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The Role of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists in the Management of Diabetic Complications

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Abstract

Evidence suggests that ACE inhibitors can be advantageous for prevention and halting progression of both micro- and macrovascular complications in patients with diabetes mellitus. ACE inhibitors are useful antihypertensive agents in both type 1 and type 2 diabetes; however, ACE inhibitor therapy often needs to be supplemented with calcium channel antagonists, β-blockers or diuretics to achieve good blood pressure control. ACE inhibitors are also indicated in non-hypertensive patients with type 1 and type 2 diabetes who have micro- or macroalbuminuria. The effect of ACE inhibitors in halting the development and progression of retinopathy and, potentially, neuropathy needs further proof in large-scale studies. More recently, angiotensin II receptor antagonists are emerging as drugs with the potential to be successfully included in the management of diabetic complications, especially when ACE inhibitors are not suitable because of adverse effects.

Angiotensin converting enzyme (ACE) inhibitors have been found to have multiple potential uses in the management of diabetes mellitus. The purpose of this review is to provide a trial-based overview of the use of these drugs in the management of macro- (usually cardiovascular death, stroke or myocardial infarction) and microvascular complications of diabetes. The focus is on the well-studied prevention of macrovascular events and diabetic kidney complications, but data on the potential uses of these medications for diabetic eye and nerve complications are also presented. Finally, some intriguing data have suggested that ACE inhibitors may even prevent or ameliorate the course of diabetes mellitus.

Although blood pressure reduction is uniformly recognised as preventive for the development of renal damage and macrovascular disease in both hypertensive and normotensive patients with diabetes, the target values to be achieved are still debated. Seemingly, the lower the blood pressure the better the protection against diabetic renal disease. Some have suggested 130/85mm Hg in patients with diabetes as a target.[1-3] The national Kidney Foundation Hypertension and Diabetes Executive Committees Working Group has recently sug-

gested 130/80mm Hg as the target blood pressure.[4] In patients with overt proteinuria values even less than 120/80mm Hg might be advisable but difficult to achieve. Thus far there is no evidence for a particular threshold blood pressure level that will provide a renoprotective effect in patients with diabetes.

1. Prevention of Macrovascular Complications

In the United Kingdom Prospective Diabetes Study (UKPDS) the effective reduction of arterial blood pressure was shown to be beneficial in patients with type 2 diabetes in reducing the macrovascular outcomes,[5] but the ACE inhibitor used (captopril) was not superior to other antihypertensives.[6] Tight control of blood pressure significantly reduced vascular complications in the UKPDS study, but no firm conclusions can be drawn as to whether ACE inhibition prevents macrovascular complications in hypertensive patients with diabetes more efficiently than other antihypertensive regimens.

The Swedish Trial in Old Patients with Hypertension (STOP)-2 trial,[7] showed that among patients with diabetes lowering of blood pressure with an ACE inhibitor to the same levels as with a calcium channel antagonist, β-blocker or diuretic, reduced the primary study end-points similarly. However, a post-hoc analysis suggested that the incidence of non-fatal myocardial infarction was reduced more with ACE inhibitors than with calcium antagonist treatment; on the other hand, there was a tendency for a lesser reduction in strokes during ACE inhibitor treatment. However, adjusting for multiple comparisons when analysing secondary outcomes in subgroups would make these small differences statistically non-significant and clinically they are not significant either. The placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial[8] showed that patients with diabetes who have isolated systolic hypertension treated with the calcium channel antagonist nitrendipine had significantly reduced total and cardiovascular mortality, stroke and all cardiovascular events. In addition, the occurrence of cardiac events tended to be lower with nitrendipine than with placebo but because of the small numbers this approximately 25% difference was not statistically significant. Thus, both ACE inhibitors and calcium channel antagonists seem to be equally effective in reducing macrovascular complications in hypertensive patients with type 2 diabetes.

The Heart Outcomes Prevention Evaluation (HOPE) study,[9] which was stopped prematurely on the recommendation of the independent data safety and monitoring board, convincingly showed the benefit of ramipril versus placebo for the reduction of cardiovascular events and overt nephropathy in patients with diabetes. Ramipril lowered the risk of major cardiovascular outcomes by 25 to 30% in high-risk, middle-aged individuals with diabetes, many of whom but not all were hypertensive. The cardiovascular benefit was greater than that attributable to the decrease in blood pressure since the reduction in diastolic blood pressure was only 3mm Hg on average. Recently, this study group reported a significant reduction of stroke in patients with diabetes receiving ramipril compared with placebo.[10]

The subgroup analysis of patients with diabetes from the Captopril Prevention Project (CAPPP) trial,[11] found a lower rate of fatal cardiovascular events in the captopril than conventional (diuretic and β-blocker) treatment group. The rate of myocardial infarctions was 66% lower in the captopril group than in the comparison group. The frequency of all cardiac events and total mortality was also lower in the captopril group, suggesting that ACE inhibition is particularly appropriate for the treatment of hypertension in patients with diabetes.[9] In a newer analysis of the patients with diabetes, the macrovascular endpoint occurred significantly less frequently among those receiving captopril than among those in the control group (relative risk [RR] = 0.59; p = 0.02). The difference was attributable to fewer cardiac events among captopril-treated patients, but there was no difference in strokes. Blood pressure level was approximately the same in both patient groups.[12]

It is evident from these studies that achievement of low blood pressure is not easy to accomplish with a single drug. Frequently three and more drugs are needed to reach the blood pressure target.[6] The use of polypharmacy for the lowering of blood pressure makes the judgement about which drug or combination of drugs the beneficial outcome can be mostly attributed, difficult. Although ACE inhibitors are often cited as the first line of therapy in hypertensive patients with diabetes, early prescription of a combination of antihypertensive drugs is necessary. It is unclear at the moment in which order calcium channel antagonists, β-blockers and diuretics should be added and how the baseline clinical characteristics of the patient influence the choice of the physician.[13]

2. Development of Diabetic Nephropathy

Diabetic nephropathy is the most common cause of end-stage renal disease in the developed world. High blood pressure is the main determinant for diabetic nephropathy. While any lowering of blood pressure reduces the risk of nephropathy,[14] ACE inhibitors have been demonstrated to be renoprotective in patients with type 1 diabetes and are now the standard of care for both hypertensive and non-hypertensive patients with type 1 diabetes used in everyday practice in patients exhibiting any level of proteinuria. The benefit of antihypertensive therapy with an ACE inhibitor in patients with type 1 diabetes can be demonstrated early in the course of the disease when microalbuminuria is the only clinical manifestation. In one study, the administration of an ACE inhibitor to normotensive patients with type 1 diabetes with microalbuminuria decreased both albumin excretion and progression to overt diabetic nephropathy when compared with patients treated with placebo.[15] Lisinopril appears to slow the progression of renal disease in normotensive patients with type 1 diabetes with little or even no albuminuria.[16] In patients with type 1 diabetes with overt nephropathy captopril was associated with a substantial reduction in the rate of decline in renal function as well as a 50% reduction in death and end-stage renal disease over a 4-year follow-up.[17]

The Candesartan and Lisinopril Microalbuminuria (CALM) study,[18] comparing the ACE inhibitor and angiotensin II AT_1 receptor antagonist effects on blood pressure and albumin excretion, and combination of these drugs, established that lisinopril and candesartan cilexetil were as effective in reducing blood pressure and urinary albumin excretion in hypertensive patients with type 2 diabetes. Importantly, the combination of both classes of drugs was more effective in reducing blood pressure (about twice) and albuminuria, and was well tolerated.

The Appropriate Blood pressure Control in Diabetes (ABCD) trial in patients with type 2 diabetes found treatment of hypertension with enalapril more efficient in preventing cardiovascular events (especially myocardial infarction) than treatment with nisoldipine.[19] But the study was not able to show any difference in incidence of nephropathy in hypertensive patients regardless of the intensity of treatment or the agent used (ACE inhibitor or calcium channel antagonist).[20] However, more recently, the study group reported that a significantly lower percentage of the 480 originally normotensive patients with type 2 diabetes in the intensively treated group (diastolic blood pressure 75mm Hg) progressed from normoalbuminuria to microalbuminuria and from microalbuminuria to albuminuria, experienced stroke or progression of retinopathy than those in the moderately treated group (diastolic pressure 80 to 89mm Hg).[21] The choice of medication still made no difference.

A study from Israel investigated the effect of enalapril versus placebo on the renal function and albuminuria in normotensive-normoalbuminuric patients with type 2 diabetes.[22] Enalapril treatment was significantly superior to placebo during the 6-year, double-blind, prospective study in preserving renal function as judged both by the creatinine clearance and albumin excretion.

Using a modelling approach, real data from conducted trials and some assumptions, it has been proposed that treating all persons with newly diag-

nosed type 2 diabetes with an ACE inhibitor might be the most cost-effective strategy for the prevention of end-stage renal disease.[23]

Recent studies have shed light on the potential mechanism of how ACE inhibitors exert their renoprotective action.[24] This renoprotective action appears to be in part independent of the effect on systemic blood pressure which explains the benefits also found in normotensive patients with diabetes. The intrarenal renin-angiotensin system is activated in individuals with diabetes by a yet unknown mechanism. The renoprotection is largely attributable to their local renin-angiotensin system inhibition in kidneys, by the dilation of renal efferent arterioles, reducing the intraglomerular pressure. However, angiotensin II is also produced in the kidneys by non-ACE enzymes and thus angiotensin II AT_1 receptor antagonists might provide even greater benefit. The ultimate purpose of the use of ACE inhibitors in microalbuminuric patients with diabetes is not just to reduce the albumin excretion rate or to prevent its progression *per se* but also to prevent a future decline in glomerular filtration rate, which would otherwise accelerate in the majority of these patients. The Irbesartan Diabetic Nephropathy Trial (IDNT)[25] and Irbesartan Microalbuminuria (IRMA)-2 study[26] both evaluated the use of the AT_1-receptor antagonist irbesartan and showed a significant preventive effect on the progression of renal disease in patients with type 2 diabetes. Another AT_1-receptor antagonist losartan may also be beneficial compared with β-blockers for the reduction of cardiovascular morbidity and mortality in patients with diabetes based on the conclusion from the recent Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.[27]

3. Diabetic Retinopathy

It is unclear if ACE inhibitors have the same benefit in diabetic retinopathy as they do in nephropathy. A preliminary report in 20 normotensive patients suggested that captopril might be associated with some benefit.[28] A more recent randomised trial assessed the efficacy of lisinopril in normotensive patients with type 1 diabetes and retinopathy.[29] Retinopathy was evaluated using a five-level scale. Retinopathy progressed by one level in 13.2% of patients receiving lisinopril versus 23.4% of those receiving placebo. Lisinopril also decreased progression by two or more levels by 73% and the progression to proliferative retinopathy by 82% compared with placebo. Tight blood pressure control in the UKPDS study significantly reduced the progression of diabetic retinopathy,[5] but treatment with captopril did not lead to a superior outcome compared with atenolol.[6] There is also evidence to contradict the efficacy of ACE inhibitors compared to calcium channel antagonists for slowing the development of retinopathy.[20]

The mechanism by which ACE inhibitors might inhibit the progression of retinopathy beyond blood pressure lowering is undefined. ACE is produced locally by vascular endothelial cells in retina,[30] which may have direct detrimental effects on retinal blood flow and vessels, independent of decrease in systemic arterial blood pressure. Increased intraocular generation of ACE could lead to the increased production of vascular endothelial growth factors that are involved in the angiogenic process of proliferative retinopathy.[31] Large scale randomised studies must be performed before these drugs can be recommended as superior to other antihypertensive agents for halting retinopathy.

4. Diabetic Neuropathy

It has been demonstrated in animal diabetes models that the ACE inhibitor lisinopril can have an ameliorating effect on neuropathy. Lisinopril was shown to normalise the motor conduction velocity,[32] improve sensory conduction velocity and normalise hypoxic resistance.[33] It was concluded that the beneficial preventative effect of lisinopril is likely to depend on a reduction of peripheral vascular resistance and improvement of tissue blood flow. However, there are few studies in humans. A study involving 13 individuals reported a significant improvement in nerve conduc-

tion velocity, temperature discrimination threshold, and vibration perception threshold measurements after 12 weeks lisinopril therapy.[34] A positive effect of ACE inhibition has also been documented on autonomic neuropathy.[35] Quinapril significantly increased parasympathetic activity in patients with diabetes which might lead to the reduction of the risk for malignant ventricular arrhythmias. The effect of trandolapril on diabetic neuropathy was assessed in 41 normotensive patients with diabetes who were randomly assigned to trandolapril or placebo. The patients receiving trandolapril had modest but significant improvement in several measures of peroneal and sural nerve physiology, but no effect on vibration perception threshold or autonomic function was seen.[36]

5. Potential Prevention/Amelioration of Diabetes

There are few data suggesting ACE inhibitors may not only benefit patients with known diabetes but also reduce the development of diabetes among individuals free of diabetes at the start of treatment.[11,37] However, in the former study[11] the conventional treatment regimen included β-blockers and that may have contributed to the deterioration of asymptomatic glucose tolerance. There have been hints that ramipril use may improve glucose control in patients with diabetes compared with placebo.[9] It appears that also AT_1-receptor antagonists may reduce the risk of developing diabetes in patients with hypertension compared with β-blockers.[38] Again, these are findings from post-hoc analyses and it will take several years before we will have more decisive data from new trials addressing this issue as the primary question. Two recently initiated studies, DREAM (Diabetes Reduction with an ACE-Inhibitor and other Medication) and ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) are currently evaluating this issue.

6. Conclusion

Evidence suggests that ACE inhibitors can be advantageous for preventing and halting progression of both micro- and macrovascular complications in patients with diabetes mellitus. ACE inhibitors are useful antihypertensive agents in both type 1 and type 2 diabetes; however, ACE inhibitor therapy often needs to be supplemented with calcium channel antagonists, β-blockers or diuretics to achieve good blood pressure control. ACE inhibitors are also indicated in non-hypertensive patients with type 1 and type 2 diabetes who have micro- or macroalbuminuria. The effect of ACE inhibitors in halting the development and progression of retinopathy and, potentially, neuropathy needs further proof in large-scale studies. More recently, angiotensin II receptor blockers are emerging as drugs with the potential to be successfully included in the management of diabetic complications, especially when ACE inhibitors are not suitable because of adverse effects.

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