Idiopathic atrial fibrillation as a risk factor for mortality

The Paris Prospective Study I

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**Aims** Idiopathic atrial fibrillation describes atrial fibrillation of unknown origin occurring without heart disease. Mortality is considered unaffected by idiopathic atrial fibrillation. We used the long follow-up period (23 years on average) of the Paris Prospective Study I to assess the mortality of idiopathic atrial fibrillation subjects in middle-aged men.

**Methods** 7746 working Frenchmen, aged 43–52 in 1967–72, underwent a physical examination plus ECG, answered questionnaires, and provided blood samples. Strict exclusion criteria were used to select idiopathic atrial fibrillation only, and men with known cardiac disease were further excluded from analysis. At 1 January 1994, vital status was unknown for 4.6% of the subjects. The analysis was conducted on the 6722 remaining subjects.

**Results** Twenty-five subjects had idiopathic atrial fibrillation at inclusion. The relative risk (and 95% confidence interval) associated with idiopathic atrial fibrillation was 4.22 [2.10–8.47] for cardiovascular mortality ($P=0.0001$) and 1.97 [1.14–3.40] for total mortality ($P=0.01$). When age, systolic blood pressure, cholesterol, body mass index and tobacco consumption were entered into a Cox model, idiopathic atrial fibrillation remained an independent risk factor for cardiovascular ($P=0.0008$) and total death ($P=0.04$).

**Conclusion** With a long follow-up period, idiopathic atrial fibrillation was associated with higher mortality in middle aged Frenchmen.

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**Key Words:** Idiopathic atrial fibrillation, mortality.

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**Introduction**

Atrial fibrillation is usually associated with an underlying cardiac disease[1–8] and various extra cardiac factors are associated with the occurrence of atrial fibrillation[9,10]. Idiopathic atrial fibrillation describes atrial fibrillation of unknown origin occurring without heart disease. Atrial histological studies in idiopathic atrial fibrillation did not reveal any characteristic lesions[11–13]. Prognosis was noted as unaffected by idiopathic atrial fibrillation in the literature[14–21], but most of the studies were carried out in clinic samples or in outpatient-derived populations[14,15,17,18,20,21].

The Framingham Heart Study recently suggested an excess mortality attributable to atrial fibrillation even in subjects free of preexisting cardiovascular disease[22].

We used the long follow-up period (23 years on average) of the Paris Prospective study I to assess the mortality of idiopathic atrial fibrillation in middle aged working men.

**Methods**

Details of the Paris Prospective Study I concerning recruitment, design and procedures have been described elsewhere[23]. Briefly, examination of 7746 native Frenchmen employed by the Paris Civil Service and aged 43 to 52 years, was carried out from 1967 to 1972. Subjects underwent an ECG and a physical examination conducted by a physician, provided blood samples for laboratory tests, and answered questionnaires administered...
by trained interviewers concerning sociodemographic factors, family and personal medical history and smoking habits. Three measurements of diastolic and systolic blood pressure were made during the examination, and the mean of those measurements was used for analysis.

Until retirement, the administrative department in charge of the population provided a list of deceased subjects annually. All available data relevant to the causes of death were collected from specific inquiries, i.e. medical records from hospital departments or general practitioners indicated by the relatives of the deceased. After retirement, cause of death was obtained from death certificates. The data were then reviewed by an independent medical committee. The ninth revision of the International Classification of Diseases was used for coding. Cardiovascular deaths include codes 390–458, 782, 795 and 798. The deadline of the follow-up period was 1 January 1994.

The vital status was not obtained for 355 subjects (4–6%). In order to select idiopathic atrial fibrillation only, subjects with preexisting cardiovascular diseases, i.e. medical history or clinical signs of angina, myocardial infarction, arteritis, cardiac failure, stroke, valvulopathy, dysthyroidism, and were considered as idiopathic atrial fibrillation subjects. The characteristics of idiopathic atrial fibrillation subjects are compared with those of the 6747 controls in Table 1. The rate of reported parental coronary disease was not significantly different between idiopathic atrial fibrillation subjects and controls. Between the two groups, there was no difference in age and in the percentage of subjects regularly practicing sport. There was a trend towards lower average tobacco consumption in the 5 years preceding the screening among the idiopathic atrial fibrillation subjects (7·8 vs 11·9 g . day

### Table 1 Characteristics and comparisons of the subjects with (n=25) and without idiopathic atrial fibrillation (n=6747) at inclusion in the Paris Prospective Study I

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects without idiopathic AF (n=6747)</th>
<th>Subjects with idiopathic AF (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental coronary diseases</td>
<td>823 (12·2%)</td>
<td>4 (16·0%)</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47·6±2·0</td>
<td>47·9±1·8</td>
<td>ns</td>
</tr>
<tr>
<td>Sport</td>
<td>1100 (16·3%)</td>
<td>2 (8·0%)</td>
<td>ns</td>
</tr>
</tbody>
</table>
| Tobacco consumption (g . day

### Results

**Characteristics of the subjects**

Of the 37/7746 (0·5%) subjects who had atrial fibrillation on an ECG at inclusion, 25/6772 (0·4%) had none of the following characteristics: medical history or signs of angina, myocardial infarction, arteritis, cardiac failure, stroke, valvulopathy, dysthyroidism, and were considered as idiopathic atrial fibrillation subjects. The characteristics of idiopathic atrial fibrillation subjects are compared with those of the 6747 controls in Table 1. The rate of reported parental coronary disease was not significantly different between idiopathic atrial fibrillation subjects and controls. Between the two groups, there was no difference in age and in the percentage of subjects regularly practicing sport. There was a trend towards lower average tobacco consumption in the 5 years preceding the screening among the idiopathic atrial fibrillation subjects (7·8 vs 11·9 g . day

**Statistical analysis**

Fisher’s exact tests were used for small samples. Chi-square and Student’s t-tests were used otherwise. Due to the skewed distribution of triglycerides, log-transformed values were used in the analysis. Comparison of ranks (Wilcoxon’s test) was used for tobacco consumption. Relative risks of mortality were estimated by Cox proportional hazards model. Relative risks are given non adjusted, and then adjusted for all confounding factors.
Causes of mortality

Among the idiopathic atrial fibrillation subjects, 13 deaths occurred during follow-up, including eight cardiovascular deaths: no stroke-related death, three ischaemic cardiac deaths, two sudden deaths, two deaths due to cardiac failure and one death due to arrhythmia. Subjects with idiopathic atrial fibrillation had the same non-cardiovascular death rate as controls (20% vs 21%), a four-fold cardiovascular death rate (32% vs 8%, \( P = 0.001 \)), and an higher total death rate (52% vs 29%, \( P = 0.01 \)).

Survival

The relative risk (and 95% confidence interval) associated with idiopathic atrial fibrillation was 4.22 [2.10–8.47] for cardiovascular mortality (\( P = 0.001 \)) and 1.97 [1.14–3.40] for total mortality (\( P = 0.01 \)).

When age, systolic blood pressure, cholesterol, body mass index and tobacco consumption were simultaneously entered into the model (Table 2), idiopathic atrial fibrillation remained an independent risk factor for total (\( P = 0.02 \)) and cardiovascular death (\( P = 0.0001 \)) with almost unchanged relative risks.

Discussion

The prevalence of idiopathic atrial fibrillation depends on the study population and on the criteria used for the diagnosis. The low prevalence of idiopathic atrial fibrillation in our study (0.4%) is explained by our middle-aged male working population, and by the severe exclusion criteria used for the diagnosis of idiopathic atrial fibrillation.

Idiopathic atrial fibrillation and mortality

Despite lower tobacco consumption, the idiopathic atrial fibrillation subjects have a four-fold higher cardiovascular mortality than controls (\( P = 0.001 \)). This is at variance with most other studies which concluded that the prognosis of idiopathic atrial fibrillation was unaffected. It may be that in the other studies the subjects were generally older and/or in hospital populations with a higher mortality among controls than in the present population, or with too short follow-up durations [14–18,20,21].

A significant increase in stroke occurrence in the group with idiopathic atrial fibrillation compared with controls has already been described [19]. More recently, the Framingham Study confirmed that atrial fibrillation was an independent hazard in persons with overt cardiac disease, and suggested that excess mortality was directly attributable to atrial fibrillation, even in the absence of pre-existing cardiovascular disease in subjects 55 to 94 years of age (mean age=73.7 years) [22].

Two other studies were already reporting a higher mortality rate among idiopathic atrial fibrillation subjects compared with controls. Kulbertus et al. [25] found a three-fold cardiovascular mortality compared with controls in 29 ambulatory subjects (mean age=68.7 years) with idiopathic atrial fibrillation discovered on an ECG and followed for 6 years; but in their study, a physical examination was not done. From the Insurance Industry’s Medical Information Bureau [26], Gajewski et al. noted that among 126 subjects (mean age about 55 years) with chronic atrial fibrillation and no major associated condition, total mortality during 3.3 years of follow-up was about eight times higher than in the standard insurance table. As pointed out by the authors, supporting diagnostic information available in the medical part of life-insurance applications is often limited, so that underlying cardiovascular disease might have been neglected or hidden.

Study limitations

Doppler echocardiography was not available in 1970. It is possible that the use of Doppler echocardiography might have discovered some underlying cardiac diseases if performed in our cohort study. However, there was no significant difference between subjects with and subjects without idiopathic atrial fibrillation in terms of parental

### Table 2

Multivariate adjusted relative risk (95% confidence intervals) of total and cardiovascular mortality in the Paris Prospective Study I

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total mortality RR (95% confidence interval)</th>
<th>( P ) value</th>
<th>Cardiovascular mortality RR (95% confidence interval)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic atrial fibrillation</td>
<td>1.95 [1.13–3.37]</td>
<td>0.02</td>
<td>4.31 [2.14–8.68]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age at inclusion</td>
<td>1.03 [1.01–1.11]</td>
<td>0.04</td>
<td>1.08 [0.98–1.19]</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.44 [1.38–1.51]</td>
<td>0.0001</td>
<td>1.51 [1.39–1.63]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.00 [0.96–1.04]</td>
<td>ns</td>
<td>1.24 [1.14–1.35]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.89 [0.85–0.94]</td>
<td>0.0001</td>
<td>1.00 [0.92–1.10]</td>
<td>ns</td>
</tr>
<tr>
<td>Tobacco consumption</td>
<td>1.40 [1.34–1.45]</td>
<td>0.0001</td>
<td>1.31 [1.22–1.41]</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Tobacco consumption is the average consumption in the 5 years preceding the screening expressed in g . day \(^{-1} \). Increased risk of an event for one standard deviation rise in variables including age at inclusion (SD=2 years), systolic blood pressure (SD=20 mmHg), cholesterol (SD=43 mg . day \(^{-1} \)), body mass index (SD=3.3 kg . m \(^{-2} \)) and tobacco consumption (SD=10.6 g . day \(^{-1} \)).
history of coronary disease, age, body mass index and ECG pattern. Subjects had no murmur at clinical examination, so the existence of an actual valvular disease remains unlikely. Moreover, they had no medical history or ECG pattern of ischaemic heart disease.

The possible influence of higher blood pressure on the occurrence of atrial fibrillation may be suspected, but no excess of left ventricular hypertrophy pattern on the ECG was observed in the cases. Even if it remains unlikely, we cannot exclude the possibility that knowledge of the presence of atrial fibrillation in the deceased may have influenced the assignment of the cause of death. Because of the limited size of the idiopathic atrial fibrillation group, specific causes of cardiovascular death should be interpreted with caution.

**Conclusion**

Our results suggested an increased mortality associated with idiopathic atrial fibrillation in middle-aged Frenchmen. Idiopathic atrial fibrillation could be the first sign of an underlying cardiovascular disorder. Thus, idiopathic atrial fibrillation clearly requires clinical attention. Further studies are needed in order to better understand the physiopathology of this disorder.

**References**


