diagnostic and therapeutic methods, the progress of AH therapy is modest: in a number of countries, far fewer than a half of all patients with AH manage to control their AH within the target range. Epidemiological data show that approx. 50 % of AH patients in Western Europe are unaware of their higher AH (i.e. they are not diagnosed with AH); among individuals with AH, just 10–15 % have satisfactory AH control [1, 6, 9].

Type 2 DM is a chronic metabolic disorder associated with progressive reduction in adequate insulin secretion by β-cells of pancreatic islets, usually as a result of insulin resistance. Type 2 DM is a prevailing form of DM globally, accounting for 90–95 % of all cases of diabetes [1, 8, 10].

This review presents results of analysis of 2010–2023 literature in PubMed, RSCI (Russian Science Citation Index), Scopus. The following keywords were used: arterial hypertension, type 2 diabetes mellitus, isolated systolic arterial hypertension, resistant arterial hypertension. The analysis includes the data of the authors conducting clinical trials to identify specific pathogenesis, clinical manifestations and management of patients with arterial hypertension and type 2 diabetes mellitus.

## Epidemiology

The International Diabetes Federation (IDF) regularly publishes epidemiological DM evaluations and prognosis; the last report was presented in 2023. There are some data from the report. According to expert IDF evaluations, in 2019, approximately 463 mln. people all over the world had diabetes (i.e. 9.3 % of all world population, of which approx. 462 mln. people had type 2 DM). It is expected that by 2030 the number of DM patients globally will reach 578 mln. (10.2 % of the world population), while by 2045 — 700 mln. (10.9 %) [4, 11,12].

According to experts, nearly a half of 463 mln. of DM patients are unaware of their condition. DM unawareness in high-income nations is 38.5 %, in average-income countries — 52.6 %, while in low-income states — 66.8 %. On top of that, 374 mln. people worldwide (7.5 % of the global population) have impaired glucose tolerance; by 2030, this number will reach approx. 54 mln. people (8.0 %), by 2045 — 548 mln. (8.6 %) [4, 11, 12].

In the Russian Federation, the number of people with confirmed DM is nearly 4.58 mln. (3.1 % of the population). It is assumed that approximately the same number of people have an undiagnosed disease; therefore, there are significant shortages in medical treatment [11].

## Prognosis

Type 2 DM is associated with a high incidence of severe, debilitating complications; it significantly contributes to mortality rates. In Eastern countries, diabetes is the leading cause of blindness; it accounts for up to 40 % of all terminal renal failure cases. A risk of myocardial infarction and cerebral stroke in type 2 DM patients is assumed to be 2–4 times higher than in individuals of the same age and sex, but having no diabetes. The incidence of low limb amputation in type 2 DM is approx. 20 (!) times higher than in individuals without diabetes. Type 2 DM reduces the life expectancy by approx. 10 years; this value is even higher with disease onset before the age of 55 years [11,12,13, 14].

AH and type 2 DM are often comorbidities and mutually enhance their adverse effects on vascular and renal prognosis. It is assumed that approx. 50 % of type 2 DM patients have AH; at the same time, approx. 20 % of AH patients have diabetes. In a recent register, patients with type 2 DM had BP of over 140/90 mm Hg or were continuously taking antihypertensives in 71 % of cases. The risk of AH in patients with type 2 DM is 2–2.5 times higher than in individuals without diabetes; and AH increases the risk of type 2 DM by 2–2.5 times. AH and diabetes mutually aggravate the course of disease: AH significantly increases the probability of diabetic macro- and microvascular complications (including diabetic nephropathy (DNP) and retinopathy); type 2 DM, being a classic independent cardiovascular factor, causes a 2-fold increase in the rate of AH-associated complications. Of importance is the information that accurate diabetes management, which ensures long-term target glycaemia values, can be associated with reduction in the probability of AH by 24 % vs. less adequate glycaemia control [5, 9, 12, 15].

## Morbid Physiology

High rates of the combination of type 2 DM and AH are a result of the similarity in a number of pathological mechanisms of these conditions. These include insulin resistance, dyslipidemia, activation of proinflammatory and prothrombotic factors, endothelial dysfunction, impaired vascular tone regulation, high salt sensitivity,

impaired sodium excretion by kidneys, etc. In patients with essential AH, the rate of insulin resistance is as high as 50 %, and individuals with such a combination have 2–3-fold increase in the cardiovascular risk severity (when using SCORE, a common European scale). It has been found that the rate of insulinemia in AH demonstrates direct correlation with BP values, and a number of specialists can treat essential AH as an insulin-resistant condition. In turn, very often higher insulin levels, observed with insulin resistance (in individuals with type 2 DM, pre-diabetes, impaired glucose tolerance), can affect insulin-sensitive tissues (e.g. kidneys) and promote AH development (e.g. promoting sodium and water retention in kidneys). It is also assumed that AH and insulin resistance can have a common genetic base. This concept is based on a higher incidence of impaired glycaemic balance in normotensive descendants of AH patients vs. children of individuals without AH [7, 10, 13, 16].

Literature sources discuss the characteristics of AH in type 2 DM patients. Points of view regarding this issue are versatile. A number of specialists emphasise that the pattern of AH in these individuals is close to the pattern in individuals without diabetes, and there are no special features. At the same time, other researchers point out to a number of aspects, which can distinguish patients with AH and type 2 DM from the general AH population.

*The most typical characteristics of a combination of AH and type 2 DM:*

- Salt sensitivity predisposition (so AH is often volume-dependant)
- Impaired circadian BP rhythm (with an increase in the relative weight of "non-dipper" and "night-peaker" categories)
- Isolated systolic AH
- Resistant AH
- Albuminuria
- Orthostatic hypotonia.

Currently, all these features are considered to be independent cardiovascular risk factors. Besides, their presence can impact AH management. For instance, in volume-dependent AH, the use of thiazid-like diuretics is justified, while individuals with albuminuria should take angiotensin-converting enzyme inhibitors (ACE inhibitors) or sartans for kidney protection. These possible characteristics of AH in type 2 DM are detailed below [5, 8, 10, 17].

## Clinical Profile and Management of the Key Pathophysiological Characteristics of AH and Type 2 DM

### *Salt sensitivity*

Higher salt sensitivity is typical of some categories of AH patients, including elderly patients, patients with DM, obesity, impaired renal function, low renin plasma activity. Also, higher salt sensitivity is observed in African Americans.

*The mechanism* of higher salt sensitivity in type 2 DM patients is still unclear. Salt sensitivity can be genetic and can be associated with hereditary reduction in the number of functional nephrons (normally, each kidney has approx. 1 mln. of nephrons), impairing the renal ability to excrete sodium and water. In this category, AH tends to rise in case of excessive consumption of sodium chloride and water; in such cases, AH demonstrates good response to dietary reduction of sodium chloride and the use of diuretics. In type 2 DM, thiazid-like diuretics (indapamide, chlortalidone) are preferable due to their metabolic neutrality and marked organ-protective properties. Thiazids (e.g. hypothiazid) are less preferable due to possible adverse effect for glucose profile (however, internationally recognised experts think they can be used also in DM patients, if thiazid-like products are unavailable). In case of impaired renal function (especially where glomerular filtration rate (GFR) is below 30–60 mL/min), loop diuretics are recommended as a component of antihypertensive therapy.

Taking into account their possible higher salt sensitivity, individuals with AH and type 2 DM may benefit from a new class of antihyperglycemic drugs — *sodium glucose linked co-transporter-2 inhibitors* (iSGLT2). In a number of large randomised controlled trials (RCTs), these drugs demonstrated a variety of organ-protective properties and the ability to improve cardiovascular and renal prognosis in type 2 DM patients (especially in chronic cardiac failure (CCF) and DNP). A significant advantage of these drugs in patients with AH and type 2 DM is their ability to enhance sodium excretion, thus, they also have marked antihypertensive effect. It is worth to discuss the mechanism of iSGLT2 action in detail [9, 13, 18].

These drugs affect sodium glucose linked co-transporter-2, which is a glucose transport protein located in the anterior part of proximal tubules of nephrons; its function is to re-absorb 80–90 % of glucose from

primary urine. Glucose is transported via tubule cell membranes from tubule opening using sodium gradient. Increased diuresis with the use of iSGLT2 is associated with osmotic effect of glucosuria and natriuresis. According to some authors, this drug effect is extremely significant and is one of the most important favourable mechanisms of iSGLT2 in CCF. It has been demonstrated that iSGLT2 can potentiate the effect of loop diuretics in CCF. It is assumed that the use of iSGLT2 is associated with a less marked rate (as compared with loop and thiazide diuretics) of reflective neurohumoral activation. Natriuretic and diuretic effects of these drugs are associated with hypotensive effect. The degree of this effect caused by iSGLT2 is clear (it can be compared with the effect of thiazide diuretics, beta-adrenoblockers (β-AB) and calcium channel blockers (CCBs), and, according to some sources, is even superior). Although the current AH therapy recommendations do not include iSGLT2 as antihypertensives, some competent experts have already put forward such proposals. Of note, this class of drugs has been included in the revised recommendations not only for type 2 DM management, but also for CCF with low, intermediate and preserved left ventricle (LV) ejection fraction (both with and without diabetes), as well as for chronic kidney disease (CKD) (including DNP and non-diabetic glomerulopathy). To conclude the discussion of the possibilities of iSGLT2, we would like to emphasise their versatile additional organ-protective and pleiotropic effects: antiinflammatory action, reduction of oxidative stress and sympathetic tone, improved vasodilation, improved energy metabolism by myocardium, reduced cardiac remodeling, reduced ischemic and reperfusion myocardial injury, reduced uricemia, better autophagy and lysosomal degradation, reduced body weight [15,18].

### *Impaired circadian BP rhythm*

Normally, during 24-hour BP monitoring, it is higher during daytime, while at night it reduces by 10–15 % vs. daytime values (dipper). A lesser reduction in BP values at night (less than < 10 % of daytime values) is called non-dipper, while higher nocturnal BP values are called night-peaker. Two latter circadian BP rhythms are pathologic. According to a number of articles. they are more common in patients with AH and type 2 DM than in AH alone; other authors suggest absence of any relation between abnormal circadian BP rhythms and type 2 DM. It is known that impaired circadian BP rhythm is associated with a higher risk of cardiovascular death irrespective of sex, age, body mass index, smoking status, and a history of cardiovascular disorders. In a number of epidemiological studies, nocturnal BP values were more reliable predictors of all cause mortality in AH than daytime BP values or BP measured at a visit to the doctor. The causes of more frequently reported circadian BP rhythm abnormalities in individuals with AH and type 2 DM vs. patients with AH alone are still not clear [12,19,20].

*To correct* such *circadian BP rhythm abnormalities,* the patient should take at least some antihypertensive before bed [12,19,20].

### *Resistant AH*

This term is used for cases when BP values remain outside the target range, despite the fact that the patient follows recommendations for lifestyle changes (including reduced consumption of sodium chloride) and takes full doses of 3 classes of compatible antihypertensives, with one of these 3 classes being a diuretic. The incidence of resistant AH (according to some US registers) is approx. 9 %. Causes of resistant AH are versatile and include poor compliance, presence of symptomatic AH (e.g. renoparenchymal, renovascular, endocrine, etc.); resistant AH is more common in obese and elderly patients, as well as (potentially) in type 2 DM patients. The mechanisms of a higher incidence of resistant AH in diabetes are unclear; endothelial function and insulin resistance are discussed among other causes.

*In order to overcome AH resistance* to therapy, the following measures are recommended: thorough review of patient's compliance to therapy and correction where necessary, ruling out symptomatic nature of AH (in case of subclinical hyperaldosteronism, it is essential to use mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone); wider use of 4–5 and more components in the therapy regimen (for instance, CCBs, thiazid or thiazid-like diuretic, ACEi or sartan, MRA, possible combined with a central-action drug, β-AB, alpha-adrenoblocker (α-AB), etc.). The role of complex multicomponent combinations of antihypertensives in such patients, their beneficial effect and safety are difficult to assess. Recently, resistant AH therapy has included some invasive procedures (catheter-based renal denervation, implantation of devices which activate carotid adrenergic receptors, etc.) [21,22].

Considering the important role played by *occult hyperaldosteronism* in resistant AH development, and the significance of MRAs in the elimination of AH resistance to therapy, we will briefly discuss their possible use in AH, including individuals with type 2 DM. Until recently, these drugs were used mainly in the management of CCF cases with low LV ejection

fraction and in post-infarction patients. Currently, they are widely used in the combined therapy of AH as a fourth drug (as an addition to traditional three-component combinations of ACE inhibitor or sartan, thiazide/thiazide-like diuretic and CCB). Spironolactone is a non-selective drug; in AH therapy, it is usually used in low, sub-diuretic doses (25–50 mg/day). The use of low doses makes it possible to minimise such adverse events as gynecomastia, decreased interest and painful menstruation. Drugs of this class are effective in reduction of BP values both in a combination with other classes of drugs and as monotherapy; however, spironolactone is superior to eplerenone in management of high BP. In a recent study PATHWAY-2 (335 participants, of which 46 individuals with type 2 DM), spironolactone 25–50 mg/day was added to a three-component combined antihypertensive therapy with ACE inhibitor (or sartan), CCB and diuretic, as compared to doxazosin and bisoprolol, and demonstrated a more prominent antihypertensive effect without any events of gynecomastia, hyperkalemia and impaired renal function. The effect and tolerability in type 2 DM patients were comparable to the effect and tolerability in non-diabetic individuals. The organ-protective effect of spironolactone is associated with LV hypertrophy regression, antifibrotic effects in myocardium and, possibly, in vascular walls, as well as with reduced microalbuminuria rates [21,22].

### *Isolated systolic AH*

This term is used for a situation when SBP values rise above 140 mm Hg without any increase in DBP, the values of which remain below 90 mm Hg. The majority of world experts consider isolated systolic AH (ISAH) to be an isolated pathology, typically observed in elderly people and associated with lower artery wall flexibility [23]. Higher SBP values are an important pathophysiological factor, contributing to LV hypertrophy; reduced DBP can result in poor coronary blood flow. The incidence of ISAH rises with age; in elderly people, it is the most common form of AH (according to Western specialist, it can account for 80–90 % of all AH cases in patients of 65 and over years of age) [24]. In elderly individuals, ISAH is associated with a significantly higher cardiovascular risk as compared to systolic-diastolic AH (with comparable SBP values) [19]. In order to assess the rate of an additional cardiovascular risk in ISAH, it is recommended to use the same SBP values, the same nomenclature for risk factors, target organ involvement and comorbidities, as in systolic-diastolic AH. At the same time, experts believe that extremely low DBP values (60–70 mm Hg and below) are associated with additional increase in the risk [16].

*The mechanism of correlation* between ISAH and type 2 DM has been understudied; it is true both for epidemiology, pathogenesis and management strategies. Considering that a lot of type 2 DM patients are elderly people, it is naturally to expect a high incidence exactly of this AH form; however, reliable epidemiological data in this regard are lacking. Since age-associated rigidity of aortic and large vessel walls is the leading cause of ISAH development, essential is the information that diabetes-associated metabolic disorders can contribute to poor vascular wall flexibility. Endothelial dysfunction, activation of local and system pro-inflammatory and profibrotic mechanisms are essential, since they are closely associated with insulin resistance, glucotoxicity, lipotoxicity and accumulation of glycation products in tissues. Reduced elasticity and damping capabilities of vascular walls are facilitated by typically early onset of type 2 DM and faster progression of atherosclerotic changes in vascular walls. An increase in systolic blood velocity resulting from higher SBP and lower DBP (as damping capabilities weaken) caused by higher vascular wall rigidity, lead to a higher pulse BP, higher mechanical load over the vascular wall with an increase in shear stress. All this contributes to the progression of vascular damage and facilitates further increase in cardiovascular risk. Of note, in type 2 DM patients, ISAH develops in younger age as compared to non-diabetic population. At the same time, it is worth mentioning that AH in middle-aged type 2 DM patients is systolic-diastolic (both SBP and DBP values rise) [7, 19, 23].

*ISAH therapy* includes standard classes of hypotensives; diuretics and CCBs are preferable [11,12].

### *Albuminuria*

Being a marker of renal damage, albuminuria is diagnosed more often in patients with AH and type 2 DM as compared to non-diabetic AH patients. Currently, the term "microalbuminuria" is outdated; in nephrology literature, this term has been replaced with albuminuria, however, the former is still used in clinical practice. Most often, albuminuria in this population is a sign of a diabetes-specific kidney damage — DNP (where glomeruli are involved most of all in the form of nodular glomerular sclerosis). Clinical manifestations of DNP usually appear 10–15 years after onset of diabetes (in type 2 DM patients, identification of this particular moment is challenging, therefore, in real time practice, this period can be significantly shorter). In type 2 DM, albuminuria, as a sign of DNP, is diagnosed in 14–20 % of cases and

often precedes AH development. It is worth noting that, if diagnosed early, albuminuria in type 2 DM patients can be reversed with the use of modern efficient kidney-protective approaches [12,25].

In developed countries, *diabetic nephropathy* is a leading cause of end stage renal disease; in dialysis patients, its share is 40 %. A very important factor in kidney damage progression in type 2 DM patients is AH. High BP values contribute both to albuminuria aggravation and its progression to proteinuria (> 0.3 g/day, then > 1.0 g/day, with possible development of nephrosis and gradual reduction in renal function) [16,20,25].

The initial stage of DNP (glomerular hyperfiltration) is asymptomatic (no albuminuria is recorded). Later, higher GFR levels drop to normal values, and albumin excretion with urine rises (albuminuria starts developing). Then, manifest DNP appears: minimal proteinuria progresses to severe condition (in this case, it is nephrosis); microscopic hematuria, cylindruria are also possible; AH appears or aggravates. GFR gradually drops, up to marked and severe kidney failure (stage 3–5 CKD). The clinical pattern (especially in type 2 DM) often presents with various cardiovascular complications, typical of diabetes in general and DNP in particular: ischemic heart disease (IHD), rhythm disturbances, CCF, and other macro- and microvascular diabetic complications [23,25].

*Efficient management of AH in type 2 DM patients* is based on a pivotal approach to kidney protection, which insures minimisation of the rate of renal damage both at early and later stages, as well as when the renal function is impaired. The most evidence-based hypertensives are renin-angiotensin system (RATS) blockers, such as ACE inhibitors or sartans [12,25]. In individuals with DNP and AH, achievement and maintenance of target AH values are associated with reduction in cardiovascular risk, as well as reduced rate of renal damage progression. Prescription of hypertensives in addition to life-style changes is recommended in DNP patients if their AH levels are ≥ 140/90 mm Hg (for patients of over 80 years of age — ≥ 160/90 mm Hg). Target values for such individuals are SBP of 120–129 mm Hg, DBP — 70–79 mm Hg (for individuals of over 65 years of age — systolic BP of 130–139 mm Hg). First-line antihypertensives for patients with DNP and DM are ACE inhibitors or sartans, supplemented with CCBs and/or thiazid/thiazid-like diuretics. Where necessary, the following drugs can be used in addition to the above-mentioned drugs: 1) loop diuretics (especially with GFR of 45 mL/min/1.73 m$^2$); 6) nitrates (in elderly patients, with IHD). During therapy, it is recommended to continuously control proteinuria, electrolyte levels and serum creatinine, GFR values [17,19,25]. The general approach to DNP management is presented in Figure 1.

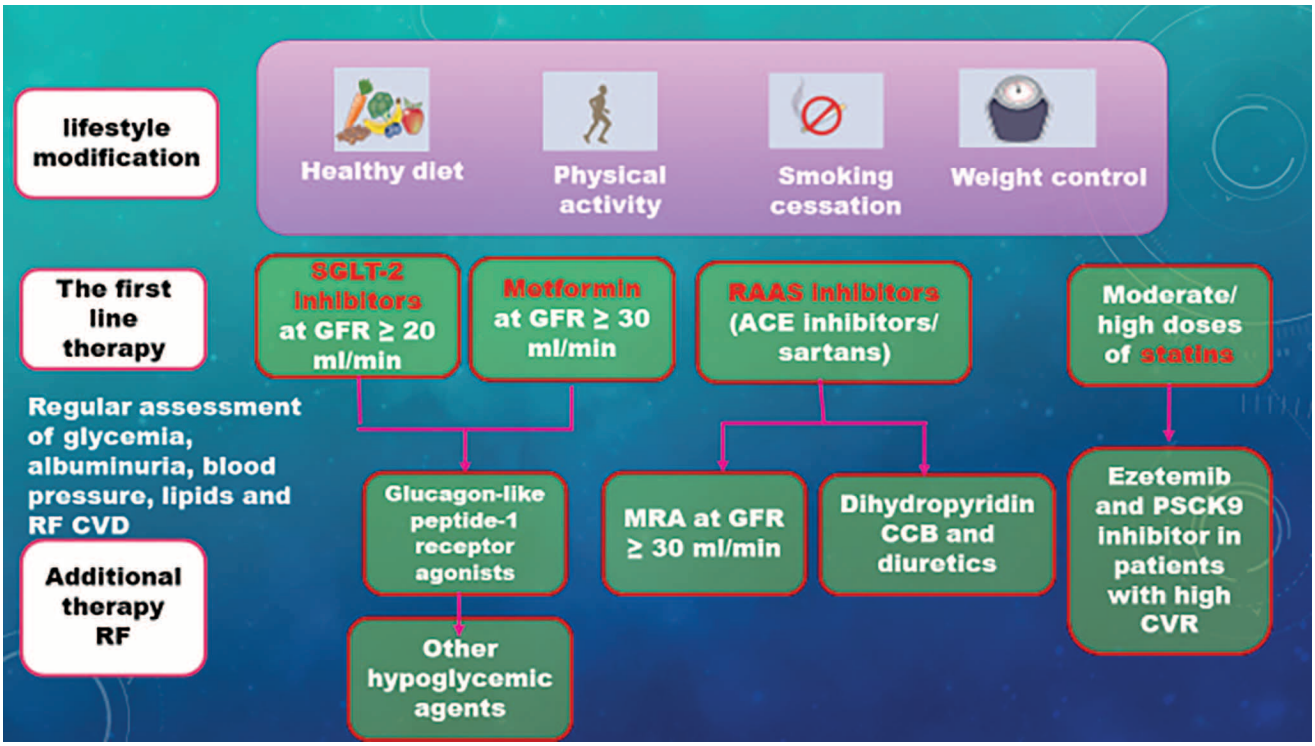


***Figure 1.*** *General view on the management of patients with DNP*
**Note:** RF — risk factors; CVD — cardiovascular diseases; CVR — cardiovascular risk; PCSK9 — proprotein convertase subtilisin-kexin type 9

### *Orthostatic hypotonia*

This term is used to describe episodes of rapid SBP reduction by ≥ 20 mm Hg or DBP by ≥ 10 mm Hg during 3 minutes after verticalisation from sitting or supine position; it is often associated with compensatory tachycardia. The incidence of orthostatic hypotonia rises with age; in elderly patients, it can reach 5–30 %. Orthostatic hypotonia is associated with a higher risk of falls and fractures [5, 16].

In quick rising, approx. 10 % of the circulating blood volume goes from chest organs to lower body vessels. Normally, BP reduction is prevented by neurohumoral system activation and changes in pressure receptor function. With age, the degree of such activation declines, thus causing lower BP during rising. Progressive orthostatic hypotonia in elderly people is characterised by slow reduction in SBP when rising (and compensatory growth in heart rate). Symptoms usually appear several minutes later. Type 2 DM patients may have episodes of orthostatic hypotonia more often than non-diabetic individuals. They are facilitated by diabetes-induced vegetative (autonomous) neuropathy, age-related baroreflex incompetence syndrome, and potential volume depletion (in case of diarrhoea, vomiting, blood loss, diuretic therapy). Often, episodes of orthostatic hypotonia are combined with postprandial hypotonia, which is caused by an increase in blood filling of GIT organs (usually 2–3 hours after a substantial meal, especially with alcohols). This is a classic mechanism of ischemic cerebral strokes (e.g. the patients comes home from work, eats a lot, lies down to rest, then rises and has both orthostatic and postprandial hypotonia, cerebral hypoperfusion, stroke) [17, 21].

*Clinical manifestations of orthostatic hypotonia* include episodes of dizziness, weakness, dyspnoea, chest pain, impaired vision associated with quick rising; hypotonia worsens in warm environment and during long-time standing. Syncopal state (also after long-time sitting — for example, during a long car ride, approx. 500–1000 mL of blood is re-distributed to lower limbs, and it contributes to the risk of syncope when rising), falls, fractures are not rare. It has been demonstrated that episodes of orthostatic hypotonia are associated with higher rates of cardiovascular and all cause deaths.

*Recommended approaches* to reduce the risk of such episodes include discontinuation of antihypertensives, which facilitate orthostatic reactions (such as thiazide diuretics, α-AB, direct vasodilators), consumption of more fluids, compression stockings, avoidance of abrupt verticalisation, avoidance of heat, overeating, hot bath or shower, high stresses (loads). Drug therapy used in type 2 DM patients can include alpha-lipoic acid products; less often — mineralocorticoids; fludrocortisone; desmopressin, a vasopressin analogue; midodrine, a sympathomimetic drug; pyridostigmine, a cholinesterase inhibitor. It has been reported that clonidine can potentially reduce orthostatic reactions, however, this information requires additional confirmation [19, 23].

Orthostatic hypotonia is a sign of cardiovascular autonomic neuropathy (CAN). Other symptoms include sinus tachycardia at rest (monotonous tachycardia); rigid rhythm (no response to physical or emotional stress); painless myocardial ischemia/silent myocardial infarction; sudden cardiac arrest/vegetative denervation. At early stages, CAN can be completely asymptomatic and can be diagnosed only after evaluation of heart rhythm variability with deep breathing. In advanced cases, patients present with tachycardia at rest, when heart rate is as high as 100 bpm, and poor exercise tolerance. Moreover, a majority of CAN cases are not associated with compensatory rise in the heart rate upon verticalisation, despite developing hypotonia (chronotropic failure). Most often CAN symptoms appear in vertical position and include dizziness, weakness, palpitations and collapse [11, 13].

Timely CAN diagnosis is essential, since this type of neuropathy in DM patients is an independent cardiovascular risk factor. CAN in type 2 DM patients is associated with higher mortality rates. CAN can become more severe with fluctuations in glycaemia levels (especially with episodes of hypoglycaemia). It has been demonstrated that reduction in heart rate variability (CAN marker) is a direct independent cardiovascular risk factor in pre-diabetes patients. Glycaemia control is essential for CAN prevention [10, 12].

## Management of Patients with AH and Type 2 DM

### *Antihypertensives*

The most commonly used antihypertensives are ACE inhibitors, sartans, CCBs, thiazide-like diuretics, MRA and β-AB. α-AB, renin inhibitors, loop diuretics, drugs for CNS activity (methyldopa or clonidine) and product to directly reduce smooth muscle strain in vessels (e.g. hydralazin), are less common. The final choice of antihypertensives depends on a number of factors, such as comorbidities, GFR and adverse effects [19, 22].

ACE inhibitors and sartans significantly reduce the number of type 2 DM cases in patients with arterial hypertension or congestive heart failure, possibly due to improved insulin secretion and better insulin sensitivity

[25, 26]. They are highly recommended as first-line therapy in patients with AH, DM and IHD; since it has been proven that they reduce cardiovascular risks in diabetic patients [25-29]. They should be added to the therapy as soon as possible in order to prevent blood vessel remodelling [30]. Besides, they should be first-line drugs in patients with AH, DM and severe albuminuria (albumin/creatinine value of > 300 mg/g) and should be considered when albumin/creatinine value is 30–299 mg/g, since they reduce the risk of kidney disease progression [31]. In the HOPE study, ramipril significantly reduced the risk of combined endpoints, all cause deaths and hospitalisations due to heart failure, when used in patients with DM and microalbuminuria [33]. In the ADVANCE RCT, addition of perindopril and indapamide reduced the rate of cardiovascular and all cause deaths and the number of macro- and microvascular complications in patients vs. placebo [32]. The ACHIEVE RCT demonstrated that ACE inhibitors and dihydropyridine CCBs are superior to the therapy with ACE inhibitors and thiazide diuretics as regards reduction of adverse cardiovascular events in patients with and without DM; however, the hydrochlorotiaside dose used in the trial was below the level required for efficient CVD reduction [33, 34].

Other drugs affecting RAT are MRAs, spironolactone and eplerenone. It has been established that the addition of spironolactone to the standard antihypertensive therapy reduces albuminuria levels in patients with DM and DNP [35]. Also, the addition of spironolactone to a minimal dose of lisinopril resulted in better renal protection in DNP patients as compared to the same dose of losartan and ACE inhibitors [36].

CCBs are recommended as a first-line therapy in DM patients, especially in elderly patients with ISAH [37]. Previous studies assumed that CCBs were able to prevent DM by inhibition of β-cell apoptosis and improvement of β-cell function; however, the meta-analysis by Noto et al. did not prove this hypothesis [38, 39].

Therefore, ACE inhibitors, BRAs, CCBs and thiazide-like diuretics are acceptable for initial antihypertensive therapy in DM patients. It is important to take into account adverse effects of antihypertensives, especially those associated with cardiometabolic consequences. Thiazide-like diuretics (e.g. chlortalidone) can result in hyperglycaemia because of their ability to enhance insulin resistance [40, 41]. Besides, a majority of β-ABs are not recommended as a first-line therapy in DM patients due to their adverse cardiometabolic effects: increased triglyceride levels, reduced HDL cholesterol levels, suppression of hypoglycaemia symptoms and reduced insulin sensitivity [42]. Also, it is assumed that they can increase the risk of DM, especially in obese individuals, as compared to alternative drugs [43]. However, not all β-ABs have adverse effect for glucose homeostasis. Carvedilol, nebivolol, labetalol not only block β-adrenoreceptors, but also have additional properties facilitating vasodilatation and causing less adverse effect for metabolism [44]. These effects were studied in the GEMINI RCT in type 2 DM patients with AH. The study compared metabolic and glycaemic effects of metoprolol tartrate and carvedilol therapy. The use of carvedilol did not affect glycaemia control and improved insulin sensitivity. It appears that the lowest probability of DM de novo resulting from antihypertensive therapy is with the use of sartans, ACE inhibitors and, to a lesser extent, CCBs [45].

### *Lipid-lowering agents*

CVRs in patients with AH and type 2 DM are high and even very high in the presence of DNP. In order to reduce CVRs, it is recommended to use lipid-lowering agents in addition to life-style changes. When lipid-lowering agents are used, it is advisable to aim to achieve the target low density lipoprotein cholesterol (LDL-C) levels, which are: 1)< 1.8 mmol/L (in high CVR) or < 1.4 mmol/L (in very high CVR), or at least 50 % reduction vs. baseline. The first-line therapy are high or maximum tolerable doses of sartans. If, despite the use of sartans, the target LDL-C levels are not achieved, it is recommended to add ezetemibe to sartans; if this combination is unable to achieve the target LDL-C values, then PCSK9 inhibitor can be used as an additional measure [46, 47].

### *Antiplatelet drugs*

In type 2 DM patients with AH, if they have DNP and atherosclerotic cardiovascular involvement, a very high risk of cardiovascular risk necessitates the use of acetylsalicylic acid (ASA) 75–100 mg/day as a preventive measure. If not tolerated, clopidogrel can be used as an alternative to ASA. A dual antiplatelet therapy comprising ASA and platelet P2Y12-receptor inhibitors (ticagrelor, clopidogrel) is recommended for patients who underwent scheduled coronary stenting (usually no more than 6 months), as well as for post-acute coronary syndrome individuals (usually no more than 12 months) [11, 27].

### *Glycaemia control*

In type 2 DM patients with chronic IHD, metformin is the leading antihyperglycemic drug; if necessary, other drug classes are added to metformin. After information from a number of RCTs has been received on the

favourable effects for cardiovascular and renal prognosis of the two new classes of antihyperglycemic drugs, glucagon-like peptide-1-receptor agonists (GLP1ra) (AWARD-7 RCT) and iSGLT2 (EMPA-REG, CANVAS, DECLARE, CREDENCE, DAPA-HF RCTs), experts give priority to these classes (usually, in addition to metformin). If GLP1ra and/or iSGLT2 cannot be prescribed in addition to metformin, other antihyperglycemic drug classes can be added (which do not improve prognosis, but are more readily available).

In type 2 DM patients with DNP who have preserved or moderately impaired renal function (stage 1–3 CKD, GFR > 30 mL/min/1.73 m$^2$), a combination of metformin with GLP1ra and/or iSGLT2 is preferable. If GLP1ra or iSGLT2 cannot be used for economic reasons, then metformin can be supplemented with DPP-4 inhibitors, sulfonylureas, pioglitazone for glycaemic control in patients with DNP and GFR > 30 mL/min/1.73 m$^2$ [11, 24].

## Conclusion

To conclude this literature review, the presented material can be summarised as follows (Fig. 2). AH is a crucial factor of a cardiovascular and renal risk both in general population in among type 2 DM patients. In turn, type 2 DM is a cause of a variety of macro- and microvascular complications; it is a separate and independent cardiovascular risk factor. Very often, AH and diabetes are comorbidities; they share common pathogenesis characteristics and mutually aggravate each other.

In the management of type 2 DM patients with AH, it is highly essential to follow the life-style change recommendations, including healthy eating, reduced sodium chloride consumption, graduated exercises, slimming, smoking cessation, reduced alcohol consumption. The most common target BP levels in this category of patients are 120–130/ 70–79 mm Hg, with target HbA1C values of 6.5–7.0 %. Literature data on the features of the course of AH and antihypertensive therapy in AH in combination of type 2 DM are very controversial. A number of specialists emphasise that the pattern of AH in these individuals is close to the pattern in individuals without diabetes, and there are no special features. At the same time, other researchers point out a number of aspects, that distinguish type 2 DM patients with AH from the general AH population, namely: salt sensitivity predisposition (so AH is often volume-dependant), a higher rate of circadian

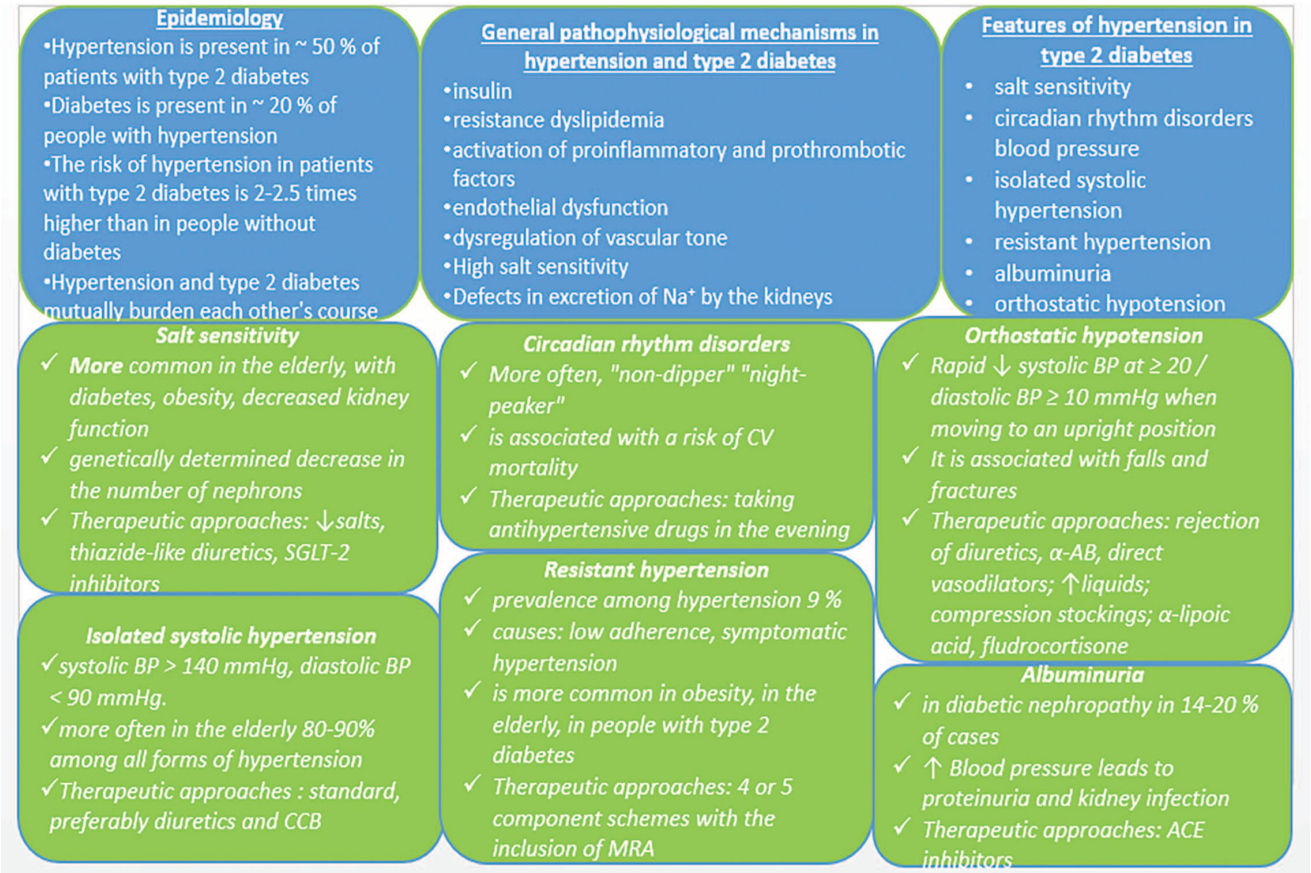


***Figure 2.*** *Arterial hypertension in type 2 diabetes mellitus*

BP rhythm abnormalities (with a higher rate of non-dippers and night-peakers), ISAH, resistant AH, a combination with albuminuria, episodes of orthostatic hypotonia. While the assumption that RATS blockers, including ACE inhibitors and sartans, have a dominant role in the management of AH with type 2 DM, is well-established, possible use of other classes of drugs in these patients, including MRAs, imidazoline receptor agonists and SGLT-2i, requires additional studies [11, 17, 23].

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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