

Significance and Management Strategies for Patients with Asymptomatic Atrial Fibrillation

Ewa Majos, MD, Rafal Dabrowski MD, PhD, FESC

Institute of Cardiology, Warsaw, Poland.

Abstract

Atrial fibrillation (AF) is a common and refractory arrhythmia. Prevalence of AF increases with age. Asymptomatic AF is a state of asymptomatic episodes of arrhythmia and its exact prevalence remains unknown. Ablation and therapy with antiarrhythmic agents may predispose to asymptomatic AF. Detection of silent AF is crucial for prevention of ischaemic stroke. Progress in continuous ECG monitoring by Holter ECG, telemetry methods or implantable devices can provide a useful tools for identifying silent AF. Simple screening procedures like pulse examination and ambulatory ECG may be helpful in arrhythmia detection and logically – ischemic stroke prevention.

Atrial Fibrillation - Epidemiology

Atrial fibrillation (AF) is the most frequent supraventricular arrhythmia affecting over 3 million people in the USA, over 4,5 million in Western Europe including France, Germany, Italy, Spain and the UK, and over 1,5 million in Japan.^{1,2,3} A 3 to 4 fold increase in arrhythmia prevalence is expected by 2050. Approximately 15 million people worldwide suffer a stroke each year. AF is associated with at least 15% of all strokes. Of this number, approximately one-third die and another third are left permanently disabled.

In the Rotterdam Study, a large population-based European cohort study, the prevalence of AF was 5.5% and was dependent on the age of the participants. It showed 0.7% in persons aged 55-59 years and 17.8% in those aged 85 years and over. The overall incidence rate was 9.9/1000 person-years and was also strictly associated with age. In the group of 55-59 years of age it was 1.1/1000 person-years, then rose to 20.7/1000 person-years in the group aged 80-84 years and finally stabilized in those aged 85 years and above. AF prevalence and incidence was higher in men than in women. The lifetime risk of developing AF at the age of 55 years was 23.8% in men and 22.2% in women.⁴ In the ATRIA study therapeutic issues in patients with AF in the United States were investigated. A total of 17 974 adults with diagnosed AF were enrolled; 45% of whom were aged 75 years or older. AF was more common in men than in women (1.1% vs 0.8%; $P < .001$). Prevalence differed from 0.1% among adults younger than 55 years to 9.0% in persons aged 80 years or older. Among persons

aged 50 years or older, prevalence of AF was higher in whites than in blacks (2.2% vs 1.5%; $P < .001$). It was estimated, that approximately 2.3 million US adults currently have AF. The authors of the study expect that this number will increase to more than 5.6 million by the year 2050, with more than 50% of affected individuals aged 80 years or older.⁵ AF is usually associated with common cardiovascular conditions, such as arterial hypertension, heart failure, coronary artery disease and diabetes mellitus, etc, which are also associated with abnormal biomarkers of a prothrombotic state. In addition, a prothrombotic state has been identified even in patients with lone AF without vascular risk factors or significant cardiovascular conditions.¹

Asymptomatic Atrial Fibrillation – Epidemiology

Patients with AF are often asymptomatic. However, in these patients cardioembolic stroke can be caused by short episodes of the arrhythmia especially if AF coexists with other comorbidities (arterial hypertension, diabetes, metabolic syndrome, obstructive sleep apnea syndrome etc).

In a prospective 19-month study of 110 patients with a previous history of AF, indications for pacing were monitored with continuous electrocardiography (ECG) using an implantable device (mean follow-up >18 months). It showed that despite optimal medical therapy, 59% of the patients had at least one period of asymptomatic device-documented AF and 38% had asymptomatic episodes lasting more than 48 hours.^{6,7} A similar conclusion comes from a sub-analysis of the SOPAT (suppression of paroxysmal atrial tachyarrhythmias) trial, that included 1033 patients with symptomatic AF for 60 months. It was observed that of the 6,165 ECG recordings with AF only 46% of patients had symptoms during these episodes.^{6,8} The same study showed that in contrast to sotalol (320 mg/day) combined therapy of quinidine and verapamil (480/240 mg/day or 320/160 mg/day) reduced the ratio of symptomatic to asymptomatic

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Corresponding Author:
Ewa Majos, MD,
Institute of Cardiology,
ul. Spartanska 1
Warsaw 02-637, Poland.

AF compared with placebo, at least in part by decreasing the heart rate.⁸

An interesting observation has been made in the DISCERN AF study (Discerning Symptomatic and Asymptomatic Episodes Pre and Post Radiofrequency Ablation of Atrial Fibrillation). In this study patients with symptomatic AF underwent implantation of an implantable cardiac monitor with an automated AF detection algorithm 3 months before and 18 months after ablation. The ratio of asymptomatic to symptomatic AF episodes increased after ablation from 1.1 to 3.7 ($p=0.002$). Asymptomatic episodes were significantly shorter and slower, with lower heart rate variability. The authors concluded, that post ablation state is the strongest predictor of asymptomatic AF. Symptoms alone underestimate post ablation AF burden, with only 12% of patients having asymptomatic recurrences.⁹

Clinical Significance Of Asymptomatic AF

Symptomatic Versus Asymptomatic Patients

Important data come from a sub analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study, which was a randomised controlled trial that included 4,060 patients with AF. It was found that asymptomatic patients (12%) had higher risk of cerebrovascular disease than symptomatic patients (17% vs 13%; $p=0.005$), but a lower incidence of coronary artery disease (28% vs 40%; $p<0.0001$). Similarly they were less prone to congestive heart failure and pulmonary disease. They were also more likely to have normal ventricular function as assessed by echocardiography, a slower average and maximum heart rate, longer duration of AF, increased exercise tolerance, and a higher global estimate of quality of life. They received fewer cardiac medications and fewer therapies to maintain sinus rhythm. At 5 years, there was a trend for better survival in asymptomatic patients (81% vs 77%, $p=0.058$), who were also more likely to be free from disabling stroke or anoxic encephalopathy, major bleeding, and cardiac arrest (79% vs 67%, $p=0.024$). However, after adjusting for left ventricular ejection fraction and history of coronary artery disease or congestive heart failure, there was no statistically significant difference between the two groups in morbidity and mortality for disabling stroke, disabling anoxic encephalopathy, major central nervous system haemorrhage, and cardiac arrest. Therefore, patients with AF should be treated for underlying heart disease, regardless of the presence or absence of symptoms.^{6,10}

Solely Asymptomatic Patients

The ASSERT study (Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial) has provided another significant observation. In this study subclinical atrial tachyarrhythmias, without clinical AF, occurred frequently in patients with pacemakers and were associated with a significantly increased risk of ischemic stroke or systemic embolism. Up to 2580 patients over 65 years old were enrolled, with hypertension and no history of AF, in whom a pacemaker/defibrillator had recently been implanted. They were monitored for 3 months for subclinical atrial tachyarrhythmias for longer than 6 minutes and afterwards followed for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. Eleven of the 51 patients had atrial tachyarrhythmias detected in the 3 month monitoring period specified by the protocol and none had had atrial fibrillation. Subclinical atrial tachyarrhythmias were predictive of the ischaemic stroke and systemic embolism after adjustment for predictors of stroke.¹¹ On the basis of the findings from the ASSERT study

temporal relationship between subclinical AF and embolic events has been investigated. Of 51 patients who experienced stroke or systemic embolism during follow-up, 26 (51%) had silent AF. In 18 patients (35%), episodes of silent AF were detected before stroke or systemic embolism. However, only 4 patients (8%) had silent AF detected within 30 days before stroke or systemic embolism, and only 1 of these 4 patients was experiencing silent AF at the time of the stroke. In the 14 patients with asymptomatic arrhythmia AF was detected over 30 days before stroke or systemic embolism, the most recent episode occurred at a median interval of 339 days earlier. Eight patients (16%) had silent AF detected only after their stroke, despite continuous monitoring for a median duration of 228 days before event. In conclusion, although asymptomatic AF is associated with an increased risk of stroke and embolism, very few patients had episodes of the arrhythmia in the month before their event.¹²

In the study by Glotzer et al. there was a trend to a doubling of the risk of stroke in the 30 days after any day in which there were at least 5.5 hours of AF.¹³

Morbidity In Atrial Fibrillation In Comparison With Patients Without Documented Arrhythmia

It has been long known, that AF is associated with an increased risk of stroke, death, heart failure, a reduced quality of life and with significant healthcare expenditures related to treating the arrhythmia and its complications.¹⁴

The impact of nonrheumatic AF on stroke incidence was examined in 5,070 participants in the Framingham Study after 34 years of follow-up. Compared with subjects free of the arrhythmia there was a near fivefold excess in stroke in patients with AF. In persons with coronary heart disease or cardiac failure AF doubled the stroke risk in men and trebled the risk in women. For those aged 80-89 years it was the sole cardiovascular condition to increase stroke incidence.¹⁵ In subjects from the original cohort of the Framingham Heart Study, AF was associated with a 1.5- to 1.9-fold mortality risk after adjustment for the preexisting cardiovascular conditions with which it was related. The decreased survival in persons with AF was present in men and women regardless of age.¹⁶

AF often accompanies heart failure. The presence of the arrhythmia in patients with left ventricular systolic dysfunction is associated with an increased risk for all-cause mortality. AF is also associated with progression of left ventricular systolic dysfunction.¹⁷ Tachycardia induced cardiomyopathy (TIC) is a reversible form of dilated cardiomyopathy that can occur with most ventricular and supraventricular arrhythmias, including AF. Its pathophysiology is not entirely understood.¹⁸ It can develop in patients with asymptomatic AF, who are not aware and not treated for the arrhythmia. It has recently been shown in a small group, that patients with AF who underwent electrical cardioversion presented an immediate increase in left ventricular ejection fraction (LVEF). After 4 to 6 weeks later LVEF increased further in patients who remained in sinus rhythm. Contrary to that, in subjects with AF relapse LVEF returned to initial values.¹⁹ Another small study results showed that heart rate control during AF without sinus conversion may result in an incomplete cure of TIC, suggesting the advantages of rhythm control with ablation in patients with TIC.²⁰

Finally, AF is an independent risk factor of all-cause mortality in patients with incident AF; as shown in a recent large trial in Sweden. The concomitant diseases that contributed most were found outside

the thromboembolic risk scores. The highest relative risk of mortality was seen in women and in the youngest patients compared with controls, and the differences between genders in each age category were statistically significant.²¹

Comparing mortality and morbidity of symptomatic and asymptomatic patients with AF to controls free of arrhythmia requires further research. This subject is difficult to evaluate, because presence of AF may be related to existing comorbidities which additionally influence risk of hospitalizations and mortality.

Detection Of Asymptomatic AF: The Longer Monitoring The Better Results

The association between silent AF and ischemic stroke or systemic embolic events seems to be logical and clear. Therefore, the search for a proper monitoring method remains a significant clinical challenge. The arrhythmia can be detected by a standard electrocardiogram (ECG), continuous 24-hour ECG recording, prolonged 7-day ECG recording, telemetric intermittent or continuous recording, implantable loop recorder (ILR) or data can be stored in memory of cardiac implantable devices.

In one of the studies the influence of Holter monitoring duration on the detection of AF episodes recurrences after RF ablation has been observed. A group of 215 patients underwent a 7-day Holter ECG at 6 months after catheter ablation. In 24-hour Holter: 59%, in 48-hour Holter: 67% and in 72-hour Holter: 80% of patients with AF, recurrences were detected, whereas a 4-day recording would have detected 91% of the recurrences that were detected with the complete 7-day recording. In conclusion, a Holter duration of less than 4 days failed to reveal a significant burden of arrhythmia, whereas a 4-day recording might offer a reasonable compromise.²²

In another trial 132 patients without known AF presenting to the diabetes, hypertension, and dyslipidaemia clinics (76 outpatients in the different clinics), or to the stroke unit (56 stroke survivors) were screened for unknown AF using a simple patient-operated, single-channel ECG recorder. Silent AF was found in 7 patients (5.3%; median CHADS₂ score: 2). The prevalence of AF was in direct proportion with a number of risk factors for stroke and AF: AF was found in 3% (1/32) of patients with hypertension and no other risk factors for AF, but in 7% (5/71) of patients with two risk factors including stroke patients (diabetes and hypertension, stroke, or stroke and hypertension), and in 11% (1/9) of patients with stroke, hypertension, and diabetes.²³

Asymptomatic AF identification is extremely important in patients with an ischemic stroke. A meta-analysis of randomized controlled trials and prospective cohort studies of patients with acute ischemic stroke has been performed. Five studies including 736 participants were analysed. All studies evaluated Holter monitoring, two also evaluated event loop recording. In studies that evaluated Holter monitoring (588 participants), new AF/atrial flutter was detected in 4.6% (95% CI: 0% to 12.7%) of patients with ischemic stroke. Duration of monitoring ranged from 24 to 72 hours. Two studies (140 participants) evaluated event loop recorders after Holter monitoring. New AF/atrial flutter was detected in 5.7% and 7.7% of consecutive patients in these two studies. The authors concluded, that screening consecutive patients with ischemic stroke with routine Holter monitoring will identify new AF/atrial flutter in approximately one in 20 patients. Extended duration of monitoring may improve the detection rate.^{24,25} Prolonged ECG monitoring

may be reasonable, but according to another trial, detection of AF in patients with ischemic stroke is often delayed. In this study, in 68% of patients AF was identified over 48 hours after presentation with stroke.^{25,26} Large trials are needed before firm recommendations can be proposed. A currently ongoing trial is CRYSTAL AF (A Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke), which has a purpose of assessing long-term ECG monitoring in patients with cryptogenic ischemic stroke and cryptogenic transient ischemic attack.^{25,27}

The question of screening for silent AF in the general population is extremely important. According to current guidelines of European Society of Cardiology (ESC) every patient aged 65 years and older who attends their general practitioner should be screened by checking the pulse, followed by an ECG in case of irregularity.²⁸ An interesting experiment of stepwise screening of arrhythmia in an older population group study (mean age 75 years) has recently been made in Sweden. All 1330 inhabitants in the municipality of Halmstad aged 75 to 76 years were invited to a stepwise screening program for AF, 848 (64%) of whom participated. As a first step, participants had 12-lead ECG and reported their relevant medical history. Those with sinus rhythm on 12-lead ECG, no history of AF, and ≥ 2 risk factors according to CHADS₂ score underwent a 2-week recording using a hand-held ECG and were asked to record 20 or 30 seconds twice daily and if palpitations occurred. Silent AF was first found in 10 (1%) among 848 individuals who recorded 12-lead ECG. Among 403 persons with ≥ 2 risk factors for stroke, who completed the hand-held ECG event recording, 30 (7.4%) were diagnosed with paroxysmal AF. In conclusion, stepwise risk factor-stratified AF screening in a 75-year-old population yields a large share of candidates for oral anticoagulation treatment on AF indication.²⁹

According to current guidelines, in patients 65 years or older, opportunistic screening by pulse palpation, followed by an ECG in those with an irregular pulse, is important to detect AF prior to the first stroke.^{28,30}

Current Recommendation for Management of AF

Treating asymptomatic AF is not different from management of symptomatic form of arrhythmia. In both cases prevention of thromboembolism is crucial. Current guidelines by European Society of Cardiology emphasise that antithrombotic therapy is recommended in all patients with AF except those at low risk or with contradictions. However, selection of therapy should be based on individualised prognosis of risk and benefit and patient preferences. CHA₂DS₂-VASC score is recommended for initial assessing stroke risk and HAS-BLED score should be used to calculate bleeding risk. Novel oral anticoagulants may be used alternatively to vitamin K antagonists.^{28,30}

Rate control should be the initial approach in elderly patients with AF and minor symptoms. Rate control agents are: β -blockers, non-dihydropyridine calcium channel antagonists and digitalis.^{28,30}

In contrast, rhythm control as an initial approach should be considered in young symptomatic patients in whom catheter ablation treatment has not been ruled out and in patients with AF secondary to a trigger or substrate that has been corrected (e.g. ischaemia, hyperthyroidism). Depending on underlying heart disease the following antiarrhythmic drugs are recommended: amiodarone, dronedarone, flecainide, propafenone, sotalol. In patients without significant structural heart disease, initial antiarrhythmic therapy

should be considered dronedarone, flecainide, propafenone, and sotalol. In subjects with severe heart failure, NYHA class III and IV or recently unstable NYHA class II, amiodarone should be the drug of choice.^{28,30}

Catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication. It may also be considered in paroxysmal AF prior to antiarrhythmic drug therapy in symptomatic patients despite adequate rate control with no significant underlying heart disease. In these patients catheter ablation is more effective than antiarrhythmic drug therapy for the maintenance of sinus rhythm.^{28,30}

Further detailed recommendations concerning therapeutic issues in AF can be found in Guidelines for the management of atrial fibrillation 2010 and 2012 focused update of the ESC Guidelines for the management of AF.^{28,30}

Conclusion

Silent AF is a significant clinical problem especially for prophylaxis of ischemic stroke. Various methods of identifying AF are being investigated for their effectiveness in detecting the arrhythmia. The role of wide screening in the primary care should be emphasized.

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