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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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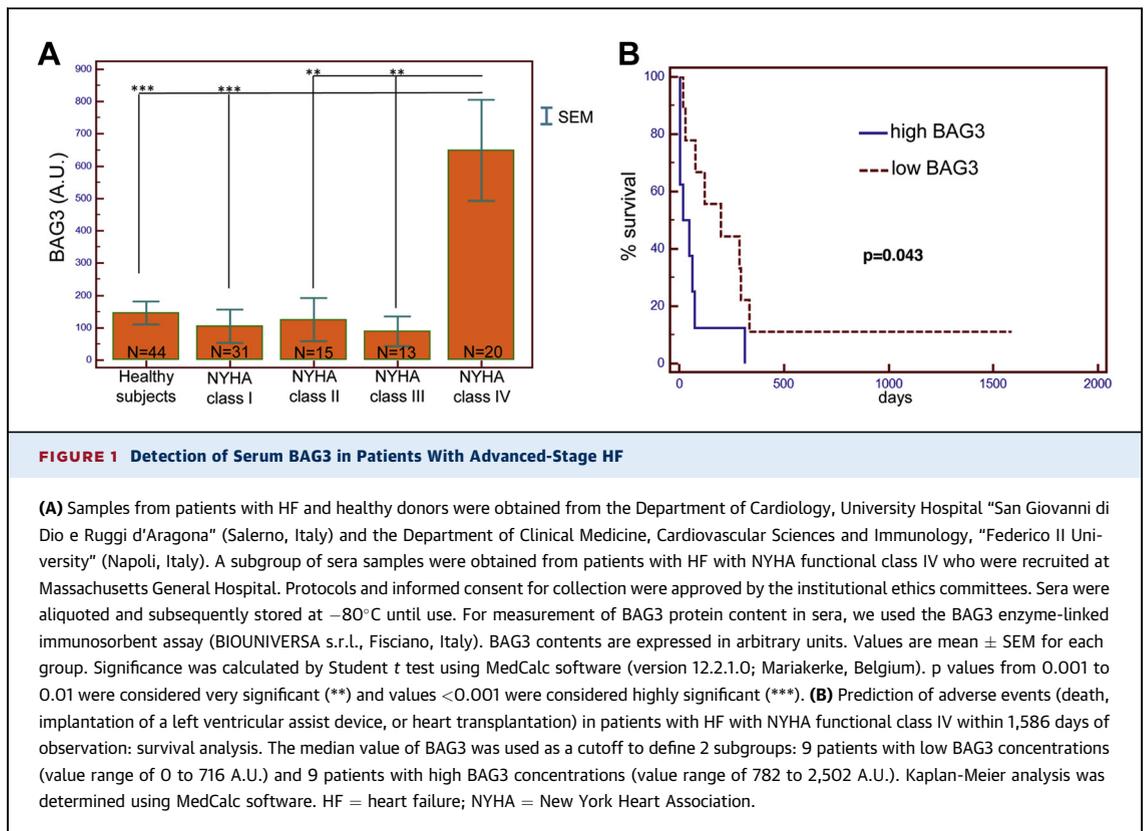
BAG3 Protein in Advanced-Stage Heart Failure



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



left ventricular assist device, or heart transplantation within 1,586 days of observation. We distinguished 2 groups: 9 patients with high BAG3 concentrations (value range of 782 to 2,502 A.U.) and median survival of 32.5 days and 9 patients with low BAG3 concentrations (value range of 0 to 716 A.U.) concentrations and median survival of 198 days ($p = 0.043$) (Figure 1B).

These findings indicate that serum BAG3 protein values, although appearing very low (close to the detection threshold) in healthy donors and patients with NYHA functional class I to III, are increased in patients with a more advanced stage of HF. Therefore, BAG3 protein appears to be a biomarker that deserves investigation to ascertain its utility in monitoring progression of HF, specifically in patients who progress from NYHA functional class II to IV or patients with functional class IV who progress to an advanced state. Furthermore, these results suggest that BAG3 enzyme-linked immunosorbent assay can be helpful, possibly in combination with other tests, to predict adverse events in patients with advanced HF.

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Please note: BIOUNIVERSA s.r.l., which produces anti-BAG3 antibodies, provided them free of charge for this study. Drs. De Marco, D'Auria, Rosati, and Turco are shareholders of BIOUNIVERSA, which provided some of the antibodies. Dr. Januzzi, Jr has received significant grant support from Roche Diagnostics, Siemens, Singulex, and Thermo Fisher; has received significant consulting income from Critical Diagnostics and Sphingotec; and he has participated in clinical endpoint committees and/or data safety monitoring boards for Novartis and Amgen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REPLY: BAG3 Protein in Advanced-Stage Heart Failure



We appreciate the interest of Dr. De Marco and colleagues in our report (1) and their interesting observations on the potential use of serum BAG3, possibly in combination with other tests, in monitoring progression of heart failure. We agree that a multiple biomarker approach may add unique diagnostic and prognostic information (2). In our study, we were not focused on chronic heart failure or long-term outcomes but rather the burden of acute heart failure on our nation's emergency departments. The high hospital admission rate and significant resource consumption suggest that strategies to safely reduce admissions, or alternatives to hospital stays, may have profound implications. We believe this challenge could be addressed with better methods to identify patients at low risk for short-term adverse outcomes and readmissions, including assessment of self-care behaviors such as symptom monitoring, medication taking, and exercise. We have previously suggested that combining physician judgment, physiological risk predictors, strategies to address barriers to ideal self-care, and shared decision making may provide this critical inertia (3,4). Unfortunately, there are currently no validated tools to identify low-risk patients with acute heart failure in the emergency department suitable for discharge or perhaps a brief period of observation (4). We suggest that previous biomarker and risk stratification efforts have not significantly affected emergency department decision making; those with no high-risk features do not necessarily equate with low risk (5). Although novel biomarkers likely will play an important role, we suggest that a more comprehensive methodology is needed to address the burden before it becomes overwhelming.

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The Effects of Dose Reduction of Furosemide on Glomerular Filtration Rate in Stable Systolic Heart Failure



Loop diuretics are effective and necessary to improve hemodynamics and relieve congestion in subjects with systolic heart failure (HF) and fluid overload. In contrast, in compensated/noncongested patients with left ventricular systolic dysfunction, reports suggest negative consequences of chronic loop diuretic therapy on the progression of HF (1,2). Others and we have also reported that in patients with compensated HF, loop diuretic therapy has deleterious neurohumoral and renal hemodynamic effects such as renal vasoconstriction and activation of the renin-angiotensin-aldosterone system (1,3). The