5-1-2013

Detectable Subclinical Myocardial Necrosis Is Associated With Cardiovascular Risk in Stable Patients With Diabetes

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Publisher's Statement

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OBJECTIVE—To investigate the relationship between different degrees of subclinical myocardial necrosis, glycemic control, and long term adverse clinical outcomes within a stable patient population with diabetes mellitus.

RESEARCH DESIGN AND METHODS—We examined 1,275 stable patients with diabetes mellitus undergoing elective diagnostic coronary angiography with cardiac troponin I (cTnI) levels below the diagnostic cut off for defining myocardial infarction (MI) (<0.03 ng/mL). The relationship of subclinical myocardial necrosis (cTnI 0.009 0.029 ng/mL) with incident major adverse cardiovascular events (MACE; defined as any death, MI, or stroke) over 3 years of follow up was examined.

RESULTS—Subclinical myocardial necrosis was observed in 22% of patients. A strong association was observed between the magnitude of subclinical myocardial necrosis and risk of 3 year incident MACE (hazard ratio, 1.98; 95% confidence interval, 1.48 2.65; $P < 0.001$) and remained statistically significant even after adjustment for traditional risk factors, high sensitivity C reactive protein, and creatinine clearance. Only a weak correlation was observed between the presence of subclinical myocardial necrosis and either glycemic control ($r = 0.06$; $P = 0.044$ for hemoglobin A_{1c} versus cTnI) or insulin resistance ($r = 0.04$; $P = 0.094$ for glucose to insulin ratio versus cTnI).

CONCLUSIONS—The presence of detectable subclinical myocardial necrosis in stable patients with diabetes mellitus is associated with heightened long term risk for MACE, independent of traditional risk factors and glycemic control.

Detection of systemic levels of cardiac troponin is associated with the presence of ongoing myocardial necrosis and fulfills the contemporary definition of myocardial infarction (MI) in the presence of ischemic symptoms (1). However, a minimal increase in cardiac troponin levels below the diagnostic range often provides clinical challenges, particularly in stable ambulatory patients without overt signs and symptoms suggestive of underlying ischemia and normal renal function (2). As biochemical assays become more and more sensitive, the ability to detect minimal myocardial damage may allow risk assessment in stable cardiac patients beyond the acute setting (3).

We recently have demonstrated that such presence of subclinical myocardial necrosis was associated with adverse long term cardiovascular risks in stable patients undergoing elective coronary angiography (4). These findings were reported in diabetic and nondiabetic patients with and without coronary artery disease and heart failure. We sought to examine the prognostic significance of detectable subclinical myocardial necrosis in the setting of diabetes mellitus, particularly to examine its relationship with underlying glycemic control.

RESEARCH DESIGN AND METHODS

The Cleveland Clinic GeneBank study is a large, prospective, cohort study that established a well characterized clinical repository with clinical data and longitudinal outcomes from consenting subjects undergoing elective diagnostic coronary angiography from 2001 to 2006. All GeneBank participants gave written informed consent approved by the Cleveland Clinic Institutional Review Board. All blood samples were collected at the time of cardiac catheterization procedure. This analysis included a cohort of 1,275 consecutive consenting subjects with a clinical diagnosis of diabetes mellitus without clinical evidence of acute coronary syndrome at the time of enrollment with 3 year follow up data. These patients underwent elective diagnostic coronary angiography within 1 year of attending outpatient appointments, scheduled coronary computed tomography angiogram scans, or computed tomography scans within 1 year of scheduled blood draws. The various reasons for the elective coronary angiography include (subjects could have more than one reason per person) the following: history of positive or indeterminate stress test (50%); evaluation for possible ischemic causes of symptoms (68%); preoperative evaluation (10%); and history of cardiomyopathy (3%). Subjects included were only those with cardiac troponin I (cTnI) <0.03 ng/mL, no history of revascularization within 30 days before enrollment, and at least 3 years of adjudicated follow up data. The diagnosis of diabetes mellitus was determined based on the latest guideline recommendations as clinical history of diabetes mellitus or fasting glucose ≥126 mg/dL or hemoglobin A_{1c} (HbA_{1c}) ≥6.5% at the time of enrollment (5).

Plasma levels of cTnI were measured using the *STAT* Troponin I assay (Abbott laboratories, Abbott Park, IL) ina research based immunoanalyzer that provides a three decimal point readout from venous blood samples collected by EDTA tubes. This assay provides highly sensitive analyt ical measuremem of cTnl with a reported limit of detection reaching 0.009 nglmL in the literature (4) and a diagnostic cut off of 0.03 nglmL for MI defined by the upper limit of normal (99th percemile cut off with 10% coefficiem of variation). Based on the analytical characteristics of the cTnl assay, we defined subclinical myocar dial necrosis as cTnl 0.009 0.029 nglmL (above level of detection). High sensitivity C reactive protein (hsCRP), HbA_{1c}, glu cose, insulin, creatinine, and fasting lipid profiles all were measured simultaneously with the cTnl assay using the same analysis platform. Treating physicians and adjudi cation commiuee were blinded to the re sults of cTnl.

We defined coronary angiography as any clinical history of MI, percutaneous coronary intervention, coronary artery $b_{y\ p}$ass graft, or angiographic evidence of significantstenosis (50%) in one or more major coronary arteries. Dyslipidemia was defined as LDL cholesterol > 130 mgldL, HDL cholesterol <50 mgldL, triglycerides > 150 mgldL, or the use of lipid lowering agents. An estimate of creatinine clearance (eCrO) was calculated using the Cockcroft Gault equation, because a large majority of subjects had relatively preserved renal function. Adjudicated outcomes were prospectively ascertained over the ensuing 3 years for all subjects after enrollmem. Maj or adverse cardiovascular event (MACE) was defined as death, nonfatal MI, or nonfatal stroke after enrollmem. Non fatal MI was defined as patients that re mained alive over the follow up period of 3 years and met the universal definition of MI, which is defined as a documented increase in cardiac biomarker in conjunc tion with evidence of myocardial ische mia (1). Nonfatal stroke in this cohort was defined as patients with a clinical diagnosis of rapid loss of brain function attributable to blood flow disturbance to the brain with accompanying imaging techniques or records of confirmed diag nosis who remained alive over the follow up period of 3 years. All cause death was ascertained by follow up (1 and 3 year) telephone interviews, Social Security Death Index that was assessed periodi cally after enrollment, official hospital record, or death certificate.

The Student *t* test or Wilcoxon rank sum test for continuous variables and x^2 test for categorical variables were used to examine the difference between the groups. Unadjusted trends (adjusted for age and sex only) for all cause mortality rates as well as nonfatal Ml/stroke rates with increasing tertiles of cTnI were eval uated with the Cochran Armitage test using a time to event approach. Adjust ments were made for individual tradi tional cardiac risk factor, Framingham risk factors (including age, sex, cigarette smoking, LDL cholesterol, HDL choles terol, and systolic blood pressure) plus log transformed hsCRP, and CrCl to pre diet incident 3 year MACE risks. Kaplan Meier analysis with Cox proportional hazards regression was used for time to event analysis to determine hazard ra tio **(HR)** and 95% confidence intervals (95% Cis) for MACE. Levels of cTnI then were adjusted for traditional coronary angiography risk factors in a multivariable model including Framing ham risk factors, log transformed hsCRP, and CrCl. We confirmed that both the proportionality hazards and linearity as sumptions were met. All analyses were performed using R 2.10.1 (Vienna, Aus tria). P < 0.05 was considered statistically significant. The authors had full access to all of the de identified data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS In our study cohort of 1,275 subjects, 22% of subjects had evidence of subclinical myocardial necro sis (with 34% detectable but in the range of 0.001 0.008 nglmL). The evem num bers for MACE in our cohort over the 3 year follow up were as follows: all cause death, 129/1,275; nonfatal MI, 62/ 1,275; and nonfatal stroke, 31/1,275.

Table *I-Baseline characteristics*

	Subclinical myocardial necrosis		
	No (*n* = 989)	Yes (*n* = 286)	p
cTnl range (nglml)	<0.01	0.01 0.03	
Demographics and clinical data			
Age (years)	64 ± 10	67 ± 10	<0.001
Male(%)	59	70	0.002
Systolic blood pressure	136 ± 21	138 ± 24	0.205
History of $h_{y\ p\ e}$ *nension* (%)	77	82	0.111
History of hean failure (%)	16	38	<0.001
Cigarette smoking (former/current %)	63	68	0.17
Previous myocardial infarction(%)	31	53	<0.001
Previous revascularization (%)	31	40	0.003
Maximal stenosis 50% (%)	77	87	<0.001
Number of coronary vessel disease			
None(%)	23	14	0.001
One(%)	19	13	0.017
Two(%)	20	21	0.606
Three(%)	38	52	<0.001
HbA_{1c} (%)	6.7 (6.1 7.7)	7.0 (6.4 8)	0.006
Laboratory data			
Fasting LDL cholesterol (mgfdl)	94 (76 114)	92 (75 112)	0.387
Fasting HDL cholesterol (mgtdl)	32.9 (27.5 40.1)	31.4 (25.7 38.1)	0.002
Fasting triglycerides (mgfdl)	128 (90 187)	126 (90 172)	0.508
hsCRP (mgfl)	2.4 (1 1 5.9)	3.6 (1.5 7.0)	<0.001
CrCI (ml./min/1. $73m^2$)	104 (78 132)	84 (61 112)	<0.001
Baseline medications			
Aspirin(%)	75	72	0.442
Statin (%)	64	62	0.58
ACE inhibitors (%)	57	70	<0.001
Beta blockers (%)	64	67	0.358
Insulin(%)	19	23	0.085
Oral glucose lowering drugs(%)	42	44	0.466

Values expressed in mean ± SD or median (interquartile range).

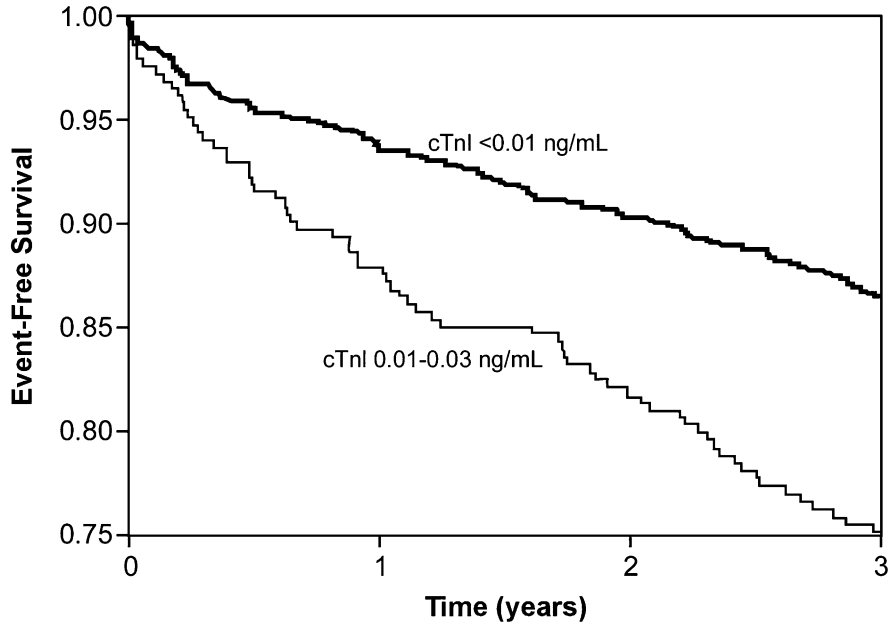

Figure 1—*Kaplan Meier analysis for 3 year major adverse clinical events, stratified according to subclinical myocardial necrosis status (rounded to the nearest 0.001 ng/mL).*

Baseline characteristics of the study population are shown in Table 1 and are stratified according to presence or absence of subclinical myocardial necrosis. Patients with evidence of subclinical myocardial necrosis were more likely to be older, with more cardiovascular risk factors and history of heart failure, and with slightly lower renal function at baseline.

Subjects with evidence of subclinical myocardial necrosis were associated with an increased 3 year risk of death (HR, 2.39; 95% CI, 1.68 3.40; $P < 0.001$), nonfatal MI or stroke (HR, 1.70; 1.09 2.66; $P = 0.019$), and MACE (HR, 1.98; 1.48 2.65; $P < 0.001$) (Fig. 1). The risk prediction appeared to be log linear as detectable cTnI levels increased (Fig. 2).

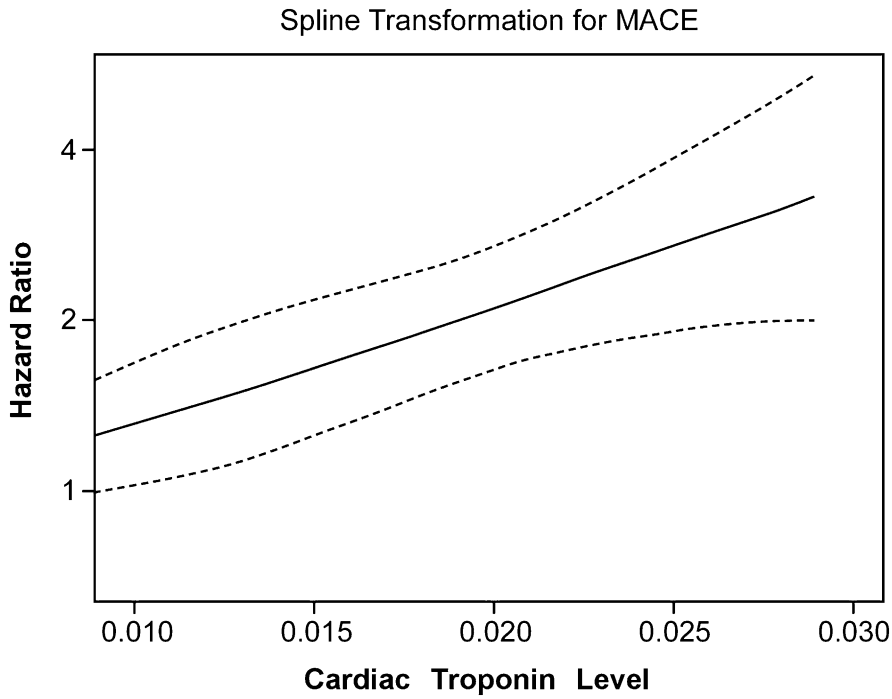

Figure 2—*Cubic spline curve of HRs for major adverse clinical events at 3 years with cTnI levels.*

After adjusting for traditional risk factors, including Framingham risk factors, hsCRP, and eCrCl, evidence of subclinical myocardial necrosis within stable cardiac diabetic patients remained a significant risk of incident MACE over the ensuing 3 years (HR, 1.48; 1.08 2.01; $P = 0.013$; Table 2).

A weak correlation was observed between the presence of subclinical myocardial necrosis and either glycemic control ($r = 0.06$ and $P = 0.044$ for HbA_{1c} versus cTnI) or insulin resistance ($r = 0.04$ and $P = 0.094$ for glucose to insulin ratio versus cTnI). Adjustments with either metabolic parameters had little impact on the prognostic value of detectable subclinical myocardial necrosis within the study cohort. Figure 3 illustrates similar risk prediction for major adverse clinical events at 3 years according to subclinical myocardial necrosis status stratified by on treatment HbA_{1c} using a cut off of 6.5%. The cTnI levels demonstrated no significant interaction with statin use or HbA_{1c} levels (P for interaction ≥ 0.20).

CONCLUSIONS The major finding of our study is the demonstration that the presence of subclinical myocardial necrosis in a respectable proportion of stable patients with diabetes mellitus has heightened long term adverse cardiovascular event risk. We further demonstrated that such risk may be independent of underlying glycemic control. These findings would appear to imply that any detectable cTnI level should warrant consideration for more globally aggressive risk reduction efforts, including closer evaluation and long term monitoring, and such intervention efforts may focus beyond glycemic control measures.

The concept of diabetes mellitus being a "coronary artery disease risk equivalent" has been suggested in several important studies (6 8) and even for those subjects with suspected acute coronary syndrome but with "normal" cardiac troponin levels (9). Guideline recommendations for routine aspirin prescription and secondary prevention therefore have been proposed (10 12). However, recent analyses have directly challenged such assertions (13,14). It is therefore conceivable that differences in risk profiles of patients with diabetes mellitus may warrant different indications of preventive interventions (5). Using the latest guideline recommendations for the definition and classification of diabetes mellitus including HbA_{1c} assessments (15), the current study provides

Table 2—*Unadjusted and adjusted HR for major adverse cardiac events at 3 year follow up*

Subclinical myocardial necrosis (*n*)	No (cTnI <0.01 ng/mL) (*n* = 989)	Yes (cTnI 0.01 0.03 ng/mL) (*n* = 286)
Death/nonfatal MI/stroke		
Unadjusted HR	1	1.98 (1.48 2.65)†
Adjusted HR (model 1)	1	1.48 (1.08 2.01)*
Adjusted HR (model 2)	1	1.56 (1.14 2.14)†
Adjusted HR (model 3)	1	1.54 (1.13 2.12)†
Adjusted HR (model 4)	1	1.49 (1.06 2.09)*

Model 1: Traditional risk factors (included age, sex, LDL, HDL cholesterol, systolic blood pressure, smoking, diabetes, CrCl, hsCRP); Model 2: Traditional risk factors + HbA_{1c}; Model 3: Traditional risk factors + HbA_{1c} + insulin-to-glucose ratio; Model 4: Traditional risk factors + HbA_{1c} + insulin-to-glucose ratio + ACE inhibitor/angiotensin receptor blocker + history of MI/coronary angiography/revascularization/heart failure/number of vessels with >50% stenosis. Values presented as HR and 95% CI. *$P < 0.05$; †$P < 0.01$.

some novel insight into the utility of detect ing subclinical myocardial necrosis as a po tential way to help identify those subjects with high versus low risks for the develop ment of future major adverse cardiac events. The implications of these findings and whether the detection of subclinical myocardial necrosis truly represents ongo ing myocardial damage that can be averted by more globally aggressive preventive efforts reducing future MACE risk com prise a hypothesis that needs further test ing by a biomarker guided therapeutic approach.

There are several potential explana tions for our findings. First, there was noticeable reduction in renal function (estimated by CrCl) associated with the cohort with definite subclinical myocar dial necrosis, which may suggest that the presence of underlying subclinical ne phropathy may have some influence on the reduced renal clearance of cTnI (16). Although we cannot definitely refute this potential explanation, our findings still indicate that the prognostic value of de tectable subclinical myocardial necrosis remained robust after statistical adjust ments for eCrCl. We also note that anal ysis of only the subset of diabetic subjects with normal eCrCl at time of study entry still showed subclinical myonecrosis to be an excellent independent predictor of in cident MACE risk over the ensuing 3 year period (adjusted HR, 1.47; 95% CI, 1.01 2.14). Second, the presence of microvascu lar diseases commonly present in patients with diabetes mellitus may contribute to progressive microvascular ischemia or mi croembolization that can be readily detect able by highly sensitive cTnI assay. Such a phenomenon has been observed in the set ting of acute coronary syndrome setting and has been demonstrated in animal mod els (17). Because silent ischemia commonly occurs in patients with diabetes mellitus, biochemical detection of subclinical myo cardial necrosis may occur without overt clinical presentation (18) and may portend further disease progression (19). Finally, there is a potential for increasing oxidative and nitrative stress in parallel with the met abolic derangements, leading to continuing decline in myocardial reserve (4). Regard less of these speculated underlying mecha nisms, our findings provided evidence to support the measurement of cTnI levels us ing contemporary and more sensitive im munoassays in a stable but relatively vulnerable patient population. This ap pears to represent a novel strategy to detect underlying cardiac vulnerability that is be yond traditional risk factors and metabolic indices that would benefit from further in vestigations.

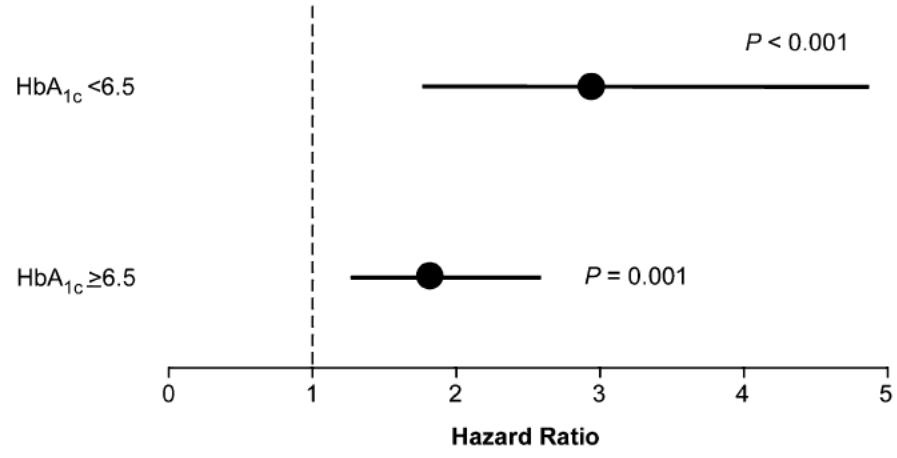

Figure 3—*Forest plot of risk prediction for major adverse clinical events at 3 years according to subclinical myocardial necrosis status stratified by HbA_{1c} at cut off of 6.5%.*

This analysis extends our previous findings by providing valuable insights into the incremental prognostic value of cTnI measurements in patients within the cohort of patients with diabetes mellitus, specifically by adjusting for glycemic con trol as well as established metabolic pa rameters. The discordance between the prognostic value of subclinical myocar dial dysfunction and glycemic control or glucose to insulin ratio is perhaps not unexpected but is worth discussion. The majority of epidemiologic data indicate the utility of adequate glycemic control in reducing microvascular rather than macrovascular disease progression (20). There have been data regarding differen tial long term cardiovascular outcomes with different glucose lowering drugs that targeted to the same HbA_{1c} (21), and there have been observations of tighter glycemic control and paradox ically higher rates of future MACE (22,23). Therefore, it would be intriguing to hypothesize that development of sub clinical myocardial necrosis in some pa tients with diabetes mellitus may, in part, contribute to these discrepant findings. It is conceivable that a tiered approach to ward cardiovascular prevention should be considered with the use of more sen sitive contemporary cardiac troponin assays in a vulnerable population in which current practice guidelines have not considered utilizing these cardiac specific biomarkers for risk prediction. By identifying those with subclinical myocardial necrosis, this "risk equiv alent" strategy of applying the most aggressive modifiable risk reduc tion strategies (both pharmacologically and nonpharmacologically) should be considered.

The strength of the current study is the ability to determine the future cardiac risk in a broad clinical population of patients with contemporary definition and management of diabetes mellitus in which cardiac troponin measurements are not routinely performed or clinically indicated at this time. However, the fact that all subjects were referred for coronary angiography, albeit electively, and that many had relatively preserved renal function, also may represent some degree of selection bias and may not be fully representative of the broad population of patients with diabetes mellitus in clinical practices. Nevertheless, the fact that we only included those with no revascularization performed within 30 days after enrollment ensured a population deemed "medically managed" for their cardiac conditions. It also should be noted that our study was limited to a single measurement and further work with serial measurements is needed to substantiate the variability of the marker for risk stratification. Moreover, serial measures will be useful because it is unclear what impact various interventions have on cTnI levels in the subclinical range in these subjects (24). It also is worth noting that limitations of our assays cannot precisely define subclinical myocardial necrosis in the lower range of 0.001 0.008 ng/mL, although the diagnostic accuracies of those with current definition of subclinical myocardial necrosis are certain. Most importantly, further studies are needed to determine if the presence of subclinical myocardial necrosis represents an underlying process that can be targeted for interventions. The presence of detectable subclinical myocardial necrosis in stable patients with diabetes mellitus is associated with heightened long term risk for MACE, independent of traditional risk factors and glycemic control.

Acknowledgments—This research was supported by National Institutes of Health grants P01HL076491, P01HL103453, P01HL098055, R01HL103866, R01HL103931, and P20HL113452 and by the Cleveland Clinic Clinical Research Unit of the Case Western Reserve University CTSA (UL1TR 000439 06).

S.L.H. is also partially supported by a gift from the Leonard Krieger endowment and by the Foundaton LeDucq. W.H.W.T. has previously received research grant support from Abbott Laboratories and has served as consultant for Medtronic and St. Jude Medical. S.L.H. reports being listed as co inventor on pending and issued patents held by the Cleveland Clinic relating to cardiovascular diagnostics and therapeutics. S.L.H. reports having been paid as a consultant or speaker for the following companies: Abbott Diagnostics, Cleveland Heart Laboratory, Esperion, Lilly, Liposcience, Merck, and Pfizer. S.L.H. reports receiving research funds from Abbott, Cleveland Heart Laboratory, Liposcience, and Pfizer. S.L.H. reports having the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics or therapeutics from the following companies: Abbott Laboratories, Cleveland Heart Laboratory, Esperion, Frantz Biomarkers, Liposcience, and Siemens. No other potential conflicts of interest relevant to this article were reported.

W.H.W.T. wrote the manuscript and researched data. Y.W. and E.B.B. researched data. N.I. researched data and contributed to discussion. S.L.H. researched data, reviewed and edited manuscript, and contributed to discussion. W.H.W.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Part of this study has been presented as a poster presentation at the 15th Annual Scientific Meeting of the Heart Failure Society of America, Boston, Massachusetts, 18 21 September 2011.

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