

Renin Angiotensin System Blockade and Nephropathy: Why Is It Being Called into Question, and Should It Be?

Norman K. Hollenberg* and Murray Epstein[†]

*Department of Radiology, Brigham and Women's Hospital, and Department of Medicine, Harvard Medical School, Boston, Massachusetts; and [†]Department of Medicine, University of Miami, Miami, Florida

Clin J Am Soc Nephrol 1: 1046–1048, 2006. doi: 10.2215/CJN.00540206

As is widely known, the first drug that was approved by the Food and Drug Administration for retarding the progression of renal injury was captopril, an angiotensin-converting enzyme (ACE) inhibitor that worked primarily through blocking the renin system (1). The study was performed in patients with type 1 diabetes. Several years later, the Food and Drug Administration approved renin-angiotensin system blockade with two angiotensin antagonists, irbesartan and losartan, for the management of nephropathy in patients with type 2 diabetes (2–4). The regulatory agency demands solid evidence, and they had it. Each of these studies, designed and conducted by experts, was large enough, used enough drug, and treated for long enough to lead to an outcome, which essentially was beyond debate. The conclusions from the major studies were supported by meta-analyses that examined additional issues, such as whether the drugs were effective in the patient who has renal injury that is not due to diabetes (5,6).

If there was debate, then it centered on an interesting issue. Whereas ACE inhibition was approved for type 1 diabetes, angiotensin receptor blockers (ARB) were approved for type 2 diabetes. This arbitrary separation reflects how the studies were done and the way large therapeutic trials typically are funded but did not have anything to do with the fundamental nature of the diseases.

We were otherwise comfortable with the current state of things. Then, suddenly, the issue of whether renin system blockade plays a special role in determining progression of renal disease was called into question. The first challenge came from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest antihypertensive study performed to date (7). The second challenge emanated from a recent meta-analysis (8). The third challenge came from an epidemiologic study in Canada (9). Indeed, they claim that not only were ACE inhibitors not protective but also that they may have contributed to the development of ESRD (9).

The ALLHAT was not designed specifically to address the issue of kidney disease, but with its massive number enrolled,

in fact, it is the largest study on diabetes yet reported. Had nephrologists designed such a study, surely they would have insisted on a better renal evaluation, including measure of proteinuria and more regular follow-up. However, it is extremely unlikely that the investigators missed ESRD.

What ALLHAT found was that patients who were treated with lisinopril did not show the anticipated protection from renal injury or renal failure. Indeed, patients who were treated with a diuretic did as well as the patients who were treated with lisinopril. The authors of the report, in fact, emphasized their failure to confirm the value of renin system blockade. The premise, not stated, was that the earlier studies were “wrong” and that the ALLHAT—presumably by virtue of the fact that it was big—provided the correct answer.

But, did it? One of the fundamentals of therapeutics is dosage (10). Each of the major clinical trials that led to approval (1–4) used very substantial dosages of the ACE inhibitor or ARB. Indeed, in one of the studies, the experimental design attempted to build a dose-response picture: The results demonstrated that whereas 150 mg/d irbesartan was effective, it was substantially less effective than 300 mg/d irbesartan (4).

What of the ALLHAT? They initiated lisinopril treatment with a daily dose of 10 mg. Few would choose to use 10 mg of lisinopril in the average patient. Experts do not hesitate to titrate upward. Physicians such as those involved in the ALLHAT, conversely, often are reluctant to uptitrate drug dosage. Information on which drug dosages the patients received was not given in the original article but has appeared recently in response to a letter to the editor (11,12). As shown in Table 1, >50% of the patients who were randomly assigned to lisinopril at year 1, year 3, and year 5 either were taking no ACE inhibitor or had remained at the lowest dosage level (Table 1). Only a little more than one third received the top dosage. We can conclude firmly that a dosage of ACE inhibitor that is inadequate is not better than other antihypertensive agents. If we did not already know that, then we at least so suspected!

The second source of dysequilibrium and one that has received substantial attention in the lay press is a recent meta-analysis that was reported in *The Lancet* (8). Their conclusion, like that of ALLHAT, was that there was little or no advantage to renin system blockade. In view of the fact that their meta-analysis involved >73,000 patients who were culled from 127 eligible studies, they were confident that their conclusion was

Published online ahead of print. Publication date available at www.cjasn.org.

Address correspondence to: Dr. Norman K. Hollenberg, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Phone: 617-732-6682; Fax: 617-232-2869; E-mail: djpagecapo@rics.bwh.harvard.edu

Table 1. Distribution of dosages of step 1 modification at 1, 3, and 5 yr in ALLHAT

Treatment	Total ^a	None (%)	Dose 1 (Low; %)	Dose 2 (Middle; %)	Dose 3 (High; %)
Year 1					
chlorthalidone	13,399	16.1	33.0	17.1	33.8
amlodipine	7888	15.9	24.6	22.4	37.1
lisinopril	7814	22.2	28.3	15.2	34.3
Year 3					
chlorthalidone	11,897	23.6	23.4	14.8	38.3
amlodipine	7080	23.0	16.3	17.6	43.1
lisinopril	6886	31.5	20.1	11.8	36.7
Year 5					
chlorthalidone	6288	28.4	17.9	12.9	40.8
amlodipine	3795	27.4	11.2	13.9	47.6
lisinopril	3630	38.5	14.0	10.4	37.1

^aNumber of participants with a valid GFR.

correct. Consequently, their predecessors must have been wrong.

The studies that led to regulatory approval shared a number of features (1–4). First, all were big enough to have the necessary power. Second, in each case, the dosage of drug was adequate to the task. Finally, in each instance, the follow-up was sufficiently long that an end point could be achieved. A useful meta-analysis would have required that all three criteria be met. Regrettably, this meta-analysis did not.

Why does duration matter? In the original study on the effect of captopril in patients with type 1 diabetes and nephropathy, no evidence of separation between the treatment and the control groups was evident at 1 yr (1). Rather, a duration that approached 2 yr was required for confidence about separation. Therefore, the shortest interval in the major trials that led to regulatory agency approval was 2 yr, and most patients had substantially more follow-up (1–4). In the literature from which the meta-analysis was culled, intervals as short as 12 mo are reported (13). Furthermore, whereas many studies aimed at 2 yr of treatment, most of the patients fell short of that interval (14–16).

Again, drug dosage is another important variable. Like the ALLHAT, many reports were initiated with very low dosages, and, commonly, the dosage remained there. Examples include captopril begun at 12.5 mg/d (17) and enalapril at 2.5 to 5.0 mg (14–16). Did addition of these studies to the meta-analysis help to answer the question? We think not.

Another fundamental in therapeutics involves the power calculation. Given a reasonable guess at effect size, how many patients would one have to enroll to achieve a statistically significant and interpretable outcome? In the quality studies that led to regulatory approval, the power calculation indicated that approximately 1800 patients were required. What are we to make, then, of studies that were included in the meta-analysis that enrolled 50 to 70 patients (13,14,16)? Why should we be confident in studies that are designed to be powered inadequately, to have inadequate dosages, and to have the patients

followed for too short an interval? Do these studies provide any useful additional information?

What is the role of meta-analysis? Certainly, the football field format with confidence intervals on each central tendency provides a useful summary of a literature, but is there a place for meta-analysis once high-quality, large, well-designed studies with adequate power and adequate drug dosage are reported? Science, like engineering, depends on an important element: The relation between signal and noise. The meta-analysis merely adds noise when poor studies are provided. Surely, reviewers and editors of journals have a responsibility to look at the quality of a study and not just the newsworthiness of its conclusion. The failure of meta-analysis to predict the outcome of large trials has been well documented (18,19).

The meta-analysis also raised the issue of BP as a determinant. Once again, we think that a careful, thoughtful, and detailed analysis from one high-quality study provides far more useful information than does the meta-analysis (20).

The most recent challenge to the contribution of renin-angiotensin system blockade to slowing progression of ESRD came from an epidemiologic study in Canada (9). The authors used a database that provides information on clinically relevant events. They concluded not only that ACE inhibition did not protect patients from ESRD but, in fact, that ACE inhibition promoted ESRD. The authors treated the groups as though the individual patients were randomly assigned to drug therapy. Nowhere does it indicate the possibility that patients who were at greater risk for ESRD received captopril and other ACE inhibitors preferentially because of that risk. Proteinuria is an important driving force in clinical decision making, and proteinuria was not listed in their database. By the early to mid-1980s, there was already substantial interest in the possibility that ACE inhibition might improve the natural history of renal disease (21).

For all of these reasons, we believe that the large, randomized, well-controlled, clinical trials that have shown the efficacy of ACE inhibition and ARB in delaying renal insufficiency in

patients who are at risk provide the correct answer—the answer that should shape policy and clinical judgment—and that recent attempts to call the results of these studies into question are based on faulty information.

References

- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; for the Collaborative Study Group: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329: 1456–1462, 1993
- Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; for the RENAAL Study investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
- Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; for the Collaborative Study Group: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
- Parving H-H, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P; for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345: 870–878, 2001
- The ACE Inhibitors in Diabetic Nephropathy Trials Group: Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta analysis of individual patient data. *Ann Intern Med* 134: 370–379, 2001
- Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, Maschio G, Brenner BM, Kamper A, Zucchelli P, Becker G, Himmelmann A, Bannister K, Landais P, Shahinfar S, de Jong PE, de Zeeuw D, Lau J, Levey AS; for the ACE Inhibition in Progressive Renal Disease Study Group: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta analysis of patient level data. *Ann Intern Med* 135: 73–87, 2001
- Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288: 2981–2997, 2002
- Casas JP, Chua W, Loukageorgakis S, Vallane P, Smeeth L, Hingorani AD, MacAlister RJ: Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. *Lancet* 366: 2026–2033, 2005
- Suissa S, Hutchinson T, Brophy JM, Kezouh A: ACE-inhibitor use and the long-term risk of renal failure in diabetes. *Kidney Int* 69: 913–919, 2006
- Hollenberg NK: Is there a pharmacologic basis for combination renin axis blockade? *Kidney Int* 68: 2901–2903, 2005
- Hollenberg NK: Omission of drug dose information [Letter]. *Arch Intern Med* 166: 368, 2006
- Rahman M, Pressel SL, Davis BR: Reply to letter to the editor: Omission of drug dose information. *Arch Intern Med* 166: 368–369, 2006
- Bannister KM, Weaver A, Clarkson AR, Woodroffe AJ: Effect of angiotensin-converting enzyme and calcium channel inhibition on progression of IgA nephropathy. *Contrib Nephrol* 111: 184–193, 1995
- Kamper AL, Strandgaard S, Leyssac PP: Effect of enalapril on the progression of chronic renal failure. A randomized controlled trial. *Am J Hypertens* 5: 423–430, 1992
- Himmelmann A, Hansson L, Hansson BG, Hedstrand H, Skogstrom K, Ohrvik J, Furangen A: ACE inhibition preserves renal function better than beta blockade in the treatment of essential hypertension. *Blood Press* 4: 85–90, 1995
- Becker GJ, Whitworth JA, Ihle BU, Shahinfar S, Kincaid-Smith PS: Prevention of progression in non-diabetic chronic renal failure. *Kidney Int Suppl* 45: S167–S170, 1994
- Zucchelli P, Zuccala A, Borghi M, Fusaroli M, Sasdelli M, Stallone C, Sanna G, Gaggi R: Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int* 42: 452–458, 1992
- Villar J, Carroll G, Belizan JM: Predictive ability of meta analyses of randomized controlled trials. *Lancet* 345: 772–776, 1995
- LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F: Discrepancies between meta analyses and subsequent large randomized, controlled trials. *N Engl J Med* 337: 536–542, 1997
- Pohl MA, Blumenthal S, Cordonnier DJ, DeAlvaro F, De-ferrari G, Eisner G, Esmatjes E, Gilbert RE, Hunsicker LG, de Faria JB, Mangili R, Moore J, Reisin E, Ritz E, Schlerthaner G, Spitalewitz S, Tindal H, Rodby RA, Lewis EJ: Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: Clinical implications and limitations. *J Am Soc Nephrol* 16: 3027–3037, 2005
- Hollenberg NK, Raj L: Angiotensin-converting enzyme inhibition and renal protection. An assessment of implications for therapy. *Arch Intern Med* 153: 2426–2435, 1993