Oral Anticoagulation and Hemorrhagic Complications in an Elderly Population With Atrial Fibrillation

Mhairi Copland, BSc, MBChB, MRCP; Isobel D. Walker, MD, FRCP, FRCPath; R. Campbell Tait, BSc, FRCP, MRCPath

Background: Warfarin sodium therapy in patients with atrial fibrillation markedly reduces the incidence of embolic stroke. However, in elderly patients warfarin therapy is often underused owing to the perceived higher risk of hemorrhagic complications.

Objectives: To assess the quality of anticoagulant control and the incidence of hemorrhagic complications and stroke in an elderly population (>75 years old) compared with a younger control group (between 60 and 69 years) and to assess the quality of anticoagulant control and incidence of hemorrhagic complications in those patients who recently commenced receiving warfarin therapy (first year of therapy).

Patients and Methods: In this retrospective follow-up study, anticoagulant control and the incidence of hemorrhagic complications and stroke were assessed in an elderly population (>75 years old) compared with a younger control group (between 60 and 69 years), all with atrial fibrillation (target international normalized ratio [INR] 2.5) and attending a hospital outpatient anticoagulant clinic.

Results: A total of 328 patients were studied over a 21-month period. There were 204 patients in the control group providing 288 patient-years of follow-up and 124 patients in the elderly group providing 170 patient-years of follow-up. The percentage of INR results in the target range was not statistically significantly different between the elderly and control groups (71.5% vs 66.1%) and the occurrences of incidences of INR greater than 7 were 4.2% in the control group and 4.7% in the elderly group (P=.96). The incidences of major hemorrhage were 2.8% per year in the elderly group and 2.9% per year in the control group (P=.96); overall incidence was 2.8% (95% confidence interval, 1.3%-4.4%). One hundred one of the 328 patients studied commenced warfarin therapy during or within 3 months of the start of the study. In this induction group, 62.1% of INRs were within the target range compared with 70.9% of INRs in patients who had been receiving warfarin therapy for more than 3 months at the start of the study (P=.002). The incidences of INR greater than 7 and major hemorrhage were 7.9% per year and 6.9% per year, respectively, in the cohort who recently began warfarin therapy compared with 3.4% per year and 1.7% per year in the group who were receiving warfarin therapy for more than 3 months.

Conclusion: While it was impossible to consider any selection bias at the level of referral to the clinic, these findings suggest that the elderly population attending our anticoagulant clinic did not have poorer anticoagulant control or an increased incidence of hemorrhage while receiving warfarin therapy.

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Atrial Fibrillation (AF) is an important independent risk factor for ischemic stroke and is associated with a 6-fold increase in risk. A recent meta-analysis of 6 randomized trials studying antithrombotic therapy for stroke prevention showed a relative risk reduction of 62% for those receiving warfarin sodium therapy compared with placebo and 36% compared with aspirin. Warfarin provides optimum protection against ischemic stroke at an international normalized ratio (INR) of 2.0 to 3.0. An INR greater than 3.0 would be protective against ischemic stroke but increases the risk of hemorrhagic complications. In patients who have AF, increasing age is a known risk factor for ischemic stroke. These patients, therefore, benefit from anticoagulation therapy. However, the elderly population is thought to have a greater risk of hemorrhagic complications, and warfarin therapy tends to be underused.

In this study, the quality of anticoagulant control and the incidence of hemorrhagic complications in the elderly population was not statistically significantly different compared with the control group. The incidence of major hemorrhage was 2.8% per year in the elderly group and 2.9% per year in the control group. Overall incidence was 2.8% (95% confidence interval, 1.3%-4.4%). One hundred one of the 328 patients studied commenced warfarin therapy during or within 3 months of the study. In this induction group, 62.1% of INRs were within the target range compared with 70.9% of INRs in patients who had been receiving warfarin therapy for more than 3 months at the start of the study. The incidences of INR greater than 7 and major hemorrhage were 7.9% per year and 6.9% per year, respectively, in the cohort who recently began warfarin therapy compared with 3.4% per year and 1.7% per year in the group who were receiving warfarin therapy for more than 3 months. While it was impossible to consider any selection bias at the level of referral to the clinic, these findings suggest that the elderly population attending our anticoagulant clinic did not have poorer anticoagulant control or an increased incidence of hemorrhage while receiving warfarin therapy.
PATIENTS, MATERIALS, AND METHODS

In a retrospective follow-up study of all patients between 60 and 69 years of age and those older than 75 years who had AF and were attending the hospital anticoagulant clinic were enrolled in this study. The only exclusion criterion was those patients who had a prosthetic heart valve.

A total of 328 patients (143 males and 185 females) were studied over a 21-month period (January 1, 1998, to September 30, 1999). Those patients receiving warfarin therapy prior to January 1, 1998, and those commencing warfarin therapy between January 1, and December 31, 1998, were included in this study. Quality of anticoagulant control was assessed by calculating the patient's percentage of attendances at the anticoagulant clinic where the INR was within an acceptable target range of 1.8 to 3.3 (mean ± standard acceptable in the United Kingdom, 2.5 ± 0.75). The incidence of hemorrhagic complications was based on the number of bleeding events per patient-year of follow-up while receiving warfarin therapy. A major hemorrhage was any bleeding event that was fatal; involved the central nervous system; or required hospitalization, blood transfusion, or surgical intervention. Statistical analyses were performed using the χ² test. P < .05 was statistically significant.

RESULTS

The subject characteristics are detailed in Table 1. There were 204 patients in the control group (mean age, 64.7 years) providing 288 patient-years of follow-up and 124 in the elderly group (mean age, 78.3 years; age range, 75-89 years) providing 288 patient-years of follow-up. Incomplete data were available for 6 patients who were lost to follow-up from the anticoagulant clinic.

A total of 3010 INRs were checked in both groups during the 21-month study period (average, 6.6 per patient-year). There were a total of 659 high INRs (>3.3), 448 in the control group (1.6 per patient-year), and 211 in the elderly group (1.2 per patient-year). There were a total of 259 low INRs (<1.8), 156 in the control group (0.6 per patient-year) and 103 in the elderly group (0.6 per patient-year). Therefore, overall 68.2% of INRs were in the target range; 60.1% in the control group and 71.5% in the elderly group (P = .13). There were 20 episodes of an INR greater than 7: 12 in the control group and 8 in the elderly group (0.7% in both groups). The incidences of major hemorrhage were 2.8% per year and 2.9% per year in the control and elderly groups, respectively (P = .96); overall incidence was 2.8% (95% confidence interval, 1.3%-4.4%). The overall incidence of intracranial hemorrhage was 0.9%; 0.7% in the control group and 1.2% in the elderly group (P = .61).

The details of patients with hemorrhagic complications are given in Table 2. All patients discontinued warfarin therapy following a bleeding episode. One patient started receiving clopidogrel therapy, and 1 patient commenced receiving aspirin therapy following colonic polypectomy. Two patients died following intracranial hemorrhage—one in the elderly group and 1 in the control group. No patients died of gastrointestinal tract hemorrhage.
however, 1 patient with mitral valve disease died of congestive heart failure following a gastrointestinal tract hemorrhage.

In the course of the study, there were 3 episodes of ischemic stroke in 2 patients in the elderly group. The patients were both women, aged 79 and 82 years with therapeutic INRs of 2.5 and 3.4, respectively, at the time of stroke. Information regarding the INR at the time of the first ischemic event in the patient having 2 strokes was unavailable. Both of these patients died of ischemic stroke.

One hundred one of the 328 patients studied commenced receiving warfarin therapy during or within 3 months of the start of the study (Table 3). In this induction group in the first year of warfarin therapy, 62.1% of INRs were within the target range compared with 70.9% of INRs in patients who had been receiving warfarin therapy for longer than 3 months at the start of the study (P=.005). The incidence of INR greater than 7 was 7.9 episodes per 100 patient-years in the cohort in the first 12 months of warfarin therapy compared with 3.4 episodes per 100 patient-years in the group receiving warfarin therapy for longer than 3 months. The incidence of major hemorrhage was 6.9 episodes per 100 patient-years in the cohort in the first 12 months of warfarin therapy compared with 1.7 episodes per 100 patient-years in the group receiving warfarin therapy for longer than 3 months (P<.005). None of the patients in the cohort who recently commenced receiving warfarin therapy bled within the first 3 months of therapy; however, 7 of the 101 patients in this group had major bleeding episodes between 5 and 12 months of therapy. There was no statistically significant difference in the risk of serious hemorrhage between the control and elderly groups (5.9% vs 7.4%, respectively) in the first year of warfarin therapy.

These findings suggest the elderly population attending our anticoagulant clinic did not have poorer anticoagulant control or an increased overall incidence of hemorrhage while receiving warfarin either in the first year of treatment or when receiving long-term therapy. These results are in accord with those of a recently published study that showed that in clinical practice the incidence of hemorrhagic complications and stroke were comparable with those in randomized studies despite statistically significant differences in patient characteristics and poorer anticoagulant control. It was impossible to consider any selection bias at the level of referral to the clinic. Potentially, referring cardiologists may have selected antiplatelet therapy for elderly patients with a complicated medical history or perceived high risk of bleeding.

Although previous studies have suggested an increased risk of intracranial hemorrhage in elderly patients, our results do not support this. Two of the 124 patients in the elderly group had intracranial bleeding compared with 2 of the 204 patients in the control group (P=.61). While the numbers are small, the outcome for patients with intracranial hemorrhage was poor with a mortality of 50% (2 of 4 patients).

These results confirm those of previous studies that recent commencement of warfarin therapy (<1 year in this study) is a strong independent risk factor for major hemorrhage. The risk was not greater in the elderly group compared with the control group. Indeed, the elderly group had superior anticoagulant control during the first year of therapy and a lower incidence of hemorrhagic complications, although the difference was not significant.

These results demonstrate that long-term anticoagulation with warfarin therapy should be considered in all patients with AF who do not have contraindications. Although there is no comparison with controls who did not receive warfarin therapy, this study provides evidence to support the cautious use of warfarin for stroke prevention in the elderly population with AF as the observed rate of ischemic stroke is low and there is no increased risk of hemorrhagic adverse effects.

**Table 3. Characteristics of Elderly and Control Groups: Long vs Short Duration of Therapy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Both Groups</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All Long Duration, &gt; 12 mo (n = 227)</td>
<td>All Short Duration, ≤ 12 mo (n = 101)</td>
<td>Control Group, Aged 60-69 y (n = 65)</td>
</tr>
<tr>
<td>Total follow-up, y (average No. of months/patient)</td>
<td>357 (18.9)</td>
<td>101 (12.1)</td>
<td>67 (12.4)</td>
</tr>
<tr>
<td>No. of INRs* (No. of INRs per patient-year) checked</td>
<td>2110 (5.9)</td>
<td>900 (8.8)</td>
<td>593 (8.8)</td>
</tr>
<tr>
<td>High INRs</td>
<td>478 (1.4)</td>
<td>181 (1.8)</td>
<td>137 (2.0)</td>
</tr>
<tr>
<td>Low INRs</td>
<td>127 (0.4)</td>
<td>132 (1.3)</td>
<td>81 (1.2)</td>
</tr>
<tr>
<td>% of INR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out of target</td>
<td>29.1</td>
<td>38.0</td>
<td>40.2</td>
</tr>
<tr>
<td>In target</td>
<td>70.9†</td>
<td>62.0†</td>
<td>59.8</td>
</tr>
<tr>
<td>No. of episodes with INR &gt; 7 (% per patient-year)</td>
<td>12 (3.4) †</td>
<td>8 (7.9) †</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>No. of hemorrhages (% per patient-year)</td>
<td>6 (1.7) †</td>
<td>7 (6.9) †</td>
<td>5 (7.4)</td>
</tr>
</tbody>
</table>

*INRs indicates international normalized ratios.
†P=.002, χ² test.
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REFERENCES


