Gal-3 has been examined as a potential diagnostic and prognostic marker for HF in humans. First studied in established HF, higher concentrations of Gal-3 were associated with an increased risk for death or recurrent HF independent of established risk factors in 4 studies ranging from 232 to 599 patients (5–8). In the largest published study (n = 895), Gal-3 was associated with HF severity and long-term outcomes, but did not add incrementally to natriuretic peptides (9). In the context of these data, Gal-3 was cleared for clinical use for prognostication in patients with established HF. However, Gal-3 does not appear useful for diagnosis of HF in patients with dyspnea (5).

Gal-3 has also been evaluated as a tool to forecast future HF. In a case-control study among patients stabilized after acute coronary syndromes, Gal-3 was associated with the risk for HF over 2 years (10). In a general population-based study of 7,968 subjects followed for 10 years, Gal-3 predicted all-cause death (11). Gal-3 was correlated with age, sex, and cardiovascular risk factors, but not the risk for cardiovascular death, leaving open whether Gal-3 is useful to identify primary prevention candidates at increased risk for developing HF.

To address this question, Ho et al. (2) measured Gal-3 in 3,353 subjects in the Framingham Offspring Cohort. In age-adjusted and sex-adjusted analyses, the risk for new HF over approximately 8 years increased by 28% for each standard deviation increase in log-transformed Gal-3 concentration. This relationship was independent of age, sex, blood pressure, diabetes, and body mass index. However, Gal-3 did not substantially improve on the clinical model for prognostication or discrimination, particularly when considering B-type natriuretic peptide. The investigators also examined the relationships between Gal-3 and left ventricular mass, systolic function, fractional shortening, and left atrial dimension assessed by echocardiography. Higher levels of Gal-3 were associated with increased left ventricular mass but not these other echocardiographic parameters.

The findings of Ho et al. (2) demonstrate for the first time a relationship between Gal-3 and future HF in the general population. Their observations are interesting and raise several questions.

Does this study establish the mechanism by which Gal-3 is associated with HF? Although experimental results implicate a direct contribution of Gal-3 to cardiac fibrosis and the unadjusted association with left ventricular mass in Ho et al’s (2) study is supportive, these data leave open whether there is a definite link between Gal-3 and cardiac structural and functional changes in humans. Future studies with cardiac magnetic resonance imaging or positron emission tomography may help elucidate these relationships. Notably, Gal-3 was only weakly correlated with B-type natriuretic peptide (r = 0.05). The lack of an association with natriuretic peptides is consistent with Gal-3 acting as an “early warning” reflecting myocardial changes before the
onset of hemodynamic strain. Supporting this concept, Gal-3 is up-regulated in animal models before the development of HF (4). Ho et al did not examine other emerging markers of hemodynamic stress or structural change, including midregional proadrenomedullin, ST2, collagen-related peptides, or high-sensitivity troponin. Also, the investigators hypothesize that renal dysfunction may mediate Gal-3’s effects on cardiac remodeling; however, additional investigation should exclude renal function as a mere confounder.

Is Gal-3 sufficiently specific as a biomarker of cardiovascular risk? In this study, Gal-3 appeared to have a stronger association with death from noncardiovascular than cardiovascular causes. Because Gal-3 is common to inflammatory processes, it is up-regulated in varied fibrotic conditions, including of the liver, lung, and kidney (3). This lack of tissue specificity is likely to have implications for consideration of Gal-3 in screening strategies.

Is there sufficient evidence to use Gal-3 for screening of HF risk? The Ho et al. (2) findings are intriguing and add support for a link between Gal-3 and the development of HF in humans, but alone are insufficient to establish a role for Gal-3 in screening apparently healthy individuals. Gal-3 did not provide substantial incremental information for predicting HF when renal dysfunction and B-type natriuretic peptide were considered; nor were other emerging biomarkers of HF reported in their study. In addition, evidence would be needed to determine whether Gal-3 is helpful for guiding effective preventive interventions. In patients with systolic HF, lower levels of Gal-3 appear to identify patients who may benefit from statin therapy (12), and preliminary data suggest interactions with use of angiotensin-converting enzyme inhibitors and device therapy. However, as yet, no interactions between Gal-3 and interventions for HF prevention have been reported. Moreover, the Ho et al. (2) echocardiographic analyses reveal that Gal-3 did not identify patients with early systolic dysfunction, for whom the early initiation of an angiotensin-converting enzyme inhibitor may be useful. Although an association with HF with preserved ejection fraction is important, therapeutic options are even more limited for this syndrome.

Nevertheless, pre-clinical studies suggest that modification of Gal-3 levels may play a role in ameliorating the progression of HF. In a mouse genetic knockout model with significantly lowered Gal-3 expression, cardiac fibrosis is reduced and ventricular function improved. In addition, as described by Ho et al. (2), Gal-3 can be inhibited with modified citrus pectin, as well as other candidates.

The study by Ho et al. (2) is a step forward in the assessment of Gal-3 in cardiovascular disease. Because Gal-3 did not add convincingly to improve discrimination or reclassification of risk, appropriately, the investigators do not argue a role for routine screening. However, their findings lend support to the notion of Gal-3 as a causal factor in human cardiac disease. Further investigation of Gal-3 may lead to advances in our understanding of cardiac fibrosis and remodeling, as well as shine a light toward new therapies for a challenging and increasingly prevalent disease.

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