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Clinical Investigations

Prognostic Value of Estimating Functional Capacity With the Use of the Duke Activity Status Index in Stable Patients With Chronic Heart Failure

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ABSTRACT

Background: Over the years, several methods have been developed to reliably quantify functional capacity in patients with heart failure. Few studies have investigated the prognostic value of these assessment tools beyond cardiorenal prognostic biomarkers in stable patients with chronic heart failure.

Methods and Results: We administered the Duke Activity Status Index (DASI) questionnaire, a self assessment tool comprising 12 questions for estimating functional capacity, to 1,700 stable nonacute coronary syndrome patients with history of heart failure who underwent elective diagnostic coronary angiography with 5 year follow up of all cause mortality. In a subset of patients (n = 800), B type natriuretic peptide (BNP) was measured. In our study cohort, the median DASI score was 26.2 (interquartile range [IQR] 15.5-42.7). Low DASI score provided independent prediction of a 3.3 fold increase in 5 year mortality risk (quartile 1 vs quartile 4: hazard ratio [HR] 3.33, 95% confidence interval [CI] 2.57-4.36; $P < .0001$). After adjusting for traditional risk factors, BNP, and estimated glomerular filtration rate, low DASI score still conferred a 2.6 fold increase in mortality risk (HR 2.57, 95% CI 1.64-4.15; $P < .0001$). **Conclusions:** A simple self assessment tool of functional capacity provides independent and incremental prognostic value for mortality prediction in stable patients with chronic heart failure beyond cardiorenal biomarkers. (*J Cardiac Fail* 2015;21:44-50)

There are nearly 6 million adults in the United States carrying a diagnosis of heart failure (HF), with the lifetime risk estimated to be 1 in 5.¹ Although current medical and device therapies for HF have dramatically improved outcomes, mortality remains high in some subgroups.² Therefore, identifying poor prognostic markers early may provide opportunities for intensifying therapy. High natriuretic peptides,³ cardiac troponin elevation,⁴ and poor performance on exercise stress testing identify HF cohorts at increased risk for death over time. Functional status impairment can occur in the setting of chronically impaired cardiac output and chronic central or peripheral venous congestion.

The Duke Activity Status Index (DASI) is a simple 12-question self-assessment tool for estimating functional capacity (table 1). DASI scores correlate well with peak oxygen uptake (Spearman rho = 0.81; $P < .0001$) and are validated (Spearman rho = 0.58; $P < .0001$) measures of functional status in patients with HF.⁵ After admission for acute decompensated HF, DASI scores predict event-free survival.⁶ However, the long-term prognosis of functional status measures in stable patients with HF has not been elucidated. In the present study, we determined the

Table 1. Duke Activity Status Index (DASI)

Can You:	Weight
Take care of yourself, that is, eat, dress, bathe, or use the toilet?	2.75
Walk indoors, such as around your house?	1.75
Walk a block or two on level ground?	2.75
Climb a flight of stairs or walk up a hill?	5.50
Run a short distance?	8.00
Do light work around the house like dusting or washing dishes?	2.70
Do moderate work around the house like vacuuming, sweeping floors, or carrying groceries?	3.50
Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	8.00
Do garden work like raking leaves, weeding, or pushing a lawn mower?	4.50
Have sexual relations?	5.25
Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a ball?	6.00
Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?	7.50

Range: 0 (worst) to 58.2 (best).

long-term prognostic value of functional status assessment in stable patients with chronic HF.

Methods

Study Population

The Cleveland Clinic Genebank study prospectively enrolled a total of 8,987 subjects who underwent coronary angiography in the absence of an acute coronary syndrome, without a history of revascularization within 30 days before enrollment, and ≥ 5 years of long term adjudicated follow up data. Detailed medical histories were obtained on all subjects (predominantly outpatients) at enrollment. Blood samples were collected at the time of cardiac catheterization after arterial sheath placement, but before the catheterization procedure or any therapy (including anticoagulation medications). Every participant gave written informed consent approved by the Institutional Review Board.

Data Collected

The present analysis included 1,700 of consecutive subjects with a medical history of HF with reduced or preserved left ventricular ejection fraction (LVEF) enrolled in Genebank, who completed the DASI questionnaire (Table 1) and with corresponding blood samples for analysis. Chronic HF was defined as a documented history of HF by treating physician in the electronic medical record and confirmed by study personnel at the time of enrollment. Heart failure was defined as a documented history of HF by the treating cardiologist in the electronic medical record at the time of enrollment.

Biomarkers and Echocardiography

B Type natriuretic peptide (BNP), creatinine, fasting lipid profiles, cardiac troponin I (TnI), uric acid, and high sensitivity C reactive protein (hs CRP) were measured on the Abbot Architect platform (Abbott Laboratories, Abbot Park, Illinois). An estimate of glomerular filtration rate (eGFR) was calculated with the use of the Modification of Diet in Renal Disease equation. LVEF was determined via transthoracic echocardiography by the Cleveland Clinic echocardiography laboratory reviewed by Board certified cardiologists with the use of chart review of the electronic medical record.

Adjudicated outcomes were prospectively ascertained over the ensuing 5 years for all subjects after enrollment.

DASI Questionnaire

Patients were asked to complete the DASI survey, supervised by study personnel, at the time of coronary angiography. The DASI is a self administered questionnaire that measures both functional capacity and quality of life aspects. It correlates well with peak oxygen uptake on stress testing.⁵ The survey attempts to capture major aspects of physical function: personal hygiene, ambulation, routine tasks, recreation, and sexual function. High scores correlate with better functional capacity. This questionnaire has been validated in similar populations.^{7,8}

Statistical Analysis

This cohort was split into quartiles of DASI score for the population. *P* values of $\leq .05$ were considered to be significant to reject the null hypothesis that there were no differences in mortality at 5 years of follow up between the highest and lowest DASI score quartiles. Independent variable was DASI score quartile, and dependent variable was mortality at 5 years. Parametric and nonparametric approaches were used to express continuous variables. Survival analyses were completed with the use of the Kaplan Meier method and log rank analysis to compare survival curves among the 4 quartiles. Cox proportional hazards models were used to compare time to event analyses to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for 5 year mortality between the 1st and 4th quartiles of DASI scores. Multivariate models were adjusted for traditional cardiac risk factors, including age, sex, systolic blood pressure, cigarette smoking, history of diabetes, and fasting low density lipoprotein and high density lipoprotein cholesterol levels. Additional adjustments were made for a subset with both measured BNP and eGFR values. Subgroups were divided according to age ≥ 60 years, LVEF $< 45\%$, eGFR $< 60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, history of coronary artery disease (CAD), TnI $\geq 0.03 \text{ ng/mL}$, sex, uric acid $\geq 9.8 \text{ mg/dL}$, hs CRP $\geq 2 \text{ mg/dL}$, history of diabetes mellitus, and history of chronic obstructive pulmonary disease (COPD). Statistical analyses were performed with the use of JMP Pro version 9 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics are described in Table 2 and are representative of a patient population with chronic HF. The reasons for cardiac catheterization within the study cohort were as follows (subjects can have > 1 reason): history of positive or abnormal stress test (30%), evaluation for possible ischemic causes of symptoms (63.5%), preoperative evaluation (24%), and history of cardiomyopathy (14%). DASI surveys were successfully completed by 1,700 study participants, and scores across this study cohort were nonparametrically distributed (Fig. 1). The median DASI score was 26.2 (interquartile range 15.5–42.7). The mean DASI scores for quartiles 1–4 were 8.7 ± 3.7 , 20.2 ± 3.2 , 33.4 ± 3.9 , and 50.0 ± 5.9 , respectively. Decreasing DASI scores were associated with increasing comorbidity (Table 2), but not with LVEF ($P = .4$). There were no differences in either angiotensin-converting

Table 2. Baseline Characteristics

Variable	DASI Score Quartile				P Value
	<15.5	15.5–26.1	26.2–42.7	>42.7	
Age (y)	68 ± 11	69 ± 11	66 ± 11	64 ± 11	<.0001
Male (%)	45.4	60.0	72.6	81.0	<.0001
BMI (kg/m ²)	29.8 (25.9–35.1)	28.4 (24.8–33.3)	28.1 (25.2–32.3)	28.9 (25.5–32.3)	.001
Diabetes mellitus (%)	49.3	44.4	35.8	27.2	<.0001
Hypertension (%)	83.0	80.0	79.3	78.2	.4
Coronary artery disease (%)	80.3	75.4	77.3	69.7	.003
Smoking history (%)	66.6	72.1	74.3	75.2	.03
LVEF (%)	45 (30–55)	40 (25–55)	40 (25–55)	40 (29–55)	.4
BNP (pg/mL)	457 (155–971)	337 (136–781)	316 (119–639)	205 (86–411)	<.0001
eGFR (mL min ⁻¹ 1.73 m ⁻²)	56.1 (41.9–74.0)	57.1 (42.8–74.1)	59.0 (46.8–75.0)	61.7 (49.9–76.0)	.001
Beta blocker (%)	66.8	68.0	68.0	65.2	.8
ACEI/ARB (%)	63.9	67.7	68.8	70.5	.2
Loop diuretic (%)	68.1	69.3	55.2	40.7	<.0001

DASI, Duke Activity Score Index; BMI, body mass index; LVEF, left ventricular ejection fraction; BNP, B type natriuretic peptide; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Values are presented as either mean ± SD or median (interquartile range) unless otherwise stated. P values were calculated with the use of analysis of variance or Kruskal Wallis test for continuous variables and chi square method for categoric variables.

enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) or beta-blocker use across DASI quartiles (P values .2 and .8, respectively).

Predicting Mortality Risk With DASI Score

In our study cohort, 1,692 study participants were followed for all-cause mortality over 5 years after study entry. By 5 years there were a total of 556 deaths and 1,023 subjects survived to the end of follow-up. 113 study participants were lost to follow-up. Kaplan-Meier estimates of survival were calculated for 1,692 participants (Fig. 2). The estimated 5-year survival rate was 67%. DASI score quartiles 1–4 had 193, 166, 120, and 77 deaths, respectively, by the end of follow-up. There were significant decrements in survival across increasing DASI score quartiles: log-rank chi-square 96.1; $P < .0001$. The lowest DASI score quartile predicted a 3.3-fold increase in risk of 5-year mortality compared with the highest DASI score quartile: HR 3.33, 95% CI 2.57–4.36; $P < .0001$; Table 3). After additional adjustment for traditional risk factors, lower DASI scores still independently predicted

an increased risk for death: HR 2.78, 95% CI 2.10–3.72; $P < .0001$. Furthermore, when stratifying DASI score by median (26.2), in addition to multivariate adjustment for traditional risk factors, the area under the receiver operating characteristic curve for 5-year mortality was 69.4%. In a sensitivity analysis with multivariate adjustment for LVEF in addition to traditional risk factors, lower DASI scores remained predictive of increased mortality: HR 2.79, 95% CI 2.10–3.72; $P < .0001$. Compared with DASI scores >40 , DASI scores ≤ 40 predicted a 2-fold increased risk for death: HR 2.00, 95% CI 1.58–2.58; $P < .0001$. Subgroup analyses reveal that DASI scores predict all-cause mortality across dichotomized subgroups of age, sex, history of coronary artery disease, history of diabetes mellitus, history of COPD, eGFR, and LVEF (Fig. 3)

Prognostic Value of DASI Adjusting for Cardiorenal Biomarkers

In a subset of patients with available BNP data (Fig. 4) at the time of the DASI questionnaire, we observed only a

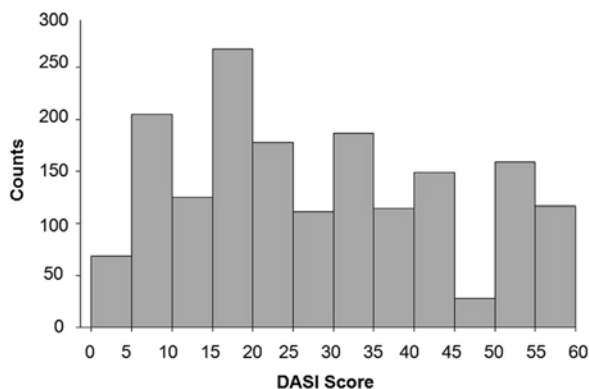


Fig. 1. Duke Activity Status Index (DASI) score distribution in study cohort (n = 1,700).

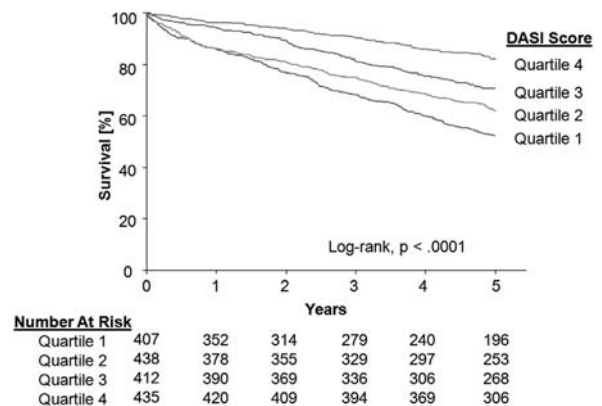


Fig. 2. Kaplan Meier estimates of 5 year survival rates according to Duke Activity Status Index (DASI) score.

Table 3. Cox Proportional Hazards Model for Risk of 5 Year Mortality Stratified According to DASI Scores

Model	HR	95% CI	P Value
Univariate	3.33	2.57–4.36	<.0001
Multivariate			
Adjusted for traditional risk factors*	2.78	2.10–3.72	<.0001
Adjusted for traditional risk factors* + BNP + eGFR†	2.57	1.64–4.15	<.0001

HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 2.

Quartile 1 versus quartile 4.

*Traditional risk factors included age, sex, systolic blood pressure, history of diabetes, smoking, low density lipoprotein cholesterol, and high density lipoprotein cholesterol.

†Subset of 800 subjects with biomarker data available.

modest correlation between BNP (Spearman rho = 0.210; $P < .0001$) and DASI score. Estimated glomerular filtration rate was also modestly correlated with DASI score (Spearman rho = 0.107; $P < .0001$) for the total cohort. Lower DASI scores still independently predicted an increased risk for death after adjusting for traditional risk factors, BNP, and eGFR: HR 2.57, 95% CI 1.64–4.15; $P < .0001$).

Discussion

There are several key findings in our study. First, we surveyed a large cohort of patients with chronic stable HF undergoing elective coronary evaluation and observed an association between lower functional status (as measured with the use of the DASI questionnaire) and greater risk of 5-year mortality. Second, this association remained robust after multivariate adjustment for traditional cardiac risk factors and, in a subset of patients, after additional adjustment for cardiorenal biomarkers. Although commonly attributed to the underlying comorbid conditions, the association between diminished functional capacity and 5-year all-cause mortality appeared to be consistent across a variety of subgroups of patients with different comorbid conditions and clinical characteristics. Taken together, these findings illustrate the potential of patient-centric insight gained by conducting a simple questionnaire developed to assess overall functional capacity.

Functional capacity is an important component of a patient-centric evaluation of HF, and recommendations for its careful assessment have been included in the latest clinical management guidelines.^{9,10} Although the DASI

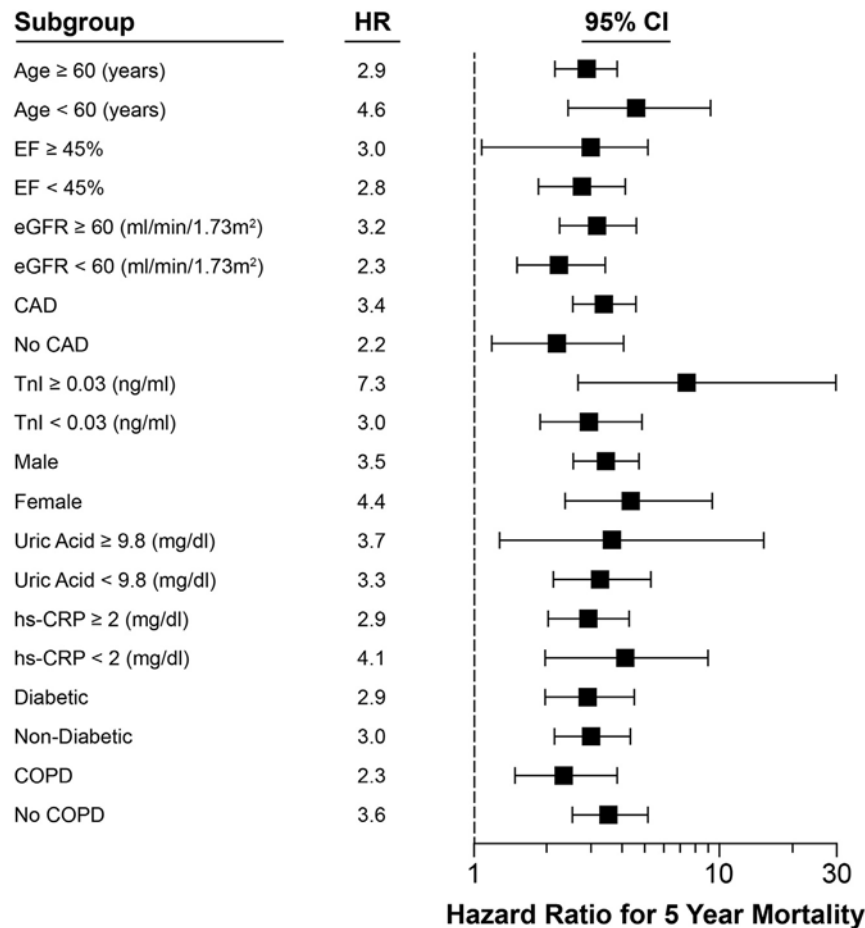


Fig. 3. Subgroup analysis of Duke Activity Status Index (DASI) score and 5 year mortality. HR, hazard ratio; CI, confidence interval; EF, ejection fraction; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; TnI, troponin I; hs CRP, high sensitivity C reactive protein; COPD, chronic obstructive pulmonary disease.

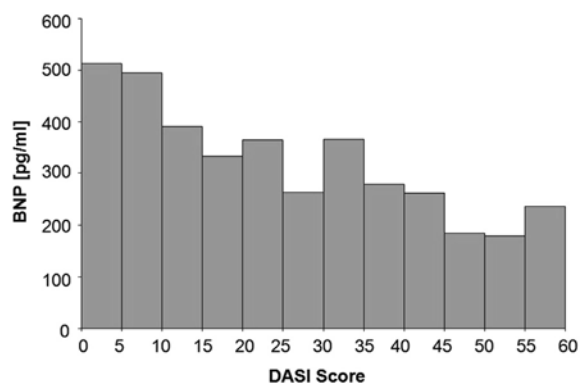


Fig. 4. Median B type natriuretic peptide (BNP) by Duke Activity Status Index (DASI) score (n = 819).

was developed > 20 years ago,⁵ its application has been largely restricted as a subjective assessment tool in clinical trials. The DASI is a simple self-administered questionnaire that assesses perceived functional status. Rather than relying on recall, it is composed of questions relating to self-assessment of one's ability to perform activities that represent major aspects of physical function. Set up as a continuous measure, DASI scores correlate with peak oxygen uptake during cardiopulmonary stress testing.⁵ The DASI has been validated in cohorts of patients with HF, obstructive CAD, and COPD.^{5,11,12} Although the accuracy of DASI score in predicting peak oxygen uptake in the setting of HF has been challenged,^{8,13} our findings support the notion that the clinical utility may likely extend beyond performance on stress testing. Indeed, a recent comparison of several commonly used objective assessments of functional capacity did not validate cardiopulmonary exercise stress testing as equivalent to other, simpler, forms of exercise capacity evaluation, such as the 6-minute walk test, in terms of prognostic utility.¹⁴

To our knowledge, this is the largest cohort of patients with HF who have completed the DASI survey and have been followed longitudinally for adverse outcomes. Our findings confirm several smaller studies that have suggested the prognostic value of functional status assessment in the setting of HF. For example, DASI scores were lower in a population of 130 patients with impaired LVEF recently hospitalized for decompensated HF who experienced adverse events after 9 months of follow-up compared with those that did not.⁶ Paired with BNP, those with low DASI scores and higher BNP levels were more likely to have lower event-free survival.⁶ In adults > 75 years old, lower functional status, as measured with the use of the pre-admission Barthel Index, was a strong predictor of 3-month mortality.¹⁵ In the setting of cardiac surgery, lower DASI scores have also been associated with higher mortality risk,¹⁶ and changes in DASI scores have been observed after surgery.¹⁷ It has been suggested that DASI scoring may vary based on factors that affect functional capacity, such as age, sex, COPD, and the presence of diabetes mellitus.¹⁸ Yet, based on our findings, its prognostic value in these

cohorts remained robust. Additionally, we found that DASI scores correlate with mortality in patients with either reduced or preserved left ventricular function and were not related to systematic differences (eg, ACEI/ARB or beta-blocker use) in medical management of HF.

There are other prognostic instruments that capture functional status as well. In a cohort of 6,975 outpatients with chronic HF from the Gruppo Italiano per lo Studio Della Streptochinasi Nell'Infarto Miocardico Heart Failure Trial (GISSI-HF), New York Heart Association (NYHA) functional classification III or IV was independently associated with a more adverse prognosis than NYHA functional classification II.¹⁹ NYHA functional class is a simple score ordinarily assessing exertional symptoms in HF. Yet it has notable limitations¹: no consistent assessment method and¹ high interoperator variability.²⁰ The Minnesota Living With Heart Failure Questionnaire (MLHFQ) is a validated HF-specific questionnaire based on a Likert scale.²¹ Data from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE) suggests that lower MHLF scores are associated with adverse outcomes in patients with HF with preserved LVEF.²² In contrast to these scores, the DASI can provide a continuum of scores, and is easily administered with simple yes/no patient responses, either oral or written.

Increasing plasma levels of natriuretic peptides have been associated with adverse outcomes in chronic HF²³ and may provide incremental prognostic information independently from clinical assessment.²⁴ Furthermore, based on an ancillary study from the Studies on Left Ventricular Dysfunction (SOLVD) trial, worsening renal function is independently associated with both mortality and disease progression in patients with LV dysfunction.²⁵ Renal function also provides additional prognostic information in patients with HF independently from functional status as measured by the 6-minute walk test.²⁶ Our observation regarding the incremental prognostic value of DASI after inclusion of BNP and eGFR in multivariate adjustment suggested that factors incremental to cardiorenal disease progression that are captured by the patient's own perception of his or her own functional status may affect long-term outcomes. For example, other underlying metabolic derangements or physical limitations may be uncovered during DASI assessment.

Our results must be interpreted in the context of several limitations in our study design. Because DASI scores were measured at only 1 point in time, we were unable to examine the variability and prognostic value of changing DASI scores over time or the impact of different therapies in the interim. Furthermore, baseline NYHA functional class was unavailable and hospitalization readmissions were not adjudicated. We cannot exclude the presence of unmeasured confounding by baseline depressive symptoms, because these were not assessed on study inclusion, or selection bias for those undergoing coronary angiography for further evaluation and management of HF at a tertiary care center, although based on baseline clinical

characteristics they appear to be relatively representative of a contemporary patient population with HF. However, the majority of the patients in this analysis had ischemic cardiomyopathy and there was low use of beta- and renin-angiotensin blocking agents. Nevertheless, based on our promising results and in the era where patient-centric outcomes are valued, further investigations into the clinical utility of baseline and serial DASI questionnaire administrations are warranted.

Conclusion

In patients with stable HF, functional status assessment, as measured by the DASI questionnaire, predicts mortality at 5 years. This assessment provides independent and additional prognostic information beyond the measurement of BNP and eGFR. Lower DASI scores predict mortality across a variety of subgroups of differing prognosis in patients with HF. These results highlight the importance of assessing functional status in patients with HF. Future studies using functional status assessment as a tool for treatment intensification in HF are warranted.

Disclosure

Dr Tang has previously received investigator-initiated research grant support from Abbott Laboratories with no personal financial payments. Dr Hazen is named as coinventor on pending patents held by the Cleveland Clinic relating to cardiovascular diagnostics; has been paid as a consultant for Abbott Diagnostics, Cleveland Heart Lab, Esperion, Lilly, Liposcience, Merck and Co, P&G, and Pfizer; has received research funds from Abbott, Cleveland Heart Lab, Liposcience, P&G, and Pfizer; and has the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics or therapeutics from Abbott Laboratories, Cleveland Heart Lab., Esperion, Frantz Biomarkers, Liposcience, and Siemens. All other authors have no relationships to disclose.

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