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The Clinical Utility of Normal Findings on Non-Invasive Cardiac Assessment in the Prediction of Atrial Fibrillation

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Abstract

Background—The absence of abnormalities found on noninvasive cardiac assessment possibly confers a reduced atrial fibrillation (AF) risk despite the presence of traditional risk factors.

Hypothesis—Normal findings on noninvasive cardiac assessment are associated with a lower risk of AF development.

Methods—We examined the clinical utility of normal findings on routine noninvasive cardiac assessment in 5,331 participants (85% white; 57% women) from the Cardiovascular Health Study (CHS) who were free of baseline AF. The combination of a normal electrocardiogram (ECG) + normal echocardiogram was assessed for the development of AF events. 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 AF.

Results—During the 10-year study period, a total of 951 (18%) AF events were detected. A normal ECG (multivariable HR=0.80, 95%CI=0.69, 0.92) and normal echocardiogram (multivariable HR=0.75, 95%CI=0.65, 0.87) were associated with a reduced risk of AF in
isolation. This association improved in those with normal ECG + normal echocardiogram (multivariable HR=0.66, 95%CI=0.55, 0.79) compared with participants who had abnormal ECG + abnormal echocardiogram (referent).

Conclusions—Normal findings on routine noninvasive cardiac assessment identify persons in which the risk of AF is low. Further studies are needed to explore the utility of this profile regarding the decision to implement certain risk factor modification strategies in older adults to reduce the burden of AF.

Keywords
risk assessment; electrocardiogram; echocardiography

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in the United States, affecting an estimated 3 to 6 million adults (1, 2). Given the projected growth among older adults (3), the prevalence of AF will inevitably increase, as the arrhythmia disproportionately affects the elderly (1). This coincides with an annual cost of 6 billion dollars to care for patients who have AF and its well-known complications (4, 5).

Noninvasive cardiovascular assessment often is performed to determine if physiological, functional, or structural abnormalities are present to determine one’s risk for adverse events. This largely is related to numerous studies which have demonstrated that abnormalities on the routine electrocardiogram (ECG) or echocardiogram confer an increased risk for future cardiovascular events (6–9). This includes reports that have shown abnormal ECG and echocardiographic findings are associated with AF development (10–14). Therefore, it is possible that normal findings on the ECG and echocardiogram are associated with a lower risk of AF development despite the presence of traditional risk factors. We explored this hypothesis in the Cardiovascular Health Study (CHS), a population-based study of community-dwelling older adults.

METHODS

Study Population
Details of CHS have been previously described (15). 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 board 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 the routine ECG and echocardiogram with regard to the risk of AF. Participants were excluded if any of the following criteria were met: baseline AF was present; baseline covariate data were missing; or follow-up data were missing.

**Electrocardiogram**

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 (16). 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 code classification (17). Participants with any major or minor abnormalities were considered to have abnormal ECGs.

**Echocardiogram**

A baseline transthoracic echocardiogram was obtained for each study participant according to previously described techniques (18). 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 ≥55%, qualitative left ventricular wall motion abnormalities were absent; left ventricular mass within sex-specific normal limits (women: <89 g/m²; men: <103 g/m²) (19). Participants who did not meet these criteria were accordingly labeled as having abnormal echocardiograms.

**Atrial Fibrillation**

AF cases were identified during the annual study ECGs that were performed annually until 1999. Additionally, hospitalization discharge data were used to identify AF events using International Classification of Diseases codes 427.31 and 427.32. Primary and secondary diagnosis codes were used to ascertain AF events. Hospital diagnosis codes for AF ascertainment have been shown to have a positive predictive value of 98.6% (20).

**Covariates**

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 ≥126 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 were 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
Baseline coronary heart disease was determined by self-reported history or by medical record adjudication of the following diagnoses: myocardial infarction, angina pectoris without myocardial infarction, or coronary revascularization procedures (angioplasty and coronary artery bypass graft surgery) (21). Baseline cases of stroke and heart failure were identified by self-reported history of a physician diagnosis followed by medical record review. Cardiovascular disease was the composite of coronary heart disease, stroke, and heart failure.

**Statistical Analysis**

We examined if a normal 12-lead ECG and normal echocardiogram, separately or in combination, were protective against the development of AF events. Therefore, in addition to using the ECG and echocardiogram separately, the following combinations were constructed: normal ECG + normal echocardiogram; normal ECG or normal echocardiogram; and abnormal ECG + abnormal echocardiogram (referent). Statistical significance for categorical variables was tested using the chi-square method and the Kruskal-Wallis procedure for continuous variables. Follow-up time was defined as the time from the initial study exam until one of the following: AF 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 AF by the above 3 groups (22). Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between each group and AF. 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, antihypertensive medications, and cardiovascular disease. The proportional hazards assumption was not violated in our analysis. Statistical significance was defined as p<0.05. SAS Version 9.4 (Cary, NC) was used for all analyses.

**RESULTS**

A total of 5,331 (85% white; 57% women) participants were included in the final analysis. There were 1,788 (34%) participants with both normal ECGs and normal echocardiograms, 2,207 (41%) with either a normal ECG or a normal echocardiogram, and 1,336 (25%) had both 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 951 (18%) AF events were detected. The 1-, 5-, and 10-year cumulative incidence estimates of AF for each category are shown in Table 2. For all time periods, the cumulative incidence of AF was lower for those with normal ECG and echocardiographic findings. The cumulative incidence estimates of AF for each group are depicted in Figure 1.

The 10-year risk estimates across levels of normal ECGs and normal echocardiograms are shown in Table 3. When we examined the predictive ability of the normal ECG and normal echocardiogram in isolation, each marker was protective of developing AF. The risk of AF
was lower for those with both normal ECGs and echocardiograms compared with either in isolation (Table 3).

**DISCUSSION**

In our study of older adults, we found that a normal 12-lead ECG and echocardiogram at baseline signified a reduced risk of future AF after adjustment of known risk factors. Our data suggest that older adults who have a normal profile on noninvasive cardiac assessment represent a group in which the development of AF is less likely. Although the clinical impact is not clear, this information possibly is informative to clinical decisions that are based on a patient’s pre-test probability for AF, such as the decision to implement anticoagulation strategies to reduce stroke risk.

Previous studies have linked abnormal findings on the ECG and echocardiogram with AF. Data from the Atherosclerosis Risk In Communities Study (10), Framingham Heart Study (11), and Copenhagen ECG Study (12, 13), have demonstrated that ECG abnormalities predict AF. Similarly, data from the Framingham Heart Study have shown that echocardiographic abnormalities are independently associated with an increased risk of non-rheumatic AF (14). The aforementioned studies clearly demonstrate the ability of abnormalities on routine ECG and echocardiographic assessment to predict AF.

Currently, there are no studies that have explored the reduced risk associated with a normal profile on either the ECG or echocardiogram regarding the prediction of AF. In this study, we have shown that the lack of ECG abnormalities and echocardiographic left ventricular dysfunction are associated with a lower risk of AF after accounting for traditional risk factors. Presumably, the elderly participants with normal findings on the ECG and echocardiogram maintained this profile through genetics, healthful behaviors, and positive psychosocial factors. Therefore, the maintenance of a normal noninvasive cardiac profile possibly is protective of AF development beyond common risk factors, and this finding underscores the importance of unmeasured cardioprotective factors.

Although the resting ECG is no longer recommended as a screening tool (23), this study demonstrates that important prognostic information is gained from a normal recording, which clinicians are more likely to encounter (24). Similarly, much information is obtained on echocardiographic assessment, and the normal definition in this study is easily interpreted by clinicians across multiple specialties. Although our normal echocardiographic profile did not include diastolic parameters, we included left ventricular mass, as abnormalities in this measurement are predictive of diastolic dysfunction (25). Overall, this study provides clinicians with valuable information regarding AF risk assessment on noninvasive cardiac assessment that is easily interpreted by the practicing clinician. It also provides a certain group of patients with information that would be missed when solely relying on biological abnormalities for risk prediction.

This study is not without certain limitations. Several baseline characteristics were self-reported and subjected our analysis to recall bias. We included several covariates in our multivariable models that likely influenced the development of AF, but we acknowledge that
residual confounding is possible similar to other epidemiological studies. The findings in this analysis are not generalizable to younger populations, as CHS was limited to whites and blacks 65 years and older. Additionally, there are no current clinical decision making tools for AF risk stratification, and it is unclear if the findings in this analysis would improve the ability to predict AF.

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References


Figure 1. 10-Year Cumulative Incidence of Atrial fibrillation.*

*The cumulative incidence curves are statistically different (log-rank p<0.001).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abnormal ECG + Abnormal Echo (n=1,336)</th>
<th>Normal ECG or Normal Echo (n=2,207)</th>
<th>Normal ECG + Normal Echo (n=1,788)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–70 (%)</td>
<td>460 (35)</td>
<td>933 (42)</td>
<td>902 (50)</td>
<td></td>
</tr>
<tr>
<td>71–74 (%)</td>
<td>333 (25)</td>
<td>528 (24)</td>
<td>414 (23)</td>
<td></td>
</tr>
<tr>
<td>75–80 (%)</td>
<td>367 (27)</td>
<td>509 (23)</td>
<td>356 (20)</td>
<td></td>
</tr>
<tr>
<td>&gt;80 (%)</td>
<td>176 (13)</td>
<td>237 (11)</td>
<td>116 (7.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>603 (45)</td>
<td>977 (44)</td>
<td>674 (38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black (%)</td>
<td>458 (34)</td>
<td>300 (14)</td>
<td>58 (3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education, high school or less (%)</td>
<td>845 (63)</td>
<td>1,261 (57)</td>
<td>956 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Income, &lt;$25,000 (%)</td>
<td>982 (74)</td>
<td>1,380 (63)</td>
<td>1,054 (59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever smoker (%)</td>
<td>686 (51)</td>
<td>1,199 (54)</td>
<td>975 (55)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>307 (23)</td>
<td>349 (16)</td>
<td>194 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, median (25th–75th percentiles), mm Hg</td>
<td>144 (130–160)</td>
<td>138 (126–152)</td>
<td>132 (122–146)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, median (25th–75th percentiles), kg/m²</td>
<td>27 (25–30)</td>
<td>26 (23–29)</td>
<td>26 (23–28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, median (25th–75th percentiles), mg/dL</td>
<td>50 (42–60)</td>
<td>52 (43–63)</td>
<td>53 (45–65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, median (25th–75th percentiles), mg/dL</td>
<td>208 (184–233)</td>
<td>210 (185–237)</td>
<td>213 (190–238)</td>
<td>&lt;0.00053</td>
</tr>
<tr>
<td>LV mass/BSA, median (25th–75th percentiles), g/m²</td>
<td>97 (90–108)</td>
<td>84 (78–90)</td>
<td>80 (75–85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive medication use (%)</td>
<td>820 (61)</td>
<td>992 (45)</td>
<td>650 (36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin use (%)</td>
<td>476 (36)</td>
<td>788 (36)</td>
<td>520 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>497 (37)</td>
<td>471 (21)</td>
<td>230 (13)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*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.
Table 2

1-, 5-, and 10-year Cumulative Incidence of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1-year (%)</th>
<th>5-year (%)</th>
<th>10-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal ECG + Abnormal Echo</td>
<td>1.9</td>
<td>12.2</td>
<td>27.9</td>
</tr>
<tr>
<td>Normal ECG or Normal Echo</td>
<td>1.0</td>
<td>8.9</td>
<td>21.1</td>
</tr>
<tr>
<td>Normal ECG + Normal Echo</td>
<td>0.6</td>
<td>5.1</td>
<td>15.2</td>
</tr>
</tbody>
</table>

ECG=electrocardiogram; Echo=echocardiogram.
### Table 3

10-year Risk of Atrial Fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Events/No at risk</th>
<th>Model 1* HR (95% CI)</th>
<th>P-value</th>
<th>Model 2† HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal ECG</td>
<td>643/3,171</td>
<td>Ref</td>
<td>-</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Normal ECG</td>
<td>308/2,160</td>
<td>0.69 (0.60, 0.80)</td>
<td>&lt;0.001</td>
<td>0.80 (0.69, 0.92)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Abnormal Echo</td>
<td>357/1,708</td>
<td>Ref</td>
<td>-</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Normal Echo</td>
<td>594/3,623</td>
<td>0.63 (0.55, 0.73)</td>
<td>&lt;0.001</td>
<td>0.75 (0.65, 0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal ECG + Abnormal Echo</td>
<td>296/1,336</td>
<td>Ref</td>
<td>-</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Normal ECG or Normal Echo</td>
<td>408/2,207</td>
<td>0.69 (0.59, 0.80)</td>
<td>&lt;0.001</td>
<td>0.81 (0.69, 0.95)</td>
<td>0.0080</td>
</tr>
<tr>
<td>Normal ECG + Normal Echo</td>
<td>247/1,788</td>
<td>0.51 (0.43, 0.61)</td>
<td>&lt;0.001</td>
<td>0.66 (0.55, 0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* 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, antihypertensive medications, and cardiovascular disease.

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