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Discussion IX

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U. Elkayam: Dr. Lipicky, the Food and Drug Administration still requires that placebo-controlled studies be performed for the approval of new drugs. However, most patients are now receiving angiotensin-converting enzyme inhibitors for heart failure. How can we carry out placebo-controlled trials at the present time?

R. Lipicky: You can perform a placebo-controlled trial in which all patients receive an angiotensin-converting enzyme inhibitor and the new drug or placebo is added to the regimen. If the new drug is better than placebo in such a study, it will be clear that the new drug is effective.

U. Elkayam: Such a trial is designed to look for an additive effect. This approach would not be able to evaluate a new drug that was similar to or exhibited a negative interaction with an angiotensin-converting enzyme inhibitor.

R. Lipicky: I do not know if there is a simple way of dealing with the problem. If one carries out a placebo-controlled exercise tolerance trial in which all patients are receiving digoxin, diuretic drugs and an angiotensin-converting enzyme inhibitor, one can assign patients randomly to placebo or active drug. If the study shows that the group receiving active therapy exercised longer than the group receiving placebo, one has learned something about the new drug. If the placebo and the active groups were similar to each other, one has also learned that there is no obvious advantage of adding the study drug to standard therapy. Hence, such a trial can produce two outcomes that can be definitively interpreted.

Of course, if the study drug is not different from placebo in such a trial, it is still possible that the study drug might be able to replace one or all of the standard medications. However, to draw such a conclusion, one would need to conduct a trial in which one or more of the standard medications were replaced by the study drug, using an active-controlled design. Certainly, we would need compelling evidence that the study drug is likely to perform as well as or better than standard therapy. Alternatively, the study could be conducted in patients who had not yet shown benefit from standard therapy. I appreciate that the problems are not easy to resolve and that the present approach may allow us to miss effective drugs for heart failure.

S. Yusuf: Dr. Lipicky, clinical trials are generally designed to evaluate the effect of treatment on symptoms or mortality, but there are intermediate end points that may be of value, particularly cardiovascular morbidity. The results of clinical trials indicate that drugs have directionally similar effects on morbidity and mortality, whereas therapy may have different effects on symptoms and mortality. I do not yet know of an example of a heart failure drug that lessened morbidity but worsened mortality. Would you consider using morbidity as an approvable outcome rather than relying on the results of an exercise test?

R. Lipicky: I do not think one should measure the effects of a drug on morbidity instead of on exercise tolerance. I would measure the effects of the drug on morbidity *in addition to* exercise tolerance. One measure of efficacy is not more important than another. If we know the effects of a drug on morbidity and mortality, it is still important to evaluate the effects of the drug on symptoms and exercise tolerance.

I disagree that exercise tolerance is a surrogate end point for symptoms. Instead, exercise intolerance is an essential component of the heart failure syndrome; it is a direct measure of something that matters to the patient. It is also one of the few simple ways of evaluating the ability of the heart to respond when faced with a demand for increased performance.

Most important, we need to understand as much as we can about a new drug and measure its effects on as many aspects of the heart failure syndrome as we can. The data base that is produced by these efforts should be internally consistent.

S. Yusuf: I am specifically thinking of a situation in which a new drug is developed that acts by a pathway similar to that of an established drug but has a different side effect profile. The number of patients required to show that the two drugs are similar in their effects on mortality is likely to be very large, perhaps as large as 10,000 patients. However, if we compared the effects of the two drugs on morbidity as well as mortality, we would need a much smaller sample size.

R. Lipicky: I have no problem with the evaluation of morbidity or with the use of a combined morbidity and mortality end point. I would have a problem if exercise tolerance had not been evaluated during the development of the drug.

M. Packer: I would like to make two points. First, I think that we need to clarify the precise issues involved in the requirement for a placebo-controlled trial. The regulatory requirement for the approval of a new drug for heart failure

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is not for a placebo-controlled study but for an adequate and well controlled study. One could carry out an active controlled trial, but it is very difficult to interpret an active controlled trial if the two treatments are not different from each other. Consequently, we should be performing placebo-controlled trials for the evaluation of new drugs. However, a placebo-controlled trial does not mean a trial carried out without background therapy. A placebo-controlled trial refers to the type of comparison not to the specifics of the background medications. If one defines a placebo-controlled trial as one carried out without background therapy, then there have been no placebo-controlled trials in the history of heart failure studies, because all of the studies with converting enzyme inhibitors enrolled patients who were already receiving background therapy with digitalis and diuretic drugs.

Second, it is important to evaluate clinically relevant end points in clinical studies. A clinically relevant end point is one that reflects how patients feel or how long they live. In this regard, exercise testing is a clinically relevant end point, because it is a measure of how well patients can perform exercise—and in many ways, heart failure can be defined in terms of how it impedes the ability to exercise. I think that it is good idea to measure the symptoms of heart failure and quality of life of patients with heart failure, but these are closely related to exercise tolerance. There has yet to be an example of a drug for heart failure that lessened symptoms and did not improve exercise tolerance.

R. Lipicky: There is enalapril.

M. Packer: Enalapril has been shown to improve quality of life and exercise tolerance in two placebo-controlled trials.

S. Yusuf: Dr. Guyatt, one of the problems we face in carrying out trials in patients with heart failure is the high rate of attrition, which is higher than that of any other disease in cardiology. In the SOLVD trial, we found that after 6 weeks, quality of life was significantly better in the active treatment group. However, this effect was no longer apparent after 12 months, presumably because different types of patients were alive in the two treatment groups. Have you found a way of handling the issue of competing risks?

G. Guyatt: For nonmortality binary end points, one solution to the problem lies in combining the end points. By adding quantity to quality of life, it is possible to develop a measure of quality of life–adjusted life-years.

R. Lipicky: We have not seen clear benefit on quality of life with any agent for heart failure. Can you explain that?

G. Guyatt: As far as I know, attempts to measure quality of life have been carried out with drugs that do not work. For drugs that do work, it has been easier to demonstrate their utility by measuring their effects on morbidity and mortality, whereas the development of quality of life instruments is still in its infancy.