

# Stroke

American Stroke  
Association<sup>SM</sup>

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American  
Heart Association



**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 Feb 18, 2010;

DOI: 10.1161/STROKEAHA.109.567800

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214  
Copyright © 2010 American Heart Association. 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/cgi/content/full/41/4/588>

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

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters  
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:  
410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

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

# 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. (*Stroke*. 2010;41:588-593.)

**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.<sup>1,2</sup> Several lines of research suggest that PVCs may be a marker of higher subclinical atherosclerotic burden, higher arrhythmogenic potential,<sup>3-5</sup> 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.<sup>6</sup> Frequent PVCs are associated with impaired ventricular relaxation<sup>7</sup> and have the potential to remodel the heart.<sup>8,9</sup> In addition to their putative arrhythmogenic 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 stud-

ied.<sup>10</sup> 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

Received September 10, 2009; final revision received October 29, 2009; accepted November 4, 2009.

From the University of North Carolina at Chapel Hill (S.K.A., G.H., M.M., R.J.S.J.), Chapel Hill, NC; Wake Forest University School of Medicine (P.R.), Winston-Salem, NC; and University of Arizona (E.S.), Tucson, Ariz.

Correspondence to Ross J. Simpson, Jr, MD, PhD, Division of Cardiology, CB #7075, UNC, Chapel Hill, NC, 27599-7075. E-mail rsimpson@med.unc.edu.

© 2010 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.109.567800

published.<sup>11</sup> 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.<sup>12</sup> 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  $\geq$ 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.<sup>13</sup> Rhythm strips were classified 3 times by independent trained coders for total supraventricular, ventricular complexes, 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 the 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.<sup>14</sup> Further PVCs were classified by the frequency of their occurrence in a 2-minute rhythm strip, that is, single PVC; 2 to 3, and  $\geq$ 4.

### Other Covariates

Covariates known to be associated with PVCs, and other atherosclerotic and embolic events, including incident stroke events, were considered during analyses.<sup>1</sup> 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.<sup>15</sup>

Standardized and validated methods were used to collect information on covariates. Detailed information about of the characterization of prevalent CHD,<sup>16</sup> hypertension (Manual 11), diabetes (Manual

10), educational attainment, medication intake history,<sup>17</sup> and Cornell voltage estimated left ventricular mass<sup>18</sup> 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.csc.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.<sup>19</sup> 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.<sup>20</sup> 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.<sup>21</sup>

### 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

**Table 1. Characteristics of Participants by Presence of PVCs at Study Baseline and Follow-Up Stroke: The ARIC Study**

Characteristics*	Baseline PVCs†		Stroke During Follow-Up	
	Yes (n=899)	No (n=13 884)	Yes (n=729)	No (n=14 054)
Age, years	56.2 (5.2)	54.0 (5.7)	56.3 (5.6)	54.0 (5.7)
Women	46.9	56.0	48.3	55.9
Black	29.6	25.8	43.3	25.2
Education (no high school)	29.9	36.3	26.3	36.4
Education (high school, no college)	40.9	41.0	35.1	41.3
Prevalent CHD	12.7	4.1	10.2	4.3
Hypertension	44.9	33.6	59.9	33.0
Diabetes	13.0	9.2	24.0	8.7
Current smoking	26.8	25.8	35.5	25.3
Systolic blood pressure, mm Hg	124.8 (19.2)	120.8 (18.7)	131.9 (22.6)	120.5 (18.3)
Low-density lipoprotein cholesterol, mg/dL	137.6 (38.9)	137.6 (39.3)	143.6 (40.2)	137.3 (39.2)
High-density lipoprotein cholesterol, mg/dL	49.9 (16.6)	51.8 (17.1)	48.8 (16.2)	51.9 (17.1)
Body mass index, kg/m <sup>2</sup>	28.4 (5.3)	27.6 (5.3)	28.8 (5.5)	27.6 (5.3)
Heart rate, beats/min	68.0 (11.0)	66.6 (10.2)	67.7 (11.3)	66.6 (10.2)
Cornell voltage,‡ mV	1.29 (0.56)	1.20 (0.53)	1.44 (0.67)	1.19 (0.52)
Serum potassium, Meq/L	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)
Serum magnesium, mmol/L	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)
Angiotensin-converting enzyme inhibitor	4.7	3.0	6.0	2.9
β-blocker medication use	12.5	10.2	18.7	9.9
Calcium channel blocker use	5.7	3.2	5.9	3.2
Other antihypertension drugs	8.2	5.4	9.3	5.4
Digoxin	3.6	1.2	3.0	1.2
Antiarrhythmic	2.9	0.5	1.1	0.7
Overall incident stroke§	7.3	4.8	...	...
Thrombotic stroke§	4.2	3.4	...	...
Embolic stroke§	2.0	0.8	...	...
Death§	31.2	16.1	46.6	16.7
Stroke§ or death§	34.0	18.8	...	...
Average follow-up duration, years	13.8 (4.4)	15.1 (3.3)	9.4 (4.3)	15.3 (3.0)

\*Characteristics expressed as percentage or means with SD of participants in respective columns.

†PVC coded by investigators using 2-minute (3-lead ECG strips) at baseline.

‡Cornell voltage was calculated in those with QRS <120 ms with nonmissing values and not having prevalent CHD.

§Incident stroke and death from study enrollment (1987 to 1989) through December 31, 2004, expressed as cumulative percentage.

included in regression models because it was considered a potential intermediary in our hypothetical pathway linking PVC to stroke.

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).

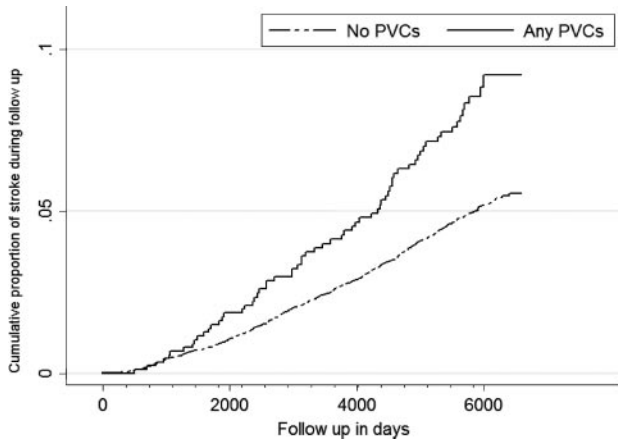
All statistical computations were performed using SAS software Version 9.1.3 (SAS Inc, Cary, NC) and STATA/IC Version 10 (StataCorp, College Station, Texas). A probability value of <0.05 for a 2-sided null hypothesis was considered statistically significant for main covariates. As is customary for tests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

epidemiological studies, a probability value of <0.2 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.



**Figure 1.** Cumulative proportion with stroke among any PVC (solid line, top, n=899 at start of follow-up) versus no PVC (dotted line, bottom, n=13 884 at start of follow-up) from the ARIC Study (1987 to 1989 through 2004).

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 adjustment for Cornell voltage. Furthermore, the estimates did not change appreciably after adjusting for baseline intake of medications such as  $\beta$ -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 3).

In the model presented in Table 2, the hazard ratio of incident stroke among those with single PVCs/2-minute, 2 to 3 PVCs/2-minute, and  $\geq 4$  PVCs compared with no PVCs were 1.55 (95% CI: 0.92 to 2.62), 1.51 (95% CI: 0.82 to 3.62), and 2.06 (95% CI: 1.24 to 3.42), respectively, without appreciable change in other estimates.

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 shown in Table 2. These estimates remained similar when using definite embolic stroke. In contrast, for stroke classified

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

Variables	Hazard Rate Ratios†	95% CIs		Pr> $\chi^2$
Any PVC‡	1.72	1.14	2.59	0.01
Age at intake per SD	1.41	1.30	1.53	<0.0001
High-density lipoprotein cholesterol per SD	0.94	0.86	1.03	0.19
Low-density lipoprotein cholesterol per SD	1.08	1.00	1.16	0.04
Potassium per SD	1.05	0.97	1.13	0.27
Magnesium per SD	0.93	0.87	1.01	0.08
Heart rate per SD	1.10	1.03	1.18	0.01
Race, black versus white	1.77	1.49	2.11	<0.0001
Gender, male versus female	1.38	1.17	1.63	0.00
Education, less than high school versus college	1.43	1.18	1.74	0.00
Education, high school versus college	1.09	0.90	1.33	0.36
Prevalent CHD	1.89	1.47	2.43	<0.0001
Hypertension	2.21	1.86	2.62	<0.0001
Current cigarette smoker	1.89	1.62	2.22	<0.0001
Diabetes	2.15	1.76	2.62	<0.0001
PVCs $\times$ hypertension	0.69	0.40	1.18	0.17
PVCs $\times$ diabetes	0.56	0.29	1.09	0.09

\*Incident stroke cases from study enrollment (1987 to 1989) through December 31, 2004.

†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.

as thrombotic, the hazard ratio comparing any PVCs versus no PVCs was 1.13 (0.78 to 1.65) among nondiabetics and 0.47 (0.21 to 1.67) among diabetics. On considering definite thrombotic stroke as the outcome, this hazard ratio was 1.03

**Table 3. Hazard Ratio for Stroke\* Contrasting Any PVC† Versus No PVC by Subgroup of Traditional Risk Factors: The ARIC Study**

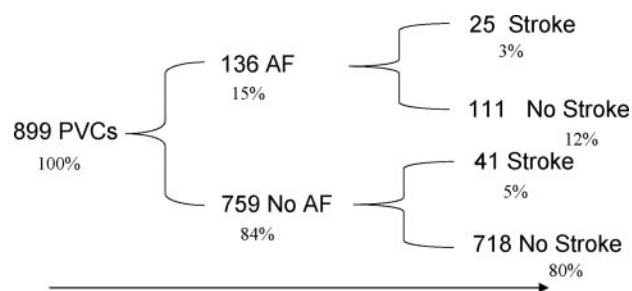
Subgroup	Hazard Ratio (95% CI)‡			Percent of Cohort
Diabetes	0.73	0.4	1.32	9
Hypertension	1.00	0.72	1.41	34
No diabetes and no hypertension	1.72	1.14	2.59	62
None of the four traditional risk factors§	2.09	1.21	3.58	44
Complete study sample	1.20	0.91	1.52	100

\*Incident stroke cases from study enrollment (1987 to 1989) through December 31, 2004.

†PVC coded by investigators using 2-minute (3-lead ECG strips) at baseline.

‡Estimates from models adjusted for age, gender, race, education, resting heart rate, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum K<sup>+</sup>, and serum Mg<sup>++</sup>; models were additionally adjusted for hypertension, diabetes, prevalent CHD, and smoking whenever appropriate.

§No diabetes, hypertension, smoking history, or CHD at study baseline.



**Figure 2.** Sketch showing the number (%) of ARIC study participants having at least single PVCs on a 2-minute rhythm strip at study baseline (1987 to 1989) and follow-up AF and stroke among them. Four participants with PVCs had missing information on incident AF and they did not have stroke. AF was diagnosed during follow-up duration using International Classification of Diseases discharge codes and ECG information from 3 yearly field center visits.

(0.62 to 1.72) among nondiabetics and 0.35 (0.11 to 1.11) among diabetics.

Lastly, the multivariable hazards of incident AF among those with any PVCs adjusted for age, gender, race, smoking status, heart rate, serum magnesium, serum potassium, prevalent CHD, diabetes, hypertension, low-density lipoprotein lipids, and high-density lipoprotein lipids was 1.56 (95% CI: 1.30 to 1.87) times higher than those with no PVCs. Figure 2 shows the cumulative proportion of follow-up AF and stroke events among those with PVCs.

## Discussion

In this large community-based cohort of white and black men and women in 4 locales of the United States, we find that PVCs are associated with incident stroke. Furthermore, this relationship is statistically significant and stronger in the subgroup without traditional risk factors for stroke such as diabetes or hypertension. Our results considering stroke subtype point toward a stronger association of PVCs with noncarotid artery embolic stroke than with thrombotic stroke (potentially caused by atherosclerosis in the cerebral circulation).

An earlier study has reported a similar but statistically nonsignificant association.<sup>10</sup> Despite the strength of 24-hour Holter recording to monitor premature complexes, this study was constrained by a small sample size, yielding only 58 incident stroke events and it included only men, mostly of white origin.<sup>10</sup> The large size of the ARIC cohort and the inclusion of women and black examinees as well as the sizeable number of incident stroke events classified as embolic and thrombotic allows us to explore this relationship with greater statistical power and by stroke subtype.

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.<sup>22</sup> 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.<sup>23</sup> It is interesting to note that despite the possibility of some misclassification of stroke subtype into as cardioembolic,<sup>20</sup> the estimates for definite and overall cardioembolic stroke

were similar. If this finding is replicated in future studies, individuals with high-frequency PVCs could be 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

1. Simpson RJ Jr, Cascio WE, Schreiner PJ, Crow RS, Rautaharju PM, Heiss G. Prevalence of premature ventricular contractions in a population of African American and white men and women: the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J*. 2002;143:535–540.
2. Rautaharju P, Rautaharju F. *Investigative Electrocardiography in Epidemiological Studies and Clinical Trials*. London: Springer; 2007.
3. Carrim ZI, Khan AA. Mean frequency of premature ventricular complexes as predictor of malignant ventricular arrhythmias. *Mt Sinai J Med*. 2005;72:374–380.
4. Meyerfeldt U, Schirdewan A, Wiedemann M, Schutt H, Zimmerman F, Luft FC, Dietz R. The mode of onset of ventricular tachycardia. A patient-specific phenomenon. *Eur Heart J*. 1997;18:1956–1965.
5. Myerburg RJ. Sudden cardiac death: epidemiology, causes, and mechanisms. *Cardiology*. 1987;74(suppl 2):2–9.
6. Malik M, Camm AJ. *Dynamic Electrocardiography*. Elmsford, NY: Blackwell Futura; 2004.
7. Topaloglu S, Aras D, Cagli K, Yildiz A, Cagirci G, Cay S, Gunel EN, Baser K, Baysal E, Boyaci A, Korkmaz S. Evaluation of left ventricular diastolic functions in patients with frequent premature ventricular contractions from right ventricular outflow tract. *Heart Vessels*. 2007;22:328–334.
8. Sun Y, Blom NA, Yu Y, Ma P, Wang Y, Han X, Swenne CA, van der Wall EE. The influence of premature ventricular contractions on left ventricular function in asymptomatic children without structural heart disease: an echocardiographic evaluation. *Int J Cardiovasc Imaging*. 2003;19:295–299.
9. Takemoto M, Yoshimura H, Ohba Y, Matsumoto Y, Yamamoto U, Mohri M, Yamamoto H, Origuchi H. Radiofrequency catheter ablation of premature ventricular complexes from right ventricular outflow tract improves left ventricular dilation and clinical status in patients without structural heart disease. *J Am Coll Cardiol*. 2005;45:1259–1265.
10. Engstrom G, Hedblad B, Juul-Moller S, Tyden P, Janzon L. Cardiac arrhythmias and stroke: increased risk in men with high frequency of atrial ectopic beats. *Stroke*. 2000;31:2925–2929.
11. The Atherosclerosis Risk In Communities (ARIC) study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989;129:687–702.
12. Jackson R, Chambless LE, Yang K, Byrne T, Watson R, Folsom A, Shahar E, Kalsbeek W. Differences between respondents and nonrespondents in a multicenter community-based study vary by gender ethnicity. The Atherosclerosis Risk In Communities (ARIC) study investigators. *J Clin Epidemiol*. 1996;49:1441–1446.
13. Vitelli LL, Crow RS, Shahar E, Hutchinson RG, Rautaharju PM, Folsom AR. Electrocardiographic findings in a healthy biracial population. Atherosclerosis Risk In Communities (ARIC) study investigators. *Am J Cardiol*. 1998;81:453–459.
14. Evenson KR, Welch VL, Cascio WE, Simpson RJ Jr. Validation of a short rhythm strip compared to ambulatory ECG monitoring for ventricular ectopy. *J Clin Epidemiol*. 2000;53:491–497.
15. Massing MW, Simpson RJ Jr, Rautaharju PM, Schreiner PJ, Crow R, Heiss G. Usefulness of ventricular premature complexes to predict coronary heart disease events and mortality (from the Atherosclerosis Risk In Communities cohort). *Am J Cardiol*. 2006;98:1609–1612.
16. Rosamond WD, Chambless LE, Folsom AR, Cooper LS, Conwill DE, Clegg L, Wang CH, Heiss G. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N Engl J Med*. 1998;339:861–867.
17. Shahar E, Folsom AR, Romm FJ, Bisgard KM, Metcalf PA, Crum L, McGovern PG, Hutchinson RG, Heiss G. Patterns of aspirin use in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J*. 1996;131:915–922.
18. Simpson RJ Jr, Cascio WE, Crow RS, Schreiner PJ, Rautaharju PM, Heiss G. Association of ventricular premature complexes with electrocardiographic-estimated left ventricular mass in a population of African-American and white men and women (the Atherosclerosis Risk In Communities). *Am J Cardiol*. 2001;87:49–53.
19. The National Survey of Stroke. National Institute of Neurological and Communicative Disorders and Stroke. *Stroke*. 1981;12:11–91.
20. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk In Communities (ARIC) cohort. *Stroke*. 1999;30:736–743.
21. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J*. 2009;158:111–117.
22. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455–2461.
23. Watanabe H, Tanabe N, Makiyama Y, Chopra SS, Okura Y, Suzuki H, Matsui K, Watanabe T, Kurashina Y, Aizawa Y. ST-segment abnormalities and premature complexes are predictors of new-onset atrial fibrillation: the Niigata Preventive Medicine Study. *Am Heart J*. 2006;152:731–735.