Premature Ventricular Complexes and the Risk of Incident Stroke

The Atherosclerosis Risk In Communities (ARIC) Study

Sunil K. Agarwal, MD, MPH; Gerardo Heiss, MD, PhD; Pentti M. Rautaharju, MD, PhD; Eyal Shahar, MD, MPH; Mark W. Massing, MD, PhD; Ross J. Simpson, Jr, MD, PhD

Background and Purpose—Premature ventricular complexes (PVCs) on a 2-minute electrocardiogram are a common, largely asymptomatic finding associated with increased risk of coronary heart disease and death. They may reflect atherosclerosis or other pathogenic pathways that predispose to arrhythmias and stroke.

Methods—We conducted a prospective evaluation of the Atherosclerosis Risk In Communities Study cohort (n = 14 783) of middle-aged men and women to assess whether the presence of PVCs at study baseline (1987 to 1989) influenced the risk of incident stroke through December 31, 2004.

Results—PVCs were seen in 6.1% of the participants at baseline, and 729 (4.9%) had incident stroke. The unadjusted cumulative proportion of incident stroke in individuals with any PVC was 6.6% compared with 4.1% in those without PVC. The unadjusted hazard ratio of incident stroke in individuals with any PVC compared with those without any PVCs was 1.71 (95% CI, 1.33 to 2.20). Among individuals without hypertension and diabetes at baseline, PVCs were independently associated with incident stroke (hazard ratio: 1.72; 95% CI: 1.14 to 2.59). Among those with either diabetes or hypertension, the presence of any PVCs did not increase the risk of stroke. The association was stronger for noncarotid embolic stroke than for thrombotic stroke and its magnitude increased with higher frequency of PVCs.

Conclusions—Frequent PVCs are associated with risk of incident stroke in participants free of hypertension and diabetes. This suggests that PVCs may contribute to atrioventricular remodeling or may be a risk marker for incident stroke, particularly embolic stroke.

Key Words: arrhythmia ■ atrial fibrillation ■ risk factors ■ stroke ■ premature ventricular complexes

Premature ventricular complexes (PVCs) are mostly asymptomatic irregular heart rhythms commonly seen on electrocardiograms (ECGs) of the middle-aged and elderly. Several lines of research suggest that PVCs may be a marker of higher subclinical atherosclerotic burden, higher arrhythmic potential, or both, thus potentially linked to stroke.

Changes in heart rate, blood pressure, and stroke volume during and after PVCs, a consequence of changes in ventricular filling, ventricular contractility, and baroreflex activity, are well known. Frequent PVCs are associated with impaired ventricular relaxation and have the potential to remodel the heart. In addition to their putative arrhythmic potential, such adverse remodeling may increase the risk of atrial fibrillation, potentially increasing the risk of clot formation and embolization.

In contrast to the established association of atrial fibrillation with incident stroke, the relationship of ventricular rhythm abnormalities with stroke has not been much studied. No published study has examined whether the association between PVCs and stroke differs by stroke subtype (embolic versus thrombotic), because this may point toward different mechanisms.

In this study, we examined an association between PVCs and incident stroke in middle-aged men and women from 4 US communities. We also explored whether such an association differs in subgroups with and without the major risk factors for stroke and we considered stroke subtypes.

Methods

Study Population

The Atherosclerosis Risk In Communities (ARIC) Study enrolled 15 792 subjects aged 45 to 64 years in 4 US communities using area-probability sampling: Forsyth County, NC; city of Jackson, Miss; 7 northwestern suburbs of Minneapolis, Minn; and Washington County, Md, at Visit 1 (1987 to 1989). Black residents were oversampled in Forsyth County, NC, whereas enrollment at the Jackson, Miss site was restricted to black residents. A complete description of the ARIC communities and of the design has been...
published. The response rate was 75% for home interviews and among those who interviewed at home, 86% to 88% came for a clinic visit for communities other than Jackson (response 63%). Whites who responded to initial home interviews but not clinic visits had poorer socioeconomic status and poorer health than nonresponders with little difference among women and blacks. The cohort participated in 4 examinations, including the baseline visit, and also annual telephone interviews. Baseline examinations of the cohort were conducted from 1987 to 1989 to collect information about socioeconomic indicators, medical history, family history, cardiovascular risk factors, serum chemistries, ECGs, and medication use. Over 90% of the surviving cohort members responded to the recent annual telephone interviews.

For the present analysis, those with missing values for the 12-lead ECGs (n=191) and the missing 3-lead 2-minute rhythm strip or on pacemakers (n=74) were excluded. Also, participants with the following cardiac rhythm disturbances were excluded: Wolf-Parkinson-White syndrome (n=6), atrial fibrillation/flutter (n=35), wandering atrial pacemaker (n=6), and supraventricular tachycardia (n=5) and not sinus rhythm (n=67). Participants with missing or invalid values for key covariates were excluded (n=619). Also, participants with missing information (n=211) or prevalent history (n=105) of stroke were excluded. Finally, we excluded 48 participants who did not identify themselves as either white or black. Some observations met >1 exclusion criteria. The remaining 14,783 (93.6% of original) cohort participants were included in this study analyses.

In a subset analysis involving adjustment for left ventricular mass using Cornell voltage, another 1009 participants with ineligible values for Cornell voltage were excluded (n=665 participants with QRS ≥120 ms, suggesting bundle branch block; n=369 with missing or 0 value for Cornell voltage).

**Premature Ventricular Complex**

A supine 12-lead ECG at rest was obtained using the MAC PC10 personal cardiogram (Marquette Electronics, Milwaukee, Wis) and a 2-minute 3-lead (V1, II, and V5) rhythm strip. Participants were requested to fast and to refrain from smoking and consuming caffeinated beverages before the examination. Electrocardiographic data processing, monitoring, and quality control have been described elsewhere. Rhythm strips were classified 3 times by independent trained coders for total supraventricular, ventricular complex, and ventricular runs, bigeminy, trigeminy, and multiform complexes. Coding for PVCs was done before this study’s hypothesis was formulated and before stroke outcomes were ascertained. Adjudication of disagreements was performed by the ECG center principal investigator or coding supervisor. PVCs and heart rate were determined from this rhythm strip.

The primary exposure was presence of any PVCs on the 2-minute rhythm ECG. PVCs seen on a 2-minute ECG rhythm strip are highly correlated with high-frequency PVCs seen on 24-hour recordings. Further PVCs were classified by the frequency of their occurrence in a 2-minute rhythm strip, that is, single PVC; 2 to 3, and ≥4.

**Other Covariates**

Covariates known to be associated with PVCs, and other atherosclerotic and embolic events, including incident stroke events, were considered during analyses. These are presented in Table 1 and were ascertained during the cohort baseline interviews and examinations. A parsimonious set of potential covariates for the relation of PVCs to incident stroke was chosen based on a strong physiological relation to PVCs (eg, electrolytes, sinus rate) or known association with stroke (eg, age, prevalent coronary heart disease [CHD], hypertension, current smoking, diabetes, ventricular hypertrophy, educational attainment, gender, ethnicity). Measures of alcohol consumption, obesity, and obstructive lung disease were not included as potential confounders due to the absence of a strong physiological link to prevalent PVCs. Standardized and validated methods were used to collect information on covariates. Detailed information about the characterization of prevalent CHD, hypertension (Manual 11), diabetes (Manual 10), educational attainment, medication intake history, and Cornell voltage estimated left ventricular mass can be located in the ARIC Study Protocol available at the study’s web site. Similarly, the definition of these covariates can be found in the variable dictionaries for Visit 1 at the study’s web site (http://www.cscu.unc.edu/ARIC/).

**Study Outcomes**

To identify incident stroke, cohort participants were followed over time through annual telephone interviews, triennial field center examinations, surveillance of the ARIC community hospitals for all cohort members’ hospitalizations, and the review of death certificates, physician questionnaires, coroner/medical examiner reports, and informant interviews. Hospital reports were reviewed for evidence of acute stroke if the discharge diagnosis included a cerebrovascular disease code (International Classification of Diseases, 9th Revision code 430 to 438), if a cerebrovascular procedure was mentioned in the summary, or if the CT or MR report showed evidence of cerebrovascular disease. Medical records for potential stroke events were forwarded to a single nurse abstractor at a central ARIC office who abstracted each record for number, type, and severity of neurological deficits and supporting angiographic, CT, MRI, spinal tap, or autopsy evidence. ARIC adapted National Survey of Stroke criteria for its stroke definition. A computerized algorithm and physician reviewer independently confirmed the diagnosis of stroke with disagreements adjudicated by a second physician reviewer. Stroke cases were further classified as definite versus probable and into further subtypes as embolic versus thrombotic stroke. Participants were followed from enrollment through December 31, 2004. Baseline ECG has no role in ascertainment of stroke.

Stroke occurs mostly in the elderly, and the chances of death due to other common causes will remove many high-risk individuals from the risk sets. This has the potential to bias the results in those with high risk of death due to other risk factors. Thus, a combined end point consisting of incident stroke or death occurring before incidence stroke was analyzed additionally.

To study whether the observed association may be mediated by incident atrial fibrillation (AF), we tested if PVCs are associated with incident atrial fibrillation occurring before incident stroke. Atrial fibrillation was defined as the presence of International Classification of Diseases, 9th Revision code 427.31 in the hospital discharge codes. Patients with a diagnosis of atrial flutter (International Classification of Diseases, 9th Revision code 427.32) not developing AF during subsequent follow-up were not considered cases. We excluded AF diagnoses occurring simultaneously with heart revascularization surgery (International Classification of Diseases, 9th Revision code 36.X) or other cardiac surgery involving the heart valves or septa (International Classification of Diseases, 9th Revision code 35.X) without evidence of AF in subsequent hospitalizations or study examinations or subsequent to an incident stroke.

**Statistical Methods**

Descriptive statistical analyses were done by presence or absence of any PVCs at study baseline, including information on important covariates and incident stroke. Rate of stroke by race, gender, and PVC categories was estimated assuming constant rate over time and Poisson distribution. Cox regression models were used to estimate the difference in log hazards contrasting presence of any PVC with no PVC. Finally, multivariable Cox regression model including interaction terms between main exposure and race, gender, and traditional risk factors for stroke after adjusting for other potential confounders associated with prevalent PVCs and possibly stroke were fitted.

These interaction terms would suggest if there is any difference in the association between PVC and stroke in the strata of race, gender, or important risk factors for stroke, that is, prevalent CHD disease, hypertension, diabetes, and current smoking status after adjusting for other potential confounders and demographic characteristics. Additionally, adjustment for left ventricular mass using Cornell voltage was done in a subset analysis because this required further exclusion of study participants. AF occurring after baseline visit was not
The proportional hazard assumption was evaluated both using graphical methods (ln-ln S graphs) and statistical tests involving continuous time interaction terms (Cox tests). The log-linearity assumption of ordinal variables was examined, and as a result, education categories were considered as nominal after violation of log-linearity.

To test if the studied association differed by race, gender, and other major risk factors for stroke, a product term between each of these and exposure variable was included. This product term if statistically significant indicates heterogeneity in the effect estimate and suggests that results be presented stratified by such variable(s).

All statistical computations were performed using SAS software Version 9.1.3 (SAS Inc, Cary, NC) and STATA/IC Version 10 (StataCorp, College Station, Texas). A probability value of <0.05 for a 2-sided null hypothesis was considered statistically significant for main covariates. As is customary for tests of interaction in epidemiological studies, a probability value of <0.02 was considered statistically significant.

### Results

PVCs on the baseline 2-minute rhythm strip were identified in 899 (6.1%) of the 14,783 study participants. The prevalence of 30 PVCs/hour, ≥60 PVCs/hour, and complex PVCs were 2.4%, 2.9%, and 0.8%, respectively. The differences in the characteristics of individuals with any PVCs versus no PVC are shown in Table 1.

Overall, 729 (4.9%) of the 14,783 participants had incident stroke. The cumulative proportion of incident stroke in individuals with any PVC was 7.3% compared with 4.8% in those without PVC. There were no differences in rate ratio for incident stroke when comparing the presence versus absence of PVC across 4 races and gender groups.
Those with PVCs had a higher rate of incident stroke (Figure 1) and combined end point than individuals without any PVCs (hazard ratio: 1.71, 95% CI: 1.33 to 2.20; and 1.70, 1.51 to 1.92, respectively). The estimates after adjusting for age, gender, and race for incident stroke and combined end point were 1.4 (1.08 to 1.80) and 1.62 (1.44 to 1.83), respectively.

Among individuals without diabetes and hypertension at baseline, the hazard ratio of incident stroke was 1.72 (95% CI: 1.14 to 2.59) for individuals with any PVC versus those without any PVCs after adjusting for potential confounders (Table 2). The hazard ratio contrasting presence of any PVCs with no PVCs was lower in those with hypertension and diabetes (Tables 2 and 3). When examining the relationship with definite stroke in the model presented in Table 2, the hazards ratio contrasting those with any PVCs versus no PVCs was 1.67 (0.92 to 3.01). The estimates did not change appreciably after adjusting for Cornell voltage. Furthermore, the estimates did not change appreciably after adjusting for baseline intake of medications such as β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, antiarrhythmic drugs, and Digoxin.

Among individuals with no major risk factors for stroke (CHD, hypertension, current smoking, and diabetes at baseline; 46.3% of study participants), the hazard ratio of incident stroke was 2.09 (95% CI: 1.21 to 3.58) for individuals with any PVC versus those without any PVCs after adjusting for potential confounders (Table 2). The hazard ratio contrasting those with any PVCs versus no PVCs was 1.67 (0.92 to 3.01). The estimates did not change appreciably after adjustment for Cornell voltage. Furthermore, the estimates did not change appreciably after adjusting for baseline intake of medications such as β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, antiarrhythmic drugs, and Digoxin.

For embolic stroke of noncarotid origin, the hazard ratio comparing any PVCs versus no PVCs was 3.48 (1.74 to 6.95) among nonhypertensive and 1.21 (0.58 to 2.53) among hypertensive after adjusting for all the potential confounders.

Table 2. Multivariable-Adjusted Cox Regression Model for Stroke*: The ARIC Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio†</th>
<th>95% CIs</th>
<th>Pr&gt;χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PVC‡</td>
<td>1.72</td>
<td>1.14</td>
<td>2.59</td>
</tr>
<tr>
<td>Age at intake per SD</td>
<td>1.41</td>
<td>1.30</td>
<td>1.53</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol per SD</td>
<td>0.94</td>
<td>0.86</td>
<td>1.03</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol per SD</td>
<td>1.08</td>
<td>1.00</td>
<td>1.16</td>
</tr>
<tr>
<td>Potassium per SD</td>
<td>1.05</td>
<td>0.97</td>
<td>1.13</td>
</tr>
<tr>
<td>Magnesium per SD</td>
<td>0.93</td>
<td>0.87</td>
<td>1.01</td>
</tr>
<tr>
<td>Heart rate per SD</td>
<td>1.10</td>
<td>1.03</td>
<td>1.18</td>
</tr>
<tr>
<td>Race, black versus white</td>
<td>1.77</td>
<td>1.49</td>
<td>2.11</td>
</tr>
<tr>
<td>Gender, male versus female</td>
<td>1.38</td>
<td>1.17</td>
<td>1.63</td>
</tr>
<tr>
<td>Education, less than high school versus college</td>
<td>1.43</td>
<td>1.18</td>
<td>1.74</td>
</tr>
<tr>
<td>Education, high school versus college</td>
<td>1.09</td>
<td>0.90</td>
<td>1.33</td>
</tr>
<tr>
<td>Prevalent CHD</td>
<td>1.89</td>
<td>1.47</td>
<td>2.43</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.21</td>
<td>1.86</td>
<td>2.62</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>1.89</td>
<td>1.62</td>
<td>2.22</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.15</td>
<td>1.76</td>
<td>2.62</td>
</tr>
<tr>
<td>PVCs x hypertension</td>
<td>0.69</td>
<td>0.40</td>
<td>1.18</td>
</tr>
<tr>
<td>PVCs x diabetes</td>
<td>0.56</td>
<td>0.29</td>
<td>1.09</td>
</tr>
</tbody>
</table>

†Hazard ratio for stroke per SD increment or for test category as compared with referent; however, estimates for PVC are for those without diabetes and hypertension and, similarly, estimates for hypertension and diabetes are for subgroup without PVCs.
‡PVC coded by investigators using 2-minute (3-lead ECG strips) at baseline.
§No diabetes, hypertension, smoking history, or CHD at study baseline.
AF. Similar to our findings, other studies have shown a
higher risk of new-onset AF among those with PVCs. It is plausible that PVCs are associated with increased risk of AF. Given the stronger association of PVCs with fibrillation.22 Given the stronger association of PVCs with embolic than with thrombotic stroke (potentially caused by atherosclerosis in the cerebral circulation).

The relationship between AF and embolic stroke is well established. Increased left atrial size reflecting cardiac remodeling has been shown to be a strong predictor of atrial fibrillation.23 Given the stronger association of PVCs with embolic than with thrombotic stroke observed in our study, it is plausible that PVCs are associated with increased risk of AF. Similar to our findings, other studies have shown a higher risk of new-onset AF among those with PVCs. It is interesting to note that despite the possibility of some misclassification of stroke subtype into as cardioembolic, the estimates for definite and overall cardioembolic stroke were similar. If this finding is replicated in future studies, individuals with high-frequency PVCs could monitored for AF as part of regular clinical encounters and promotion by promoting self-monitoring of heart rhythm in such individuals. A proactive management of other risk factors of stroke could also be considered in individuals with high-frequency PVCs.

The strengths of our study include its large sample size, the length and completeness of its follow-up, and its population base that provides for inference to the general population. Because 2-minute rhythm strips are highly specific but less sensitive than 24-hour ambulatory ECG recordings, the strength of the associations with PVCs reported here could be underestimated, however. An alternate interpretation of the lack of association between PVCs and stroke among hypertensive individuals is the influence of medications that can suppress PVCs. This has the potential to induce bias resulting in failure of detecting a true association (Type 2 error) in ways that are not amenable to quantification in our data. As an additional note of caution, stroke occurs mostly among elderly and death due to other atherosclerotic processes also has the potential to induce a similar bias. Although a modification of the effect estimate by various established risk factors for stroke was studied, the statistical power to detect such interaction(s) was relatively limited. Also, a criterion probability value of 0.2 for the interaction test may result in a false-positive statistical interaction (Type 1 error); however, the difference in the size of the estimates supports such interaction. Lastly, time-varying comorbid conditions were not considered in these analyses because the main exposure itself varies over the course of follow-up and we lack information on such intraindividual variability.

These results, if replicated in other future studies, have potential clinical implications. PVCs may well turn out to be important risk markers for stroke, particularly embolic stroke, especially in the absence of established risk factors for stroke. In parallel, these results suggest that PVCs seen on a short rhythm strip may point to more than an atherosclerotic phenomenon such as an indication of an increased tendency toward formation of thrombi or embolization through cardiac remodeling and possibly AF and other serious arrhythmias.

In conclusion, the presence of high-frequency of PVCs in an ECG may help in stratifying individuals who are otherwise considered low risk for stroke due to the absence of important risk factors. The observed findings possibly point to PVCs as markers of a pathological process beyond atherosclerosis.

Acknowledgments
We thank the staff and participants of the ARIC Study for their important contributions. Thanks to Emily O’ Brien and Randi Foraker for their valuable comments on an early draft.

Sources of Funding
The ARIC Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022.

Disclosures
None.
References


Premature Ventricular Complexes and the Risk of Incident Stroke: The Atherosclerosis Risk In Communities (ARIC) Study
Sunil K. Agarwal, Gerardo Heiss, Pentti M. Rautaharju, Eyal Shahar, Mark W. Massing and Ross J. Simpson, Jr

Stroke. 2010;41:588-593; originally published online February 18, 2010;
doi: 10.1161/STROKEAHA.109.567800
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/4/588

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/