Bleeding with anticoagulant treatments

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Summary
Anticoagulation with vitamin K antagonists (VKAs) is effective in the prevention and treatment of thrombotic complications in many clinical conditions, including atrial fibrillation (that represents today the most frequent indication for anticoagulant treatment), venous thromboembolism, acute coronary syndromes and after invasive cardiac procedures. Bleeding is the most important complication of VKAs and a major concern for both physicians and patients, limiting a more widespread prescription of the treatment. As a result, a non negligible proportion of all the subjects who would have a clear clinical indication for anticoagulation do not receive an effective treatment.

This review analyses the treatment- and person-associated risk factors for bleeding during VKAs. New oral anticoagulant drugs seems to overcome at least some of the limitations of VKAs. Potentially, they can allow a less demanding and more stable anticoagulant treatment, with less side-effects allowing that more patients can receive an appropriate anticoagulant treatment. Based on the so far available phase III clinical studies, it is possible to assume that these new drugs are associated with a risk of bleeding, that is probably related to the intensity of treatment.

Antithrombotic treatments affect the haemostatic system and are therefore associated with a risk of bleeding.

In particular, bleeding is the most important complication of anticoagulation and is a critical point for a widespread use of this treatment.

Reported rates of major bleeding among individuals treated with anticoagulants vary widely in clinical studies. These different rates reflect the differences in the adopted classifications of bleeding events and in the designs of studies.

Classification of bleeding

The adopted classification of bleeding events markedly influences the rate of complications reported in clinical studies. Unfortunately, a wide variety of classifications have been adopted in clinical studies probably accounting for the major differences in the bleeding rates reported in different studies. Usually bleeding events are distinguished between major and minor. According to the ISTH recommendation for non-surgical patients, major bleeds include (1):

- fatal bleeding,
- symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intrarticular or pericardial, or intra-muscular with compartment syndrome, and/or
- those bleeds causing a fall in haemoglobin level of 20 g/l or
- leading to transfusion of two or more units of whole blood or red cells.

More recently many authors prefer a classification that focuses more directly on the relevance to the patient-centred outcomes. Bleeding can therefore be classified as:

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• clinically relevant (that may include bleeds causing death or being life-threatening, those requiring operation or medical intervention to stop bleeding, or causing permanent symptomatic organ damage, or permanent changes in antithrombotic therapy),
• clinically non-relevant major bleeds (requiring cessation of antithrombotic therapy, and or change in therapeutic management), or
• minor (with minimal impact on clinical status of patients).

Clinical trials or observational studies

Clinical trials on anticoagulant therapy often include only highly selected patients, with a low bleeding risk profile, good adherence to treatment, younger, with less comorbidities and co-medications than we encounter in clinical practice. For these reasons, bleeding rates reported from trials are often lower than those that can be expected in clinical practice. Observational studies give more reliable results on safety of the therapy and reflect more accurately what can be expected in clinical practice, especially if they include prospectively consecutive non-selected patients and first-time takers of anticoagulant drugs; for these reasons higher rates of bleeding complications are often recorded in these studies.

Bleeding complications

Rates with vitamin K antagonists

The risk of bleeding on vitamin K antagonists (VKAs) in prospective studies has been reported to be:
• 0.1–1.0% patient-years of treatment for fatal episodes,
• 0.5–6.5% for major episodes and 6.2–21.8% for minor bleeding.

The absolute risk in specialised anticoagulation services ranged from 0% to 0.25% per year for fatal bleeding and from 0.32% to 2.1% per year for major bleeding complications(3). A significant clinical impact of bleeding in patients anticoagulated for VTE has been demonstrated in a recent meta-analysis of available clinical trials that reported a case-fatality rate of major bleeding of 13.4% in all patients, with a rate of ICH of 1.15% per year (4).

Risk factors

Determinants of VKA-induced bleeding include personal- or treatment-dependent factors. Some patient characteristics are bleeding predisposing factors such as
• genetic polymorphisms,
• age,
• prior stroke,
• history of bleeding,
• anaemia,
• presence of co-morbidity (especially hypertension, renal insufficiency, liver disease) and
• co-medications (antiplatelet agents, NSAIDs and drugs affecting the actual intensity of anticoagulation).

Important treatment-associated risk factors for bleeding include the
• intensity of anticoagulation and also
• quality of monitoring services provided.

Personal-dependent factors

Genetic factors

Many genes have been associated with the metabolism and action of warfarin. Some polymorphisms of genes that encode for the vitamin K epoxide reductase enzyme (VKORC1) and for the cytochrome P-450–2C9 enzyme (CYP2C9) are the most important factors responsible for the large inter-individual variations in dose requirements and may lead to overdosage conditions and a higher risk of bleeding (5).

VKAs function by directly inhibiting the enzyme VKORC1 whose action is necessary for a complete reduction of vitamin K epoxide. The lack of completely reduced vitamin K impedes an adequate post-translational gamma-carboxylation of vitamin K-dependent coagulation factors, including factor II, VII, IX, and X, and also protein C and protein S, which is essential for the activity of these factors. The enzyme CYP2C9 regulates the metabolic clearance of S-entiomer of warfarin. The presence of the variants CYP2C9*2 and CYP2C9*3 is associated with a reduced warfarin catalysis that in turn leads to a higher sensitivity to VKAs and lower dose requirements (6). The frequent presence of mutations in VKORC1 gene is associated with a 50% reduction in activity compared to the wild type; thus the carriers require lower VKA doses (7). Carriers of CYP2C9 variants, compared with non-carriers, achieve stable dose significantly later, spend more time above range at the beginning of anticoagulation and have higher risk of INR values >5; whereas, the effect of VKORC1 variants is a higher risk of INR >5 (8). Some studies (9), though not all (10), reported an association between the presence of these gene variants and incidence of bleeding. Several dosing algorithms have been proposed based on genotype of VKORC1 and CYP2C9, on top of other factors, such as age, gender and weight, to improve management of initial anticoagulation and reduce the risk of bleeding (11).

A rare mutation in factor IX propeptide has been described leading to a marked reduction in the levels of this factor during VKA treatment and to increased incidence of bleeding (12). The alteration is revealed by particularly increased aPTT results but not higher than expected INR values.

Age

Most ((13–15), though not all (16, 17), available observational studies report higher rates of bleeding in elderly people. A recent review of the studies (18) reported rates of 3.2% and 0.64% patient-years, for major and fatal bleeding respectively in subjects aged 69 years or older compared to 0.6% and 0.12% patient-years in subjects aged 40 years or less. The risk of ICH is particularly increased in advanced age (19). Its incidence is estimated to be 0.2% to 1.0% patient-years in all anticoagulated patients (20). A large, prospective, multicenter, nested, case-control study (21) showed a higher risk of major (2.1% pt/y versus 1.1% pt/y) and fatal (6 versus only 1, all due to ICH) complications in patients aged >75 years than in matched (for sex, main indication for therapy and treating centre) younger controls aged less than 70 years. A recent study (22) reported an adjusted odds ratio of 2.5 (95% CI, 13–4.7) of ICH in pa-
patients aged 85 or more versus a reference group of patients of 70–74 years. In line with previous reports (21), this study showed that values of INR less than 2.0 were not associated with lower risk of ICH compared with values between 2.0 and 3.0. These results have been confirmed by subsequent studies (22).

Several reasons can be at the basis of the higher risk for bleeding complications in elderly subjects. They require lower anticoagulant doses than younger subjects and the commonly used daily dose of 5 mg per day to start anticoagulation may lead to overtanticoagulation for some of them. Elderly patients more frequently present comorbid conditions and are more likely to be taking interacting drugs (23). The incidence of gastrointestinal haemorrhage increases sharply with age, due to more frequent presence of diverticulosis, malignancy, angiodysplasias, and other alterations (24). Finally, more frequently they have pathological changes in cerebral vessels, such as leuкоaraisis and amyloid angiopathy, conditions that are likely to be predisposing factors to occurrence of ICH (25).

**Indication for treatment**

Some data show that the risk of bleeding is higher when the indication for anticoagulant treatment is the presence of arterial disease. A high incidence of major bleeding (3.9% pt/yr) has been reported in patients with ischemic stroke of arterial origin, but it was mainly confined to the first months of treatment and in elderly patients (26). The higher incidence of bleeding in cerebrovascular or other “arterial” patients in comparison with patients with other indications raises the question whether the risk of bleeding during anticoagulation outweighs the benefits in those conditions (27); however, more recent studies showed a lower incidence of major bleeds in these patients, likely due to use of more moderate anticoagulation intensity (28, 29).

**Concomitant diseases and comedications**

Prospective observational data clearly showed that concomitant diseases, present since the beginning of the treatment or occurring during it, are a factor that increases the risk of bleeding (13). Certainly, the history of gastrointestinal haemorrhaging is a risk factor for bleeding during VKA treatment (30), though the presence of a peptic ulcer disease without previous haemorrhaging is not (31). Various studies have consistently shown that the presence of cancer in patients treated for venous thromboembolism is associated with a higher rate of bleeding as well as with more frequent treatment failures (32–34).

Many patients treated with VKAs, especially the elderly, are plurimedicated. Two meta-analysis have shown an increased relative risk of major bleeding when VKAs were combined with aspirin (2.4 and 2.5, respectively) (35, 36). The risk of upper gastrointestinal bleeding in patients using VKAs is further increased when combined with aspirin and/or clopidogrel (37). It has been shown that the combined use of VKAs and NSAIDs results in a markedly higher risk of hospitalization for gastro-intestinal bleeding as compared to the general population (38).

**Lesions or injuries related to the site of bleeding**

The presence of organic lesions, already known or still latent, is an important factor for bleeding. Most frequently lesions accounting for anticoagulant-related bleeding are found in the gastrointestinal or genitourinary tracts and soft tissues. Important remediable lesions or injuries related to the site of bleeding were detected in 42% of patients with major bleeding and, what is more, the bleeding event led to the discovery of a remediable lesion (especially in the gastrointestinal or urogenital tracts) in 17% of patients (39). It is more likely to diagnose previously unknown lesions when bleeding occurs at therapeutic or sub therapeutic INR values.

**Treatment-dependent factor**

**Intensity of anticoagulation**

Several experimental trials have shown a clear relationship between the intensity of anticoagulation and the risk of bleeding (40). Bleeding may occur in association with in-range or even below the range INR values; however, its incidence increases in relation to the intended intensity of anticoagulation and especially the actually achieved intensity. The inception-cohort, observational ISCOAT study (13) showed a clear relationship between the achieved intensity of anticoagulation and temporally related risk of bleeding: The lowest rate of bleeding (4.8 %pt-yr) was found in the 2.0–2.9 INR category, whereas the bleeding incidence increased exponentially for INR values > 4.5.

**Time course of anticoagulant treatment**

A higher frequency of bleeding early in the course of VKA treatment, especially during the first 90 days, has been reported in many studies (13, 42). Several factors may contribute to the increased risk of bleeding in the early period of anticoagulant courses. First, anticoagulant therapy can unmask a cryptic lesion; second, the dosage adjustment of therapy may be less well controlled at the start of treatment. For this reason studies that examine non-inception cohort patients and/or include patients who have resumed the treatment for a second course after an interval period are likely to underestimate the true risk of bleeding by either missing early events or excluding from any second course patients who had bled in the first course.

**Type and quality of anticoagulation monitoring**

The quality of monitoring anticoagulated patients is certainly an important factor affecting the risk of bleeding complications. A measure to evaluate the quality of anticoagulation monitoring is to calculate the time spent within the therapeutic range (time-in-range). A relationship between time-in-range and bleeding or thromboembolic rates has been reported in many studies (43). The quality of anticoagulation control is affected by many factors: the use of long-lasting instead of short half-life coumarin drugs (44); an adequate patient information and education (45); the system adopted for monitoring the treatment.

It is generally accepted, confirmed by some studies (46), that less bleeding (and also thrombotic) complications occur when patients are monitored by dedicated anticoagulation services compared to rou-
tine care. Other strategies have also been shown to be effective in improving the quality of treatment: patients’ self-management is feasible, safe and improves the quality of anticoagulation control (47). The use of computer-assisted dosage is also effective in improving the quality of oral anticoagulation management, as shown by a recent European collaborative study (48).

**Rates with other anticoagulants**

The rates of major bleeds in patients treated with heparin or derivatives, or fondaparinux for different clinical indications, as reported in clinical trials or calculated by meta-analysis, range from 1.6% to 6% (Table 1). It should be noticed, however, that the highest rate (6%) has been recorded in patients with cancer (condition at high risk for haemorrhage) treated for acute venous thromboembolism (VTE) (49). Furthermore, in some studies (those with fondaparinux in VTE) the reported rates include major as well as clinically relevant non-major bleeding. Unfortunately, results from observational studies with these drugs are still lacking and it is therefore not easy to extrapolate what can be the real risk of bleeding with these anticoagulants in clinical practice.

The situation is similar for the so-called new oral anticoagulants, a series of newly developed different drugs that are targeted to selectively inhibit thrombin (factor IIa) or activated factor X. For some of these agents results from phase III clinical trials for chronic treatment in patients with atrial fibrillation or VTE have already been published. However, results of their use in clinical practice are not available, as yet (Table 2). In the RE-LY study (50), where dabigatran (a selective thrombin inhibitor) was given to patients with atrial fibrillation for prevention of thrombotic complications, the rates of major bleeding were 3.36% in the warfarin group and 2.71% (significantly lower: p = 0.003) and 3.11% per year in the groups that received 110 mg bid or 150 mg bid of dabigatran, respectively. In the RE-COVER study (51) dabigatran was given to patients with acute VTE at the dose of 150 mg bid and the rate of major bleeds was 1.6% versus 1.9% in those treated with warfarin. In the Einstein study (52) patients with acute VTE were treated with 20 mg oid of rivaroxaban, a selective inhibitor of activated factor X, or warfarin and the rates of major bleeding were 0.8% and 1.2%, respectively.

**Conflict of interest**

The author declares, that he has no conflict of interest.

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**Tab. 1 Bleeding rates for some anticoagulant treatments**

<table>
<thead>
<tr>
<th>agent</th>
<th>indication</th>
<th>major bleeding (incidence; %patients/year)</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>unfractionated</td>
<td>VTE treatment (metaanalysis)</td>
<td>2.0</td>
<td>(53)</td>
</tr>
<tr>
<td>heparin</td>
<td>acute coronary syndromes (systematic overview)</td>
<td>4.5</td>
<td>(54)</td>
</tr>
<tr>
<td>enoxaparin</td>
<td>VTE treatment (metaanalysis)</td>
<td>2.1</td>
<td>(53)</td>
</tr>
<tr>
<td>dalteparin</td>
<td>VTE treatment (clinical trial in cancer patients)</td>
<td>6.0</td>
<td>(49)</td>
</tr>
<tr>
<td></td>
<td>acute coronary syndromes (clinical trial)</td>
<td>3.3</td>
<td>(55)</td>
</tr>
<tr>
<td>tinzaparin</td>
<td>VTE treatment (clinical trial)</td>
<td>2.0</td>
<td>(56)</td>
</tr>
<tr>
<td>fondaparinux</td>
<td>VTE treatment (DVT/PE studies)</td>
<td>4.5/5.8*</td>
<td>(57)</td>
</tr>
<tr>
<td></td>
<td>VTE secondary prophylaxis (clinical trials)</td>
<td>4.5*</td>
<td>(58)</td>
</tr>
<tr>
<td></td>
<td>acute coronary syndromes (clinical trial)</td>
<td>1.6–2.8</td>
<td>(59)</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism

* The rates include major and clinically relevant non-major bleeds.

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**Tab. 2 Treatment with new oral anticoagulants (NOAC) or comparators in recent trials in different clinical indications: Rates of major bleeding complications and intracranial hemorrhages**

<table>
<thead>
<tr>
<th>complications</th>
<th>agent</th>
<th>indication (trial)</th>
<th>NOAC</th>
<th>comparator</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>major bleeding</td>
<td>dabigatran (anti-IIa agent)</td>
<td>atrial fibrillation (RE-LY)</td>
<td>110 mg bid = 2.71%</td>
<td>3.36% warfarin</td>
<td>(50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>150 mg bid = 3.11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rivaroxaban (anti-Xa agent)</td>
<td>VTE treatment (RE-COVER)</td>
<td>150 mg bid = 1.6%</td>
<td>1.9% warfarin</td>
<td>(51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rivaroxaban (anti-Xa agent)</td>
<td>VTE treatment (Einstein)</td>
<td>20 mg oid = 0.8%</td>
<td>1.2% warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>axiptaban (anti-Xa agent)</td>
<td>atrial fibrillation (ROCKET)*</td>
<td>20 mg oid = 3.6%</td>
<td>3.45% warfarin</td>
</tr>
<tr>
<td>intracranial</td>
<td>dabigatran (anti-IIa agent)</td>
<td>atrial fibrillation (RE-LY)</td>
<td>110 mg = 0.23%</td>
<td>0.74% warfarin</td>
<td>(50)</td>
</tr>
<tr>
<td>haemorrhages</td>
<td></td>
<td></td>
<td>150 mg = 0.30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rivaroxaban</td>
<td>(ROCKET)*</td>
<td>0.49%</td>
<td>0.74% warfarin</td>
<td>(60)</td>
</tr>
<tr>
<td></td>
<td>apixaban</td>
<td>(AVERROES)</td>
<td>0.4%</td>
<td>0.4% ASA</td>
<td>(61)</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; ASA: acetyl salicylic acid; * available as abstract; ¹ p = 0.003
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