POLICY FORUM: MEDICINE

Placebo-Controls in Short-Term Clinical Trials of Hypertension

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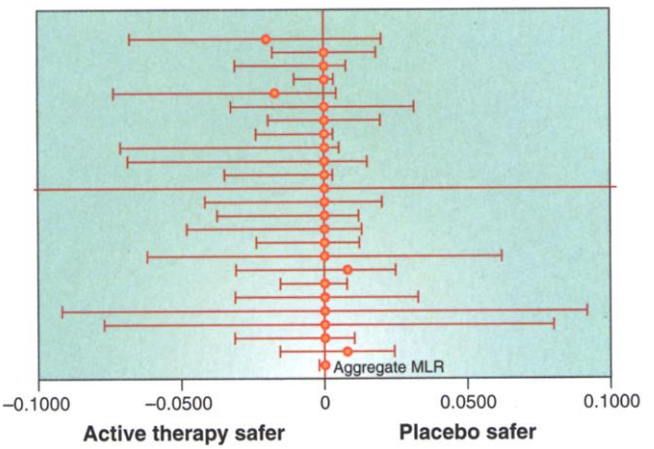
The current version of the Declaration of Helsinki addresses the selection of appropriate controls: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." (*1*). However, the E10 report issued by the International Conference for Harmonization considers the use of placebo-controls in clinical trials ethical, even if an effective treatment is available for the condition under study, if withholding the effective treatment leads to no serious harm and if patients are fully informed about available therapies and the consequences of delayed treatment (*2*). In addition, in a recent appraisal of the ethical and scientific issues of placebo-controlled trials, Temple and Ellenberg argue that if patient-subjects are not likely to be harmed through exposure to placebo and they can give voluntary informed consent, it is permissible to use placebo-controls in some trials, despite the existence of a known effective therapy (*3*).

There are reasons why placebo-controls, when appropriate, are preferred to active controls (*3*). One important reason is that placebo-controlled trials contain internal evidence of assay sensitivity (that is, the ability to distinguish an effective treatment from a less effective treatment). As such, these trials do not rely on external information to support a conclusion of effectiveness. In contrast, "equivalence" trials rely on evidence of effectiveness of the active control obtained in previous trials and on the assumption that the active control would be effective under the conditions of the present trial. Also, comparing the experimental therapy to placebo generally requires a smaller sample size to attain statistical significance than does comparing the experimental therapy to another treatment. As a consequence, trials may be conducted faster and at a lower cost, exposing fewer subjects to the potential risks of the experimental therapy.



Difference in event rates by the maximum likelihood method. Each horizontal line represents the 95% CI surrounding the maximum likelihood ratio (MLR) estimate of the risk differences for the placebo group and the active treatment group in a given study. Negative MLR indicates that those exposed to active therapy were safer, whereas a positive MLR indicates that those administered placebo were safer. ○, Maximum likelihood ratio for a study.

Such problems with using active controls must be accepted if patient-subjects are likely to die, suffer serious adverse events, or develop irreversible morbidity as a result of participating as research subjects. If these problems with active controls cannot be overcome, development of new products must be abandoned.

However, where patient-subjects are unlikely to be harmed, the use of placebo-controls may be acceptable. This situation is present in most trials of symptomatic treatments and appears often to be the case for risk-factor interventions like short-term studies of antihypertensive agents, oral hypoglycemics, or lipid-lowering agents that typically employ secondary outcome measures such as blood pressure, blood glucose, and lipid profile. In such trials, placebo-controls are commonly used on the assumption that withholding active therapy for a short time is unlikely to result in harm. Further, secondary measures as these tend to correlate with harmful outcomes, but in and of themselves may not be harmful.

Hypertension is a common disorder whose prevalence in the U.S. population exceeds 60% after the age of 70 years (*4*). Hypertension is a well-established risk factor for stroke, myocardial infarction, congestive heart failure, and premature cardiovascular death (*4*, *5*). A 1990 review of 14 long-term randomized trials of antihypertensive drugs including 37,000 patients concluded that antihypertensive therapy reduced the risk of stroke by 42% ($P < 0.0001$), coronary artery disease by 14% ($P < 0.01$), and vascular mortality by 21% ($P < 0.0002$) (*5*). In 1991, SHEP (Systolic Hypertension in the Elderly Program) and STOP-Hypertension (Swedish Trial in Old Patients with Hypertension) found similar benefits of antihypertensive therapy in elderly patients with hypertension (*6*, *7*). Thus, there is strong evidence that patients with hypertension benefit from long-term antihypertensive therapy.

Given this strong evidence, the use of placebo-controls in clinical trials of agents to control hypertension has been challenged as unethical, because patient-subjects enrolled in clinical trials should generally be assured of the best "proven" treatment. (*8*). This challenge is persuasive if patients in such trials would be harmed, but it is not known that participants in short-term placebo-controlled studies of antihypertensive agents are harmed as a result of receiving placebo. Available data do not address the possibility of some increased risk to the placebo-treated patients. Nevertheless, these trials are still being approved by institutional review boards and being conducted. We, therefore, conducted a quantitative systematic review of short-term randomized placebo-controlled clinical trials of hypertension published in 1997 and 1998 to determine whether the use of placebos in these trials is safe.

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A summary of the methods and results of this meta-analysis and a list of the corresponding references are included in supplemental material (*9*).

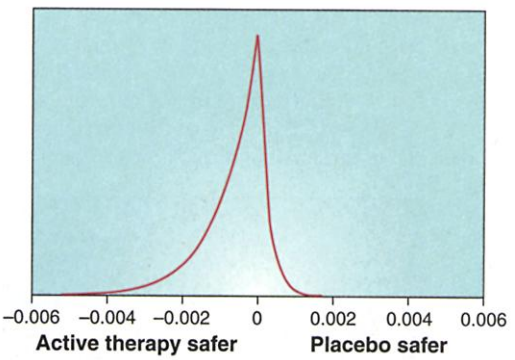
In this meta-analysis, we combined the data for death, stroke, myocardial infarction, and congestive heart failure from 25 randomized trials examining the efficacy of antihypertensive therapy as compared with placebo (see the figure on page 2013). Each study is relatively small (sample size range 20 to 734), but the group of combined trials is large enough (sample size 6409) to allow the detection of differences in the rates of serious adverse events (death, stroke, myocardial infarction, and congestive heart failure) for the two treatment groups, if such differences exist (had power to detect 2.5 in 1000 difference). We found that the difference in the incidence of event rates between the two treatment groups was 0, and, at worst, did not exceed 6 in 10,000 (see the figure on this page). Thus, short-term exposure to placebo in clinical trials of hypertension does not seem to be associated with an increased risk of serious adverse events.

Several facts could explain the findings of this meta-analysis. First, the combined studies are relatively short in duration. As exposure to placebo in these studies is limited, the risk of serious adverse events is expected to be low. Second, only patients with mild to moderate hypertension, either with no history of significant medical illnesses or with no recent history of myocardial infarction or stroke, were enrolled in these studies. As such, it is likely that only patients who were deemed at very low risk of being harmed from participation in these studies were included. Third, patient-subjects were apparently closely monitored during these studies, and they were withdrawn if they had a persistently elevated blood pressure or once they were determined to be at risk of serious harm. Such close monitoring has most certainly contributed to the prevention of serious adverse events.

Thus, when patient-subjects are carefully selected and adequately monitored, limited exposure to placebo in clinical trials of hypertension is not associated with increased risk of serious adverse events. Using placebo-controls in such trials, therefore, would seem ethically permissible.

In concordance with our findings, a recent study by Preston and co-workers showed that the rate of serious adverse events among patients with stage 1 and stage 2 hypertension was not significantly different between the placebo and active drug groups (*10*). In that study, patients who did not meet criteria for successful control of blood pressure at interim visits during the trial were dropped from the study, reinforcing the importance of continuous monitoring of patients in such trials (*10*).

Of course, the findings of this meta-analysis are only applicable to short-term studies of mild to moderate hypertension. Longer exposure to placebo in clinical trials of hypertension is associated with a higher risk of serious adverse events. In the Syst-Eur study, Staessen and co-workers showed that 200 (8.7%) of 2297 patients administered placebo had a serious adverse event as compared with 140 (5.8%) of 2398 patients administered active therapy (*11*). Likewise, Keane *et al.* reported an analysis of three studies of enalapril in hypertensive patients with renal impairment that showed the rate of serious adverse events to be 11% among patients assigned to placebo and 3% among those assigned to active therapy (*12*). Thus, the use of placebo in long-term studies of hypertension is not safe, and it has generally been appropriately abandoned.



Difference in event rates by the Bayesian method. Using the Bayesian method, the difference in event rates is interpreted according to the probability expressed as the area under the curve. If placebo was worse, the peak of the curve would be to the left of zero; if placebo was better the peak of the curve would be to the right of zero.

Concerns have been raised regarding the use of placebo-controls in clinical trials involving investigational agents for other diseases such as diabetes, peptic ulcer disease, and schizophrenia (*13–15*). Certainly, where there is evidence of long-term benefit of treatment, investigators and those charged with oversight of research (institutional review boards and data and safety monitoring committees) need to carefully consider the need for, and ethical basis for, placebo-controlled trials of a particular duration and in a particular population. In part, this involves a careful evaluation of both the available evidence that the treatment has favorable effects on outcomes and the duration of treatment needed to confer such benefits. In some cases, systematic reviews such as ours may help provide such safety information and ought to be employed in the design and oversight of clinical trials so as to inform decisions about the appropriate selection of controls. It should be noted, however, that in many symptomatic conditions, such as allergic rhinitis, harm from omitting treatment during a long-term study is highly implausible, unless evidence can be provided to substantiate long-term outcome effects (favorable or adverse) from treatment. As such, placebos could appropriately be used to study these conditions without the need to provide evidence of safety. Finally, in still other settings including research on certain psychiatric disorders such as schizophrenia, collaborative research to determine whether placebo use is appropriate warrants additional attention, but that is beyond the scope of our work.

When it comes to decision-making regarding the use of placebos in clinical research, general edicts should give way to a more nuanced consideration of their true risks, benefits, and appropriate use. In this way, the rights and interests of patient-subjects enrolled in research will be protected while usable scientific data are gathered.

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