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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