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Utility of Normal Findings on Electrocardiogram and Echocardiogram in Individuals 65 Years of Age

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Abstract

The lack of abnormalities found on noninvasive cardiac testing possibly improves cardiovascular disease (CVD) risk stratification efforts and conveys reduced risk despite the presence of traditional risk factors. This analysis included 3,805 (95% white; 61% women) participants from the Cardiovascular Health Study (CHS) without baseline CVD. The combination of a normal electrocardiogram (ECG) and echocardiogram was assessed for the development of CVD. A normal ECG was defined as the absence of major or minor Minnesota code abnormalities. A normal echocardiogram was defined as the absence of contractile dysfunction, wall motion abnormalities, or abnormal left ventricular mass. Cox regression was used to compute the 10-year risk of developing coronary heart disease (CHD), stroke, and heart failure events. There were 1,555 (41%) participants with normal findings on both measures. After accounting for traditional CVD risk factors, a protective benefit was observed for all outcomes among participants who had normal ECG and echocardiographic findings (CHD: HR=0.56, 95%CI=0.46, 0.69; stroke; HR=0.57, 95%CI=0.43, 0.76; heart failure: HR=0.36, 95%CI=0.29, 0.41). The addition of this normal profile resulted in significant net reclassification improvement (NRI) of the Framingham risk score for heart failure (NRI=4.3%, 95%CI=1.0%, 8.0%). In conclusion, normal findings on routine noninvasive cardiac assessment identify persons in whom CVD risk is low.

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Disclosures

None.

Keywords

risk assessment; electrocardiogram; echocardiography

INTRODUCTION

Attempts to reduce overall cardiovascular disease (CVD) burden have stemmed from the identification of risk factors (e.g., serum cholesterol, blood pressure, cigarette smoking) and their biological role in CVD progression. Consequently, numerous preventive measures have been implemented and reductions in CVD mortality have been observed.^{1,2} In this framework, abnormal profiles clearly are associated with adverse cardiac outcomes. In contrast, several reports have demonstrated that low-risk status (e.g., favorable blood pressure and cholesterol level, no cigarette use) confers a reduced risk of CVD-related mortality and improved longevity.^{3,4} The use of noninvasive cardiac assessment, such as the widely available electrocardiogram (ECG) and transthoracic echocardiogram, have further permitted the assessment of CVD progression from the healthy to subclinical state. Accordingly, several reports have demonstrated that abnormalities in both measures are predictive of future CVD events.^{5–10} However, less is known about the predictive ability of persons who have normal findings on these common tests. The lack of abnormalities found possibly confers a reduced risk for adverse cardiac events beyond traditional risk factors, thus identifying a group of patients in whom intense risk factor modification strategies are unnecessary. Therefore, the purpose of this analysis was to examine the clinical utility of normal findings on two commonly used noninvasive cardiac assessment tools in a population-based cohort study of older community-dwelling adults.

METHODS

Details of CHS have been previously described.¹¹ Briefly, CHS is a prospective population-based cohort study of risk factors for coronary heart disease (CHD) and stroke in individuals 65 years and older. A total of 5,888 participants with Medicare eligibility were recruited from 4 field centers located in the following locations in the United States: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. Subjects were followed with semi-annual contacts, alternating between telephone calls and surveillance clinic visits. CHS clinic exams ended in June of 1999 and since that time 2 yearly phone calls to participants were used to identify events and collect data. The institutional review boards at each site approved the study and written informed consent was obtained from participants at enrollment. In this analysis, we examined the clinical utility of normal findings on routine noninvasive cardiac assessment (e.g., ECG and echocardiogram) with regard to the risk of adverse CVD outcomes (e.g., CHD, stroke, and heart failure). Participants were excluded if any of the following criteria were met: baseline CHD, stroke, or heart failure were present; baseline covariate data were missing; or follow-up data were missing.

Identical electrocardiographs (MAC PC, Marquette Electronics Inc., Milwaukee, Wisconsin) were used at all clinic sites, and resting, 10-second standard simultaneous 12-lead ECGs

were recorded in all participants.¹² ECGs were automatically processed at a central ECG core lab (Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston-Salem, NC) using GE Marquette 12-SL program (GE, Milwaukee, Wisconsin). ECG abnormalities were classified using the standards of Minnesota ECG classification.¹³ Participants with any major or minor abnormalities were considered to have abnormal ECGs.

A baseline transthoracic echocardiogram was obtained for each study participant according to previously described techniques.¹⁴ Trained echocardiographers who were blind to CHS data analyzed and interpreted all echocardiographic data at a centralized reading center. Echocardiograms were defined as normal if the following criteria were met: ejection fraction $\geq 55\%$, qualitative left ventricular wall motion abnormalities were absent; left ventricular mass within sex-specific normal limits (women: $<89 \text{ g/m}^2$; men: $<103 \text{ g/m}^2$).¹⁵ Participants who did not meet these criteria were labeled as having abnormal echocardiograms.

The outcomes of interest were the development of fatal and non-fatal CHD, stroke, and heart failure events. The ascertainment and adjudication of baseline and incident cases of CVD events in CHS have been previously described.^{16–18} Adjudicated incident CHD was defined as one of the following: fatal or non-fatal myocardial infarction, angina pectoris without myocardial infarction, coronary revascularization procedures (angioplasty and coronary artery bypass graft surgery), or other fatal CHD events. All suspected stroke events and stroke-related deaths were reviewed by the Cerebrovascular Adjudication Committee and included fatal and non-fatal ischemic strokes. Heart failure events were determined from both the physician diagnosis and/or treatment defined by a current prescription for typical therapies (e.g., diuretics, digitalis, and vasodilators). Additionally, typical symptoms, signs, and chest X-ray findings of heart failure were reviewed by the CHS Events Committee. Probable and definite heart failure cases were included. A detailed description of the ascertainment of each clinical event is described in the Supplemental Document.

Participant characteristics were collected during the initial CHS interview and questionnaire. Age, sex, race, income, education, and smoking status were self-reported. Annual income was dichotomized at \$25,000, and education was dichotomized at “high school or less.” Smoking was defined as current or ever smoker. Participants’ blood samples were obtained after a 12-hour fast at the local field center. Measurements of total cholesterol, high-density lipoprotein cholesterol, and plasma glucose were used in this analysis. Diabetes was defined as self-reported history of a physician diagnosis, a fasting glucose value $\geq 126 \text{ mg/dL}$, or by the current use of insulin or oral hypoglycemic medications. Blood pressure was measured for each participant in the seated position and systolic measurements was used in this analysis. The use of aspirin and antihypertensive medications was self-reported. Body mass index was computed as the weight in kilograms divided by the square of the height in meters.

Categorical variables were reported as frequency and percentage while continuous variables were recorded as mean $\pm$ standard deviation. Statistical significance for categorical variables was tested using the chi-square method and the Kruskal-Wallis procedure for continuous variables. We examined if a normal 12-lead ECG and normal echocardiogram, separately or

in combination, were protective against the development of common CVD events. Therefore, in addition to using ECG and echocardiogram separately, the following 4 combinations were constructed: normal ECG + normal echocardiogram; abnormal ECG + normal echocardiogram; normal ECG + abnormal echocardiogram; and abnormal ECG + abnormal echocardiogram (referent). Follow-up time was defined as the time from the initial study exam until one of the following: CVD development, death, loss to follow-up, or end of follow-up. Follow-up was truncated at 10 years to increase the clinical utility of our findings. Kaplan-Meier estimates were used to compute the 1-, 5-, and 10-year cumulative incidence of each outcome by the above 4 groups.¹⁹ Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association of each group with each outcome of interest. Multivariable models were constructed as follows: Model 1 adjusted for age, sex, race, education, and income; Model 2 adjusted for Model 1 covariates plus smoking, systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol, aspirin, and antihypertensive medications. The proportional hazards assumption was not violated in our analysis. We also assessed the added predictive ability of normal ECG + normal echocardiogram in the Framingham risk scores for CHD,²⁰ stroke,²¹ and heart failure.²² A modified version of the Framingham risk score for heart failure was used that did not separate men and women. We computed absolute and relative integrated discrimination improvement (IDI). These measures quantify the increase in the difference between mean predicted risks for participants who do and do not develop the outcome of interest after adding the new covariate (e.g., normal ECG + normal echocardiogram) to the model.²³ Additionally, net reclassification improvement (NRI) which quantifies any desirable change in predicted risk was computed using the following risk categories: <10%, 10–20%, and >20%.²⁴ Confidence intervals for both IDI and NRI were computed using bootstrapping with 1000 replicates.²³ Statistical significance was defined as $p < 0.05$. SAS Version 9.4 (Cary, NC) was used for all analyses.

RESULTS

A total of 3,805 (95% white; 61% women) participants were included in the final analysis. There were 1,555 (41%) participants with normal ECGs and normal echocardiograms at baseline. Of those with normal ECGs ($n=1,703$), 91% had normal echocardiograms. In contrast, 51% of those with normal echocardiograms ($n=3,072$) had normal ECGs. Also, 585 (15%) participants had abnormal ECGs and abnormal echocardiograms. Baseline characteristics for the study population are shown in Table 1.

During the 10-year study period, a total of 783 CHD events, 414 strokes, and 576 cases of heart failure were detected. The 1-, 5-, and 10-year cumulative incidence of each outcome are shown in Table 2. For all time periods, the cumulative incidence of each outcome was lower for those with normal ECG and echocardiographic findings compared with each condition in isolation (Figure 1).

The 10-year risk estimates across levels of normal ECGs and normal echocardiograms are shown in Table 3. The risk for all outcomes was lowest for those with normal ECGs and echocardiograms. The addition of normal ECG + normal echocardiogram resulted in significant reclassification of the Framingham risk score heart failure (Table 4). A large

proportion of participants who did and did not experience CVD events in the intermediate risk groups were reclassified with inclusion of these normal measures into the model (Table 4). The reclassification tables for CHD, stroke, and heart failure are shown in Supplemental Tables 1, 2, and 3, respectively.

DISCUSSION

The findings of this analysis demonstrate that normal findings on the routine 12-lead ECG and echocardiogram confer a reduced risk for the development of future CVD events in persons ≥ 65 years of age, independent of traditional cardiovascular risk factors. Additionally, the inclusion of normal ECG and echocardiographic findings in commonly used risk scores for CHD, stroke, and heart failure was able to reclassify intermediate-risk participants into low- and high-risk categories. Overall, our data suggest that persons who have normal ECG and echocardiographic findings represent a group in which the risk for future CVD events is low.

Several reports have demonstrated that abnormalities detected on the ECG and echocardiogram are associated with an increased risk for CVD events and mortality.^{5–10} However, less is known about the CVD risk associated with normal findings on both commonly used tools. The present study aimed to determine if the risk of CVD events associated with normal findings on the routine ECG and echocardiogram were associated with a lower risk of future events after accounting for traditional risk factors. Accordingly, we have demonstrated that persons who have such a normal cardiac profile have a lower CVD risk than persons with abnormalities. Additionally, participants who were labeled intermediate-risk based on common scoring systems were reclassified to low and high risk for each outcome examined. These findings have important implications regarding the clinical decision to initiate certain risk factor modification strategies in older adults, especially when normal ECG and echocardiographic findings are present. Therefore, the identification of this normal cardiac profile possibly is beneficial, especially when contemplating invasive strategies to reduce CVD risk.

The aim of this study was to use a simple and easy characterization scheme with which to define a normal cardiac profile that the practicing clinician would be able to interpret. Although the prevalence of ECG abnormalities will vary, the practicing clinician is more likely to encounter a normal tracing.²⁵ The resting ECG is no longer recommended as a screening tool due to inconsistencies in risk prediction and its inability to change clinical practice,²⁶ but much information, as evidenced in this report, is obtained from a normal tracing. Additionally, normal echocardiographic findings were defined by the presence of normal ejection fraction, the absence of qualitative left ventricular wall motion abnormalities, and normal left ventricular mass. Despite the detailed information that is obtained during echocardiographic assessment, the definition used in this study is easily interpreted across multiple specialties. Also, the definition used was highly protective of future CVD events, indicating that the criteria used were adequate to describe a normal echocardiographic profile for risk assessment. Overall, this study provides clinicians with valuable information regarding risk assessment that would be missed when solely relying on the detection of biological abnormalities.

We must also mention that 91% of participants with a normal ECG had a normal echocardiogram. This would imply that the ECG is able to be used in lieu of the echocardiogram for CVD risk assessment, especially when a normal tracing is obtained. This was most evident for stroke and heart failure prediction, as similar risk estimates were obtained when a normal ECG and normal echocardiogram were present. As we strive for cost-effective options within our health care system, the ECG possibly has a role in reclassifying CVD risk rather than relying on costly imaging modalities which are unlikely to change clinical practice.²⁷ However, further studies are needed to explore the utility of this profile to reduce CVD burden in older adults before clinical practice recommendations are made.

Our findings should be interpreted in the context of certain limitations. Several baseline characteristics were self-reported and possibly resulted in misclassification. We included several covariates in our multivariable models, and we acknowledge that residual confounding is possible. The Framingham scoring system has been shown to perform poorly in populations of older adults.²⁸ Accordingly, we did not use the C-statistic to examine model performance, as the primary goal of our analysis was to determine if each participant's risk would be altered with the inclusion of a normal noninvasive cardiac profile into the model. Therefore, more appropriate measures (e.g., IDI, NRI) were used. Lastly, the population of CHS was limited to whites and blacks older than 65 years of age and limits the generalizability of our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. 10-Year Cumulative Incidence of CHD (A), Stroke (B), and Heart Failure (C).*

*The cumulative incidence curves are statistically different (log-rank $p < 0.001$) for CHD (A), stroke (B), and heart failure (C).

CHD=coronary heart disease.

Table 1

Baseline Characteristics (N=3,805)

Characteristic	Normal ECG + Normal Echo (n=1,555)	Abnormal ECG + Normal Echo (n=1,517)	Normal ECG + Abnormal Echo (n=148)	Abnormal ECG + Abnormal Echo (n=585)	P-value *
Age (years)					
65–70	802 (52%)	667 (44%)	67 (45%)	194 (33%)	
71–74	367 (23%)	352 (23%)	38 (26%)	149 (25%)	
75–80	296 (19%)	335 (22%)	29 (20%)	156 (27%)	
>80	90 (6.0%)	163 (11%)	14 (9.0%)	86 (15%)	<0.001
Men	563 (36%)	643 (42%)	65 (44%)	234 (40%)	0.0035
Black	50 (3.2%)	83 (5.5%)	6 (4.1%)	34 (5.8%)	0.0090
Education, high school or less	824 (53%)	834 (55%)	83 (56%)	353 (60%)	0.025
Income, <\$25,000 yearly	894 (57%)	914 (60%)	84 (57%)	398 (68%)	<0.001
Current or former smoker	835 (54%)	822 (54%)	66 (45%)	277 (47%)	0.0057
Diabetes mellitus	142 (9.1%)	197 (13%)	28 (19%)	119 (20%)	<0.001
Systolic blood pressure, mean $\pm$ SD (mm Hg)	135 $\pm$ 18	139 $\pm$ 20	139 $\pm$ 20	145 $\pm$ 20	<0.001
Body mass index, mean $\pm$ SD (kg/m ²)	26 $\pm$ 3.8	26 $\pm$ 3.8	28 $\pm$ 4.5	27 $\pm$ 4.0	<0.001
HDL cholesterol, mean $\pm$ SD (mg/dL)	57 $\pm$ 16	55 $\pm$ 16	54 $\pm$ 15	53 $\pm$ 15	<0.001
Total cholesterol, mean $\pm$ SD (mg/dL)	217 $\pm$ 38	216 $\pm$ 39	220 $\pm$ 44	212 $\pm$ 39	0.024
LV mass/BSA, mean $\pm$ SD (g/m ²)	80 (7.3)	83 (8.5)	87 (9.3)	99 (14)	<0.001
Antihypertensive medication use	479 (31%)	576 (38%)	62 (42%)	287 (49%)	<0.001
Aspirin use	401 (26%)	467 (31%)	51 (34%)	183 (31%)	0.0032

* Statistical significance for continuous data was tested using the Kruskal-Wallis procedure and categorical data was tested using the chi-square method.

BSA=body surface area; ECG=electrocardiogram; Echo=echocardiogram; HDL=high-density lipoprotein; LV=left ventricular; SD=standard deviation.

Table 2

1-, 5-, and 10-year Cumulative Incidence Estimates of Cardiovascular Outcomes

Outcome	1-year	5-year	10-year
<i>Coronary Heart Disease</i>			
Abnormal ECG + Abnormal Echo	2.9 (%)	20.1 (%)	36.8 (%)
Normal ECG + Abnormal Echo	2.0 (%)	11.9 (%)	25.5 (%)
Abnormal ECG + Normal Echo	1.9 (%)	10.6 (%)	22.3 (%)
Normal ECG + Normal Echo	1.4 (%)	9.2 (%)	18.2 (%)
<i>Stroke</i>			
Abnormal ECG + Abnormal Echo	1.2 (%)	7.7 (%)	18.6 (%)
Normal ECG + Abnormal Echo	2.0 (%)	6.8 (%)	12.4 (%)
Abnormal ECG + Normal Echo	1.3 (%)	5.7 (%)	14.1 (%)
Normal ECG + Normal Echo	0.6 (%)	2.6 (%)	8.1 (%)
<i>Congestive Heart Failure</i>			
Abnormal ECG + Abnormal Echo	2.4 (%)	14.0 (%)	35.0 (%)
Normal ECG + Abnormal Echo	0.7 (%)	5.6 (%)	14.0 (%)
Abnormal ECG + Normal Echo	0.9 (%)	7.1 (%)	18.4 (%)
Normal ECG + Normal Echo	0.4 (%)	3.3 (%)	10.2 (%)

ECG=electrocardiogram; Echo=echocardiogram.

Table 3

10-year Risk of Cardiovascular Outcomes (N=3,805)

Outcome	Events/No at risk	Model 1* HR (95%CI)	P-value	Model 2† HR (95%CI)	P-value
Coronary Heart Disease					
Abnormal ECG	485/2,102	1.0 (ref)	-	1.0 (ref)	-
Normal ECG	298/1,703	0.75 (0.65, 0.87)	<0.001	0.81 (0.70, 0.94)	0.0062
Abnormal Echo					
Abnormal Echo	217/733	1.0 (ref)	-	1.0 (ref)	-
Normal Echo	566/3,072	0.57 (0.48, 0.66)	<0.001	0.63 (0.54, 0.74)	<0.001
Abnormal ECG + Abnormal Echo					
Abnormal ECG + Abnormal Echo	183/585	1.0 (ref)	-	1.0 (ref)	-
Normal ECG + Abnormal Echo	34/148	0.66 (0.45, 0.95)	0.024	0.70 (0.49, 1.01)	0.059
Abnormal ECG + Normal Echo	302/1,517	0.56 (0.46, 0.67)	<0.001	0.61 (0.51, 0.74)	<0.001
Normal ECG + Normal Echo	264/1,555	0.49 (0.40, 0.59)	<0.001	0.56 (0.46, 0.69)	<0.001
Stroke					
Abnormal ECG	281/2,102	1.0 (ref)	-	1.0 (ref)	-
Normal ECG	133/1,703	0.60 (0.49, 0.74)	<0.001	0.66 (0.54, 0.82)	<0.001
Abnormal Echo					
Abnormal Echo	108/733	1.0 (ref)	-	1.0 (ref)	-
Normal Echo	306/3,072	0.66 (0.53, 0.82)	<0.001	0.76 (0.60, 0.95)	0.015
Abnormal ECG + Abnormal Echo					
Abnormal ECG + Abnormal Echo	91/585	1.0 (ref)	-	1.0 (ref)	-
Normal ECG + Abnormal Echo	17/148	0.75 (0.45, 1.26)	0.27	0.82 (0.49, 1.37)	0.44
Abnormal ECG + Normal Echo	190/1,517	0.77 (0.60, 0.99)	0.044	0.86 (0.67, 1.11)	0.26
Normal ECG + Normal Echo	116/1,555	0.48 (0.36, 0.63)	<0.001	0.57 (0.43, 0.76)	<0.001
Congestive Heart Failure					
Abnormal ECG	416/2,102	1.0 (ref)	-	1.0 (ref)	-
Normal ECG	160/1,703	0.48 (0.40, 0.58)	<0.001	0.53 (0.44, 0.64)	<0.001
Abnormal Echo					
Abnormal Echo	185/733	1.0 (ref)	-	1.0 (ref)	-
Normal Echo	391/3,072	0.47 (0.40, 0.56)	<0.001	0.56 (0.47, 0.67)	<0.001
Abnormal ECG + Abnormal Echo					
Abnormal ECG + Abnormal Echo	167/585	1.0 (ref)	-	1.0 (ref)	-
Normal ECG + Abnormal Echo	18/148	0.38 (0.23, 0.62)	<0.001	0.40 (0.25, 0.65)	<0.001
Abnormal ECG + Normal Echo	249/1,517	0.51 (0.42, 0.62)	<0.001	0.59 (0.48, 0.72)	<0.001
Normal ECG + Normal Echo	142/1,555	0.30 (0.24, 0.37)	<0.001	0.36 (0.29, 0.46)	<0.001

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* Adjusted for age, sex, race, education, and income.

[†] Adjusted for Model 1 covariates plus smoking, systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol, aspirin, and antihypertensive medications.

CI=confidence interval; ECG=electrocardiogram; Echo=echocardiogram; HR=hazard ratio.

Table 4

Reclassification of Framingham Risk Scores for Coronary Heart Disease, Stroke, and Heart Failure

Outcome	IDI (95%CI)	Relative IDI (95%CI)	NRI* (95%CI)	Proportion of Intermediate Risk Events/Non-Events Reclassified
<i>Coronary Heart Disease[†]</i>				
Framingham + Normal ECG/Echo	0.16% (0.10%, 0.26%)	2.7% (1.1%, 4.5%)	2.4% (−0.07%, 4.8%)	13.8%/14.9%
<i>Stroke[‡]</i>				
Framingham + Normal ECG/Echo	0.25% (0.13%, 0.36%)	5.5% (2.8%, 8.0%)	2.2% (−0.72%, 5.5%)	24.3%/24.0%
<i>Congestive Heart Failure^δ</i>				
Framingham + Normal ECG/Echo	0.67% (0.44%, 0.90%)	9.8% (6.3%, 13%)	4.3% (1.0%, 8.0%)	27.2%/39.3%

* Presented for the following risk categories: <10%, 10–20%, >20%.

[†] Model covariates included age, sex, smoking, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and antihypertensive medications.

[‡] Model covariates included age, systolic blood pressure, diabetes, smoking, atrial fibrillation, left ventricular hypertrophy, and antihypertensive medications.

^δ Model covariates included age, left ventricular hypertrophy, heart rate, systolic blood pressure, valve disease, diabetes, and body mass index.

ECG=electrocardiogram; Echo=echocardiogram; IDI=integrated discrimination improvement; NRI=net reclassification improvement.