Premature Ventricular Complexes on Screening Electrocardiogram and Risk of Ischemic Stroke

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Background and Purpose—Premature ventricular complexes (PVCs) detected from long-term ECG recordings have been associated with an increased risk of ischemic stroke. Whether PVCs seen on routine ECG, commonly used in clinical practice, are associated with an increased risk of ischemic stroke remains unstudied.

Methods—This analysis included 24,460 participants (aged, 64.5±9.3 years; 55.1% women; 40.0% blacks) from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study who were free of stroke at the time of enrollment. PVCs were ascertained from baseline ECG (2003–2007), and incident stroke cases through 2011 were confirmed by an adjudication committee.

Results—A total of 1415 (5.8%) participants had at least 1 PVC at baseline, and 591 developed incident ischemic stroke during an average (SD) follow-up of 6.0 (2.0) years. In a cox proportional hazards model adjusted for age, sex, race, geographic region, education, previous heart disease, systolic blood pressure, blood pressure–lowering medications, current smoking, diabetes mellitus, left ventricular hypertrophy by ECG, and aspirin use and warfarin use, the presence of PVCs was associated with 38% increased risk of ischemic stroke (hazard ratio [95% confidence interval], 1.38 [1.05–1.81]).

Conclusions—PVCs are common on routine screening ECGs and are associated with an increased risk of ischemic stroke. (Stroke. 2015;46:1365-1367. DOI: 10.1161/STROKEAHA.114.008447.)

Key Words: hypoxia-ischemia, brain ▪ stroke ▪ ventricular premature complexes

Premature ventricular complexes (PVCs) are common findings on the resting ECG. In a recent report from the Atherosclerosis Risk in Communities (ARIC) study, the presence of PVCs on 2-minute ECG rhythm strips was associated with a higher risk of ischemic stroke. Notably, however, recording 2-minute ECG is not a common practice in clinical settings. Whether PVCs detected by the more conventional short-term routine ECG are associated with increased risk of ischemic stroke remains unknown.

Methods

The goals and design of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study have been published. REGARDS was designed to investigate causes of regional and racial disparities in stroke mortality, oversampling blacks, and residents of the southeastern (stroke belt) United States. Individuals were recruited from a commercially available list of residents using mail and telephone contact. Demographic information and medical history were obtained by standardized telephone interview. A brief physical examination was conducted after the telephone interview, including standardized measurements of risk factors, collection of blood and urine, and recording of resting ECG. Participants are followed up every 6 months by telephone for possible stroke events. Participants provided informed consent, and the study was approved by all institutional review boards.

Of the 30,239 participants enrolled in REGARDS, we excluded 2953 with prevalent stroke or transient ischemic attack, 698 with poor quality ECG, and 2128 with missing covariates.

Details on stroke event adjudication have been previously published. In summary, reports of possible stroke during follow-up generated a request for retrieval of medical records that were centrally adjudicated by physicians. Stroke events were defined following the World Health Organization definition. Events not meeting the World Health Organization’s definition but with symptoms lasting <24 hours and neuroimaging consistent with acute ischemia were classified as clinical strokes. This analysis included World Health Organization–defined and clinical ischemic stroke and its subtype cardioembolic stroke. Participants with incident hemorrhagic stroke were excluded.

Statistical Analysis

Cox proportional hazards models were used to examine the association between PVCs with incident ischemic stroke through 2011 with incremental adjustment for potential confounders as follows: (1) age, sex, race, geographic region, and education; (2) further adjustment for blood pressure–lowering medications, systolic blood pressure,
current smoking, diabetes mellitus, left ventricular hypertrophy, atrial fibrillation, and previous heart disease, (5) further adjustment for warfarin use and aspirin use.

All statistical computations were performed using SAS-9.2 (SAS Institute, Cary, NC). A value of \( P < 0.05 \) was considered statistically significant.

## Results

Of the 24,460 participants (aged, 64.5±9.3 years; 55.1% women; 40.0% blacks) included in this analysis, 1415 (5.8%) had at least 1 PVC at baseline. Differences in the characteristics of participants with and without PVCs are shown in Table 1.

During an average (SD) follow-up of 6.0 (2.0) years, 591 participants developed ischemic stroke, of which 162 was defined as cardioembolic stroke. The incidence rate of ischemic stroke was higher in those with versus without PVCs (6.7 versus 4.2 per 1000 person-years; \( P < 0.01 \)). The Figure shows the cumulative proportion of stroke events by the PVCs status.

Table 2 shows the results of the association between PVCs and ischemic stroke. PVCs were associated with a 38% (95% confidence interval, 5%–81%) increased risk of ischemic stroke. The association between PVCs and cardioembolic stroke was of similar strength (hazard ratio [95% confidence interval], 1.47 [0.98–2.43]), but the association did not reach a statistical significance possibly because of lack of enough power.

## Discussion

In this analysis from the REGARDS study, one of the largest US cohort studies, the presence of PVCs on routine screening ECG was associated with higher risk of ischemic stroke. To our knowledge, this is the first study examining the relationship between PVCs detected by routine ECG recording and incident ischemic stroke. Previous studies were based on long-term ECG recordings that are not routinely used at clinical settings.3,8

The pathophysiologic mechanism through which PVCs may increase stroke risk is not yet well understood. The presence of PVCs has been associated with an increased risk of atrial fibrillation.3,9 This means that the association between PVCs and ischemic stroke could potentially be mediated by AF; although in our study, the association between PVC and stroke did not change after adjusting for baseline AF. PVCs are known to cause sudden changes in heart rate, blood pressure, and stroke volume.2 Also, frequent PVCs have been associated with an abnormal left ventricular diastolic function and have the potential for cardiac remodeling,10,11 which in turn may enhance thromboembolism.

Strengths of our study include its large sample size, the length, and thoroughness of its follow-up, and its diverse population. Few key limitations include our inability to explore

### Table 1. Baseline Characteristics of the Participants by the Presence of PVCs

<table>
<thead>
<tr>
<th></th>
<th>PVCs Present (n=1415)</th>
<th>PVCs Absent (n=23,045)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.3±9.2</td>
<td>64.3±9.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Women</td>
<td>642 (45.4)</td>
<td>12828 (55.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Black</td>
<td>593 (41.9)</td>
<td>9193 (39.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No high school</td>
<td>219 (15.5)</td>
<td>2570 (11.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High school/no college</td>
<td>372 (26.3)</td>
<td>5889 (25.6)</td>
<td></td>
</tr>
<tr>
<td>College or professional</td>
<td>824 (58.2)</td>
<td>14586 (63.3)</td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Non-Belt</td>
<td>667 (47.2)</td>
<td>10128 (43.9)</td>
<td></td>
</tr>
<tr>
<td>Belt</td>
<td>480 (33.9)</td>
<td>8019 (34.8)</td>
<td></td>
</tr>
<tr>
<td>Buckle</td>
<td>268 (19.0)</td>
<td>4898 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>184 (13.0)</td>
<td>3219 (14.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Previous heart disease</td>
<td>359 (25.4)</td>
<td>3509 (12.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>915 (64.7)</td>
<td>12958 (56.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130.1±16.9</td>
<td>126.9±16.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>309 (21.8)</td>
<td>4408 (19.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.2±6.1</td>
<td>29.3±6.2</td>
<td>0.61</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>134 (9.7)</td>
<td>1768 (7.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>158 (11.2)</td>
<td>2171 (9.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>49 (3.5)</td>
<td>620 (2.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>681 (48.1)</td>
<td>9429 (40.9)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

PVCs indicate premature ventricular complexes.
dose–response effect and mediation of putative association through incident AF (as seen in the ARIC study) because of lack of data.

In conclusion, we showed that presence of PVCs on a routine ECG is associated with increased risk of ischemic stroke, independent of traditional risk factors of stroke. These findings suggest that incidentally detected PVCs, typically dismissed as benign findings, may be a risk marker for future stroke. Whether suppression of frequent PVCs with β-blockers or use of antiplatelet agents may reduce observed stroke risk remains unstudied.

Acknowledgments
We thank the participants, staff, and investigators of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study for their valuable contributions. A full list of REGARDS investigators and institutions can be found at http://www.regardsstudy.org.

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Disclosures
Dr Kissela participates in stroke event adjudication in a clinical trial. The other authors report no conflicts.

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