Recent Clinical Trials
The Good, the Bad, and the Misleading

Norman M. Kaplan

Results of 3 major clinical trials on the treatment of hypertension have been published recently or presented. In addition, the validity of data provided in an often-quoted publication of another trial that had a major impact on nephrological practice has been seriously questioned.

First, the good trial, Treatment of Hypertension in Patients 80 Years of Age or Older, addressed a major unsettled issue: should antihypertensive drug therapy be given to the very elderly? The need for such a study is obvious, because people >80 years of age are the fastest growing part of our population, and systolic hypertension is almost invariably among them. The few data available previously on the benefit versus danger of treating them were not encouraging.

Fortunately, Treatment of Hypertension in Patients 80 Years of Age or Older turned out very well, so well that it was stopped prematurely after an average of 1.8 years of treatment because of the strong evidence of benefit with an average blood pressure that was 15/6 mm Hg lower than in the placebo group. Death from cardiovascular disease was reduced by 23%, death from any cause by 21%, stroke by 30%, and heart failure by 64%. As with all trials, some methodologic issues are noted: (1) the subjects were healthier than most people over age 80 years; (2) only one third had isolated systolic hypertension, the usual form of hypertension in the elderly; (3) only half reached the goal of 150/80 mm Hg; and (4) therapy was limited to the diuretic indapamide and the angiotensin-converting enzyme (ACE) inhibitor perindopril.

Nonetheless, the outcome data are very impressive and will call for extension of drug treatment to patients at any age who are not suffering from terminal illness or severe dementia. The suggestive evidence that ACE inhibition may reduce the risk of Alzheimer disease by increasing degradation of amyloid-β will likely add to the rush toward ACE inhibitor therapy in the elderly.

The Misleading Trial
The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) compared an ACE inhibitor with an angiotensin receptor blocker (ARB) and with a combination of the ACE inhibitor and the ARB.

The trial was patterned after the Heart Outcomes Prevention Evaluation Trial with the same principal investigators. It was designed to show noninferiority of the ARB to the ACE inhibitor, which was shown. In particular, the equal cardioprotection by the 2 agents should settle the claim than ARBs are less effective than ACE inhibitors for myocardial protection. The combination was associated with more progressive renal dysfunction, likely from excessive lowering of blood pressure in vulnerable patients.

In view of the equivalence of the 2 drugs, a not-surprising result, the major issue leading clinicians to choose one or the other would logically depend on adverse effects. In ONTARGET, the incidence of the most common adverse effect of ACE inhibitors, cough, was reported in only 4.2% to be the cause for discontinuation of the ACE inhibitor, whereas the same dose of the same ACE inhibitor was the cause for discontinuation in 7.3% of the Heart Outcomes Prevention Evaluation Trial (both 4.2% and 7.3% are below the usual reported incidence of cough, 10% to 15%, but the larger incidences are for the occurrence of cough and not the cause of discontinuation of treatment).

Why the lower incidence of ACE inhibitor–induced cough? The reasons are obvious and should have at least been mentioned in the discussion of ONTARGET if not taken into account in establishing the protocol. These are as follows: (1) 60% of enrollees were already on an ACE inhibitor, weeding out those who were intolerant; (2) those who were known to be intolerant to an ACE inhibitor were shunted to a parallel study, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease, which has not yet been published; and (3) ramipril was given for a 3- to 4-week run-in so that, again, those who were quickly intolerant of an ACE inhibitor were not enrolled.

Thus, the major adverse effect of ACE inhibitors was minimized by design, negating the well-known lesser adverse effect profile of ARBs. This may be the reason why the editorialist commenting on ONTARGET stated, “ARBs have more side effects than ACE inhibitors,” despite the common knowledge that they do not.

The Unpublished Trial
Results of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial were presented as a “late breaker” at the March 2008 meeting of the American College of Cardiology, but as of June 30, 2008, the data remained unpublished. A preliminary publication describes excellent control of blood pressure in both arms, the combined diuretic plus ACE inhibitor and the combined calcium channel blocker plus ACE inhibitor. The oral report indicated that the combina-

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tion of ACE inhibitor and calcium channel blocker was much better than the diuretic and ACE inhibitor in reducing all of the end points.

Obviously, the publication of the results of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial will be of great interest. If, as reported, it shows better effects of combining a calcium channel blocker over a diuretic, and if this finding is replicated in another large randomized, controlled trial, current practice may need to be modified.

The Bad Trial

During their review of the literature to prepare a meta-analysis of the effect of monotherapy and combination therapy of inhibitors of the renin-angiotensin system on proteinuria in patients with renal disease, Kunz et al\textsuperscript{14} stated that they, “excluded one eligible trial\textsuperscript{4} because of serious implausibilities that contact with the publishing journal could not re-solve.” These included a highly unusual balance in the distribution of 3 key baseline variables across 3 treatment groups, discrepancy between the reported statistical method and the results in the article, and problems with patient satisfaction. In a separate letter to the editor of The Lancet, where the original article\textsuperscript{4} was published, Kunz et al\textsuperscript{6} went even further in their critique stating, “The number and seriousness of the inconsistencies found in the Nakao article led us to wonder whether it is possible that this is only a case of extremely sloppy reporting or a hint toward more severe problems with the data.” This could be of little concern except that the results have been accepted by expert nephrologists\textsuperscript{5,15} and have been incorporated into clinical practice. Perhaps the main conclusion from this unfortunate episode is that reviewers and journal editors should be much more careful before publishing novel results and much quicker to admit mistakes.

Conclusions

Large clinical trials are hard to do and expensive, so that, other than for some landmark trials sponsored by the National Institutes of Health, only pharmaceutical companies are willing to pay for them. The marketers of telmisartan, used in ONTARGET, are to be congratulated for their willingness to fund trials where their products might not be better than the comparator. However, the former editor of the British Medical Journal, Richard Smith, believes that substantial biases are virtually inherent in clinical trials and that journals should only publish critiques of trials, so they could, “prevent journals from being an extension of the marketing arm of pharmaceutical companies in publishing trials that favor their products.”\textsuperscript{16}

Dr Smith is not the first to call attention to the dangers of designing and reporting clinical trials. Nonetheless, clinical trials are needed to inform clinical practice, as more and more drugs are marketed. Moreover, other than occasionally from the National Institutes of Health, pharmaceutical compa-

nies are virtually the only current source of funding of large-outcome trials. Their results should be published in peer-reviewed journals, but caution must be taken in accepting their results to be more than marketing tools. Their study design should be independently reviewed before initiation, and rigorous examination of their results should be provided by peer reviewers with statistical expertise.

Disclosures

None.

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