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Incremental Value of Biochemical and Echocardiographic Measures in Prediction of Ischemic Stroke: The Strong Heart Study

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Abstract

Background and Purpose—American Indians suffer high rates of stroke. Improved risk stratification could enhance prevention, but the ability of biochemical and echocardiographic markers of preclinical disease to improve stroke prediction is not well defined.

Methods—We evaluated such markers as predictors of ischemic stroke in a community-based cohort of American Indians without prevalent cardiovascular or renal disease. Laboratory markers included C-reactive protein (CRP), fibrinogen, urine albumin-creatinine ratio (UACR), and glycohemoglobin (HbA1c), while echocardiographic parameters comprised left atrial (LA) diameter, left ventricular mass, mitral annular calcification (MAC), and mitral E/A ratio. Predictive performance was judged by indices of discrimination, reclassification and calibration.

Results—After adjustment for standard risk factors, only HbA1c, albuminuria, and LA diameter were significantly associated with first ischemic stroke. Addition of HbA1c, though not UACR, to a basic clinical model significantly improved the C-statistic (0.714 vs. 0.695, p=0.044), whereas LA diameter modestly enhanced integrated discrimination improvement (IDI=0.90%, p=0.004), but not the C-statistic (0.701, p=0.528). When combined with HbA1c, LA diameter further increased IDI (1.81%, p<0.001), though not the C-statistic (0.716). No marker achieved significant net reclassification improvement (NRI).

Conclusions—In this cohort at high cardiometabolic risk, HbA1c emerged as the foremost predictor of ischemic stroke when added to traditional risk factors, affording substantially improved discrimination, with a more modest contribution for LA diameter. These findings bolster

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the role of HbA1c in cardiovascular risk assessment among persons with glycometabolic disorders, and provide impetus for further study of the incremental value of echocardiography in high-risk populations.

Keywords

Stroke; Echocardiography; Biomarkers

Cardiovascular disease (CVD) is the leading cause of death in American Indians, a population with high prevalences of obesity, diabetes and associated risk factors.[1] In particular, the incidence of stroke is exceedingly high in this population, surpassing that of US whites and blacks.[2] Identification of laboratory or imaging measures capable of enhancing stroke risk stratification could improve targeting of primary prevention efforts in American Indians and similar high-risk populations.

Several biochemical markers, in particular CRP,[3] fibrinogen,[4] UACR,[5] and HbA1c[6] have been shown to be independent predictors of CVD in cohorts with and without diabetes. These markers of inflammation, thrombosis and preclinical end-organ damage have also been associated with stroke.[3, 4, 6, 7] Similarly, several structural and functional cardiac measures available routinely from transthoracic echocardiography have predicted CVD in population-based studies.[8–11] Such measures, namely, LA diameter,[12] left ventricular (LV) mass,[13] MAC,[14] and the ratio of mitral E/A diastolic velocities,[15] have also been associated with ischemic stroke independent of traditional risk factors.

Beyond the documented associations, whether such biochemical and echocardiographic measures, individually or jointly, improve prediction of first ischemic stroke over standard clinical risk factors has not been formally studied. We addressed this question in a cohort at high cardiometabolic risk.

Methods

Participants

The Strong Heart Study (SHS) is a population-based investigation of risk factors for CVD in 13 American Indian communities.[16] Tribal members ages 45–74 were recruited from all eligible individuals, yielding 4,549 participants. Baseline assessment, including standardized determinations of blood pressure (BP), anthropometry, and laboratory measures, was performed at an initial examination (1989–1992). Subjects were invited to return for a 2nd examination (1993–1995), at which echocardiography was added. The return rate for survivors was 89%, of whom 97% had echocardiograms (n=3,501). Herein, we focused on participants in the 2nd exam without clinical or echocardiographic evidence of CVD, atrial fibrillation (AF), or renal insufficiency (serum creatinine ≥2.0 mg/dL). After exclusion of 147 participants with missing data for traditional CVD risk factors, this left 2,391 eligible for analysis.

Definitions

Diabetes was defined as fasting glucose ≥126 mg/dL or glucose-lowering treatment, and metabolic syndrome by NCEP criteria. Clinical CVD included definite coronary heart disease or myocardial infarction, congestive heart failure, and definite or possible stroke, adjudicated using previously described procedures.[1] AF was diagnosed by electrocardiography, supplemented by absence of a transmitral diastolic A wave by echocardiography owing to a catastrophic disk crash and resulting loss of electrocardiographic data.[14] Echocardiographic CVD was defined by LV ejection fraction

<50% or segmental abnormalities; left-sided valvular disease comprised more than mild regurgitation, any stenosis, or prior prosthetic replacement.

The primary endpoint was non-fatal and fatal ischemic stroke. Strokes were adjudicated based on the International Diagnostic Criteria, as previously reported.[2, 14] Event ascertainment through December 2008 was 99% complete.

Laboratory Methods

Laboratory methods have been detailed previously.[17] Plasma fibrinogen was assessed by modification of the Clauss method, CRP by immunoassay, and HbA1c by high-pressure liquid chromatography.[18] Urine albumin and creatinine were measured in a morning sample.[16]

Echocardiography

Evaluation was performed with phased-array echocardiographs by a standardized protocol.[11] Standard approaches were used to determine LV internal dimension and wall thicknesses, LA anteroposterior dimension, mitral E and A diastolic velocities, and presence of MAC.[11, 14, 19] As reported elsewhere,[9] validated methods were applied to calculate LV mass and LV ejection fraction from end-diastolic and end-systolic dimensions or volumes. The ratio of mitral E and A inflow waves was calculated as a measure of LV diastolic function.[11]

Statistical Analysis

Comparisons of categorical variables employed the Chi-square test; continuous variables used Student's t or the Mann-Whitney U test. The relationships of biochemical and echocardiographic measures with incident ischemic stroke were evaluated with Cox Models. All measures were assessed both as continuous and dichotomous variables except for MAC, which was available only dichotomously, and mitral E/A, which was categorized as abnormal LV relaxation (<0.6), normal relaxation (0.6–1.5), or restrictive filling (>1.5).[11] Increased LA diameter and LV mass (indexed to height$^{2.7}$) were defined by previously derived partition values,[19] as were elevations in CRP, fibrinogen, HbA1c, and UACR.[9, 20] All biochemical markers underwent logarithmic transformation to achieve normality. Values for all measures were missing in ≤2.3% of cases, except for LV mass (7.1% missing).

The relations of candidate biochemical or echocardiographic measures with ischemic stroke were adjusted by a panel of standard clinical and laboratory variables obtained routinely in clinical practice. Additional adjustment was then undertaken by laboratory or echocardiographic measures that exhibited significant associations with outcome in the clinically adjusted models. Relative performance of risk-prediction models was assessed with indices of discrimination (Harrell's C statistic and IDI[21]), reclassification (NRI),[21] and calibration (Hosmer-Lemeshow goodness-of-fit). For reclassification analyses, we selected risk categories of <5%, 5–9.9%, and 10% and chose to use the entirety of follow-up, instead of truncating at 10 years, to achieve meaningful numbers of participants in each risk stratum. NRI gives the proportion of individuals reclassified correctly into higher or lower risk categories based on whether they did or did not experience the outcome. IDI has the advantage of not depending on an arbitrary choice of risk categories, demonstrating instead the degree to which the new model improves average sensitivity without compromising average specificity.

Analyses were conducted with SPSS version 18.0 (SPSS Inc., Chicago, IL) or Stata version 11.0 (StataCorp, College Station, TX). Two-tailed $p<0.05$ was the threshold for significance, except for IDI, for which $p<0.01$ was used.[21]

Results

During 12 years of mean follow-up, 138 (5.8%) participants suffered an ischemic stroke (19 fatal). As summarized in Table 1, these individuals were older, with higher systolic BP and more diabetes, metabolic syndrome or smoking than those without an event. Participants who developed ischemic stroke also had higher HbA1c, UACR, LA diameter and prevalent MAC.

Among biochemical markers, CRP and fibrinogen were moderately strongly correlated (r=0.48), as were UACR and HbA1c (r=0.44), but remaining pairwise correlations were more modest (CRP and UACR, r=0.11; fibrinogen and UACR, r=0.29; CRP and HbA1c, r=0.18; fibrinogen and HbA1c, r=0.27) (all $p<0.001$). Correlations between biochemical markers and LA diameter were weak or absent (all $r\leq0.07$).

Table 2 shows the relations of biochemical and echocardiographic measures with ischemic stroke. When examined as continuous variables, UACR and HbA1c, but not CRP or fibrinogen, were each significantly associated with ischemic stroke after adjustment for basic clinical covariates, as well as for each other. Only HbA1c was significantly associated with ischemic stroke upon inclusion of echocardiographic predictors. When binary categories were evaluated, HbA1c and macroalbuminuria were significantly related to outcome after adjustment for clinical covariates, an association that persisted only for macroalbuminuria after further adjustment for biochemical, but not echocardiographic, measures. Among echocardiographic parameters, continuous LA diameter, but not LV mass index, showed a significant association with ischemic stroke following adjustment for clinical covariates. This relationship for LA diameter remained significant after additional adjustment for biochemical markers and for MAC. Dichotomous LA diameter was also a significant predictor of ischemic stroke in models adjusted for clinical covariates, but the association was marginally non-significant for MAC. The relationship for binary LA diameter persisted after adjustment for biochemical markers and, additionally, for MAC. By contrast, mitral E/A categories were not significantly associated with outcome. There was no evidence of interaction between HbA1c ($p=0.675$) or UACR ($p=0.580$) and diabetes, although stratification did show lower risk estimates for UACR among participants without than with diabetes (clinically adjusted HR=1.15 per SD, 95% CI=0.73–1.81 vs. HR=1.32, 95% CI=1.07–1.64), and less so for HbA1c (adjusted HR=1.46 per SD, 95% CI=0.85–2.50 vs. HR=1.54, 95% CI=1.17–2.30).

The relative performance characteristics of different models are presented in Table 3. Addition of HbA1c, but not UACR, to the basic model significantly improved discrimination by the C-statistic, yet neither biochemical marker significantly enhanced IDI. Joint inclusion of HbA1c and UACR did achieve a significantly greater IDI, with near-significant improvement in the C-statistic as compared with the basic model. But addition of UACR to the model containing HbA1c demonstrated no significant improvement in either discrimination index. Neither HbA1c nor UACR, singly or jointly, increased NRI. In turn, addition of LA diameter to the basic clinical model improved integrated discrimination, though not the C-statistic or NRI. Inclusion of MAC achieved no significant improvement in performance. When biochemical and echocardiographic measures were combined, greater improvements in IDI were observed. Notably, LA diameter significantly increased integrated discrimination when added to the model containing HbA1c, as well as HbA1c and UACR. The latter improvements, however, were not accompanied by significant increases in C-statistics. C-statistics from combined models, while numerically higher, also had broader 95% CI's, failing to reach significance even in comparisons to the basic model. Further addition of MAC and UACR led to the highest IDI, but neither significantly improved discrimination. Nor did any of the combined models lead to reclassification

improvement. (Reclassification tables for all models are provided in the Online Supplement.) There was no evidence of inadequate calibration among the models considered (all p>0.10).

Discussion

This study demonstrates that the biochemical markers HbA1c and UACR, together with echocardiographic LA diameter, are significantly associated with first ischemic stroke independent of clinical covariates in American Indians at high cardiometabolic risk. By contrast, neither CRP nor fibrinogen, LV mass, mitral E/A or (marginally) MAC was significantly related to long-term risk of ischemic stroke in this cohort after adjustment for clinical covariates. Moreover, HbA1c and LA diameter emerged as the most robust predictors, retaining significant associations with ischemic stroke even after additional adjustment for biochemical and echocardiographic factors. Indeed both HbA1c and LA diameter, but not UACR, individually improved discrimination indices of prediction-model performance, although only HbA1c significantly enhanced the C-statistic, the standard conservative measure for assessing discrimination.

To our knowledge, this is the first study to examine laboratory and echocardiographic biomarkers jointly in stroke-risk prediction, and to assess formally the extent to which such markers enhance prediction-model performance. Prior studies have documented positive associations with stroke for albuminuria,[7] CRP,[3] fibrinogen,[4] and HbA1c,[6] wherein such measures of renal microvascular disease, inflammation and/or thrombosis, and glycosylative damage signaled an increased risk of cerebral vascular occlusion. Likewise, previous reports have linked echocardiographic measures of preclinical cardiac damage to heightened risk of cerebral infarction.[12–15] The current report extends earlier findings by documenting that, among such biomarkers, HbA1c is the foremost risk predictor for ischemic stroke in persons at high cardiometabolic risk, and that, while LA diameter is a more modest contributor to prediction-model performance, the prognostic information contained in these biochemical and echocardiographic measures is complementary.

Our finding regarding HbA1c serves to reinforce its usefulness for prognostication of ischemic stroke. Several, though not all,[22] prior studies in cohorts with[23] or without[6] diabetes have shown a significant association between HbA1c and stroke, but none has previously documented this alongside measures of preclinical renal and cardiac disease, inflammation, and thrombosis. Of note, the addition of HbA1c did not reach our conservative threshold for significance for IDI, nor did it boost NRI. In the latter respect, the widespread failure of biomarkers to improve NRI in the face of significant or near-significant improvements in C-statistics and IDI likely reflects a preponderance of participants in the low and middle-risk categories (Online Supplement), suggesting that even the low partition values chosen for ischemic stroke risk may be too high in the context of a younger population free of prevalent CVD. Yet the sizable improvement in the C-statistic observed is a true credit to the predictive accuracy of HbA1c, and all the more supportive of its clinical utility in that it pertains to only one of the several important macrovascular and microvascular complications of hyperglycemia. As such, the finding provides firm support for recommendations to incorporate HbA1c for assessment of glycemic and cardiovascular risk.[20]

UACR was the only other biochemical candidate to be significantly associated with ischemic stroke independent of clinical covariates, and also of HbA1c, yet this marker did not significantly improve any of the performance indices examined. While there was no significant evidence of interaction by diabetes status, the association of UACR with ischemic stroke did show higher risk estimates in the diabetic subset. This suggests that

UACR's influence on risk-prediction performance for ischemic stroke could be greater in participants with diabetes, which would accord with the current recommendation for standard testing of albuminuria in the management of type 2 diabetes.[20] The present investigation lacks sufficient power, however, to evaluate this question appropriately within our diabetic stratum.

Turning to echocardiographic measures, addition of LA diameter to the basic model did not significantly increase the C-statistic or NRI, but did result in enhanced integrated discrimination. This was also the case when LA diameter was added to the basic model plus HbA1c (and/or UACR), leading to a combined model with 1.81% better average sensitivity relative to the latter model, and 2.33% as compared with the basic model. Additional inclusion of MAC, using information already available from routine echocardiography, did not significantly enhance indices of discrimination or reclassification further.

Yet, because HbA1c testing is already recommended for patients at cardiometabolic risk or with type 2 diabetes, and albuminuria screening may well be extended beyond diabetes to hypertension and the metabolic syndrome,[24] the real benefit of echocardiographic measures needs to be considered incrementally to such biochemical markers. In this regard, inclusion of LA diameter and MAC afforded a net increase of 1.60% in average sensitivity to the model containing HbA1c and UACR, which is at least comparable to the increment in IDI achieved by adding HbA1c and UACR to the basic model. In view of the greater cost associated with echocardiography than with automated laboratory assays, and given the lack of significant corresponding increases in C-statistics or NRI, additional studies evaluating the prognostic value of various echocardiographic findings for all cardiovascular outcomes, and not just stroke, are required to determine the cost-benefit ratio of echocardiographic screening in populations at high cardiometabolic risk. In such studies, assessment of contemporary echocardiographic measures such as tissue Doppler annular velocities and, particularly, LA volume could make echocardiography more attractive.

There are several limitations to this study. First, the number of endpoints was moderate, although this proved sufficient for adequate model fitting. While there was no evidence of heterogeneity in our findings based on diabetes status, power to detect an interaction was modest, and the sample size among corresponding strata inadequate to permit separate assessment of performance indices. Second, as noted above, we applied existing imaging technology at the time of the 2nd SHS examination. In particular, we lack measures of LA volume, which have since been recommended for incorporation in routine echocardiography.[25] We are therefore unable to determine its incremental contribution to risk prediction here. Third, baseline electrocardiography was only available in 41.9% of the cohort. This precluded comparative assessment of echocardiographic and electrocardiographic LA enlargement, and also necessitated use of the transmitral-Doppler profile to aid in detection of AF. While the latter method may be less reliable than electrocardiography, the prevalence of AF among participants with available electrocardiograms was 0.2%, and transmitral Doppler correctly identified all of these cases. The very low baseline prevalence of AF, coupled with the observed accuracy of the transmitral-Doppler profile, suggests that misclassification based on lost electrocardiograms was minimal, and that underdetection of prevalent AF is unlikely to account for the predictive value of LA diameter documented here. Last, the present findings in a cohort of American Indians do not necessarily apply to other ethnic groups. Nevertheless, findings from SHS have been generally consistent with other population-based cohorts, and may bear particular relevance to the broader population given the growing epidemics of obesity and diabetes affecting modern societies.

Conclusions

The present findings bolster the value of HbA1c in risk-assessment of persons at elevated cardiometabolic risk, although the incorporation of echocardiography will require investigation of the prognostic utility of modern echocardiographic techniques for aggregate macrovascular complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics*

Characteristic	Ischemic Stroke(n=2,391)	
	Yes(n=138)	No(n=2,253)
Age(yr)	62±8*	59±8*
Women(%)	66.7	64.5
BMI(kg/m^2)	31.0±5.8	31.3±6.2
Diabetes(%)	60.9*	44.4*
Systolic BP(mmHg)	134±22*	128±19*
Antihypertensive therapy(%)	34.1	28.0
LDL(mg/dL)	119±30	119±34
HDL(mg/dL)	40±15	42±13
Metabolic syndrome(%)	78.8*	65.4*
Current smoking(%)	39.1†	30.9†
Serum creatinine(mg/dL)	0.9±0.2	0.9±0.2
UACR(mg/g)	21.3(7.7,101.8)*	12.3(6.0,45.9)*
CRP(mg/L)	3.9(2.1,6.5)	3.7(2.0,7.0)
Fibrinogen(mg/dL)	352(315,403)	348(306,397)
HbA1c(%)	7.1(5.5,9.9)*	5.8(5.1,8.3)*
LA diameter(cm)	3.6±0.5†	3.5±0.4†
LV mass(g/m$^{2.7}$)	41.3±9.9	39.9±9.0
MAC(%)	14.5†	8.5†
Mitral E/A ratio		
<0.6(%)	7.2	4.4
>1.5(%)	0	2.1

Continuous variables are presented as means±SD or medians(IQR) in their original scale.

* $p \leq 0.001$

† $p > 0.05$

Table 2

Relations of Biochemical and Echocardiographic Variables with Ischemic Stroke

	Hazard Ratio (95% CI),*p*	
	Continuous (per SD)	**Dichotomized**
Biochemical Markers		
CRP(SD=2.6 mg/L)(Elevated CRP≥3.0 mg/L)		
Model 1*	1.11(0.94–1.31),0.230	1.27(0.89–1.81),0.189
Model 2†	1.09(0.91–1.30),0.372	1.22(0.84–1.75),0.296
Model 3‡	1.07(0.89–1.29),0.460	1.20(0.83–1.74),0.337
Model 4§	1.08(0.90–1.30),0.412	1.21(0.83–1.75),0.322
Fibrinogen(SD=1.2 mg/dL)(Hyperfibrinogenemia≥400 mg/dL)		
Model 1*	1.26(1.04–1.52),0.016	1.19(0.81–1.76),0.379
Model 2†	1.18(0.97–1.44),0.094	1.02(0.69–1.52),0.917
Model 3‡	1.09 (0.89–1.34),0.408	0.88(0.58–1.34),0.552
Model 4§	1.10(0.89–1.35),0.395	0.85(0.56–1.30),0.464
HbA1c(SD=1.4%)(Elevated HbA1c ≥6.5%)		
Model 1*	1.60(1.36–1.88),>0.001	2.22(1.58–3.14),>0.001
Model 2†	1.55(1.22–1.96),>0.001	1.70(1.04–2.78),0.034
Model 3‡	1.45(1.19–1.76),>0.001	1.55(0.92–2.59),0.097
Model 4§	1.47(1.21–1.78),>0.001	1.50(0.90–2.51),0.121
UACR(SD=6.1 mg/g)(Microalbuminuria=30–299 mg/g)		
Model 1*	1.45(1.24–1.69),>0.001	1.79(1.22–2.64),0.003
Model 2†	1.32(1.09–1.59),0.005	1.44(0.95–2.19),0.090
Model 3‡	1.24(1.02–1.52),0.031	1.31(0.85–2.02),0.225
Model 4§	1.20(0.98–1.46),0.075	1.34(0.87–2.07),0.189
UACR(Macroalbuminuria≥300 mg/g)		
Model 1*	--	2.73(1.69–4.42),>0.001
Model 2†	--	2.07(1.20–3.59),0.009
Model 3‡	--	1.78(1.01–3.13),0.046
Model 4§	--	1.64(0.92–2.91),0.095
Echocardiographic Measures		
LA Diameter(SD=0.4 cm)(LA Enlargement, Men>4.2 cm, Women>3.8 cm)		
Model 1*	1.31(1.11–1.54),0.001	1.81(1.20–2.72),0.005
Model 2†	1.34(1.12–1.61),0.002	1.80(1.17–2.76),0.007
Model 3‡	1.36(1.31–1.64),0.001	2.03(1.34–3.22),0.001
Model 4§	1.35(1.12–1.62),0.002	1.99(1.28–3.07),0.002

	Hazard Ratio (95% CI),*p*	
	Continuous (per SD)	**Dichotomized**
LV Mass(SD=9.1 g/m$^{2.7}$)(LV Hypertrophy, Men>50g/m$^{2.7}$, Women>47 g/m$^{2.7}$)		
Model 1*	1.12(0.95–1.32),0.185	1.11(0.73–1.70),0.630
Model 2†	1.04(0.86–1.26),0.662	0.94(0.59–1.50),0.801
Model 3‡	1.03(0.84–1.25),0.799	0.97(0.60–1.55),0.884
Model 4§	0.98(0.80–1.20),0.829	0.91(0.56–1.46),0.684
MAC(Present vs. Absent)		
Model 1*	--	1.67(1.03–2.71),0.037
Model 2†	--	1.59(0.97–2.60),0.065
Model 3‡	--	1.54(0.93–2.52),0.091
Model 4§	--	1.40(0.84–2.34),0.192
Mitral E/A Ratio(E/A<0.6) □		
Model 1*	--	1.29(0.67–2.49),0.455
Model 2†	--	1.09(0.56–2.11),0.810
Model 3‡	--	1.00(0.51–1.96),0.991
Model 4§	--	0.95(0.49–1.85),0.874

Hazard ratios for continuous CRP, fibrinogen, UACR and HbA1c are for log-transformed values; those for LA diameter and LV mass are on the original scale.

*Adjusted for age and sex

†Adjusted for age, sex, BMI, systolic BP, antihypertensive therapy, diabetes, LDL, HDL, current smoking, and serum creatinine

‡Adjusted for covariates in † plus UACR and HbA1c

§Adjusted for covariates in ‡ plus LA diameter and MAC

□There were no strokes in participants with E/A>1.5, precluding calculation of HR's.

Table 3

Comparison of Discrimination and Reclassification Indices*

	C-statistic	95% CI	*p*†	IDI (%)	*p*†	NRI (%)	*p*†
Clinical Model‡	0.695	0.652–0.738	--	--	--	--	--
Biochemical Markers							
Clinical Model+UACR	0.706	0.664–0.749	0.168	0.44	0.139	3.03	0.475
Clinical Model+HbA1c	0.714	0.673–0.755	0.044	0.95	0.021	5.00	0.241
Clinical Model+HbA1c+UACR	0.717	0.675–0.758	0.056	1.20	0.009	1.45	0.770
(vs. Clinical Model+HbA1c)	--	--	0.575	0.29	0.229	−2.61	0.507
Echocardiographic Measures							
Clinical Model+LA Diameter	0.701	0.657–0.744	0.528	0.90	0.004	0.84	0.821
Clinical Model+MAC	0.698	0.655–0.742	0.444	0.13	0.592	1.18	0.661
Clinical Model+LA Diameter+MAC	0.703	0.659–0.748	0.368	1.01	0.004	2.11	0.595
Biochemical and Echocardiographic Measures							
Clinical Model+LADiameter+HbA1c	0.716	0.673–0.759	0.101	2.33	<0.001	4.82	0.348
(vs. Clinical Model+HbA1c)	--	--	0.767	1.81	<0.001	−1.56	0.735
Clinical Model+LA Diameter+	0.719	0.675–0.762	0.105	2.26	0.001	6.64	0.215
HbA1c+UACR							
(vs. Clinical Model+HbA1c)	--	--	0.639	1.74	<0.001	5.33	0.274
(vs. Clinical Model+HbA1c+UACR)	--	--	0.822	1.05	0.003	3.22	0.459
Clinical Model+LA Diameter+MAC+HbA1c	0.718	0.674–0.761	0.092	2.41	<0.001	6.19	0.233
(vs. Clinical Model+HbA1c)	--	--	0.676	1.89	<0.001	5.40	0.255
Clinical Model+LA Diameter+MAC+UACR+HbA1c	0.720	0.676–0.763	0.093	2.81	<0.001	6.65	0.219
(vs. Clinical Model+HbA1c+UACR)	--	--	0.731	1.60	<0.001	3.72	0.407
(vs. Clinical Model+HbA1c+LA Diameter)	--	--	0.533	0.47	0.147	2.46	0.434
(vs. Clinical Model+LA Diameter+MAC+HbA1c)	--	--	0.632	0.40	0.098	0.37	0.892

All indices are for continuous variables except for MAC.

* For C-statistics, all values calculated in subset with available data for all biochemical and echocardiographic measures (n=2286). For IDI and NRI, all values calculated in subsets with available data for all biochemical markers (n=2306), all echocardiographic measures (n=2371), or both (n=2286), depending on the comparisons.

† Compared to basic clinical model, unless otherwise indicated.

‡ See Model 2, Table 2