Vuk Vrhovac Institute, University Clinic for Diabetes,
Endocrinology and Metabolic Diseases,
Dugi dol 4a, HR-10000 Zagreb, Croatia

Review
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APPROACH TO ARTERIAL HYPERTENSION IN PATIENTS WITH DIABETES MELLITUS

Lea Duvnjak, Krishna Mohan Sepuri, Nikica Car, Željko Metelko

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SUMMARY

In diabetic patients, the presence of hypertension implies an increased risk of cardiovascular disease. Approximately two-thirds of such patients die from cardiovascular complications. Over the last decade extensive randomized trials showing a clinically significant benefit in outcomes with lowering of blood pressure levels have led to a revision of the definition of hypertension in diabetic population. According to recent guidelines, a target blood pressure of <130/80 mm Hg is recommended. The diagnosis of hypertension should be based on three or more separate measurements, after 5-minute rest in supine and standing position. A wider cuff should be used if midarm circumference is greater than 33 cm. Noninvasive ambulatory blood pressure measurement is becoming ever more widely used in diabetic patients for some advantages over standard sphygmomanometer, particularly due to the close relation with a range of target organ damage. Pharmacologic therapy needs to be individualized to fit the patient's needs and combinations of drugs are often necessary to achieve target levels of blood pressure control. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, calcium channel blockers and beta-blockers have all been documented as effective pharmacologic therapies. Because of the proven beneficial effects on the progression of nephropathy, the established practice of choosing an angiotensin-converting enzyme inhibitor or AT antagonist as first line agent in type 1 and type 2 diabetics is reasonable. Beta-blockers, diuretics and calcium channel-blockers should be used as second-line agents, and alpha-blockers in specific indications.

Correspondence to: Assist. Prof. Lea Smirčić-Duvnjak,M.D., Vuk Vrhovac Institute, University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Dugi dol 4a, HR-10000 Zagreb, Croatia
E-mail: lea.smircic-duvnjak@idb.hr

INTRODUCTION

The overall significance of arterial hypertension in diabetic population relies on two facts: 1.5-3 times higher prevalence in patients with diabetes compared with nondiabetics and approximately 86% of deaths in diabetics caused by cardiovascular disease (1,2). Hypertension as one of the major cardiovascular risk factors affects about 20%-60% of diabetic patients, depending on the criteria used on its definition (2,3).

DEFINITION

Previous epidemiologic studies defined hypertension as a systolic blood pressure of 160 mm Hg or greater and/or diastolic blood pressure of 90 mm Hg or greater. Over the last decade, studies in the general population indicating an increase in cardiovascular disease by 20%-30% with the increase in diastolic or systolic blood pressure of 5 mm Hg have led to a revision of the definition of hypertension (1,4,5). In 1999, the World

Health Organization (WHO) – International Society of Hypertension (ISH) and British Hypertension Society guidelines for the management of hypertension proposed a lower value of 140/90 mm Hg as a threshold for the definition of hypertension (6,7). Extensive randomized trials in diabetic patients showing a clinically significant benefit in outcomes with further lowering of blood pressure levels have also led to a revision of the definition of hypertension in diabetic population (1,3). In 1997, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) recommended a target value of 140/90 mm Hg for general population and a lower value of 130/85 mm Hg for diabetic patients (8). Recently published JNC VII guidelines recommend a target blood pressure of <130/80 mm Hg in diabetic patients. JNC VII have also introduced a new category, prehypertension, classified as a systolic blood pressure of 120-139 or diastolic blood pressure of 80-89 mm Hg (9). Many other authors have argued against this category, wondering if a person can be "prediseased" and emphasize that there is no single value dividing normotension from hypertension (10).

The recently published European Society of Hypertension (ESH), European Society of Cardiology (ESC) guidelines are shown in Table 1. The authors state the term prehypertension could only be applied to patients with an additional high risk. The threshold for the initiation of blood pressure treatment should be determined on the basis global cardiovascular risk including associated risk factors, risk of future organ damage, and target blood pressure values (10).

Table 1. **ESH-ESC guidelines**

	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal blood pressure	<120	and	<80
Normal blood pressure	120-129	and	80-84
High normal blood pressure	130-139	or	85-89
Hypertension			
1 mild	140-159	or	90-99
2 moderate	160-179	or	100-109
3 severe	≥180	or	≥110
	≥140	and	<90

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PREVALENCE AND CHARACTERISTICS OF HYPERTENSION IN DIABETIC PATIENTS

The prevalence of hypertension in patients with either type of diabetes is on an increase, although the timing and presentation differ between the two groups of patients (1,3). In type 1 diabetic patients, hypertension affects approximately 30% of individuals. It is usually not present at diagnosis, develops after several years of the disease, and closely correlates with the development of nephropathy. The increase in systolic and diastolic blood pressure is proportional (1,11). In type 2 diabetic patients, hypertension is usually present at the time of diagnosis, is not significantly related to the development of nephropathy, and the increase in systolic pressure is higher compared to diastolic blood pressure. In these patients, hypertension is closely associated with obesity, age, and hyperlipidemia. Although these confounding factors make the assessment of the prevalence of hypertension attributable to diabetes difficult, approximately 20%-60% of type 2 patients will develop hypertension (2,11).

Hypertension causes macroangiopathy and microangiopathy. Large vessel disease is nonspecific to diabetes but in diabetics it occurs at an earlier age and with a greater frequency. Coronary artery disease and myocardial infarction are two times, and cerebrovascular accidents 2-6 times more common in diabetics (12-14). Peripheral arterial disease including intermittent claudication, rest pain, foot ulceration, and peripheral gangrene is extremely common in diabetics and significantly correlates with systolic pressure (2,3,13). The essential lesion is accelerated atherosclerosis, with alterations in endothelial cells, platelet interactions, and lipid and glucose metabolism (12). Small vessel disease affecting the eyes (retinopathy), kidneys (nephroangiosclerosis, glomerulosclerosis, diabetic nephropathy) and peripheral neurons (neuropathy, vasa vasorum lesion) is specific to diabetes (15-17). The pathogenesis includes susceptibility factors such as duration of diabetes and metabolic control, functional abnormalities within the microcirculation, and consequences of hyperglycemia (advanced glycosylation end products) and hypertension (11,16).

Diabetic cardiomyopathy is a specific entity representing myocardial dysfunction in the absence of extensive coronary atherosclerosis with intramural coronary artery disease and interstitial myocardial accumulation of glycoprotein and collagen (13).

DIAGNOSTIC APPROACH

On clinical assessment and investigations in diabetic patients with newly diagnosed hypertension, some important points should be considered. The type and duration of diabetes, therapy for diabetes, family history of hypertension, and presence of microvascular or macrovascular complications should be established. Emphasis should be placed on the assessment of overall cardiovascular risk, contributory factors (obesity, alcohol intake), and secondary causes of hypertension (primary aldosteronism, Cushing's syndrome, pheochromocytoma, acromegaly, hyperparathyroidism, thyreotoxicosis, renovascular disease) (1,3). Physical examination includes body mass index (BMI) and waist to hip ratio (WHR) measurement. Signs related to other endocrinopathies should be noted. Glycosylated hemoglobin, lipid profile, urinary albumin excretion, creatinine clearance and serum electrolytes should be determined, and other hormones (catecholamine, growth hormone, thyroid hormones) if necessary. It is advisable to routinely perform chest radiography and electrocardiography, ophthalmoscopy, neurologic and peripheral artery examinations (1,2).

Special care should be taken when measuring blood pressure. The diagnosis should be based on three or more separate measurements, which must be accurately performed after 5-minute rest in supine, sitting and standing position. A wider cuff should be used if the midarm circumference is greater than 33 cm (3,18).

Noninvasive ambulatory blood pressure measurement (ABPM) is being ever more widely used in diabetic patients for offering some advantages over standard sphygmomanometer. This method eliminates the observer bias, the "white coat" effect, is quiet in operation and highly reproducible. It measures blood pressure during normal daily activities and sleeping period, and usually averages over 20 measurements to obtain the blood pressure status. If the normal 24-hour blood pressure is preserved, the values are lower at night, with a decline in systolic and diastolic blood pressure by more than 10/5 mm Hg compared with daytime measurement (the nocturnal deep). ABPM is more closely related to a range of target organ damage in comparison with clinical measurements. The target organ damage includes left ventricular hypertrophy, microalbuminuria, cerebral infarctions, and retinal vessel abnormalities (3,18,19).

THERAPEUTIC APPROACH

The aim of antihypertensive treatment is to reduce the mortality and morbidity from cardiovascular (congestive heart failure, coronary artery disease, stroke) and microvascular (nephropathy, retinopathy, neuropathy) complications (1,3,7). In patients with blood pressure values between 130/80 and 139/89 mm Hg, behavioral treatment may be used for at least three months. This treatment including dietary management with sodium restriction, weight reduction, increased physical activity, alcohol restriction and smoking cessation may often prove inadequate to reach target values. Although it is important to incorporate changes in unhealthy lifestyle that aggravates the underlying pathology, it has been recognized that once blood pressure rises above the threshold of 140/90 mm Hg, it is necessary to introduce medical therapy (3,7,10,20). Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, diuretics, and ß-blockers have all been documented to be effective pharmacologic therapies (3,20). Based on the results of a number of studies demonstrating improvement in the range of renal outcomes, agents that inhibit the renin-angiotensin system (RAS), i.e. ACE inhibitors and ARBs, are considered first line antihypertensive agents in type 1 and type 2 diabetic patients with microalbuminuria (3,9). Approaches to antihypertensive therapy in type 1 and type 2 diabetic patients are shown in Figures 1 and 2.

The objective in the development of these drugs was RAS inhibition for protection of target organs, in addition to the expected benefit of blood pressure reduction. Intrarenal effects of ACE inhibitors on renal microcirculation are independent of the systemic blood pressure lowering effect and present in normotensive patients with microalbuminuria. Vasodilation of efferent arterioles with intraglomerular blood pressure decrease leads to prevention or delay of progression of diabetic nephropathy.

Figure 1. **Approach to antihypertensive therapy in type 1 diabetic patients**

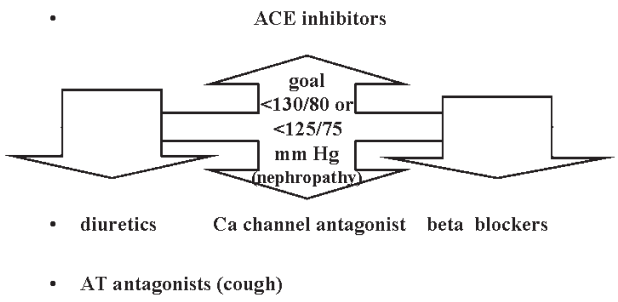
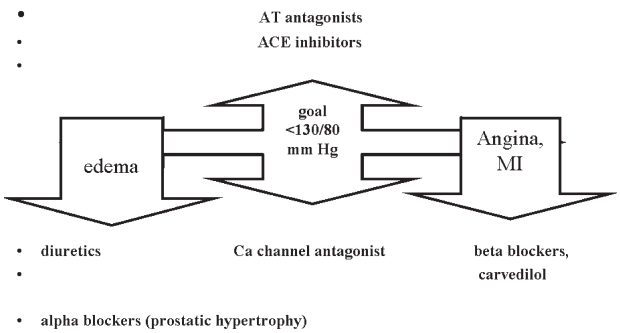


Figure 2. **Approach to antihypertensive therapy in type 2 diabetic patients**



The antihypertensive effects of ACE inhibitors include a decrease in elevated systemic vascular resistance without reflex sympathetic activation, enhanced perfusion of vital organs, and reversal of cardiac hypertrophy; reduction of sympathetic tone and decreased cardiac oxygen demands, decreasing both the preload and afterload. ACE inhibitor is also effective in preventing or delaying the progression of diabetic retinopathy.

ACE inhibitors have no adverse metabolic effects, glucose and lipid metabolism is not affected. Side effects include first dose hypotension, often present in patients receiving diuretics, cough with a tickling sensation in the throat that diminishes with time, and worsening of renal impairment. Caution is needed in elderly patients with atherosclerosis related renal artery stenosis (20-25).

Numerous clinical trials showed beneficial effects of ACE inhibitors in type 1 diabetic patients: regression to normoalbuminuria from microalbuminuria in normotensive and hypertensive patients, and delay in the progression to overt proteinuria in hypertensive patients with microalbuminuria (20-25) The Eurodiab Controlled Trial of Lisinopril in Insulin Dependent Diabetes confirmed the effect of ACE inhibitors on the reduction of the progression of retinopathy in normotensive patients (26).

Recent trials also documented beneficial effects of ACE inhibitors in type 2 diabetic patients: they decreased the risk of the development of micro- and macrovascular complications, decreased mortality in patients with cardiovascular risk factors or previous cardiovascular disease, and reduced the progression of retinopathy (27-29).

According to recent recommendation, ARBs represent first line therapy in type 2 diabetic patients with microalbuminuria or more advanced stages of nephropathy (3,9). These drugs act on AT1 specific angiotensin II receptors (vessels, kidney, heart, liver, brain) inhibiting the activity of angiotensin II on vasoconstriction, contractility, aldosterone and sodium reabsorption. In comparison with competitive agents, ACE inhibitors, these agents cause specific inhibition of angiotensin II and non-ACE angiotensin II pathways (cardiac chymase), and are not associated with cough and "first dose" hypotension (30,31).

Recent trials documented the beneficial effects of ARBs in type 2 diabetics with hypertension on the progression of microalbuminuria and more successful reduction of proteinuria in comparison with amlodipine with a similar degree of blood pressure decrease (32,33). Treatment with ARBs was also associated with a significant reduction in cardiovascular events compared to atenolol-based therapy, despite equivalent blood pressure reduction, and with a 25% lower incidence of new onset diabetes (34).

Monotherapy basically intended to increase the chosen agent dosage until the blood pressure begins to decrease was for long time considered as a traditional option to control hypertension. However, it should be emphasized that two-thirds of patients will require more than one agent to achieve the target value of blood pressure.

Beta-blockers are the appropriate choice as second drug or initial therapy in diabetic patients, unless contraindicated. These agents reduce cardiac output, heart rate and renal blood flow, increase peripheral vascular resistance, showing cardioprotective and good blood pressure lowering effect. In the UKPDS, atenolol

was as effective as an ACE inhibitor in decreasing the risk of the development of micro- and macrovascular complications in type 2 diabetics (27).

In diabetic patients, selective beta 1 receptor blockers (bisoprolol, atenolol, metoprolol) should be used. Nonselective beta 2 receptor blockers decrease insulin release, prolong hypoglycemia by inhibiting glycogenolysis in muscles and lipolysis in adipose tissue, and impair perception of hypoglycemia symptoms and recovery from insulin-induced hypoglycemia. However, it should be taken into consideration that both beta 1 and 2 receptor blockers increase triglycerides and lower HDL cholesterol, and cause deterioration in peripheral vascular disease. Peripheral vascular resistance and peripheral blood flow play a central role in mediating the metabolic side effects of the beta-blocking agents, as the vasodilating action (either *via* beta(2) stimulation or alpha 1-blockade) seems to more than offset the detrimental effects of the blockade of beta (or beta(1)) receptors.

For these reasons, vasodilating beta-blockers (dilevalol, carvedilol, celiprolol), combinations of nonselective beta-blockers and alfa 1 receptor blockers are very useful in diabetic patients.

The beneficial characteristics of these newer beta-adrenoreceptor blockers suggest that these vasodilating beta-blocking agents could be advantageous for hypertensive patients with insulin resistance or type 2 diabetes (1,3,35).

Thiazide diuretics reduce total body sodium through natriuretic action and show vasodilatory effects. Because of the proven benefits for cardiovascular outcomes, they seem to be appropriate choice as second drugs or initial therapy in diabetic patients without proteinuria.

Recently, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in high-risk hypertensive patients, including those with diabetes, demonstrated that chlorthalidone, a thiazide-type diuretic, was superior to an ACE inhibitor, lisinopril, in preventing one or more forms of cardiovascular disease (1,3,36).

Calcium channel blockers are commonly part of an effective multi-drug regimen in diabetic patients. These agents show additional benefits in terms of symptom control and inhibit calcium influx through membrane-bound voltage-dependent calcium channels, resulting in a decrease of intracellular calcium levels and vasodilation. They show antianginal, cardioprotective and antiarrhythmic properties and neutral effects on metabolic parameters.

Dihydropyridines (nifedipine, amlodipine) have mainly vasodilatory effects, and benzodiazepines (diltiazem) and phenylalkylamines (verapamil) moderate vasodilatory effects, negative inotropic and chronotropic effects. Renal disease does not influence their pharmacokinetics and side effects are minor, including peripheral edema and flushing.

Trials using dihydropyridine calcium-channel blockers in combination with ACE inhibitors and ß-blockers do not appear to show any increased morbidity or mortality from cardiovascular disease, as has been implicated in the past for dihydropyridine calcium-channel blockers alone (1,3,37,38).

Alpha receptor blockers represent a class of agents for which longterm data on efficacy in improving outcomes in diabetic patients are lacking, thus they should be used for specific indications (prostatic hypertrophy) or when additional drugs are needed to obtain a target blood pressure value (3,39). Caution is needed in patients with autonomic neuropathy because of the side effect of orthostatic hypotension.

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