Use of Placebo in Heart Failure Research

To the Editor:

The recently published Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH), a multinational study of 844 patients with class II to III systolic congestive heart failure (CHF), investigated the effects of the angiotensin II receptor blocker candesartan cilexetil on exercise time and the signs and symptoms of CHF. In the 59% of patients who were receiving prior therapy with angiotensin-converting enzyme (ACE) inhibitors, the ACE inhibitors were withdrawn. A 2-week washout period was followed by a 4-week placebo run-in. At that point, patients were randomized to receive placebo or 4, 8, or 16 mg of candesartan cilexetil daily for an additional 12 weeks. No patient received an ACE inhibitor for a minimum of 16 to 18 weeks. In addition, none of the patients were treated with either an ACE inhibitor or an angiotensin II receptor blocker for 4 to 6 weeks and, in the placebo arm, 25% of all patients (n=211) did not receive an ACE inhibitor or an angiotensin II receptor blocker for the duration of the entire study (ie, for 16 to 18 weeks). Concomitant therapy with cardiac glycosides, long-acting nitrates, or diuretics was kept constant, and the use of other cardioactive agents was not permitted.

The authors state that “the study was conducted according to the Declaration of Helsinki, the European Guidelines on Good Clinical Practice, and relevant national and regional authority requirements and ethics committees.” It was not specifically disclosed whether informed consent was obtained or how the placebo arm was explained to subjects.

We are concerned about the apparent discrepancy between the authors’ assurance of compliance and the explicit statements regarding the use of placebo contained in the Declaration of Helsinki. In patients with symptomatic CHF, treatment with ACE inhibitors has proven efficacy in both symptom reduction and prolonged survival. The greatest effect of ACE inhibitors on survival is seen in the first 3 months of therapy. Evidence of their efficacy in providing symptom relief and in improving survival is so strong that the American College of Cardiology/American Heart Association Task Force on Practice Guidelines supports the use of ACE inhibitors “in all patients with symptomatic heart failure, unless the inhibitors are contraindicated or not tolerated.” It follows that in patients with symptomatic CHF, the use of placebo seems to violate the Declaration of Helsinki, which states that “The potential benefits, hazards, and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods,” and that “In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.”

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Response

The Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH) investigated the effects of candesartan cilexetil on exercise time and the signs and symptoms of congestive heart failure in patients with heart disease. The first patient was enrolled in January 1996 and the last case was completed in June 1997. The study was approved by a total of 52 independent ethical committees in Germany (n=17), the Czech Republic (n=34), and the Slovak Republic (n=1), and it fulfilled all regulatory requirements. All patients gave informed consent, as stated in the declaration of Helsinki. In addition, the informed consent form and patient information leaflet were approved by the ethical committees. In the patient information leaflet, it was stated that angiotensin-converting enzyme inhibitor treatment would be withdrawn and background medication with digoxin and diuretics would be optimized. The patients were randomized into 4 groups, 1 of which was placebo. At any time during the study, the patients and/or their physicians could stop the trial medication.

To avoid harm to patients, those with an ejection fraction <30% were excluded from the study. This was done on the basis of the results of the most important and most appropriate controlled trial, the Studies of Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure (SOLVD). In this trial, the investigators analyzed predefined subgroups with respect to the end point death and the combined end point of death or hospitalization. They divided the baseline ejection fraction by terciles. No significant benefit in either end point was observed between ejection fractions of 30% and 35% during an average follow-up of 41.4 months. The restriction of the ejection fraction in our study, in fact, resulted in the recruitment of patients with a mean ejection fraction between 38.6% and 39.0%. This value is near the lower limit of a normal ejection fraction, as measured by echocardiography.

To avoid the inclusion of unstable patients in the trial after randomization, a relatively long wash-out/run-in phase was chosen. During this phase, the patients were seen every 2 weeks and could be excluded at any time and treated appropriately by their physician. If any problems arose for the patients, the same applied after randomization. The STRETCH study design was thoroughly reviewed by the ethical committees, and all possible safeguards were included. Furthermore, during the entire study period, the trial was scrutinized by an independent expert safety committee, which consisted of a cardiologist, statistician, and epidemiologist.

The STRETCH study had the confidence of all the relevant regulatory and ethics committees involved, was performed under the scrutiny of an independent expert safety committee, and was conducted using the highest standards. Therefore, we do not share the concerns of Drs Littmann and Stell.

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