Warfarin for non-rheumatic atrial fibrillation: five year experience in a district general hospital

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Objectives: To assess the long term efficacy of and risks associated with computer aided oral anticoagulation for non-rheumatic atrial fibrillation (NRAF) in a district hospital setting.

Design: Retrospective, age stratified, event driven clinical database analysis.

Setting: District general hospital.

Participants: 739 patients receiving warfarin for NRAF between 1996 and 2001. Patients were selected from an anticoagulation database through appropriate filter settings.

Main outcome measures: Anticoagulation control (international normalised ratio (INR)) and hospitalisations for bleeding complications, thromboembolic events, and stroke.

Results: Over 1484 patient-years, computer assisted anticoagulation was uncontrolled in 38.3% of patients (INR < 2.0 or > 3.0). No significant differences in INR control were observed with respect to patient age (< 65, 65–75, and > 75 years), although to achieve adequate control of anticoagulation, the frequency of testing increased significantly with age. Annual risks of bleeding complications, thromboembolism, and stroke were 0.76%, 0.35%, and 0.84%, respectively. No significant differences in these events were observed between the three age groups studied. Patients who had thromboembolic events and haemorrhagic complications were significantly more likely to have been under-anticoagulated (INR < 2.0) and over-anticoagulated (INR > 3.0), respectively, at the time of their clinical event.

Conclusions: Computerised long term oral anticoagulation for NRAF in a community setting of elderly and diverse patients is safe and effective. Anticoagulation control, bleeding events, thromboembolic episodes, and stroke rates are directly comparable with those reported in major clinical trials. The authors therefore support the strategy of rate control with long term oral anticoagulation for NRAF in general clinical practice.

C hronic non-rheumatic atrial fibrillation (NRAF) is the most common sustained cardiac arrhythmia,1 which untreated results in a doubling of cardiovascular morbidity and mortality.2 Although atrial fibrillation affects 0.89% of the population, the majority of cases (> 80%) are confined to patients aged > 65 years.3

Management of NRAF is controversial, since disordered atrial activity predisposes to thromboembolic complications, and long term oral anticoagulation is not without risk.4 The benefits of rate limiting treatment with long term oral anticoagulation compared with no anticoagulation have been confirmed in several clinical trials.4–5 More recently, similar outcomes were reported when a policy of rate control with long term oral anticoagulation was compared with strategies of rhythm control and short term anticoagulation.6–11

The implications of these studies are that even greater numbers of patients (including the elderly) should be treated with long term oral anticoagulation.12 This raises the critical issue regarding the risk:benefit ratio of this treatment in general clinical practice. We therefore aimed at assessing the reliability, efficacy, and associated risks of computer aided long term oral anticoagulation for NRAF over a five year period in a district general hospital.

METHODS

This study was conducted at a district general hospital serving a population of 250 000. Geographic factors and the semirural locality preclude migration to nearby hospitals, thus ensuring a stable patient base. The investigation was an event driven retrospective clinical database analysis between September 1996 and September 2001.

The management of NRAF within our unit is based on accepted guidelines.13 In particular, our target international normalised ratio (INR) is 2.5 (range 2.0–3.0). INR values < 2.0 and > 3.0 indicate suboptimal anticoagulant control, and values > 8.0 indicate potentially serious breaches requiring urgent treatment. All patients presenting to our unit with stroke or transient neurological deficit while taking warfarin undergo computer tomographic imaging for further assessment.

Anticoagulation database

Since 1995, all outpatient oral anticoagulation with warfarin at our institution has been centralised and computer assisted. The software (TelePath anticoagulation module v1.3; iSOFT Systems plc, Manchester, UK) uses an accepted protocol (Charles’ algorithm).14 Frequent internal validations ensure compliance with operational standards.

For each patient, the indication for long term oral anticoagulation, target INR, intended duration of treatment, co-morbidities, and concurrent medication are mandatory input fields. Appropriate database filtering therefore enables precise identification of patient groups. At each visit, the current INR is compared with the patient’s characteristics, previous INR values, and dosing history. These variables are used to generate a schedule.

Abbreviations: AFASAK, atrial fibrillation, aspirin, and anticoagulation; BAATAF, Boston area anticoagulation trial for atrial fibrillation; INR, international normalised ratio; NRAF, non-rheumatic atrial fibrillation; PAS, patient administration system; SPINAF, stroke prevention in non-rheumatic atrial fibrillation
recommending any changes in subsequent warfarin dosage and the next test date.

The database was accessed to identify all patients receiving warfarin for NRAF. Patients receiving treatment for < 12 months were excluded. For each patient, profiles comprising age at inception, sex, number of INR tests, INR values, and dosing intervals were constructed. In addition, episodes where INR values measured < 2.0, > 3.0, and > 8.0 were identified.

**Patient administration system database**

Our hospital subscribes to the national patient administration system (PAS) (ISOFT plc, Manchester, UK), which records all inpatient episodes against a discharge diagnosis (*International classification and coding of diseases, 10th revision*). Details of patients with NRAF receiving long term oral anticoagulation (obtained from the anticoagulation database) were cross referenced with the PAS database to identify inpatient episodes over the five year study period. For each matching record, hospitalisation dates and discharge diagnoses were recorded. Discharge diagnoses were subsequently categorised with respect to (a) haemorrhagic risks of long term oral anticoagulation (any bleeding event leading to hospitalisation); (b) thromboembolic episodes (transient ischaemic cerebrovascular event, systemic arterial embolism, or pulmonary embolism); and (c) stroke (with radiological confirmation).

**Radiology database**

Details of patients presenting with stroke (from the PAS database) were cross referenced with a proprietary radiology database (PAS) (ISOFT plc, Manchester, UK), which records all inpatient episodes against a discharge diagnosis (*International classification and coding of diseases, 10th revision*). Details of patients with NRAF receiving long term oral anticoagulation (obtained from the anticoagulation database) were cross referenced with the PAS database to identify inpatient episodes over the five year study period. For each matching record, hospitalisation dates and discharge diagnoses were recorded. Discharge diagnoses were subsequently categorised with respect to (a) haemorrhagic risks of long term oral anticoagulation (any bleeding event leading to hospitalisation); (b) thromboembolic episodes (transient ischaemic cerebrovascular event, systemic arterial embolism, or pulmonary embolism); and (c) stroke (with radiological confirmation).

**Statistical analysis**

Age stratified data (patients aged < 65, 65–75, and > 75 years) are presented as mean (SD). Events are expressed as prevalence within each age group or as an annualised prevalence. Two way analysis of variance with Bonferroni post hoc testing was used for parametric between group comparisons. Fisher’s exact test was used to compare non-parametric data (InStat v3.01; GraphPad Software Inc, San Diego, California, USA). Significance was considered to be p < 0.05.

**RESULTS**

There were 739 patients with NRAF receiving long term oral anticoagulation for > 12 months during the five year study period, for a total of 1484 patient-years of treatment. Their mean (SD) age was 73.1 (4.0) (range 21–97 years) and 52.1% were men. One hundred and forty nine patients (20.2%) were > 75 years. The prevalence of female sex increased from 33% of patients aged < 65 years to 55% of patients > 75 years (p < 0.01).

**Anticoagulation control**

During the five year study period, 27 026 INR tests to monitor anticoagulant control were performed. The frequency of testing increased significantly and the interval between tests shortened significantly with advancing age (table 1). Table 1 shows the mean (SD) INR for all patients (2.43 (0.23)) and age related mean INR values. Overall, 22.9% of INRs measured < 2.0, 14.3% measured > 3.0, and in 37.2% of cases, anticoagulation was uncontrolled (INR < 2.0 or > 3.0). No significant differences in anticoagulation control were observed with respect to a patient’s age (table 1).

**Clinical events**

Figure 1 shows haemorrhagic complications of long term oral anticoagulation requiring hospitalisation (n = 28), thromboembolic events (n = 13), and stroke (n = 31). No significant differences in bleeding complications and embolic events were demonstrable between the three age groups. Similarly, the annualised combined event rate of bleeding complications, thromboembolic events, and stroke was similar in patients aged < 65 (1.48%), 65–75 (1.97%), and > 75 years (2.16%) (fig 1).

**Clinical events versus anticoagulation control**

Figure 2 shows INR control at the time of clinical events. Compared with the study group as a whole, patients who had thromboembolic and cerebrovascular events were significantly more likely to have been under anticoagulated (INR < 2.0) at the time of the event (69.2% v 22.9%, p < 0.01; 58.1% v 22.9%, p < 0.05, respectively). Similarly, the prevalence of overanticoagulation (INR > 3.0) was greater in patients experiencing a haemorrhagic complication than in the rest of the study group (42.9% v 14.3%, p < 0.05). During the five year study, 24 episodes where the INR measured > 8.0 were recorded. The prevalence of INR readings > 8.0 was similar across the three patient groups (< 65 years, n = 7 (4.7%); 65–75 years, n = 9 (3.2%); and > 75 years, n = 8 (2.6%)).

**DISCUSSION**

Over nearly 1500 patient-years of treatment in a community setting, we have shown that computer assisted dosing of warfarin can be safe and effective. In addition, we have observed that outcomes reported in clinical trials examining the use of long term oral anticoagulation in NRAF are reproducible in general clinical practice.

To date, five major randomised clinical studies of long term oral anticoagulation in NRAF have been conducted. Although the studies differed with respect to patient numbers, entry criteria, levels of anticoagulation, control group treatment (aspirin or no antiplatelet treatment), and

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**Table 1** Patient demographics and international normalised ratio (INR) tests

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>n</th>
<th>Mean age (years)</th>
<th>Men</th>
<th>Mean INR</th>
<th>Number/ patient/year</th>
<th>Dosing interval (days)</th>
<th>INR control</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>149</td>
<td>56.4 (7.8)</td>
<td>67.1%</td>
<td>2.4 (0.3)</td>
<td>17.4 (5.1)</td>
<td>21.0 (2.6)</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>65–75</td>
<td>284</td>
<td>69.8 (2.7)</td>
<td>63.0%</td>
<td>2.4 (0.2)</td>
<td>36.8 (6.7)</td>
<td>9.9 (2.2)</td>
<td>&lt;2.0 or &gt;3.0</td>
</tr>
<tr>
<td>&gt;75</td>
<td>306</td>
<td>80.3 (2.8)</td>
<td>45.4%</td>
<td>2.5 (0.3)</td>
<td>43.7 (6.0)</td>
<td>8.1 (6.9)</td>
<td>&lt;3.0</td>
</tr>
</tbody>
</table>

Data are mean (SD) or percentage.

Number of INR tests increased significantly with age: <65 v 65–75 years (p < 0.01) and 65–75 v >75 years (p < 0.01). Correspondingly, the interval between tests shortened significantly with increasing age: <65 v 65–75 years (p < 0.01) and 65–75 v >75 years (p < 0.01). No significant between group differences were observed with respect to INR control.
end points (combined and individual), all studies were
terminated prematurely after significant benefits were shown
for patients receiving long term oral anticoagulation. Table 2
compares isolated end points—anticoagulation control,
bleeding complications, thromboembolic events, and ischae-
mic strokes—from these trials with our experience (table 2).

Patients in the present study were more representative of
the general population compared with those recruited to
clinical trials. For example, patients in the current investiga-
tion were on average 4–8 years older (mean age 73 years
\(\text{v} 65–69 \text{ years}\))\(^5\–8\); only median age was reported in the AFASAK
(atrial fibrillation, aspirin, and anticoagulation) study\(^9\).

More of our patient population were women (48% \(\text{v} 24–
47\%))\(^5\–7\),\(^9\); SPINAF (stroke prevention in non-rheumatic atrial
fibrillation)\(^8\) was an all male study.

Annual ischaemic stroke rates observed in the present
study are comparable with the rates reported from clinical
trials (0.84\% \(\text{v} 0.4–2.5\%))\(^5\–9\). This is an important observation
suggesting that in this setting, clinical trial data (involving
selected and relatively young patients) may be extrapolated
to the general population. At the same time, haemorrhagic
complications observed in the current investigation (0.76\% a
year) were less frequent than expected (7–18.3\% a year).\(^5\–9\)
This difference may relate to variable trial definitions of
major and minor bleeding and the methods we used, which
recognised only hospitalised events. Our observed prevalence
of thromboembolic events (including transient ischaemic
cerebral events) is comparable with the rates reported in
clinical trials (0.35\% \(\text{v} 0–1.6\%\) a year)\(^5\–9\) and probably reflects the
fact that most of these events result in hospitalisation. Trial
data regarding thromboembolic events, however, are defi-
cient, since embolic episodes were not reported in BAATAF
(Boston area anticoagulation trial for atrial fibrillation),\(^5\) no
events were observed in AFASAK,\(^9\) and embolic rates for the
remaining studies\(^6\–8\) have been derived from composite
outcomes.

Our anticoagulation control (38% uncontrolled) is directly
comparable with the levels experienced in trials (uncon-
trolled range 17–56\%).\(^5\–9\) To achieve these levels, we found
that the frequency of testing and intervals between tests had
to be more rigorous for the elderly. This probably relates to
compliance issues\(^15\) and increasing polypharmacy\(^16\) among
patients of advancing age.

Where INR values were beyond the target range, they
tended to be \(< 2.0\), rather than \(> 3.0\). This is a feature of our
software with in-built protocols that tend to underdose
rather than overdose warfarin.\(^14\) Although this policy
safeguarded against the development of haemorrhagic complica-
tions, underanticoagulated patients were predisposed to a
threelfold increased risk of a thromboembolic event (fig 2).
Although initially alarming, these data are reassuring, since
they endorse the value of long term oral anticoagulation
(target INR of 2.5) in this group of patients.

**Study limitations**

This study has several limitations. Firstly, our methods
allowed only for the identification of hospitalised episodes
to our institution. As a result, we were apt to miss events
managed at home or at another hospital and out of hospital
Table 2 Results of landmark randomised clinical trials of long term oral anticoagulation for non-rheumatic atrial fibrillation compared with a five year experience in a district general hospital (DGH)

<table>
<thead>
<tr>
<th></th>
<th>BAATAF5</th>
<th>AFASAK9</th>
<th>SPINAF8</th>
<th>SPAF-15</th>
<th>CAFA7</th>
<th>DGH</th>
</tr>
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<td>C C</td>
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</tr>
<tr>
<td>Number</td>
<td>212</td>
<td>208</td>
<td>335</td>
<td>336</td>
<td>337</td>
<td>260</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 (9)</td>
<td>68 (9)</td>
<td>– –</td>
<td>67 (7)</td>
<td>67 (7)</td>
<td>67 (7)</td>
</tr>
<tr>
<td>Men</td>
<td>75%</td>
<td>70%</td>
<td>53%</td>
<td>55%</td>
<td>54%</td>
<td>100%</td>
</tr>
<tr>
<td>INR control</td>
<td>1.5–2.7</td>
<td>2.8–4.2</td>
<td>Aspirin</td>
<td>Placebo</td>
<td>1.4–2.8</td>
<td>Placebo</td>
</tr>
<tr>
<td>Under target</td>
<td>8%</td>
<td>26%</td>
<td>29%</td>
<td>15%</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Over target</td>
<td>9%</td>
<td>1%</td>
<td>24%</td>
<td>– –</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>17%</td>
<td>27%</td>
<td>44%</td>
<td>28%</td>
<td>57%</td>
<td>39%</td>
</tr>
<tr>
<td>Outcomes (%/year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding episodes</td>
<td>8.58</td>
<td>6.97</td>
<td>7.00</td>
<td>2.00</td>
<td>2.00</td>
<td>1.14</td>
</tr>
<tr>
<td>Embolic events</td>
<td>– –</td>
<td>– –</td>
<td>0.00</td>
<td>1.34</td>
<td>1.31</td>
<td>1.56</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.41</td>
<td>2.98</td>
<td>2.00</td>
<td>4.13</td>
<td>4.19</td>
<td>0.90</td>
</tr>
</tbody>
</table>

AFASAK, atrial fibrillation, aspirin, and anticoagulation; BAATAF, Boston area anticoagulation trial for atrial fibrillation; C Control; CAFA, Canadian atrial fibrillation anticoagulation; SPAF, stroke prevention in atrial fibrillation; SPINAF, stroke prevention in non-rheumatic atrial fibrillation; W, warfarin.

Conclusions

Long term administration of warfarin for NRAF based on computer assisted protocols in the community is safe and effective. Our experience approaching 1500 patient-years suggests that satisfactory anticoagulant control is possible (60% of measures within target range) and comparable with levels reported from landmark clinical trials.

Assuming control group event rates in clinical trials are also applicable, long term oral anticoagulation for NRAF in general clinical practice remains a highly beneficial treatment, with annual bleeding, thromboembolic event, and stroke rates of 0.76%, 0.35%, and 0.84%, respectively.

We therefore endorse the practice of computer aided dosing of warfarin and recommend its wider use for NRAF in the community, which includes elderly and heterogeneous patients after appropriate clinical assessment.

References


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