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EDITORIAL COMMENT

More Risk Factors Affecting Heart Failure Outcomes!

Time for Hope or Despair?*

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Tremendous progress has been made over the last two decades in the management of patients with heart failure due to left ventricular dysfunction. Recent large randomized beta-blocker trials in these patients have shown a single-digit annual mortality rate (range 7.2% to 8.8%) and a reduction in hospitalization rate in excess of 20% (1–3). Despite these improvements, the road ahead is humbling. Due to the extremely high prevalence, the actual morbidity and mortality associated with heart failure remains astronomical. It is estimated that currently there are over 5 million people in U.S. who have heart failure, with an annual incidence rate of over 500,000. Heart failure still accounts for over 250,000 deaths and over a million hospitalizations annually (4). In fact, both the incidence and the prevalence of heart failure continue to increase. This is attributable to a combination of the aging of the population in general and improved outcomes from other acute cardiovascular diseases, which in turn provide patients a chance to live, albeit with abnormal ventricular function. Another less well-studied possibility is that the risk factors for development of heart failure may also be increasing in the general population.

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Thus, despite the overall decrease in mortality rate with newer therapies in recent years, if the current epidemic continues to evolve, the absolute number of deaths due to heart failure at the population level may actually increase rather than decrease in the future. Moreover, many recent heart failure therapies that once showed promise failed to replicate the same beneficial results in larger trials (5). In short, heart failure burden continues to increase; although outcomes have improved, they are still unacceptable, and the benefits with newer therapies seem to be reaching a plateau.

Given these realities, where do we go from here? One answer is to discover new risk factors for heart failure and explore novel therapies. Two studies in this issue of the *Journal* have done exactly this. Doehner et al. (6) have reported on the importance of insulin resistance as a risk factor for adverse heart failure outcomes. Although the relationship between insulin resistance and coronary artery disease has been researched for some time now, its association with survival in heart failure patients is not well documented. Prospectively investigating 105 male patients with an ejection fraction of 28 ± 2%, the investigators compared outcomes based on patients' state of insulin sensitivity. During a mean follow-up period of 44 ± 4 months, almost half the patients died. For comparative purposes, patients were divided into those with above and those below median insulin sensitivity measured for the cohort. Patients with lower insulin sensitivity had lower ejection fraction (24 ± 2% vs. 33 ± 3%) and peak exercise oxygen consumption (16.8 ± 1.0 ml/kg/min vs. 19.9 ± 1.0 ml/kg/min). Patients with lower insulin sensitivity had worse survival than did those with above-median values, and when adjusted for various differences between the two groups, higher insulin sensitivity predicted better survival.

In the second study, Meyer et al. (7) assessed the importance of impaired endothelium-dependent flow-mediated vasodilation in patients with heart failure. They studied 75 patients with depressed ejection fraction. The primary end point for this study was a combined outcome of either patient death or conversion to United Network for Organ Sharing (UNOS) status 1 while awaiting cardiac transplantation. Event-free survival rate was higher in patients with flow-mediated vasodilation above the median value compared with those below. Only 19% of patients above the median cut-off value, but 63% below it, reached the combined end point. Flow-mediated vasodilation was independently related to the risk of reaching the combined end point.

Although both these results are interesting and have potential therapeutic implications, they have to be viewed cautiously. In the study by Doehner et al. (6), the overall one-year mortality rate was 22%. This is higher than expected for a group of patients with an average peak exercise oxygen consumption of 17.9 ± 0.7 ml/kg/min and would suggest sub-optimal management. Indeed, this is the case. Only 20% of these patients were on beta-blockers, and we do not have the information on defibrillator use. It is anyone's guess whether this relationship between insulin resistance and mortality would remain true if all eligible patients were on standard therapy. What is almost certain is that even if there were an adverse link between insulin resistance and mortality identified in such an idealized treatment paradigm, it would be of a different (perhaps lesser?) magnitude. Another interesting issue is the emerging data on differences in beta-blockers with respect to their effect on insulin sensitivity, and how that would affect these results (8).

In the study by Meyer et al. (7), the event rate is driven primarily by the patient's conversion to UNOS status 1 and

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not by mortality. How to account for transplantation and ventricular assist device use in heart failure studies is an unresolved problem. Conversion to UNOS status 1, which presumably was primarily related to continuous inotrope use, is even more subjective. The study by Meyer et al. (7) would have been more convincing if there was an adverse relationship demonstrated with mortality. Another issue is whether this relationship represents a risk factor or a risk marker for adverse outcomes. Many correlates of impaired flow-mediated vasodilation are also associated with worsening heart failure itself (e.g., oxidative stress and neurohormonal activation). However, impaired flow-mediated vasodilation may worsen heart failure progression through ischemia and changes in ventricular afterload, as stated by the authors. Finally, the "independent" prognostic power of any risk factor depends largely on what it is compared against, and in this study we do not have the information on some of the standard risk predictors in heart failure.

However, the epidemiologic and therapeutic implications of these results are enormous. Western society is facing a growing obesity, insulin resistance, and metabolic syndrome challenge. These studies suggest a possibility of improving heart failure outcomes by treating insulin resistance. Indeed, a recent study showed significant benefit with insulin sensitizers in heart failure patients with diabetes (9). If these results are replicated, it would not be surprising that such drugs like thiazolidinediones may become part of the therapeutic armamentarium for heart failure. A recent clinical trial showed significant survival benefit in heart failure patients with carvedilol as compared to metoprolol tartarate (3). Could this be in part related to differences in insulin sensitivity profile (8) between these agents? If insulin resistance is a determinant of heart failure outcomes, the differences between various beta-receptor antagonists will become even more clinically relevant, providing additional evidence to support the superiority of carvedilol over beta-1 selective adrenergic antagonists. With insulin resistance and diabetes, the heart uses an excess of free fatty acids and has reduced metabolism of glucose. Thus one may expect drugs that optimize myocardial metabolism in patients with insulin resistance to potentially improve heart failure outcomes. Indeed, ranolazine is associated with an improvement in left ventricular function in animal models of heart failure (10).

Similarly, will drugs that improve flow-mediated vasodilation (e.g., statins) improve heart failure outcomes? Studies suggest improved heart failure outcomes with statins, and a clinical trial is underway (11). Another interesting question that arises is whether the impaired flow-mediated vasodilation and insulin resistance are related, and are these two studies both leading us in the same direction (12). Finally, based on these findings, novel pharmacologic agents may be developed that target these pathophysiologic abnormalities.

In short, both groups of investigators should be congratulated for their interesting findings. However, the hard work of proving these hypotheses, replicating the results, and, more importantly, translating them into therapeutic advances needs to begin soon.

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