ATRIAL FIBRILLATION IN STROKE PATIENTS
ADMITTED TO HOSPITAL

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Summary
Aims: To determine the prevalence of atrial fibrillation in stroke and to examine the current practice of anticoagulation use in the secondary prevention of stroke for such patients.

Methods: Retrospective analysis of hospital notes of all patients admitted, via the Emergency Department of Palmerston North Hospital, New Zealand with a final diagnosis of stroke during the eighteen month period from April 1995 to September 1996, inclusive.

Results: There were 261 patients in the study, 27.2% (71) were in atrial fibrillation at the time of admission. The 30-day mortality rate was significantly higher in patients with atrial fibrillation (43.7% versus 22.1%, p=0.0006). Those in atrial fibrillation were significantly older (mean age of 77.1 years versus 72.9 years, p=0.005) and were more likely to be hypertensive (71.0% versus 54.8%, p=0.02). Of the 71 patients in atrial fibrillation, 35 had contraindications to warfarin and, of the remaining 36 patients, 31 received warfarin. Those who received anticoagulants were significantly younger than those who didn’t (74.1 years versus 79.3 years, p=0.03). The leading reasons for not starting anticoagulation were, firstly, that the severity of the stroke was such that active treatment was not warranted, and secondly, the patient died within 24 hours of admission.

Conclusions: Atrial fibrillation is common amongst stroke patients and it carries a high mortality. Utilisation of warfarin in these patients is becoming increasingly common and elderly people should not be denied this form of therapy, as they may have the most to benefit.

Introduction
Atrial fibrillation is a common arrhythmia in clinical practice, with a prevalence of 4% in the adult population. According to the Framingham study, the prevalence rises from 0.5% in those aged 50-59 to 8.8% in the 80-89 age group. In addition, they found that patients with non rheumatic atrial fibrillation (the most common form) have a fivefold increase in the risk of developing an ischaemic stroke when compared to the general population. This translates into a yearly risk of 5-7%. Alternately, approximately 14-20% of stroke patients will also have atrial fibrillation. While this association might not always be causal, it is believed that atrial fibrillation is the cause of 7-31% of all strokes in the over 60 age group. The pathogenesis is thought to be due to stagnation of blood in the fibrillating left atrium with subsequent thrombus formation and embolisation. Based on this, clinical trials using warfarin to prevent the development of strokes were started. At present, the results of 6 major clinical trials have been published. Of these, only two studied the use of warfarin in the secondary prevention of stroke. The remainder were strictly primary prevention trials. All the studies have, to varying degrees, shown that warfarin is effective in reducing the risk of ischaemic stroke. A meta analysis of 5 of the 6 clinical trials came to the conclusion that warfarin reduced the risk of stroke by 68% and death by 33%, without significantly increasing the risk of major bleeding (annual frequency of 1.3% in warfarin treated versus 1% in controls). In addition, the analysis found that increasing age, history of hypertension, previous transient ischaemic attack (TIA) or stroke, and diabetes mellitus were independent risk factors for the development of stroke. Based on these studies, Blackshear et al suggested the use of warfarin for “all (those with atrial fibrillation) in whom it is safe or, alternatively, warfarin for those with risk factors (these being increasing age, diabetes mellitus, hypertension, and previous TIA or stroke) and aspirin for those without risk factors.” While there is abundant evidence that warfarin is effective, in the setting of a clinical trial, at least, questions have been raised about its value in clinical practice. There is concern at the risk of bleeding complications associated with its use, as well as
doubts about its effectiveness in clinical practice given the highly selective groups of patients enrolled in the trials.14

This study was undertaken with three main aims. First, to determine what percentage of stroke patients have atrial fibrillation on admission. Second, to ascertain what the current management, in Palmerston North Hospital, of these patients is, with regard to the need (or not) for anticoagulation. Third, to compare this with recommendations or guidelines in the literature.

Palmerston North city is in the North Island of New Zealand and the hospital serves a population of approximately 150,000.

Methods

All patients admitted, via the Emergency Department of Palmerston North Hospital during the 18-month period from April 1995 to September 1996 inclusive, with a possible diagnosis of stroke or transient ischaemic attack, as well as those who presented with falls, confusion, collapse, hemiparesis or speech difficulty were eligible for the study. Excluded from the data analysis were those who were subsequently found not to have a stroke, and those with a final diagnosis of transient ischaemic attack, subdural or subarachnoid haemorrhage or a brain tumour.

The study is retrospective, with the source of data being hospital notes. Data collected included demographics, history of hypertension prior to presentation, history of previous stroke or transient ischaemic attack, diabetes mellitus, current smoking, and whether the patient was on aspirin or warfarin therapy prior to admission. A patient was defined as being in atrial fibrillation (AF) if an irregularly irregular ventricular rate was noted on an ECG at the time of admission.

Results of any CT scans done were divided into subcategories as follows: normal for the patient’s age, evidence of recent infarction with or without secondary haemorrhage, haemorrhage, or other. Whether a patient had an echocardiogram during the course of the admission was also noted.

Additional data gathered, for patients in AF, included: whether they were started on warfarin or aspirin, if so, how long after admission and if not, what were the reasons. Mortality rates were based on patients who died within 30 days of admission.

Data analysis was carried out using Microsoft Excel. Tests of statistical significance were calculated using the Student’s t-test for continuous data and the Chi-squared test for categorical data.

Results

The sample consisted of 444 patients. 183 were excluded. The leading reason for patient exclusion was a diagnosis of transient ischaemic attack (71) while 3 patients did not have an ECG at the time of admission.

![Figure 1. Flow chart indicating the number of patients screened, the exclusions and the numbers included for analysis.](image)

The valid study population was 261: 48.3% were males and 51.7% were females. The mean age was 74.0 (range: 31-99) years. A total of 71 patients were in AF at the time of admission to hospital, giving a prevalence of 27.2%. The remaining 190 patients were in sinus rhythm. Of the patients in AF, 40.8% were males and 59.2% were females; their mean age was 77.1 years, compared to 72.9 years for those not in AF (p=0.005) (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>AF group (n=71)</th>
<th>Non AF (n=190)</th>
<th>Total (n=261)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40.8 (29)</td>
<td>51.1 (97)</td>
<td>48.3 (126)</td>
<td>0.1</td>
</tr>
<tr>
<td>Female</td>
<td>59.2 (42)</td>
<td>49.9 (93)</td>
<td>51.7 (135)</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean age in yrs</td>
<td>77.1 (35-91)</td>
<td>72.9 (31-99)</td>
<td>74.0 (31-99)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71.0 (49)</td>
<td>54.8 (102)</td>
<td>59.0 (151)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14.3 (10)</td>
<td>13.7 (26)</td>
<td>13.9 (36)</td>
<td>0.9</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>44.3 (31)</td>
<td>40.2 (76)</td>
<td>41.3 (107)</td>
<td>0.6</td>
</tr>
<tr>
<td>On aspirin at admission</td>
<td>44.3 (31)</td>
<td>40.0 (76)</td>
<td>41.2 (107)</td>
<td>0.5</td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>43.7 (31)</td>
<td>2.1 (42)</td>
<td>28.0 (73)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

1. AF=atrial fibrillation;
2. Hypertension referred to a history of hypertension prior to presentation;
3. No data available for hypertension in 6 patients (2 in AF), diabetes mellitus in 1 AF patient, prior stroke in 2 patients (1 in AF), and aspirin on admission for 1 patient in AF.
History of hypertension was the most common risk factor for stroke with an overall prevalence of 59.0%, followed by prior stroke (71.0% versus 54.8%, p=0.02). The prevalence of other risk factors was similar in both groups. (Table 3) A small of patients (18) had an echocardiogram, 4 of whom were in AF.

Mortality Rates

The overall 30-day mortality rate was 28.0%. Those in AF had a significantly higher 30-day mortality rate (43.7% versus 22.1%, p=0.0006). The mean age of those who died was not significantly different from those who didn’t (77.8 years versus 76.5 years, p=0.6 in the AF group and 72.9 years versus 72.9 years, in the non AF group). However, those who died in the AF group were significantly older than the corresponding patients in the non AF group (77.8 years versus 72.9 years, p=0.05).

Head CT Scan Results (Table 2)

The majority, 76.6% had a CT scan as part of their investigations. The most common result was an infarct without secondary haemorrhage in 59.0%, followed by a normal scan in 22.5%. Primary intracerebral haemorrhage was noted in 15% of CT scans. Only 3 patients in AF had a primary haemorrhage, 2 of whom were already on warfarin. Their INR levels on admission were 2.9 and 3.1. The remaining patient was on aspirin.

Table 2. Head CT scan results

<table>
<thead>
<tr>
<th></th>
<th>AF % (No.)</th>
<th>Non AF % (No.)</th>
<th>Total % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>34.0 (17)</td>
<td>18.7 (28)</td>
<td>22.5 (45)</td>
</tr>
<tr>
<td>Infarct without haemorrhage</td>
<td>60.0 (30)</td>
<td>58.7 (88)</td>
<td>59.0 (118)</td>
</tr>
<tr>
<td>Infarct with 2ry haemorrhage</td>
<td>0</td>
<td>2.0 (3)</td>
<td>1.5 (3)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>6.0 (3)</td>
<td>18.0 (27)</td>
<td>15.0 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2.7(4)</td>
<td>2.0 (4)*</td>
</tr>
<tr>
<td>Not Done</td>
<td>29.5 (21)</td>
<td>21.0 (40)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation; *old infarcts not consistent with neurological deficit

CT scans were not performed in 21 of those in AF; 17 of these patients were not eligible for anticoagulation (6 died within 24 hours, 8 had severe strokes for which active treatment was not warranted, and 3 had other contraindications). Those who had a CT scan were significantly younger than those who didn’t (75.1 (range: 35-91) years versus 81.8 (range: 69-91) years, p=0.002).

Anticoagulation Practices

Of those in AF, 44.3% were on aspirin at the time of admission, compared to 40.0% of the non AF group (p=0.5, non significant). A total of 11 patients were already on warfarin at the time of admission, 9 of whom were in AF. Reasons for being on warfarin were as follows: 6 for AF, 2 for prosthetic heart valves, 2 for recurrent transient ischaemic attacks, and 1 for paroxysmal AF.

Of the 71 patients in AF, 31 were started on warfarin, and 35 had contraindications to warfarin. The mean time from admission to warfarinisation was 4.3 (range: 0-19) days. In all but two cases, warfarin was commenced after obtaining the result of a CT scan demonstrating the absence of haemorrhage. Those started on warfarin were significantly younger than those who weren’t (74.1 years versus 79.3 years, p=0.03). Excluding those with contraindications to warfarin (35 patients) left 5 patients who did not receive warfarin. Their mean age was 85.0 years, and this was significantly older than those started on warfarin (mean age 74.1 years, p=0.005).

Of the 40 patients who did not receive warfarin, 11 did not have contraindications to aspirin. Aspirin (dose: 150 mg/day) was started in 10 of these patients. One patient developed a gastrointestinal bleed and was taken off aspirin, leaving a total of nine patients on aspirin at discharge.

Reasons Not To Anticoagulate (Table 3)

The most common reason for not starting warfarin was the patient’s condition being such that active treatment was not warranted, a decision made in consultation with relatives and/or patients (18). Of the 18 patients not considered for active treatment, 14 died within two weeks of admission. Other reasons for not starting anticoagulation were shown in Table 3.

Table 3. Reasons not to anticoagulate

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active treatment not justified (in consultation</td>
<td>18</td>
</tr>
<tr>
<td>with relatives and/or patient)</td>
<td></td>
</tr>
<tr>
<td>Early death of patient (within 24 hours)</td>
<td>7</td>
</tr>
<tr>
<td>Risk of falls/dementia/compliance problem</td>
<td>4</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>3</td>
</tr>
<tr>
<td>Recent gastrointestinal bleed</td>
<td>2</td>
</tr>
<tr>
<td>High alcohol intake</td>
<td>1</td>
</tr>
<tr>
<td>No reasons found</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
</tr>
</tbody>
</table>
Discussion

Atrial fibrillation is a common finding in stroke patients. According to our study, the prevalence approaches 30%. Furthermore, the presence of atrial fibrillation heralds a poor outcome, as the 30-day mortality rate of 43.7% is almost double those in sinus rhythm (22.1%). The Oxfordshire Community Stroke Study also found the 30-day mortality rate to be significantly higher amongst stroke patients with atrial fibrillation than those without (23% versus 8%)\textsuperscript{4}. However, their prevalence (17%) and mortality rates are lower than that observed in our study. These differences reflect the greater severity of stroke being managed in the hospital as opposed to the community.

While atrial fibrillation, in itself, may account for the increased mortality in stroke patients with this cardiac arrhythmia\textsuperscript{15}, various other features also affect prognosis adversely. These include increasing age, the severity of neurological deficit, coma, cardiac failure, diabetes mellitus, and urinary incontinence\textsuperscript{15,16}. Of note, Lai et al\textsuperscript{16} found that a history of hypertension or transient ischaemic attacks did not increase mortality in stroke patients who survived at least 30 days. Therefore, it is likely that increasing age would have contributed to the higher mortality observed in the atrial fibrillation group of our study as they were significantly older than those without this arrhythmia (p=0.005).

Although there has been recent improvement in the utilisation of anticoagulants in patients with atrial fibrillation, physicians remain somewhat reluctant to initiate anticoagulation in the elderly\textsuperscript{17-19}. This reflects fear of an increased incidence of bleeding complications in these patients.

According to the SPAF2 study, the incidence of major haemorrhage increased from 1.7%, in those 75 years or younger, to 4.2% in those over 75, despite similar anticoagulation intensity\textsuperscript{20}. This is unfortunate as the elderly stand to benefit most from anticoagulant therapy, given that the risk of atrial fibrillation associated stroke rises significantly from 7.3% in the 60-69 age group, to 30.8% in 80-89 year olds\textsuperscript{21}.

The American Heart Association, after reviewing the available evidence, concluded that patients over 75 years of age should not be denied anticoagulants, if deemed appropriate; however, they advocated close monitoring of INR levels due to the possibility of increased bleeding complications\textsuperscript{22}. Our study suggests that increasing age was a deterrent to the initiation of anticoagulation, as those who received warfarin were significantly younger than those who didn't (74.1 years versus 79.3 years, p=0.03) and the age difference became even more significant (74.1 years versus 85 years, p=0.005) when we excluded those who did not receive warfarin because of valid contraindications. This is further reinforced by our finding that those who had a CT scan, an essential investigation prior to commencing anticoagulants, were significantly younger than those who didn't (75.1 years versus 81.8 years, p=0.002). Unfortunately, this situation, whereby elderly patients are denied appropriate treatment, for no other reason than their age, is mirrored in other clinical settings. The use of thrombolytics in acute myocardial infarction is a case in point\textsuperscript{23}.

While primary prevention trials have received the most attention, secondary prevention is equally as important, given that those who have had a stroke are at high risk of having another (2-15% in the first year and 5% per year thereafter)\textsuperscript{10}. One secondary prevention trial (the EAFT study) found that using warfarin in patients who had either a transient ischaemic attack or minor stroke reduced the incidence of recurrent stroke from 12%/year to 4%/year, a risk reduction of 66%\textsuperscript{10}. The authors concluded that treating 1000 patients with anticoagulants for one year would prevent 90 vascular events, predominantly strokes, from occurring. Fortunately, physicians are now recognising the importance of secondary prevention. This is borne out by a recent study by McCrory et al\textsuperscript{19}, which found that over 90% of physicians would start anticoagulants for patients in atrial fibrillation and who had suffered a recent embolic stroke. In our study, only 5 out of 36 patients without contraindications for warfarin were not anticoagulated. This compares quite favourably with the study by Lawson et al\textsuperscript{17} where 10 out of 35 patients without contraindications to warfarin were not anticoagulated.

It is interesting to note, in our study, the two most common reasons for not anticoagulating a patient were, firstly that active treatment was not warranted (18 patients, 14 of whom died within two weeks) and secondly, that the patient died within 24 hours (7 patients). This further reiterates that atrial fibrillation and stroke are a lethal combination and that prevention is of utmost importance.

Clinical trials have shown that warfarin is an effective means of reducing atrial fibrillation associated stroke and mortality; however, there remain several unresolved issues. When to start warfarin, and the optimal intensity of anticoagulation are examples.

The Cerebral Embolism Study found that early
anticoagulation of patients with large infarcts resulted in an increased risk of haemorrhagic transformation of the infarct\(^\text{25}\). They recommended that a delay of “several days” before initiating anticoagulation in patients with large infarcts would be “prudent”. Patients with smaller infarcts may be anticoagulated earlier, as long as a CT scan ruled out the presence of haemorrhage. These recommendations have been adopted by the American Heart Association\(^\text{22}\). In our study, warfarin was started, on average, 4.3 days after admission, ranging from the day of admission to nineteen days later, indicating the lack of a firm guideline on when to start warfarin.

With the ever present danger of causing a haemorrhagic complication by using warfarin, recent studies have examined what the optimal intensity of anticoagulation should be. Hylek et al\(^\text{25}\) found that there was a substantial increase in the risk of an ischaemic stroke in those patients with INR levels of less than two compared to those with INR levels of two. The increased risk ranged from 1.2 times to 17.6 times that associated with an INR level of two, for INR levels of 1.9 to 1.0, respectively. Another study conducted by the EAFT study group found that INR levels between 2.0 to 3.9 conferred the most protection against thromboembolic events in atrial fibrillation, while most bleeding complications occurred at INR levels above 5.0\(^\text{26}\). These two studies support the current recommendations\(^\text{22}\) that the INR should be maintained between 2.0 and 3.0.

Whether aspirin is an effective alternative is not certain. The AFASAK study\(^\text{6}\) using 75mg of aspirin per day in their trial, found that aspirin was no better than placebo in preventing strokes. In contrast, the SPAF1 study\(^\text{8}\) found that 325mg of aspirin per day reduced the risk of ischaemic stroke or systemic embolisation by 42%. Meta analysis of these two studies concluded that aspirin did reduce the risk of stroke by 36%\(^\text{12}\). The SPAF2 study\(^\text{20}\) compared aspirin (at doses of 300mg per day) to warfarin, and found that there was no statistically significant difference between the efficacy of aspirin and warfarin. Nevertheless, the current recommendation from the American Heart Association is to use aspirin in those patients in whom anticoagulation is not safe\(^\text{25}\). Use of aspirin was generally low in our study, with only nine patients being discharged on 150 mg per day of aspirin.

The SPAF3 study was undertaken in an attempt to reduce the haemorrhagic complications of warfarin therapy\(^\text{27}\). They compared adjusted-dose warfarin (INR 2-3) to low intensity, fixed dose warfarin (initial INR of 1.2-1.5) and 325mg/day of aspirin. The results were very much in favour of adjusted dose warfarin, with the rate of primary events (ischaemic stroke and systemic embolism) being significantly lower with this form of anticoagulant therapy (1.9%/year versus 7.9%/year, \(p<0.0001\)) and the risk of major bleeding being similar in both groups.

In summary, atrial fibrillation in stroke is common, and is associated with a high mortality. The message that warfarin is effective at preventing strokes in patients with atrial fibrillation is getting through, as evidenced by the high levels of utilisation of warfarin in those without contraindications. Unfortunately, age seems to have a negative effect on the likelihood of a patient receiving warfarin, most likely due to fear of bleeding complications. Recent studies suggest that the optimal form of therapy is adjusted dose warfarin to maintain the INR between 2 and 3.

**Acknowledgments**

The authors would like to express thanks to the Palmerston North Hospital Medical Trust for financial assistance.

**References**

Some time ago, a senior manager asked me across the meeting table, “Why do you think is the Geriatric Day Hospital (GDH) so expensive?” “Most available evidence actually showed that GDH is cost-effective,” I replied, “allowing of course for some publication bias.” He seemed to accept the answer.

I had subconsciously called upon EBM (Evidence-based medicine) to rescue. Strangely so, for I do not consider myself fully converted to the doctrine of EMB, in vogue as it may be. In particular, I am often puzzled by many meta-analyses.

I recently came across a meta-analysis of post-stroke depression (PSD) in which 225 relevant papers from 1985 to 1995 were reviewed. The author critically discussed the available information with respect to subject selection, instrumentation, biochemical markers, etc. The scenario presented was dismal: DSM-IV criteria are not helpful in diagnosing PSD, somatic symptomatology is unreliable, validity of depressive symptoms by patient reporting is doubtful, and neurobehavioral sequelae of stroke such as emotional lability confuse the clinical picture. Since patient-reporting is not reliable, the author justifiably called for future “systematic multi-dimensional approach to collection of information about the patient’s mood”. One hopeful approach proposed was dexamethasone suppression test. The author’s affinity to neurochemistry is also reflected in enthusiastic discussion of CSF 5-HIAA levels and SSRIs antidepressants.

Such nihilistic picture of PSD diagnosis by meta-analysis is misleading. The difficulty of diagnosing depression in stroke patients is real; nonetheless, good bedside clinical diagnosis is possible: not by cookbook criteria, not by hurried patient reporting, but by good all-rounded history taking and assessment. Disciplined observation can distinguish frontal lobe emotionalism from sad tearfulness, facial weakness from “down” appearance, aprosody (loss of voice tone modulation from non-dominant hemisphere lesion) from “depressed voice”.

Alas, for the individual patient, clinical evidence in assessment is not restricted to RCTs (randomized controlled trials) or meta-analyses. Neither is clinical insight in management. Few Chinese elderly people tolerate textbook dosage of colchicine in treatment of gouty attack; they also seem to re-