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LEADING ARTICLE

Diabetes and hypertension a position statement by the American Diabetes Association: comments of Russian experts

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Summary
In September 2017 the experts of the American Diabetes Association (ADA) published a new document dedicated to diagnostics and treatment of arterial hypertension (AH) in patients with diabetes mellitus (DM). AH is one of the main risk factors in people with DM, and its prevalence depends on many circumstances and reaches 80%. It has been proved that BP control with antihypertensive therapy reduces the frequency of cardiovascular diseases related to atherosclerosis, heart failure, and microvascular complications. Published document consists of several parts that include detection, screening and diagnostics of AH, information about target BP levels, AH treatment with lifestyle change and pharmacological therapy, management of several groups of patients and treatment of resistant hypertension. This article contains the comments of leading Russian experts on key points of the new position statement of ADA.

Key words
Arterial hypertension, diabetes mellitus, guidelines.

Introduction
In September 2017 the experts of the American Diabetes Association (ADA) published a new document dedicated to diagnostics and treatment of arterial hypertension (AH) in patients with diabetes mellitus (DM). The previous version of this document was published in 2003.

The importance of this problem is doubtless. AH is one of the main risk factors in people with DM, its occurrence reaches 80% according to major clinical studies, and it depends on type of diabetes and its duration, age, gender, race/ethnic group, history of glycemic control, and presence of kidney disorders. AH is not only the risk factor of atherosclerosis, but also of heart failure and microvascular lesions. It has been proved that BP control with antihypertensive therapy (AHT) reduces the frequency of above-mentioned complications. Nevertheless, these characteristics can be improved with control of several risk factors. The fact that since 1990 significant improvement of BP control has led to reduction of atherosclerosis complications in patients with DM proves this hypothesis.

Recently published document consists of several sections:

- Definitions, screening, and diagnostics of AH with blood pressure targets;
- AH treatment including lifestyle management and pharmacologic therapy;
- Resistant AH;
- Management of pregnant women with AH and DM;
- AH treatment in older adults;
- AHT in the absence of hypertension;

The comments of leading Russian experts on key points of the new ADA statement are published in this review

Definitions, screening, and diagnostics of AH with blood pressure targets
AH is defined as continuing BP elevation ⩾ 140/90 mm Hg. Diagnostics can be complicated in case of masked hypertension and white-coat hypertension. Masked hypertension is defined as normal BP in hospital or in office (<140/90 mm Hg) and BP elevation at home (⩾135/85 mm Hg). White-coat hypertension is a phenomenon when patient exhibits BP above normal range (⩾ 140/90 mm Hg) in a clinical setting and normal BP at home (<135/85 mm Hg) [2]. Traditionally, BP monitoring at home and 24-h BP monitoring are used for diagnostics of these disorders. Orthostatic BP measurement should be performed for initial evaluation of hypertension and sometimes during follow-ups or if patient manifests the symptoms of orthostatic hypotension, and it should be done regularly if patient is diagnosed with orthostatic hypotension. The new ADA statement reports classic rules of BP measurement.

Automated office BP measurement is an alternative method to measure BP. This method was used in two large clinical studies ACCORD [3] and SPRINT [4]. Generally there is some difference between automated office BP measurement and standard office BP measurement. It means that the results of the trials in which this technique was used cannot be directly applied to standard BP measurement. Another important method of BP control is BP self-control at home. Cuff size is very important, since a small cuff would give BP higher than real ones, and a large cuff would give BP values lower than actual BP.

Orthostatic hypotension is an important problem and it correlates with increased risk of death and heart failure [5]. It is known that orthostatic hypotension can be caused by diabetic autonomic neuropathy and that it can be additionally aggravated with antihypertensive drugs [6]. Orthostatic hypotension is defined as reduction of systolic BP by 20 mm Hg or as reduction of diastolic BP by 10 mm Hg within 3 min in comparison measured at sitting or supine position [7]. It is important to evaluate the symptoms of orthostatic hypotension in order to individualize blood pressure goals, choose the most appropriate antihypertensive agents and minimize adverse effects of AHT. More than that, type of antihypertensive drug or timing (switch to nocturnal dosing) may require correction. In particular, α-blockers and diuretics may need to be stopped. People with orthostatic hypotension can use compression stockings or other approaches [8].

AH treatment including lifestyle management and pharmacologic therapy

Epidemiologic and prospective studies show that BP≥115/75 mm Hg is associated with increased rate of atherosclerotic vascular lesions [9], heart failure, retinopathy, kidney disease, and it indicates prognostic value of BP control in patients with DM [10, 11, 12, 13, 14]. Pharmacological treatment of BP ≥140/90 mm Hg is reasonable. According to the UKPDS study, targeting BP <150/85 mm Hg versus BP < 180/105 mm Hg contributes to reduction of macro- and microvascular complications by 24% [15].

In the majority of cases patients with AH and DM should reach systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg during treatment. Lower systolic and diastolic BP values (<130/80 mm Hg) may be appropriate for selected groups of patients with high risk of cardiovascular diseases.

Is there the need of intensive BP control in patients with AH and DM?

The ACCORD BP study examined the effects of intensive BP control (systolic BP <120 mm Hg) comparing with standard BP control (systolic BP <140 mm Hg) in patients with DM 2 type. Intensive BP control did not result in reduction of combination of total major cardiovascular events (myocardial infarction (MI), stroke, or cardiovascular death, hazard ration (HR) 0,88, 95% confidence interval (CI) 0,73 to 1,06), but the risk of stroke was reduced by 41% (HR 0,59, 95% CI from 0,39 to 0,89). Intensive AHT was associated with serious adverse effects in some cases (in 3,3% versus 1,3%) due to increased frequency of hypotension, electrolyte abnormalities and elevated serum creatinine concentration.

Taking into account these analyses, antihypertensive treatment is beneficial when initial average BP is ⩾ 140/90 mm Hg or if target BP values after AHT are ⩾ 130/80 mm Hg [16, 17-19]. In general, between the studies with lower initial or achieved BP AHT reduced the risk of stroke, retinopathy and albuminuria, but its effects on other complications and heart failure were not obvious. Taken together, these meta-analyses consequently demonstrate that treatment of patients with baseline BP ⩾ 140 mm Hg up to reaching target BP levels < 140 mm Hg is beneficial, whereas more intense goals may have additional but lest trustworthy advantages.

Lately the individualization of target BP levels is widely discussed. It is caused by the fact that advantages and risks related to the intensity of therapy may vary in patients depending on the presence of concomitant diseases (for example the risk of progressing kidney disease), glycemic status, age, etc. At the same time it is necessary to take into account the risks associated with treatment (adverse effects), absolute risk of cardiovascular events and expected lifespan.

Patients with higher risk of cardiovascular events (like the risk of stroke) or albuminuria who can reach intensive BP control easily without severe adverse effects may correspond better to intensive BP control. And patients with condition more common in older adults like functional limitations, polypharmacy, and multimorbidity suit better to less intense BP control.

Notably, there are no convincing data available for definition of target BP levels in DM type 1. Association of BP with macro- and microvascular outcomes in DM type 1 are generally similar with the ones of DM type 2 and general population [20]. Although there are no proved results, young people with DM 1 can achieve intense BP control easier and gain some significant long-term benefit from it.

Lifestyle management in patients with DM

For the first time official ADA statement on AH treatment in DM included lifestyle management that has not been defined well for this category of patients in the corresponding section of ADA DM treatment guidelines 2017 ("ADA Standards")

This document reports that lifestyle change is an important aspect of AH treatment in patients with DM 2 type that reduces BP levels, increases the effectiveness of several hypotensive drugs, improves vascular condition and is normally accompanied with lower number of adverse effects of treatment. Nowadays it is well known that all patients with DM and systolic BP > 120 mm Hg or diastolic BP > 80 mm Hg belong to the group of risk to develop AH and its complications [21, 22], and that lifestyle modification helps to prevent or to slow down AH development and the need of pharmacological therapy. To achieve stable change of patient's behavior, his lifestyle should correspond to his needs, and it is also necessary to discuss this aspect together with DM treatment in general. Consulting of moderate and active lifestyle modification in subgroup of patients with risk factors including DM had positive effect on such intermediate outcomes like BP levels, lipids' concentration, fasting blood glucose concentration, body weight especially within 12-24 month period [23]. One recent meta-analysis proved that lifestyle change help to reduce BP in patients with DM 2 type [24].

Diet is the most important lifestyle restriction in this category of patients. Although by now no well-controlled trials dedicated to following diet during the treatment of elevated BP or AH in patients with DM have been conducted, the DASH study (Dietary Approaches to Stop Hypertension) evaluated the influence of different aspects of healthy diet in patients without DM. It has been demonstrated that hypotensive effect of such diet was comparable with the effect of therapy with one pharmacological agent [25]. This diet consists of calories restriction, restriction of sodium intake (<2300 mg/day), increased consumption of fruits and vegetables (up to 8-10 portions per day) and non-fat milk products (2-3 portions per day), and refusal of excessive alcohol consumption [26]. These recommendations are stricter comparing with the ADA standards that includes the Mediterranean diet [27] and various vegetable diets [28] together with the DASH diet. More than that, these standards highlight the negative influence of alcohol on patients with DM receiving insulin and insulin secretion stimulators due to the risk of hypoglycemia. Similarly, the ADA standards recommend refusing smoking and using tobacco products and electronic cigarettes for all patients with DM including the ones with concomitant AH.

Sodium is one of important dietary microelements which concentration correlated directly with BP level. Restriction of sodium intake in patients with DM has not been studied in controlled clinical trials. At the same time, the results of studies performed in patients with primary hypertension demonstrated that moderate restriction of sodium consumption (from 200 mmol [4600 mg] to 100 mmol [2300 mg]) reduced systolic BP by 5 mm Hg and diastolic BP by 2-3 mm [29]. Decreased sodium consumption was characterized with dose-dependent effect. Patients who received hypotensive pharmacological agents and simultaneously restricted sodium consumption demonstrated improved response to these drugs due to reduction of volume-dependent component of hypertension. Notably, comparing with the Russian clinical guidelines for diagnostics and treatment of AH (2013) and with the European ones (ESH (European Society of Hypertension)/ESC (European Society of Cardiology) 2013) allowable daily consumption of sodium is reduced more than twice (from 5-6 g to < 2,3 g) that reflects stricter diet management in patients with DM. Together with this, the ADA standards warn about possible danger of excessive sodium reduction (<1500 mg/day) since several studies demonstrated possible negative effects of such restriction [30, 31].

Physical activity is another important lifestyle aspect in patients with AH and DM. It has been shown that moderate physical activity (30-45 minutes of fast walking for most of the week) decreased BP [32]. The "Standards..." include more detailed recommendations on physical exercise: duration of moderate or intensive physical activity should be 150 min per week or more and it should be distributed for at least 3 days of the week, and duration of any period without physical activity should be not more than 2 days. More than that, in case of long forced staying in sitting position patient should make breaks every 30 minutes to improve the control of glycaemia. Regular physical exercise may reduce BP and require correction of the dose of AHT [33]. Physical activity should be recommended to all patients including older patients with restricted physical abilities. Type and intensity of physical activity should correspond to patient's preferences and functional condition and also patient's pharmacological therapy should be taken into account. For

example, beta-blockers can reduce the tolerability of maximal physical exercise, and diuretics increase the risk of dehydration.

Regular physical activity has another positive effect: it reduces body weight. It is known that the loss of 1 kg of weight correlated with BP reduction approximately by 1 mm Hg [34]. According to the ADA standards, weight loss may be achieved in case of daily energy intake of 1200-1500 kcal for women and 1500-1800 kcal for men. Many patients with DM and obesity have to reduce body weight more than by 5% in order to achieve positive outcomes of glycemic control, and weight loss of 7% and more is considered optimal. Together with this, some drugs promoting weight loss can increased BP and should be taken with caution. Many obese patients have obstructive sleep apnea, and weight loss reduces significantly apnea symptoms, and this, in its turn, leads to additional BP decrease [35]. All above-mentioned strategies of lifestyle modification may influence positively glycemic control and lipid levels, so they should be advised even to patients with light BP increase.

Particular attention of the ADA guidelines 2017 for treatment of AH in DM is paid to regular analysis of pharmacological agents that patient receives, since drugs with possible hypertensive effect can be present between them, including self-administered drugs and plant-derived agents. For example, one of meta-analyses demonstrated that non-steroid anti-inflammatory drugs increase systolic BP by 5 mm Hg [36].

The section dedicated to the lifestyle modification is concluded with the following recommendation of the ADA for patient with systolic BP > 120 mm Hg or diastolic BP > 80 mm Hg: lifestyle change should include weight loss (for patients with excessive body weight or obesity); following the DASH diet that considers reduced sodium consumption, increased potassium intake, increased intake of fruits and vegetables, restriction of alcohol consumption, and increased physical activity (level of evidence – B).

Pharmacological treatment of AH in patients with DM

Lifestyle modification is an important aspect of AH correction, but the choice of the optimal therapy that would have not only hypotensive but also organ-protective effect is not less important. Analysis of previously performed placebo-controlled trials demonstrated that renin-angiotensin-aldosterone system (RAAS) blockers had advantages for cardiovascular and renal events' prevention in patients with DM comparing with other pharmacological agents, independently on their hypotensive effectiveness. According to the ADA guidelines [37], RAAS blockers with nephroprotective effect have a priority for AH treatment in all patients with DM independently on the presence of abnormal kidney function, but these guidelines are based on placebo-controlled trials that had been finished 15-20 years ago [38]. Early prescription of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor type I blockers (sartans, ARB) is reasonable in patients with DM an high cardiovascular risk [39] and/or congestive heart failure [40]. At the same time, other classes of drugs, especially calcium channel blockers and beta-blockers with proved efficacy for treatment and prevention of cardiovascular diseases are frequently used in DM population.

In 2013 ESH/ESC working group for AH treatment proposed to use all groups of hypotensive drugs in patients with DM, but to prescribe RAAS blockers as the first line medications. Also the attitude to BP levels appropriate for starting AHT has changed: it increased from 130/80 mm Hg to 140/90 mm Hg [41]. This change is based on the results of the ACCORD study that demonstrated no additional advantages of target BP levels 130/80 mm Hg for cardiovascular events' prevention.

In the end, the last statement from the Joint National Committee on prevention, detection, evaluation, and treatment of high BP in patients with DM recommended all hypotensive agents' groups, but if there is microalbuminuria or proteinuria the treatment should be started from RAAS blockers [42].

Meta-analysis of 19 randomized controlled trials that included 25414 patients with DM was performed in 2016 due to the absence of single distinct opinion on AHT prescription in patients with DM and AH [43]. It evaluated RAAS blockers efficacy comparing with other classes of hypotensive drugs. This analysis did not include placebo-controlled trials and did not analyze patients with clinically significant chronic heart failure (CHF), for whom the benefit of ACE inhibitors or ARB has been proved.

The results of this analysis demonstrated that RAAS blockers' efficiency had no significant advantages over other antihypertensive agents (calcium channel blockers, beta-blockers, thiazide diuretics) in DM population in the following aspects: total mortality risk (HR 0,99, 95% CI 0,93-1,05), cardiovascular mortality (HR 1.02, 95% CI 0.83-1,24), stable angina, (HR 0.80, 95% CI 0.58-1,11), myocardial infarction (MI)

(HR 0.87, 95% CI 0.64-1,18), stroke (HR 1.04, 95% CI 0.92-1,17), CHF (HR 0.90, 95% CI 0.76-1,07), and the necessity of myocardial revascularization (HR 0,97, 95% CI 0,77-1,22). There was no significant difference in kidney disease progression (HR 0,99, 95% CI 0,78-1,28). RAAS blockers demonstrated significantly lower risk of CHF development just in comparison with calcium channel blockers (HR 0,78, 95% CI 0,70-0,88).

This analysis did not demonstrate the advantage of RAAS blockers over other antihypertensive agents for prevention of poor cardiovascular outcomes in patients with DM. The only exception was fair for patients with DM and CHF. These results prove the recommendations of ESH/ESC guidelines (2013) and the 8th statement of the Joint National Committee on prevention, detection, evaluation, and treatment of high BP (2014) that demonstrated that any class of antihypertensive drugs may e used in patients with DM especially without impaired renal function.

The last ADA guidelines published in summer 2017 maintain the position of hypotensive therapy "concretization" in patients with DM. They take into account the stage of diabetic nephropathy, degree of BP elevation and cardiovascular risks that may influence the choice and intensity of AHT. RAAS blockers have advantage in patients with diabetic nephropathy (urinary albumin-to-creatinine ratio ⩾ 300 mg/g or from 30 to 299 mg/g to blood creatinine level). The possibility to prescribe other classes of hypotensive drugs in case of necessity is preserved. Particular attention is paid to precise monitoring of creatinine and potassium levels for treatment with RAAS blockers. Recommended target BP level is < 140/90 mm Hg, and there are no strict limitations on available therapy.

In general, the last ADA statement widened the possibility of clinical practitioners to rely on their knowledge, intuition and experience and increased their responsibility for AH treatment in patients with DM.

Influence of glucose-lowering agents on BP levels

Hyperinsulinemia and exogenous insulin administration in theory can lead to BP elevation due to vasoconstriction and sodium and liquid retention [44]. Insulin by itself had direct vasodilating action, and basal insulin treatment comparing with the standard one is not connected with BP change in patients with DM type 2 or pre-diabetes (the ORIGIN study [45]).

Taking into account the fact that hyperinsulinemia and insulin resistance are physiological components of BP regulation, activation of sympathetic vegetative system plays the leading role in realization of their effects [42].

In its turn, renal hypersympaticotony being a particular feature of insulin-induced AH, develops as the consequence of hyperinsulinemic stimulation of central mechanisms of sympathetic nervous system and it results in increased noradrenalin secretion in sympathetic synapses of kidney due to activation of renal tissue rennin-angiotensin system during insulin resistance [46].

Sodium/glucose cotransporter 2 inhibitors (iSGLT2) are associated with moderate diuretic effect and BP reduction (systolic BP by 3-6 mm Hg and diastolic BP by 1-2 mm Hg) [47, 48].

This principally new class of glucose-lowering agents has been introduced into clinical practice relatively recently. iSGLT2 reduce glucose reabsorption in kidney and increase glucose excretion with urine up to 60-80 g/day [49].

iSGLT2 potential is not restricted just to glucose homeostasis and partial elimination of glucose from blood.

Additional advantage of this group is BP reduction (systolic BP by 2-4 mm Hg, and diastolic BP by 1-2 mm Hg). More than that, increased glucose excretion and moderate osmotic diuresis induce several systemic effects including the once modeling cardiovascular factors apart from BP reduction: weight loss because of fat tissue, reduction of albuminuria, ureic acid concentration decrease, reduced risk of hypoglycaemia, improved sensitivity of muscular tissue to insulin [50].

Possible mechanisms underlying iSGLT2 hypotensive effect include osmotic diuresis, increased sodium concentration in renal tubuli in macula densa zone that may be considered as a signal for decreased renin secretion by cells of juxtaglomerular apparatus, and possible non-direct effect of NO released in response to reduced oxidative stress in case of improved glycemic control [51].

Glucagone-like peptide-1 agonists (aGLP-1) are also associated with BP decrease [104]. Therapy with aGLP-1 (in particular liraglutide and exenatide) demonstrated moderate reduction of systolic BP [52]. Meta-analysis of observation of 12469 patients, 41% of whom received liraglutide and the rest received exenatide, demonstrated higher hypotensive effect in the group of aGLP-1 comparing with the control group (by 2,22 mm Hg (95% CI: -2,97; -1,47))independently from initial BP levels or degree of HbA1c reduction [53].

August. 25 of 2017 after the results of the LEADER study the U.S. Food and Drug Administration (FDA) approved new indication for aGLP-1 drug liraglutide: reduction of main undesirable cardiovascular events in adult patients with DM 2 type and concomitant cardiovascular diseases. This decision of FDA was partially based on hypotensive effects of this drug [54].

Management of pregnant patients with AH and DM

AH occurs in 8-10% of pregnant women. During the last years there is an obvious increase of frequency of hypertensive complications during pregnancy due to increased age of pregnant women and high prevalence of obesity and DM. AH during pregnancy can manifest for the first time after 20 week (gestational AH) or before (chronic AH), and in both cases it may be complicated with pre-eclampsia development (AH with proteinuria). AH increases the risks of such undesirable maternal and perinatal outcomes like premature birth, surgical delivery, birth of underweight children, and perinatal mortality.

The majority of guidelines on AH management during pregnancy are based on few empiric observations and they vary a lot. The following recommendations on AH treatment in pregnant women with DM have E level of evidence and represent the consensus opinion of experts.

Nowadays the discussion about efficacy of AH treatment during pregnancy is still ongoing due to possible problems with fetal growth. Control of severe AH is recommended for reduction of maternal morbidity and mortality. In case of moderate AH the benefit of AHT for pregnancy outcomes has not been proved in clinical studies. Treatment of moderate AH is capable to prevent development of severe AH. At the same time AHT may cause impaired fetal growth. AHT did not decrease total risk of pre-eclampsia. It is necessary to take into consideration the fact that stricter BP control with target diastolic BP 85 mm Hg comparing with less strict control of BP 105 mm Hg did not improve pregnancy outcomes and did not decrease the risk of birth of underweight children, but together with it decreased the risk of severe AH.. Additional advantages of AHT are focused on reduction of short-term and long-term maternal morbidity, mortality due to stroke and other vascular and organ lesions.

Thus, the guidelines on AH management in pregnant women with DM are formulated in the following way: at first, AHT is not indicated during chronic AH or moderate gestational AH with systolic BP < 160 mm Hg, diastolic BP < 105 mm Hg, and without the symptoms of target organ lesions; at second, target BP levels for chronic AH and previously performed AH may vary in the range of 120-160/80-105 mm Hg.

The American college of obstetricians and gynecologists does not recommend AHT for moderate gestational AH (systolic BP < 160 mm Hg or diastolic BP < 110 mm Hg), since there are no advantages for pregnancy outcomes and potential risks of therapy are enough high. For pregnant women with high risk of pre-eclampsia low-dose aspirin is recommended starting from 12 weeks of gestation. Aspirin improves the deepness of placenta attachment and circulation in spiral arteries. There are evidences that low-dose aspirin reduces the risk of pre-eclampsia in 10-24% of cases, and in general it improves perinatal outcomes, decreases the frequency of delayed fetal development and premature birth. The signs of serious adverse effects from aspirin therapy like increased perinatal death or increased frequency of intracranial hemorrhage of fetus or post-partum hemorrhage for mother have not been identified. Also Russian guidelines indicate the necessity of low-dose aspirin administration starting from 12 weeks of gestation in women with high risk of pre-eclampsia. DM 1 and 2 type are the high risk factors for pre-eclampsia development.

Target BP levels in the range of 120-160 mm Hg for systolic BP and 80-105 mm Hg for diastolic BP are considered safe both for mother and fetus. It is better to avoid lower BP values since BP lower than 120/80 mm Hg may cause impaired fetal growth. It is advised to consider the possibility to reach target BP levels < 140/90 mm Hg in pregnant women with AH and signs of target organ lesions including cardiovascular and kidney diseases in order to prevent progressing of organ lesions during pregnancy.

Recommendations on choice of antihypertensive drug are restricted by warning against ACE inhibitors, ARB, and spironolactone since these agents have teratogenic effects and are contraindicated during pregnancy. Updated ADA guidelines on AH treatment (2017) named antihypertensive drugs effective and safe during pregnancy: metildopa, labetalol, hydralazine, and extended-release nifedipine. In the Russian Federation the following drugs are recommended for administration during pregnancy: metildopa (the first line), extended-release nifedipine (the second line), and beta-blockers (metoprolol, propranolol, sotalol, bisoprolol). Beta-blockers are not advised for treat-

ment of AH in pregnant women with DM due to unfavorable effects on perinatal outcomes, decreased body weight, and increased risk of intrauterine growth retardation. During post-partum period women with gestational AH and pre-eclampsia should be examined for not less than 7-10 days together with precise BP monitoring within first 72 h after delivery due to high risk of complications development. Even normotensive women have a tendency to BP elevation during post-partum period; BP reaches the maximal values by 5th day after the childbirth, and it is the consequence of physiological increase of liquid volume and its mobilization into vascular system. Patients with AH preserve the same trend. The choice of pharmacological agent during post-partum period is mostly determined by lactation, but normally the same drugs that woman received during pregnancy and after delivery are recommended. Long-term observation of these patients is advised since they have higher risks of cardiovascular complications in long-term period.

AH treatment in older adults (≥65 years)

In this section ADA experts concentrate on several key questions related to AH treatment in older patients with DM.

At first, the importance of patient's functional status, comorbidity, and polypharmacy for the choice of AHT strategy and target BP levels is highlighted. The choice of AHT strategy and target BP levels should be made based on estimation of older patient's condition: in fitter patients, a therapeutic strategy similar to that used in younger individuals should be used, whereas in the patients with loss of autonomy and functional limitations (like the need of help for basic daily routines) higher levels of target BP (140-150 mm Hg) and reduced intensity of AHT in the presence of BP <130 mm Hg and orthostatic hypotension should be considered. In this context the ADA statement goes along with the documents prepared by geriatric communities that highlight impossibility of using the same therapeutic regimens tested in multiple randomized clinical trials on fitter patients for older patients with senile asthenia [55].

At second, this document highlights the role of high arterial stiffness as the cause of high systolic BP (that is the goal of AHT) and difficulties related to its achievement. It's recommended to be careful with possible excessive lowering of diastolic BP below 65-70 mm Hg in patients with high arterial stiffness (pulse BP ≥60 mm Hg) , since reaching this levels may increase the risk of coronary complications.

At third, the statement mentions the high risk of iatrogenic complications including hypoglycemia (use of beta-blockers is restricted by their ability to mask hypoglycemia), orthostatic hypotension (should be monitored for any antihypertensive drug prescribed) and reduction of circulating blood volume (may be worsened with diuretics).

Conclusion

AH is a potent modifiable risk factor of diabetic macro- and microvascular complications' development. Numerous clinical studies demonstrated the efficacy of AH correction using several classes of antihypertensive drugs for prevention of cardiovascular and microvascular complications. Meta-analysis of clinical studies demonstrates the benefit of reaching target BP < 140/90 mm Hg in the majority of patient with DM. Lower values of BP may be useful for several patients with high risk of cardiovascular disorders in case of good tolerability of long therapy, and these goals should be evaluated on a case-by-case basis. Apart from lifestyle change, it is necessary to prescribe several classes of antihypertensive agents in order to achieve target BP. It has been shown that ACE inhibitors, sartans, dihydropyridine calcium channel blockers and thiazide-like diuretics improve clinical outcomes and are preferable for BP control in patients with DM. ACE inhibitors or sartans should be included in therapy of patients with albuminuria. Treatment should be individualized for each separate patient based on the presence of concomitant diseases, their expected benefit for cardiovascular diseases related to atherosclerosis, heart failure, progressing nephro- and retinopathy, and the risk of unfavorable events.

Thus, the position statement of ADA systematized the data of AH diagnostics, target BP levels and treatment approaches including lifestyle modification, use of various groups of drugs both in general population of patients with AH and DM and in selected categories of patients.

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References

1. Ian H. de Boer, Sripal Bangalore, Athanase Benetos, Andrew M. Davis, Erin D. Michos, Paul Muntner, Peter Rossing, Sophia Zoungas and George Bakris. Diabetes Care 2017 Sep; 40(9): 1273-1284.
2. Franklin SS, Thijs L, Hansen TW, O'Brien E, Staessen JA. White-coat hypertension: new insights from recent studies. Hypertension 2013;62:982–987

3. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
4. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116
5. Fleg JL, Evans GW, Margolis KL, et al. Orthostatic hypotension in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial: prevalence, incidence, and prognostic significance. Hypertension 2016;68:888–895
6. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40:136–154
7. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci 2011;161:46–48
8. Briasoulis A, Silver A, Yano Y, Bakris GL. Orthostatic hypotension associated with baroreceptor dysfunction: treatment approaches. J Clin Hypertens (Greenwich) 2014;16:141–148
9. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. JAMA 2017;317:165–182
10. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110–1130
11. Fox CS, Golden SH, Anderson C, et al.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research; American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2015;38:1777–1803
12. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883
13. Adamsson Eryd S, Gudbjörnsdottir S, Manhem K, et al. Blood pressure and complications in individuals with type 2 diabetes and no previous cardiovascular disease: national population based cohort study. BMJ 2016;354:i4070
14. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913
15. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
16. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615
17. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:i717
18. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011;123:2799–
19. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. J Hypertens 2017;35:922–944
20. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation. 2014;130:1110–1130
21. Whelton PK, Appel L, Charleston RN, et al. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I[published correction appears in JAMA 1992;267:2330]. JAMA 1992;267:1213–1220
22. Appel LJ, Champagne CM, Harsha DW, et al.; Writing Group of the PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. JAMA 2003;289:2083–2093
23. Lin JS, O'Connor EA, Evans CV, Senger CA, Rowland MG, Groo m HC. Behavioral Counseling to Promote a Healthy Lifestyle for Cardiovascular Disease Prevention in Persons With Cardiovascular Risk Factors: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force [Internet], 2014. Rockville, MD, Agency for Healthcare Research and Quality (US), 2014. Available from http://www.ncbi.nlm.nih.gov/books/NBK241537/. Accessed 11 November 2016
24. Chen L, Pei J-H, Kuang J, et al. Effect of lifestyle intervention in patients with type 2 diabetes: a meta-analysis. Metabolism 2015;64:338–347
25. Azadbakht L, Fard NRP, Karimi M, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. Diabetes Care 2011;34:55–57

26. Sacks FM, Svetkey LP, Vollmer WM, et al.; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3–10
27. Sundström J, Arima H, Woodward M, et al.; Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet 2014;384:591–598
28. Whelton PK, Appel L, Charleston RN, et al. The effects of non-pharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I [published correction appears in JAMA 1992;267:2330]. JAMA 1992;267:1213–1220
29. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. Diabetes Care 2002;25:134–147
30. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. Cochrane Database Syst Rev 2011;Oct 5:CD004184
31. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. Diabetes Care 2011;34:1270–1276
32. Brook RD, Appel LJ, Rubenfire M, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. Hypertension 2013;61:1360–1383
33. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2065–2079
34. Semlitsch T, Jeitler K, Berghold A, et al. Long-term effects of weight-reducing diets in people with hypertension. Cochrane Database Syst Rev 2016;Mar 3:CD008274
35. Shaw JE, Punjabi NM, Naughton MT, et al. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. Am J Respir Crit Care Med 2016;194:486–492
36. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289–300
37. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–967
38. Fox CS, Golden SH, Anderson C, et al.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research; American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2015;38:1777–1803
39. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615
40. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:i717
41. Arauz-Pacheco C, Parrott MA, Raskin P; American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2003;26(Suppl. 1):S80–S82
42. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110–1130
43. Arauz-Pacheco C, Parrott MA, Raskin P; American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2003;26(Suppl. 1):S80–S82
44. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. Lancet 2012;380:601–610
45. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
46. Fox CS, Golden SH, Anderson C, et al.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research; American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2015;38:1777–1803
47. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014;16:457–466
48. Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. J Am Soc Hypertens 2014;8:330–339
49. Arauz-Pacheco C, Parrott MA, Raskin P; American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2003;26(Suppl. 1):S80–S82
50. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615
51. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–967

52. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:i717
53. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011;123:2799–2810
54. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. J Hypertens 2017;35:922–944
55. Benetos A, Bulpitt CJ, Petrovic M, et al. An expert opinion from the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the management of hypertension in very old, frail subjects. Hypertension 2016;67:820–825