

Letters

TO THE EDITOR

Predicting Sudden Cardiac Death in Heart Failure



Ahmad et al. (1) suggest that biomarkers related to myocardial stress and fibrosis add some weight to the prediction of mode of death in patients with heart failure-reduced ejection fraction (HF-REF), particularly pump failure as opposed to sudden cardiac death (SCD). A variety of biomarkers have been shown to predict adverse ventricular remodeling/progressive pump failure, including natriuretic peptides and various markers of matrix turnover, but the holy grail of outcome prediction in HF-REF is the discovery of a robust predictor of SCD at the point of diagnosis. The decision as to whether to implant a defibrillator early after diagnosis of de novo HF-REF is one of the most challenging, balancing the potential for recovery of left ventricular function with evidence-based pharmacotherapy against the risk of SCD while awaiting possible functional recovery. Although certain biomarkers may provide some information to this effect, none are particularly powerful predictors, including galectin-3 and ST2, which were investigated in the study by Ahmad et al. (1). This may be because risk of SCD in HF-REF is more appropriately predicted by electrical and structural data than by biomarkers, but perhaps there is a role for biomarkers in combination with electrical and structural abnormalities in the prediction of SCD.

Detailed analysis of the 12-lead surface electrocardiogram (ECG) recorded at the time of diagnosis of HF-REF reveals certain anomalies that increase the risk of SCD, including QRS dispersion, heart rate variability, short-term variability of the QT interval, and the independent finding of a QRS duration in excess of 160 ms (2). If routine Holter monitoring is performed at the point of diagnosis of HF-REF, the absence of nonsustained ventricular tachycardia is associated with reduced risk of SCD (3). The use of basic and more advanced imaging techniques has resulted in the detection of a number of characteristics that increase the risk of SCD in HF-REF, ranging from echocardiographic left atrial size and

severity of mitral regurgitation to the detection of myocardial fibrosis/scarring using late gadolinium enhancement on cardiac magnetic resonance (4). Indeed, the presence (and not necessarily the extent or distribution) of late gadolinium enhancement in patients with HF-REF is an independent predictor of SCD (4).

The true role of biomarkers in predicting SCD in HF-REF may lie in combination with clinical, electrocardiographic, and structural findings. N-terminal pro-B-type natriuretic peptide, when added to a model comprising clinical, ECG, and echocardiographic variables, enhanced the ability to predict SCD in patients with HF-REF (5). Studies to establish risk prediction models for SCD in HF-REF should combine baseline electrocardiography, modern imaging techniques (particularly cardiac magnetic resonance), and existing and novel biomarkers. Could the authors speak to whether ECG and/or imaging data are available from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) cohort described in their report and, if so, whether inclusion of such data influenced the predictive efficacy of the biomarkers studied?

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Please note: Dr. Weir has served on an endpoint committee for the REMINDER trial, sponsored by Pfizer (USA).

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REPLY: Predicting Sudden Cardiac Death in Heart Failure



We thank Dr. Weir for the insightful comments in regard to our recent report (1). We wholeheartedly agree with the assertion that biomarkers may play a role in prediction of risk of sudden cardiac death in combination with electrical and structural assessments of the heart.

It would be expected that inclusion of specifics of the surface electrocardiogram such as QT variability and novel imaging modalities such as late gadolinium enhancement on cardiac magnetic resonance could potentially add both accuracy and precision to the prediction of sudden cardiac death. However, such detailed phenotyping was not performed in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study. Furthermore, patients with chronic heart failure have an increased risk of death from a variety of causes other than sudden cardiac death, and extremely accurate predictors of one mode of death might not be clinically feasible in the setting of these competing risks. Risk of sudden cardiac death is also not static, and frequent detailed assessments of cardiac structure and electrocardiography may not be practical in the clinical setting. With these unanswered questions in mind, there is an unmet need to compare various predictors of sudden cardiac death to assess their comparative prognostic and cost effectiveness.

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BAG3 Protein in Advanced-Stage Heart Failure



We read with interest the report by Storrow et al. (1), which shows that a high proportion of patients with acute heart failure (HF) are admitted to emergency departments annually, with high readmission rates and costs. Accurate monitoring is critical to guide clinical management of HF and identify high-risk patients who may be considered for advanced therapy. It is increasingly evident that analysis of multiple biomarkers reflecting various pathophysiologies in HF may add unique information to gauge the severity and/or progression of the disease, assist in stratifying risk, and ultimately improve the care of patients with HF, resulting in better outcomes and lower health care costs (2,3). In this respect, novel identification of molecules released by failing cardiomyocytes may contribute to the available apparatus of diagnostic and prognostic tools while simultaneously extending our understanding of biological processes in HF.

Cardiomyocytes express BAG3, a protein involved in homeostatic response to mechanical stress; mutations in BAG3 have been implicated in several cardiomyopathies (4). We recently described for the first time an extracellular form of BAG3 released by stressed cardiomyocytes. The protein was identifiable using mass spectroscopy of serum samples from patients with chronic HF (left ventricular ejection fraction <45%); release of BAG3 appeared to trigger an immune response because serum anti-BAG3 antibodies were also measurable in these patients. However, using a specific enzyme-linked immunosorbent assay for measuring BAG3 protein concentration in serum samples, we could not detect significant differences between BAG3 values in healthy subjects and patients with HF using New York Heart Association (NYHA) functional class I to III symptom severity (5).

In the present analysis, we report that BAG3 protein concentration was significantly higher in serum samples from 20 patients with HF with NYHA functional class IV compared with 44 healthy subjects or 59 patients with NYHA functional class I to III (Figure 1A). Differences were greatest ($p < 0.001$) between healthy controls and patients with NYHA class I versus patients with NYHA class IV and remained quite significant ($p < 0.01$) when highly symptomatic patients were compared with those with NYHA class II to III symptoms. Notably, high concentrations of BAG3 were associated with death, implantation of a