Natriuretic Peptide and High-Sensitivity Troponin for Cardiovascular Risk Prediction in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

Diabetes Care 2016;39:677–685 | DOI: 10.2337/dc15-1760

Mauro Gori,[1,2] Deepak K. Gupta,[1,3] Brian Claggett,[1] Elizabeth Selvin,[4] Aaron R. Folsom,[5] Kunihiro Matsushita,[6] Natalie A. Bello,[1,7] Susan Cheng,[1] Amil Shah,[1] Hicham Skali,[1] Orly Vardeny,[8] Hanyu Ni,[9] Christie M. Ballantyne,[10] Brad C. Astor,[11] Barbara E. Klein,[12] David Aguilar,[13] and Scott D. Solomon[1]

[1]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA
[2]Cardiovascular Department, Azienda Ospedaliera Papa Giovanni XXIII Hospital, Bergamo, Italy
[3]Vanderbilt Heart and Vascular Institute, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
[4]Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore MD, and Department of Epidemiology and the Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
[5]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN
[6]Department of Epidemiology, Johns Hopkins University, Baltimore, MD
[7]NewYork-Presbyterian/Columbia University Medical Center, New York, NY
[8]Department of Pharmacy, University of Wisconsin School of Pharmacy, Madison, WI
[9]National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, MD
[10]Section of Atherosclerosis and Vascular Medicine, Department of Medicine, Baylor College of Medicine, Houston, TX
[11]Departments of Medicine and Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI
[12]Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI
[13]Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, TX

Corresponding author: Scott D. Solomon, ssolomon@rics.bwh.harvard.edu.

Received 11 August 2015 and accepted 27 November 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-1760/-/DC1.

M.G. and D.K.G. equally contributed to the manuscript.

OBJECTIVE

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in diabetes; yet, heterogeneity in CVD risk has been suggested in diabetes, providing a compelling rationale for improving diabetes risk stratification. We hypothesized that N-terminal prohormone brain natriuretic peptide (NTproBNP) and high-sensitivity troponin T may enhance CVD risk stratification beyond commonly used markers of risk and that CVD risk is heterogeneous in diabetes.

RESEARCH DESIGN AND METHODS

Among 8,402 participants without prevalent CVD at visit 4 (1996–1998) of the Atherosclerosis Risk in Communities (ARIC) study there were 1,510 subjects with diabetes (mean age 63 years, 52% women, 31% African American, and 60% hypertensive).

RESULTS

Over a median follow-up of 13.1 years, there were 540 incident fatal/nonfatal CVD events (coronary heart disease, heart failure, and stroke). Both troponin T ≥14 ng/L (hazard ratio [HR] 1.96 [95% CI 1.57–2.46]) and NTproBNP >125 pg/mL (1.61 [1.29–1.99]) were independent predictors of incident CVD events at multivariable Cox proportional hazard models. Addition of circulating cardiac biomarkers to traditional risk factors, abnormal electrocardiogram (ECG), and conventional markers of diabetes complications including retinopathy, nephropathy, and peripheral arterial disease significantly improved CVD risk prediction (net reclassification index 0.16 [95% CI 0.07–0.22]). Compared with individuals without diabetes, subjects with diabetes had 1.6-fold higher adjusted risk of incident CVD. However, participants with diabetes with normal cardiac biomarkers and no conventional complications/abnormal ECG (*n* = 725 [48%]) were at low risk (HR 1.12 [95% CI 0.95–1.31]), while those with abnormal cardiac biomarkers, alone (*n* = 186 [12%]) or in combination with conventional complications/abnormal ECG (*n* = 243 [16%]), were at greater risk (1.99 [1.59–2.50] and 2.80 [2.34–3.35], respectively).

CONCLUSIONS

Abnormal levels of NTproBNP and troponin T may help to distinguish individuals with high diabetes risk from those with low diabetes risk, providing incremental risk prediction beyond commonly used markers of risk.

See accompanying articles, pp. 664, 668, 686, 694, 701, 709, 717, 726, 735, and 738.

Cardiovascular disease (CVD) is the major cause of morbidity and mortality among persons with diabetes (1). However, substantial heterogeneity in CVD risk has been described among individuals with diabetes (2–4). As the incidence and prevalence of diabetes continue to rise worldwide, there is a compelling rationale for improving CVD risk prediction provided by commonly used markers of risk, such as traditional risk factors, abnormal electrocardiogram (ECG), and conventional measures of diabetes complications, in particular to identify persons at the lowest risk, who may derive less benefit from preventive measures, and those at highest risk, who may derive the greatest benefit.

Recently, the circulating cardiac biomarkers, including N-terminal prohormone brain natriuretic peptide (NTproBNP) and troponin T (TnT), have been proposed as predictors of adverse cardiovascular outcomes in the general population and among persons with diabetes (5–12). However, these prior studies of diabetes were limited in their assessment of event discrimination or examined clinical trial cohorts, which may lack applicability to the broader population. Furthermore, whether circulating cardiac biomarkers improve CVD risk prediction beyond that achieved not only with traditional risk factors but also with other risk markers routinely assessed in diabetes, such as ECG findings and conventional measures of diabetes complications, has not been specifically tested.

Therefore, among participants with prevalent diabetes in the Atherosclerosis Risk in Communities (ARIC) study, we hypothesized *1*) heterogeneity in the risk of incident CVD and *2*) enhancement of CVD risk prediction with NTproBNP and high-sensitivity TnT beyond commonly used markers of risk.

RESEARCH DESIGN AND METHODS

Study Population

The ARIC study is an ongoing prospective observational study of the natural history of atherosclerotic diseases and cardiovascular risk factors. Detailed study rationale, design, and procedures have previously been published (13). The original cohort was recruited between 1987 and 1989 using probability sampling of middle-aged (45–64 years old) men and women from four communities in the U.S. (Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD). Subsequent short-term follow-up visits occurred at 3-year intervals up to 1998, with annual telephone interviews conducted between visits and to the present. A fifth visit was completed in 2011–2013.

The fourth visit (1996–1998) is the baseline for the current study. The study population included participants without prevalent CVD, with further categorization according to the presence (n = 1,510) or absence (n = 6,892) of diabetes. Prevalent diabetes was defined according to *1*) fasting glucose ≥126 mg/dL or nonfasting glucose ≥200 mg/dL or *2*) use of hypoglycemic drugs or a reported physician diagnosis of diabetes at visit 4 or any prior visit (14). Although diabetes type has not been formally assessed in ARIC, approximately one-third of individuals in this study population were known to be diagnosed with diabetes at ARIC visit 1 (age 45–64 years), while 62% of our study population developed diabetes after visit 1. The known prevalence of type 1 versus type 2 diabetes suggests that the majority of the patients with diabetes at baseline would be classified with type 2 diabetes, and all patients diagnosed after baseline can be classified with type 2 diabetes, in keeping with previous publications from ARIC (15). Thus, the vast majority of our study sample comprised persons with type 2 diabetes. Prevalent CVD was defined as a prior history of coronary heart disease (CHD), heart failure (HF), and/or stroke according to previously published criteria (16–19). Anthropometric and demographic data, medical history, blood pressure, and lipid assessments were obtained at visit 4 as previously described (20).

Conventional measures of diabetes complications included retinopathy, nephropathy, and peripheral arterial disease (PAD). Retinopathy was evaluated via retinal photography during visit 3 (1993–1995) and was considered to be present if any characteristic lesion as defined by the Early Treatment Diabetic Retinopathy Study severity scale was present (21). Nephropathy was defined by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or urine albumin-to-creatinine ratio (UACR) ≥30 mg/g (22). eGFR was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine and cystatin C equation, using covariates obtained at visit 4. UACR was calculated from a random urine sample collected at visit 4 (23). PAD was assessed as previously described in ARIC (24) and included intermittent claudication determined from the Rose Questionnaire, PAD-related hospitalization by ICD-9 code, or ankle-brachial index (ABI) <0.9 detected at visit 4 or at visit 3 (n = 365) or 1 (n = 302) if ABI at visit 4 was missing (25).

Major ECG abnormalities at visit 4 were defined according to the Minnesota coding system and ARIC study procedures as previously described (26) and included the presence of ventricular conduction defect, left ventricular hypertrophy, isolated major ST segment or T-wave (ST-T) wave abnormalities, or atrial fibrillation/flutter. Myocardial infarction (MI) by ECG was excluded, as it was part of the definition for prevalent CHD.

NTproBNP was measured from stored plasma samples collected from participants during visit 4, using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics) with a lower limit of detection ≤5 pg/mL and interassay coefficient of variation 3.5–4.7% (27). We dichotomized NTproBNP using a fixed cutoff value of 125 pg/mL as previously suggested (28).

TnT was measured using a high-sensitivity assay (hs-TnT), Elecsys Troponin T (Roche Diagnostics, Indianapolis, IN), with a lower limit of detection of 3 ng/L. TnT levels were categorized as abnormal based on the manufacturer's proposed 99th percentile in a healthy reference population (≥14 ng/L) (29), a value significantly lower than the 99th percentile detected in our population with diabetes (50 ng/L).

Of the 11,656 participants who attended visit 4, we initially determined status regarding prevalent diabetes (n = 2,936 with diabetes and n = 8,720 without diabetes). Among participants with prevalent diabetes, we excluded those with missing data on diabetes (n = 548) and participants with missing or prevalent HF, CHD, or stroke at visit 4 (n = 591), since for some clinical outcomes patients with prevalent disease were not followed up for postbaseline

in ARIC. Additionally, we sequentially excluded those with ethnicity other than black or white (n = 5), underrepresented in ARIC, and those with missing data on cardiovascular risk factors (n = 123) and with missing data on conventional complications of diabetes or cardiac biomarkers (n = 159), leading to a final population of 1,510 subjects with diabetes. Similarly, from the group without prevalent diabetes, we excluded subjects with missing or prevalent HF, CHD, or stroke at visit 4; with ethnicity other than black or white; and with missing data on cardiovascular risk factors, leading to 6,892 subjects without diabetes.

Outcomes

The primary outcome was a composite of incident fatal or nonfatal CVD events, including CHD (definite fatal CHD, definite or probable MI, or coronary revascularization) (16,17), HF (based on ICD-9 or -10 codes from hospital discharges or death certificates) (18), and/or stroke (validated definite or probable nonfatal stroke) (19). As a sensitivity analysis, we excluded coronary revascularization procedures from the composite outcome. Secondary end points included the individual component outcomes of incident CHD, HF, or stroke. The follow-up period was defined as the time elapsed from the date of visit 4 to 31 December 2011.

Statistical Analysis

The 1,510 participants with diabetes were categorized into four groups according to the presence or absence of conventional complications of diabetes, abnormal ECG, and/or abnormal levels of circulating cardiac biomarkers. Group I included participants with neither conventional complications of diabetes/abnormal ECG nor abnormal levels of circulating cardiac biomarkers (n = 725 [48%]). Group II comprised participants with at least one conventional complication of diabetes or abnormal ECG but negative circulating cardiac biomarkers (n = 356 [24%]). Group III included participants with at least one abnormal circulating cardiac biomarker but no conventional complications of diabetes or abnormal ECG (n = 186 [12%]), and group IV consisted of participants with abnormalities of both (n = 243 [16%]). Clinical characteristics were compared across these four groups. Right-skewed variables (triglycerides, UACR, and NTproBNP) were log transformed prior to analysis. Pack-years of cigarettes was log transformed after adding 1 to the observed value, such that nonsmokers were coded as 0 after transformation. Continuous variables were expressed as mean $\pm$ SD or median (25th, 75th percentiles) and compared with ANOVA, while categorical variables were compared using a χ^2 test.

CVD incidence rates for each measure of diabetes complication, abnormal ECG, or cardiac biomarkers and within each of the four aforementioned categories were calculated. The risk of adverse cardiovascular outcomes was assessed with sequential Cox proportional hazards regression models. Our multivariate model comprised variables derived from well-known risk scores (Framingham risk model, UK Prospective Diabetes Study [UKPDS] risk engine, ARIC CHD risk score) (30–32), therapeutic strategies known to affect CVD risk in diabetes, and variables based on noted baseline differences between the groups and/or on prior literature (33–35). Model 1 was adjusted for age, sex, race, and field center. Model 2 was adjusted for variables in model 1 as well as smoking status, log-transformed pack-years of cigarettes (packs of cigarettes smoked per day times number of years smoked), BMI, waist-to-hip ratio, systolic blood pressure, hypertension medication use, lipid-lowering medication use, aspirin use, education level, total-to-HDL cholesterol ratio, log-transformed triglycerides, and duration of diabetes. (As a sensitivity analysis, we adjusted model 2 also for glycated hemoglobin, detected in ARIC at visit 2.) Model 3 was further adjusted for conventional measures of diabetes complications (retinopathy, nephropathy, PAD) and ECG abnormalities, while model 4 also included cardiac biomarkers (abnormal TnT and abnormal NTproBNP). We also assessed CVD incidence rates in participants without diabetes and compared CVD risk with that of the four groups of participants with diabetes while adjusting for variables included in model 2. Additionally, we performed a sensitivity analysis also considering carotid artery intima-media wall thickness (cIMT) as a conventional measure of diabetes complications, since previous studies have suggested that persons without known CVD with increased cIMT are at increased risk for cardiac events and stroke (36).

Using the Harrell C statistic, continuous net reclassification index (NRI), and integrated discrimination improvement (IDI) statistics (37), we assessed whether inclusion of abnormal levels of circulating cardiac biomarkers (alone or together) improved the discriminatory abilities of models 2 and 3 for the primary outcome. Although it has been suggested that the more objective way to compare across studies is to use the continuous NRI version, we have also performed a sensitivity analysis with categorical NRI analysis for completeness, applying a conservative approach considering many cutoffs ($<$10, 10–20, 20–30, 30–50, and $>$50%), to solve the issues regarding the absence of standard risk thresholds in diabetes, heterogeneity of the population studied, and existence of different meaningful categories for the considered outcome.

In order to compare cardiac biomarkers and conventional measures of diabetes complications on the same scale, using Cox regression models we estimated hazard ratios (HRs) corresponding with a change of 1 SD for parameters with a continuous distribution (UACR, eGFR, TnT, and NTproBNP), maintaining dichotomous variables for retinopathy, PAD, and ECG abnormalities. To allow for flexible, potentially nonlinear relationships, we utilized restricted cubic spline models (38) applied to a fully adjusted model. Furthermore, to assess whether the prognostic relevance of the considered biomarkers may be a simple surrogate for renal dysfunction, we performed a sensitivity analysis excluding patients with eGFR $<$60 mL/min/1.73 m^2. For all analyses, two-sided P values of $<$0.05 were considered statistically significant. No adjustments were made for multiple comparisons. All analyses were performed using Stata, version 13 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics According to Markers of Risk in Diabetes (Conventional/ECG Versus Cardiac Biomarkers)

Clinical characteristics significantly differed across the four categories of participants with diabetes (Table 1). Out of 26 characteristics considered, 19 were

Table 1—Baseline characteristics of ARIC participants with diabetes, without prevalent HF, CHD, and stroke, by categories of conventional diabetes complications/ECG/cardiac biomarker

	Overall	No markers of risk	Only conventional/ECG	Only cardiac biomarker	Both	*P*
n (%)	1,510	725 (48)	356 (24)	186 (12)	243 (16)	
Age (years)	63 ± 6	62 ± 5	62 ± 5	65 ± 6*^	65 ± 6*^	<0.001
Female	52	51	61*	49^	44^	<0.001
African American	31	29	43*	19*^	30^#	<0.001
BMI (kg/m^2)	31.2 ± 5.8	31.0 ± 5.7	31.5 ± 6.1	31.3 ± 5.9	31.0 ± 5.3	0.67
Waist-to-hip ratio	0.98 ± 0.06	0.97 ± 0.06	0.98 ± 0.06	0.98 ± 0.07	0.98 ± 0.06	0.20
Low education‡	25	21	31*	17^	32*#	<0.001
Cigarettes (pack-years)	2 (0, 26)	1 (0, 24)	1 (0, 26)	6 (0, 26)	3 (0, 34)	0.40
Hypertension†	60	50	68*	59^	76*^#	<0.001
SBP (mmHg)	132 ± 18	128 ± 16	134 ± 18*	132 ± 18	139 ± 23*^#	<0.001
DBP (mmHg)	71 ± 10	71 ± 9	71 ± 11	70 ± 11	70 ± 12	0.85
Antihypert. Rx	57	47	64*	57*	77*^#	<0.001
Triglyceride (mg/dL)	142 (100, 206)	137 (100, 203)	148 (101, 206)	139 (103, 205)	142 (103, 213)	0.41
LDL (mg/dL)	122 ± 34	125 ± 34	122 ± 34	119 ± 30	118 ± 38	0.042
Total-to-HDL chol. ratio	4.8 ± 1.6	4.8 ± 1.4	4.8 ± 1.6	4.8 ± 1.6	4.9 ± 1.9	0.75
Lipid-lowering Rx	16	16	16	10^	23*#	0.002
Aspirin Rx	56	54	56	58	59	0.48
Creatinine (mg/dL)	0.89 ± 0.57	0.84 ± 0.18	0.85 ± 0.24	0.86 ± 0.18	1.13 ± 1.33*^#	<0.001
eGFR (mL/min/1.73 m^2)	93 ± 19	98 ± 14	94 ± 20*	91 ± 14*	79 ± 24*^#	<0.001
UACR (mg/g)	4.3 (1.5, 12.9)	3.0 (1.2, 6.7)	7.5 (2.0, 45.6)*	4.2 (1.7, 8.6)	17.6 (4.0, 90.9)*^#	<0.001
Glucose (mg/dL)	137 (117, 180)	133 (116, 170)	151 (126, 209)*	134 (113, 168)^	135 (116, 177)	<0.001
Longer diabetes duration[c]	38	31	44*	37^	51*^#	<0.001
Drug therapy for diabetes	44	36	53*	38^	57*^#	<0.001
Insulin	15	9	23*	10^	26*#	<0.001
ABI	1.14 ± 0.16	1.18 ± 0.13	1.08 ± 0.19*	1.18 ± 0.14^	1.10 ± 0.19*#	<0.001
hs-TnT (ng/L)	6 (3, 10)	5 (3, 7)	6 (3, 8)	10 (5, 17)*^	14 (7, 20)*^#	<0.001
NTproBNP (pg/mL)	54 (25, 107)	39 (20, 67)	43 (23, 73)	149 (51, 212)*^	192 (120, 356)*^#	<0.001
Retinopathy	13		35		32	
Nephropathy	19		40		58	
PAD	8		25		16	
Abnormal ECG	12		22		41	
NTproBNP >125 pg/mL	20			65	74	
TnT ≥14 ng/L	14			43	52	

Data are mean ± SD, median (25th, 75th percentiles), or percentage unless otherwise indicated. Retinopathy: ≥1 sign of retinopathy according to Early Treatment Diabetic Retinopathy Study severity scale. Nephropathy: eGFR <60 mL/min/1.73 m^2 or albuminuria ≥30 mg/g. PAD: ABI <0.9 at visit 4 (or 1 or 3 if not available at visit 4), hospitalization for PAD prior to visit 4, or intermittent claudication symptoms at follow-up questionnaire before visit 4. ECG abnormalities: ventricular conduction defect, left ventricular hypertrophy, isolated major ST-T wave abnormalities, or presence of atrial fibrillation. Antihypert., antihypertension; chol., cholesterol; DBP, diastolic blood pressure; Rx, prescription; SBP, systolic blood pressure. ‡Low education level defined as less than high school degree. [c]Longer duration of diabetes: disease diagnosed at the first ARIC study visit. †Hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current use of any antihypertension medications. *$P < 0.05$ compared with absence of all markers/measures. ^$P < 0.05$ compared with only conventional measures/abnormal ECG. #$P < 0.05$ compared with only cardiac biomarkers.

nominally statistically significant. Participants in group II (only conventional complications/abnormal ECG) were more commonly African American. Conversely, participants in group III (abnormal circulating cardiac biomarkers alone) were more commonly white, less frequently hypertensive, had the lowest use of therapies for diabetes and antihypertension and lipid-lowering therapy, and had shorter duration of diabetes. Finally, participants in group IV (both abnormal cardiac biomarker and conventional complication/abnormal ECG) were more commonly men, were more hypertensive, and had higher prevalence of treatments directed against risk factors and the longest duration of diabetes.

Cardiovascular Risk in Subjects With Diabetes Compared With Subjects Without Diabetes

Over a median follow-up time of 13.1 years (25th, 75th percentiles 6.9, 14.4), an incident CVD event occurred in 540 (36%) participants with diabetes and in 1,331 (19%) participants without diabetes. Compared with subjects without diabetes, in multivariable models adjusted for demographics and traditional cardiovascular risk factors (model 2) participants with diabetes had a higher risk of incident CVD event (HR 1.60 [95% CI 1.44–1.79], $P < 0.001$). However, subjects with diabetes with normal cardiac biomarkers, normal ECG,

and no conventional diabetes complications (group I) had only a mildly increased risk of events (1.12 [0.95–1.31], $P = 0.18$), while people with conventional complications/abnormal ECG alone (group II) had ~1.5-fold higher risk of incident CVD (1.68 [1.39–2.02], $P < 0.001$). Similarly, participants in group III (abnormal circulating cardiac biomarkers alone) had ~2.0-fold higher risk (1.99 [1.59–2.50], $P < 0.001$), while subjects in group IV (combined abnormality of cardiac biomarker and conventional diabetes complication/ECG) had a 3.0-fold higher risk (2.80 [2.34–3.35], $P < 0.001$) (Fig. 1).

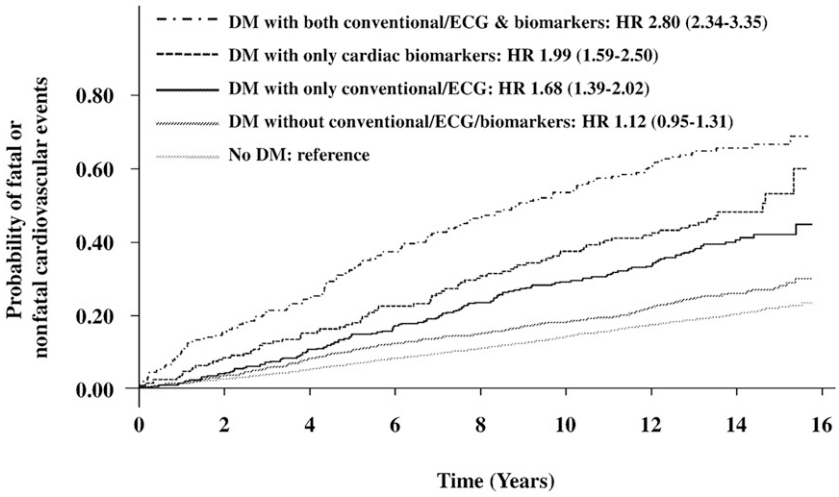

Figure 1—Kaplan-Meier curves for probability of fatal and nonfatal cardiovascular events. HRs are adjusted for demographic characteristics and cardiovascular risk factors. DM, diabetes.

Cardiovascular Risk Associated With Individual Markers

Dichotomous indicators of retinopathy, nephropathy, PAD, ECG abnormalities, elevated NTproBNP, and elevated TnT were individually associated with significantly increased risks of CVD when accounting for age, sex, race, and field center (model 1). However, with simultaneous adjustment for traditional cardiovascular risk factors and all six markers (model 4), retinopathy, nephropathy, ECG abnormalities, and elevated cardiac biomarkers remained significantly associated with increased risks for CVD, while PAD was not (Fig. 2). The prognostic relevance of cardiac biomarkers was confirmed looking at the risk associated with 1 SD change of UACR (log transformed) and eGFR, even when tested with restricted cubic spline models (Supplementary Table 1 and Supplementary Fig. 1). The results were similar in a sensitivity analysis excluding coronary revascularization as a component of the CHD outcome or adjusting model 2 for glycated hemoglobin assessed at visit 2 (data not shown). Additionally, when cIMT was considered as a conventional measure of diabetes complications, this marker was also significantly associated with the primary outcome in fully adjusted analysis (Supplementary Fig. 2).

Multivariable models adjusted for traditional cardiovascular risk factors as well as all six markers (model 4) were repeated for the individual components of the primary outcome, i.e., HF, CHD, and stroke (Fig. 3). The only marker consistently associated with increased risk for each of these secondary outcomes was TnT.

Incremental Prognostic Value of Circulating Cardiac Biomarkers

Abnormal levels of circulating cardiac biomarkers improved the discriminatory ability of traditional cardiovascular risk factors (model 2), conventional markers of complications of diabetes, and abnormal ECG (model 3), as shown by modest increases in Harrell *C* statistic, and significant improvement in continuous NRI and IDI statistics (Tables 2 and 3), with a similar additive value provided by each cardiac biomarker (Table 2). As compared with the continuous NRI analysis with categorical biomarkers, results were generally consistent in the sensitivity analyses incorporating log-transformed NTproBNP and hs-TnT as linear predictors and in the categorical NRI (Supplementary Table 2), even though we found that using continuous log-transformed biomarkers gave slightly stronger results, while using categorical NRI gave slightly weaker results.

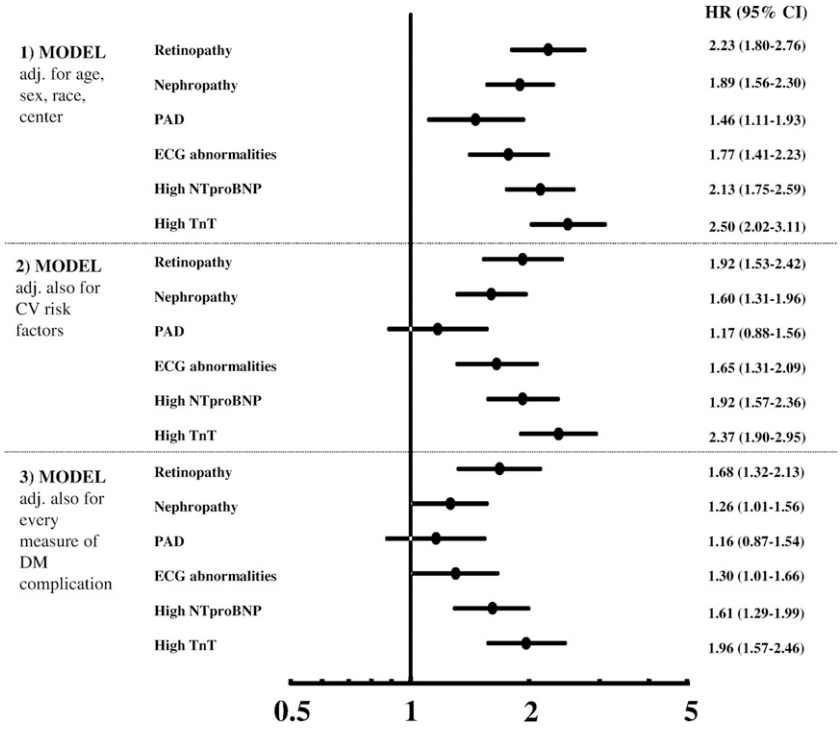

Figure 2—Forest plot of HRs for the primary outcome of fatal/nonfatal cardiovascular events for each conventional measure of diabetes complications, abnormal ECG, and cardiac biomarkers with hierarchical adjustment across models. adj., adjusted; CV, cardiovascular.

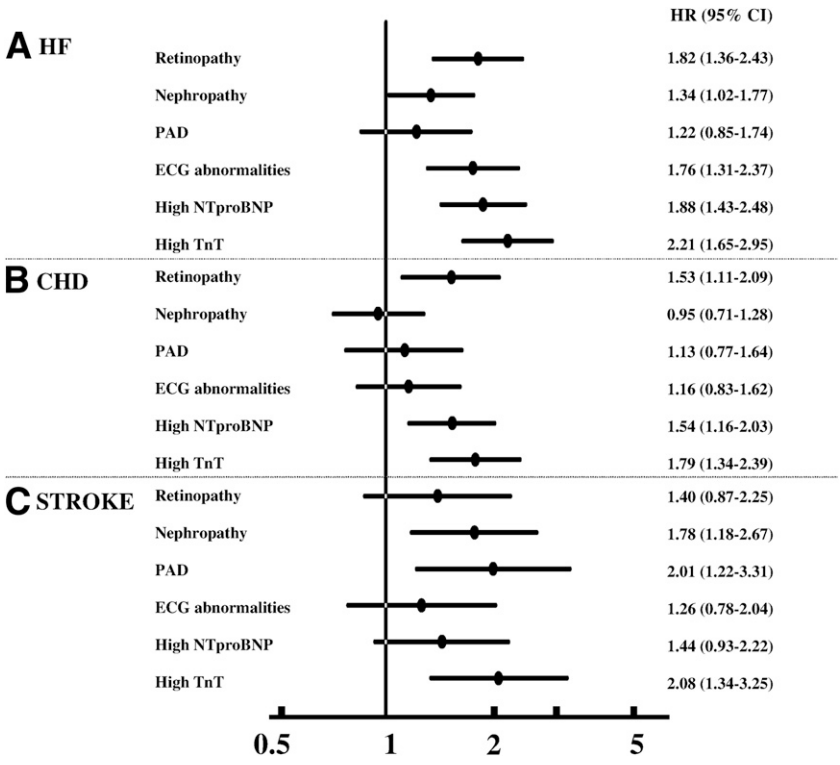

Figure 3—Forest plot of HRs (from models fully adjusted: model 4) for the secondary outcomes of HF (*A*), CHD (*B*), and stroke events (*C*) for each conventional measure of diabetes complications, abnormal ECG, and cardiac biomarkers in ARIC participants with diabetes.

Adding cIMT to conventional measures of diabetes complications did not result in discrimination improvement (Supplementary Table 3). A sensitivity analysis conducted excluding patients with eGFR $<$60 mL/min/1.73 m^2 produced nearly identical results (data not shown).

CONCLUSIONS

Among participants of the ARIC study with prevalent diabetes, there was substantial heterogeneity in the risk of incident CVD. The presence or absence of abnormal levels of circulating cardiac biomarkers aided in the differentiation of individuals with diabetes at the greatest or lowest risk of events, respectively. Importantly, the inclusion of cardiac biomarkers significantly improved CVD risk assessment in persons with diabetes above and beyond factors currently used in clinical practice, such as traditional cardiovascular risk factors, ECG abnormalities, and conventional measures of diabetes complications. Collectively, these findings may help refine risk stratification and potentially inform clinical management recommendations regarding CVD prevention strategies among individuals with diabetes.

Comparison With Previous Data

The prognostic importance of TnT and NTproBNP has previously been shown in the general population (5,6). However, relatively few data are available in persons with diabetes. Small studies of clinically referred patients (7–9) and one prospective population-based study (12) have shown a role for NTproBNP as a marker of CVD risk in subjects with diabetes. Another community study of women described the prognostic relevance of hs-TnT in subjects with diabetes (10). These prior evaluations demonstrated the predictive value of cardiac biomarkers for cardiovascular disease; however, whether circulating biomarkers added incremental value to existing risk factors was not examined. One recent study of persons with diabetes evaluated both troponin and NTproBNP in their ability to reclassify CVD and mortality risk (11). However, this study was a post hoc analysis of a randomized trial, which may lack applicability to the broader population, and the authors considered a population at higher risk, including also subjects with a known history of MI, stroke, or HF at baseline. Furthermore, in contrast to the study by Hillis et al. (11), we also used a threshold response analysis and examined the incidence of HF, which is increasingly recognized as an important end point in diabetes.

Our results in ARIC extend the observations from all prior studies. We included a broad community-based middle-aged population of individuals

Table 2—Reclassification and discrimination statistics (95% CI) for 10-year risk of the primary outcome (fatal and nonfatal HF, CHD, or stroke) by circulating cardiac biomarkers among ARIC participants with diabetes

	C statistic	IDI	NRI
Model 2	0.668 (0.645–0.691)		
Model 2 + hs-TnT	0.687 (0.665–0.709) (P = 0.001)	0.04 (0.02–0.06) ($P < 0.001$)	0.11 (0.03–0.18) (P = 0.007)
Model 2 + NTproBNP	0.682 (0.659–0.704) (P = 0.009)	0.02 (0.01–0.04) ($P < 0.001$)	0.11 (0.04–0.17) (P = 0.013)
Model 2 + hs-TnT and NTproBNP	0.694 (0.672–0.716) ($P < 0.001$)	0.05 (0.03–0.08) ($P < 0.001$)	0.20 (0.11–0.26) ($P < 0.001$)
Model 3	0.688 (0.665–0.710)		
Model 3 + hs-TnT	0.698 (0.676–0.720) (P = 0.018)	0.02 (0.01–0.04) ($P < 0.001$)	0.07 (0.00–0.15) (P = 0.06)
Model 3 + NTproBNP	0.694 (0.672–0.716) (P = 0.08)	0.01 (0.00–0.02) ($P < 0.001$)	0.09 (0.03–0.16) (P = 0.013)
Model 3 + hs-TnT and NTproBNP	0.703 (0.681–0.725) (P = 0.004)	0.03 (0.02–0.05) ($P < 0.001$)	0.16 (0.07–0.22) ($P < 0.001$)

Model 2 adjusted for age, sex, race, center, smoking status, log-transformed pack-years of cigarettes (packs of cigarettes smoked per day times number of years smoked), BMI, waist-to-hip ratio, mean systolic blood pressure, hypertension medication use, lipid-lowering medication use, aspirin use, education level, total-to-HDL cholesterol ratio, log-transformed triglycerides, and duration of disease. Model 3 adjusted for variables in model 2 plus ECG abnormalities and conventional complications of diabetes (retinopathy, nephropathy, PAD).

Table 3—Reclassification and discrimination statistics (95% CI) for 10-year risk of each secondary outcome (HF, CHD, or stroke) by circulating cardiac biomarkers among ARIC participants with diabetes

	C statistic	IDI	NRI
HF events (*n* = 317)			
Model 3	0.747 (0.719–0.774)		
Model 3 + cardiac biomarkers	0.768 (0.742–0.794) (*P* = 0.004)	0.04 (0.01–0.07) (*P* = 0.007)	0.22 (0.06–0.30) (*P* = 0.027)
CHD events (*n* = 321)			
Model 3	0.692 (0.664–0.719)		
Model 3 + cardiac biomarkers	0.703 (0.675–0.730) (*P* = 0.09)	0.02 (0.01–0.05) (*P* < 0.001)	0.14 (0.05–0.22) (*P* < 0.001)
Stroke events (*n* = 128)			
Model 3	0.741 (0.697–0.784)		
Model 3 + cardiac biomarkers	0.749 (0.706–0.791) (*P* = 0.35)	0.02 (0.00–0.07) (*P* < 0.001)	0.22 (0.03–0.32) (*P* = 0.027)

Model 3 adjusted for variables in model 2 (age, sex, race, center, smoking status, log-transformed pack-years of cigarettes [packs of cigarettes smoked per day times number of years smoked], BMI, waist-to-hip ratio, mean systolic blood pressure, hypertension medication use, lipid-lowering medication use, aspirin use, education level, total-to-HDL cholesterol ratio, log-transformed triglycerides, and duration of disease) plus ECG abnormalities and conventional complications of diabetes (retinopathy, nephropathy, PAD).

with diabetes. The risk of incident CVD was examined over >10 years of follow-up. NTproBNP and hs-TnT were analyzed both as categorical variables, according to well-known cutoffs to facilitate clinical application, and as continuous variables with similar results. The robustness of our findings regarding cardiac biomarkers was further supported by the demonstration of additive value for CVD risk prediction beyond established cardiovascular risk factors included in the Framingham risk model and conventional diabetes complications, including retinopathy, a potent predictor of adverse CVD outcomes.

Clinical Implications

The increased risk for CVD in diabetes causes a growing economic and public health burden. Despite improvements in risk factor control, recently it has been shown that almost half of U.S. adults with diabetes did not meet the recommended goals for diabetes care (39). Furthermore, we encountered a wide heterogeneity of CVD risk in diabetes, as recently suggested (2–4). The suboptimal implementation of preventive strategies and heterogeneity in risk emphasizes the need to refine CVD risk stratification to better identify higher- and lower-risk individuals with diabetes. Our findings may help to inform clinical decisions regarding recommendations for preventive strategies, e.g., intensity of statin therapy and aspirin use (1). While regular screening for retinopathy, nephropathy, PAD, and ECG abnormalities is recommended in persons with diabetes (1), our results suggest that measurement of NTproBNP and TnT may be incrementally informative among individuals with diabetes. Importantly, the absence of all these six markers identified a subject with diabetes (prevalence 48% in this study population) with a low risk of incident CVD events. In contrast, 12% of the study population had high values of cardiac biomarkers alone. Compared with the other categories of diabetes complications, this subgroup was characterized by a lower burden of cardiovascular risk factors and shorter duration of diabetes. Nonetheless, elevated cardiac biomarkers were associated with higher risk of incident cardiovascular events, which may justify intensive multifactorial interventions to reduce diabetes-related CVD risk, although this theory remains to be tested. Furthermore, it is conceivable that cardiac biomarkers may be used as screening tests to detect individuals with diabetes more suitable for comprehensive assessment of silent heart disease, such as echocardiography and stress testing, as recently suggested (40).

Finally, contemporary data further underscore the clinical utility of cardiac biomarkers, not only to risk stratify subjects with diabetes, but also to select appropriate therapy and to guide its optimization. Recently, it had been shown that accelerated uptitration of renin angiotensin system antagonists and β-blockers to maximum tolerated dosages was an effective and safe intervention for the primary prevention of cardiac events in patients with diabetes preselected using NTproBNP (41). Furthermore, in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial, which enrolled patients with diabetes and a history or risk of cardiovascular events, the rates of hospital admission for HF were significantly higher with saxagliptin than with placebo in patients with the highest concentrations of NTproBNP at study baseline (42). These data suggest that the choice of antihyperglycemic agents in patients at risk for developing HF may also be guided by cardiac biomarkers.

Some limitations of this analysis should be noted. First, ABI in ARIC was measured only on one leg and upper extremity. Furthermore, ABI data for some participants were obtained antecedent to visit 4, while retinal photography was performed at visit 3. This may have led to a possible underestimation of the risk associated with these measures of diabetes complications. Second, residual confounding remains a possibility. For example, in the ARIC study echocardiography was performed only in African Americans at visit 3 (1993–1995). Thus, we did not adjust for this variable in our analysis, which used visit 4 (1996–1998) as baseline. Finally, statin prescription was low at baseline in this cohort, according to guidelines at the time of ARIC visit 4. However, the identification of a subgroup of participants with diabetes, but low incidence of CVD over a long follow-up period despite low statin prescription at the beginning, further underscores the heterogeneity in diabetes and the necessity of individualizing treatment strategies.

In conclusion, in a community sample of middle-aged individuals with diabetes abnormal levels of cardiac biomarkers were significantly associated with increased CVD risk and provided incremental risk prediction over traditional cardiovascular risk factors, abnormal ECG, and conventional measures of

diabetes complications. We encountered a wide range of CVD risk in diabetes, and our data suggest that one way to help distinguish high from low risk is to risk stratify according to cardiac biomarkers.

Acknowledgments. The authors thank the staff and participants of the ARIC study for their important contributions.

Funding. The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). This work was also supported by NHLBI cooperative agreement NHLBI-HC-11-08 (Brigham and Women's Hospital). D.K.G. was supported by National Institutes of Health (NIH)/NHLBI T32-HL-094301-02 and K12-HL-109019. N.A.B. is supported by NIH/NHLBI T32-HL-007374-34. S.C. is supported in part by NIH/NHLBI K99-HL-107642 and a grant from the Ellison Foundation. A.S. is supported in part by NIH/NHLBI K08-HL-116792.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.G. and D.K.G. designed this study, undertook the statistical analyses, and wrote the initial drafts of the manuscript. B.C. undertook the statistical analyses and revised the initial drafts of the manuscript for scientific content. E.S., A.R.F., K.M., N.A.B., S.C., A.S., H.S., O.V., H.N., C.M.B., B.C.A., B.E.K., D.A., and S.D.S. revised the initial drafts of the manuscript for scientific content. S.D.S. 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.

References

1. American Diabetes Association. Standards of medical care in diabetes—2015. Diabetes Care 2015;38(Suppl. 1):S1–S93
2. Barkoudah E, Skali H, Uno H, Solomon SD, Pfeffer MA. Mortality rates in trials of subjects with type 2 diabetes. J Am Heart Assoc 2012;1:8–15
3. Boyko EJ, Meigs JB. Does diabetes always confer coronary heart disease risk equivalent to a prior myocardial infarction? Implications for prevention. Diabetes Care 2011;34:782–784
4. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med 2009;26:142–148
5. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367–1376
6. Di Angelantonio E, Chowdhury R, Sarwar N, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. Circulation 2009;120:2177–2187
7. Bhalla MA, Chiang A, Epshteyn VA, et al. Prognostic role of B-type natriuretic peptide levels in patients with type 2 diabetes mellitus. J Am Coll Cardiol 2004;44:1047–1052
8. Tarnow L, Gall MA, Hansen BV, Hovind P, Parving HH. Plasma N-terminal pro-B-type natriuretic peptide and mortality in type 2 diabetes. Diabetologia 2006;49:2256–2262
9. Huelsmann M, Neuhold S, Strunk G, et al. NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus. Eur Heart J 2008;29:2259–2264
10. Everett BM, Cook NR, Magnone MC, et al. Sensitive cardiac troponin T assay and the risk of incident cardiovascular disease in women with and without diabetes mellitus: the Women's Health Study. Circulation 2011;123:2811–2818
11. Hillis GS, Welsh P, Chalmers J, et al. The relative and combined ability of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide to predict cardiovascular events and death in patients with type 2 diabetes. Diabetes Care 2014;37:295–303
12. Bruno G, Landi A, Barutta F, et al. N-terminal probrain natriuretic peptide is a stronger predictor of cardiovascular mortality than C-reactive protein and albumin excretion rate in elderly patients with type 2 diabetes: the Casale Monferrato population-based study. Diabetes Care 2013;36:2677–2682
13. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol 1989;129:687–702
14. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811
15. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. JAMA 2000;283:2253–2259
16. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. J Clin Epidemiol 1996;49:223–233
17. Rosamond WD, Chambless LE, Folsom AR, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. N Engl J Med 1998;339:861–867
18. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol 2008;101:1016–1022
19. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30:736–743
20. Atherosclerosis Risk In Communities study manuals [Internet], 2015. Available from http://www2.cscc.unc.edu/aric/cohort-manuals. Accessed 11 August 2015
21. Klein R, Sharrett AR, Klein BE, et al.; ARIC Group. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: the Atherosclerosis Risk in Communities study. Ophthalmology 2002;109:1225–1234
22. Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the National Kidney Foundation (NKF) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Am J Kidney Dis 2003;42:617–622
23. Hsu CC, Brancati FL, Astor BC, et al. Blood pressure, atherosclerosis, and albuminuria in 10,113 participants in the Atherosclerosis Risk in Communities study. J Hypertens 2009;27:397–409
24. Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR. HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care 2006;29:877–882
25. Weatherley BD, Nelson JJ, Heiss G, et al. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord 2007;7:3
26. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 2009;158:111–117
27. Apple FS, Panteghini M, Ravkilde J, et al.; Committee on Standardization of Markers of Cardiac Damage of the IFCC. Quality specifications for B-type natriuretic peptide assays. Clin Chem 2005;51:486–493
28. Rehman SU, Januzzi JL. Natriuretic Peptide testing in primary care. Curr Cardiol Rev 2008;4:300–308
29. Saenger AK, Beyrau R, Braun S, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. Clin Chim Acta 2011;412:748–754
30. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–187
31. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–679
32. Chambless LE, Folsom AR, Sharrett AR, et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. J Clin Epidemiol 2003;56:880–890
33. Loehr LR, Rosamond WD, Poole C, et al. Association of multiple anthropometrics of overweight and obesity with incident heart failure: the Atherosclerosis Risk in Communities study. Circ Heart Fail 2009;2:18–24
34. Agarwal SK, Chambless LE, Ballantyne CM, et al. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. Circ Heart Fail 2012;5:422–429
35. Lutsey PL, Alonso A, Michos ED, et al. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2014;100:756–764
36. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1999;340:14–22
37. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive

ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–172; discussion 207–212
38. Harrel FE. *Regression Modeling Strategies With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York, NY, Springer, 2001
39. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med 2013;368:1613–1624
40. Nadir MA, Rekhraj S, Wei L, et al. Improving the primary prevention of cardiovascular events by using biomarkers to identify individuals with silent heart disease. J Am Coll Cardiol 2012;60: 960–968
41. Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol 2013;62:1365–1372
42. Scirica BM, Braunwald E, Raz I, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579–1588