Recent Landmark Clinical Trials: How Do They Modify the Therapeutic Paradigm?

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Despite intense investigation and clinical attention, many challenges remain in the management of the hypertensive patient. It is clear that hypertension remains inadequately controlled worldwide, with the control rate in the United States approximating 27%. Furthermore, several recent studies have underscored that it is frequently difficult to attain control at goal blood pressure (BP) with monotherapy and that adequate control of hypertension based on the newer more intensified BP goals necessitates multiple drug therapy. Indeed, in the recently published landmark trials of angiotensin I receptor antagonists, including the Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of Endpoints in Non–insulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL), multiple antihypertensive drugs were required to attain goal. A pivotal class of drug required to comprise this regimen is the calcium antagonists. For example, in RENAAL, 78% of patients randomized to losartan required add-on therapy with a calcium antagonist. Calcium antagonists are an important and often necessary component of this multiple drug regimen. Am J Hypertens 2002;15:82S–84S © 2002 American Journal of Hypertension, Ltd.

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Data from the US Renal Data System Registry indicate that the incidence of end-stage renal disease (ESRD) is increasing steeply. The two disease entities driving this increase are diabetic nephropathy and, secondarily, hypertension. This review examines the specific trials in relation to diabetes mellitus and hypertension, and appropriate therapeutic intervention.

Clinical Trials

Diabetic Nephropathy and Secondary Hypertension

Because diabetes is steadily increasing, this disease entity appropriately was selected for study in numerous recently conducted intervention trials, including the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, the Irbesartan Diabetic Nephropathy Trial (IDNT), and the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA 2) study.

The Diabetes Collaborative Study Group of Lewis et al was the first proof-of-concept study to address the question of: Do agents such as angiotensin converting enzyme (ACE) inhibitors possess mechanisms independent of antihypertensive effects that are renoprotective? Four hundred nine patients with type 1, or insulin-dependent, diabetes mellitus (IDDM) were randomized to one of two interventions, either so-called usual care or an ACE inhibitor. The three end points selected to assess renal progression were time to doubling of serum creatinine concentration; renal survival, defined as that point in time when dialysis or renal replacement therapy is initiated; and mortality. The investigators demonstrated that patients randomized to the ACE inhibitor arm had slower progression to ESRD.

Despite the broad and expanding use of ACE inhibitors since 1993, the ensuing years have seen no leveling off of the incidence of diabetic nephropathy. Thus, there must be factors in addition to modulation of the renin-angiotensin system that constitute determinants of renal progression. Recent clinical trials have focused on this dilemma. The UK Prospective Diabetes Study (UKPDS) investigated the role of tight blood pressure (BP) control and the resultant risk of macrovascular or microvascular complications in type 2, or non–insulin-dependent, diabetes mellitus (NIDDM) patients. More intensive BP lowering demonstrated a clearcut difference on risk reduction. Indeed, a 32% risk reduction in diabetes-related death and a 44% risk reduction in stroke were demonstrated. Microvascular disease was reduced 37% and heart failure 56%. The resulting BP in the conventional therapy group was 154/87 mm Hg, compared to the tight control group where the achieved BP was 144/82 mm Hg (P < .0001 in both groups).
groups). To achieve these BP reductions in the tight control group, approximately one-third of the patients required three or more antihypertensive drugs. Two take-home messages are derived from UKPDS: lower is better, and monotherapy often does not suffice to achieve goal BP.

A similar trial, completed within months of UKPDS, was the Hypertension Optimal Treatment (HOT) study. More than 18,000 patients worldwide were enrolled, but essentially, the hypothesis tested was the same: Is lower BP better? Patients were randomized to three cohorts, in which the goal was a diastolic pressure of 90 mm Hg or less, 85 mm Hg or less, or 80 mm Hg or less. The objective of the study was to determine whether a relationship existed between goal BP and major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death). The investigators found a clear and linear relationship between BP and cardiovascular events in the diabetic patient cohort such that for the group randomized to the lowest goal (a diastolic pressure of 80 mm Hg), the cardiovascular event rate was reduced by one half. In all three groups, the majority of patients required at least two different antihypertensive drugs to reach goal, but for the group with the lowest goal (a diastolic pressure of 80 mm Hg), the need was most apparent, with 74% of patients requiring two or more antihypertensive drugs. Thus, HOT demonstrated the need for multiple antihypertensive drugs.

**Appropriate Therapeutic Intervention**

In September 2000, the National Kidney Foundation issued a consensus recommendation asserting that, on the basis of new data, the paradigm for adults with diabetes and hypertension deserved revision. Data from five major well-controlled landmark studies formed the basis of the recommendation. The UKPDS, HOT, the African American Study of Kidney Disease and Hypertension (AASK), the Modification of Diet in Renal Disease (MDRD) study, and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial were the studies included. Fig. 1, which is adapted from the National Kidney Foundation report, shows the average number of antihypertensive agents needed to achieve goal BP in these studies. In AASK, the patients randomized to the group with the lowest goal, 125/75 mm Hg, required an average of more than three and a half different drugs to achieve that goal. Patients with renal dysfunction and hypertension also required three and a half drugs. Patients with type 2 diabetes from the ABCD trial required in the range of two and a half to three agents. Thus, in patients with established hypertension and some complicating feature, such as diabetes or renal disease, monotherapy often will not suffice to achieve the desired goal.

Recently, results defining the role of angiotensin I (AT-I) receptor antagonists in the management of type 2 diabetes were reported in three landmark studies. The RENAAL study investigated the role of the AT-I receptor antagonist losartan. One thousand five hundred thirteen patients with established nephropathy were randomized to either standard care or losartan. The renal end point was a composite of time to first event, doubling of serum creatinine, ESRD, or death. The composite end point showed a 16% risk reduction for patients randomized to losartan. The average number of agents needed to achieve goal BP was approximately four; monotherapy did not suffice. During the RENAAL study, 78% of patients on the losartan arm required the addition of a calcium channel blocker (CCB) as part of the antihypertensive regimen to achieve goal BP. It is generally accepted that ACE inhibitors and/or AT-I receptor antagonists should be used as the initial intervention for this patient population, yet equally important is one of the conclusions in RENAAL, which states that "simultaneous therapy with a calcium channel antagonist did not detract from the beneficial effects of losartan despite the recent controversy regarding the role of the calcium-channel antagonists in the protection of the kidneys and the heart.”

A second AT-I receptor antagonist study, the IDNT study, was similar to RENAAL, with two exceptions. The number of patients exceeded 1700, and, importantly, rather than having two arms, it had three. These included the AT-I receptor antagonist irbesartan (300 mg daily), the CCB amlodipine (10 mg daily), and placebo. Again, the end points were similar to those in the RENAAL study. There was greater renal benefit with respect to renal protective effects for the AT-I receptor antagonist. Yet, similar to the results of the RENAAL study, monotherapy was again insufficient to reach goal BP, therefore intervention with multiple drug therapy was initiated. However, with
respect to cardiovascular end points, the amldipine arm generally fared as well as the AT-I receptor arm.

What the RENAAL and IDNT studies show collectively is the necessity for multiple drug therapy. Patients who are more difficult to treat are unlikely to achieve goal BP with a monotherapeutic approach. As illustrated in the RENAAL study, the antihypertensive regimen often requires the addition of a CCB to achieve goal BP.

The remaining unanswered questions are: How do CCBs influence the kidney? Is there evidence that CCBs stabilize renal function over time? If they do, how do they compare to ACE inhibitors?

The renal portion of the ABCD study [11] addressed this issue. Four hundred seventy patients with type 2 diabetes were randomized to either an ACE inhibitor or a long-acting dihydropyridine. Creatinine clearance, corrected for surface area determined during a 5-year period, showed no discernible difference between the ACE inhibitor and dihydropyridine. Thus, if intensive treatment is given with a low BP goal and metabolic factors are also controlled during 5 years, no discernible difference in creatinine clearance is seen in type 2 diabetics. Tarnow et al [12] reported similar findings in type 1 diabetic patients. These recent data support the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI), [13] which stated: "The most important action to retard progression of renal disease is to lower blood pressure to goal." This goal is generally recognized to be 130/80 mm Hg. The overwhelming majority of diabetic hypertensive patients are initially treated with a renin-modulating drug, an ACE inhibitor, or an AT-I receptor antagonist. But this, in and of itself, may be insufficient. It is unlikely that any single antihypertensive agent will suffice to achieve this degree of tight BP control in complex patients. One must not only make the right initial intervention but also follow through and treat to goal with a combination of drugs. Calcium channel blockers are an important and often a necessary component of this multiple drug regimen.

References