

NON-VALVULAR ATRIAL FIBRILLATION AND STROKE: IMPLICATIONS FOR MANAGEMENT

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ABSTRACT

Nonvalvular Atrial Fibrillation is more prevalent with increasing age. It is associated with a six-fold excess risk of stroke; and a cumulative lifetime stroke risk of 35%. 15% of ischaemic strokes are directly attributable to it. Five trials have established the safety of warfarin in reducing the risk by 70% in well selected patients, with stringent monitoring. Thromboembolism, cardiac failure, hypertension and echocardiographic abnormalities identify higher risk patients. The management of NVAF is changing from rate control, to cardioversion and anticoagulation (or use of antithrombotics) to reduce the embolic risk.

Keywords: *NVAF, embolism, cardioversion, anticoagulation, antithrombotics.*

Introduction

Atrial fibrillation (AF) has been described as "the grandfather" of cardiac arrhythmias, being known as "The Arrhythmia Perpetua" in the 19th century whence its management has remained almost unchanged, depending mainly upon digoxin and other drugs, and more recently on D.C. cardioversion.

Incidence and Prevalence of AF

The Framingham study found an overall incidence of AF of 1.7%¹, other studies have revealed higher rates depending upon the source of the population studied. An average of 2.5% of those over 60 years are said to be in atrial fibrillation with the incidence increasing with age. One 5-year study found a prevalence of 50 rising to 90 per thousand in the elderly², while the Framingham study revealed a prevalence of up to 8.8% at 80 - 89 years. Campbell et al carried out an electrocardiographic survey of over 65 year olds registered in clinics, and found that 2% of 64 year to 70 year olds were in AF, rising to 5% in the over 75 year olds³. There was no significant difference between the sexes in all the studies.

Causes of AF

Atrial fibrillation (AF) is found six times more frequently in rheumatic heart disease and cardiac failure¹. It is associated with hypertension only

TABLE I - Precursors of Atrial Fibrillation

A. Cardiac:

- Rheumatic heart disease
- Cardiac failure
- Hypertensive heart disease with left ventricular hypertrophy
- "Lone" atrial fibrillation
- Cardiomyopathies
- Wolf-Parkinson White Syndrome
- Pre-excitation
- Sinus node disease
- "Holiday" heart (Alcohol induced)
- Atrial septal defect

B. Non-Cardiac:

- Hyperthyroidism
- Chronic lung disease
- Post-operative (pulmonary surgery)
- Hodgkin's disease.

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in the presence of left ventricular hypertrophy, when there is an excess risk of developing AF of 1.6-1.8. "Lone" atrial fibrillation describes a generally benign condition, in those under 60 years, with no clinical, radiological or echocardiographical evidence of heart disease. Hyperthyroidism and alcohol are well known causes of AF, the latter causing the so-called "Holiday heart".

In the Framingham study, diabetes mellitus was also found to be associated with a 2 to 3 fold risk of developing AF¹.

The basic pathology is thought to be myocardial damage predisposing to atrial dilatation; interestingly ischaemic heart disease was not significantly related to the development of AF¹.

Prognosis of AF

This is described as 'grave' in the Framingham Study¹; the mortality is doubled and within this figure, the cardiovascular mortality is doubled¹. As regards morbidity, AF was associated with a six-fold increased risk of strokes, which were large with disabling residual deficits.

Stroke appeared to predispose to AF; it is thought that in these cases paroxysmal AF was occurring, throwing off emboli, then reverting to sinus rhythm. The incidence of embolism is higher than is generally thought (see Table II). Similar figures have been found by Hurst et al in patients with mitral valve disease and coronary artery disease (1964), and by Aberg (1969) in a study of 642 cases with AF. An epidemiological study of 'Lone' AF based on life insurance records also showed an increased mortality⁵, which seems contrary to other studies⁶. Overall this information shows that AF is not as benign as was previously thought. Further evidence to support this will now be discussed.

Atrial Fibrillation and Stroke

Atrial fibrillation has been found in 15% of all ischaemic strokes, and 2-8% of patients with transient ischaemic attacks. There is an annual incidence of 2.5% of ischaemic stroke in non-valvular AF (NVAF) with a cumulative lifetime risk of 35%⁴. Lone AF has been found to have a low stroke risk of 0.4-1% annually⁶.

Secondary emboli, that is embolisation after a stroke are most frequent in the first year, especially in the first two weeks. The stroke

recurrence rate is 15% in the first year, and 5% thereafter. The mortality after embolic stroke is 5%, with NVAF being the most common embolic source. It is note-worthy that 26% of NVAF patients with no history of cerebrovascular ischaemia are found to have silent infarcts on CT brain scans⁷; perhaps this fact explains why a lower incidence of infarcts was found clinically in younger subgroups of patients with NVAF. This information has been available for some years; however whether to treat with antithrombotics was controversial until recently.

AF: An Independent Risk Factor for Stroke

AF can coexist with atheroma, indeed there is an increased frequency of both in the elderly, however a number of factors point to an independent risk status. Following the onset of sustained AF, the embolic risk factor is particularly high - thyrotoxic AF is associated with a 30% embolic rate⁸. The Framingham study showed a low association between ischaemic heart disease and AF, but AF patients have a four fold increase in stroke. Autopsy studies have shown that ischaemic stroke in AF due to cardiogenic embolus varies from 50-71%⁹. Furthermore, angiography has shown significant cervical carotid artery stenosis in fewer than 10% of stroke patients with AF, this is much lower than expected in the average stroke population¹⁰.

Lacunar infarcts are thought to be due to small vessel disease (and very rarely to embolism), were found to be infrequently associated with AF in the Oxfordshire Community Stroke project¹¹.

Finally, newer imaging techniques such as transoesophageal echocardiography and ultrafast CT scan have made it easier to exclude intracardiac abnormalities which might be sources of embolism.

Obviously some ischaemic strokes in AF are due to concomitant cerebrovascular disease, but the exact number is uncertain and controversial, and when all factors are considered NVAF is found to be an independent risk factor¹².

Can Patients with AF be Stratified into Different Risk Groups for Embolism?

A number of factors can be used to stratify risk levels, for example younger patients with 'Lone' AF have been shown to have an annual stroke risk of less than 0.5%^{6,13}.

TABLE II - AF and Embolism

| Association | Prevalence of embolism |
|---|------------------------|
| Mitral valve disease and AF | 41 % |
| Sinus rhythm with ischaemic heart disease | 7 % |
| Chronic AF with ischaemic heart disease | 35 % |

Hinton et al (1977) 4.

At the onset of paroxysmal or sustained AF there is a particularly high risk of embolism.¹⁴

Embolic risk varies from 2.5% to 7.2% if either hypertension or congestive cardiac failure within the last three months or previous thromboembolism are present. Where two of these factors occur together, the risk rises to 17.6%¹⁵. Left atrial size and left ventricular dysfunction at echocardiography are also associated with a 5% thromboembolic risk, increased from 1% with a normal echocardiogram¹⁶.

Can Stroke be Prevented in NVAF?

This question has been addressed by five studies¹⁷⁻²¹; comparing warfarin, aspirin and placebo. All have been terminated early, within two years, because the warfarin group had shown significant benefit and it was considered unethical to continue the trials. The average age of the patients was just under 70 years. Overall there was a reduction of ischaemic and embolic strokes in the warfarin group from 5% to 2%, which represents a 70% reduction in risk level. These figures applied to a carefully selected group with a high exclusion rate (up to 93%) and stringent haematological monitoring. For every 1000 patients treated, there was an increase of three major haemorrhages, but in general the safety and efficiency of warfarin in the elderly was remarkable.

On this data there was consensus that all patients with NVAF should be considered for anticoagulation, unless some contraindication existed.

What Role for Aspirin?

Until March 1994, the place of Aspirin was not established; it was compared in the AFASAK

study¹⁷ and the SPAF study¹⁹ and was not as convincing as Warfarin. It seemed to reduce the risk of stroke by 25%, but the 95% confidence interval included zero benefit.

The Stroke Prevention in Atrial Fibrillation II Study (SPAFII)²² published in 1994 clarified the role of aspirin. 1,105 patients were randomised to warfarin (International Normalized Ratio (INR) 2-4.5), or Aspirin 325mgs daily to detect a reduction in primary ischaemic or systemic embolic events. There were two sub-groups divided by the age of 70 years, and the trial was designed to detect a 2% reduction in the events described above in the under 75 year olds, and a reduction of 4% in those over 75 years. Warfarin seemed to be more effective than Aspirin in the prevention of ischaemic strokes but the absolute reduction was small, and there was an increase in haemorrhagic strokes. Both drugs were equally effective in preventing total or disabling strokes. The absolute rate of events with aspirin in low risk under 75 year olds (ie no heart failure, thromboembolism or hypertension) was 0.5% annually. This implied that patient age and thromboembolic risk should be considered in tailoring antithrombotic treatment of NVAF. This study did not address the relative risks of the subgroups, however bearing in mind the factors affecting thromboembolic risk, patient selection should be based upon the clinical and echocardiographic findings.

Who Should be Treated?

This still requires the results of ongoing trials to define the subgroups of patients, the dosages and possible combinations of aspirin and warfarin. In the meantime it is clear that patients with a previous transient ischaemic attack or minor stroke should be anticoagulated²³.

In the light of SPAF II²², it seems that warfarin is also indicated in the presence of cardiac abnormalities as demonstrated by clinical or echocardiographic findings. Transoesophageal echocardiography may be helpful in stratifying the risk by better imaging of intracardiac thrombi and the left atrial appendage.

The five studies originally addressing this problem¹⁷⁻²¹ suggested that increasing age should not be a barrier to anticoagulation. On the contrary, the older the patient, the higher the risk of embolism and so the higher the benefit. However older patients also face an increased risk of bleeding, apart from problems due to

dementia/forgetfulness, difficulty in mobility and therefore access to an anticoagulant clinic. The studies had an exclusion rate of up to 93%, and in practice it is still unclear whether the stringent haematological control they achieved can be reproduced in routine clinics. In practice this means that one must balance the risks and benefits of each treatment and tailor therapy accordingly, so as to reduce the embolic risk of NVAf.

What Level of Anticoagulation?

Differing levels of anticoagulation were used in the trials with the INR varying from 1.4-4. The Veterans Affairs Study used prothrombin time, because INR was not as yet in general usage in North America. At present other trials are in progress and until they are completed an INR of 2-3 as recommended by the American College of Chest Physicians²⁴ is thought to be reasonable, assuming the haematological monitoring is of good quality.

The average rate of intracerebral haemorrhage was 0.3% in the five trials¹⁷⁻²¹; this was probably due to careful selection and follow up in the trials. However out-patient studies have shown serious haemorrhages in 5 to 11% of patients and fatal bleeds in 2% in one year of routine medical care²⁵. Moreover, one study showed that the risk of intracerebral haemorrhage was increased ten-fold whilst on anticoagulant therapy, independently of age²⁶. Overall anticoagulant treatment is justified if the rate of serious cerebral bleeding is low: should it rise beyond 2% annually the complication rate would be too high to justify both medically and economically²⁷. No figures are available for the Local Anticoagulant Clinic but in view of the increasing numbers of referrals for atrial fibrillation²⁸, they are necessary for guidance.

What of the Secondary Prevention of Stroke?

The European Atrial Fibrillation Trial (EAFT)²⁴, supports anticoagulating patients who are in AF

and have sustained a minor ischaemic stroke or Transient Ischaemic Attack (TIA). The risk of stroke was reduced from 12% to 4%. These patients were a selected subgroup with small strokes or TIA's, and the trial did not address the problem of those with larger strokes. Consideration should also be given to the wisdom and practicality of anticoagulating patients who are probably elderly, hypertensive and disabled, but in view of this data the possibility should at least be reviewed^{29,30}.

Is the Long Term Benefit Really Established?

All the studies were concluded within two years, so the question as to whether the risk of thromboembolism is constant in AF is unlikely to be formally evaluated.

What are the Implications Regarding the Treatment of NVAf?

In view of the inherent risks of AF, and the treatment necessary to reduce these risks, there ought to be a more aggressive approach in attempting to restore sinus rhythm. The action of digoxin is equivalent to placebo in restoring sinus rhythm,³¹ so other therapeutic agents have to be considered. A rational approach could be a pharmacological trial of a class III - Antiarrhythmic Agent (eg. amiodarone or sotalol) for one month. Should this be successful in restoring sinus rhythm a small maintenance dose as prophylaxis would seem reasonable³², failing this, DC cardioversion could be attempted. A full discussion of the possible antiarrhythmic therapy is beyond the scope of this article but is available elsewhere³². Anticoagulation should be continued for one month after restoration of sinus rhythm.

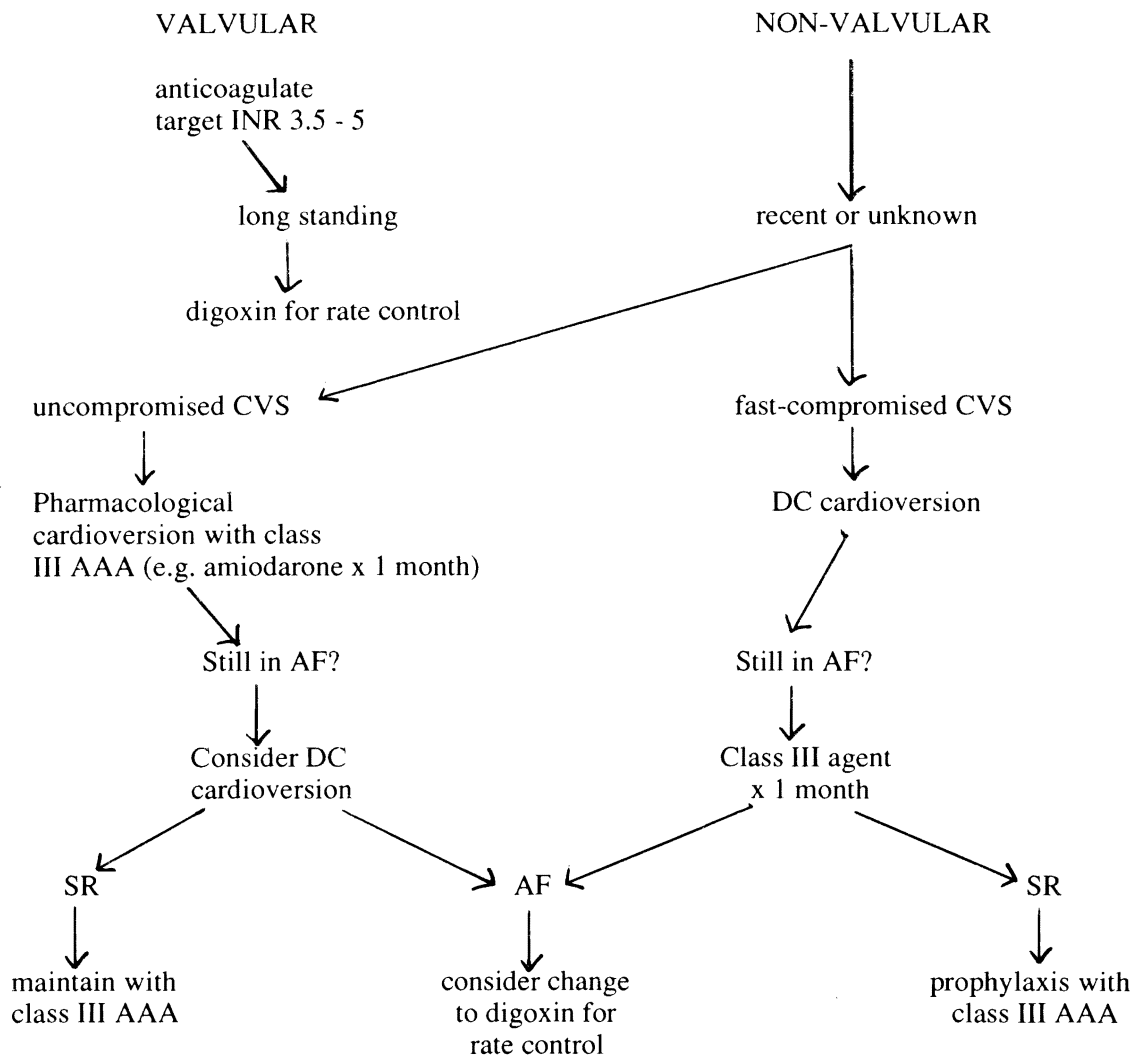
A study in the British Heart Journal³³ showed a reluctance to consider cardioversion or anticoagulation for NVAf, however optimum management will require increasing consideration of such factors.

CLINICAL ALGORITHM: MANAGEMENT OF ATRIAL FIBRILLATION (AF)

*Identify any cause and treat.
Aim to restore sinus rhythm wherever possible.*

A. ARRHYTHMIA

*Consider thyroid function tests, echocardiogram
holter monitor (? sick sinus syndrome)*



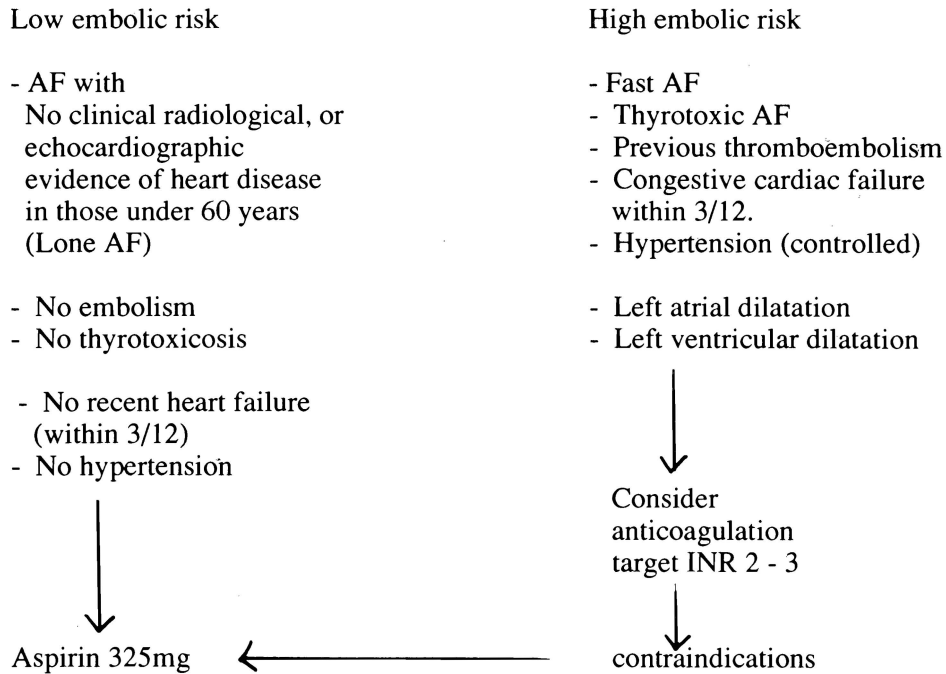
DC = Direct current AAA = Anti-arrhythmic agent CVS = Cardiovascular system

CLINICAL ALGORHYTHM: MANAGEMENT OF ATRIAL FIBRILLATION (AF)

*Identify any cause and treat.
Aim to restore sinus rhythm wherever possible.*

B. ANTICOAGULATION

Assess embolic risk and treat



A and B are to be considered concurrently

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