Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment

Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation

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Background—Vitamin K antagonist (VKA) therapy is increasingly being used for the prevention of venous thromboembolism and stroke in atrial fibrillation. Bleeds are the major concern for VKA prescription, especially in very old patients who carry many risk factors for bleeding. We performed a large multicenter prospective observational study that enrolled very old patients to evaluate the quality of anticoagulation and the incidence of bleedings.

Methods and Results—The study included 4093 patients ≥80 years of age who were naïve to VKA for thromboprophylaxis of atrial fibrillation or after venous thromboembolism. Patients’ demographic and clinical data were collected, and the quality of anticoagulation and the incidence of bleeding were recorded. The follow-up was 9603 patient-years; median age at the beginning of follow-up was 84 years (range, 80 to 102 years). We recorded 179 major bleedings (rate, 1.87 per 100 patient-years), 26 fatal (rate, 0.27 per 100 patient-years). The rate of bleeding was higher in men compared with women (relative risk, 1.4; 95% confidence interval, 1.12 to 1.72; P=0.002) and among patients ≥85 years of age compared with younger patients (relative risk, 1.3; 95% confidence interval, 1.0 to 1.65; P=0.048). Time in therapeutic range was 62% (interquartile range, 49% to 75%). History of bleeding, active cancer, and history of falls were independently associated with bleeding risk in Cox regression analysis.

Conclusion—In this large study on very old patients on VKA carefully monitored by anticoagulation clinics, the rate of bleedings was low, suggesting that age in itself should not be considered a contraindication to treatment. Adequate management of VKA therapy in specifically trained center allows very old and frail patients to benefit from VKA thromboprophylaxis. (Circulation. 2011;124:824-829.)

Key Words: atrial fibrillation ■ elderly ■ hemorrhage ■ venous thromboembolism ■ warfarin

O ral anticoagulant therapy with vitamin K antagonists (VKA) is increasingly being used for the prevention and treatment of vascular disease. Its effectiveness has been clearly established for the secondary prevention of venous thromboembolism (VTE) and for the prevention of systemic embolism in patients with atrial fibrillation (AF). The incidence of both VTE and AF grows with age; therefore, an increasing number of elderly patients have indications for this treatment. However, few data are available on the bleeding risk in very old patients on VKA,1–3 who are usually underrepresented in clinical trials. Their real risk of bleeding is still uncertain; therefore, it is not always easy to determine the benefit-to-risk ratio of anticoagulation in very old subjects.

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Therapy with VKA needs specific management and is not free of bleeding complications. Bleeds are the major concern for clinicians when they prescribe VKA. Many factors considered to be risk factors for bleeding and relative contraindications to the use of VKA are common in elderly patients such as multiple comorbidities, multiple drugs, hypertension, renal failure, and reduced functional status with increased risk for falls. Indeed, current guidelines4,5 report age as a risk factor for both hemorrhage and stroke, determining uncertainty about the optimum treatment of elderly. These uncertainties are present in clinical practice and concur with the current undertreatment of elderly patients. Several studies, in fact, indicate that fewer than half of elderly patients who would benefit from anticoagulation actually receive warfarin.6–11 In the view of these uncertainties, we performed a large multicenter prospective observational study enrolling very old patients in daily practice to evaluate the quality of their anticoagulant treatment and the associated incidence of bleeding events. The present prospective observational study

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The collaborators are listed in full in the Appendix.
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included 4093 very old patients who started VKA treatment after 80 years of age for thromboprophylaxis of AF or after VTE (first event or recurrence). All patients were maintained at the intended international normalized ratio (INR) therapeutic range of 2.0 to 3.0.

Methods

Centers

Twenty-seven centers affiliated with the Italian Federation of Anticoagulation Clinics (FCSA) participated in the study. The FCSA centers are required to give patients who start the treatment adequate education on the purpose of the treatment, the risk of complications, INR values, and treatment management. They follow up patients by periodic INR measurements; establish the date for the subsequent visits; prescribe the daily VKA dosages; and monitor and record changes in patients' habits, diet, comedinations, intercurrent illnesses, bleeding, and thrombotic complications through patient interviews. All centers take part in the specifically designed laboratory external quality control program, which runs 3 times yearly and uses lyophilized plasma samples obtained from anticoagulated patients.12

Patients

The present prospective observational study (Elderly Patients followed by Italian Centres for Anticoagulation [EPICA study]) included 4093 very old patients who started VKA treatment after 80 years of age for thromboprophylaxis of AF or after VTE (first event or recurrence). All patients were maintained at the intended INR therapeutic range of 2.0 to 3.0. Patients' demographic information, indications for VKA, and clinical data were collected. Patients were classified as hypertensive if they were taking medications to lower blood pressure. Diabetes mellitus was defined according to American Diabetes Association criteria.13 Coronary artery disease was defined on the basis of a history of myocardial infarction or stable and unstable angina. Heart failure was defined as the presence of signs and symptoms of right or left ventricular failure or both and confirmed by noninvasive or invasive measurements demonstrating objective evidence of cardiac dysfunction. Patients who had ≥2 accidental falls in the last year were defined as being at high risk for falls.

Creatinine clearance was calculated by the Cockcroft-Gault formula.14 Renal failure was defined as a calculated creatinine clearance ≤30 mL/min. Quality of anticoagulation was calculated as the time in the therapeutic range using linear interpolation method by Rosendahl et al.15 This calculation started at the beginning of treatment.

Follow-Up and End Points

Follow-up visits were scheduled every 2 to 4 weeks for INR monitoring. Patients who missed check-ups for >2 months were contacted (personally or through their family or general practitioner), and the reason for interrupting treatment monitoring was recorded. In the case of death, further information about its cause was requested. Deaths for all causes were recorded.

Major end points of the study were first major bleeding, defined fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal bleeding: when surgery or an invasive maneuver was necessary to stop bleeding; when transfusion of >2 U blood was required; or when hemoglobin was reduced by >2 g/dL. All cases of clinically relevant bleeding events that were not classified as major were considered minor.1 The INR was defined as temporally related to the adverse event when it was obtained at the time of the event or during the preceding 8 days. Follow-up was stopped after the first major bleed occurred, after the cessation of oral anticoagulation, or when a patient was no longer monitored by the participating center.

Statistical Analysis

The SPSS software for Windows, version 11.5 (SPSS Inc, Chicago, IL) and Stata, version 11 statistical software package (Stata Corp, College Station, TX) were used for data processing. We used descriptive analysis expressed as median and interquartile range. Incidence rates of adverse events were calculated as the number of events per 100 patient-years of observation. For this calculation, observation started at the beginning of follow-up and ended when patients experienced a major outcome or were censored.

Analyses were performed with the Fisher exact test (categorical data), unpaired t test (normally distributed data), and Mann-Whitney test (nonnormally distributed data). A 2-sided value of P<0.05 was chosen for statistical significance. The univariate effect of risk factors was investigated by computing incidence rate ratios as estimates of the relative risks and using the exact significance test (categorical data).16 All incidence rate ratios are given with their 95% confidence intervals. All variables found to be significant in univariate analysis were subsequently entered in a multivariate survival regression model. Given the elderly age of the patients, nonhemorrhagic death could prevent a significantly fraction of the subjects to ultimately develop hemorrhage, therefore biasing estimates based on the right censoring used in Cox regression. Thus, we modeled hemorrhagic risk using a competing-risk regression according to Fine and Gray17 and considering nonhemorrhagic death as a competing risk.

Results

We prospectively followed up 4093 patients (1762 men; 43%) who started VKA treatment at ≥80 years of age for stroke prevention in AF or for secondary prevention after venous VTE. The total observation period was 9603 patient-years, and the median age of patients at the beginning of follow-up was 84 years (range, 80 to 102 years). Clinical characteristics of the entire population are reported in Table 1. The majority of patients (2831 of 3651, 77.5%) lived with their family, 532 of 3651 (14.6%) lived alone, and 288 of 3651 (7.9%) lived in nursing homes. All patients received concomitant medications (mean, 4.4±2.2). Renal failure (serum creatinine ≥1.5 mg/dL) was recorded in 385 of 3172 patients (12.1%). During follow-up, 385 patients died (total mortality rate, 4.0 per 100 patient-years): 26 (6.8%) of

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>(%)</th>
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<tr>
<td>Atrial fibrillation</td>
<td>3015 (73.7)</td>
<td></td>
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<tr>
<td>Venous thromboembolism</td>
<td>1078 (26.3)</td>
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<tr>
<td>History of major bleeding</td>
<td>114/3933 (2.9)</td>
<td></td>
</tr>
<tr>
<td>History of falls</td>
<td>151/3595 (4.2)</td>
<td></td>
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<tr>
<td>≥3 Associated drugs</td>
<td>2367/3817 (60.6)</td>
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<tr>
<td>Creatinine clearance ≥30 mL/min</td>
<td>251/2477 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance ≥50 mL/min</td>
<td>1500/2477 (60.6)</td>
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<tr>
<td>Quality of anticoagulation (IQR), %</td>
<td>50 (49–75)</td>
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<tr>
<td>Time in the therapeutic range</td>
<td>11 (5–18)</td>
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<tr>
<td>Time below the therapeutic range</td>
<td>24 (13–35)</td>
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IQR indicates interquartile range; VKA, vitamin K antagonist. Data are expressed as mean (SD) or median (IQR) as appropriate. For history of major bleeding, history of falls, number of associated drugs, and creatinine clearance, the denominators indicate the available data.
hemorrhagic complications, 112 (29.1%) of cardiovascular disease, 34 (8.8%) of sudden death, 12 (3.1%) of stroke, 56 (14.5%) of cancer, and 145 (37.7%) of other disease not related to VKA treatment.

The clinical characteristics of patients in relation to the indication for VKA treatment, AF or VTE, are reported in Table 2. The AF patients more frequently showed cardiovascular risk factors, renal failure, and use of antiplatelet drugs and associated other drugs compared with VTE patients. The VTE patients had a higher incidence of cancer (Table 2).

Quality of Anticoagulation
In the whole population, time in the therapeutic range was 62% (interquartile range, 49% to 75%). A significant difference was observed between AF and VTE patients owing to a lower quality in the latter (P=0.000; Table 2).

Bleeding Events
During the whole observation period, 179 major bleedings were recorded (rate, 1.87 per 100 patient-years), of which 53 (rate, 0.55 per 100 patient-years) were intracranial and 26 (rate, 0.27 per 100 patient-years) were fatal (Table 3); 38 (21.2%) occurred in the first 3 months of treatment. When we split the follow-up period into ≤3 and >3 months, the rates of bleeding were 3.87 and 1.63 per 100 patient-years, respectively (relative risk, 2.4; 95% confidence interval, 1.66 to 3.37; P=0.000). The rate of bleeding events was higher in men (n=93; rate, 2.23 per 100 patient-years) compared with women (n=86; rate, 1.59 per 100 patient-years; relative risk, 1.4; 95% confidence interval, 1.12 to 1.72; P=0.002) and among patients aged ≥85 years of age compared with patients <85 years of age (relative risk, 1.3; 95% confidence interval, 1.0 to 1.65; P=0.048; Table 3).

The distribution of bleeding events in relation to indication for VKA treatment is reported in Table 4. The rate of bleeds was higher among patients on VKA for VTE compared with patients on VKA for AF (relative risk, 1.4; 95% confidence interval, 1.1 to 1.8; P=0.03; the Figure).

No difference was found in time in the therapeutic range between patients with bleeding and those without bleeding events (P=0.7). Bleeding events occurred at an INR of ≥3.5 in 30 of 179 patients (16.8%). Additional risk factors associated with bleeding at univariate analysis are reported in Table 5. In multivariate competing-risk regression analysis, only history of bleeding, active cancer, and history of falls were confirmed to be independently and strongly associated with bleeding risk (Table 6).

### Discussion

Bleeding Events
To the best of our knowledge, this is the largest observational study on very old patients on VKA treatment for AF or VTE. In our study, the rate of major bleedings was 1.87 per 100 patient-years. All patients were followed up for anticoagulation management by specifically devoted centers and showed a good quality of anticoagulation expressed as time in the therapeutic range. All patients started VKA after 80 years of age and were followed up from the beginning of therapy. The recorded rate of bleedings was slightly lower than that...
previously reported in a study conducted in a similar setting. However, unlike our study, that study also enrolled patients with a target INR of >2.5 such as patients with prosthetic heart valves and patients with arterial thrombosis, who are at higher risk for bleeding. Our results are similar to those observed in a previous study conducted in a single center among AF patients and in a small cohort of patients followed up by Kagansky et al. Recently, a similar bleeding rate was found in a randomized controlled trial that compared warfarin and aspirin in elderly AF patients for stroke prevention. In particular, in that study, bleeding risk in patients on VKA was similar to that in patients on aspirin, suggesting the prevalent benefit of warfarin over aspirin for stroke prevention in elderly patients. Conversely, in the study of Hylek et al, the rate of bleeds was markedly higher, probably because of the elevated concomitant use of aspirin in that cohort of patients.

Factors Associated With Bleeding

An increased bleeding risk was recorded with increasing age, with a significantly higher rate among patients ≥85 years of age compared with those <85 years of age. In addition, we confirmed that the first 3 months of treatment are associated with a high risk of bleeding (relative risk, 2.4), as previously reported.

Bleeding risk was lower among AF than VTE patients; the significantly lower time in the therapeutic range among patients with VTE compared with those with AF may, at least in part, explain this finding. In addition, VTE patients were more frequently affected by active cancer, and it is known that cancer is associated with higher bleeding risk. On the other hand, it should be noted that AF patients are more frequently affected by classic cardiovascular risk factors. In addition, even if the use of antiplatelets drugs in our cohort is limited, AF patients are treated with these drugs more frequently than VTE patients.

Renal failure was associated with an increase in bleeding, confirming previous reports. Interestingly, renal failure with a creatinine clearance ≤30 mL/min was recorded in >12% of patients, but more than half of the entire cohort showed a creatinine clearance ≤50 mL/min. This will be an emerging problem when new anticoagulants with prevalent renal excretion, which is different from VKA, are used in clinical practice in the future. Considering the advanced age of these frail patients and their possible further worsening of renal function, more than half of the patients should be carefully controlled over time for renal function if treated with these new drugs.

The bleeding risk was significantly associated with history of previous bleeding events, history of falling, and active cancer. Patients with previous major bleeds therefore carry a higher risk of developing a new bleeding event if treated with VKAs. In particular, in agreement with previous data, patients with prior gastrointestinal bleedings are especially prone to recurrence (hazard ratio, 6.2). Patients at risk for falling showed a risk of major bleedings ~5-fold higher than
the other patients, in agreement with previous data. In particular, Gage et al., examining a cohort of elderly AF patients at high risk for falling, found a similar increase in bleeding risk. However, these authors concluded that the bleeding risk did not exceed the risk of stroke and estimated that these patients appear to still benefit from anticoagulant therapy, especially if they have multiple risk factors for stroke. Examining the number of concomitant medications, we observed that all patients were on multiple drugs, and when the number of associated drugs was ≥3, the bleeding risk increased. We cannot exclude that this could be an effect of the associated comorbidities because it was not significantly related to bleeding risk when other variables were included in the model. In any case, the complexity of VKA treatment is further amplified by the elevated number of comediations, a condition that requires careful management and adequate information for patients and caregivers. It is known that well-informed patients carry a lower risk for adverse events during VKA treatment. In Italy, centers devoted to the management of patients on VKA usually perform patient education, including the goals of treatment, the risk of complications, and information on INR values. In addition, family members and caregivers are involved in the education program. The good quality control in the management of patients conducted by these centers, probably explains the low bleeding risk recorded in our cohort of very old patients.

Limitations
This study enrolled very old patients who were referred to centers for the management of VKA treatment. Therefore, they were selected for anticoagulation, probably excluding patients judged to be too frail for treatment. Indeed, only 7.9% of our patients lived in a nursing home. However, the study was conducted in a real-life setting and represents a broad spectrum of patients who, for the major part, are on treatment for stroke prevention with a good life expectancy to justify warfarin prophylaxis. Patients undergoing treatment for a recent episode of VTE have a high risk of recurrent VTE if anticoagulation is not given; therefore, their risk-to-benefit ratio is judged in favor of treatment.

Because no adjudication panel was planned for the study, we accepted as major bleeding or death all events indicated by each participating center. However, participating centers were required to clearly describe all adverse events, and for all events that lacked adequate description in the data set, the coordinating center requested further information to ascertain the real occurrence of the event. When the event did not fulfill the definition, it was not included.

Another limitation is the exclusion of patients with an elevated INR target, who make up a group of patients at high bleeding risk. However, we choose to limit the observation to AF and VTE, which are the great majority of indications for anticoagulation. In addition, the treatment of these patients is still being debated in relation to the risk-to-benefit ratio of this therapy.

In the evaluation of renal failure, we applied the Cockroft-Gault formula, which was not validated for very old patients. However, numerous studies have attempted to identify a replacement for serum creatinine as a filtration marker, but no single marker has been definitely established, particularly for the elderly. Therefore, despite acknowledged weaknesses, estimates of glomerular filtration rate based on serum creatinine will remain the mainstay of clinical assessment of renal function.

Conclusions
In this large study on very old patients on VKA treatment, the rate of bleeding complications was low, suggesting that age in itself should not be considered a contraindication to treatment. Adequate management of VKA therapy through careful monitoring of patients in specifically trained centers allows very old and frail patients to benefit from VKA thromboprophylaxis.

Appendix
Participating Investigators and Centers
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Disclosures
None.
References

CLINICAL PERSPECTIVE

Vitamin K antagonists therapy is increasingly being used for the secondary prevention of venous thromboembolism and the prevention of stroke in atrial fibrillation. Bleeds are the major concern for vitamin K antagonist prescription, especially in very old patients who carry many risk factors for bleeding. We aimed to assess the incidence and risk factors for bleedings in patients who started on vitamin K antagonist at ≥80 years of age. The observed rate of major bleeding was acceptably low, notwithstanding the particularly advanced age of the patients. This could be explained at least in part by the good quality of the international normalized ratio control obtained in this cohort of patients, who were managed in experienced centers. We confirmed that the first 3 months of treatment carry the highest risk of bleeding, and we found a lower risk of bleeding in atrial fibrillation compared with venous thromboembolism patients. The presence of renal failure was significantly associated with bleeding risk. This is particularly important given that more than half had moderate renal failure, suggesting the need for careful monitoring of renal function over time, especially when the new anticoagulant drugs with a prevalent renal route of excretion are introduced. Bleeding risk was also significantly associated with history of previous bleeding events, previous falls, and cancer. This large study suggests that age in itself should not be considered a contraindication to vitamin K antagonist treatment. An adequate management of this therapy with careful monitoring of patients in specifically trained centers allows very old and frail patients to benefit from vitamin K antagonist thromboprophylaxis.
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