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# The occurrence of cardiovascular disease during 5-year follow-up in patients with idiopathic atrial fibrillation

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## Aims

Idiopathic atrial fibrillation (AF) may be an expression of as yet undetected underlying heart disease. We found it useful for clinical practice to study the long-term development of cardiovascular disease (CVD) in patients diagnosed with idiopathic AF.

## Methods and results

Forty-one consecutive idiopathic AF patients ( $56 \pm 10$  years, 66% male) were compared with 45 healthy control patients in permanent sinus rhythm. Patients were free of hypertension, antihypertensive and antiarrhythmic drugs, diabetes, congestive heart failure, coronary artery or peripheral vascular disease, previous stroke, thyroid, pulmonary and renal disease, and structural abnormalities on echocardiography. Baseline characteristics and echocardiographic parameters were equal in AF cases and controls. During a mean follow-up of  $66 \pm 11$  months, CVD occurred significantly more often in idiopathic AF patients compared with controls (49 vs. 20%,  $P = 0.006$ ). Patients with idiopathic AF were significantly younger at the time of their first CV event compared with controls ( $59 \pm 9$  vs.  $64 \pm 5$  years,  $P = 0.027$ ), and had more severe disease. Multivariable Cox regression analysis revealed that age, a history of AF, and echocardiographic left ventricular wall width were significant predictors of CVD development.

## Conclusion

Patients originally diagnosed with idiopathic AF develop CVD more often, at younger age, and with a more severe disease profile compared with healthy sinus rhythm control patients. The detection and treatment of CVD in an early stage could improve the prognosis of these patients. At present it seems prudent to regularly check idiopathic AF patients for the insidious development of CVD.

## Keywords

Idiopathic atrial fibrillation • Cardiovascular disease • Follow-up

## Introduction

Idiopathic atrial fibrillation (AF) refers to the occurrence of the arrhythmia in the absence of a cardiovascular or pulmonary disease generating the pathophysiological substrate for the arrhythmia. Follow-up data in patients diagnosed with idiopathic AF are sparse and mainly based on two large observational population studies.<sup>1–3</sup>

Data from the Olmsted County database suggest that idiopathic AF is a benign disease with comparable risk of thromboembolism, congestive heart failure, and mortality as the general population. In contrast, data from the Framingham Heart Study and the Paris

Prospective Study show that idiopathic AF is associated with increased mortality and co-morbidity.<sup>1–4</sup> Presumably, differences regarding the definition of idiopathic AF in these studies are the main cause of these ambivalent results. Translating the data of these studies into daily clinical practice is not easily established due to the long follow-up duration (mean of 23 years), and the focus on the occurrence of major adverse cardiovascular and cerebrovascular events [MACCE: death, stroke/transient ischaemic attack (TIA), myocardial infarction, embolism, or major bleeding] instead of cardiovascular disease (CVD) itself. More recent observational studies show that ageing, development of CVD, and

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## What's new?

- Idiopathic AF is often described as a benign disease; this study shows that in clinical practice almost half of the patients originally diagnosed with idiopathic AF develops CVD within merely 5 years follow-up.
- Cardiovascular disease develops not only more often, but also at younger age and with a more severe disease profile in idiopathic AF patients compared with healthy sinus rhythm controls.
- Patients who developed CVD during follow-up more often showed an increase in atrial size over time compared with patients who did not develop CVD.

increased left atrial (LA) volume relate to long-term prognosis of idiopathic AF patients.<sup>2,5,6</sup>

The detection and treatment of CVD in an early stage could improve the prognosis of these patients. Since idiopathic AF may be an expression of as yet undetected underlying heart disease, we found it useful for clinical practice to study the development of CVD over time in patients diagnosed with idiopathic AF.

## Methods

### Study population

We prospectively studied 41 consecutive idiopathic AF patients and 45 healthy sinus rhythm control patients, who were referred to the outpatient clinic of one of our cardiologists (RGT) between 2004 and 2007 for a standard transthoracic echocardiographic examination (in the work up for AF or for cardiovascular screening purpose in the sinus rhythm control patients). The study was approved by the local Ethics Committee and complied with the declaration of Helsinki. Informed consent of all patients was obtained.

Atrial fibrillation patients had to be in AF at time of enrolment or had a previous documented history of paroxysmal or persistent AF defined as a documented episode of AF lasting 30 s or more. Idiopathic AF and healthy sinus rhythm were strictly defined as the absence of any CVD including hypertension [no antihypertensive drug use (diuretics, angiotensin-converting enzyme inhibitors, aldosterone receptor blockers, aldosterone receptor antagonists, non-dihydropyridine calcium antagonists, other), all previously recorded systolic blood pressures not exceeding 140 mmHg, diastolic blood pressures not exceeding 90 mmHg, and absence of left ventricular hypertrophy (interventricular septum width  $>10$  mm, posterior wall width  $>10$  mm)], diabetes (fasting blood glucose  $>7.0$  mmol/L), or hypercholesterolaemia (total fasting cholesterol  $>6.4$  mmol/L and no statin use). In addition, no coronary artery disease (i.e. absence of typical exercise-related angina pectoris, an exercise stress test with significant ST-segment depression, previous acute coronary syndrome, percutaneous or surgical coronary revascularization, or previous angiographically documented coronary disease), no peripheral vascular disease (intermittent claudication, or previous percutaneous or surgical revascularization), no congestive heart failure (no clinical signs or symptoms, left ventricular ejection fraction  $>50\%$ , normal diastolic function parameters), no previous stroke, no thyroid or pulmonary disease, no significant renal dysfunction (estimated MDRD<sup>7</sup> glomerular filtration rate  $<60$  mL/min), no malignancy,

and no evidence for structural CVD on echocardiography including valvular heart disease.

During follow-up we collected all emerging CVDs, including cardiovascular death, thromboembolic complications (stroke, TIA), congestive heart failure, coronary artery disease (acute coronary syndrome, percutaneous or surgical coronary revascularization, or angiographically documented coronary disease with angina pectoris), and new onset hypertension [antihypertensive drug use (diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, aldosterone receptor antagonists, dihydropyridine calcium-channel blockers), systolic blood pressures exceeding 140 mmHg, diastolic blood pressures exceeding 90 mmHg, or development of left ventricular hypertrophy (interventricular septum width  $\geq 10$  mm, posterior wall width  $\geq 10$  mm, according to the American Society of Echocardiography-convention) during follow-up echocardiography].

### The electrocardiogram

At the time of inclusion and during follow-up, all patients underwent 12-lead electrocardiographic (ECG) recording obtained in the supine position (MAC 5000, Marquette Medical Systems, Milwaukee, WI, USA).

### Echocardiographic examination

The echocardiographic examination consisted of a standard two-dimensional echocardiogram, including M-mode and Doppler echocardiography (Sonos 5500, Philips Medical Systems, Andover, MS, USA) during continuous ECG monitoring according to the recommendations as described in the American Society of Echocardiography guidelines. After we obtained baseline echocardiographic data, all measurements for study purposes were made by an independent observer who was blinded for arrhythmia history and other patient characteristics. Echocardiography during follow-up was left at the discretion of the treating physician.

### Data collection

Patient characteristics, including medication, (arrhythmia) history, ECGs, visits to cardiac emergency department, hospital admissions, and major cardiovascular events at the time of echocardiography and during follow-up were obtained and cross-checked by two independent observers. Data were derived from the patient charts (both hospital and general practitioner), electronic medical records and the electronic ECG database, which stores all ECGs and Holter recordings, performed in our hospital. Progression of AF was defined as follows: development of new-onset AF during follow-up in control patients or paroxysmal AF at baseline becoming persistent or permanent AF during follow-up. Since the Maastricht University Medical Centre has a strong regional community care function, none of the patients were lost to follow-up. At the end of follow-up, general practitioners were contacted in order to obtain additional follow-up data.

### Statistical analysis

Continuous variables are expressed as mean and standard deviation; categorical variables are expressed as absolute numbers and percentages.

Baseline variables were compared with an independent *T*-test (two-tailed) after performing Levene's test for equality of variances in all normally distributed continuous variables and Mann–Whitney test (two-tailed) in all not normally distributed variables. Categorical variables were tested with two-sided Fisher's exact test.

All parameters showing a significant Cox regression univariate relation with the occurrence of CVD during follow-up (age, AF history,

posterior wall width) were included as covariates in a Cox regression model (retention level set at 0.1), odds ratios and 95% confidence intervals were calculated and results were checked for collinearity (off note, Vitamin K antagonist (VKA) use and interventricular septum width were not included since these are directly related to respectively AF history and posterior wall width).

Statistical analysis was performed with SPSS statistical software (SPSS, Inc. release 18.0) and statistical significance was assumed for  $P < 0.05$ .

**Table 1** Baseline characteristics in patients with sinus rhythm compared with patients with idiopathic atrial fibrillation

	Sinus rhythm (n = 45)	Atrial fibrillation (n = 41)	P value
Demographics			
Age (median, interquartile range)	57 (46–62)	58 (46–64)	0.465 <sup>a</sup>
Male	23 (51)	27 (66)	0.194 <sup>b</sup>
Body mass index (kg/m <sup>2</sup> )	26 (4)	27 (4)	0.348 <sup>c</sup>
AF history duration (months) (median, interquartile range)	–	1 (0.6–11)	
Medication			
Oral anticoagulation	0	14 (34)	<0.001 <sup>b</sup>
Aspirin	5 (11)	18 (44)	0.001 <sup>b</sup>
Beta-blocker	7 (16)	13 (32)	0.124 <sup>b</sup>
ECG			
Heart rate (b.p.m.)	70 (12)	66 (11)	0.176 <sup>c</sup>
P-wave duration (ms)	86 (17)	88 (20)	0.521 <sup>c</sup>
PQ duration (ms)	153 (29)	158 (24)	0.304 <sup>c</sup>
QRS duration (ms)	93 (17)	93 (11)	0.987 <sup>c</sup>
QTc duration (ms)	411 (19)	410 (18)	0.820 <sup>c</sup>
Echocardiography			
Aorta diameter (mm)	33 (3)	34 (4)	0.056 <sup>c</sup>
Left atrial diameter (mm)	38 (4)	39 (5)	0.254 <sup>c</sup>
Left ventricular end diastolic diameter (mm)	48 (4)	49 (4)	0.191 <sup>c</sup>
Left ventricular end systolic diameter (mm)	32 (4)	33 (3)	0.261 <sup>c</sup>
Interventricular septum width (mm)	8.7 (0.9)	8.6 (0.8)	0.763 <sup>a</sup>
Posterior wall width (mm)	8.4 (0.8)	8.5 (0.7)	0.693 <sup>a</sup>
Left ventricular ejection fraction (%)	62 (5)	62 (4)	0.976 <sup>c</sup>

Data are presented as mean ( $\pm$  SD) or n (%) unless otherwise specified.

<sup>a</sup>Non-normal distribution, Mann–Whitney U test.

<sup>b</sup>Categorical data, Fisher's exact test.

<sup>c</sup>Normal distribution, Levene's independent samples T-test.

## Results

The overall mean (SD) age was 54 (11) years and just over half of patients was male (58%). Baseline characteristics, ECG, and standard echocardiographic parameters were equal in AF cases and controls (Table 1). Particularly, mean  $\pm$  SD age ( $56 \pm 10$  vs.  $53 \pm 12$  years,  $P = 0.465$ ), P-wave duration ( $88 \pm 20$  vs.  $86 \pm 17$  ms,  $P = 0.521$ ) and LA diameter ( $39 \pm 5$  vs.  $38 \pm 4$  mm,  $P = 0.254$ ) did not differ between AF patients and controls. A few sinus rhythm patients were on aspirin or a beta-blocker because their referring physician deemed these drugs necessary due to the suspicion of CVD (not found at enrolment after full work-up including echocardiography). A total of 14 (34%) AF patients used oral anticoagulation despite low cardiovascular risk profile. Atrial fibrillation duration showed a statistically significant but weak correlation to LA size (Spearman's correlation coefficient: 0.365,  $P = 0.024$ ).

Follow-up was completed in all patients; mean follow-up duration was  $66 \pm 11$  months (Table 2). Cardiovascular disease occurred significantly more often in idiopathic AF patients compared with sinus rhythm controls (49 vs. 20%,  $P = 0.006$ ). The Kaplan–

**Table 2** Atrial fibrillation progression, cardiovascular disease, and medication during follow-up

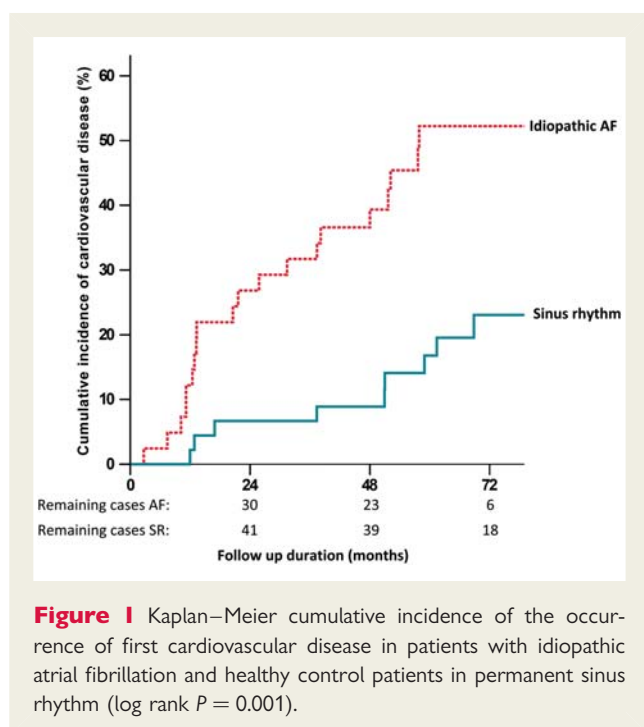
	Sinus rhythm (n = 45)	Atrial fibrillation (n = 41)	P value
Demographics			
AF progression in follow-up	2 (4)	6 (15)	0.144 <sup>c</sup>
Visits cardiac emergency department	2 (4)	21 (66)	<0.001 <sup>c</sup>
Cardiovascular (related) disease in follow-up <sup>a</sup>			
Cardiovascular death	0	1 (3)	1.0 <sup>c</sup>
Myocardial infarction	0	1 (3)	1.0 <sup>c</sup>
Cerebrovascular accident	0	2 (5)	0.218 <sup>c</sup>
Congestive heart failure	0	3 (8)	0.100 <sup>c</sup>
Coronary artery disease	4 (9)	5 (12)	0.299 <sup>c</sup>
New onset hypertension	7 (16)	12 (30)	0.191 <sup>c</sup>
Medication			
Oral anticoagulation	1 (2)	18 (45)	<0.001 <sup>c</sup>
Aspirin	10 (22)	15 (38)	0.231 <sup>c</sup>
Beta-blocker	5 (12)	12 (30)	0.058 <sup>c</sup>
Statins	7 (16)	7 (18)	1.000 <sup>c</sup>
Antihypertensive drug use <sup>b</sup>	7 (16)	12 (30)	0.191 <sup>c</sup>

Data are presented as mean ( $\pm$  SD) or n (%).

<sup>a</sup>The tabulations of cardiovascular diseases during follow-up include the first event for each patient.

<sup>b</sup>ACE-inhibitor, angiotensin receptor blocker, diuretics, calcium channel blocker.

<sup>c</sup>Categorical data, Fisher's exact test.



Meier 6-year cumulative risk for occurrence of CVD was significantly increased for patients with idiopathic AF (Figure 1).

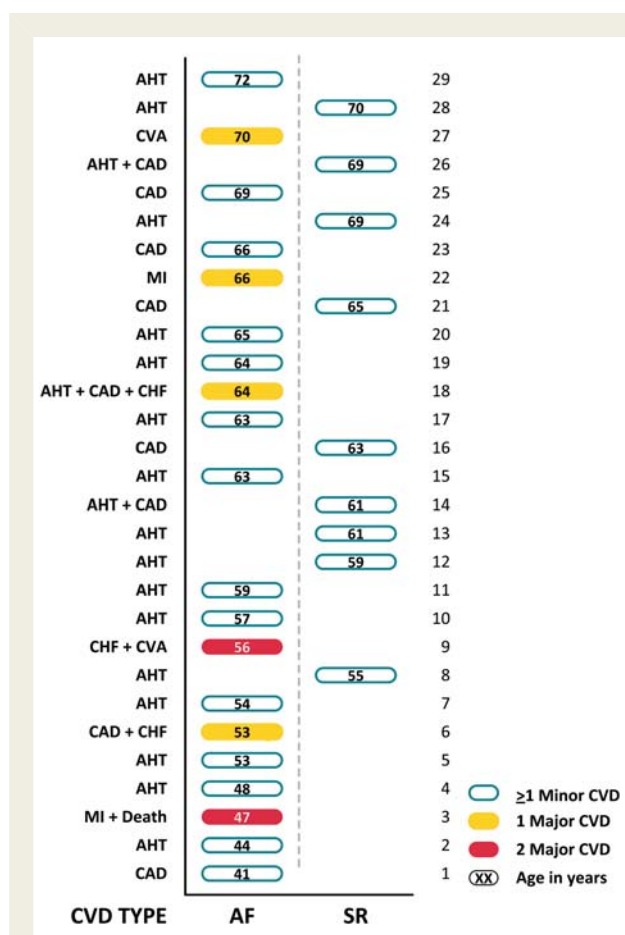
Three patients (7%) with idiopathic AF died (one due to myocardial infarction, one due to malignancy, and the other developed a cerebrovascular accident and died later in follow-up due to malignancy), whereas none of the control patients died during follow-up. Hypertension (33 vs. 16%,  $P = 0.123$ ) and coronary artery disease (12 vs. 9%,  $P = 0.299$ ) developed most frequently. Patients with idiopathic AF were significantly younger at the time of cardiovascular event or associated disease ( $59 \pm 9$  vs.  $64 \pm 5$  years,  $P = 0.027$ ) and had developed a more severe disease profile compared with controls (Figure 2).

Echocardiography during follow-up was available in 34 patients (20 AF, 14 controls). Left atrial diameter increased in 23 patients [AF: 15 (75%) vs. SR: 8 (57%),  $P = 0.485$ ] with a mean increase of  $3.0 \pm 4$  mm in patients with idiopathic AF vs.  $0.8 \pm 3$  mm in controls ( $P = 0.099$ ). Patients who developed CVD during follow-up more often showed an increase in atrial size compared with patients who did not develop CVD [17 (90%) vs. 6 (40%),  $P = 0.003$ ] (Figure 3).

The following baseline parameters showed a significant Cox regression univariate relation with the occurrence of CVD during follow-up: age, AF history, VKA use, interventricular septum width, and posterior wall width (Table 3). Multivariable Cox regression analysis revealed that age, a history of AF, and posterior wall width were predictors of CVD development (Table 4).

## Discussion

This study is one of the few following idiopathic AF patients for the development of CVD in general instead of focusing on major cardio- and cerebrovascular events only, and comparing them

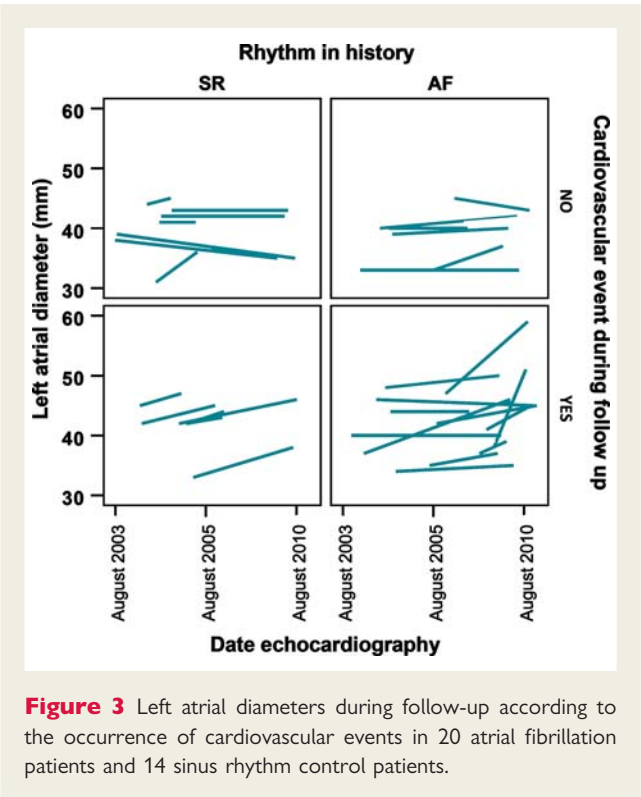


**Figure 2** Occurrence and severity of cardiovascular disease in follow-up per patient and according to age in patients with idiopathic atrial fibrillation and healthy control patients in permanent sinus rhythm. Minor cardiovascular disease: arterial hypertension (AHT), coronary artery disease (CAD); Major CVD: congestive heart failure (CHF), cerebrovascular accident (CVA), myocardial infarction (MI), death.

with patients in sinus rhythm without a cardiovascular diagnosis. It shows that in clinical practice almost half of the patients originally diagnosed with idiopathic AF develops CVD within merely 5 years follow-up. Cardiovascular disease develops more often, at younger age and with a more severe disease profile, in these patients compared with healthy sinus rhythm controls. This suggests that idiopathic AF is an expression of as yet undetected underlying CVD and that these patients should be checked regularly for the development of CVD.

Longitudinal studies on idiopathic AF are rare and the definitions used in these studies are mostly not identical and often lenient. The presence of arterial hypertension for instance was not an exclusion criterion in the Framingham Heart study on idiopathic atrial fibrillation.<sup>1</sup> We used a very strict definition for idiopathic AF so riskwise, all patients were at low risk and similar at the outset. Yet, almost half of the patients with idiopathic AF developed CVD or MACCE. This suggests that not only advanced AF but also idiopathic AF is associated with CVD and events. To what extent AF on itself contributes is difficult to say. With increased





levels of thrombogenesis and uncontrolled heart rate, AF could act as a mechanism in the development of stroke and congestive heart failure.<sup>8–11</sup> But it is difficult to find a similar role for AF in the development of arterial hypertension (i.e. AF may induce hypertension through concealed insidious adrenergic activation due to high heart rates) or coronary artery disease.<sup>12,13</sup> In these cases, AF could be seen as a whistleblower of as yet undetected, clinically concealed coronary artery disease, or arterial hypertension.

Arterial hypertension is a major risk factor for the development of AF and cardiovascular events but is often not recognized. This so called masked or latent hypertension has been described in patients initially diagnosed with idiopathic AF.<sup>14,15</sup> Although patients with hypertension or left ventricular hypertrophy were excluded in the present study, posterior wall width—although within normal limits—was a predictor of CVD. This might suggest the presence of masked hypertension or pre-hypertension (systolic blood pressure of 120–139 mmHg and diastolic blood pressure of 80–89 mmHg) in patients participating in this study. It also suggests that even normal wall sizes show a variation representing preclinical disease once wall width is found to be at the high end of normal. These patients seem to be at an increased risk of developing CVD or AF compared with those with normal blood pressure levels.<sup>16–19</sup> The present study corroborates the findings by Katritsis et al., supporting the notion that hypertension may develop or become apparent in many idiopathic AF patients (30% during 5-year follow-up) and emphasizes the importance of regular 24 h ambulatory blood pressure monitoring and adequate treatment of early hypertension in patients with idiopathic AF since it relates to their vascular prognosis.

Many clinical parameters are only indirectly related to AF. However, the true ‘scene of calamity’ are the atria. Increased LA

**Table 3** Baseline characteristics in patients who did not vs. did develop cardiovascular disease during follow-up

	No CVD (n = 56)	≥1 CVD (n = 29)	P value
Demographics			
Age	52 (12)	59 (8)	0.003 <sup>a</sup>
Male	31 (54)	19 (66)	0.363 <sup>b</sup>
Body mass index (kg/m <sup>2</sup> )	25 (4)	28 (4)	0.172 <sup>c</sup>
Atrial fibrillation in history	21 (37)	20 (69)	0.005 <sup>b</sup>
Follow-up duration (months)	67 (11)	65 (10)	0.609 <sup>a</sup>
Medication			
Oral anticoagulation	5 (9)	9 (31)	0.013 <sup>b</sup>
Aspirin	15 (26)	8 (28)	1.0 <sup>b</sup>
Beta-blocker	13 (23)	7 (24)	1.0 <sup>b</sup>
Echocardiography			
Aorta diameter (mm)	33 (3)	34 (4)	0.168 <sup>c</sup>
Left atrial diameter (mm)	38 (4)	41 (4)	0.447 <sup>c</sup>
Left atrial volume (cc)	51 (17)	57 (17)	0.744 <sup>c</sup>
Left ventricular end diastolic diameter (mm)	48 (4)	50 (5)	0.402 <sup>c</sup>
Left ventricular end systolic diameter (mm)	32 (3)	34 (4)	0.109 <sup>c</sup>
Interventricular septum width (mm)	8.4 (0.8)	9.0 (0.9)	0.006 <sup>a</sup>
Posterior wall width (mm)	8.3 (0.6)	8.8 (0.8)	0.005 <sup>a</sup>
Left ventricular ejection fraction (%)	63 (4)	61 (5)	0.294 <sup>c</sup>

Data are presented as mean (±SD) or n (%).  
<sup>a</sup>Non-normal distribution, Mann–Whitney U test.  
<sup>b</sup>Categorical data, Fisher’s exact test.  
<sup>c</sup>Normal distribution, Levene’s independent samples T-test.

**Table 4** Multivariable Cox regression analysis: demographic and clinical variables related to occurrence of cardiovascular disease

	OR	95% CI	P
History of AF	3.265	1.470–7.250	0.004
Posterior wall width (mm)	1.993	1.249–3.181	0.004
Age (years)	1.059	1.013–1.106	0.010

size is associated with increased risk of AF onset and recurrence, other CVD and mortality.<sup>6,20</sup>

In this study, LA sizes at the outset were equal between patients with and without AF and were not related to the occurrence of CVD in the overall population. On the other hand, patients with LA increase during follow-up were prone to develop CVD. These results confirm previous findings during three decades follow-up in idiopathic AF patients.<sup>6</sup>

Idiopathic AF is often described as a benign disease.<sup>3,21</sup> However, our data suggests that not every idiopathic AF patient has the same cardiovascular prognosis. It seems that patients with idiopathic AF can be divided into two groups following divergent courses regarding CVD development. Those who are at true low risk on one hand, and those with deterioration of CVD in the years after idiopathic AF diagnosis as reflected by AF progression, development of CVD and events. This study shows that within 5 years follow-up almost 50% of the patients initially suffering from idiopathic AF develops CVD. During long-term follow-up in the Olmsted County population, the same number of those with idiopathic AF (50%) developed *major* adverse cardiovascular events.<sup>6</sup> It is plausible that the patients in our study are the same as the patients in the Olmsted County cohort but caught somewhat later in their vascular career. Apparently, it is possible to identify these patients since they have in common that atrial size appears to increase during follow-up. At present, it seems judicious to closely follow these patients at the outpatient department for the development of CVD. Repeated blood pressure measurements and echocardiography (including LA size and posterior wall width) seem prudent in patients with idiopathic AF.

## Limitations

The study result was obtained in a relatively small and—by its nature—highly selected population and should be reproduced in other cohorts. Nevertheless, it seems reasonable to state that a substantial part of patients originally diagnosed with idiopathic AF develop CVD during short-term follow-up. Since sinus rhythm patients were referred for cardiovascular screening purposes rather than AF, referral bias may have played a role but would—if anything—have led to a higher incidence of events in the control population rather than the reverse. Although we meticulously tried to rule out hypertension, specific cases of masked hypertension could be missed since 24 h ambulatory blood pressure monitoring was not performed. Follow-up echocardiography was not available in all patients. As a result, potential surveillance bias due to echocardiography being performed for renewed suspicion or actual development of cardiac disease could not be excluded. However, this bias holds for both groups and, in addition, does not invalidate the relationship between size increase and disease development.

## Conclusion

Patients originally diagnosed with idiopathic AF develop CVD more often, earlier in time and at younger age compared with healthy sinus rhythm control patients. Age, history of AF, and posterior wall width are significant predictors of CVD development. The detection and treatment of CVD in an early stage could improve the prognosis of these patients. At present it seems prudent to regularly check idiopathic AF patients for the development of CV disease.

## Contributorship

All authors contributed significantly to the submitted work and have read and approved the manuscript.

**Conflict of interest:** none declared.

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