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

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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, losartan and irbesartan, 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, 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...
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. Regretfully, 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

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Totala</th>
<th>None (%</th>
<th>Dose 1 (Low; %)</th>
<th>Dose 2 (Middle; %)</th>
<th>Dose 3 (High; %)</th>
</tr>
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<tbody>
<tr>
<td><strong>Year 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>chlorthalidone</td>
<td>13,399</td>
<td>16.1</td>
<td>33.0</td>
<td>17.1</td>
<td>33.8</td>
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<td>amlodipine</td>
<td>7888</td>
<td>15.9</td>
<td>24.6</td>
<td>22.4</td>
<td>37.1</td>
</tr>
<tr>
<td>lisinopril</td>
<td>7814</td>
<td>22.2</td>
<td>28.3</td>
<td>15.2</td>
<td>34.3</td>
</tr>
<tr>
<td><strong>Year 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chlorthalidone</td>
<td>11,897</td>
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<td>23.4</td>
<td>14.8</td>
<td>38.3</td>
</tr>
<tr>
<td>amlodipine</td>
<td>7080</td>
<td>23.0</td>
<td>16.3</td>
<td>17.6</td>
<td>43.1</td>
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<tr>
<td>lisinopril</td>
<td>6886</td>
<td>31.5</td>
<td>20.1</td>
<td>11.8</td>
<td>36.7</td>
</tr>
<tr>
<td><strong>Year 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chlorthalidone</td>
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<td>12.9</td>
<td>40.8</td>
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<td>47.6</td>
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<tr>
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<td>38.5</td>
<td>14.0</td>
<td>10.4</td>
<td>37.1</td>
</tr>
</tbody>
</table>

*aNumber of participants with a valid GFR.*
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