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Editorial Comment

Prognostic Factors in Heart Failure: Poverty Amidst a Wealth of Variables*

JAY N. COHN, MD, FACC

Minneapolis, Minnesota

Although life expectancy is a concept that everyone understands, and attempts to prolong life are widely appreciated, the traditional physician-patient relation usually is based on short-term goals, such as an improvement in quality of life, rather than on the more nebulous attempt to delay death. Nonetheless, early death occurs with such alarming frequency in patients with chronic heart failure that a reduction in its incidence has emerged as an important goal in the management of these patients. Because death is such a noncontroversial endpoint for therapeutic trials, a reduction in the number of deaths is now a primary goal of many on-going studies.

Surrogates for a poor prognosis. In evaluating a patient with heart failure, the physician usually seeks to classify the severity of the disease with the assumption that the greater the severity the poorer its prognosis. But on what should the definition of severity be based? On the degree of congestion? On the degree of exercise intolerance? On the severity of left ventricular dysfunction? We now know that these signs and symptoms correlate poorly with each other so that patients with, for example, a severely dilated and poorly functioning left ventricle may exhibit no symptoms and no exercise intolerance (1).

The problem is that heart failure is a multisystem disease that involves the heart, the peripheral vasculature, the kidney, the sympathetic nervous system, the renin-angiotensin system, other circulating hormones, local paracrine and autocrine systems and metabolic derangements in skeletal muscle. No single criterion may therefore be adequate to characterize either the severity of the symptoms or the likelihood of early death (2). If one chooses to use multiple variables, the list of potential candidates is growing all the time. The search for surrogates of mortality certainly has merit, however, if not for help in clinical care, then certainly in an effort to select patients with a more precisely defined risk of death for a clinical trial designed to test a therapy to reduce mortality.

Mechanism of death. To influence mortality in this syndrome, it is important to understand the mechanism of death. Most heart disease mortality can be classified into that due to mechanical dysfunction of the heart (pump failure) and that due to a lethal arrhythmia. Although patients with heart failure usually have left ventricular dysfunction, recent trials (3) have suggested that as many as 50% of the deaths may be related to an arrhythmic episode rather than to an aggravation of the underlying mechanical deficit. An attempt to sort out the mechanism of death in heart failure is of utmost importance if one is to know whether an intervention to prevent ventricular fibrillation or an intervention to improve pump function is the more rational approach in a given patient. This distinction depends on the precision with which the mechanism of death can be defined. Unfortunately, in dealing with symptomatic patients whose lifestyle has been altered by disease, a clear distinction between pump failure and a lethal arrhythmia is not always possible. Even the documentation of ventricular fibrillation in a bedridden patient with advanced pump failure does not suggest that prevention of that ventricular arrhythmia would have strikingly prolonged life. Furthermore, instantaneous unexpected death of the type assumed to be caused by an arrhythmia has now been documented on several occasions to be due to electromechanical dissociation. Thus, the key question—how best to prevent death—may be more difficult to answer than might have been suspected.

The present study. In this issue of the Journal, Gradman and associates (4) report an analysis of the previously published digoxin-captopril trial aimed at delineating those baseline factors that were predictive of overall mortality and "sudden death" in patients with heart failure not classified as severe. The data base was only modest in size, resulting in only 47 deaths for analysis, and the three treatment arms in the study (placebo, digoxin, captopril) had to be merged despite the possibility that these interventions could have altered the pattern of mortality. Furthermore, the authors did not utilize life table analysis, which would have corrected for varying follow-up intervals, but apparently simply analyzed dead versus living patients regardless of the time of death or the follow-up interval for the survivors. Despite these weaknesses in power and analysis, however, the data are useful in contributing to a growing insight into the factors influencing prognosis in heart failure.

Left ventricular function. As in most previous trials that have included enough patients with a sufficiently wide range of left ventricular ejection fraction (5), the ejection fraction

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From the Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota 55455.

Address for reprints: Jay N. Cohn, MD, Box 488, University of Minnesota Medical School, Minneapolis, Minnesota 55455.

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was statistically a highly significant predictor of mortality. Ejection fraction itself is a rather crude measurement, and even in the best of circumstances it is a less than ideal measure of the functional capacity of the left ventricle. Therefore, these repeated confirmations of ejection fraction as a critical determinant of survival suggest that a more precise technique for evaluating ventricular function, if it were available, might be an even more sensitive marker for prognosis. The critical prognostic importance of left ventricular dysfunction should not necessarily be taken as evidence that the severity of the underlying etiology-specific myocardial disease is the major risk factor. Left ventricular dysfunction may progress because of the interplay of biochemical, hemodynamic and structural changes that may bear little relation to the initial myocardial insult. Thus a dilated, poorly functioning ventricle may largely represent the impact of various self-perpetuating processes within the myocardium rather than the end result of an episode of massive myocardial injury.

Symptomatic indexes of severity of heart failure have been less tightly linked to prognosis than has left ventricular dysfunction. That the New York Heart Association functional classification can distinguish the likelihood of dying is hardly surprising and hardly useful, because this classification is perhaps too crude to be very helpful. Because exercise tolerance is a continuous variable that can be quantitated more precisely and can be monitored during therapy, its possible value as a prognostic factor is of considerable importance. The study of Gradman et al. (4) unfortunately did not confirm that quantitative exercise tolerance is an independent predictor of survival. However, in a larger data base of men in whom gas exchange was monitored during exercise, the Veterans Administration Cooperative Study (V-HeFT) demonstrated that peak oxygen consumption ($\dot{V}O_2$) is an independent predictor of prognosis in heart failure (6).

The attempt of Gradman et al. (4) to analyze separately the group with "sudden death" raises concerns already addressed about the definition of this event and the unjustified assumption that it is due to an arrhythmia. Nonetheless, the data do tend to support the notion that ventricular tachycardia in heart failure is a poor prognostic marker and may increase the risk for an arrhythmic death.

One of the risks of identifying a surrogate for mortality is that clinical investigators may be attracted to using the surrogate as a substitute for mortality data. Demonstration of an association between a variable and a high risk of death does not imply that a favorable alteration in this surrogate is necessarily a good prognostic sign. Indeed, the complexity of the heart failure syndrome has been further muddled by growing concern that a favorable effect of therapy on one measurement of the severity of the disease may not be reflected in a favorable effect on another. For example, there has long been concern that some drugs may improve left ventricular function but have an adverse effect on survival (7). Furthermore, the recent early termination of two treatment arms of The Cardiac Arrhythmia Suppression Trial was precipitated by overwhelming evidence that type Ic drugs that suppress ventricular premature beats cause an increase in cardiac mortality. These concerns mean that we must now address not only the surrogates for mortality from the so-called natural history of the disease but also the surrogates for an adverse response to specific therapeutic agents. And these surrogates may not be the same!

Conclusions. Heart failure is a complicated syndrome. As in most complex diseases involving regulatory systems, our analysis is limited to measurements we know how to make. There may yet be exciting observations in the blood, heart, peripheral vasculature or neuroendocrine system waiting to be discovered. In the meantime, attempts to identify factors affecting prognosis in heart failure have value not only for our efforts to improve clinical decision making, but also for our goal to gain better insight into the crucial mechanisms that influence the syndrome and may yield to therapeutic efforts. The story is still unfolding.

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