Bleeding During Warfarin and Aspirin Therapy in Patients With Atrial Fibrillation

The AFASAK 2 Study

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Background: Treatment with warfarin sodium is effective for stroke prevention in atrial fibrillation but many physicians hesitate to prescribe it to elderly patients presumably because of the associated risk for bleeding and the inconvenience of frequent blood tests for the patients.

Methods: In the Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK 2) Study, we studied the rate of bleeding events associated with the incidence of thromboembolic events in patients receiving warfarin sodium, 1.25 mg/d; warfarin sodium, 1.25 mg/d, plus aspirin, 300 mg/d; aspirin, 300 mg/d; or adjusted-dose warfarin therapy aiming at an international normalized ratio of the prothrombin time ratio (INR) of 2.0 to 3.0. The study was scheduled for 6 years from May 1, 1993, but owing to evidence of inefficiency of low-intensity therapy plus aspirin from another study it was prematurely terminated on October 2, 1996. Minor and major bleeding events were recorded prospectively. The rate of bleeding was calculated using the Kaplan-Meier method and risk factors were identified by the Cox proportional hazards model.

Results: Of 677 included patients, 130 (median age, 77 years; range, 67-89 years) experienced bleeding. One woman and 12 men experienced major bleeding. Four had intracranial bleeding: 2 cases were fatal and 2 were nonfatal. During treatment with mini-dose warfarin, warfarin plus aspirin, aspirin, and adjusted-dose warfarin, the annual rate of major bleeding was 0.8%, 0.3%, 1.4%, and 1.1%, respectively (P = .20). After 3 years of treatment the cumulative rate of any bleeding was 24.7%, 24.4%, 30.0%, and 41.1% (P = .003), respectively. Increasing INR value (P < .001) and prior myocardial infarction (P = .001) were independent risk factors for bleeding, whereas increasing age was not.

Conclusions: Fixed mini-dose warfarin and aspirin alone or in combination were associated with both minor and major bleeding. The small number of major bleeding events in patients receiving adjusted-dose warfarin therapy as compared with those receiving less intensive antithrombotic treatments and the finding of no significant influence of age on the risk for bleeding indicate that even elderly patients with atrial fibrillation tolerate adjusted-dose warfarin therapy (INR, 2.0-3.0).

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SUBJECTS AND METHODS

The AFASAK 2 Study was a randomized controlled trial conducted from a single center recruiting outpatients with chronic atrial fibrillation. The design and methods of the study have been described elsewhere.8

SUBJECTS

Patients older than 18 years with nonvalvular chronic atrial fibrillation were eligible. In summary, exclusion criteria were lone atrial fibrillation in patients younger than 60 years, recent stroke or transient ischemic attack, concomitant disease or other conditions increasing the risk for bleeding, and ongoing or planned oral anticoagulant therapy.

Participants were recruited from general practices in Copenhagen, Denmark, and the surrounding areas. Before randomization, patients were interviewed and examined by 1 of 3 investigators. Baseline characteristics were recorded in standardized case record forms.

The study protocol was approved by the regional ethics committees and the Danish National Board of Health, and the trial was performed according to the Second Declaration of Helsinki. All patients received oral and written information about the background and procedures of the trial, and signed informed consent was obtained.

RANDOMIZATION AND STUDY TREATMENTS

According to computer-generated randomization, eligible patients were assigned to treatment with (1) warfarin sodium, 1.25 mg/d; (2) warfarin sodium, 1.25 mg/d, plus aspirin, 300 mg/d; (3) aspirin, 300 mg/d; or (4) adjusted-dose warfarin therapy in the intensity of INR 2.0 to 3.0. Warfarin (tablets of 2.5 mg and 1.25 mg; Marevan) and aspirin (nonenteric-coated tablets of 150 mg; Hjertemagnyl) were supplied by Nycomed DAK A/S, Roskilde, Denmark. The treatment was not blinded. Discontinuation of the study treatment was allowed for a maximum of 4 weeks per year.

THERAPY MONITORING

Treatment with adjusted-dose warfarin sodium was initiated with a loading dose of 10 mg and during the following days dose adjustments were made to achieve an INR of 2.0 to 3.0. When the intended anticoagulation level was reached, INR determinations were performed with a maximum interval of 4 weeks.

After an introduction with weekly monitoring, INR values in patients receiving 1.25-mg/d warfarin sodium with or without aspirin were monitored once every 3 months.

Blood samples were analyzed with the automatic coagulation analyzers Nycomatic (Nycomed Pharma A/S, Oslo, Norway), Thrombolyser (Behringwerke AG, Marburg, Germany), and ACL 200 (Instrumentation Laboratory, Milan, Italy). The thromboplastins used were Nycostest PT (Nycomed Pharma A/S) with an international sensitivity index of 0.97 and SPA (Diagnostica Stago, Asnieres-sur-Seine, France) with an international sensitivity index of 1.04.

Aspirin therapy was not monitored by blood tests.

FOLLOW-UP

Patients receiving treatment were followed up with physical examinations 3 and 6 months after inclusion, and then at 6-month intervals until termination of the trial. By the end of the study all patients were interviewed concerning major bleeding events and end points that might have occurred since the last evaluation in the study center.

HEMMORRHAGIC EVENTS

Hemorrhagic events were classified as minor or major according to the loss of blood and the severity and rate of bleeding.

A major bleeding event was defined as being fatal, life-threatening, or potentially life-threatening. Bleeding leading directly to death was characterized as fatal; bleeding requiring surgical or angiographic intervention to stop the loss of blood and bleeding leading to cardiopulmonary arrest or irreversible damage such as myocardial infarction, stroke, or blindness was characterized as life-threatening. Hemorrhagic events leading to 2 of the following 3 consequences were considered potentially life-threatening: (1) severe loss of blood requiring transfusion of more than 3 U of erythrocytes (1 U equals 250-300 g of erythrocytes), (2) decline in systolic blood pressure to below 90 mm Hg, or (3) critical anemia, ie, a hemoglobin substance concentration below 6.0 mmol/L. All reports on major bleeding events were confirmed by hospital records.

Minor bleeding events were nonthreatening and included overt or occult gastrointestinal tract bleeding, hemoptysis, gross hematuria, nose bleeding, bruising, symptomatic anemia ascribed to bleeding, and chronic bleeding with minor or moderate loss of blood.

OUTCOME EVENTS

The primary end point was a stroke (ischemic and hemorrhagic) or a systemic thromboembolic event. The secondary end points were acute myocardial infarction, transient ischemic attack, and death not due to other end points. These events have been defined elsewhere.8

STATISTICAL ANALYSES

Sample size estimations have been reported elsewhere.15 Baseline comparisons among the 4 groups were performed using the χ² test for categorical data and analysis of variance for continuous data.

Patients who experienced both major and minor bleeding events were categorized as patients with major bleeding. For the 4 groups the cumulative rates of total hemorrhagic events were calculated using the Kaplan-Meier method,16 and the log-rank statistics were used for comparison of the event rates in the 4 groups. Time until a hemorrhagic event was analyzed using the Cox regression model.17 In patients with more bleeding events, the time to the first hemorrhagic event was used in the analysis. Backward selection was used to identify significant risk factors. The INRs were calculated using linear interpolation for days on which INR was not observed and were consequently included as time-dependent covariates in the risk factor analysis. Because of the small number of major bleeding events, the risk factor analysis was performed for all bleeding events together.

The mean rate of major and minor bleeding (the number of patients with bleeding per patient-year, ie, from randomization to a hemorrhagic or thromboembolic event or to termination of the trial) was calculated to facilitate comparison with other studies.
Of the 677 randomized patients, 130 (19.2%) experienced bleeding (Table 2). The male-female ratio in patients with bleeding was 3:2 and the mean age was 74.4 years (median age, 77 years; range, 67-87 years).

A total of 13 major and 139 minor bleeding events were noted. In 3 patients a minor bleeding event was succeeded by a major bleeding event, and 16 patients had more than 1 minor hemorrhagic event. No hemorrhagic events were reported in withdrawn patients.

**MAJOR BLEEDING**

Thirteen patients (1 woman and 12 men) had a major hemorrhagic event. The patients were aged between 69 and 87 years (median age, 79 years; mean ± SD, 78.2 years) and major bleeding occurred from 14 to 830 days (median, 202 days; mean ± SD, 235 days) after initiation of treatment.

Detailed information on the major hemorrhagic events is reported in Table 3. Four hemorrhagic events were intracerebral, 8 were gastrointestinal, and 1 was retinal. In 1 patient receiving aspirin (patient 5) and in 1 receiving adjusted-dose warfarin therapy (patient 11) intracerebral bleeding occurred spontaneously, whereas the fatal intracerebral bleeding in patient 12 and the nonfatal intracerebral bleeding in patient 3 were traumatic. Four patients receiving aspirin monotherapy who experienced major gastrointestinal tract bleeding all had a lesion in the stomach. Only 1 patient receiving combined warfarin and aspirin therapy (patient 4) had a major gastrointestinal bleeding event, which was ascribed to diverticulitis in the colon. In 2 patients receiving low-dose therapy (patients 1 and 2) with lower gastrointestinal tract bleeding and anemia, the source of bleeding was not identified. Only 1 patient with major bleeding (patient 13) had a neoplasm. Retinal bleeding resulting in permanent blindness in 1 eye occurred in 1 patient receiving adjusted-dose warfarin therapy.

**MINOR BLEEDING**

A total of 139 minor hemorrhagic events were noted in 120 patients. Twenty-nine cases of gastrointestinal tract bleeding, 52 cases of nose bleeding, 23 cases of gross hematu-
bleeding, however, was significantly more frequent in patients receiving adjusted-dose warfarin therapy than in patients receiving any of the other treatments ($P = .02$). Anemia was the first sign of bleeding in 3 patients with minor bleeding. They were all evaluated in the hospital.

A total of 10 patients with minor nose bleeding had acute treatment in the hospital emergency department, but the events did not fulfill the criteria of major bleeding.

### RATE OF BLEEDING

After 3 years of treatment, the cumulative rate of bleeding was 24.7%, 24.4%, 30.0%, and 41.1% in patients receiving mini-dose warfarin, warfarin plus aspirin, aspirin, and adjusted-dose warfarin, respectively. The cumulative incidence was significantly higher in patients receiving adjusted-dose warfarin than in the other groups ($P = .003$), but the difference was ascribed only to a higher rate of minor bleeding. The probability of survival on treatment without any bleeding in the 4 groups is illustrated in the **Figure**.

The annual risk for minor respective major bleeding events according to assigned treatment are listed in Table 2. The rate of major bleeding ranged from 0.3% to 1.4% per year among the 4 groups. The very small number of major events and consequently the low incidence rates do not allow for statistical comparison, but the events seem equally distributed among the 4 groups. Minor bleeding, however, was significantly more frequent in patients receiving adjusted-dose warfarin than any of the other treatments ($P = .02$).

### ANTICOAGULANT INTENSITY PRIOR TO BLEEDING

Patients treated with adjusted-dose warfarin had an INR between 2.0 and 3.0 for 73% of the time of treatment, above this range for 9%, and below this range for 18%. None of the patients who experienced major bleeding during warfarin therapy had an INR above 2.8 at the last evaluation in the study laboratory, but 1 patient who was severely injured after a fall down a staircase had an INR of 3.9 at admission to the hospital. One patient receiving fixed low-dose warfarin therapy had an INR of 1.5 five days before a major gastrointestinal bleeding event. He had a prothrombin time ratio of 0.11 at admission to the hospital. The sudden pronounced anticoagulant effect of 1.25-mg/d warfarin sodium was ascribed to interaction with aspirin, of which the patient had taken 3 to 4 g/d for 1 week. The bleeding was caused by gastric ulcers. In the 4 patients who experienced a major bleeding episode during adjusted-dose therapy, the intensity of anticoagulation was stable with the last 3 INR values within or just below the intended range.

### RISK FACTORS FOR BLEEDING

Prior myocardial infarction ($P = .001$) and allocation to adjusted-dose warfarin therapy ($P < .001$) were the only independent risk factors for bleeding. The risk for bleeding increased by increasing INR value. There was no significant impact of age, sex, history of stroke or transient ischemic attack, diabetes, cigarette smoking, left ventricular fractional shortening, or arterial hypertension on the occurrence of bleeding. Risk

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Table 3. Cases of Major Bleeding*

<table>
<thead>
<tr>
<th>Treatment Group†</th>
<th>Patient No./Sex/Age, y</th>
<th>Time to Bleeding, d</th>
<th>Hb at Presentation, mmol/L</th>
<th>Need of Transfusion‡</th>
<th>Rate of Bleeding§</th>
<th>Severity¶</th>
<th>Description and Localization of Bleeding Event</th>
<th>Anticoagulation Level at Presentation</th>
<th>Most Recent INR in Study Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>1/M/82</td>
<td>341</td>
<td>4.3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>Melena and anemia</td>
<td>PT = 0.11</td>
<td>1.5 (5 d before)</td>
</tr>
<tr>
<td></td>
<td>2/M/55</td>
<td>552</td>
<td>5.8</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>Melena and anemia</td>
<td>INR = 2.1</td>
<td>1.1 (20 d before)</td>
</tr>
<tr>
<td></td>
<td>3/M/79</td>
<td>51</td>
<td>...</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>Traumatic IC hemorrhage</td>
<td>PT = 0.55</td>
<td>1.2 (22 d before)</td>
</tr>
<tr>
<td>Warfarin + aspirin</td>
<td>4/M/87</td>
<td>299</td>
<td>4.3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>Colon diverticulitis</td>
<td>...</td>
<td>1.1 (60 d before)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>5/F/80</td>
<td>830</td>
<td>...</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>IC hemorrhage (fatal)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>6/M/74</td>
<td>61</td>
<td>6.6-5.7†</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>Gastric ulcer</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>7/M/75</td>
<td>21</td>
<td>7.2-6.1†</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>Gastric ulcers</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>8/M/77</td>
<td>104</td>
<td>...</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>Gastric cyst</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>9/M/69</td>
<td>14</td>
<td>6.4-3.8¶</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>Gastric ulcer</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>INR</td>
<td>10/M/78</td>
<td>213</td>
<td>...</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>Subretinal hemorrhage</td>
<td>...</td>
<td>2.8 (12 d before)</td>
</tr>
<tr>
<td></td>
<td>11/M/69</td>
<td>63</td>
<td>...</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>IC hemorrhage</td>
<td>PT = 0.55</td>
<td>1.3 (3 d before)</td>
</tr>
<tr>
<td></td>
<td>12/M/80</td>
<td>202</td>
<td>4.2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>Traumatic IC hemorrhage (fatal)</td>
<td>INR = 3.9</td>
<td>2.3 (8 d before)</td>
</tr>
<tr>
<td></td>
<td>13/M/81</td>
<td>308</td>
<td>8.1-5.8¶</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>Adenoma in rectum</td>
<td>INR = 2.0</td>
<td>2.2 (7 d before)</td>
</tr>
</tbody>
</table>

*Hb indicates hemoglobin substance concentration; INR, international normalized ratio of the prothrombin time ratio (PT); ASA, aspirin; IC, intracerebral; and ellipses, no available data.
†Warfarin was given as warfarin sodium, 125 mg; aspirin, 300 mg; and INR, range of 2.0-3.0.
‡1 indicates 1-2 U of blood; 2, 3 U of blood; and 3, >3 U of blood.
§1 indicates >7 d; 2, 3-7 d; and 3, >3 d.
¶Decline in hemoglobin concentration during observation in hospital.
factor analysis for only patients receiving adjusted-dose warfarin therapy did not identify increasing age as a risk factor for bleeding.

Interestingly, a bleeding complication related to the study treatment was identified as an independent risk factor for a thromboembolic event later in the study period (P = .006) in patients who did not stop taking the study treatment after the bleeding event.

THERAPEUTIC CONSEQUENCES OF BLEEDING

In all patients with major bleeding the antithrombotic treatment was discontinued and the patients were permanently withdrawn from the study.

All patients who reported minor bleeding were encouraged to visit their primary care physician for further examination and 7 patients were admitted to the hospital for examination and/or treatment of an underlying disorder. These examinations, however, were not coordinated with the study center, and follow-up information on minor bleeding events was not systematically recorded.

The study treatment was permanently discontinued in 4 (19%) of 21 patients who experienced a minor bleeding event while receiving mini-dose warfarin therapy, in 12 (43%) of 28 receiving combined warfarin and aspirin therapy, in 6 (23%) of 26 receiving aspirin therapy, and in 15 (36%) of 42 receiving adjusted-dose warfarin therapy (P = .22).

COMMENT

In the AFASAK 2 Study the number of major bleeding events was very small, with no significant difference among the 4 groups. Considering all minor and major hemorrhagic events, the cumulative rate of bleeding was significantly higher in patients receiving adjusted-dose warfarin than in those receiving the other antithrombotic treatments.

In patients receiving adjusted-dose warfarin therapy in the present study, the annual incidence of major bleeding of 1.1% was comparable to the rate of major bleeding in the first trials on stroke prevention in atrial fibrillation. In the Stroke Prevention in Atrial Fibrillation (SPAF) II Study, the overall risk of major bleeding in patients receiving warfarin aiming at an INR of 2.0 to 4.5 was 2.3% per year, which was slightly higher than in the previous trials. The higher rate of bleeding events may partly be ascribed to the relatively high intensity of anticoagulation therapy used in that study. The rate of bleeding in the SPAF II subgroup of patients older than 75 years will be discussed later. For comparison, the rates of major bleeding during antithrombotic therapy in various atrial fibrillation trials are listed in Table 4.

The relatively large number of major hemorrhagic events in patients receiving aspirin in the present study is important to note as aspirin is suggested as an alternative treatment for patients in whom warfarin is considered inappropriate. The risk for gastrointestinal tract bleeding has been shown to be proportional with the dose of aspirin, and in the AFASAK 2 Study a relatively large dose of non–enteric-coated aspirin was used. Other studies, however, have indicated that neither coating nor a small dose of aspirin ensures a small risk for gastrointestinal tract bleeding. As aspirin may be associated with a risk for major bleeding very close to that of adjusted-dose warfarin therapy, we find that the only reason for choosing aspirin instead of warfarin should be expected poor compliance during oral anticoagulant therapy.

In our study the combination of warfarin and aspirin was associated with a risk for major bleeding of 0.3% per year. This was unexpectedly low as compared with both adjusted-dose warfarin therapy (1.1% per year) and aspirin monotherapy (1.4% per year) and indicates that combined low-intensity warfarin and aspirin therapy can be safe even in the elderly. It should, however, be noted that 1 pa-
tient receiving mini-dose warfarin therapy who unaware took aspirin 3 to 4 g/d for approximately 1 week developed pronounced hypoprothrombinemia and had a major gastrointestinal bleeding event. Our experience with combined warfarin and aspirin therapy in respect to major bleeding is in accordance with the findings in other recent trials. In patients with prosthetic heart valves treated with warfarin alone aiming at INR of 2.5 to 4.0 or in combination with 100 mg of aspirin, the combined treatment increased the risk for minor bleeding but not for major bleeding. In the SPAF III Study, excretion of fecal hemoglobin was increased in patients receiving combined therapy compared with those receiving adjusted-dose warfarin therapy, whereas no difference in the rate of major bleeding was found. In contrast to this, patients with intracoronary stent placement receiving combined warfarin and aspirin therapy had a high risk for upper gastrointestinal tract bleeding as compared with patients receiving aspirin mono-therapy.

In the present study, the incidence of minor bleeding of 11.8% per year in patients receiving adjusted-dose warfarin therapy was significantly higher than in the other study groups but it was comparable to the rate of minor bleeding in prior atrial fibrillation trials, in which the rate ranged from 1.5% to 14.0% per year in the warfarin groups. The large spread in the incidences of minor bleeding may be explained by different operational definitions and follow-up schedules and by the patients’ susceptibility to report harmless bleeding such as bruising and nose bleeding rather than by a real difference in the number of minor bleeding events.

We found it important, however, to obtain data on even minimal bleeding events, as such events were expected to reflect compliance and to influence withdrawal and dropout from the trial. In fact, bleeding was a major reason for both withdrawal and dropout. Although insignificant, the dropout ratio seemed elevated in patients receiving warfarin plus aspirin or adjusted-dose warfarin, suggesting that a complicated treatment and polypharmacy influence the patients’ willingness to continue the treatment after even minor adverse events.

By stepwise multiple regression analysis we found that prior myocardial infarction and allocation to adjusted-dose warfarin therapy were the only independent risk factors for bleeding. The risk for bleeding increased with increasing INR. The finding of myocardial infarction as a risk factor for bleeding was surprising. An explanation could be that some of these patients previously had been told always to take aspirin and maybe still took it in addition to the study medication. The literature does not explain this finding. A risk factor analysis for only major bleeding events was not performed as the number of events was considered insufficient, but it is remarkable that only 1 of 13 patients with major bleeding was female. An explanation for this is not evident, but compliance may have been better or comorbidity less frequent in female participants.

Older age as a potential risk factor for bleeding is an important issue of debate as many patients may be withheld from relevant warfarin therapy only because of their age. In the SPAF II Study, the risk of major bleeding was high in the elderly, ie, 4.2% per year in the subgroup of patients older than 75 years. When interpreting the results of the SPAF II Study, however, it should be kept in mind that increasing age was identified as an independent risk factor for bleeding for the entire study population. Thus, it is not surprising that a subgroup of the study population consisting of only persons older than 75 years had a very high risk for hemorrhage. Since the publication of the SPAF II Study, many physicians have been reluctant to prescribe warfarin therapy to the elderly, who may, however, benefit most from the treatment. Among other investigators, Launbjerg et al also noted that age over 75 years was an individual risk factor for bleeding. In a recent prospective cohort study of patients with various diseases receiving oral anticoagulant therapy, the rate of bleeding was higher in patients older than 75 years than in those younger, and more bleeding events were major or fatal in the elderly. Opposite to these findings, the present and other studies have shown that it may be safe to treat even elderly patients with warfarin.

The intensity and variability of anticoagulation therapy have also been determined as risk factors for bleeding. In our study the last 3 control INRs were below 3.0 in all patients who experienced major bleeding during adjusted-dose warfarin therapy, but at admission to the hospital the level of anticoagulation was more intense than intended in 2 of the patients. In 1 case it was a consequence of accidental interaction between low-dose warfarin and high-dose aspirin and in the other case the patient was severely traumatized.

Prior studies have demonstrated that a history of stroke or arterial hypertension increases the risk for intracerebral bleeding during oral anticoagulant treatment. Such a relationship could not be confirmed by the AFASAK 2 Study, but it should be remembered that patients with uncontrolled arterial hypertension and recent stroke were not included in the study. In the European Atrial Fibrillation Trial, which included patients with a recent stroke or transient ischemic attack, no intracranial bleeding was noted in 225 patients with atrial fibrillation receiving oral anticoagulant therapy—a result contradicting that a history of stroke increases the risk for warfarin-associated bleeding. In both the AFASAK 2 Study and the European Atrial Fibrillation Trial, however, the cause of death was not clarified in several patients who unexpectedly died at home.

We did not find that minor bleeding could predict the risk for major bleeding, as only 3 patients experienced both minor and major hemorrhage, but the finding of bleeding as a risk factor for thromboembolic events should be noticed as it may indicate unsteady intake of the study medication.

Drug interaction caused major bleeding in only 1 patient, but in more patients without bleeding elevated INRs could be ascribed to drug interaction. Aspirin was the most frequent interacting agent, but amiodarone, cetidime, and nalidixic acid also were recorded.

This study showed that treatment with mini-dose warfarin given alone or in combination with aspirin implies a nonnegligible risk for bleeding. Traditional warfarin therapy was not associated with a higher risk for major bleeding than aspirin and the other “low-risk” antithrombotic treatments, and increasing age was not a risk factor for bleeding. Thus, this study indicates that even elderly patients with atrial fibrillation tolerate and should
receive adjusted-dose warfarin therapy (INR, 2.0-3.0) provided there are no contraindications for the treatment and patients are carefully monitored.

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Reprints not available from the authors.

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