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Individual Components of the Romhilt-Estes Left Ventricular Hypertrophy Score Differ in Their Prediction of Cardiovascular Events: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—It has been recently reported that the Romhilt-Estes (R-E) Score, originally proposed for detection of left ventricular hypertrophy (LVH) from the electrocardiogram (ECG), is a strong predictor of all-cause mortality. Whether the R-E score is also predictive of cardiovascular disease (CVD) and whether its individual components differ in their ability to predict different CVD outcomes is not well established.

Methods—This analysis includes 13,261 participants from the Atherosclerosis Risk in Communities (ARIC) study who were free of cardiovascular disease at baseline (1987–1989). Incident CVD, coronary heart disease (CHD), heart failure (HF) and stroke were ascertained by an adjudication committee through December 2010. R-E LVH score was measured from automatically processed baseline ECG data. Cox proportional hazard models were used to examine the association between baseline R-E overall score (overall) and each of its six individual components separately, with each of the CVD outcomes.

Results—During a median follow-up of 21.8 years, 3,579, 2,205, 1,814, and 731 CVD, CHD, HF, and stroke events, respectively, occurred. In multivariable adjusted models, R-E score ≥ 4 points (compared to 0 points) was associated with increased risk of CVD, CHD, HF and stroke (HR (95%CI): 1.66(1.41–1.96), 1.66 (1.34–2.07), 1.97(1.60–2.43) and 1.49(1.07–2.07), respectively). The six component of the R-E score varied in their relationship with different CVD outcomes.

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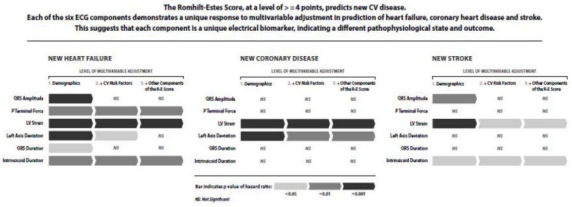
Conclusions—The R-E score is predictive of CVD outcomes. The six R-E score components differ in their associations with different CVD outcomes, indicating that they may be electrical biomarkers of different physiological events within the myocardium.

Graphical abstract



The Romhilt-Estes Score, at a level of > = 4 points, predicts new CV disease.

Each of the six ECG components demonstrates a unique response to multivariable adjustment in prediction of heart failure, coronary heart disease and stroke.

This suggests that each component is a unique electrical biomarker, indicating a different pathophysiological state and outcome.

Keywords

Romhilt-Estes Score; Left Ventricular Hypertrophy; ARIC study

Introduction

We recently have shown that the electrocardiographic Romhilt-Estes Point Score (R-E Score) (1) is associated with an increased risk of all-cause mortality in the general population, and that different score components show different predictive abilities (2). These results suggest that the R-E Score and its components, which were originally intended for the electrocardiographic diagnosis of left ventricular hypertrophy (LVH), could become a useful tool for clinicians in identifying patients at higher risk for adverse outcomes.

We sought to extend our previous work that examined the association between R-E score and all-cause mortality to cardiovascular disease (CVD) outcomes. We hypothesize that different components of the R-E score will be associated with different CVD outcomes (heart failure (HF), coronary heart disease (CHD), stroke, and a composite of these outcomes referred herein as composite CVD). This hypothesis is based on our belief that ventricular hypertrophy and the ECG changes historically used to indicate its presence are independent, but related phenomena. That is to say, the components of the R-E Score are distinct electrical characteristics involving both atrial and ventricular, and both depolarization and repolarization phases of myocardial electrical activity, and that they will be associated with different clinical outcomes.

We examined our hypothesis using data from the Atherosclerosis Risk in Communities (ARIC) Study, one of the largest biracial longitudinal cohort studies in the United States (US).

Methods

The Atherosclerosis Risk in Communities (ARIC) Study includes 15,792 participants, aged 45 to 64 years, from four US communities: Forsyth County, NC, Jackson, MS, Minneapolis, MN, and Washington County, MD. The subjects were selected by probability sampling in three communities. In Jackson, MS only blacks are included in the sample. The selection methods and study details have been described elsewhere (3). The first examinations were begun in 1986, and the first cycle of the study completed in 1989. Follow-up visits were carried out in 1990–1992 (93% return rate), 1993–1995 (86%), 1996–1998 (80%) and 2011–2013 (65%).

ARIC studies are approved by the institutional review boards of the participating community study sites. All participants also provided written informed consent.

For this analysis, we excluded 196 who had no ECG, 136 with ECGs of inadequate quality, 429 with an external pacemaker, Wolff-Parkinson-White pattern or complete bundle branch block, and 47 who were not African-American or white in ethnic origin. Also, 1,723 participants with baseline CVD, defined as coronary heart disease (CHD), heart failure (HF), stroke or atrial fibrillation (AF), were also eliminated. After all exclusions, 13,261 participants remained and are included in this analysis.

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Electrocardiography

At each study exam, a standard supine 12-lead resting ECG was recorded with a MAC PC Personal Cardiograph [Marquette Electronics, Milwaukee, Wisconsin, USA] and transmitted to the ARIC ECG Reading Center [Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, NC] for reading and coding.

ECGs were automatically processed using Marquette 12-SL Version 2001 [GE, Milwaukee, Wisconsin, USA]. R-E score was calculated from six ECG features with a specific value of points for each feature as follows: QRSAMP—R or S wave in any limb lead ≥2 mV, or S wave in V1 or V2≥3 mV., or R wave in V5 or V6 ≥3 mV. [3 points]; PTFV1—P terminal force defined as terminal negativity of P wave in V1≥ 0.10 mV in depth and ≥ 0.04 sec in duration [3 points]; LVSTR—left ventricular strain defined as ST segment and T wave in opposite direction to QRS in V5 or V6, without digitalis [3 points]; LAXDEV—left axis deviation defined as QRS axis ≤ −30 degrees [2 points]; QRSDUR—QRS duration ≥0.09 sec [1 point]; and INTRNS—intrinsicoid deflection duration in V5 or V6 ≥ 0.05 sec [1 point].

Cardiovascular Outcomes

The outcomes of stroke, heart failure, and CHD were determined by physicians, using validated adjudication protocols. Stroke was defined as sudden neurologic insult of = or > 24 hour duration or a neurologic insult associated with death without evidence of a non-

stroke cause of death (4). Strroke events were ascertained from surveillance of ARIC participant hospitalizations using ICD-9 codes 430–438 through 1997 and codes 430–436 thereafter. Strokes were classified by physician review and computer algorithm with standardized criteria and determined as hemorrhagic or ischemic.

Heart failure was ascertained by review of hospitalization records and death certificates for a heart failure diagnosis. Specifically, incident cases with an ICD-9 code of 428 (428.0–428.9) or ICD Tenth Revision 150 were classified as heart failure (5). CHD was determined using study surveillance and adjudicated as described (6,7). Symptoms, biomarkers, and electrocardiography were incorporated into a computerized algorithm. Disagreement between discharge coding and computer algorithm were adjudicated by the ARIC Mortality and Morbidity Classification Committee. For the present analysis, CHD was defined as definite or probable myocardial infarction or definite fatal CHD. Incident CVD was defined as the first occurrence of any of a composite of CHD, stroke or HF.

Covariates

Baseline age, sex, race, education level, income and smoking status were determined by self-report. Body mass index [BMI] at baseline was calculated as weight [in kilograms] divided by height [in meters] squared. Blood samples were obtained after an 8-hour fasting period. Diabetes was defined as a fasting glucose level ≥126 mg/dL [or non-fasting glucose ≥200 mg/dL], a self-reported physician diagnosis of diabetes, or use of diabetes medications. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or use of blood pressure lowering medications. Prevalent CVD was identified by self-reported history or a previous physician diagnosis.

Statistical analysis

Baseline R-E scores for all participants were calculated, and various baseline characteristics of the population were tabulated and compared across increasing score levels, grouped as follows: score=0, 1–3, and ≥4. Incidence rates of new CVD per 1000 person-years in each of the three R-E score levels occurring during follow-up (from Visit 1 to December 2010) were calculated.

Cox proportional hazards analysis was used to examine the association between R-E score and each of the outcomes (CVD, CHD, HF, and stroke) in a series of models as follows: Model 1, adjusted for age, sex, and race; and Model 2. adjusted for the Model 1 variables plus: field center, BMI, systolic blood pressure, smoking status, education, hypertension, diabetes mellitus, family history of CHD, total cholesterol/high-density lipoprotein ratio, blood glucose, serum creatinine and serum uric acid. In these models, R-E score 0 was the reference group and risk of new CVD was evaluated across the three groupings of the R-E score (0, 1–3, ≥4).

The associations between each of the six components of the R-E score: QRSAMP, PTFV1, LVSTR, LAXDEV, QRSDUR, and INTRNS, as a baseline ECG finding, with different CVD outcomes were also examined. Each of the R-E score components was evaluated separately as present/absent at the baseline visit, with the absent value group as the reference group. Models were adjusted in a similar fashion as mentioned above, but with an additional

model 3 in which adjustments for each and all of the six components were added to those present in model 2.

We examined the assumption of proportional hazards by computation of Schoenfeld residuals and inspection of log(−log[survival function]) curves, and they were met. Statistical significance for all analyses was $p<0.05$. Analyses were conducted using SAS 9.3 [SAS Institute, Cary, NC.]

Results

A total of 13,261 participants [age 53.8±5.3 years; 56.9% females; 26.3% African Americans] were included in this analysis. Table 1 shows the participant characteristics across different levels of the R-E score. Participants characteristics found to be positively associated with increasing levels of R-E score were age, African-American ethnicity, male sex, body mass index, systolic blood pressure, total cholesterol, blood glucose, serum creatinine, uric acid, lower education level, smoking, diabetes, hypertension, and use of blood-pressure lowering drugs.

During a median follow-up of 21.8 years, 3,579, 2,205, 1,814, and 731 CVD, CHD, HF, and stroke events, respectively, occurred. The incidence rates of these outcomes were lowest in those with R-E score = 0 and highest in those with an R-E score ≥ 4 points. R-E score ≥ 4 points (compared to R-E score= 0 point) was significantly associated with increased risk of CVD, CHD, HF and stroke after adjustment for common CVD risk factors and potential confounders (Table 2).

Table 3 shows the associations between the individual components of the R-E score and incident CVD outcomes. As shown, all of the six R-E score were predictive of CVD events in the demographic adjusted model. However, after further adjustment for CVD risk factors and potential confounders (model 2) or when the six components were entered together in the model (model 3), only PTFV1, LVSTR and LAXDEV retained their significant associations with CVD.

Table 4 shows the associations between each component of the R-E score at baseline with individual CVD outcomes (HF, CHD and stroke). As shown, various components of the R-E score showed different levels of associations with CVD outcomes. Specifically: 1) All of the six components were significantly associated with HF in the demographic adjusted models. However, after further adjustments for CVD risk factors and potential confounders (model 2), QRSAMP and QRSDUR lost their significant associations with HF, and when all the six components were included in the model (model 3), LAXDEV lost its significant association with HF as well; 2) Only LVSTR and LAXDEV were significantly associated with CHD in all models; and 3) Only LVSTR and INTRNS were significantly associated with incident stroke in all models, with QRSAMP only showing significant association in the demographic adjusted model.

The nature and extent of the differing profiles described above can be better visualized in Figure 1.

Discussion

There are two key findings from this analysis. First, a R-E score greater than 4 points (compared to R-E= 0 points) is predictive of CVD, CHD, HF and stroke. Second, different components of the R-E score show different levels of associations with different CVD outcomes, as seen in Table 4 and Figure 1.

For several years there has been growing speculation that the ECG abnormalities used for decades as an indication of LVH are not directly related to cardiac mass or volume, but are related to an unknown predecessor of both. Our results, showing that the six components of the R-E score are unique in their relationship with different CVD outcomes, adds a new dimension to that speculation: each of the ECG abnormalities might indicate a different predecessor state. Each of the six ECG findings might prove to be a unique electrical biomarker, sharing with the others the ability to predict LVH, all-cause mortality, and incident CVD, but each, individually, predicting a *different* antecedent pathophysiological state, and perhaps a different clinical outcome as well.

Evidence that ECG-LVH and cardiac mass/volume are not directly related comes from a number of independent observations. First is the long recognized fact that many individuals have increased cardiac mass/volume and no ECG findings. Most recognized ECG-LVH diagnosis systems have a sensitivity well below 50% and usually below 30% (8). In 2001, Sundstrom and colleagues (9) reported that Echo-LVH and ECG-LVH predicted mortality independently of each other in a population of elderly Swedish men. Bacharova and colleagues (10) showed that both ECG-LVH and MRI-LVH predicted mortality to the same general level, but differed widely in their detection of LVH, leading to the conclusion that the two methods were likely to be distinct but somehow related phenotypes.

More evidence is found in genetic studies. Mayosi and coworkers (11) found that Sokolow-Lyon voltage measures of LVH displayed a greater heritability than echocardiographic measures of LVH. In a later genome-wide linkage analysis of ECG-LVH and Echo-LVH in families with hypertension, there were stronger linkages for the former, and the genetic determinants of each appeared to be distinct from the other (12). Shah (13) has reported heritability of ECG-LVH identified by four commonly utilized ECG measures, and Hong (14) has reported, in a genome wide association study in a Korean population, variations on the *RYR1* gene in patients with ECG/LVH.

None of the above studies have considered the relationships between genetic variations and specific ECG patterns and/or specific CV outcomes. Thus the nature of the proposed pathophysiological states remains speculative. The above evidence suggests that ECG wave forms associated with LVH are not rare occurrences with genetic variants. It is possible that a series of genetic variations exist, each of which produces subtle and specific changes in the basic physiology of the myocardial cell. The specific ECG changes might result from the basic genetic defect, or from changes in myocardium initiated by the basic defect acting over many years, such as the accumulation of fibrin within the myocardium, or the development of inflammatory vascular lesions. The importance of our observations will be determined by future research.

These results call for much more intensive studies of the relationships between the ECG components and genetic variants, and further study of the relationships between these same components and the plethora of chemical biomarkers.. It these relationships are present, then the ease of obtaining ECG information, the objectivity of its measurement, and its relatively low cost would greatly accelerate the pace of discovery and understanding of these relationships and their role in cardiac disease. The ultimate goal of all of this would be finding better tools for identifying individuals at higher risk for specific patterns of cardiovascular disease. In the context of our findings, the R-E score with its unique six components could be the infrastructure upon which such a tool could be built.

Limitations

This study shares the same limitations as all population studies. They are dependent on the generalizability of findings from a specific group to the larger population. These findings must be confirmed in other population groups, especially other ethnic groups. Similar studies must be carried out using other ECG abnormalities and other cardiovascular outcomes.

Conclusions

The R-E score is predictive of incident cardiovascular events. The six individual ECG components of the score all share in this predictive ability, but all have an independent and unique ability to predict specific CVD outcomes, defined in this study as HF, CHD, and stroke. The unique nature of response is revealed in the profiles of response of each ECG criterion to multivariable adjustments in the prediction of CV disease, suggesting a different pathophysiological state and outcome. These results call for further studies of the relationships between the components of the R-E score with other ECG abnormalities, genetic variants, and blood biomarkers.

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The authors acknowledge the contribution of Elizabeth Smith of Tenten Design, Chattanooga, TN in the design and production of Figure 1.

Disclosures: Dr. Estes has filed a provisional application for a patent related to automated generation of a risk score from an ECG, delivering the score to the physician as a part of the machine generated report.

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Figure 1.

This figure depicts the ability of each of the six components of the R-E Score in detecting three cardiovascular outcomes: heart failure, coronary heart disease, and stroke. The response of each ECG component to three levels of correction are shown. The first level corrects for demographic factors (age, sex, race). The second level corrects for these *plus* CV risk factors. The third corrects for these two *plus* the other components of the R-E Score. The color of the bar indicates the p value of the hazard ratio (see key).

Table 1

Baseline participants characteristics stratified by levels of Romhilt/Estes score

N=13,261	Score =0 n=5860	Score ≤3 n=7037	Score ≥4 n=364	P value
Age (years)	54 (5.8)	54 (5.7)	56 (5.8)	<.0001
Body mass index (kg/m2)	27 (5.4)	28 (5.1)	27 (5.3)	<.0001
Systolic blood pressure (mmHg)	119 (18.1)	121 (17.8)	137(25.6)	<.0001
Total cholesterol (mg/dL)	216 (42.1)	213 (41.0)	213 (40.3)	0.0012
High-density lipoprotein (mg/dL)	55 (17.2)	50 (16.7)	53 (18.4)	<.0001
Blood glucose (mg/dL)	107 (38.9)	108 (37.2)	113 (50.9)	0.0043
Serum creatinine (mg/dL)	1.1 (0.3)	1.1 (0.2)	1.3 (1.2)	<.0001
Uric acid (mg/dL)	5.6 (1.4)	6.2 (1.6)	6.5 (1.7)	<.0001
Women (%)	74.9	42.7	42.0	<.0001
African-American (%)	28.5	23.0	54.1	<.0001
Education (≤ high school) (%)	56.1	53.5	62.6	0.0001
Smoke (current) (%)	26.5	24.5	33.9	<.0001
Diabetes (%)	9.9	10.2	16.1	0.0009
Hypertension (%)	28.2	32.2	62.2	<.0001
Use of blood pressure lowering drugs (%)	22.7	25.8	45.9	<.0001
Family history of coronary heart disease (%)	39.1	39.1	34.3	0.1859

Table-2

Baseline Romhilt-Estes score and risk of incident cardiovascular disease

	Event rate		Model-1		Model-2	
	n/N	%	HR (95%CI)	P-value	HR (95%CI)	P-value
Incident Cardiovascular Disease						
Score = 0	1375/5860	23.5	1.00 (ref)		1.00 (ref)	
Score 1–3	2030/7037	28.9	1.10 (1.02–1.18)	0.0098	1.07 (0.99–1.15)	0.0879
Score ≥ 4	174/364	47.8	2.03 (1.73–2.39)	<.0001	1.66 (1.41–1.96)	<.0001
Incident Coronary Heart Disease						
Score = 0	788/5860	13.5	1.00 (ref)		1.00 (ref)	
Score 1–3	1316/7037	18.7	1.10 (1.00–1.21)	0.0510	1.09 (0.99–1.19)	0.0874
Score ≥ 4	101/364	27.8	1.94 (1.57–2.39)	<.0001	1.66 (1.34–2.07)	<.0001
Incident Heart Failure						
Score = 0	731/5793	12.6	1.00 (ref)		1.00 (ref)	
Score 1–3	970/6943	14.0	1.12 (1.01–1.24)	0.0289	1.02 (0.92–1.13)	0.7678
Score ≥ 4	113/356	31.7	2.52 (2.06–3.08)	<.0001	1.97 (1.60–2.43)	<.0001
Incident Stroke						
Score = 0	304/5860	5.2	1.00 (ref)		1.00 (ref)	
Score 1–3	381/7037	5.4	1.08 (0.86–1.18)	0.9147	0.96 (0.81–1.12)	0.5779
Score ≥ 4	46/364	12.6	2.06 (1.50–2.82)	<.0001	1.49 (1.07–2.07)	0.0178

Model-1: Adjusted for age, sex and race;
Model-2: Adjusted for variables in model 1 plus study site, body mass index, systolic blood pressure, smoking status, education, hypertension, diabetes mellitus, cardiovascular disease status, family history of coronary heart disease, ratio of total cholesterol/high-density lipoprotein, blood glucose, serum creatinine, and uric acid (all at baseline).

Table 3

Baseline Romhilt-Estes score components and risk of incident cardiovascular disease

	Event rate (%)		Model-1[a]	Model-2[b]	Model-3[c]
	Absent	Present	HR (95%CI)	HR (95%CI)	HR (95%CI)
QRSAMP	26.8	40.8	1.40 (1.10–1.77)‡	1.17 (0.92–1.50)	1.04 (0.81–1.33)
PTFV1	26.9	38.3	1.51 (1.12–2.03)‡	1.41 (1.03–1.91)†	1.42 (1.04–1.93)†
LVSTR	26.5	48.0	2.28 (1.93–2.70)§	1.65 (1.38–1.96)§	1.62 (1.36–1.94)§
LAXDEV	26.6	39.5	1.34 (1.16–1.56)§	1.21 (1.04–1.42)†	1.19 (1.02–1.39)†
QRSDUR	24.2	29.4	1.09 (1.01–1.16)†	1.07 (1.00–1.15)	1.06 (0.98–1.14)
INTRNS	26.8	32.7	1.26 (1.04–1.52)†	1.20 (0.99–1.45)	1.17 (0.96–1.41)

†Denotes P<0.05;

‡P<0.01;

§P<0.001 for P values of hazard ratios

[a]Model-1: Adjusted for age, sex and race;

[b]Model-2: Adjusted for variables in model 1 plus field center, body mass index, systolic blood pressure, smoking status, education, hypertension, diabetes mellitus, family history of coronary heart disease, ratio of total cholesterol/high-density lipoprotein, blood glucose, serum creatinine, and uric acid (all at baselien)

[c]Model-3: Adjusted for variables in Model 2 plus all of the six R-E score components.

QRSAMP—R or S wave in any limb lead ≥2.0 mV, or S wave in V1 or V2 ≥3.0 mV, or R wave in V5 or V6 ≥3.0 mV;
PTFV1—P terminal force defined as terminal negativity of P wave in V1 ≥0.10 mV in depth and ≥ 0.04 sec in duration;
LVSTR—Left ventricular strain defined as ST segment and T wave in opposite direction to QRS in V5 or V6, without digitalis;
LAXDEV—Left axis deviation defined as QRS axis ≤ −30 degrees;
QRSDUR—QRS duration ≥0.09 sec;
INTRNS—Intrinsicoid deflection duration in V5 or V6 ≥0.05 sec;

Table 4

Baseline Romhilt/Estes score components and risk of incident heart failure, coronary heart disease and stroke

Score Components	Model	Incident HF	Incident CHD	Incident Stroke
QRSAMP	Model 1[a]	1.53 (1.12–2.09)[‡]	1.13 (0.80–1.59)	2.20 (1.47–3.27)[‡]
	Model 2[b]	1.27 (0.92–1.75)	1.03 (0.72–1.46)	1.45 (0.96–2.21)
	Model 3[c]	1.05 (0.75–1.45)	0.91 (0.63–1.30)	1.33 (0.87–2.04)
PTFV1	Model 1[a]	1.94 (1.34–2.80)[‡]	1.46 (0.98–2.17)	1.16 (0.58–2.34)
	Model 2[b]	1.76 (1.20–2.58)[‡]	1.39 (0.93–2.08)	1.09 (0.54–2.21)
	Model 3[c]	1.75 (1.19–2.57)[‡]	1.40 (0.93–2.10)	1.06 (0.52–2.15)
LVSTR	Model 1[a]	2.89 (2.36–3.55)[§]	2.40 (1.94–2.97)[§]	2.22 (1.58–3.11)[§]
	Model 2[b]	2.13 (1.72–2.63)[§]	1.76 (1.41–2.20)[§]	1.54 (1.09–2.18)[†]
	Model 3[c]	2.09 (1.68–2.59)[§]	1.75 (1.40–2.19)[§]	1.48 (1.04–2.11)[†]
LAXDEV	Model 1[a]	1.50 (1.23–1.84)[§]	1.45 (1.21–1.75)[§]	1.12 (0.78–1.59)
	Model 2[b]	1.24 (1.01–1.53)[†]	1.36 (1.13–1.64)[‡]	0.99 (0.69–1.42)
	Model 3[c]	1.21 (0.99–1.49)	1.33 (1.10–1.60)[‡]	0.98 (0.68–1.41)
QRSDUR	Model 1[a]	1.11 (1.00–1.22)[†]	1.08 (0.98–1.18)	1.02 (0.87–1.19)
	Model 2[b]	1.04 (0.94–1.15)	1.08 (0.99–1.18)	0.99 (0.85–1.15)
	Model 3[c]	1.01 (0.91–1.12)	1.07 (0.98–1.18)	0.95 (0.81–1.12)
INTRNS	Model 1[a]	1.60 (1.25–2.06)[‡]	1.05 (0.82–1.34)	1.59 (1.08–2.36)[†]
	Model 2[b]	1.48 (1.14–1.91)[‡]	1.01 (0.79–1.30)	1.55 (1.05–2.31)[†]
	Model 3[c]	1.46 (1.13–1.89)[‡]	0.99 (0.76–1.27)	1.53 (1.03–2.29)[†]

[†]Denotes P<0.05;

[‡]P<0.01;

[§]P<0.001 for P values of hazard ratios.

CHD- coronary heart disease; HF- heart failure

[a]Model-1: Adjusted for age, sex and race;

[b]Model-2: Adjusted for variables in model 1 plus field center,, body mass index, systolic blood pressure, smoking status, education, hypertension, diabetes mellitus, family history of coronary heart disease, ratio of total cholesterol/high-density lipoprotein, blood glucose, serum creatinine, and uric acid (all at baseline).

[c]Model-3: Adjusted for variables in Model 2 plus all of the six R-E score components.