Potential Impact of Exclusion Criteria on Results of Hypertension Trials

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Recent trials of antihypertensive therapy, including the Veterans Administration trials, the Hypertension Detection and Follow-up Program, the Multiple Risk Factor Intervention Trial, the Australian Mild Hypertension Trial, and the British Medical Research Council Trial, are reviewed with a particular emphasis on the criteria leading to the exclusion of potentially eligible participants. The observation of all-cause and cause-specific mortality rates in the group ultimately selected to participate in the trial is suggested as an index to the general applicability of trial results. Because end-point rates are fundamental for determining sample size, substantial reduction in these end-point rates by patient exclusion should be taken into account by the trial design. Some recent trials may have generated end-point-event rates so low that the power of the trial to detect reasonable treatment effects was substantially reduced. Future trials should attempt to take this important factor into account at the design stage. *(Hypertension* 1989;13(suppl I):I-66-I-68)

Since the landmark publication of the Veterans Administration randomized, double-blind, placebo-controlled trials 20 years ago, clinical evaluation of antihypertensive therapy has made a great deal of progress. Since the Veterans Administration trials, studies like the Hypertension Detection and Follow-up Program, the Multiple Risk Factor Intervention Trial, the Australian Mild Hypertension Trial, and the British Medical Research Council Trial have presented occasionally contradictory but generally comparable results. All these trials showed some benefit from the identification, treatment, and control of elevated blood pressure although such elevation may have been at only modest levels. The clinical evaluation of antihypertensive treatment has progressed to the point where investigators can now examine, in greater detail, the effects of antihypertensive treatment on specific forms of morbidity, especially morbidity from arteriosclerotic heart disease. Finally, there is considerable interest in the selection of specific medications for first-step therapy, and, for this purpose, trials like the Treatment of Mild Hypertension Study are attempting to provide simultaneous comparisons of representatives of several classes of medication.

As treatment technology improves and as the major relatively crude questions concerning the safety and efficacy of antihypertensive medication are answered, it is inevitable that somewhat more subtle and refined questions will be asked and that trials will be designed to answer such questions. However, as investigators progress from relatively crude to relatively refined hypotheses, the demands on trial design will increase. For example, the expected therapeutic benefits resulting from studies with more refined hypotheses or with comparisons among relatively effective drugs will be relatively small, thereby increasing the required sample sizes. Furthermore, much more attention will need to be given to the characteristics of hypertensive patients admitted to and excluded from such trials.

This latter point requires emphasis. The Veterans Administration trials were classic double-blind, placebo-controlled, essentially fixed-dose designs. Dosages could be increased to a limited extent because each increase must be matched by appropriately designed placebos. In this case, the criteria for admission of patients to the study were also relatively tightly specified, and blood pressures, for example, were required to fall within relatively narrow ranges and to remain there for some time. Patient exclusions were thus relatively extensive, and, in addition to excluding individuals with intercurrent disease, other criteria related to cooperativeness were used to exclude potential participants. These characteristics were probably appropriate to the state of the art at that time. The investigators were interested in learning whether general antihypertensive treatment could reduce mortality and morbidity directly associated with the consequences of blood pressure elevation.
The hypotheses investigated by the Hypertension Detection and Follow-up Program, a trial that was initiated soon after the Veterans Administration trial results were reported and that still continues through the late phases of data analysis, were substantially different. This trial was community based and sought to identify all hypertensive subjects within residentially or occupationally designed intact groups. Such individuals were subject to a two-stage screening phase and were then allocated to stepped- or referred-care treatment plans. That trial showed a significant reduction in all-cause mortality among stepped-care participants, both overall and in those patients with the most modest elevations of diastolic blood pressure. It should be noted that an important guide to the representativeness of the individuals participating in the trial is provided by the overall mortality rates in the group. These rates were roughly comparable to rates in the general population as observed by follow-up studies, like those reported in the Pooling Project, for example.

The Multiple Risk Factor Intervention Trial sought to enroll individuals at high risk of arteriosclerotic heart disease. This goal was to be accomplished with use of the upper percentiles of a logistic regression function. However, for a variety of reasons, the investigators adopted relatively stringent exclusion criteria, which apparently led to the elimination of many potential participants at the highest risk of end-point events. At any rate, the observed mortality rates were hardly different from those of the general population. Had these actual rates been contemplated in the original design, a much larger trial would have been needed. One can only speculate whether the results of the Multiple Risk Factor Intervention Trial would have been somewhat more clear-cut had this factor been taken into account.

In the case of the British Medical Research Council Trial, patients seen in general practice clinics were used for the major portion of the study. The investigators initially identified 46,350 patients whose blood pressures made them eligible for the trial, but exclusion factors were so extensive that less than one half of these individuals were considered eligible for participation. The main point is that an exclusion rate of more than 50% was applied to patients who were otherwise eligible on the basis of blood pressure level. The results of this trial produced ultimate mortality rates much lower than expected in general populations with similar elevations of blood pressure.

In clinical trial methodology for hypertension and other diseases, we have become accustomed to believing that randomization and blindness largely protect us against reaching biased estimates of true treatment effects, even in patient groups not comparable to the general patient population. This assumption may have been true for the early trials that were designed to answer relatively crude hypotheses, that is, those trials in which the major interest was to determine whether there was a treatment effect of any substantial magnitude. The assumption is surely less true for trials that have been designed to compare the relatively small differences in groups of low natural mortality. The assumption must also be a problem when comparing different drugs of potentially similar efficacy. In other words, as investigators move beyond the first-stage clinical trials designed to test general hypotheses to trials that attempt to quantify relatively subtle differences, design characteristics must become similarly refined.

Patient exclusion criteria represent a vast wasteland of clinical trial design. Investigators have tended to be relatively precise in defining the characteristics of the therapeutic regimens under study, in defining the characteristics of patients initially admitted into a trial, in describing the analytical methodology, in providing general estimates of sample size, and in defining criteria for patient follow-up. However, many investigators have been very crude in defining patient exclusion criteria. There are exceptions to this rule, of course, but in general, trials in antihypertensive treatment have tended to describe exclusion criteria with a brief statement, a list of specific diagnostic entities, or such global phrases as "serious intercurrent disease" or "normally accepted indications for antihypertensive treatment."

Individuals designing therapeutic trials at this stage of understanding of hypertension must adopt much more stringent and carefully specified criteria for exclusion of potential participants. The burden of such exclusion criteria in terms of reducing the numbers of participants should be estimated in advance, as are all other important trial characteristics. The effect of such exclusions on control-group end-point responses should be estimated. Finally, sample-size estimates should be adjusted to reflect the number of individuals actually expected to become final participants in the trial. Only in this way can we avoid some of the surprises and even some of the inconsistencies among trials that now plague a more complete understanding of the implications of antihypertensive treatment. Perhaps the main point is that whether sample sizes (and the consequent statistical power to detect real differences) are too small because of the initial design or because of the systematic exclusion of high-risk participants, the net effect is the same: outcomes reflect inadequate control of random variation.

Few would question the benefits of antihypertensive medication, even in mild hypertensive subjects, as a kind of first-stage conclusion. Many, however, would disagree concerning the details of those effects. For example, how do such effects vary by race, by sex, or by indications of intercurrent disease, like relatively nonspecific electrocardiographic changes, presence of mild diabetes, and others? If the answers to such questions are needed, and if well-designed randomized trials constitute an important portion of the methodology for providing
such answers, then a much more rigorous trial design must be established, particularly with respect to exclusion criteria.

The problems of inference from trials to patient populations are perplexing. Strictly speaking, a statistical inference can be made only to the population from which trial participants are actually drawn, exclusion criteria and all. However, there is general agreement that inferences must be extended beyond the limits permitted by the probability structures that underlie significance tests or confidence intervals. In the case of hypertension, there is a problem. There are differences among comparisons involving subtle distinctions. How can a relatively uniform stance with respect to patient management be adopted, a stance based, to the greatest possible extent, on experimental data and valid interpretation of those data? This can be accomplished only by careful attention to the details of study design that previously have been treated in a relatively casual manner. At stake is the ability to reach conclusions that are needed to manage these important conditions and to reduce the mortality and morbidity burden they place on the general population.

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