Therapeutic Controversies in Hypertension Management: Angiotensin Converting Enzyme (ACE) Inhibitors or Angiotensin Receptor Blockers for Diabetic Nephropathy? A Case for ACE Inhibitors

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INTRODUCTION

Diabetic nephropathy is the number one cause of endstage renal disease (ESRD) in the United States. Blockade of the renin angiotensin system (RAS) is important in the treatment of diabetic nephropathy. With the reports of recently completed trials examining the role of angiotensin receptor blockers (ARBs) in type 2 diabetic nephropathy, the question has arisen as to which agents are best to block the RAS in type 2 diabetes. ACE inhibitors have been to preserve renal function in type 1 diabetics with nephropathy in large, randomized, placebo controlled trials, but such data is lacking in type 2 diabetes. Nevertheless, ACE inhibitors have been recommended for use in type 2 diabetic nephropathy for some time. In type 2 diabetics, ACE inhibitors may have a role in preventing development of nephropathy, and, importantly, ACE inhibitors have been shown to reduce cardiovascular disease in diabetics with and without nephropathy. In addition, ACE inhibitors have beneficial effects on other diabetic complications such as retinopathy and neuropathy. Until better comparative data between ACE inhibitors and ARBs on nephropathy and cardiovascular outcomes is available, ACE inhibitors should remain an important consideration for treatment of diabetic nephropathy. (Ethn Dis. 2002;12[suppl3]:S3-49–S3-52)

Key Words: Diabetic Nephropathy, ACE Inhibitor, Angiotensin Receptor Blocker, Hypertension

ACE Inhibitors in Diabetic Nephropathy

The finding that diabetic nephropathy was associated with hyperfiltration and increased glomerular pressure led to the hypothesis that agents that lower intraglomerular pressure would preserve renal function. ACE inhibitors, via their effects on angiotensin II and the efferent arteriole, decrease intraglomerular pressure and, therefore, were hypothesized to be of benefit in diabetes. Indeed, trials in Europe and the United States demonstrated the beneficial effects of ACE inhibitors in type 1 diabetics.

The Collaborative Study Group examined the effects of the ACE inhibitor captopril vs placebo in type 1 diabetics with at least 500 mg of proteinuria. Calcium antagonist (nifedipine), diuretics, and other agents were used to control blood pressure as necessary. Treatment with captopril improved renal survival, as demonstrated by the fact that those in the captopril group were less likely to exceed the endpoints of doubling of serum creatinine, ESRD or transplantation, or death. The effects of ACE inhibition was noticed early in the course of the 3.5-4 years of followup and were more apparent in those with initial serum creatinine greater than 1.5 mg/dL.

At the time of these studies, the majority of diabetics in the ESRD program were type 1 diabetics. However, that situation has now changed as type 2 diabetics outnumber type 1 diabetics in the ESRD population. This is likely a result of the significant increase in obesity and overweight in this country with the resultant "epidemic" in type 2 diabetes. The results of the studies in type 1 diabetics with nephropathy were extrapolated to type 2 diabetics and ACE inhibitors have been recommended in both types 1 and 2 diabetic nephropathy for some time. While a study similar in design to those described above has not been done to investigate effects of ACE inhibitors in type 2 diabetics,

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other studies have focused on different questions. Ravid et al asked if ACE inhibition would be of benefit in delaying progression of nephropathy in normotensive type 2 diabetics with microalbuminuria and normal renal function. Subjects were treated with enalapril (10 mg/day) or placebo using nifedipine to treat increased blood pressure as necessary. Renal function, assessed by change in inverse creatinine, remained stable in the enalapril group but declined by 13% in the placebo group.

In a subsequent study the same investigators asked if treatment with enalapril for normotensive type 2 diabetics without albuminuria would delay or prevent progression of nephropathy. Transition to microalbuminuria occurred in 19% of the placebo group vs 6.5% of enalapril recipients (absolute risk reduction of 12.5%). In addition, the enalapril group had a lower rate of decline in creatinine clearance over the 6 years of followup.

A meta-analysis of the effects of ACE inhibitors in diabetic and non-diabetic renal disease demonstrated that ACE inhibitors prolong renal survival. The authors reviewed almost 3 decades of published reports in their overview. ACE inhibitors were found to significantly decrease the risk of developing microalbuminuria among diabetics with microalbuminuria. In addition, among diabetics and non-diabetics with proteinuria and renal insufficiency the presence of an ACE inhibitor significantly decreased the risk of doubling of the serum creatinine or developing ESRD.

In general, the data demonstrates a favorable effect of ACE inhibitors on proteinuria and renal disease progression in diabetics. ACE inhibitors have been shown to have other effects, which may be beneficial in the treatment of diabetic nephropathy, independent of their hemodynamic effects. For example, ACE inhibitors have also been shown to decrease the level of transforming growth factor –β1 (an important cellular mediator of diabetic nephropathy) in diabetics. The totality of this data has led to the general recommendation that all diabetics with albuminuria (micro or macro) and/or hypertension be given an inhibitor of the renin angiotensin system (RAS). Should the blockade of the RAS be with an ACE inhibitor or an ARB?

**AN ARGUMENT FOR ACE INHIBITORS IN TYPE 2 DIABETIC NEPHROPATHY**

The major cause of morbidity and mortality in type 2 diabetes is cardiovascular disease (CVD). The rates of CVD are significantly increased in type 2 diabetics with nephropathy compared to diabetics without nephropathy. Again, blood pressure control may be the most important factor in preventing CVD in diabetics. Here, too, ACE inhibitors have been shown to have a significant impact on lowering CVD morbidity and mortality in diabetics. However, other agents like calcium antagonists, diuretics, and β-blockers have been shown to reduce CVD disease in diabetics if blood pressure targets are met.

There are several trials that have demonstrated the beneficial effects of ACE inhibitors on CVD in diabetics. The Captopril Prevention Project was designed to compare the potential benefits of ACE inhibitors vs a “conventional” antihypertensive regimen of diuretics and β-blockers on CVD morbidity and mortality. In this study of diabetic and non-diabetic hypertensives, captopril (initial dose 50 mg/day) was compared to the β-blocker (atenolol or metoprolol) or diuretics (hydrochlorothiazide and bendrofluzazide). There was a trend for the captopril group to have lower CVD mortality. Of interest, fatal and non-fatal stroke was increased in the captopril group. However, when diabetics were considered separately, captopril had a significantly lower rate of fatal and non-fatal CVD events.

The Heart Outcome Prevention Evaluation (HOPE) Study demonstrated that treatment of diabetics and non-diabetics at risk for CVD with the ACE inhibitor ramipril reduced CVD events and mortality. In addition, these investigators found an association of albuminuria and reduced renal function with increased CVD events and mortality. The presence of ramipril in these 2 groups lowered CVD risk.

The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial was designed to answer 2 questions: 1) to determine the appropriate blood pressure in hypertensive type 2 diabetics with nephropathy to retard progression of renal disease; and 2) to determine if the choice of antihypertensive agents used to get to blood pressure goal was important. The investigators randomized patients to an ACE inhibitor (enalapril) or the calcium antagonist (nifedipine). This trial was terminated early because of a significant reduction in fatal and non-fatal myocardial infarction (MI) in the enalapril group. It should be noted that the rate of MI in the calcium antagonist group was not elevated compared to other studies in similar populations, but rather, the rate of MI in the ACE inhibitor group was reduced. This indicated that ACE inhibitors offered “protection” from MI in type 2 diabetics with nephropathy.

Taken together, these data provide the most compelling reasons to support the use of ACE inhibitors in type 2 diabetics with nephropathy. ACE inhibitors provide cardiovascular protection that may be beyond that seen with blood pressure control alone. Given the high rate of CVD in type 2 diabetics with renal disease, cardiovascular protection is of the utmost importance.

To be fair, there has been a recently published study (Losartan Intervention for Endpoint Reduction [LIFE]) that demonstrates similar findings with the ARB losartan in hypertensive patients with left ventricular hypertrophy. Similar to CAPPP, losartan was compared to
the β-blocker atenolol. The losartan group had a distinct reduction in fatal and non-fatal stroke and a tendency for less CVD death. The rates of MI were similar. In a subanalysis of the diabetic patients, losartan was found to significantly reduce CVD morbidity and mortality and all cause mortality.\textsuperscript{26} However, in the recent trials with ARBs in type 2 nephropathy, the effects of ARBs on CVD were modest. Losartan was shown to lower first-time hospitalizations for CHF in comparison to placebo, but there was no effect on other CVD outcomes.\textsuperscript{7} Irbesartan was not shown to have a better CVD profile than amlopipine.\textsuperscript{8} The fact that ARBs did not demonstrate a significant impact on CVD may be the result of the lower blood pressure goals (and attainment) in these more recent trials.

### Other Important Benefits of ACE Inhibitors

ACE inhibitors have been shown to have other beneficial effects that are of importance in the diabetic patient. Similar to their effects on nephropathy, ACE inhibitors delay the development and progression of diabetic retinopathy.\textsuperscript{27} There may be some distinction between ACE inhibitors and ARBs in diabetic retinopathy. For example, in an experimental animal model, the ACE inhibitor lisinopril, but not losartan, was found to decrease levels of vascular endothelial growth factor and its type 2 receptor RNA.\textsuperscript{28} Similarly, ACE inhibitors appear to have a beneficial effect on diabetic neuropathy.\textsuperscript{29} These effects of ACE inhibitors are important as the quality of life of diabetics is strongly associated with preservation of sight and limbs.

Another beneficial effect of ACE inhibitors is that they may improve glycemic control and they are at least neutral in their effects on lipids. In fact, ACE inhibitors have been shown to be associated with a lower risk of the development of diabetes.\textsuperscript{20,21,30} These effects may be shared with ARBs, as losartan was shown to lower the incidence of diabetes, in comparison to atenolol, in the LIFE trial.\textsuperscript{25}

### Conclusions

It is clear that ACE inhibitors are beneficial in type 1 and type 2 diabetics with nephropathy. The lack of a specific randomized, placebo-controlled trial examining their role in type 2 diabetic renal disease has led some to state that the evidence supports using ARBs in type 2 diabetics with albuminuria.\textsuperscript{31} However, there is data in placebo-controlled trials that demonstrate the importance of ACE inhibition in delaying the development of nephropathy in hypertensive type 2 diabetics\textsuperscript{10} and normotensive type 2 diabetics.\textsuperscript{11} These studies are, arguably, of more importance than other traditional trials in diabetic nephropathy because they address prevention.

It is important to remember that the trials with ARBs did not allow use of ACE inhibitors and there are not strong comparative trials in this population. A large-scale comparative trial between ACE inhibitors and ARBs in diabetic nephropathy is not likely to occur for several reasons. One important reason is the probable lack of financial benefit to the drug manufacturers. Secondarily, given the similar effects of both agents, it will require a large number of patients in order to get significant differences.

Because the major cause of morbidity and mortality in diabetics, and particularly diabetics with nephropathy, is CVD, it is most important that our strategies to control hypertension in this population address this issue. ACE inhibitors have a significant protective effect on CVD in diabetics.\textsuperscript{20,21,24} It appears that the reduction in CVD disease observed with ACE inhibitors may be independent of blood pressure control, however, there are studies now that may argue otherwise.\textsuperscript{5,22,33} This CVD protective effect may be strongest in type 2 diabetics with nephropathy\textsuperscript{24} and has not been corroborated to the same extent as with ARBs. Therefore, the beneficial effects on ACE inhibitors on CVD disease, and, to a lesser extent, on diabetic retinopathy and neuropathy, and glycemic control provide strong support for the continued use of ACE inhibitors in diabetic nephropathy.

In summary, the evidence from recent trials examining the use of ARBs in type 2 diabetic nephropathy is not robust enough to favor ARBs over ACE inhibitors. This conclusion was shared by the Federal Drug Administration when considering whether to grant an indication to irbesartan for type 2 diabetic nephropathy. On the other hand, there is compelling evidence that the combination of ACE inhibitors and ARBs are beneficial in those with significant albuminuria.\textsuperscript{34,35} In conclusion, practitioners should continue to strongly consider the benefits of ACE inhibitors in type 1 and 2 diabetics with and without nephropathy.

### References

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AUTHOR CONTRIBUTIONS

Design and concept of study: Crook, Preddie
Acquisition of data: Crook, Preddie
Data analysis and interpretation: Crook, Preddie

Manuscript draft: Crook, Preddie