Background and Purpose—With the exception of atrial fibrillation (AF), little scientific attention has been given the associations between cardiac arrhythmias and incidence of stroke. We sought to study whether atrial and ventricular arrhythmias assessed during a 24-hour ambulatory ECG registration are associated with incidence of stroke.

Methods—The population-based cohort “Men Born in 1914” was examined with 24-hour ambulatory ECG registrations at 68 years of age. Four hundred two men without previous myocardial infarction or stroke were included, and 236 of them had hypertension ($160/95$ mm Hg or treatment). Fourteen-year rates of stroke (fatal and nonfatal) and all-cause mortality were updated from national and regional registers. Frequent or complex ventricular arrhythmias was defined as Lown class 2 to 5. A high frequency of atrial ectopic beats (AEB) was defined as the fifth quintile (ie, $\geq 218$ AEB per 24 hours).

Results—Fifty-eight men suffered a first stroke during the follow-up. Stroke rates (per 1000 person-years) among men with AF ($n=14$), with frequent AEB ($n=77$), and without AF or frequent AEB ($n=311$) were 34.5, 19.5, and 11.6, respectively. The corresponding values among men with hypertension were 40.7, 32.3, and 14.7, respectively. Frequent AEB (compared with absence of AF and frequent AEB) was significantly associated with stroke among all men (relative risk $= 1.9; 95\% \text{ CI}, 1.02$ to 3.4; $P=0.04$) and among hypertensive men (relative risk $= 2.5; 95\% \text{ CI}, 1.3$ to 4.8; $P=0.009$) after adjustments for potential confounders. The increased stroke rates among men with Lown class 2 to 5 did not reach statistical significance.

Conclusions—A high frequency of AEB is associated with an increased incidence of stroke. (Stroke. 2000;31:2925-2929.)

Key Words: arrhythmia ■ cerebrovascular disorders ■ electrocardiography

Subjects and Methods
Six hundred twenty-one men, representing a random 50% sample of all 68-year-old men living in Malmö, Sweden, were invited to participate in a prospective study on cardiovascular diseases when they were close to their 68th birthday. Five hundred men (80.5%) participated. The baseline examination included an examination of cardiovascular history and status. Previous studies from the cohort have shown that ventricular arrhythmias are associated with increased mortality and cardiac event rates. Frequent or complex ventricular arrhythmias have been reported in a sizeable proportion, approximately one third, of healthy elderly individuals. However, with the exception of AF, the associations between incidence of stroke and cardiac arrhythmias have received little scientific attention.

“Men Born in 1914,” from Malmö, Sweden, is a population-based prospective study of cardiovascular diseases and its major determinants. Previous studies from the cohort have shown that ventricular arrhythmias are associated with increased mortality and cardiac event rates. The objective of the present follow-up was to study whether incidence of stroke is associated with the occurrence of ventricular arrhythmias and atrial ectopic beats (AEB) assessed during 24-hour ambulatory ECG registrations.

Assessments of Health Status
Blood pressure was measured in the morning with the subjects in a sitting position. Pressure was measured to the nearest 5 mm Hg with a mercury sphygmomanometer and a 12×26-cm rubber cuff. Men with systolic blood pressure $\geq 160$ mm Hg or diastolic blood pressure $\geq 95$ mm Hg and men with medical treatment for hypertension were classified as hypertensive.

History of angina pectoris was assessed by means of the Rose questionnaire.
TABLE 1. Mortality and Stroke During 14 Years Among All Men in Relation to Findings From 24-Hour Ambulatory ECG Recordings

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Mortality</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Deaths, n (%)</td>
</tr>
<tr>
<td>Not AF or frequent AEB</td>
<td>311</td>
<td>130 (42)</td>
</tr>
<tr>
<td>Frequent AEB, not AF</td>
<td>77</td>
<td>40 (52)</td>
</tr>
<tr>
<td>AF</td>
<td>14</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Lown class 0–1</td>
<td>259</td>
<td>107 (41)</td>
</tr>
<tr>
<td>Lown class 2–5</td>
<td>143</td>
<td>74 (52)</td>
</tr>
<tr>
<td>All men</td>
<td>402</td>
<td>181 (45)</td>
</tr>
</tbody>
</table>

PY indicates person-years.

Smoking was assessed by means of a structured interview. Men who never smoked or who had stopped smoking at least 1 month before the examination were categorized as nonsmokers.

Total plasma cholesterol was analyzed at the laboratory of the Malmö University Hospital with standard methods. Blood samples for determination of lipids and glucose were drawn after a minimum fasting period of 8 hours. Diabetes mellitus was defined as fasting blood glucose ≥7.0 mmol/L or medication for diabetes mellitus. All cases were validated by review of hospital records.

Ambulatory 24-Hour ECG Recordings

The procedures of the 24-hour ECG recordings and analyses of arrhythmias were described previously.7,11 An ECG tape recorder (Oxford Medilog II, FM type) with 2 bipolar electrodes in the V2 and V6 positions was used. An interactive computer (Oxford Medilog MA 14/20) was used for interpretation of type of ventricular arrhythmia. In addition, all tapes were analyzed by a well-trained technician.

Ventricular arrhythmia was categorized with regard to number and type according to Lown and Wolf15; class 0, no ventricular ectopic beats; class 1, <720 per 24 hours; class 2, ≥720 per 24 hours; class 3, multifocal, bigeminal, or trigeminal; class 4a, couplets; class 4b, ventricular tachycardia; and class 5, R-on-T type. Frequent or complex ventricular arrhythmias were defined as Lown class 2 to 5.11,15

The following criteria were used for detection of AEB: a reduced RR interval of ≥25%, presence of a P wave, and a QRS width ≤0.12 seconds. Categorization of AEB is based on distribution of the present sample. High frequency was defined as the fifth quintile (ie, ≥218 AEB per 24 hours). Absence of P waves and irregular ventricular activity or irregular ventricular activity in presence of F waves was used as a criterion of AF. Men with single episodes or intermittent AF were classified as having AF.

Mortality Rates

All probands were followed from the baseline examination until their death or December 31, 1996. Mean follow-up time was 11.1±4.0 years (range, 0.3 to 14.3 years). Mortality data were obtained from the Mortality Register of the Swedish National Bureau of Statistics. In 59% the cause of death was based on autopsy or studies of hospital records. Mean follow-up time to the stroke event was 10.6±4.2 years (range, 0.3 to 14.3 years).

Statistical Analysis

The Mann-Whitney U test and Pearson’s $\chi^2$ test were used for comparisons of groups. The Kaplan-Meier method18 with Breslow statistics was used for comparisons of stroke and survival rates in relation to ECG findings. The Cox proportional hazard model19 was used to adjust these associations for potential confounders. Significance testing ($P<0.20$) of the cardiovascular risk factors in categories of cardiac arrhythmias was used to identify potential confounders. The fit of the proportional hazard model was confirmed by plotting the hazard functions in different categories of risk factors over time.

Results

Stroke and Death Rates

Fifty-eight men suffered a stroke during the follow-up, 6 had intracerebral hemorrhage (ICD-9 code 431), 36 an ischemic stroke (ICD-9 code 434), and 16 had an unspecified stroke (ICD-9 code 436). Eight (14%) of the subjects with strokes died within 28 days. In all, 181 (45%) died during the follow-up, 89 (49%) of them from cardiovascular disease (ICD-9 codes 390 to 448).

Two hundred thirty-six men (58.7%) had hypertension ($\geq160/95$ mm Hg or treatment). Forty-four of them had a stroke (4 intracerebral hemorrhage, 27 ischemic strokes, and 13 unspecified strokes). Fourteen strokes (2 intracerebral hemorrhage, 9 ischemic strokes, and 3 unspecified strokes) occurred among men with normal blood pressure. Stroke and death rates among men with hypertension were significantly higher than they were among men with normal blood pressure (stroke: 18.5 versus 7.5 per 1000 person-years, $P=0.002$; mortality: 46.8 versus 32.3 per 1000 person-years, $P=0.02$).

Incidence of Stroke and Death in Relation to Atrial and Ventricular Arrhythmias

Prevalence of men with AF, frequent AEB, and ventricular arrhythmias in Lown class 2 to 5 in the entire cohort and among men with hypertension is presented in Tables 1 and 2.

Rates of stroke were higher among men with a high frequency of AEB (19.5 versus 11.6 per 1000 person-years, $P=0.068$) and in men with AF (34.5 versus 11.6 per 1000 person-years; $P=0.007$) than it was among men without frequent AEB or AF (Table 1). Among men with hypertension, the stroke rates were similarly higher among men with frequent AEB (32.3 versus 14.7 per 1000 person-years; $P=0.01$) and among men...
with AF (40.7 versus 14.7 per 1000 person-years; \( P = 0.03 \)) (Table 2). The increased stroke rate among men with arrhythmias in Lown class 2 to 5 was not statistically significant (Tables 1 and 2).

Within the group with high frequency of AEB, the number of premature beats was higher among those who had a stroke during the follow-up (median number of AEB per 24 hours, 1988 [range, 272–12 355] versus 726 [range, 218 – 8152]; \( P = 0.02 \)). When the number of AEB among men with and without stroke was studied in relation to the circadian distribution, the difference in number of AEB was highest between 12 and 6 PM (median number of cases, 1274 [range, 29 –3587]; controls, 151 [range, 6 –2358]; \( P = 0.003 \)) and smallest between 0 and 6 AM (median number of cases, 242 [range, 8 –3013]; controls, 215 [range, 2–2328]; \( P = 0.39 \)).

### Cardiovascular Risk Factors in Relation to Occurrence of Arrhythmias

The distribution of cardiovascular risk factors in relation to occurrence of cardiac arrhythmias is presented in Table 3. There were no significant differences with regard to use of antihypertensive medication, systolic blood pressure, mean heart rate, smoking habits, alcohol consumption, plasma cholesterol, diabetes, or history of angina pectoris (all \( P > 0.20 \)) between men with and without a high frequency of AEB. Diastolic blood pressure was lower among men with a high frequency of AEB (90.7±10 versus 93.1±11 mm Hg; \( P = 0.16 \)) than it was among men with a low frequency of AEB. Distribution of cardiovascular risk factors in hypertensive men with and without a high frequency of AEB was also similar.

### Characteristics of Strokes With and Without Frequent AEB

Twenty-eight-day case fatality rate after stroke showed no significant differences between cases with and without frequent AEB (n=3 [20%] versus n=5 [13%], respectively). Median time from the baseline examination to the stroke event was 7.2 years (range, 0.4 to 13.8 years) among cases with frequent AEB and 8.5 years (range, 0.6 to 13.5 years) among cases without frequent AEB (\( P = \text{NS} \)). There was no significant overrepresentation of ischemic strokes in the group with high frequency of AEB.

With the purpose of exploring the extent to which strokes with a high frequency of AEB at baseline had developed AF...
at the time of the stroke event, the routine 12-lead resting ECGs at the time of the hospital admission were investigated. Among the 15 stroke patients who had frequent AEB at baseline, 6 had AF at the time of stroke, 8 had sinus rhythm, and in 1 case the resting ECG was unavailable.

**Multivariate Analysis**

The increased incidence of stroke among men with high frequency of AEB was statistically significant after adjustments for systolic blood pressure, history of angina pectoris, smoking, and diabetes (all men: relative risk = 1.9; 95% CI, 1.02 to 3.4; P = 0.04; hypertensive men: relative risk = 2.5; 95% CI, 1.3 to 4.8; P < 0.01) (Table 4).

**Discussion**

As in many other studies, hypertension was associated with an increased incidence of stroke. There were, however, substantial differences between hypertensive men with and without frequent AEB. A high frequency of AEB was significantly associated with an increased risk. This association was independent of other major risk factors.

Associations between AF and stroke have been described in many previous studies.\(^1\)\(-6\) Left ventricular hypertrophy, major T-wave inversion, and ST depression (ie, signs of hypertension and ischemic heart disease) are other resting ECG findings that have been associated with stroke.\(^6\)\(-20\)\(-24\)

However, few have studied incidence of stroke in relation to 24-hour ambulatory ECGs. Frishman et al\(^9\) reported significant association between cerebrovascular accidents among other subjects with slow heart rate (<60 bpm) or AV block. No significant association was found between cerebrovascular accidents and AF, atrial tachycardia, or ventricular arrhythmias. However, subjects with previous myocardial infarctions were included in their study, and the number of events was smaller.

To the best of our knowledge, this is the first study reporting frequent AEB to be an independent risk factor. Although AEB often is considered a benign phenomenon, it has been shown in clinical practice that frequent AEB could be an early sign of heart failure and may precede AF.\(^25\)

However, of the patients with frequent AEB at baseline, a majority had sinus rhythm at the time of the stroke event. Although it seems likely that a higher proportion developing AF contributes to the increased risk among men with frequent AEB, there also may be other explanations. Frequent AEB could be a marker of other risk factors, eg, severe and longstanding hypertension, asymptomatic atherosclerosis, or structural abnormalities that cause embolism. Frequent AEB could be a marker of mitral valve calcification or left atrial enlargement, which in turn could cause increased thrombus formation and embolism.\(^26\)

In has been shown that frequent or complex ventricular arrhythmias are common among older individuals both with and without evidence of atherosclerotic disease.\(^8\) The associated prognostic significance of ventricular arrhythmias is different, however, with increased mortality and cardiac event rates if frequent arrhythmias occur in individuals with atherosclerosis.\(^8\) Hypertensive men with frequent or complex arrhythmias had higher rates of stroke in the present study. This association did not reach significance, however. Whether the absence of a significant association between stroke and ventricular arrhythmias should be interpreted in terms of lack of effect or lack of statistical power due to the comparatively small number of individuals and events remains to be evaluated. With respect to AF, however, lack of statistical power seems to be the most likely explanation for the nonsignificant association, since only 14 men had AF during the ECG recording.

Change of exposure during follow-up is a source of bias inherent in all prospective studies of risk factors. Although use of antihypertensive therapy showed small differences between the groups at baseline, it is possible that men without ECG abnormalities used antihypertensive drugs more often during the follow-up. Even though this explanation seems unlikely, it remains a potential confounder.

Vital status was updated by data linkage with the National Cause of Death Registry. None was lost to follow-up. The Stroke Registry of Malmö has continuously been recording and validating all cerebrovascular events in Malmö since 1989. Ninety-seven percent of the cases were validated by studies of hospital records or autopsy. The comparatively high proportion of unspecified strokes could be explained by the fact that CT scan was not performed on all patients during the 1980s. According to other epidemiological studies from the city, there is no reason to believe that biased retrieval or validation of end points confounded the results.\(^27\)

Frequent AEB assessed by means of 24-hour ECG monitoring was associated with stroke in this population-based cohort of older men. We conclude that a high frequency of AEB is associated with an increased incidence of stroke.

**Acknowledgment**

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**TABLE 4. Multivariate Analysis of Atrial Arrhythmias in Relation to Stroke and All-Cause Mortality**

<table>
<thead>
<tr>
<th></th>
<th>All Men</th>
<th>Hypertensive Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroke Mortality</td>
<td>Stroke Mortality</td>
</tr>
<tr>
<td>Not frequent AEB, no AF</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Frequent AEB</td>
<td>1.9 (1.02–3.4)*</td>
<td>2.5 (1.3–4.8)†</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.2 (1.1–9.6)*</td>
<td>3.2 (0.92–11.4)‡</td>
</tr>
</tbody>
</table>

Values are relative risks (95% CI), adjusted for systolic blood pressure, diabetes, history of angina pectoris, and smoking.

\( ^* P < 0.04, ^† P < 0.009, ^‡ P = 0.07 \)
References


Cardiac Arrhythmias and Stroke: Increased Risk in Men With High Frequency of Atrial Ectopic Beats
Gunnar Engström, Bo Hedblad, Steen Juul-Möller, Patrik Tydén and Lars Janzon

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