

BENEFITS OF RENIN ANGIOTENSIN SYSTEM INHIBITORS IN HYPERTENSIVE PATIENTS WITH DIABETES MELLITUS

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REZUMAT

Hipertensiunea arterială este o afecțiune frecvent întâlnită la pacienții cu diabet zaharat, prevalența ei fiind de aproximativ 20-60%. Prezența hipertensiunii arteriale în diabetul zaharat crește riscul pentru complicații microvasculare și macrovasculare. Din aceste motive, în diabetul zaharat, tratarea hipertensiunii arteriale este la fel de importantă ca și reducerea hiperglicemiei. Agenții farmacologici hipotensori trebuie să contracareze mecanismele fiziopatologice ale hipertensiunii arteriale, să prevină complicațiile acestea și nu doar să reducă valorile crescute ale tensiunii arteriale. Activarea sistemului renină-angiotensină joacă un rol important în patogeniza hipertensiunii arteriale. În plus, are un impact negativ asupra micro- și macroangiopatiei, nu doar prin creșterea presiunii arteriale, ci și prin mecanisme adiționale: stimulează recrutarea leucocitelor la nivel endotelial, activarea macrofagelor, proliferarea celulelor endoteliale, hipertrofia și migrarea celulelor musculare netede, depunerea de collagen la nivelul peretelui vascular și favorizează tromboza. Numeroase studii clinice randomizate au evidențiat eficacitatea inhibitorilor enzimei de conversie și blocanților receptorilor angiotensinei II de a reduce valorile crescute ale tensiunii arteriale, morbiditatea și mortalitatea cardiovasculară și complicațiile microvasculare la pacienții cu diabet zaharat. În câteva studii importante efectul benefic al inhibitorilor sistemului renină-angiotensină a fost superior celui atribuit reducerii valorilor tensiunii arteriale, probabil fiind determinat de contracararea efectelor adiționale ale angiotensinei II. Aceste argumente justifică alegerea de primă intenție a unui inhibitor de enzimă de conversie ca agent hipotensor la pacienții diabetici cu hipertensiune arterială, cu sau fără nefropatie diabetică asociată. La pacienții cu diabet zaharat tip 2 și nefropatie diabetică, blocanții receptorilor angiotensinei II au avut efecte renoprotective importante. La acești pacienți, în prezența macroalbuminuriei (albuminurie >300mg/24 de ore) sau în prezența insuficienței renale cronice se recomandă administrarea unui blocant al receptorilor angiotensinei II.

Cuvinte cheie: hipertensiune arterială, inhibitori ai enzimei de conversie a angiotensinogenului, blocanți ai receptorilor angiotensinei II, complicații macrovasculare, nefropatie diabetică, boli cardiovasculare.

ABSTRACT

Hypertension is an extremely common diabetes comorbidity, affecting approximately 20 to 60% of diabetic patients. Hypertension further increases the risk for both micro- and macrovascular complications in diabetes. Activation of the renin-angiotensin system (RAS) plays an important role in the pathogenesis of hypertension, atherosclerosis, heart failure, diabetic and hypertensive nephropathy. Angiotensin II (AT II), the active component of RAS, has a negative impact on micro- and macroangiopathy not only through elevating blood pressure but through several additional mechanisms (stimulation of leukocytes recruitment, macrophages activation, proliferation of endothelial cells, hypertrophy and migration of smooth muscle cells, collagen deposition in the vascular wall, thrombosis). Several long-term randomized controlled trials have demonstrated the efficacy of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in lowering high blood pressure, reducing cardiovascular morbidity and mortality, total mortality and microvascular complications in diabetic patients. Some of these studies have suggested that RAS inhibitors may have additional beneficial effects independent of the blood pressure lowering action. These evidences justify the use of ACEIs as the first-line hypotensive agents in diabetic patients with mild or more severe hypertension, with or without nephropathy. In type 2 diabetic patients with diabetic nephropathy, ARBs have been shown to have considerable renoprotective effects. In these patients, in the presence of macroalbuminuria (albuminuria > 300mg/day) or renal insufficiency, ARBs should be strongly considered.

Key Words: hypertension, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, renin angiotensin system, cardiovascular disease, diabetic nephropathy

RENIN ANGIOTENSIN SYSTEM (RAS)

Any initial treatment for arterial hypertension should specifically address its pathophysiologic mechanisms and should aim at preventing or reversing

its complications and not merely lowering elevated blood pressure.

Activation of the renin-angiotensin system (RAS) plays an important role in the pathogenesis of hypertension, atherosclerosis, heart failure, and diabetic nephropathy.¹

Most of the physiologic effects of AT II, the active component of RAS, are mediated through the activation of angiotensin II type 1 (AT 1) receptors. These effects include vasoconstriction, proximal tubular sodium reabsorption, secretion of aldosterone from the adrenal glands, activation of the sympathetic nervous system, and cell proliferation. Angiotensin II type 2 (AT 2) receptors, abundantly represented during fetal life, are

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expressed during adulthood only in a few organs, including the heart, the adrenal gland, and the kidney. The number of these receptors increases during certain disease states. Their function is not completely understood. AT II induces vasodilatation, mediated by bradykinin, nitric oxide, and cyclic GMP through the activation of its type 2 receptors.¹

Several effects of AT II are involved in the pathogenesis of hypertension: vasoconstriction, vascular myocyte hypertrophy which enhances the vasoconstrictive response to vasopressors, plasma volume expansion (by increased secretion of aldosterone and antidiuretic hormone and by hemodynamic renal effects) and activation of the sympathetic nervous system.

AT II is also involved in atherogenesis through up-regulation of vascular cell adhesion molecules expression, stimulation of leukocytes chemotaxis, macrophages activation, enhanced formation of superoxide anion (which promotes production of oxidized LDL cholesterol), stimulation of vascular myocyte migration from medial to intimal vascular layer and increased deposition of tissue collagen in the vascular wall, increased platelet adhesiveness and increased plasminogen activator inhibitor type 1. AT II within the cardiac wall promotes left ventricular hypertrophy and congestive heart failure through cardiac myocyte hypertrophy and fibroblast proliferation. In the kidney, AT II promotes sodium retention, shifts pressure natriuresis toward higher blood pressure, increases transforming growth factor-beta.²

Therefore, it is obvious that AT II has a negative impact on micro- and macroangiopathy through additional mechanisms rather than through merely elevating blood pressure, and seems logical that a drug that reduces or eliminates the effects of AT II should be effective in hypertension treatment.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

The antihypertensive effect of ACEIs results from the transient reduction of circulating AT II, inhibition of tissular AT II production and the accumulation of bradykinin since the converting enzyme is also a kinase II, the enzyme responsible for degradation of bradykinin.² Inhibition of circulatory and tissular angiotensinogen converting enzyme (ACE) decreases the production of AT II and its vasoconstrictive, proliferative and prothrombotic effects. Also, increased bradykinin levels associated with the use of ACEIs leads to increased PGI₂ release, NO and tissue-plasminogen

activator production and has vasodilator, antiproliferative and fibrinolytic effects and might be responsible for the improvement in insulin sensitivity.³ The elevation of bradykinin levels may also contribute to the occurrence of ACEIs side effects, such as cough and angioedema.

Several long-term randomized controlled trials have demonstrated the beneficial effects of ACEIs in lowering elevated blood pressure, reducing cardiovascular morbidity and mortality, total mortality and microvascular complications in diabetic patients. Some of these studies have suggested that ACEIs may have additional beneficial effects independent of blood pressure lowering action.

Cardiovascular protective effects of ACEIs

The Heart Outcomes Prevention Evaluation (HOPE) study investigated the effects of ACE inhibition on the development and progression of atherosclerotic process.^{4,5} In this study 9297 patients with established atherosclerotic disease or diabetes with at least one other cardiovascular risk factor, i.e., hypertension, hypercholesterolemia, smoking, or microalbuminuria, were randomized to treatment with ramipril, versus placebo.

At the beginning of the study 38% of participants had diabetes, and 47% had mild elevated blood pressure. After a 4.5-year follow-up period, a 22% reduction in the primary outcome (combined incidence of myocardial infarction, stroke and death from cardiovascular disease) was reported in the ramipril-treated group. The incidence of myocardial infarction was reduced by 22%, stroke by 33%, all-cause mortality by 24%, and overt nephropathy by 24%, despite only modest reduction of blood pressure (-3/2 mm Hg). The lower cardiovascular risk in the ramipril group persisted after adjustment for blood pressure differences, therefore, it has been suggested that part of the cardioprotective properties of ACE inhibition are independent of their antihypertensive effects.⁴

The results of comparative trials of ACEIs, diuretics, beta blockers (BBs) and calcium channel blockers (CCBs) are discordant. The United Kingdom Prospective Diabetes Study (UKPDS)^{6,7} and Swedish Trial in Old Patients with Hypertension (STOP-2)⁸ found that ACEIs were equivalent to BBs and diuretics, while in Captopril Prevention Project Study (CAPPP)⁹, ACEIs were superior in hypertensive diabetics. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attacks Trial (ALLHAT)¹⁰ compared ACEIs, CCBs and thiazide diuretics. In a prespecified subgroup analysis of 12,063 patients with type 2 diabetes, no significant differences were seen

between the groups in the primary outcomes of nonfatal acute myocardial infarction plus coronary heart disease death or all-cause mortality.

However, the risk for heart failure was lowest in the diuretic group. In addition, the ACEI group had a borderline elevated risk for combined cardiovascular disease compared with the diuretic group.⁵ The conclusion of this study that diuretics are superior to ACEIs and CCBs seems excessive because the study included a large number of African Americans, which have poorer response to ACEIs, systolic blood pressure was significantly higher in ACEI and CCB treated groups and the antihypertensive therapeutic combinations were inappropriate for ACEI.¹¹

The Appropriate Blood Pressure Control in Diabetes study (ABCD)¹² and the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET)¹³ demonstrated that ACE inhibition is superior to calcium-channel blockade in the reduction of cardiovascular events in patients with diabetes. Results of FACET have shown that, despite similar metabolic of both medications, fosinopril significantly lowered the risk for combined outcome of stroke, myocardial infarction, and hospitalization for congestive heart failure, compared to amlodipine therapy. It should be noticed that patients treated with both fosinopril and amlodipine had the fewest cardiovascular events.¹⁴

A meta-analysis of the ABCD, CAPPP and FACET trials showed a significant advantage of ACEIs over alternative treatment modalities in reducing acute myocardial infarction (63% reduction), cardiovascular events (51% reduction), and all-cause mortality (62% reduction).¹⁴ These findings were not observed in the UKPDS, which compared captopril with atenolol. The ACEIs did not appear to be superior to other agents for the stroke outcome in any of the trials.¹⁴

In some of the above-mentioned studies, the greater benefit of ACEIs in major cardiovascular events was not explained by differences in blood pressure control, metabolic control, or other measured risk factors.¹⁴ Other mechanisms linked to ACE inhibition may have played an additional role in the prevention of major clinical events. One of the possible mechanisms is improvement of insulin sensitivity by ACEIs.¹⁵ The HOPE trial also demonstrated that ramipril use results in a 34% reduction in the development of new cases of diabetes.

Similarly, the CAPPP showed a reduction of 11% in the new cases of diabetes with the use of an ACEI.⁹ It has been suggested that endogenous AT II, through its effects on insulin signalling, is involved in insulin resistance.¹⁶ Also, accumulation of bradykinin during chronic treatment with ACEIs could be involved in

reducing insulin resistance.¹ Other favorable metabolic effects of ACEIs include reduction of low-density lipoprotein particle oxidation¹⁷, counteraction of hypercoagulation¹⁸, reduction of oxidative stress¹⁹, and enhancement of endothelial nitric oxide function.²⁰ ACEIs may also enhance endothelial integrity by decreasing expression of vascular cell adhesion molecules²¹ and normalizing vascular permeability.²²

Renoprotective effects of ACEIs in type 1 diabetic patients

Several randomized, placebo-controlled studies performed in hypertensive and non-hypertensive type 1 or type 2 diabetic patients with microalbuminuria or macroalbuminuria have shown significant reductions in urinary albumin excretion rate with the use of different ACEIs. A large randomized placebo-controlled trial using captopril²³ showed a significant decrease in the progression of diabetic nephropathy in proteinuric hypertensive type 1 diabetic patients. Captopril treatment was associated with a 48% reduction in the doubling of serum creatinine and a 50% reduction in the incidence of end-stage renal disease or death. The differences in systolic and diastolic blood pressure levels between the two groups (placebo and captopril) studied were small, suggesting that ACEIs have a renal protective effect independent of their antihypertensive effect.¹

Renoprotective effect of ACEIs in type 2 diabetic patients

In the MICRO-HOPE study, ramipril compared with placebo reduced the relative risk of developing overt proteinuria from microalbuminuria by 24% ($P < 0.027$).⁴

Some limited evidence showed that ACEIs may have hypertension-independent renoprotective effects in patients with type 2 diabetes: some short-term trials²⁴⁻²⁶ and the placebo-controlled study of Ravid et al.²⁷

Development of microalbuminuria or overt proteinuria did not differ in patients receiving captopril or atenolol in the UKPDS study,⁷ or in those receiving either enalapril or nisoldipine in the ABCD studies.¹² So far, there are no long-term trials comparing angiotensin II receptor blockers with ACEIs in patients with diabetes. Early data on renal outcomes appear to be equivalent²⁸ and effects on intermediate endpoints such as blood pressure control seem to be similar, although angiotensin II receptor blockers may be slightly better tolerated.⁵

Diabetic retinopathy and ACEIs

In the UKPDS, tight blood pressure control was

associated with a significant reduction of 34% in the number of patients requiring photocoagulation and showing deterioration of the retinopathy by two or more steps, and a 47% reduction in the risk of decreasing vision in both eyes.^{6,7} This benefit was achieved with either ACEI or BB, suggesting that the reduction in blood pressure, rather than ACE inhibition itself, may be of primary importance.

ACEI therapy has been associated with lower levels of vascular endothelial growth factor in patients with proliferative diabetic retinopathy,²⁹ and studies on animal models strongly suggest a potential benefit for ACE inhibition as a treatment for diabetic retinopathy.³⁰ Although conclusive proof of a specific and independent benefit for ACE inhibition in treating diabetic retinopathy has not been demonstrated, clinical trials are now under way to further elucidate these issues.

ANGIOTENSIN II RECEPTOR BLOCKERS

AT 1 receptor blockers prevent the binding of AT II, generated both in the classic pathway of ACE and in the non-ACE, altern pathway, and consecutively lower blood pressure through vasodilatation, reduction of sympathetic activity, decreased aldosterone synthesis, decreased retention of sodium and water. They determine an increase in circulant AT II and stimulate AT 2 receptors (if they are expressed). Lack of AT 2 receptor blocking permits the maintenance of favorable effects of AT II mediated through these receptors: vasodilatation with increased coronary blood flow, a better myocardial oxygenation, myocardial protection during ischemic events and antiproliferative effects. Angiotensin II receptor blockers (ARBs) do not interfere with bradikinin and substance P catabolism, thus avoiding ACEIs side effects (cough, bronchospasm).³¹

Currently, there is a large range of AT 1 receptor blockers, known as sartans: losartan, irbesartan, candesartan, valsartan, telmisartan, eprosartan, and olmesartan. The selectivity for AT 1 receptors compared to AT 2 receptors is extremely important. This selectivity is over 20,000 for valsartan, over 10,000 for candesartan, over 8,000 for irbesartan, over 3,000 for telmisartan and over 1,000 for eprosartan and losartan.

All ARBs have a duration of action of approximately 24 hours, that allows administration once daily.

Monotherapy with ARBs achieves blood pressure control in over 50% of subjects with grade 1 and grade

2 hypertension. When associated with other blood pressure lowering agents, target values are reached in over 80% of the patients.^{32,33} Sartans can be associated with BBs, CCBs, ACEIs, and diuretics. The association with ACEIs is extremely useful, as it decreases both circulating AT II and its action on AT 1 receptors.

ARBs do not interfere with carbohydrate and lipid metabolism. Side effects during sartan therapy are rare and side effect-related treatment drop-out rate is low.

Renoprotective effects of ARBs

Several studies in type 2 diabetic patients with hypertension have showed that ARBs reduce albuminuria, may even restitute normoalbuminuria and retard development and progression of nephropathy. In most studies ACEIs had renoprotective effects that exceeded the benefits attributable to lowering blood pressure.

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study³⁴ examined the effect of losartan vs. placebo when added to conventional antihypertensive therapy in 1513 diabetic type 2 subjects with diabetic nephropathy. Patients in the losartan group had a 16% risk reduction in the composite primary endpoint (doubling of serum creatinine, end-stage renal disease, or death), a 25% risk reduction in the doubling of serum creatinine, and a 28% reduction in the end-stage renal disease. The benefits exceeded those attributable to changes in blood pressure.

In Irbesartan Diabetic Nephropathy Trial (IDNT),³⁵ the effect of irbesartan added to conventional therapy was compared with amlodipine and placebo also added to conventional therapy in 1715 hypertensive diabetic type 2 patients with overt nephropathy. Treatment with irbesartan (300 mg) was associated with a reduction of the risk of the primary composite endpoint (doubling of serum creatinine, development of end stage renal disease or death) of 20% compared with the placebo group and 23% compared with the amlodipine group. The risk of doubling serum creatinine was 33% lower compared with the placebo group and 37% lower compared with the amlodipine group (daily dose - 10 mg). The relative risk of end stage renal disease was 23% lower in the irbesartan group than in the placebo or amlodipine groups. These differences were not explained by the blood pressure reduction achieved.

Microalbuminuria in Hypertensive Patient with Type 2 Diabetes Mellitus (IRMA 2) study³⁶ examined the effect of irbesartan (100 mg or 300 mg daily) vs. placebo on the development of diabetic nephropathy in 590 type 2 hypertensive diabetic subjects with

microalbuminuria. The results have shown a dose-dependent beneficial effect of irbesartan on the level of microalbuminuria and a more frequent restauration of normoalbuminuria in the 300 mg irbesartan group. Although both doses of irbesartan produced comparable reductions in blood pressure, only the 300 mg dose was renoprotective. It was concluded that irbesartan had a renoprotective effect independent of any blood pressure-lowering effect.

ACEIs and/or ARBs for renoprotection in hypertensive type 2 diabetic patients

So far there are no long-term trials comparing angiotensin II receptor blockers with ACEIs in patients with diabetes. Early data on renal outcomes appear to be equivalent²⁸ and effects on intermediate endpoints such as blood pressure control seem to be similar, although angiotensin II receptor blockers may be slightly better tolerated.⁵ Several small studies have showed the benefits of combining lower doses of ACEIs and ARBs. In the Candesartan and Lisinopril Microalbuminuria (CALM) study, dual blockade of the RAS using candesartan and lisinopril for 6 months found that the combination of both agents reduced blood pressure and urinary albumin levels to a greater extent than either medication alone.³⁷ However, published studies of ACEI plus ARB combinations have important shortcomings, including small numbers of study subjects and short-term follow-up (1 to 6 months).³⁸

Cardiovascular protective effects of ARBs

Long-term data on cardiovascular outcomes using this class of drugs are limited. The RENAAL study³⁴ compared the effects of losartan vs. placebo when added to conventional antihypertensive therapy in hypertensive type 2 diabetic patients. There were no differences between the two groups for all-cause mortality and the composite outcome of mortality and morbidity from cardiovascular causes. Rate of first hospitalization for heart failure was 32% lower on losartan. In the IDNT study³⁵ there were no significant differences in the rates of death or cardiovascular composite outcomes, between the groups treated with irbesartan, amlodipine or placebo in addition to conventional antihypertensive therapy. The addition of valsartan to chronic ACEI treatment in patients with heart failure in the Valsartan in Heart Failure Trial (Val-HeFT) study³⁹ did not reduce mortality but was associated with a 27.5% reduction in hospitalization. Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Trial⁴⁰ has demonstrated a 25% reduction of risk for composite endpoint (represented

by cardiovascular mortality, myocardial infarction, and stroke) in the subgroup of diabetes patients and a 38% reduction of general mortality risk.

CONCLUSIONS

Because many studies demonstrated the benefits of ACEIs on multiple adverse outcomes in patients with diabetes, including macrovascular and microvascular complications, in patients with either mild or more severe hypertension and in type 1 and type 2 diabetes, an ACEI should be the drug of choice as the first-line therapy for high blood pressure in most patients. In patients with type 1 diabetes, with or without hypertension, with any degree of albuminuria, ACEIs proved to be effective in delaying the progression of nephropathy. In patients with type 2 diabetes, hypertension and microalbuminuria, ACEIs and ARBs have been shown to delay the progression to macroalbuminuria. In those with type 2 diabetes, hypertension and macroalbuminuria (>300 mg/day) or renal failure, an ARB should be strongly considered.

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