ACE Inhibitors versus Angiotensin Receptor Blockers in Diabetic Nephropathy: Is There a Winner?

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The review by Wilmer et al. (1) and the comments from Brenner (2) reflect the dilemma facing physicians regarding the optimal approach to the blockade of the renin-angiotensin system in diabetic nephropathy. The publication of “The Effect of Angiotensin-Converting-Enzyme Inhibition in Diabetic Nephropathy” evoked a change in the standard of care for these patients (3). The agent used in this trial, captopril, in the modest dose of 25 mg thrice daily, was approved by the Food and Drug Administration as a “renoprotective agent.” On the basis of this trial, many physicians began therapy with angiotensin-converting enzyme inhibitors (ACEI), in not only in type 1 but also type 2 diabetic nephropathy. The logical progression of clinical trial research may well have dictated a subsequent study of ACE inhibition in overt type 2 diabetic nephropathy; however, there was dwindling patent protection for those pharmaceutical companies interested in this question. In addition, the priority for such a clinical trial was low at the National Institute of Diabetes, Digestive and Kidney Diseases. Hence the funding mechanisms that supported “The Captopril Trial” were no longer available. What emerged was an opportunity to employ angiotensin receptor blockers (ARB), which appeared to have several advantages beyond the financial considerations attendant the undertaking of a clinical trial. When compared with ACEI, ARB appeared safe and well tolerated, lacked the side effects of cough and angioedema, and had a pharmacologic advantage. It was well known that the competitive inhibitory characteristics of ACEI led to a compensatory increase in angiotensin I production, which could overcome the renin-angiotensin system blockade. The ARB provided a therapeutic avenue that involved noncompetitive kinetics at the level of the receptor, which would not be overcome by an increase in generated angiotensin II (4). In both a practical and theoretical sense, ARB appeared to have the advantage in a test of renoprotective effect. For these reasons, the Irbesartan Diabetic Nephropathy Trial (IDNT) was designed utilizing a member of a new class of pharmacologic agents, ARB (5). Irbesartan proved to be renoprotective in this patient population (6). It was inevitable that comparisons would arise with regard to the relative clinical efficacy of ARB and ACEI with respect to both the renoprotective and cardioprotective properties of these two classes of compounds.

A number of studies have analyzed the effects of the inhibition of the renin-angiotensin system upon the risk for cardiovascular complications in patients with diabetes (7–11). ACEI were utilized in the Heart Outcomes Prevention Evaluation (HOPE) Study (7), the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial (8), the Swedish Trial in Old Patients with Hypertension-2 (STOP Hypertension-2) (9), and the Valsartan versus Amlodipine Cardiovascular Events Trial (FACET) (10). Angiotensin-receptor blocker was administered in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Trial (11). The Valsartan in Acute Myocardial Infarction (VALIANT) Study and the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM “Added”) Trial attempted to compare the cardioprotective efficacy of an ACEI with an ARB in specific clinical situations (12,13). None of these studies included enough patients with overt diabetic nephropathy to provide a conclusive recommendation in the clinical population pertinent to this discussion. In these trials, agents that inhibited the renin-angiotensin system were efficacious with respect to cardiovascular outcomes. The beneficial cardioprotective effects of one of these classes over the other did not appear to be compelling.

The extensive meta-analysis carried out by the Blood Pressure Lowering Treatment Trialists’ Collaboration revealed favorable results when ARB-based regimens were compared with control regimens in trials that recorded a composite of major cardiovascular events. Similar results were reported when ACEI were compared with placebo and other therapeutic regimens (14). The overall conclusion of this meta-analysis was that BP management is a more important determinant of cardiovascular outcome than specific treatment regimens. The VALIANT study in post–myocardial infarction patients and the CHARM study in patients with heart failure were designed to compare the results with ACEI versus ARB. Both trials imply equivalence or an advantage to ARB in those specific patient populations (12, 13).

Results in the IDNT demonstrated a protective effect of irbesartan with respect to the development of congestive heart failure (6,15). Similar results were reported in the Reduction of Endpoints in NIDDM with the Angiotensin-II Antagonist Losartan (RENAAL) trial and the subgroup analysis of patients with diabetes in the LIFE trial (11,16). These findings accord
with results of clinical trials that have used ACEI (17). A recently reported meta-analysis by the Cochrane Group implied that diabetic nephropathy patients treated with ACEI had a reduced mortality rate compared with those treated with ARB (18). However, since the relevant studies in patients receiving ACEI were carried out in type 1 diabetic nephropathy (the mean age in the “Captopril Trial” was 35 yr [3]) and studies utilizing ARB were carried out in patients with type 2 diabetic nephropathy (the mean age in the IDNT and RENAA L was 59 yr and 60 yr, respectively [6,16]), one is forced to conclude that this reported difference is meaningless. The faulty logic employed in this meta-analysis does not test the therapeutic efficacy of ACEI versus ARB, rather, it demonstrates that younger patients with type 1 diabetic nephropathy have fewer cardiovascular events over a finite follow-up period than do older patients with type 2 diabetic nephropathy. In fact, during the Captopril Trial, few deaths or cardiovascular events were seen in either the placebo or the captopril groups (3). It is relevant that there were no significant mortality differences between ARB and the respective comparator groups in either IDNT or RENAA L (6,16).

The preponderance of studies with ACEI and ARB indicate that both classes of agents are associated with improved cardiovascular outcomes in defined settings. In the current state of our knowledge, evidence regarding the beneficial effect of one class of these agents over the other is less compelling. For the practitioner who is struggling with the question of treatment of patients with diabetic nephropathy, the overwhelming evidence from controlled clinical trials supports the recommendation of ACEI in type 1 diabetic nephropathy and ARB in type 2 diabetic nephropathy. In the absence of comparative studies of either cardioprotection or renoprotection in patients with overt type 2 diabetic nephropathy, the issue of whether ACEI are equivalent therapy to ARB remains unresolved.

Currently the strategy of combining ACEI and ARB therapy has been proposed as ultimately providing a solution to the problem (19). However it is important to emphasize caution, as the latter approach has not been thoroughly explored with respect to the optimal pharmacologic relationships of the two classes of drugs, the dose-response profile, or most importantly, the safety and efficacy profiles in this growing population of complex patients. This convenient answer therefore awaits appropriate scientific inquiry.

References
patients with type 2 diabetes and overt nephropathy. 


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