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Discussion V

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M. Packer: Dr. Colucci, you made a number of excellent points in your presentation. One point that should be emphasized is the importance of dose. The dose of milrinone that was evaluated in the PROMISE trial was arbitrarily chosen to produce a significant positive inotropic effect. That might not have been the correct decision. I do not think that the results of the PROMISE trial are related to patient selection because the proarrhythmic actions and serious cardiovascular side effects of milrinone were observed in patients in both functional class III and class IV.

A. Coats: I want to make a point about the importance of dosing frequency for positive inotropic agents. The original animal experiments with dobutamine used infusions of short duration. When these studies were translated to the care of patients, a 48-h infusion was used. Perhaps better results would have been found if the duration of the infusion had been shorter. We recently completed a trial of dobutamine using half-hour infusions/day for 3 weeks. This dosing regimen improved exercise tolerance and caused up-regulation of beta-receptors. Hence, it may be inappropriate to administer an inotropic drug so as to produce a pharmacologic effect for 24 h/day.

W. Colucci: There are few published data on the safety of intermittent dobutamine therapy. Many of the deaths in the dobutamine study were sudden deaths that occurred during the infusion of the drug at home. One wonders whether dobutamine would have increased mortality if infusion of the drug had been more closely monitored.

P. Poole-Wilson: I am not convinced that the results of controlled clinical trials with digitalis support a role for the drug in the treatment of heart failure. Most of the studies demonstrating its utility are withdrawal studies. Such studies, even if apparently positive, are difficult to interpret and are compatible with a deleterious effect of the drug. For example, if a drug injures the heart but still produces a hemodynamic effect, withdrawal of the drug will result in clinical deterioration, but such deterioration might not have occurred if the patient had not been exposed to long-term therapy with the drug. Withdrawal studies do not address the fundamental question concerning digitalis: In a patient receiving appropriate doses of a diuretic drug and an angiotensin-converting enzyme inhibitor, does the addition of digoxin produce further benefit? My answer to this question at the present time is no. The data from the RADIANCE study (Packer et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. N Engl J Med 1993;329:1–7) simply is not relevant to this question.

T. Smith: I find it hard to agree with your interpretation of the results of the RADIANCE Study. In that study, a group of patients with heart failure were maintained on diuretic drugs and angiotensin-converting enzyme inhibitors in optimal doses. For these patients, it made a great deal of difference whether or not they were also receiving digoxin.

P. Poole-Wilson: One of the key points of the study was that the withdrawal of digoxin led to an increased requirement for diuretic drugs and an angiotensin-converting enzyme inhibitor. This is a problem. The study should have been designed to permit increases in the dose of the latter two agents throughout the study whenever the clinical need arose. Then we could assess whether patients treated with digoxin fared any better than patients not receiving the drug.

M. Packer: Actually, that suggestion was followed in the RADIANCE trial. Before enrollment in the study, the patients' medical regimen was optimized using three drugs: digoxin, diuretic drugs and a converting enzyme inhibitor, and while using these drugs, most patients had only mild symptoms of heart failure (class II). Then, patients were randomly assigned to continue digoxin or to have placebo substituted for digoxin. Patients randomized to placebo had a 6-fold increase in the risk of worsening heart failure during the 12-week follow-up period, and this risk was not simply manifested as an increase in the need for diuretic drugs. In this study the withdrawal of digoxin led to serious clinical problems—including hospitalization for worsening heart failure—despite appropriate increases in the doses of diuretic drugs.

B. Pitt: I am concerned about the use of digitalis. In animal models in which recurrent episodes of myocardial ischemia are produced, we know that digitalis sensitizes the myocardium to the development of catecholamine-induced arrhythmia.

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Dr. Colucci, I am concerned about your suggestion that we administer positive inotropic agents primarily to patients with mild heart failure. Such patients are at greater risk of sudden death than are patients with severe heart failure and should probably not receive drugs that can exacerbate ventricular arrhythmias. Furthermore, mild heart failure can progress rapidly to severe heart failure at any time, so that we cannot confine the use of positive inotropic agents to patients with mild disease.

W. Colucci: I did not propose that we do that. I merely wanted to point out that we have not really explored the possibility. The fact that patients progress from functional class III to class IV makes it almost impossible to give a drug to a patient in class III that is known to be dangerous to a patient in class IV. Yet if safer agents were developed in the future, one would be interested in knowing whether they were useful in mild heart failure.

M. Thames: In addition to its positive inotropic effects, digitalis reduces the activation of neurohormonal systems by enhancing the responsiveness of cardiac baroreflexes, in a manner similar to that of the veratrum alkaloids. Hence, we do not really understand which mechanism of action (inotropic or neurogenic) contributes to the clinical effect of the drug. Dr. Smith, you have worked with many different digitalis compounds. Is it possible to design a digitalis type of drug that exerts effects primarily on neurogenic mechanisms rather than on cardiac contractility? One of the unique features of digitalis is that it causes sympathetic withdrawal at the same time that it has an inotropic effect on the myocardium. This inotropic effect supports the myocardium as sympathetic stimulation is withdrawn. Is the balance between these two effects the same among the large number of derivatives of digitalis?

T. Smith: Many years ago we produced a variety of digitalis derivatives by adding a positive or negative charge to the molecule. The charged drug did not penetrate into the cerebrospinal fluid—unlike digitalis itself. Yet, the charged derivatives were just as toxic as the parent drug. These studies were difficult to interpret, however, because digitalis exerts its neuroexcitatory effects by acting on the area postrema, but this region is one of the few areas of the central nervous system that does not have a blood-brain barrier (Mudge GH, Lloyd BL, Greenblatt DJ, Smith TW. Inotropic and toxic effects of a polar cardiac glycoside derivative in the dog. Circ Res 1978;43:847–54).

A. Katz: We have an excellent way of reducing sympathetic stimulation of the heart without the side effects of positive inotropism: beta-blockers.

M. Thames: Beta-blockers only block the effects of the sympathetic nervous system on the myocardium. They do not affect the vasoconstrictor effects of the system on the peripheral circulation, although they may decrease the release of renin by the kidney. The reason for emphasizing the neurogenic effect of digitalis is to underscore the importance of the periphery. I do not think we can focus only on the heart when we talk about heart failure.

A. Katz: I think that the heart is the problem in heart failure and the periphery just responds to the primary abnormality in the heart.

S. Yusuf: In the Digitalis Trial sponsored by the National Heart, Lung, and Blood Institute, 50% of the patients have never previously received digitalis whereas 50% have had long-term treatment with the drug. Given this distribution, we will be able to determine whether the results of trials of digoxin withdrawal can be extrapolated to trials in which digoxin is introduced.