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Assessing bleeding risk in patients taking anticoagulants

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Abstract Anticoagulant medications are commonly used for the prevention and treatment of thromboembolism. Although highly effective, they are also associated with significant bleeding risks. Numerous individual clinical factors have been linked to an increased risk of hemorrhage, including older age, anemia, and renal disease. To help quantify hemorrhage risk for individual patients, a number of clinical risk prediction tools have been developed. These risk prediction tools differ in how they were derived and how they identify and weight individual risk factors. At present, their ability to effective predict anticoagulant-associated hemorrhage remains modest. Use of risk prediction tools to estimate bleeding in clinical practice is most influential when applied to patients at the lower spectrum of thromboembolic risk, when the risk of hemorrhage will more strongly affect clinical decisions about anticoagulation. Using risk tools may also help counsel and inform patients about their potential risk for hemorrhage while on anticoagulants, and can identify patients who might benefit from more careful management of anticoagulation.

Keywords Anticoagulation · Hemorrhage · Risk stratification · Warfarin

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Introduction

Anticoagulants are commonly used medications in the prevention and treatment of thromboembolic disease [1]. Vitamin K antagonists (VKAs), primarily warfarin, have been the most frequently used agents for patients requiring chronic anticoagulation [1]. More recently, novel oral anticoagulants including the direct thrombin inhibitors and factor Xa inhibitors have become available [2–6].

Despite the high efficacy of oral anticoagulation, concerns about their related hemorrhagic complications prevent many patients from being prescribed or maintained on therapy [1]. The use of accurate bleeding risk assessment tools based on patients' individual risk factors can contribute important information about the potential risks of therapy that can be incorporated into clinical decision making.

This article reviews currently available bleeding risk assessment tools for outpatients taking anticoagulants. Our goals are to review the epidemiology and individual risk factors for anticoagulation-related hemorrhagic complications, to highlight situations where bleeding risk tools may be most useful in clinical care, and to compare the features of the various risk tools.

Anticoagulant-related hemorrhagic complications

Multiple studies have described the risk of hemorrhagic complications in patients taking anticoagulants. Estimates of the effect of anticoagulants find an approximately two-fold increase in bleeding rates for patients on warfarin [7].

In a recent analysis of clinical studies characterized by careful monitoring of anticoagulant intensity, it has been calculated that VKA treatment in atrial fibrillation increases the risk of major bleeding by 0.3–0.5 % per year [7, 8].

In these studies the risk of intracranial hemorrhage, which is the major cause of death and disability associated with VKA treatment, is increased by approximately 0.2 % per year when compared to controls.

In patients with venous thromboembolism (VTE), bleeding rates have been generally higher than in atrial fibrillation patients, most likely due to different concomitant comorbid conditions and with a greater proportion of patients who are newly started on short-duration of therapy. In patients anticoagulated for VTE, the risk of major bleeding is 7.2 events per 100 person-years and the risk of fatal bleeding is 1.31 per 100 person-years, with a case-fatality rate of 13.4 % from major bleeding [9].

Although extracranial hemorrhages, predominantly gastrointestinal in origin, are much more common than intracranial hemorrhages, intracranial events are usually more devastating in impact. Only 5.1 % of extracranial hemorrhages on warfarin result in death at 30 days, compared to a nearly 50 % mortality rate in patients with warfarin-associated intracranial hemorrhage [10, 11].

Individual risk factors for anticoagulant-associated hemorrhage

Because of the clinical importance of identifying those patients who are at particularly high risk from warfarin-related complications, numerous studies have attempted to identify factors associated with hemorrhage.

Demographic and predisposing clinical conditions

Advanced age is associated with an increased risk for major hemorrhage, particularly intracranial hemorrhage [12]. In addition, many individual comorbid medical conditions have been associated with elevated risks for bleeding on anticoagulant treatment. These include a history of congestive heart failure, cerebrovascular disease, hepatic or renal disease, and diabetes mellitus [13]. A history of bleeding (especially in the gastrointestinal tract) and anemia are highly predictive of subsequent bleeding complications [14]. Liver disease potentiates the response to VKAs by impairing synthesis of coagulation factors and make control of anticoagulation more difficult [13].

Hypertension has often been linked to bleeding risk, and in particular may elevate intracranial hemorrhage risk [15]. A modest reduction in blood pressure halves the occurrence of intracranial hemorrhage in patients on anti-platelet therapy [15].

The association between malignancy and VTE is well established. The ISCOAT study showed that malignant disease was significantly more common in patients who started oral anticoagulation for VTE than in patients who were treated with VKAs for other indications (11.3 vs. 2.9 %, respectively; $p < 0.0001$) [16]. Many studies report a higher rate of major and minor bleeding in patients with malignancy during oral anticoagulant therapy. One study showed that patients with cancer spent more time at higher-than intended anticoagulation levels than patients without cancer, reflecting the unpredictable fluctuations in the INR due to concomitant medications and co-morbid diseases [16]. In part because of these issues, as well as a greater efficacy in preventing recurrent thrombosis, prolonged low molecular weight heparin mono-therapy is the recommended initial treatment for cancer-related thrombosis.

Although falls are often cited as a concern for anticoagulated patients, the evidence linking fall risk and hemorrhage is limited [17]. High fall risk does appear to be linked to increased intracranial hemorrhage risk [18]. However, it is estimated that patients with atrial fibrillation need to fall about 300 times per year before the risk of intracranial hemorrhage outweighs the net benefits of anticoagulation in terms of stroke prevention [19].

Finally, at least 30 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 responsible for about 40 % of the inter-individual variations in warfarin dose requirements. It is possible that genetic polymorphisms could predispose to a higher risk of bleeding [20].

Concomitant medications

Antiplatelet agents that are co-administered with anticoagulants significantly raise the hemorrhage risk. The addition of aspirin to VKAs increases the risk of hemorrhage by 2.5 (95 % CI, 1.7–3.7) [21]. Compared with warfarin monotherapy, triple antithrombotic therapy (with warfarin, aspirin, and clopidogrel) more than threefold increased the risk of both nonfatal and fatal bleeding [21]. Other medications also increase hemorrhage risk, notably non-steroidal anti-inflammatory drugs (NSAIDs) and should be avoided if possible in patients taking chronic anticoagulation [21].

Anticoagulation intensity and control of vitamin K antagonists (VKAs)

The intensity and quality of anticoagulation control have major impact on the risk of hemorrhage. The incidence of major bleeding for patients with a target international normalized ratio (INR) above 3.0 is twice as high as in those with a target INR between 2.0 and 3.0 [8]. Both major bleeding and mortality rates have been reported to be significantly higher in patients with time in therapeutic range (TTR) less than 60 % (3.85 and 4.20 %, respectively)

compared with those with TTR above 75 % (1.58 and 1.69 %, respectively) [8].

Specialized anticoagulation clinics have been associated with improved anticoagulation control. Self-monitoring for oral anticoagulation may also be potentially beneficial for selected patients, although has not been proven to reduce the risk of major hemorrhagic events (HR, 0.88; 95 % CI, 0.74–1.06) [22].

Novel anticoagulants versus VKAs

Newer oral anticoagulants, namely the oral direct thrombin inhibitors and factor Xa inhibitors, have generally been associated with lower rates of major hemorrhage and a significant reduction in the risk of fatal bleeding and intracranial hemorrhage [23]. However, the effect may vary somewhat by the category of anticoagulant. In addition, elderly patients and those with renal impairment may be at elevated risk of extracranial bleeding on dabigatran [24].

Bleeding risk assessment tools

Although numerous risk factors have been linked to a higher bleeding risk, noting the presence of these risk factors is not sufficiently informative to help clinicians gauge a patient's hemorrhage risk. In response, a number of risk stratification tools have been developed to try and better quantify a given patient's risk of hemorrhage and to help distinguish which patients are at low or high risk [13, 14, 25–32]. Table 1 lists risk schemes that have been developed to predict anticoagulant-associated hemorrhage. Note that these risk schemes were all developed in patients taking VKAs and it is not clear whether they can be applied to the oral factor Xa and direct thrombin inhibitors.

Development of risk schemes

Most of the hemorrhage risk schemes were developed from cohorts of patients newly prescribed or already taking anticoagulants, and as such reflect patients who were considered suitable for anticoagulation therapy. Patients with extremely high bleeding risk may therefore not be well-represented by these risk tools, as they are less likely to be deemed appropriate for anticoagulation. Several risk schemes were specifically developed in patients with atrial fibrillation and others in cohorts of venous thromboembolism and so some risk scores contain disease-specific risk factors. The Outpatient Bleeding Risk Index (OBRI) was the only one that had a mixed group of indications for anticoagulation and was primarily developed in a group of patients newly starting warfarin for cardiac surgery/prosthetic heart valves. Other risk schemes were developed in subgroups of clinical trial participants community-based outpatients or recently hospitalized patients. Differences in the derivation populations contributed to higher and lower observed bleeding rates. In addition, the risk scores had differences in how they identified or defined bleeding events, as well as what clinical risk factors were available to be tested.

Clinical risk factors included in risk schemes

Not surprisingly, many of the individual risk factors contained within the various risk schemes overlap considerably, although their relative impact are not weighted the same. Older age was a consistent risk factor in all schemes, although the exact definition of older age varied. Renal disease, history of bleeding, and anemia were other factors included in most of the risk scores. Labile INR/poor anticoagulation control was included in the HAS-BLED and 9th ACCP Guidelines risk schemes and not in the others. Requiring measurement of INR control limits the utility of these schemes to patients being newly considered for warfarin therapy and may not apply to patients on newer anticoagulants that do not require INR monitoring. Some risk factors, such as genetic testing, may not be universally available.

Performance of risk schemes

Because each of the hemorrhage risk schemes was developed in very different patient populations or clinical settings, the hemorrhage rates reported in the original risk score vary widely. The OBRI, for example, was developed in recently hospitalized patients newly starting warfarin, many with high target INR ranges, and observed an average bleeding rate of 7 % per year. In comparison, the ATRIA bleeding risk index was developed in a more contemporary community-based cohort of outpatients, many of whom were already on anticoagulants and reported an average bleeding rate of only 1.4 % per year. When the OBRI was applied to the ATRIA cohort, the high-risk group had a hemorrhage rate of 3.96 %, compared to 48 % in the original study. Such variation in bleeding rates supports the case that these risk schemes should be tested in separate and independent populations to provide a range of rates in different populations.

Validation studies have been performed in subgroups of clinical trials [33], outpatients with atrial fibrillation [34, 35], prospective cohorts [36, 37], and administrative databases of hospitalized patients [38, 39]. From these studies a range of observed hemorrhage rates have been reported (Table 1). In general, the majority of studies have found that these risk schemes are only modestly predictive in patients with atrial fibrillation, with c-statistics largely in

Table 1 Risk prediction tools for anticoagulant-associated hemorrhage

Risk scheme	Study description	Risk score calculation	Hemorrhage outcomes	Risk categories (points)	Number of patients (%)	Major bleeding rates in original cohort	Major bleeding rates in other studies
Outpatient bleeding risk index, OBRI [25]	Developed in 565 patients with cardiac surgery, atrial fibrillation, or venous thromboembolism newly starting warfarin on hospital discharge and followed for 48 months. Most common indication was cardiac surgery	1 point for each of the following: age ≥65 years, prior stroke, prior GI bleeding 1 point if any of the following: recent myocardial infarction, diabetes mellitus, hematocrit <30 %, creatinine >1.5 mg/dL	Major bleeding: fatal, life-threatening, potentially life-threatening, led to severe blood loss, led to surgical treatment or led to moderate blood loss	Low (0) Intermediate (1–2) High (3–4)	164 (31 %) 331 (58 %) 61 (11 %)	3 % at 12 months 11 % at 2 months 17 % at 2 months	3 % at 12 months 7.6 % at 12 months 8.6 % at 12 months
Modified outpatient bleeding risk index, mOBRI [14]	Refinement of previous OBRI in 565 patients with cardiac surgery, atrial fibrillation, or venous thromboembolism newly starting warfarin on hospital discharge and followed for 48 months. Most common indication was cardiac surgery. Then prospectively tested in 264 patients in a separate cohort	1 point for each of the following: age ≥65 years, prior stroke, prior GI bleeding 1 point if any of the following: recent myocardial infarction, diabetes mellitus, hematocrit <30 %, creatinine >1.5 mg/dL	Major bleeding: overt bleeding leading to a loss of at least 2.0 units in 7 days or less, or life-threatening	Low (0) Intermediate (1–2) High (3–4)	186 (33 %) 336 (59 %) 34 (6 %)	3 % at 12 months 12 % at 2 months 48 % at 12 months	0–1.5 % per year 2–5 % per year 0–11 % per year
Kuijer et al. [26]	Developed in 241 patients with new venous thromboembolism enrolled in a clinical trial and followed for 3 months	Age >60 years (1.6 points), female sex (1.3 points), presence of malignancy (2.2 points)	Major bleeding: clinically overt and associated with a decline in hemoglobin concentration of at least 20 g/L, need for transfusion of 2 units or more of red blood cells, retroperitoneal or intracranial, warranted permanent discontinuation of treatment	Low (0) Intermediate (>0 and <3) High (≥3)	170 (22 %) 460 (59 %) 150 (19 %)	0.5 % at 3 months 1.7 % at 3 months 7 % at 3 months	0.6 % at 3 months 1.5–4.4 % at 3 months 1.8–7 % at 3 months
Kearon et al. [32]	Developed in patients with acute venous thromboembolism enrolled in a clinical trial	1 point for each of the following: age ≥65, prior stroke, prior peptic ulcer disease, prior GI bleeding, creatinine >1.5, anemia or thrombocytopenia, liver disease, diabetes mellitus	Prospectively determined major bleeding: clinically overt and decrease in Hgb ≥2.0 g/dL, transfusion of ≥2 units PRBCS, or in a critical site	Low (0–1) Intermediate (2–3) High (≥4)	654 (89 %) 84 (11 %) –	0.2–2.0 per 100 person-years 1.0–2.3 per 100 person-years –	0.6–2.5 per 100 person-years 2.3–9.3 per 100 person-years 5.5–15.3 per 100 person-years

Table 1 continued

Risk scheme	Study description	Risk score calculation	Hemorrhage outcomes	Risk categories (points)	Number of patients (%)	Major bleeding rates in original cohort	Major bleeding rates in other studies
$HEMORR_2HAGES$ [28]	Developed from the National Registry of Atrial Fibrillation (NRAF) in 3791 hospitalized Medicare patients with atrial fibrillation discharged on warfarin and followed for 36 months	1 point for each of the following: hepatic or renal disease, alcohol abuse, malignancy, age >75 years, reduced platelet count or function, hypertension (uncontrolled), anemia, genetic factors, excessive fall risk, and stroke 2 points for: previous hemorrhage	Authors used ICD-9-CM codes for bleed in any location	Low (0–1) Intermediate (2–3) High (≥4)	717 (45 %) 694 (43 %) 193 (19 %)	2 % at 12 months 5 % at 12 months 9 % at 12 months	0.7–2.5 % per year 2.5–8.4 % per year 4.0–12.3 % per year
Shireman et al. [27]	Developed from 26,345 hospitalized Medicare patients older than 65 years with atrial fibrillation discharged on warfarin and followed for 3 months	Risk score = 0.4 (age ≥70) + 0.32 (female) + 0.58 (remote bleed) + 0.62 (recent bleed) + 0.71 (alcohol/drug abuse) + 0.27 (diabetes) + 0.86 (anemia) + 0.32 (antiplatelet use)	Hospitalization for bleeding events identified from claims data	Low (≤1.07) Intermediate (>1.07 and <2.19) High (≥2.19)	– – –	0.9 % at 3 months 2 % at 3 months 5.4 % at 3 months	0.9–5.7 % at 12 months 3.2–9.9 % at 12 months 6.7–14.3 % at 12 months
RIETE risk scheme [29]	19,274 patients presenting to hospital with acute venous thromboembolism followed for 3 months	Recent major bleeding (<15 days prior to thrombotic event) (2 points) creatinine >1.2 mg/dL (1.5 points) anemia (1.5 points) malignancy (1 point), pulmonary embolism (1 point) age >75 years (1 point)	Major bleeding: overt, requiring a transfusion of 2 or more units of blood, retroperitoneal, spinal, intracranial, fatal	Low (0) Intermediate (1–4) High (>4)	1340 (21 %) 4891 (74 %) 341 (5.2 %)	0.3 % at 3 months 2.6 % at 3 months 7.3 % at 3 months	0.6–4.3 % at 12 months 1.9–7.1 % at 12 months 10.2–15.4 % at 12 months
HAS-BLED [30]	Developed from the Euro Heart Survey on AF in 3,456 patients with atrial fibrillation followed for 12 months	1 point for each of the following: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, or drug/alcohol use concomitantly	Major bleeding: any bleed requiring hospitalization or causing a decrease in hemoglobin level of 2 g/L or requiring blood transfusion that was not a hemorrhagic stroke	Low (0) Intermediate (1–2) High (≥3)	798 (26 %) 2030 (66 %) 243 (8 %)	1.13 per 100 person-years 2.90 per 100 person-years 3.74 per 100 person-years	0.8–2.8 % at 12 months 3.3–6.9 % at 12 months 3.1–9.5 % at 12 months
ATRIA risk score [31]	Developed in 9186 atrial fibrillation patients enrolled in a large integrated healthcare system and followed for 6 years	Anemia (3 points), severe renal disease (3 points), age ≥75 yrs (2 points), prior bleed (1 point), hypertension (1 point)	Potential events identified by ICD-9 CM codes and validated using chart review. Major bleeding: fatal, requiring transfusion of ≥2 units blood, or hemorrhage into a critical site	Low (0–3) Intermediate (4) High (5–10)	83 % person-years 7 % person-years 10 % person-years	0.76 % per 100 person-years 2.62 % per 100 person-years 5.76 % per 100 person-years	1.5–5 % per year 2.1–4.6 % per year 2.8–11.6 % per year

Table 1 continued

Risk scheme	Study description	Risk score calculation	Hemorrhage outcomes	Risk categories (points)	Number of patients (%)	Major bleeding rates in original cohort	Major bleeding rates in other studies
ACCP 9th [13]	Evidence-based review of the literature	Age >65 years, age >75 years, previous bleeding, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia,previous stroke, diabetes, anemia, antiplatelet therapy, poor anticoagulant control, comorbidity and reduced functional capacity, recent surgery, frequent falls, alcohol abuse	N/A	Low (0)	N/A	1.6 % within 3 months, 0.8 % per year after the first 3 months	2.1 % at 90 days
				Intermediate (1)	N/A	3.2 % within 3 months, 1.6 % per year after the first 3 months	5 % at 90 days
				High (≥2)	N/A	12.8 % within 3 months, ≥6.5 % per year after the first 3 months	5.2 % at 90 days

the 0.6–0.7 range. No single risk score was consistently superior to others in predicting hemorrhage.

The one study that specifically examined the performance of risk schemes for venous thromboembolism found very mediocre performance [36]. Among this cohort of 663 older patients presenting with acute venous thromboembolism, the rate of bleeding was 4.2 % within 90 days. The four bleeding risk schemes tested performed only marginally better than chance alone, with an observed hemorrhage rate in the high bleeding risk groups of 3.1–6.6 %.

Use of bleeding risk tools in clinical practice

When evaluating the performance of a risk score, it is important to consider whether the ability to categorize a patient at high or low risk for an outcome would change the decision to anticoagulate or not. In many situations, the rates of bleeding that have been seen in patients categorized even at high bleeding risk are generally not high enough to dissuade from anticoagulation, because the negative consequences of thromboembolism largely outweigh the consequences of bleeding. None of the available risk schemes were specifically designed to predict intracranial hemorrhage, the only outcome comparable to ischemic stroke in severity. Although some risk schemes have been associated with a higher risk of intracranial hemorrhage, it is not clear there is a threshold at which the risk of intracranial hemorrhage is clearly excessive, given the limited power of studies to detect this rare outcome [35, 38]. For the most part therefore, bleeding risk tools seem to be most useful for patients at the lower end of thrombotic risk, where the net benefits of anticoagulation are smaller and the risk of bleeding may be more influential. Bleeding risk tools can also be useful in identifying low-risk groups of patients who can be reassured that they are unlikely to have significant bleeding complications.

When considering which risk scheme to use, several factors should be considered. One is whether the individual risk factors are readily available. For example, knowledge of anticoagulation control or genotyping may not be available at the start of therapy. One should also consider whether the risk score applies to the patient population. For example, the RIETE risk scheme was developed in patients with venous thromboembolism and the risk factor "clinically overt pulmonary embolism" is not applicable to patients with atrial fibrillation. Several risk schemes were developed in inception cohorts of patients newly started on anticoagulants examining the short-term risk of bleeding, while others were based in outpatient settings. In order to most effectively counsel patients about their actual risk of bleeding, it is worth considering which risk scheme most directly applies to a particular target patient until there is more evidence supporting the effectiveness of a given risk scheme.

Summary

Tools to predict bleeding risk on oral anticoagulants can provide clinicians and patients valuable information about the potential risks of bleeding, information that can be used to aid in informed decision-making. Unfortunately, none of the available risk tools are highly predictive and are not able to effectively predict intracranial hemorrhage. Bleeding risk tools can help in counseling patients about the risks of bleeding and identify patients who might benefit from more careful anticoagulation or targeted reduction of risk factors.

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