Bleeding in patients receiving vitamin K antagonists who would have been excluded from trials on which the indication for anticoagulation was based

Marcel Levi,1 G. Kees Hovingh,1 Suzanne C. Cannegieter,2 Marinus Vermeulen,3 Harry R. Bülfer,1 and Frits R. Rosendaal2

1Department of Internal Medicine/Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam; 2Department of Clinical Epidemiology, Leiden University Medical Center, Leiden; and 3Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Vitamin K antagonists (VKAs) are effective antithrombotic agents and advocated in guidelines for the management of cardiovascular disease. However, in the trials underlying these guidelines, many patients were excluded. We performed a case-control study in 993 patients receiving VKAs, who required hospitalization for bleeding, and contrasted them to 993 matched control patients on VKAs, who were hospitalized for an infection. We analyzed whether patients and controls would have been eligible for the clinical trials on which their indication for anticoagulation was based, and estimated the risk of hemorrhage associated with exclusion criteria as applied in those trials. Approximately one quarter (23% [95% CI: 21%-26%]) of controls had one or more exclusion criteria for the trials, supporting the use of anticoagulation for their condition. Forty percent of patients presenting with bleeding had one or more exclusion criteria (95% CI: 37%-43%). Having one exclusion criterion resulted in a 2.9-fold increased risk of bleeding (95% CI: 2.2-3.9), and this risk increased sharply when more than one exclusion criterion was present. VKAs are often prescribed to patients who would not have qualified for clinical trials, and in these patients a careful consideration should be made regarding the expected efficacy and the risk of bleeding. (Blood. 2008;111:4471-4476)

Introduction

Anticoagulant treatment with vitamin K antagonists has shown to be an effective preventive or therapeutic strategy for arterial and venous thromboembolism. The 3 most frequent indications for the use of vitamin K antagonist are prevention of emboli in patients with atrial fibrillation, (secondary) prevention and treatment of venous thromboembolism, and (secondary) prevention of arterial thrombosis after a coronary atherothrombotic event. Indeed, for each of these indications, clinical trials have shown a favorable balance between efficacy and safety in favor of vitamin K antagonists, even though most clinical trials show a considerable risk of major bleeding complications related to the use of these anticoagulant agents.

Approximately 15 to 20 per 1000 subjects in the Western world use vitamin K antagonists,1,2 and this number is increasing, probably due to aging of the population and increasing adherence to guidelines. However, it is not clear whether the population in which vitamin K antagonists are used accurately mirrors the population that was included in the trials that generated the clinical evidence for efficacy and, importantly, safety of these agents. This may be relevant since the balance between efficacy and safety for certain indications is critical. Hypothetically, in a population with different characteristics, this balance might be less favorable for vitamin K antagonists. We here show that a large proportion of patients, who were admitted to the hospital because of bleeding while on vitamin K antagonist treatment, would not have been eligible for the trials on which their indication for anticoagulation was based. We also show that this proportion is significantly larger for patients who present with bleeding than for matched control patients on vitamin K antagonists, who were admitted for a respiratory or urinary tract infection.

Methods

Patients and controls

We selected all adult patients who were admitted to all departments of the Academic Medical Center, a teaching hospital in Amsterdam, The Netherlands, between January 1, 2002, and December 31, 2005, with an admission diagnosis of hemorrhage. From this group of 11 061 patients, 1184 patients were using vitamin K antagonists (acenocoumarol or phenprocoumon) at the time of admission. From this group, we selected patients who used vitamin K antagonist for (1) prevention of arterial embolism during atrial fibrillation, (2) prevention and treatment of venous thromboembolism, and (3) secondary prevention of arterial thrombosis in patients with a history of myocardial infarction or unstable angina. Of each of these patients, data were collected from the individual patient file. Both selection procedures and initial chart review were done using the Hospital Information System, which includes detailed information on diagnosis, medication, clinical data, correspondence, and laboratory results. If required, additional information was retrieved from the paper charts or by contacting the general practitioner.

The control group consisted of patients who had no hemorrhage but were admitted to the hospital for a respiratory or urinary tract infection while using vitamin K antagonists. Patients and controls were frequency matched for age, sex, and duration of anticoagulant treatment. Also from the control patients, individual data were retrieved from their files and—if required—paper charts.

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Laboratory data at admission (international normalized ratio [INR], creatinine level, liver enzymes, and bilirubin level) of each patient were collected, and presence or absence of diabetes (elevated fasting glucose, for which therapy was started) was recorded. The presence of liver insufficiency (defined as bilirubin level > 35 μM) or serious kidney insufficiency (defined as creatinine level > 150 μM) was noted. The site of bleeding was confirmed by endoscopy for gastrointestinal bleeding, computed tomography (CT) scan for intracranial bleeding, gynecologic or urologic analysis and imaging for genitourinary bleeding, and ultrasound or CT scan for retroperitoneal, muscle, or joint bleeding.

The protocol for the study was approved by the Medical Ethics Committee of the Academic Medical Center.

**Literature search and assessment of exclusion criteria**

We sought the pivotal trials on which the indication for the use of anticoagulation in the 3 diagnosis groups (atrial fibrillation, venous thromboembolic disease, and coronary atherothrombosis) is based. Therefore, we looked at the studies mentioned in the major guidelines for the use of antithrombotic agents, that is, The Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines and the relevant guidelines of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology. In addition, we performed a MedLine search using the text words and MESH terms “atrial fibrillation,” “venous thrombosis,” “pulmonary embolism,” “myocardial infarction,” “unstable angina,” and “acute coronary syndrome” in combination with “warfarin,” “coumadin” or “vitamin K-antagonist,” aiming to identify randomized controlled trials that were not mentioned in the guidelines. The selected studies were screened for exclusion criteria, and the number of patients that was excluded from the study because of these criteria was recorded.

**Statistical analysis**

Means, proportions, and their 95% confidence intervals (CIs) are reported. To determine the overall presence of exclusion criteria in subjects using vitamin K antagonists for any of the 3 indications, we calculated proportions of each criterion by indication in the controls. Odds ratios as a measure of the relative risk for bleeding were calculated using logistic regression models. Age and sex were consistently included in the model, to take the effect of matching of the controls on age and sex into account. Ninety-five percent confidence intervals were derived from the model.

**Results**

**Patient and control characteristics**

In the group of 1184 patients who presented with bleeding while using vitamin K antagonists, 186 patients were excluded because they received anticoagulant agents for other indications (artificial heart valves, n = 138; vascular prostheses, n = 28; cerebrovascular disease, n = 17; unknown indication, n = 3). Detailed information could be obtained in 993 of the remaining 998 cases. The control group consisted of 993 patients who used vitamin K antagonists and who were admitted with a respiratory or urinary tract infection. Characteristics of cases with bleeding and controls are shown in Table 1. The mean age was 66.9 years, and more than half of all subjects were male. The mean duration of anticoagulation was 3.1 years. The majority of all subjects (n = 1286) had atrial fibrillation, the group of patients with venous thromboembolism consisted of 288 patients, and there were 412 patients with a history of an acute coronary event. The majority of cases (n = 596, 59.7%) presented with upper or lower gastrointestinal bleeding, whereas approximately 15% of cases presented with either intracranial bleeding (n = 151) or urogenital bleeding (n = 153). In 6.4% (n = 64) of cases there was muscle or joint bleeding. Bleeding patterns did not essentially differ between the 3 diagnosis groups, except for a low proportion of upper gastrointestinal bleeding and intracranial bleeding in the venous thromboembolism group and a high proportion of these bleeding localizations in the coronary atherothrombosis group.

**Comparison of bleeding and nonbleeding patients**

In the group of patients with bleeding, INR at admission was higher than in the controls (4.1 [95% CI: 4.0-4.2] vs 2.9 [95% CI: 2.8-3.0]), which was apparent in all 3 diagnosis groups (Table 2). The number of patients with an INR of 5.0 or more was much higher in the group of patients with bleeding (30.0% compared with 4.5% in the control group [OR: 9.6; overall 95% CI: 6.7-13.7]). Mean creatinine levels were higher in patients with

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All patients with bleeding, cases</th>
<th>All patients without bleeding, controls</th>
<th>AF patients with bleeding, cases</th>
<th>AF patients without bleeding, controls</th>
<th>VTE patients with bleeding, cases</th>
<th>VTE patients without bleeding, controls</th>
<th>ACS patients with bleeding, cases</th>
<th>ACS patients without bleeding, controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>993</td>
<td>993</td>
<td>638</td>
<td>648</td>
<td>141</td>
<td>147</td>
<td>214</td>
<td>198</td>
</tr>
<tr>
<td>Age, y</td>
<td>66.8</td>
<td>67.0</td>
<td>68.4</td>
<td>68.8</td>
<td>59.4</td>
<td>59.9</td>
<td>67.0</td>
<td>66.3</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>56.6</td>
<td>56.5</td>
<td>56.5</td>
<td>58.2</td>
<td>45.4</td>
<td>42.9</td>
<td>64.5</td>
<td>61.1</td>
</tr>
<tr>
<td>Duration of anticoagulation, y</td>
<td>3.2</td>
<td>3.0</td>
<td>3.7</td>
<td>3.5</td>
<td>1.9</td>
<td>2.2</td>
<td>2.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Localization of bleeding (%)

- Upper GI: 311 (31.1%), NA 196 (30.6%), NA 31 (22.0%), NA 85 (39.7%), NA
- Lower GI: 285 (28.7%), NA 190 (29.8%), NA 49 (34.8%), NA 46 (21.5%), NA
- Intracranial: 151 (15.2%), NA 96 (15.0%), NA 11 (7.8%), NA 44 (20.6%), NA
- Urogenital: 153 (15.4%), NA 100 (15.7%), NA 28 (19.9%), NA 25 (11.7%), NA
- Retro/muscle/joint: 64 (6.4%), NA 39 (6.1%), NA 15 (10.6%), NA 10 (4.7%), NA
- Other: 29 (2.9%), NA 18 (2.8%), NA 7 (5.0%), NA 4 (1.9%), NA

GI indicates gastrointestinal; retro, retroperitoneal; and NA, not applicable.

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**Table 2. Risk factors for bleeding**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>All patients with bleeding, cases, n = 993</th>
<th>All patients without bleeding, controls, n = 993</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR at admission</td>
<td>4.1</td>
<td>2.9</td>
<td>—</td>
</tr>
<tr>
<td>INR of 5.0 or higher</td>
<td>301 (30.3%)</td>
<td>43 (4.5%)</td>
<td>9.6 (6.7-13.7)</td>
</tr>
<tr>
<td>Mean creatinine level, μM</td>
<td>98.0</td>
<td>83.6</td>
<td>—</td>
</tr>
<tr>
<td>Creatinine level higher than 150 μM, no.</td>
<td>59 (5.9%)</td>
<td>27 (2.7%)</td>
<td>2.3 (1.5-3.7)</td>
</tr>
<tr>
<td>Liver failure, no.</td>
<td>24 (2.4%)</td>
<td>10 (1.0%)</td>
<td>2.5 (1.2-5.3)</td>
</tr>
<tr>
<td>Diabetes, no.</td>
<td>195 (19.6%)</td>
<td>191 (19.2%)</td>
<td>1.0 (0.8-1.3)</td>
</tr>
</tbody>
</table>

— indicates not applicable.
bleeding (98.0 μM; CI: 92.7-103.4) compared with patients without bleeding (83.6 μM; CI: 79.8-87.5), and the risk of hemorrhage was 2.3-fold increased in the group with a creatinine level higher than 150 μM (95% CI: 1.5-3.7). Serious renal insufficiency was seen mostly in the group of patients who had an acute coronary syndrome. Liver failure was a relatively rare comorbidity in both groups, but bleeding patients more often had impaired liver function than controls (OR: 2.5; CI: 1.2-5.3). The prevalence of diabetes was not different between the groups (OR: 1.0; CI: 0.8-1.3).

Exclusion criteria in the pivotal trials

We identified 6 randomized trials on which the indication for the use of vitamin K antagonists in patients with atrial fibrillation is based.6-11 In all 6 trials, patients judged not to be suitable for anticoagulation (such as incompliant patients, patients who could not be controlled regularly, patients with recent [≤ 1 year] hemorrhage or a presumed increased bleeding risk, or patients with an alcohol or drug dependency) were excluded. In addition, in 5 of 6 trials, cardiac comorbidity or stroke within the previous 2 years was an exclusion criterion. Further, in 5 of these 6 trials, patients using alternative antithrombotic agents (in particular platelet inhibitors) were excluded. The trials included a total of 4348 patients, whereas 28 787 patients were screened but excluded from these studies (87.4%).

Six randomized controlled trials, including a total of 3534 patients, formed the principal basis for the guidelines to use vitamin K antagonists for treatment and secondary prevention of venous thromboembolism.12-17 In 4 of these 6 trials, patients judged not to be suitable for anticoagulation were excluded, 5 trials excluded patients with comorbidity, such as cancer or a previous venous thromboembolic event, in 4 trials patients with risk factors for thrombosis, including pregnancy, were excluded, and none of the 6 trials allowed the use of antithrombotic comedication, notably antiplatelet agents. Based upon these criteria, a total of 1434 patients (28.9% of screened patients) were excluded from the 6 studies.

The use of vitamin K antagonists in specific patient groups with a history of acute myocardial infarction or unstable angina is based on 5 randomized controlled trials.18-22 All trials excluded patients who were judged not to be suitable for anticoagulation or patients with serious comorbidity, such as malignancy. Three of the 5 trials excluded the use of other antithrombotic medication, including antplatelet agents, in patients on vitamin K antagonists. A total of 14 614 patients were included in these 5 studies, whereas 22 331 patients were excluded (67%).

Eligibility of controls for the pivotal clinical trials

Overall, 23% of the controls in our study had one or more of the major exclusion criteria for the clinical trials and would therefore probably have been excluded from these trials (Table 3). In the group of controls with atrial fibrillation, the 2 by far most frequently encountered exclusion criteria were “not suitable for anticoagulant treatment” (n = 94, 15%) and “use of other antithrombotic medication” (n = 87, 13%). The 2 most frequently occurring exclusion criteria in controls who used vitamin K antagonists for venous thromboembolism were “not suitable for anticoagulant treatment” (n = 14, 10%) and “comorbidity” (n = 7, 5%). In patients who used vitamin K antagonists for (secondary) prevention of coronary atherothrombosis, the use of antithrombotic comedication (n = 25, 13%) and “not suitable for anticoagulant

| Table 3. Occurrence of exclusion criteria in patients with or without bleeding |
|---------------------|---------------------|---------------------|
| All patients        | ACS patients        | VTE patients        |
| All patients        | AF patients         | VTE patients        |
| All patients        | AF patients         | ACS patients        |
| Without bleeding    | With bleeding       | Without bleeding    | With bleeding       | Without bleeding    | With bleeding       |
| n                    | n                   | n                   | n                   | n                   | n                   |
| 933                  | 933                 | 933                 | 933                 | 933                 | 933                 |
| No exclusion criteria | 907 (96.6%) | 374 (98.6%) | 174 (17.5%) | 40 (4.3%) | 14 (1.7%) | 20 (6.2-68.6) |
| 1 exclusion criterion | 305 (20.6%) | 123 (24.4%) | 102 (10.3%) | 15 (4.6%) | 5 (3.5-28.1) |
| 2 exclusion criteria | 122 (12.4%) | 51 (20.8%) | 42 (4.2%) | 5 (4.1%) | 1 (0.7%) | 0 (0.0-0.8) |
| More than 2 exclusion criteria | 17 (1.7%) | 8 (0.8%) | 15 (1.5%) | 2 (1.9%) | 1 (0.7%) | 0 (0.0-0.8) |

All odds ratios are adjusted for age and sex to take the effect of frequency matching on these factors into account.

— indicates not applicable.
treatment” (n = 13, 7.2%) were most frequently observed. Interestingly, the majority of controls with a diagnosis of venous thromboembolism had no or one exclusion criterion (84%), whereas a higher proportion of controls who used vitamin K antagonists for atrial fibrillation or for (secondary) prevention of coronary thrombosis had 2 or more exclusion criteria (13% and 7%, respectively). The frequency of each specific inclusion criterion for each of the 3 indications is shown in Table 4.

### Eligibility and the risk of bleeding

In the group of patients that presented with hemorrhage, the proportion with one or more major exclusion criteria was considerably greater (40%; 95% CI: 37%-43%) than in the control group (23%; 95% CI: 21%-26%). Having one exclusion criterion increased the risk of bleeding 3-fold (OR: 2.9; 95% CI: 2.2-3.9) compared with no exclusion criterion. The bleeding risk increased sharply with having more exclusion criteria compared with none: having 2 versus none increased the risk 4-fold (OR: 3.8; 95% CI: 2.7-3.9), while in subjects with 3 or more the risk was 15 times increased (OR: 14.9; 95% CI: 4.7-46). Having a high INR at admission was not related to the number of exclusion criteria present; hence adjustment for INR did not essentially change these estimates.

Both in patients with atrial fibrillation and in patients with coronary atherothrombosis, the exclusion criterion that was most prominently present in patients who presented with bleeding in comparison with controls was the use of other antithrombotic agents (26.8% vs 13.4% [OR: 3.6; 95% CI: 2.6-5.1] in patients with atrial fibrillation and 32.7% vs 6.6% [OR: 9.3; 95% CI: 4.6-18.8] in patients with coronary atherothrombosis, respectively; all ORs adjusted for age and sex).

### Discussion

We found that approximately one-quarter of subjects who use anticoagulation for prevention of thromboembolic complications do not fulfill the eligibility criteria of the trials that demonstrated efficacy and safety of this treatment for the 3 most important indications. This proportion was higher (40%) in anti–vitamin K users admitted for bleeding. Hence, the risk of hemorrhage was 3-fold increased for patients with exclusion criteria. It rose sharply with the number of exclusion criteria present, up to a 15-fold increased risk for subjects with more than 2 exclusion criteria. This suggests that in patients who have characteristics that are different from those that were included in the clinical trials, the balance between efficacy and safety has shifted and that the conclusions from these trials are not applicable to this group. It should be stressed that in the case of vitamin K antagonists for prevention of arterial or venous thromboembolism, the window between efficacy and safety is quite narrow,23,24 and therefore the overall benefit of treatment may be radically different in patient populations with different characteristics.

In clinical trials, exclusion criteria are often used to exclude patients who have a presumed high risk of complications of the intervention. In several studies, certain comorbidities have been stated to be exclusion criteria, because they would interfere with the main outcome of the trial. These exclusion criteria may therefore not directly be regarded as risk factors for an adverse outcome, however, may cause a selection of patients that has also another risk/benefit profile as the general eligible population. It is remarkable that in the major clinical trials underlying the indication for the use of anticoagulation in various clinical settings, very large groups of patients were excluded from the trials, for various reasons, but often because the intervention with a vitamin K antagonist was thought not to be safe. These subtleties are, however, not very often expressed in the guidelines on the use of anticoagulant agents.3-5 We therefore suggest that in the development of guidelines for clinical practice based on evidence from clinical studies, besides efficacy and safety and strength of the clinical evidence, a new dimension is added, that is, the applicability of the evidence (or lack thereof) to specific patient populations.

Our observations are not unique, since previous studies on other topics have shown similar results when it comes to the risk of extrapolation of results obtained in trials. After the publication on the beneficial effect of spironolactone in patients with severe heart failure, for example, the prescription of this agent in patients who would never have been admitted to the original clinical trial resulted in excess rates of hyperkalemia and related morbidity and mortality.25,26 Similarly, a cross-sectional study in patients with heart failure demonstrated that less than one-third of Medicare beneficiaries older than 64 years with heart failure met the enrollment criteria for major studies determining evidence-based treatment in these patients, although it is not clear what the effect of this mismatch was on the efficacy of treatment or the incidence of adverse events.27 In cancer patients, a similar difference between populations in clinical trials and those seen in clinical practice was observed.28 On top of that, the management of medical treatment of patients in clinical trials is commonly considered somewhat better organized than the management of usual care. In our study, the anticoagulation therapy in all patients was regulated by specialized anticoagulation clinics, which has been shown to be superior over usual care of anticoagulation. Nevertheless many bleeding events occurred, and one can hypothesize that the bleeding risk in subjects with exclusion criteria in usual care would be even higher.

There were various differences between patients who presented with bleeding in comparison with control patients who did not bleed. A very high INR (> 5.0) increased the risk of bleeding almost 10-fold. It can be argued that anticoagulation treatment in subjects with serious comorbidity is more likely to become excessive, so that in these people it was in fact the high INR that caused the bleeding, rather than the presence of exclusion criteria. However, our analysis showed that this was not the case. Another interesting finding was the higher mean creatinine level and the
2-fold increased risk of bleeding in patients with creatinine levels higher than 150 μM. Since there is no direct effect of kidney function on the metabolism or mode of action of vitamin K antagonists, this may suggest that patients with kidney failure may have a high bleeding risk due to other factors, such as thrombocytopenia or other consequences of uremia. Impaired kidney function as a risk factor for anticoagulation-associated bleeding was also demonstrated in a recent study in patients with acute coronary syndromes.29

Although the proportion of patients that would have been excluded from the clinical trials was larger in patients with bleeding for all 3 indications of anticoagulation that we analyzed in our study, it seems that the proportion of patients treated for venous thromboembolism that was not eligible for the clinical studies was relatively small. Indeed, most of these studies do not have many exclusion criteria. Moreover, patients with venous thromboembolism in our sample were relatively young and had less comorbidity. Another important distinction between these patients and the other 2 groups was the relatively low proportion of intracranial hemorrhage, which may also be due to the young age and less comorbidity in this group. It seems that patients with venous thromboembolism form a discrete group with specific risk characteristics that differ from patients for whom vitamin K antagonists are prescribed for arterial thromboembolism.

One of the most frequently occurring exclusion criterion that was present in our patient population was the use of other antithrombotic agents, mostly antiplatelet agents, in particular aspirin, sometimes in combination with clopidogrel. A recent population-based case-control study confirmed the high risk of upper gastrointestinal bleeding in patients using vitamin K antagonists in combination with aspirin and/or clopidogrel.30 Indeed, we found a relatively high frequency of upper gastrointestinal bleeding in patients who used vitamin K antagonists for (secondary) prevention of coronary atherothrombosis, and in this group the combined use of vitamin K antagonists and antiplatelet agents was relatively frequent.

The design of our study has some limitations. As a control group, we selected patients on vitamin K antagonists, who were admitted because of a respiratory or urinary tract infection. Although not likely, it may be that this control group represents a specific subset of patients with different characteristics than the general population of patients that uses vitamin K antagonists. In addition, our approach might carry the risk that we missed specific conditions, such as prior hemorrhage or peptic ulcer disease, which may have affected the bleeding risk as well. Lastly, collecting data from patient records and computer files could have introduced bias, although we tried to overcome this by blinding the chart abstractors for case or control status. Another issue is that we collected the data regarding the eligibility for the clinical trials and presence of potential exclusion criteria in our patients and controls at the time of admission to the hospital. It may well be that exclusion criteria were not present at the time of initiating vitamin K antagonist treatment and had developed over time. That would implicate that the individual benefit/risk assessment of vitamin K antagonist treatment in a patient should not only be made when starting this treatment but should also be re-evaluated when the clinical condition of the patient changes.

In conclusion, approximately one-quarter of patients do not fulfill the inclusion criteria for clinical trials that form the basis for the indication of vitamin K antagonists in their situation. The risk of bleeding increases strongly with the number of exclusion criteria present in subjects treated with vitamin K antagonists. It is likely that differences in patient characteristics between those who use vitamin K antagonist in clinical practice and those who were admitted in the clinical trials result in a less favorable safety profile of these agents and may cause a shift in the balance between efficacy and safety. We do not recommend that patients who would have fulfilled one or more exclusion criteria for the clinical trials should not be treated with anticoagulants. However, we feel that in these patients a more careful and individual consideration should be made regarding the expected efficacy and the estimated risk of adverse events, in particular bleeding. Further, more intensive monitoring of the intensity of anticoagulation may be required in these patients. In addition, we suggest that guidelines that are based on clinical trials should pay more attention to the profile of patients who were included in these trials.

References


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