Risks of Oral Anticoagulant Therapy With Increasing Age

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Background: Oral anticoagulation in the elderly is a dilemma. Although many elderly patients have strict indications for treatment with coumarin derivatives, the tendency toward an increased bleeding risk with age is a matter of concern. We investigated the risk of hemorrhage and thromboembolism according to age in patients who were treated with oral anticoagulants in the routine setting of an anticoagulation clinic.

Methods: All patients of the Leiden Anticoagulation Clinic (Leiden, the Netherlands) who were treated because of mechanical heart valve prostheses (target, international normalized ratio [INR] of 3.5), atrial fibrillation (target, INR of 3.0), or after a myocardial infarction (target, INR of 3.0) between 1994 and 1998 were included in the study and grouped by age at the start of follow-up. We calculated incidence rates of major hemorrhage and thromboembolism per age group.

Results: We included 4202 patients: 842 patients younger than 60 years; 1200 patients aged between 60 and 70 years; 1464 patients aged between 71 and 80 years; and 696 patients older than 80 years. The incidence rate of major hemorrhage rose gradually with age from 1.5 per 100 patient-years for patients younger than 60 years to 4.2 per 100 patient-years for patients older than 80 years, yielding a hazard ratio of 2.7 (95% confidence interval, 1.7-4.4). The incidence rate of major thromboembolism rose from 1.0 per 100 patient-years for patients younger than 60 years to 2.4 per 100 patient-years for patients older than 80 years (hazard ratio, 2.2; 95% confidence interval, 1.2-4.2).

Conclusions: The incidence of both bleeding and thromboembolic events increases sharply with advanced age. Because higher thromboembolic risk with age often makes it unfeasible to withhold oral anticoagulation from elderly patients, future studies should focus on ways to lower the bleeding risk.

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ORAL ANTICOAGULANT therapy has proven to be effective in the prevention of arterial thromboembolism in patients with potential cardiac sources such as atrial fibrillation,1 heart valve replacement with a mechanical prosthesis,2 or myocardial infarction.3 These cardiac diseases are more frequent among the elderly: atrial fibrillation occurs in 0.5 per 1000 person-years before age 50 years compared with 9.7 per 1000 person-years after age 70 years.4 Calcific aortic valve disease, the most common valvular lesion in elderly patients and the main reason for aortic valve replacement in patients older than 75 years, is present in its severe form in 1% to 2% of persons aged 75 to 76 years, up to 6% in those aged 86 years.5 The incidence of myocardial infarction increases 2- (men) to 3-fold (women) in individuals older than 65 years compared with those aged 35 to 64 years. Hence, Western society with its aging population will be confronted with a dramatic increase of these diseases in the next decades and thereby an increasing number of elderly patients might be considered for anticoagulation with coumarin derivatives. Oral anticoagulant therapy in the elderly, however, is a dilemma because many studies have shown a tendency toward a higher bleeding risk in these patients.6

Much of our knowledge on the relationship between bleeding risk and age comes from clinical trials in which the very old and diseased are often excluded. These studies therefore provide little information relevant to routine clinical care and virtually no information concerning the very old or frail. Observational studies on the bleeding risk in routinely anticoagulated cohorts7,8 therefore give a more useful indication regarding day-to-day practice; unfortunately, most published studies lack data on thromboembolic risks. Because the risk of thromboembolism also
increases with age, \(^{9,10}\) bleeding risk cannot be judged fully without taking the thromboembolic risk into account. We studied the relationship between age and bleeding or thromboembolic events in a large group of patients of a Dutch anticoagulation clinic who were treated for mechanical heart valve prostheses, atrial fibrillation, or after myocardial infarction.

### METHODS

#### ANTICOAGULATION CLINIC

In the Netherlands, all outpatients who receive oral anticoagulant therapy are treated by regional anticoagulation clinics. On average, patients visit the clinic or are visited at home once per 3 weeks. During each visit, a nurse fills out a small questionnaire concerning hospital admissions, adverse events, and intercurrent diseases and takes an antecubital blood sample. The prothrombin time is measured and expressed as international normalized ratio (INR).

The target intensities for anticoagulant treatment in the Netherlands were altered in 1996 during the time window of the study. For patients with mechanical heart valve prostheses, the target intensity (range) were lowered from an INR of 4.0 (3.6-4.5) to an INR of 3.5 (3.0-4.0). The target intensity (range) were lowered from an INR of 4.8 (4.0-5.6) to an INR of 3.5 (3.0-4.0). The target intensities for anticoagulant treatment in the Netherlands were altered in 1996 during the time window of the study. For patients with mechanical heart valve prostheses, the target intensity (range) were lowered from an INR of 4.0 (3.6-4.5) to an INR of 3.5 (3.0-4.0). The target intensity (range) were lowered from an INR of 4.8 (4.0-5.6) to an INR of 3.5 (3.0-4.0). The target intensities for anticoagulant treatment in the Netherlands were altered in 1996 during the time window of the study. 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#### PATIENTS

We selected all patients of the Leiden Anticoagulation Clinic (Leiden, the Netherlands) who were treated because of mechanical heart valve prostheses, atrial fibrillation, or myocardial infarction between 1994 and 1998 and grouped them by age at entry in the cohort (<60, 60-70, 71-80, and >80 years).

#### DATA COLLECTION

We collected the following information from the computerized records of the Leiden Anticoagulation Clinic: date of birth, sex, indication and duration of treatment, and dates and results of routine INR measurements, hospital admissions, and death. In addition, we collected discharge letters for all hospital admissions, completed with the results from radiography, computed tomography (CT), laboratory tests, and autopsy to adjudicate outcome events.

#### OUTCOME EVENTS

Outcome events were major hemorrhage and major thromboembolism, whichever event occurred first. The incidence of venous thromboembolism was not studied. All possible outcome events were judged by a panel of experts according to the following definitions that were previously applied. The members of the expert panel were at all times blinded for the INRs.

Thromboembolism consisted of cerebral infarction, myocardial infarction, and peripheral arterial embolism. Cerebral infarction was defined as an acute neurologic deficit, proven by CT or autopsy. The diagnosis of myocardial infarction required 2 or more of the following: history of chest discomfort, typical rise of specific cardiac enzymes, or the development of new Q waves on the electrocardiogram. Periodal arterial embolism was defined as sudden peripheral ischemia, proven by duplex scanning, angiography, surgery, or autopsy.

#### INTENSITY OF ANTICOAGULATION

Because incidence rates of hemorrhage and thromboembolism depend highly on the achieved intensity of anticoagulant treatment, \(^{11}\) we compared the outcomes of INR measurements between the age groups by calculating the percentage of time-in-range by the method of Rosendaal et al. \(^{12}\)

To investigate whether the relationship of risk with increasing age also held for lower INR ranges than those used in this cohort, we assessed the risk of adverse events by achieved INRs and only those lower than 3.0. Because this reduced the number of events, we compared 2 age groups (ie, <70 and ≥70 years). For each group we determined the total time spent at INRs under 3.0 by linear interpolation \(^{12}\) and calculated the incidence of adverse events by only counting those occurring at INRs of lower than 3.0.

#### STATISTICAL ANALYSIS

The incidence rates of outcome events within each patient group and their 95% confidence intervals (CIs) were derived by standard calculations, assuming a Poisson distribution of the numbers of events. We compared the occurrence of outcome events in the age groups as hazard ratios (HRs), which were obtained from Cox proportional hazard models.

#### RESULTS

**PATIENTS**

In the 3-year time window of the study, we included 4202 patients for a total of 7788 patient-years (Table 1) and created 4 patient groups: 842 patients were younger than 60 years (range, 2-60 years; 1574 patient-years in total);
1200 patients aged between 60 and 70 years (2358 patient-years); 1464 patients aged between 71 and 80 years (2742 patient-years); and 696 patients older than 80 years (range, 80-95 years; 1114 patient-years in total). With increasing age, the relative number of women in the study population rose from 22% in the patients younger than 60 years to 58% in the patients older than 80 years. Also the distribution of the indications for treatment changed with increasing age, with a preponderance of atrial fibrillation in the elderly.

ACHIEVED INTENSITIES OF ORAL ANTICOAGULATION

No major differences in the quality of anticoagulation were found between the age groups. On average, 65% of the follow-up time was spent within the target ranges in patients younger than 60 years vs 68% in patients aged between 60 and 70 years, 66% in patients aged between 71 and 80 years, and 61% in patients older than 80 years. The percentage of follow-up time under the target ranges was 19% for the patient group younger than 60 years, 16% for patients aged between 60 and 70 years, 17% for patients aged between 71 and 80, and 23% for patients older than 80 years. The percentage of follow-up time above the target ranges did not differ much by age (16%, 16%, 17%, and 16%, respectively).

OUTCOME EVENTS

Hemorrhage

The incidence rate of all major bleeding events combined rose gradually with increasing age, from 1.5 (95% CI, 1.0-2.2) per 100 patient-years in those younger than 60 years to 4.2 (95% CI, 3.1-5.5) per 100 patient-years in those older than 80 years (Table 2). The incidence rate of fatal hemorrhage, which consisted predominantly of intracranial bleeds, was 0.3 per 100 patient-years in all age groups except for patients younger than 60 years, who tended to have a lower rate of 0.1 per 100 patient-years. As given in Table 3, the HR for major hemorrhage was 1.3 (95% CI, 0.8-2.0) for patients aged between 60 and 70 years and increased up to 2.7 (95% CI, 1.7-4.4) in patients older than 80 years, all compared with patients younger than 60 years. When we adjusted the HRs for sex and the indication for anticoagulant treatment, these results did not change essentially. When age was entered in the model as a continuous variable, the risk of hemorrhage increased 2% per 1-year increase in age (HR, 1.02; 95% CI, 1.01-1.04).

Thromboembolism

The incidence rate of major thromboembolism increased with age, from 1.0 (95% CI, 0.6-1.6) per 100 patient-years in those younger than 60 years to 2.4 (95% CI, 1.6-3.4) per 100 patient-years in those older than 80 years (Table 2). The incidence of fatal thromboembolism, which consisted exclusively of myocardial infarction, was constant in the different age groups (0.3 per 100 patient-years), except for patients older than 80, who had a higher rate of fatal myocardial infarction at 0.5 per 100 patient-years. The increase of nonfatal thromboembolism with age was mainly due to the increased incidence of non-

### Table 2. Incidence Rates of Bleeding and Thromboembolic Events According to Age Category

<table>
<thead>
<tr>
<th>Event</th>
<th>Age, y</th>
<th>Events, No. (n = 40)</th>
<th>Incidence* (95% CI)</th>
<th>Events, No. (n = 81)</th>
<th>Incidence* (95% CI)</th>
<th>Events, No. (n = 111)</th>
<th>Incidence* (95% CI)</th>
<th>Events, No. (n = 74)</th>
<th>Incidence* (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Hemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fatal</td>
<td></td>
<td>2 0.1 (0.0-0.4)</td>
<td>8 0.3 (0.1-0.6)</td>
<td>9 0.3 (0.1-0.6)</td>
<td>3 0.3 (0.0-0.7)</td>
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<tr>
<td>Intracranial</td>
<td></td>
<td>2 0.7</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Extradural</td>
<td></td>
<td>0 1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td></td>
<td>22 1.4 (0.9-2.1)</td>
<td>41 1.7 (1.2-2.3)</td>
<td>59 2.2 (1.6-2.7)</td>
<td>44 4.0 (2.8-5.2)</td>
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<td></td>
<td></td>
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<tr>
<td>Intracranial</td>
<td></td>
<td>2 5</td>
<td>5</td>
<td>10</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Extradural</td>
<td></td>
<td>20 5</td>
<td>36</td>
<td>49</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td>24 1.5 (1.0-2.2)</td>
<td>49 2.1 (1.5-2.7)</td>
<td>68 2.5 (1.9-3.1)</td>
<td>47 4.2 (3.1-5.5)</td>
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<td><strong>Thromboembolism</strong></td>
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<tr>
<td>Fatal</td>
<td></td>
<td>4 0.3 (0.1-0.6)</td>
<td>6 0.3 (0.1-0.5)</td>
<td>7 0.3 (0.1-0.5)</td>
<td>6 0.5 (0.2-1.1)</td>
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<tr>
<td>Cerebral ischemia</td>
<td></td>
<td>0 0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Myocardial infarction</td>
<td></td>
<td>4 0</td>
<td>6</td>
<td>7</td>
<td>6</td>
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<td></td>
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<tr>
<td>Nonfatal</td>
<td></td>
<td>12 0.8 (0.4-1.3)</td>
<td>26 1.1 (0.7-1.6)</td>
<td>36 1.3 (0.9-1.8)</td>
<td>21 2.0 (1.2-2.8)</td>
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<tr>
<td>Cerebral ischemia</td>
<td></td>
<td>1 0</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td></td>
<td>10 1</td>
<td>16</td>
<td>28</td>
<td>15</td>
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<tr>
<td>Peripheral embolism</td>
<td></td>
<td>1 0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td>16 1.0 (0.6-1.6)</td>
<td>32 1.4 (0.9-1.9)</td>
<td>43 1.6 (1.1-2.1)</td>
<td>27 2.4 (1.6-3.4)</td>
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</table>

Abbreviation: CI, confidence interval.
*Incidence rate per 100 patient-years. Incidence totals may slightly deviate from the sum of fatal and nonfatal events because of rounding.
fatal myocardial infarction. The risk for thromboembolic events was twice as high in patients older than 80 years compared with patients younger than 60 years (HR, 2.2; 95% CI, 1.2-4.2). Adjusting for sex and indication for anticoagulant therapy made these results more pronounced (Table 3). When age was entered in the model as a continuous variable, the risk of thromboembolism increased 2% per 1-year increase in age (HR, 1.02; 95% CI, 1.00-1.04).

**INDICATION FOR TREATMENT**

In patients who were treated because of atrial fibrillation or myocardial infarction, the incidence of major hemorrhage increased gradually with age (Table 5). In patients with atrial fibrillation, the incidence of major hemorrhage rose from 0.5 per 100 patient-years in those younger than 60 years to 2.8 per 100 patient-years in those older than 80 years. In patients with mechanical heart valve prostheses, atrial fibrillation, or myocardial infarction, the incidence rate rose from 0.3 to 1.8 per 100 patient-years, and in patients treated after a myocardial infarction, the incidence rate rose from 1.6 to 3.6 per 100 patient-years.

**RISKS AT LOWER INRS**

When we only included person-time and events at INRs of 3.0 and lower, we observed 7 adverse events over 440 person-years in those younger than 70, and 21 events over 520 person-years in those older than 70, yielding an HR of 2.5 (95% CI, 1.6-3.8).

We studied the influence of age on the occurrence of major thromboembolic and bleeding events among a large cohort of anticoagulated patients of the Leiden Anticoagulation Clinic who were treated because of mechanical heart valve prostheses, atrial fibrillation, or myocardial infarction. We found that the incidence rate of major hemorrhage increased from 1.5 per 100 patient-years to 4.2 per 100 patient-years when we compared patients younger than 60 years with patients older than 80 years (1.9 per 100 patient-years).

For major thromboembolism, an increasing incidence with age for all 3 indications was found. In patients with mechanical heart valve prostheses, the incidence rate rose from 0.5 per 100 patient-years in those younger than 60 years to 2.8 per 100 patient-years in those older than 80 years. In patients with atrial fibrillation, the incidence rate rose from 0.3 to 1.8 per 100 patient-years, and in patients treated after a myocardial infarction, the incidence rate rose from 1.6 to 3.6 per 100 patient-years.

**COMMENT**

When only included person-time and events at INRs of 3.0 and lower, we observed 7 adverse events over 440 person-years in those younger than 70, and 21 events over 520 person-years in those older than 70, yielding an HR of 2.5 (95% CI, 1.6-3.8).
tradicory with regard to an increasing risk of hemorrhage with increasing age. While some authors described an increasing bleeding risk with age, other studies were less definite or revealed no added risk. Our study shows that the risk increases sharply with advanced age.

Because of the large number of patients followed in the routine setting of an anticoagulation clinic, this study provides risk estimates without the selection bias and bias due to intense monitoring that are inevitable parts of clinical trials. Obviously, some selection is present, since referring physicians decide which patients are treated with oral anticoagulants. However, most of our patients have a very explicit indication for oral anticoagulant treatment (eg, mechanical heart valve prosthesis and atrial fibrillation) for which international guidelines recommend a strict anticoagulant policy. Exclusion of large groups of patients, even elderly patients, is therefore unlikely.

The same guidelines also recommend different anticoagulant strategies for different age groups in patients with atrial fibrillation. Younger patients (age <60 years) without concurrent heart disease (lone atrial fibrillation) or without risk factors like previous stroke, left ventricular ejection fraction under 0.35, or a history of hypertension have a low risk of arterial thromboembolism and can be treated with aspirin. It should therefore be noticed that the patients younger than 60 years who are treated by the Leiden Anticoagulation Clinic form a selected group with already extended cardiovascular disease. Nevertheless, their thromboembolic risk was lowest. Guidelines also suggest lowering the target intensity for atrial fibrillation in patients older than 75 years who are considered to have an increased bleeding risk. Although this practice is not widespread, elderly patients in general are anticoagulated more cautiously, as was demonstrated in our study by patients older than 80 years having the highest percentage of treatment time spent under the target range. Still, their bleeding risk is highest.

Target INRs in our patient population were higher than those currently used in most centers. Although it does not seem likely that the association of risk of adverse events with age would be different for different target ranges, we performed an analysis by achieved INRs. We found that for time spent at INRs under 3.0 and events occurring at INRs under 3.0, elderly individuals had a higher risk of adverse events compared with younger patients.

Many authors have speculated why elderly patients have a higher risk of bleeding events when receiving oral anticoagulation. Many factors are likely to play a role. One cause is comorbidity, which is very common in elderly patients and has several aspects. First, potential bleeding sites may result from other diseases. An example of this mechanism is leuko-araioisis, a white matter abnormality on computed tomographic scan, which is an evoking factor for intracerebral bleeding. Second, other diseases might worsen bleedings that already exist (hypertension) or delay healing (diabetes mellitus). Third, pharmacokinetics of coumarins may change as in heart failure, leading to instability of oral anticoagulant therapy. Another cause is comedication, which might directly contribute to the bleeding risk (anti-inflammatory drugs) or interfere with the metabolism of coumarins (amiodarone and antibiotics). We observed a similar quality (time in range) of anticoagulant control in the various age groups, which renders instability an unlikely cause.

In patients treated for atrial fibrillation or myocardial infarction, the bleeding risk rose gradually with age, with the highest incidence in patients older than 80 years. In patients with mechanical heart valve prostheses, however, the older patients and the younger patients both had an increased bleeding risk. An explanation for this finding may be the higher target intensity for patients with mechanical heart valve prostheses that contributes to more traumatic bleeding events in young, physically active patients. Another explanation might be that some valve diseases that require heart valve replacement also lead to vascular malformations in the gut, causing more gastrointestinal hemorrhage. It should be pointed out that the subgroup of patients with mechanical heart valve prostheses was the smallest, and as the overlapping CIs indicate, we could not rule out the absence of age-related risk differences. A gradual increase, as for myocardial infarction and atrial fibrillation, however, is unlikely based on these data.

We conclude that anticoagulant treatment in elderly patients presents a major clinical dilemma. While the risk of thromboembolism and the subsequent need for proper anticoagulant therapy increases sharply with age, the bleeding risk rises as well. The question is whether an overall benefit remains for elderly patients who are treated with oral anticoagulants. In patients with atrial fibrillation older than 75 years, the estimated annual stroke risk is 6% or higher despite aspirin therapy. This risk can rise gradually as additional risk factors are present. Prior stroke in patients with atrial fibrillation yields a stroke rate of 12%. An important clinical implication of these findings is that it is not feasible to withhold oral anticoagulant therapy from elderly patients. Hence, all attempts must be focused on ways to lower the bleeding risk.

More frequent monitoring of the achieved levels of oral anticoagulation in elderly patients might minimize the amount of treatment time spent above the target range. Lowering the target ranges for elderly patients might also be considered. However, it is not known whether the protective effects of oral anticoagulation in elderly patients are preserved when lower target intensities are applied. In our data set, the numbers of adverse events per indication were too small to calculate optimal anticoagulation levels for the different age categories. Further studies are needed to tailor our efforts to improve the safety of oral anticoagulant therapy in elderly patients.

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