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Review Article

Atrial Fibrillation Revisited —With a Special Reference to Primary Prevention—

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Atrial fibrillation (AF) is common arrhythmia and results in a rapid and irregular rhythm. Patients with this arrhythmia may be asymptomatic but AF often causes palpitation or chest discomfort especially when it develops in its paroxysmal form and patients might develop fatigue easily or reduced working capacity. Because of a loss of atrial contribution to ventricular filling, AF results in a decrease of cardiac output by 15% at rest and up to 30% upon exercise.[1] Long-standing tachycardia leads to cardiac dysfunction known as tachycardia-induced cardiomyopathy[2] and AF can be the cause of such cardiomyopahty and results in atrial stunning.[3]

The prevalence of AF increases with advanced age: 0.4% in the general population but less than 6% in those >80 years[4,5] and the elder patients are prone to develop heart failure. Rarely, AF can be fatal in WPW syndrome when rapid ventricular activation occurs via the Kent bundle.[6]

In addition to such morbidity, AF is the major cause of stroke and is associated with increased mortality and morbidity.[7–9] For stroke in patients with AF, several risk factors have been established[8–13] and in animal model, altered gene expression predisposing to coagulation was confirmed in the endocardium of the paced-atrium.[14] To reduce stroke, efficacy of anticoagulant therapy by Warfarin is well established.[12,13] Aspirin seems to be inefficacious especially in Japan to prevent stroke due to AF.[15]

For AF, antiarrhythmic drugs are prescribed to prevent recurrence but with limited efficacy. The best result in preventing the recurrence of AF is that reported by CTAF using amiodarone, wherein the AF free rate was 60% at the 600th day of therapy.[16] However, the drug might be withdrawn because of side effects and paroxysmal AF progresses eventually to chronic AF over time.[17]

Recently, catheter ablation has been established as a new promising therapy to prevent the recurrence of AF[18] but it would be difficult to apply catheter ablation to every patient because of the large number of patients. For these reasons, we have to seek other possibilities and the prevention of the occurrence of AF in the general population is very important. We hereby, review the epidemiology and the underlying diseases of AF from the point of view of primary prevention of AF.

Associated Disorders and Genesis of AF

Though AF can occur in subjects without disease and with normal cardiac function,[19] it occurs more often in association with familiar diseases.

The prevalence of AF associated with well-known cardiac or non-cardiac diseases is shown in **Table 1** which was presented in the guideline of AF treatment in this country.[20] The prevalence of each disorder was determined in the institutions of the committee members.

A more precise prevalence of AF was determined in 19,825 patients who visited cardiovascular clinics of 13 hospitals in Hokkaido, Japan.[21] AF, was found in 14% and increased with age: for the age groups of <40, 40–50, 50–60, 60–70, 70–80 and >80 were 3.5%, 6.9%, 10.4%, 13.5%, 18.7% and 25.4%,

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Table 1 The prevalence of atrial fibrillation (Ref. 20).

1	Hypertension: 7% (8.8%/5.0%)
2	Ischemic HD: 7% (7.3%/6.3%)
3	Dilated CM: 38% (36.3%/40.7%)
4	Hypertrophic CM: 10–20%
5	Valvular HD: 14–26%
6	Heart Failure: 20–35%
7	Hyperthyroidism: 1.7% (2.8%/1.4)
8	WPW syndrome: 15–30%
9	Sick sinus syndrome: 15–30%*
10	Lone AF: 1–10%**

HD: Heart Disease. CM: Cardiomyopathy. (Men/Women)
*: Rose to 40–60% in Brady-tachy syndrome.
**: Age dependent (<1%, 4–7% and 10% in <60, 70–79, >80 years of age)

respectively. The underlying heart diseases of AF were hypertension (29%), valvular heart disease (19%), ischemic heart disease (11%), cardiomyopathy (5%), sick sinus syndrome (1%), WPW syndrome (5%) and others (33%). The prevalence of AF in these two reports was higher than that determined in the general population.

The main factor causing AF in these diseases is considered to be stretching of the left atrium[22,23] as found in heart failure, hypertension, myocardial infarction and cardiomyopathy and the prevalence and the incidence of AF increases as the cardiac function worsens: the prevalence of AF can be found in 10–15%, 26%, and up to 50% for NYHAI–II, III–IV and IV, respectively.[24]

When the atrium undergoes stretching, the renin-agniotensin system (RAS) is considered to be activated in the atrium and plays a major role in inducing structural remodeling or expression of oxidative stress.[26–29] This activation has been confirmed in the atrium with AF[26] and in the rapidly paced atrium.[27,28] In spontaneously hypertensive rats (SHR), oxidative stress expression and fibrosis was detected. This finding suggests that both fibrosis and oxidative stress occur prior to the onset of AF and they were found to be attenuated by hypotensive therapy: most effectively by angiotensin II type-1 receptor blockade.[30]

Altered autonomic nerve activities is another precipitating factor of AF[31,32] and some patients develop AF exclusively at night or show a distinct circardian rhythm in the occurrence of AF.[33] A shortening of the effective refractory period of atrial myocytes by vagal activity will result in AF in these patients since shortening of the effective refractory period is considered to facilitate the development of AF.[34,35]

Recently, gene mutations of ionic channels have been reported as the cause of familial AF.[36–39] These mutations are associated with abnormal function of ionic channels and shortening of the refractory period.[38,39] AF develops in hyperthyroidism but the cause has yet to be determined. We then, confirmed that the thyroid hormone (T3) induces gene expression of Kv1.5: the potassium channel, and reduces the gene expression of the L-type calcium channel.[40] This altered gene expression will result in a shortening of the action potential duration and this might be the mechanism of frequent AF in hyperthyroidism.[34,35] The ionic channels can be altered by congenital abnormalities or by some other disorders such as hyperthyroidism rendering the atrium to develop AF easily. Of these underlying diseases, recent clinical trials have been shown the incidence of AF might be efficiently reduced by some drugs and will be discussed later.

Prevalence of AF in the General Population and Risk Factors

The epidemiology of AF has not been well known until recently in this country.[41,42] We have determined the prevalence of AF in the general population.[41] The subjects underwent an annual health examination which was recommended for those who were not under medication for either cardiac or non-cardiac diseases, but 12.6% had been receiving medication for hypertension, diabetes etc. In 2003, 83,367 men (31.1% of the total male residents) and 159,770 women (39.6% of the total female residents) underwent the examination. ECG at the time of the examination showed AF in 1.25% and the prevalence of AF was higher in men than women and in the elderly than in younger subjects (**Figure 1**). These results were similar to those obtained in the national survey in 300 districts conducted every 10 years in Japan.[42] From these results, the number of Japanese adults with AF might be estimated as more than one million: 598,000 men and 457,000 women.

Risk factors leading to development of AF have been elucidated in population-based studies.[43–48] In the Framingham study,[43] a total of 2,090 men and 2,641 women free of a history of AF between the ages of 55 and 94 years were followed for 38 years. AF developed in 12.6% of men and 11.3% of women and in the multivariable model, odds ratio (OR) of developing AF for each decade of advancing age was 2.1 for men and 2.2 for women. In addition, diabetes mellitus (DM), hypertension, congestive heart failure and valve disease were associated with OR (men/women) of 1.4/1.6, 1.5/1.4, 4,5/5.9 and

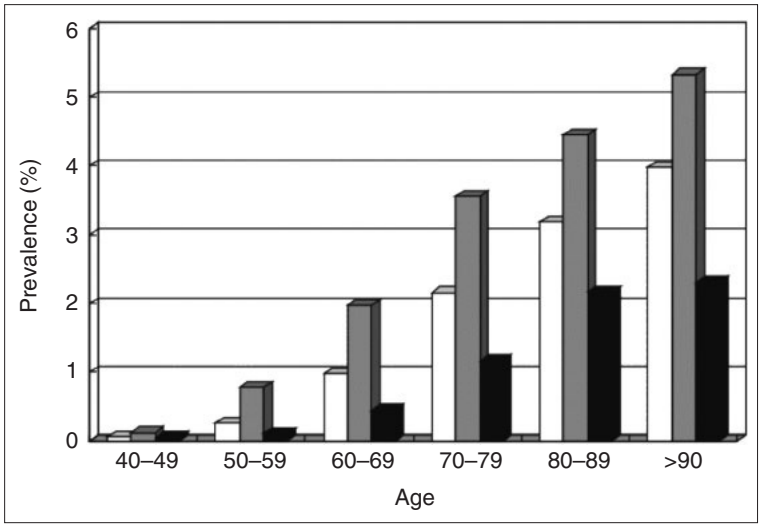

Figure 1 Age distribution of atrial fibrillation in Japanese people.
White: Total. Grey: Men. Black: Women (from references 41 and 42).

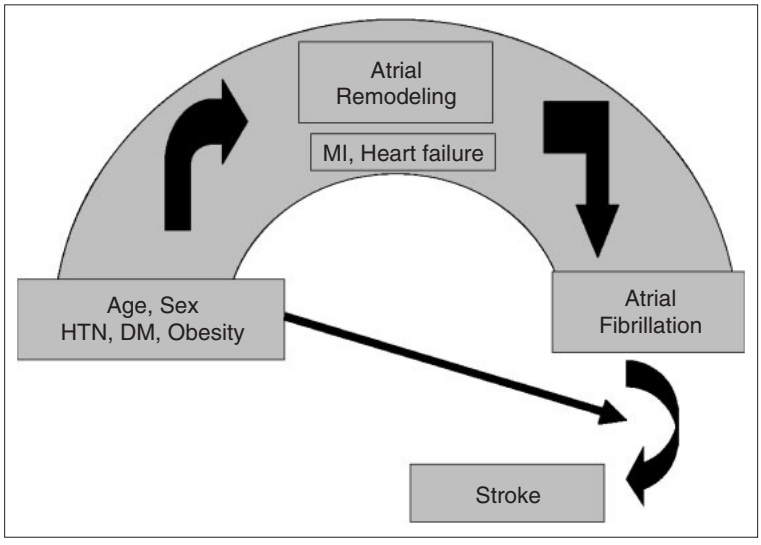

Figure 2 Development of atrial fibrillation and common risk factors with subsequent stroke.
Common diseases such as hypertension (HTN), diabetes mellitus (DM) or obesity are believed to provide the arrhythmogenic substrate in the atrium leading to development of atrial fibrillation (AF). These risk factors including age or sex(male) are the risks for stroke. Though not shown, heart failure is another risk factor. Structural and electrical remodeling are involved for the development of AF.

1.8/3.4, respectively. Myocardial infarction was a risk factor in men (OR = 1.4). The incidence of AF in the general population is considered to be 0.5 per 1000 person-years in those under 50 years and rose to 9.7 per 1000-person years in those 70 years of age.[44] A similar age-dependent rise of the incidence of AF was reproted by Psaty et al:[45] 17.2 per 1000-persons-years for those between 65–74 years and 42.7 per 1000 person-years for those between 75–84 years.

Risk factors for newly developed AF was observed in this country and the incidence was found to be lower than Western countries.[48] The study was conducted in 63,386 subjects aged ≥50 years, without baseline AF, structural heart disease, or heart failure, who completed the annual examination during a 10-year follow-up period (1991–2002). AF developed in 873 subjects (1.38%). The incidence was 1.3 per 1000 person- years: 2.6 per 1000 person-years for men and 0.9 per 1000 person- years for women.

Age, male sex, body mass index, hypertension, systolic and diastolic blood pressure, and diabetes were significant risk factors for the development of AF (**Figure 2**). In multivariable logistic regression analysis adjusted for these risk factors, electrocardiographic left ventricular hypertrophy (odds ratio [OR], 1.43), ST-segment abnormality without left ventricular hypertrophy (OR, 1.89), and the presence of premature complexes during a 10-second recording (OR, 2.89) were significantly associated with AF, whereas neither right nor left bundle branch block was a risk factor.

Among risk factors in developing AF, some were

closely related to a metabolic abnormality: DM, obesity and obstructive sleep apnea (OSA) as risk factors for newly developed AF was reported in the literature.

DM and/or metabolic syndrome is increasing in developed countries and is a risk factor for the new AF.[45] In type II DM (n = 293,124), AF occurred in 14.9% DM patients vs. 10.3% in the non-matched control without DM but with hypertension: OR = 2.13 (95% CI:2.10 to 2.16, p < 0.0001).[50] The causal link can be indirect via coronary artery disease, hypertension or autonomic neuropathy but it can be more direct. In the atrium of diabetic rats, overexpression of oxidative stress was verified and most likely it plays a role as a causative factor of AF.[51]

Obesity is said to be reaching epidemic proportions with nearly 65% of the population overweight and nearly 31% obese in the USA[52] and this has been associated with new AF and cerebral stoke events in AF patients.[53–55] In the Framingham study,[50] 5,282 participants (mean age, 57 ± years; 2,898 women) without baseline AF were included. During the mean follow-up of 13.7 years, 526 participants (234 women) developed AF. The age-adjusted incidence rates for AF increased across the 3 BMI categories in men and were 9.7, 10.7, and 14.3 per 1000 person-years and in women 5.1, 8.6, and 9.9 per 1000 person-years. The excess risk of AF in obesity is considered to be mediated by left atrial dilatation.[53–55] Furthermore, the increased iuncidence of AF in obesity appeared partially mediated by DM.[54]

OSA is found in about 40% of obese individuals[56–58] and patients with OSA were reported to be significantly frequent in the AF group than in the general cardiology group (49% versus 32%, P = 0.0004): OR for the association between AF and OSA was 2.19 (95% CI 1.40 to 3.42, P = 0.0006).[56]

In OSA, autonomic, hemodynamic and hypoxemic surges caused by apnea will activate some ionic channels leading to greater focal discharges. Pulmonary or systemic hemodynamics, lung physiology restricted by morbid obesity or both can elevate atrial pressures and trigger ectopy. Furthremore, enhanced vagal reflexes activities in OSA would lead to a shortening of the atrial refractory period and might promote the conduction of focal discharges from the pulmonary vein to the left atrium and trigger AF.[56–58] Elevated C-reactive protein (CRP), a marker of risk of a cardiovascular event[59] has been associated with obesity, metabolic syndrome, severity of OSA and AF.[59–61] Obesity, OSA or both is believed to promote atrial structural remodeling via mechanical or inflammatory stress.

Prevention of AF

Whether proper management of underlying diseases or disorders can prevent the occurrence of AF or not is an important clinical issue (**Figure 2**). So far, clinical trials in heart failure and hypertension have shown that ACE-inhibitors and ARB have been effective in reducing the development of AF.

ACE inhibitors were suggested to reduce the occurrence of arrhythmias and cardiac remodeling[25] and Trandolapril showed that it reduces the incidence of AF after acute myocardial infarction with left ventricular dysfunction. Of 1,749 patients randomized to trandolapril or placebo, 1,577 had sinus rhythm at baseline ECG.[62] In the trandopril group, 2.8% developed AF while in the placebo group, 5.3% developed AF during the follow-up of 2–4 years (P < 0.05). Such reduction of the occurrence of AF was confirmed in the SOLVD study.[63] Of 391 patients with sinus rhythm and depressed left ventricular ejection fraction (<0.35) and asymptomatic or mild symptoms of heart failure, 5.4% in the enalapril group and 24% in the placebo group developed AF during the follow-up period of 2.9 ± 1.0 years (P < 0.0001).

In the Val-Heft study,[64] new AF was observed in 287 (6.53%) among the 4,395 patients patients who had sinus rhythm at baseline during 23 months of follow-up. Multivariable analysis showed that the brain natriuretic peptide (BNP) levels at baseline above the median value, age over 70 years, and male sex were risk factors for new AF. AF was reported in 113/2,205 (5.12%) allocated to the valsartan group and in 174/2,190 (7.95%) to the placebo group (P = .0002). Valsartan reduced the incidence of AF by 37%. The occurrence of AF was independently associated with a higher all-cause mortality and with combined mortality/morbidity.

In the CHARM program,[65] 7,601 patients with symptomatic heart failure and reduced or preserved left ventricular systolic function were randomly administered candesartan or placebo and followed for 37.7 months on average. Of these, 392 (6.15%) developed AF during the follow-up, 177 (5.55%) in the candesartan group and 215 (6.74%) in the placebo group (OR 0.812, 95% CI 0.662–0.998, P = .048).

The recurrence rate of AF after cardioversion of persistent AF was reduced by ACE-inhibitor or ARB.[66,67] The beneficial effect of ACE-inhibitors or ARBs was seen in meta-analysis.[68,69] A rise in the atrial pressure or an increased atrial size is believed to be important in developing AF but, it was difficult

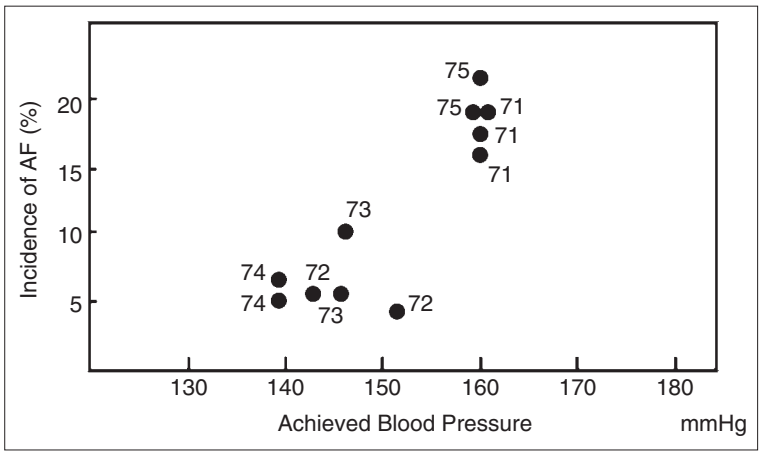

Figure 3 Incidence of AF vs achieved blood pressure in hypotensive therapy.
The incidence of AF against the achieved blood pressure (systolic) in 5 clinical trials of hypotensive therapy were plotted. Number means the reference number (from references 71–75).

to predict the occurrence of AF from clinical or hemodynamic variables in heart failure.[70] Decreased mitral flow velocity might be observed prior to AF.[70]

Hypertension is an important risk factor for the occurrence of AF and can be regarded as the major source of AF in the community. In the STOP-Hypertension 2 trial,[71] 6,614 elderly patients were included and the incidence of the cardiovascular events were assessed in 3 treatment regimens; conventional antihypertensive drugs (atenolol, metoprolol, pindolol or hydrochlorothiazide plus amiloride) and newer drugs at that time (enalapril, lisinopril, fledipine, or isradipine). New AF developed in 16.5/1,000 person-years but the incidence was not affected by drugs. The incidence was relatively high compared to subsequent studies[72–74] and this might be due to the patients being aged 70–84 years and some had severe hypertension: blood pressure $\geq$180 mmHg systolic, or $\geq$105 mmHg diastolic. More importantly, the attained blood pressure was high, around 159 mmHg (systolic).

The Nordic Diltiazem (NORDIL) study[72] was another prospective, randomised, open, blinded endpoint study and 10,881 patients, aged 50–74 years were treated in two treatment regimens: diltiazem with diuretics, beta-blockers, or both. Blood pressure fell similary in both groups from $174 \pm 18/105 \pm 5$ to $152 \pm 16/88 \pm 8$ mmHg in the diltiazem group and from $173 \pm 18/106 \pm 5$ to $149 \pm 17/87 \pm 8$ mmHg in the other group and new AF occurred in 4.2 vs. 5.1 per 1000-person years respectively. The two studies showed no difference in the incidence of AF among drugs used.

However, in the LIFE study,[73] the patients with hypertension associated with ECG-documented left ventricular hypertrophy were followed for 4.8 ± 1.0 years and losartan or atenolol was administered. New-onset AF occurred in 150 patients randomly administered with losartan vs. 221 with atenolol (6.8 vs. 10.1 per 1,000 person-years; the relative risk was 0.67, 95% confidence interval [CI] 0.55 to 0.83, $p < 0.001$) despite similar blood pressure reduction. Finally, the most recent study of VALUE[74] investigated the outcomes in 15,245 high-risk hypertensive subjects who were treated with valsartan- or amlodipine-based regimens. For the first time, the attained systolic blood pressure fell below 140 mmHg on average in this study. AF developed newly in 4.8/1,000 person-years in the valsaratan group and lower compared to the calcium channel blocker amlodipine group: 5.8/1,000 person-years. Thus, recent studies showed ARB reduces the incidence of AF in hypertensive therapy.

The studies and results of hypotensive therapy were summarized in **Figure 3**. It is of note that the incidence of AF was high in the STOP-Hypertension-2 study but low in the VALUE study.[71,74] One reason can be the finding that attained blood pressure was high:160 mmHg in the former but in the VALUE study, the attained blood pressure was for the first time below 140 mmHg. Another reason can be that the age of the patients: in the STOP Hypetension-2 was high (>80 years) compared to those of VALUE. However, the CAPP study included younger aged patients: 20–66 years[75] and the attained blood pressure and the incidence of AF were similar to STOP-Hypertension-2. Therefore, in hypotensive therapy, it seems very important to treat hypertension strictly and also to choose either an ACE-inhibitor or ARB. Such therapy can be a promising upstream therapy of AF.[76]

In summary, AF is a common arrrhythmia and develops in association with common diseases (**Figure 2**). Once AF occurs, AF is associated with

increased morbidity and mortality and the proper therapy of AF is mandatory: anticoagulant therapy to prevent stroke and antiarrhythmic agents or catheter ablation to prevent recurrence of AF. The risk factors to develop AF are also risk factors for stroke to occur and the proper treatments are warranted.[7–9,12,13,43] However it is to be stressed that AF might be reduced by the proper use of drugs which inhibit RAS and the strict control of the underlying diseases as proved in heart failure and hypertension.

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