Diabetic nephropathy is the number one cause of endstage renal disease in the United States. Blood pressure is most important in delaying the progression of renal disease in persons with diabetes and, agents that block the renin angiotensin system (RAS) should be the primary agents used to achieve blood pressure reduction. There is debate regarding which method of RAS blockade should be used as primary therapy in persons with diabetes. There are not significant differences between angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) with regard to renal outcomes. Consideration of the enormously high rates of cardiovascular disease (CVD) in persons with diabetes and renal disease is the primary factor in choosing agents for blood pressure reduction. The ACE inhibitors and ARBs have been shown to reduce cardiovascular events in persons with diabetes and, there are recent comparable trials between the 2 classes. Some studies and meta-analyses show ACE inhibitors as being superior with regard to cardioprotection. In our nephrology clinic, we find that patients who presented on an ACE inhibitor had significantly lower CVD than those on ARBs (49.2% vs 70.1% prevalence of CVD, ACE inhibitor vs ARB respectively, \( P = .042 \)). We conclude that ACE inhibitors should be strongly considered as the primary method of RAS inhibition in persons with diabetes. (Ethn Dis. 2004; 14[suppl 2]:S2-1–S2-4)

**Key Words:** Angiotensin Converting Enzyme (ACE) Inhibitor, African American, Angiotensin Receptor Blocker (ARB), Cardiovascular Disease, Diabetes, Hypertension

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**INTRODUCTION**

As the number one cause of endstage renal disease (ESRD) in the United States, diabetic nephropathy and its optimal treatment has deservedly received much attention. Blood pressure control is the most important factor in delaying the progression of renal disease in patients with diabetic nephropathy.\(^1,2\) Lowering blood pressure with any antihypertensive agent is likely to delay renal disease progression in diabetes;\(^3\) however, angiotensin converting enzyme (ACE) inhibitors have been shown to reduce cardiovascular events in persons with diabetes.\(^4,5\) These studies show that ACE inhibitors have antiproteinuric effects similar to those of ARBs and are superior to other antihypertensive agents.\(^6,8\) Since ACE inhibitors have not been studied in large, appropriately designed trials in type 2 persons with diabetes, there is argument that the evidence for preventing renal disease progression in this population favors ARBs.

Clearly RAS inhibition is indicated in all persons with diabetes with albuminuria and/or reduced glomerular filtration rate. Both ACE inhibitors and ARBs have beneficial effects in the kidney of persons with diabetes. Both agents have been found to prolong renal survival compared to a placebo and, both are more likely to result in a regression of microalbuminuria to normoalbuminuria. Only small or short-term comparative studies have been done. Some comparative studies with proteinuria and blood pressure as endpoints suggest that, at maximum doses, ACE inhibitors may have more of an antiproteinuric effect than ARBs.\(^11\) However, at this time, there are no sig-
significant differences between these 2 classes with regard to renal outcomes.

**AN ARGUMENT FOR ACE INHIBITORS AS PRIMARY ANTIHYPERTENSIVE AGENT IN PERSONS WITH TYPE 2 DIABETES**

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 persons with diabetes with nephropathy compared to persons with diabetes without nephropathy. Again, blood pressure control appears to be the most important factor in preventing CVD in persons with diabetes. The ACE inhibitors have a significant impact on lowering CVD morbidity and mortality in persons with diabetes, however, calcium antagonists, diuretics and β-blockers have been shown to reduce CVD disease in persons with diabetes if blood pressure targets are met.

As mentioned earlier, two years ago we concluded that, because ACE inhibitors reduce CVD events and mortality, they should be the first line agent for lowering blood pressure in type 2 persons with diabetes. At that time, the evidence for CVD reduction with ARBs was not as strong as indicated by the data with ACE inhibitors. The Losartan Intervention for Endpoint Reduction (LIFE) study was the only study demonstrating the efficacy of ARBs at reducing CVD events.

In addition, other trials with ARBs in type 2 persons with diabetes with nephropathy showed only modest effects of ARBs on CVD. Losartan was shown to lower first-time hospitalizations for congestive heart failure (CHF) in comparison to placebo, but there was no effect on other CVD outcomes. While irbesartan did reduce CHF hospitalizations compared to amloidipine in the Irbesartin Diabetic Nephropathy Trial (IDNT), surprisingly, patients treated with amloidipine had lower rates of myocardial infarction (MI) and stroke. This is in contrast to FACET where fosinopril was superior to amloidipine in CVD outcomes in persons with type 2 diabetes.

Recently completed trials have provided more information on the relative effects of ACE inhibitors and ARBs on CVD. In the OPTIMAAL trial, captopril showed a strong trend toward superiority over losartin in reducing death (P=.069), the primary endpoint, in patients with acute MI and heart failure. In this large trial (N=5,477) captopril was significantly superior at reducing cardiovascular death (P=.032). The Valsartan in Acute Myocardial Infarction (VALIANT) Study and the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM-Added) Trial compared ACE inhibitors to ARBs or a combination of both agents. Superiority of one class over the other was not observed in either study.

Two meta-analyses have examined the effects on ACE inhibitors and ARBs on CVD outcomes. The meta-analysis by the Blood Pressure Lowering Treatment Trials’ Collaboration showed that both ACE inhibitors and ARBs reduced CVD events and mortality. There was no notion of superiority of one class relative to the other, and, independent of agent, blood pressure control was thought to be the most important factor to lower CVD. The second analysis was by the Cochrane Group. They included studies where ACE inhibitors or ARBs were compared and trials where there was a common comparator to either class. They found no difference between the 2 classes with regard to renal-specific outcomes; however, in their analysis, ACE inhibitors reduced all-cause mortality while ARBs did not. This approach has been questioned recently because several of the large ACE inhibitor trials included in the analysis were conducted with type 1 persons with diabetes who were much younger and had fewer CVD events.

To examine this question further, we examined our database. We have performed a cross-sectional analysis of persons with diabetes seen in our academic nephrology clinic during 2001 and 2002. The study was approved by the IRB of Wayne State University School of Medicine. This analysis includes 387 patients (326 [84.2%] African American). Cardiovascular disease (CVD) outcomes, CVD risk factors, and factors thought to have an effect on renal survival were specifically extracted from charts. The ACE inhibitors were used much more commonly than ARBs in this population that had more type 2 persons with diabetes (>95%) and female (64.2%) participants. At presentation to clinic, 193 patients were on ACE inhibitors, 28 on ARBs, and 2 were on a combination of both classes.

**Table 1. Prevalence of cardiovascular disease in diabetics presenting to Academic Nephrology Clinic by ACE inhibitor or ARB status**

<table>
<thead>
<tr>
<th></th>
<th>ACE Inhibitor (N=193)</th>
<th>ARB (N=28)</th>
<th>P (square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>31.4%</td>
<td>56.0%</td>
<td>.023</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>26.9%</td>
<td>37.0%</td>
<td>.359</td>
</tr>
<tr>
<td>Combined heart disease</td>
<td>40.1%</td>
<td>64.0%</td>
<td>.024</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>20.4%</td>
<td>7.14%</td>
<td>.120</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>49.2%</td>
<td>70.1%</td>
<td>.042</td>
</tr>
</tbody>
</table>

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; TIA=transient ischemic attack. Coronary artery disease: unstable angina, asymptomatic occlusive coronary disease on coronary angiogram, myocardial infarction.

Combined heart disease: coronary artery disease and/or congestive heart failure.

Cardiovascular disease: combined heart disease and/or stroke/TIA.

Prevalence rates shown as percentages as data not available on all subjects in every category.
In this analysis we only included those on either an ACE inhibitor or an ARB at presentation to clinic but not those on combination therapy. There was no difference in age, initial blood pressure, initial renal function, or protein excretion between the 2 groups. Renal survival, as determined by progression to end stage renal disease (ESRD) or combined ESRD and/or doubling of serum creatinine, was not different between groups. However, we did observe lower prevalence rates of CVD in patients presenting on an ACE inhibitor when compared to those on an ARB (Table 1). This difference appeared to be due to significantly lower rates of coronary artery disease in patients presenting on an ACE inhibitor when compared to those on ARBs (see table). Incident CVD after presentation was not different between the 2 groups.

CONCLUSIONS

Because the major cause of morbidity and mortality in persons with diabetes, and particularly persons with diabetes with nephropathy, is CVD, it is most important that our strategies to control hypertension in this population address this issue. While the debate as to whether there is a significant difference between ACE inhibitor and ARBs still rages, at the present time, we still favor using ACE inhibitors as the primary agent in persons with type 2 diabetes, hypertension and extreme CVD risk—that is CVD risk factors beyond that of diabetes and hypertension. While there are definitely limitations to our retrospective data presented above, we did observe a significantly lower prevalence of CVD in patients presenting on an ACE inhibitor when compared to ARBs. This is particularly relevant as it is a predominantly African-American population with type 2 diabetes and renal disease—arguably the group at highest risk for CVD in the United States. In conclusion, practitioners should continue to strongly consider the benefits of ACE inhibitors in persons with type 1 or type 2 diabetes with and without nephropathy, and they should feel comfortable using them rather than an ARB.

REFERENCES

Ethnicity & Disease - Crook and Penumalee


