A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO)

AMAR RASH1, TOM DOWNES1, ROBIN PORTNER2, WILF W. YEO2, NICOLETTE MORGAN1, KEVIN S. CHANNER3

1 Northern General Hospital, Medicine for the Elderly, Sheffield, UK
2 Royal Hallamshire Hospital, Academic Unit of Clinical Pharmacology, Sheffield, UK
3 Royal Hallamshire Hospital, Cardiology, Sheffield, UK

Address correspondence to: K. S. Channer. Tel: +44 (0)114 271 3473. Email: kevin.channer@sth.nhs.uk

Abstract

Background: atrial fibrillation (AF) is the commonest chronic arrhythmia with a prevalence of 9% in octogenarians and accounts for 24% of the stroke risk in this population. Although trials demonstrate reductions in stroke with warfarin, audit data show that it is still underused. However, anti-coagulation in the very elderly is not without risk.

Methods: randomised open labelled prospective study of primary thromboprophylaxis for AF. Patients aged >80 and <90 were randomised to receive dose-adjusted warfarin (INR 2.0–3.0) or aspirin 300 mg. All patients had permanent AF, were ambulant, had Folstein mini mental score >25 and had no contraindications to either treatment. Follow-up was for 1 year with 3 monthly visits. The primary outcome measure was a comparative frequency of combined endpoints comprising death, thromboembolism, serious bleeding and withdrawal from the study.

Results: seventy-five patients (aspirin 39; warfarin 36) were entered (mean age 83.9, 47% male). There were significantly more adverse events with aspirin (13/39; 33%) than warfarin (2/36; 6%), P = 0.002. 10/13 aspirin adverse events were caused by side effects and serious bleeding; there were three deaths (two aspirin, one warfarin).

Conclusion: dose-adjusted warfarin was significantly better tolerated with fewer adverse events than aspirin 300 mg in this elderly population. Although aspirin 75 mg may have been better tolerated, there is no evidence for efficacy in AF at this dose.

Keywords: randomised controlled trial, thromboprophylaxis, atrial fibrillation, tolerability, elderly, warfarin, anti-coagulation, low dose aspirin, stroke prevention

Thromboprophylaxis in octogenarians with atrial fibrillation


Received 11 July 2006; accepted in revised form 6 November 2006
A. Rash et al.

Introduction

Atrial fibrillation (AF) is the commonest chronic arrhythmia. Its prevalence increases with age, affecting approximately 9% of octogenarians [1]. Stroke is the major adverse phenomenon associated with AF and in people 80–90 years old AF accounts for 24% of the risk of stroke [2]. Pooled data from randomised controlled trials have demonstrated a reduction in the risk of stroke by about 2/3 in patients treated with warfarin and 1/3 in patients treated with aspirin [3–7]; however, these trials did not specifically recruit patients over the age of 80. The risks of anti-coagulation are not insignificant (the annual risk of major bleeding with warfarin is 2% compared to 1% with aspirin [8]) and increases in the very elderly [9]. The risk increases dramatically when the INR is greater than 4.5 [10]. Existing data have not clearly defined the risks and benefits of treatment with warfarin and aspirin specifically in people 80–90 years old, yet it is this group of patients who may gain most from therapy. Audit data suggest that anti-coagulants are underused, particularly in elderly patients [11]. Part of the explanation for this is the reluctance of physicians to expose their patients to the risk because of an absence of clear trial evidence of benefits [12]. When making treatment decisions it is also important to consider drug tolerability and compliance, as adherence with prescribed medication can influence efficacy [13].

This study aimed to evaluate oral anti-coagulation with dose-adjusted warfarin (INR 2.0–3.0) and aspirin 300 mg to address the differences between risks and benefits in octogenarians. A sub-study was designed to evaluate adherence with prescribed medication.

Methods

Study design

This was a randomised open labelled prospective study. The main study and sub-study were granted ethical approval by the North Sheffield Committee on Medical Research Ethics. Patients were recruited from main study and sub-study if they had any one of the following: one or more falls (without formal gait assessment) or syncopal episode within the last 12 months; epileptiform seizures; alcoholic liver disease or excess alcohol intake (>21 and >14 units per week, males and females, respectively); previous history of thromboembolism (stroke, transient ischaemic attack, systemic embolus); gastrointestinal or genitourinary bleeding in the previous 6 months; previous intracranial haemorrhage; BP>180/100; abnormal resting prothrombin time; Folstein mini mental state examination score <26; previous intolerance/allergy to warfarin or aspirin; already taking warfarin.

Baseline assessment

Patients attended a baseline screening clinic and a proforma was used to record a full medical history and examination findings. During this visit, patients also completed the Folstein mini mental state examination and Barthel index. Blood was taken for full blood count, urea and electrolytes, glucose, clotting, liver function and thyroid function tests and a 12-lead electrocardiograph was recorded. A chest X-ray and echocardiogram were done prior to randomisation. Written informed consent was obtained from all the patients.

Randomisation

Eligible and consenting patients were randomised to receive either dose-adjusted warfarin (INR 2.0–3.0) or aspirin 300 mg. Randomisation was performed by opening sealed envelopes in numbered sequence, prepared by an individual not otherwise involved in the study and prepared from a computer-generated random numbers program. Patients randomised to receive warfarin were initiated on treatment at the baseline screening clinic by the low dose regimen (2 mg per day for 2 weeks with their first anti-coagulation clinic visit at 2 weeks; the INR measured after 2 weeks dosing at 2 mg per day predicts the maintenance dose) [14]; INR monitoring was through the usual hospital based anti-coagulation clinics.

Follow-up

Patients were followed up for 1 year at 3-monthly intervals. All adverse events and reasons for withdrawal were recorded.

Compliance sub-study

Compliance was assessed using the Medication Event Monitoring System (MEMSV). This is an electronic system that is designed to compile the dosing histories of ambulatory patients prescribed oral medications. The system comprises two parts: a standard plastic vial with threaded opening and a top for the vial that contains a micro-electric circuit that registers when the vial is opened and when it is closed. Patients randomised to receive warfarin were initiated on treatment at the baseline screening clinic by the low dose regimen (2 mg per day for 2 weeks with their first anti-coagulation clinic visit at 2 weeks; the INR measured after 2 weeks dosing at 2 mg per day predicts the maintenance dose) [14]; INR monitoring was through the usual hospital based anti-coagulation clinics.

Statistical analysis

The study aimed to address the differences between risk and benefit in the two treatment arms. Assumptions made for power calculation: (all events are annual rates) death rate of 10% in the population studied [15]; warfarin to decrease the risk of thromboembolism from 7 to 2.5% [16] and aspirin from 7 to 5% [6]; significant bleed rate of 2% for warfarin and 1% for aspirin [8]; withdrawal from the study 38% with warfarin and 13% with aspirin [3].
The primary outcome measure was a comparative frequency of combined endpoints comprising death, thromboembolism (stroke, transient ischaemic attack, systemic embolus), serious bleeding (intracranial haemorrhage, fall in haemoglobin by >2 g/dl, need for blood transfusion) and withdrawal from the study (voluntary refusal to continue with the study, intolerance/side effects of treatment and INR>4.5 on two occasions).

The secondary outcome measures were: compliance; minor bleeding; percentage time in target INR range (warfarin only). The study would need 70 patients in each arm to show a combined endpoint difference of 23% between warfarin and aspirin with 80% power at P<0.05.

Data from the main study was entered onto an Excel spreadsheet. Differences between the baseline characteristics of the two groups were measured using the Mann–Whitney test for quantitative variables and the chi-squared test for categorical variables, except LV function where the Kendall tau-b test was used. Differences in outcomes were measured using Fisher’s exact test and the chi-squared test. Analysis was performed using Statistical Package for the Social Sciences (SPSS) version 11.5. Data from the MEMSV vials was downloaded with its own Powerview software and analysed using the Mann–Whitney test. Percentage time in target INR range was calculated by the Rosandaal method using the Dawn AC Time in Range Calculator.

Results

Patients were recruited from medical outpatient clinics and ECG clinics. A number of clinicians referred potentially eligible patients to be considered for entry into the study and were aware of the inclusion and exclusion criteria. Accurate data regarding the percentage of octogenarians screened that were ineligible to participate were therefore not available. A total of 75 patients were entered into the study over an 18 month period; 36 patients were randomised to receive dose-adjusted warfarin (INR 2.0–3.0) and 39 patients to receive aspirin 300 mg. There were no significant differences in baseline demographic characteristics between the two groups (Table 1). The median age of all patients was 83 years (range 80–90) and 47% were male. A total of 30 patients were recruited and entered into the compliance sub-study, of which 17 were receiving aspirin and 13 warfarin.

Primary outcomes (Table 2)

A total of 17/39 (44%) patients reached an endpoint in the aspirin group versus 9/36 (25%) in the warfarin group (difference 19%, 95% CI 2–40, P = 0.144, Fishers exact test). A total of 13/39 (33%) had an adverse event in the aspirin group versus 2/36 (6%) in the warfarin group (difference 27%, 95% CI 11–45, P = 0.002, Fishers exact test). Of the 13 patients randomised to receive aspirin who had an adverse event, 7 cases were due to intolerable side effects (gastrointestinal disturbance) and 3 were due to serious bleeding. There were 11/75 (15%) voluntary withdrawals from the study (4 from the aspirin group and 7 from the warfarin group, P = 0.26) and the reasons for withdrawal were similar between groups. These were either too much travelling or a desire not to continue with the study except for two patients who later decided to stop warfarin treatment because of concerns over its safety.

There were two deaths in the aspirin group and one death in the warfarin group. The relative risk of an adverse event occurring in the aspirin group was 6 (95% CI 1.5–24.8) versus the warfarin group.

Secondary outcomes

Compliance sub-study (Figure 1)

There were two withdrawals from the sub-study, one from each treatment arm. The median percentage of days with a correct daily dose taken by the warfarin group (n = 12) was 96.4% versus 100% for the aspirin group (n = 16) (difference 3.6%, 95% CI 0.0–7.1, P = 0.08 adjusted for ties, Mann–Whitney test).

### Table 1. Baseline characteristics (n = 75)

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n = 36)</th>
<th>Aspirin (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age</td>
<td>83.5 (80–90)</td>
<td>82.6 (80–90)</td>
<td>0.25</td>
</tr>
<tr>
<td>Male (%)</td>
<td>14 (39%)</td>
<td>21 (54%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>17 (49%)</td>
<td>18 (46%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>4 (11%)</td>
<td>11 (28%)</td>
<td>0.07</td>
</tr>
<tr>
<td>No. of regular drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1–8)</td>
<td>4 (8–12)</td>
<td>0.61</td>
</tr>
<tr>
<td>Four or more (%)</td>
<td>17 (49%)</td>
<td>21 (54%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Cardiomegaly on chest X-ray (%)</td>
<td>25 (69%)</td>
<td>19 (49%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Left ventricular systolic function on echocardiogram</td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Normal (%)</td>
<td>29 (76%)</td>
<td>24 (71%)</td>
<td></td>
</tr>
<tr>
<td>Mildly impaired (%)</td>
<td>4 (11%)</td>
<td>8 (24%)</td>
<td></td>
</tr>
<tr>
<td>Moderately impaired (%)</td>
<td>5 (13%)</td>
<td>2 (6%)</td>
<td></td>
</tr>
<tr>
<td>Median (range) LA size (mm)</td>
<td>44 (35–54)</td>
<td>45 (27–56)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

### Table 2. Primary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n = 36)</th>
<th>Aspirin (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined outcome</td>
<td>9 (25%)</td>
<td>17 (44%)</td>
<td>0.114</td>
</tr>
<tr>
<td>Adverse events</td>
<td>2 (6%)</td>
<td>13 (33%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other embolic</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Serious bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intol/side effects</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2 INR 4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voluntary withdrawal</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
A. Rash et al.

Figure 1. Percentage of days with a correct daily dose taken by warfarin (n = 12) and aspirin (n = 16) treated patients.

Minor bleeding

10/75 (13%) patients experienced minor bleeding at some point during follow up (four from the aspirin group and six from the warfarin group, P = 0.39). In all instances minor bleeding was due to epistaxis or haematuria and was not to an extent that required withdrawal from the study (as per protocol).

Percentage time in INR range

For the patients randomised to receive warfarin the mean percentage (SD) time in the target INR range of 2.0–3.0 was 69.2% (17.7).

Discussion

The results of our study suggest an advantage of dose-adjusted warfarin (INR 2.0–3.0) over aspirin 300 mg in this population, although it was underpowered for the difference to reach statistical significance. However, in terms of safety there were significantly fewer adverse reactions with warfarin than aspirin and adherence to medication was equivalent in both treatment arms.

Of the patients randomised to receive aspirin 300 mg who withdrew from the study because of side effects, the reason in all cases was gastrointestinal disturbance. The three patients who had significant bleeds all experienced a fall in haemoglobin of more than 2 g/dl and were referred for further investigation. This may be because of increasing intolerability of aspirin with increasing age. It is also suggested that the gastro-toxicity of aspirin is dose related [13] and it could be argued that aspirin 75 mg would have been better tolerated by this elderly group of patients. However, we chose 300 mg daily as this is the dose which had the best evidence of efficacy for thromboprophylaxis in patients with atrial fibrillation [6, 17, 18] and is the dose recommended by the American Heart Association. Gastro-protection with a proton pump inhibitor was not prescribed as routine as by the American Heart Association. Gastro-protection with a proton pump inhibitor may have reduced the number of adverse events in the aspirin group. There were no serious bleeding events in the group randomised to receive dose-adjusted warfarin and only one patient had two or more INR readings over 4.5. The use of a low dose initiation regime (2 mg per day for up to 2 weeks) [14] and the monitoring of the INR by an effective and responsive anti-coagulation clinic may have played an influential role in these observations. We also reported a much lower rate of voluntary withdrawal from the warfarin group than we had expected. Only 19% withdrew compared to the 38% that we had previously anticipated [3]. This could be explained by the strict exclusion criteria used in selection, resulting in a relatively ‘fit’ group of octogenarians included in the study—we only observed three deaths whereas the expected annual death rate in this age group is 10% [15]. However, as this group of patients age, they may become frailer and exhibit deterioration in mobility and cognitive function. The number of warfarin related adverse events and voluntary withdrawals would therefore be expected to increase. A longer period of follow-up would be required to detect these events and it is a limitation of this study that follow up was only for 12 months.

Most authorities recommend a target INR of 2.0–3.0 with warfarin treatment for thromboprophylaxis in AF and this was the target range used in our study. The anti-coagulation control was good in this group, with a mean time in target INR range of 69.2%. This compares with other studies, which have shown that patients with access to anti-coagulation clinics have INRs within the target range over 60% of the time [19, 20]. Compliance with warfarin treatment was also very good as shown in the sub-study, with the median percentage of correct daily dose of 96.4% despite the perceptions that warfarin treatment may be too complicated for the very elderly.

Concern over the risk/benefit ratio has led to physicians being cautious about the use of warfarin in octogenarians. There are no previous trial data to support its routine use in this cohort. Studies from around the world have shown that only a minority of patients over 80 years are anti-coagulated with warfarin for prophylaxis against stroke in association with atrial fibrillation—and this remains the case [21–35] (Table 3). Taking all patients over 65 years of age, warfarin is used in less than 50% in all surveys published since 1990 (Table 3).

While our study was not powered to detect the differences in benefit between dose-adjusted warfarin and aspirin 300 mg in terms of thromboembolic risk (the proposed BAFTA trial will address this [36]), it did show that in a selected group of octogenarians warfarin is safe, well tolerated and acceptable with well controlled anti-coagulation in such patients.

Key points

• Atrial fibrillation is the commonest chronic arrhythmia and stroke is the major adverse event associated with it in 80–90 year olds.
Warfarin was significantly better tolerated with fewer adverse events than aspirin 300 mg in a selected group of octogenarians.

Acknowledgements
The authors would like to thank the following colleagues for their support and help: Chris Austin, Liz Benton, Mike Jennings, Peter Lawson, Tracey Young and all the staff based at Sheffield Teaching Hospitals’ anti-coagulation clinics and cardiology departments.

Conflicts of interest
None.

Declaration of sources of funding
None.

Provenance of equipment
Medication Event Monitoring System (MEMSV), Aardex Ltd, Switzerland. Dawn AC Time in Range Calculator provided by 4S Dawn Software, 4S Information Systems Ltd, 4 The Square, Milnthorpe, Cumbria, LA7 7QJ, UK.

References
A. Rash et al.


