The Key to Unraveling the Mystery of Mortality in Heart Failure
An Integrated Approach
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Heart failure (HF) is a growing public health problem in the United States. Nearly 5 million Americans suffer from HF, and an estimated 550,000 new cases of HF are diagnosed each year.1 HF is the No. 1 discharge diagnosis in patients ≥65 years of age and results in a substantial burden on healthcare expenditures. It is estimated that in 2001, more than $24 billion was spent as direct cost for the care of patients with HF.1 Furthermore, HF is associated with a significant increase in morbidity and mortality.

Although considerable progress has been made in our approach to the pharmacological management of patients with HF, most patients remain at increased risk of cardiac death. To further improve outcomes in patients with HF, newer therapeutic modalities, including devices such as biventricular pacemaker, automatic internal cardioverter-defibrillators (AICDs), and left ventricular assist devices, have been increasingly utilized. Several recent randomized controlled trials have shown that such devices can indeed further improve the outcome in patients with HF.2–4 However, these devices are expensive, and their widespread or injudicious application in unselected patients with HF is likely to have a substantial impact on healthcare expenditures. On the other hand, appropriate use of device therapy in properly selected patients (who are at high risk of mortality) is essential to improve clinical outcome. Thus, there is a need to develop a strategy to accurately identify those patients with HF who are at increased risk of mortality. The paper by Vrtovec and associates5 in the present issue of Circulation provides such a strategy by showing that routinely available diagnostic tests, such as measurement of QT interval on 12-lead ECG and measurement of B-type natriuretic peptide (BNP), can indeed identify HF patients who are at increased risk of overall mortality, sudden cardiac death, and death due to pump failure.

Prognostic Predictors of Mortality in HF

HF is associated with a significant increase in overall mortality. It has been stated that mortality in HF is comparable to that observed in many cancers. The total number of deaths attributable to HF is also on the rise in the United States, increasing by 148% between 1979 and 2000.1 This increase is likely to continue as the overall number of patients with HF increases as a result of the aging of the US population, as well as improved survival of patients with myocardial infarction. Despite significant advances in therapy for HF, many patients with HF remain at increased risk of death.6 Because the clinical diagnosis of HF includes a whole host of patients with a wide spectrum of clinical presentations and functional status, there is considerable variation in their prognosis. Recent data indicate that, on the basis of the degree of severity of HF, the mortality rate for patients with HF can range between 10% and 50% per year.6 Clearly, the patients with advanced HF are at the highest risk of death. The mode of death can also vary according to the severity of HF. For example, patients with New York Heart Association (NYHA) class II/III HF are at increased risk of sudden cardiac death, whereas patients with NYHA class IV HF are at greater risk of dying from pump failure.

Mortality in patients with HF also varies according to the degree of hemodynamic and biochemical abnormalities, the extent of ventricular dilation and dysfunction, electrophysiological changes, and the use of various drugs. The Table shows a variety of different parameters that have been frequently described as predictors of mortality in HF. In total, more than 60 parameters have been related to mortality in HF. Whereas all of the listed parameters have been shown to have significant predictive value in the univariate model, many of them do not retain their predictive value in the multivariate regression analyses.6 It is obvious that the clinician cannot effectively utilize all of these predictors in clinical practice to stratify HF patients into high- and low-risk categories. Furthermore, because many of these predictors do not have significant independent predictive value when combined with other parameters, it might not be clinically meaningful or necessary to evaluate them for risk prediction. It is, therefore, necessary to use an integrated approach to find the most cost-effective strategy for risk stratification of patients with HF. A variety of different models have been utilized and described previously for risk stratification of patients with HF.7–8 For example, in 1989 we had described that, in a multivariate regression model in patients with mild to moderate HF, left ventricular ejection fraction was the best predictor of total mortality, whereas the presence of nonsustained ventricular tachycardia was a better predictor for the risk of sudden cardiac death.7 Subsequently, the predictive value of nonsustained ven-
tricular tachycardia for sudden death was also shown in patients with severe HF.\(^8\) More recently, studies have utilized the newer biochemical markers such as BNP and revealed that measurement of BNP can also identify HF patients at increased risk of sudden cardiac death.\(^9\)

**An Integrated Approach**

Although many of the previous studies utilized a number of established parameters that are predictive of mortality, the available results are of limited value because some studies have failed to utilize all of the commonly available predictors of outcome. The study by Vrtovec et al\(^2\) published in this issue of *Circulation* has attempted to overcome some of those deficiencies by including most of the commonly utilized parameters that have been shown to have predictive value for risk of mortality in patients with advanced HF. They have utilized an interesting strategy by first identifying patients with advanced HF by measuring plasma BNP levels and selecting only the patients who have BNP levels >400 pg/mL. Then, they compared the predictive value of QT\(_c\) interval obtained from leads II and V\(_4\) on a standard 12-lead ECG against many of the previously established and commonly available parameters for determining the risk of all-cause mortality, cardiac mortality, sudden cardiac death, and death due to pump failure. By using such an integrated approach, Vrtovec et al\(^2\) have been able to demonstrate that such simple parameters as QT\(_c\) interval and plasma BNP levels can indeed accurately identify subgroups of patients with HF who are at increased risk of overall mortality, sudden cardiac death, and death due to pump failure. The results from this study should be of considerable clinical interest because the most powerful and independent predictors in their study were prolonged QT\(_c\) (>440 ms) and increasing levels of BNP. It is interesting to note that not only did patients with prolonged QT\(_c\) have a 5- and 9-fold increased risk of all-cause mortality and death due to pump failure, respectively, but also the risk of sudden death was increased 6-fold in those with QT\(_c\) >440 ms.\(^5\) Furthermore, their results indicate that the progressive increase in BNP levels was also an independent predictor of all-cause, cardiac, and pump failure deaths but not of sudden cardiac death.\(^5\) These data demonstrate the advantage of such an integrated approach because a recent study that did not utilize QT\(_c\) interval had shown that levels of BNP were predictive of increased risk of sudden cardiac death.\(^6\) The discrepancy in the results of these two studies suggests that, unless one utilizes an integrated approach using most of the commonly available parameters, the studies can provide data that might have limited clinical utility.

The study by Vrtovec et al\(^5\) has some limitations. For example, they have not utilized the cardiothoracic ratio available from chest x-rays in their multivariate regression model. It would have been important to utilize such information because of the fact that a previous study had failed to show independent predictive value of QT or JT intervals when the cardiothoracic ratio was used in patients with mild to moderate HF.\(^11\) Also, the investigation by Vrtovec et al\(^5\) did not give any information about ventricular arrhythmias and heart rate variability measured on 24-hour Holter monitoring, both of which have been shown to provide independent predictive information about the risk of sudden cardiac death. Regardless of these limitations, the present study by Vrtovec and associates has important clinical value.

**Clinical Implications and Future Direction**

Despite significant advances in medical therapy, patients with HF remain at increased risk of overall mortality and sudden cardiac death. The results of several recent trials indicate that
AICD implantation can reduce the risk of sudden cardiac death. Also, devices such as biventricular pacing for resynchronization therapy and left ventricular assist devices can improve the clinical outcome in patients with HF. However, because of the significant cost, these devices cannot be utilized for all patients with HF. An integrated approach such as the one utilized by Vrtovec et al in this issue of Circulation can help identify those patients who are at increased risk of overall mortality, sudden cardiac death, and pump failure death. By using such a risk stratification strategy to identify high-risk individuals, the clinician should be able to more effectively utilize the limited healthcare resources while providing the necessary and proven therapy to those who need it the most. Such a strategy is essential to provide proven therapies to patients who are most likely to benefit. Future studies should be conducted to prospectively examine the clinical usefulness and merit of such an integrated approach to prescribe treatment with expensive devices such as resynchronization with biventricular pacing and/or AICDs. Unless we utilize such a strategy, the cost of health care for HF patients could break the bank without necessarily providing the optimal care for those who really need it.

References

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