

Review Article

Bleeding with anticoagulation therapy – Who is at risk, and how best to identify such patients

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Summary

Anticoagulation with vitamin K antagonists (VKAs) has been shown to be effective in the prevention and treatment of thrombotic complications in various clinical settings, including atrial fibrillation (AF), venous thromboembolism (VTE), 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. The occurrence of bleeding during treatment is not only important for the treated subjects, but also for a correct and complete use of this therapy in all the subjects

Keywords

Anticoagulation, bleeding, vitamin K antagonists, clinical prediction rules

who have a clear clinical indication for anticoagulation. This review analyses the treatment- and person-associated risk factors for bleeding during VKAs and their combination in clinical prediction rules that have been proposed in the attempt to identify those patients at higher risk for bleeding. The clinical prediction rules may help physicians stratify patients into categories of risk and thus to evaluate their individual risk/benefit ratio of starting or prolonging an anticoagulant treatment.

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Introduction

Anticoagulation is a very common form of medical intervention which is increasingly used for primary or secondary prevention of thrombotic complications of vascular disease. Oral anticoagulation with vitamin K antagonists (VKAs), mainly warfarin, is almost the unique tool for chronic anticoagulant treatment in clinical practice, although newer anticoagulants have already been approved or evaluated in clinical studies. Anticoagulation with VKAs has been shown to be effective in the prevention and treatment of thrombotic complications in various clinical settings, including atrial fibrillation, venous thromboembolism (VTE), acute coronary syndromes and after invasive cardiac procedures. In spite of the sharp increase in the number of anticoagulated subjects which has occurred in recent years (an increase of 45% of warfarin prescriptions between 1998 and 2004 has been recorded in the USA [1]), numerous studies have documented an under-use of anticoagulation in subjects, especially elderly, who would benefit from this therapy (2, 3). Adequate treatment with VKAs is rather demanding, for both the patients and the health care systems, because periodic laboratory monitoring is necessary to maintain the effect of the drug in a thera-

peutic range and to minimize adverse events (4–6). Bleeding is the most important complication of VKAs and a major concern for both physicians and patients.

The aim of this selective review is to analyse the factors affecting the risk of bleeding during VKAs, and to review the clinical rules proposed to predict the individual risk for haemorrhage when starting VKAs.

The expected incidence of bleeding: Clinical trials and observational studies

The incidence of bleeding varies widely in published studies. In part, the difference in reported rates can be attributed to the diverse classification of bleeding events (major, life-threatening and minor) adopted in single studies. However, differences in study design, patient populations and quality of monitoring may well have a more important role in explaining such differences. Studies of experimental type (randomised clinical trials) can be expected to record lower rates of bleeding than observational studies because they usually include only highly selected patients. Very elderly patients are almost always excluded in these

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studies, as well as patients with personal risk factors for bleeding who, however, can be encountered in clinical practice. Up to one third of patients evaluated for participation in clinical trials on VKAs use in atrial fibrillation were judged ineligible, primarily for a high perceived bleeding risk (7, 8). Retrospective observational studies may underestimate the risk of bleeding, as well as studies not performed on a clearly defined inception cohort of patients. It is, in fact, well known that the first few months of treatment are associated with a higher rate of complications (9, 10).

Such studies may therefore underestimate the rate of bleeding by missing early complications and early cessation of VKA in patients at a high risk of bleeding. In a recent analysis of clinical studies characterised by careful monitoring of anticoagulant intensity, it has been calculated that VKA treatment increases the risk of major bleeding by 0.3–0.5% per year. In these studies the risk of intracranial hemorrhage (ICH), which is the major if not the exclusive cause of death and disability associated with VKA treatment (11), is increased by approximately 0.2% per year when compared to controls (12).

The absolute risk of major bleeding complications in specialised anticoagulation services ranged from 0.32% to 2.1% per year, and of fatal bleeding from 0% to 0.25% per year (13). 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 (95% confidence interval [CI], 9.4% to 17.4%), with a rate of ICH of 1.15% patient-years (95% CI, 2.5% to 21.7%) (14). The Food and Drug Administration (FDA)'s Adverse Event Reporting System indicated that warfarin is among the 10 top drugs for the adverse events reported during the 1990 and 2000 decades (1).

Major bleeding with VKA treatment can be not only life-threatening, such as ICH, but also associated with significant morbidity, while even minor bleedings may be important for the related inconvenience to the patients. Altogether, the risk of bleeding associated with VKAs limits their more widespread use and denies many patients the benefits of a useful therapy. It has been shown (15) that the occurrence of VKA-associated adverse events has an impact on the prescription of this treatment, since physicians are less likely to prescribe VKAs after observing major bleeding during VKA treatment in their patients. The study reported that patients with atrial fibrillation (AF), who were treated by physicians in the 90 days after a major bleeding event occurred in other patients in a physician's own practice, had a 21% reduced odds of receiving VKAs compared with patients treated by the same physicians before the bleeding event occurred. In contrast, the occurrence of a thromboembolic stroke in a patient with AF not on anticoagulation did not influence the odds that a physician would use VKAs in subsequent patients with AF (15). These results demonstrate the relevance of bleeding occurrence during VKA treatment not only for the treated subjects, but also for a correct and complete use of this therapy in all the subjects who have a clear clinical indication for anticoagulation (16–18).

Risk factors for bleeding during VKA therapy: Treatment-associated factors

Intensity of anticoagulation

The intensity and duration of anticoagulation are main factors associated with the risk of bleeding. A strong relationship between the intensity of anticoagulation and the risk of bleeding has been demonstrated by several experimental trials (in various clinical conditions) in which patients were randomised to different anticoagulation levels (12). Though bleeding is not always related to a high intensity of anticoagulation and may occur even in association with very low international normalised ratio (INR) values (< 2.0), the intended intensity of anticoagulation and especially the actually achieved intensity are major determinants of anticoagulation-induced bleeding. The increase in bleeding incidence becomes exponential for INR values > 4.5, while the lowest rate is associated with INR results between 2.0 to 3.0 INR (9). The risk of death is also strongly related to the INR level, with a minimum risk at 2.2 INR. High INR values are associated with an excess mortality as well: for one unit INR increase above 2.5 there is a two-fold risk increase (19).

Timing from starting of anticoagulation

The first period of anticoagulation and in particular the first 90 days are associated with a higher rate of haemorrhages (9, 10). This can be attributed to different factors: occult lesions can be unmasked at the beginning of anticoagulant therapy, and/or the dose adjustment may be less adequate in that period. Studies examining patients not included in inception cohorts and/or those undergoing a second course of VKAs after an interval period are likely to underestimate the true risk of bleeding because they either miss early events or exclude patients who had bled in the first course from any second course.

Quality of monitoring

A poor control of anticoagulation is undoubtedly an important factor leading to an increased risk of complications. A way to evaluate the quality of anticoagulation control is to calculate the time spent within the therapeutic range (time-in-range). A strong relationship between time-in-range and bleeding or thromboembolic rates has been observed in many studies, involving different patient populations and different target ranges (20). Higher rates of annual mortality and major bleeding events have been recorded in a poor control group of patients (4.20% and 3.85%, respectively) compared to a good control group (1.69% and 1.58%) (21). Many factors may affect the quality of anticoagulation monitoring. A better overall quality of treatment and a more stable anticoagulation has been reported by using coumarin drugs with long-lasting action, such as warfarin (22) or phenprocoumon (23), versus the short half-life drug acenocoumarol. Patient information and education and the systems adopted for INR control are also factors affecting the quality of treatment. A better quality control in patients who had received a satisfactory education has been reported (24), as well as an improvement in their time-in-range in highly unstable patients after a supplementary education course (25).

Other strategies have been shown to be effective in improving the time-in-range in chronically anticoagulated patients. Many patients can manage their treatment safely and reliably themselves. Several studies have shown that patients' self-management is feasible, safe and improves the quality of anticoagulation control together with the quality of life (for a review see [26, 27]). Moreover, it has recently been demonstrated that self-management was superior for the prevention of major thromboembolic and bleeding complications and for the quality of anticoagulation control compared to routine care in a population at particularly high risk of complications during VKA treatment such as elderly patients (28). The use of computer-assisted dosage has been demonstrated to improve the quality of oral anticoagulation management. A recent large collaborative study showed that the use of two different marketed computer programs not only improved the achievement of target INR in comparison with experienced medical staff dosage at the centers with established interest in anticoagulation, but also led to a significant prevention of clinical events in some patient groups (29).

Person-dependent factors

Genetic factors

Though for decades VKAs have been the most used antithrombotic drugs, only recently our understanding of their mechanisms of action and of the broad inter-individual variability in the sensitivity to these drugs has greatly improved thanks to the knowledge on their pharmacogenetics (for a complete review see [30]).

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 the large inter-individual variations in dose requirements, and can predispose to overdosage conditions and a higher risk of bleeding (31, 32).

The VKORC1 is the target enzyme of VKAs that function by directly inhibiting reduction of vitamin K epoxide by VKORC1. As a result, VKAs block the complete vitamin K reduction, which is essential for the post-translational gamma-carboxylation of vitamin K-dependent coagulation factors, including factor II, VII, IX, and X, and also protein C and protein S. The enzyme CYP2C9 regulates the metabolic clearance of S-enantiomer of warfarin. The presence of the allelic variants CYP2C9*2 and CYP2C9*3 is associated with a reduction in S-enantiomer catabolism that in turn leads to a higher sensitivity to VKAs and lower dose requirements (33, 34).

The CYP2C9 polymorphism can cause a delayed stabilization of VKA treatment; its effect, however, is not of the same magnitude on all VKAs, being least pronounced in the case of phenprocoumon (35). As regards to VKORC1, studies have shown the presence of frequent mutations leading to different sensitivities to VKA action. The haplotype A/A is associated with a 50% reduction in activity compared to the wild type; thus the carriers require lower VKA doses (36, 37). By contrast, other mutations lead to a condition of coumarin resistance (30, 38, 39).

CYP2C9 variants are significantly more frequent among patients with highly unstable response to VKAs than in stable controls (25). It has been reported that carriers of CYP2C9 variants,

compared with non-carriers, achieve stable dose significantly later, spend a higher proportion of time above range in the initial phase of anticoagulation and have higher risk of INR values > 5; whereas, the only significant effect of VKORC1 variants was a higher risk of INR > 5 (40). Other studies reported that specifically patients with A/A VKORC1 haplotype had a decreased time to first therapeutic INR (41).

Though only some (42), but not all studies (41) have found these gene variants to be associated with the incidence of bleeding, it is, however, well proven that they are associated with particular VKA dose requirements in the initial phase of VKA anticoagulation. To improve management of initial anticoagulation and reduce the risk of bleeding in early phases of treatment, several dosing algorithms have been proposed based on genotype of both VKORC1 and CYP2C9, on top of other previously known factors that influence VKA dose, such as age, gender and weight (43).

Another genetic factor has been demonstrated to affect VKA pharmacodynamics. A rare mutation in factor IX propeptide has been described leading to a marked reduction in the levels of this factor (up to 1–3%) during VKA treatment and to an increased incidence of bleeding (44). This alteration cannot be revealed by higher than expected INR values but only by particularly increased aPTT results (45).

Age

Throughout most (9, 46–49), though not all (50, 51), studies age is generally regarded as a risk factor for bleeding during VKA treatment. A recent review of the studies (52) 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, the most important and feared type of haemorrhage during VKA, is particularly increased in advanced age (47). Its incidence is estimated to be 0.2% to 1.0% patient-years in all anticoagulated patients (53), but increases to 1.1% patient-years in patients above 75 years (54). A recent study (55) reported an adjusted odds ratio of 2.5 (95% CI, 1.3–4.7) of ICH in patients aged 85 or more versus a reference group of patients of 70–74 years. In line with previous reports (54), 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.

Elderly subjects are exposed to higher risk for bleeding complications during VKA for several reasons. They require lower anticoagulant doses than younger subjects, mainly because of reduced metabolic clearance (56) especially in older women. It has been recently shown that, when warfarin is being initiated, the commonly used starting daily dose of 5 mg per day may lead to overanticoagulation for the majority of elderly patients and a lower initiation and maintenance dose has been recommended for these patients (57). Elderly patients have a higher prevalence of co-morbid conditions (58) and are more likely to be taking interacting drugs. They more frequently have pathological changes in cerebral vessels, such as leukoaraiosis and amyloid angiopathy, that may increase the risk of ICH (59, 60). They are at higher risk for falls with a subsequent substantially increased risk of intracranial haemorrhage (61). The incidence of gastrointestinal haemorrhage increases sharply with age (62), due to the

more frequent presence of diverticulosis, malignancy, angiodysplasias, and ischaemic colitis, all more common in the elderly population. Although reported to be similar in elderly and younger patients (63), non-compliance to VKAs may contribute to the complexity of the drug regimen and a higher instability of anticoagulation levels. A lack of a clear understanding of the purpose and mechanisms of this treatment by the elderly (25) who are also prone to mental impairment (64) may also contribute to a low compliance with the treatment.

Physicians are therefore faced with a dilemma. The elderly are considered to be at higher risk of bleeding during VKAs, but an increasing number of elderly patients are candidates for, and could benefit from, anticoagulation. A recent randomised study has shown that warfarin anticoagulation in subjects with atrial fibrillation aged over 75 years was more effective than antiplatelet agents at reducing stroke risk without leading to a significantly higher incidence of bleeding (65). These results support therefore anticoagulation therapy in elderly subjects with atrial fibrillation, unless there are evident contraindications.

It can be concluded that elderly patients should not be excluded from anticoagulation therapy only because of their age if they are otherwise good candidate to the treatment. These subjects should, however, be monitored carefully and frequently to maximise their stability during anticoagulation and to reduce the risk of complications.

Gender

A greater risk of bleeding (66) or of borderline significance (67) was reported in women than in men treated for atrial fibrillation, although no significant difference in bleeding rate between males and females was found in observational studies enrolling patients with various indications for VKA (9). Pengo et al. (68) found a higher frequency of major bleeding in females treated for atrial fibrillation at univariate analysis.

Personal characteristics, life habits and environmental factors

Good patient compliance is necessary to achieve a safe and effective anticoagulation with VKAs. Non-compliant patients were found to be more frequently young, male and not having already experienced a thromboembolic event (63). Unstable patients, more frequently than stable ones, reported they were poorly informed on the reasons and the clinical importance of anticoagulation for their health; many of them also had insufficient knowledge of VKA mechanism of action, the rules of treatment-monitoring, and the risk of thrombotic and bleeding complications (25). A relationship between patient knowledge of anticoagulation mechanisms and quality of control has been reported (69, 70). Moreover, patient education on VKAs and anticoagulation training has been effective in reducing the risk of major bleeding in older patients (71). These data indicate that patient knowledge of VKAs treatment and its management is a primary determinant of the quality of anticoagulation control and that appropriate education and information of patients is one of the most important tasks of services dedicated to anticoagulation monitoring.

Dietary modification has long been recognised as a key factor for instability of anticoagulated patients. Patients who increase their dietary vitamin K intake may become resistant to

VKA effect (72, 73). On the contrary, a lower intake of vitamin K has been demonstrated to increase sensitivity to VKAs (74, 75). A reduction in dietary vitamin K intake should be expected in sick patients who are treated with antibiotics and intravenous fluids without vitamin K supplementation and in patients who have states of fat malabsorption. It is possible that at least part of the instability of anticoagulation control in patients on VKA therapy is attributable to a low dietary intake and/or low reserves of vitamin K. A low-dose vitamin K supplementation (100 to 200 mcg daily) proved to be effective in improving the quality of anticoagulation control (76, 77), a result that has been confirmed by two recent trials (78, 79).

Fever or other hypermetabolic states, such as hyperthyroidism, may increase VKAs responsiveness, probably by increasing the catabolism of vitamin K-dependent coagulation factors.

The use of nutritional supplements and/or herbal products is particularly problematic in VKA-treated patients for the little or no standardisation of their content and for the possible effects on anticoagulation stability. Unfortunately, such products are frequently taken by patients monitored in anticoagulation clinics (80) often without informing the doctors in charge.

Co-morbid conditions

The presence of co-morbidities may represent a significant risk factor for bleeding during treatment. A recent analysis of results of a clinical trial on treatment of patients with AF (the AFFIRM Study [81]) reported that congestive heart failure, hepatic or renal disease and diabetes were conditions, among others, significantly associated with major bleeding. A history of bleeding (especially in the gastro-intestinal tract) is the patient related factor most frequently reported to be predictive for the risk of further bleeding complications (82). Liver diseases potentiate the response to VKAs by impairing synthesis of coagulation factors and usually make a good control of anticoagulation more difficult. In a recent review (83) of the available studies, several possible predisposing factors have been analysed: history of bleeding, history of myocardial infarction and previous cerebrovascular events were all factors associated with higher risk of bleeding complications.

Blood pressure control is a critical factor for bleeding complications during VKA. A higher prevalence of history of hypertension in anticoagulated patients with bleeding versus patients without bleeding complications was found in some (84), though not all studies (55). No relationship was found between quartiles of systolic blood pressure and bleeding complications in the SPORTIF cohorts (85). These results can reflect the optimal management and close monitoring typical of a clinical trial setting. It has been reported that a modest blood pressure-lowering halves the occurrence of ICH during antiplatelet therapy (and likely during anticoagulation) (86).

The association between malignancy and VTE is well established. The ISCOAT study showed that a 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; $p < 0.0001$) (87). Most studies (87–89), but not all (90), have reported a higher rate of major and minor bleeding in patients with malignancy during oral anticoagulant therapy. One study (87)

Table 1: Factors that affect the quality of treatment and the risk of bleeding complications in patients on chronic anticoagulant treatment with vitamin K antagonists (VKAs).

Better control quality / reduced bleeding risk	Worse control quality / increased bleeding risk
A) Treatment-associated factors	
Duration and timing from initiation of treatment	
Short duration	First 3–6 months of therapy
Intensity of anticoagulation	
Low-to-moderate intensity INR target	High INR target
2.0–3.0 actual INR values	> 4.5 INR values
Quality of anticoagulation monitoring	
Organized systems for monitoring (e.g. anticoagulation clinics)	
Use of long half-life VKA drug	Use of short half-life VKA drug
Good anticoagulation control (high % time in range)	Poor anticoagulation monitoring
Self-management	
Use of computer-assisted dosage	
B) Person-dependent factors	
Genetic factors	
	Polymorphisms of VKORC1 and CYP2C9
	Mutation in factor IX propeptide (low factor IX levels)
Natural conditions	
	Advanced age
	Women
Personal characteristics/life habits	
	Tendency to falls
	Insufficient information and education to the treatment
	Poor compliance
	Poor dietary intake of vitamin K
	Nutritional supplements and herbal products
	Alcohol abuse
	Absence of familial or social support
Co-morbid conditions	
	History of major bleeding (especially GI)
	History of atherosclerotic stroke
	Uncontrolled hypertension
	Cancer
	Congestive heart failure
	Liver diseases
Co-medication	
	Antiplatelet drugs
	NSAIDs
	Drugs affecting pharmacokinetics or pharmacodynamics of VKAs

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. It was found, however, that different intensities of INR were associated with similar high rates of bleeding in cancer patients, thereby suggesting that even very close monitoring of the INR may not help to reduce the risk of bleeding in this patient group. The lack of correlation between the bleeding rate and INR levels suggests that local sources, rather than anticoagulation intensity, may be the main causes of bleeding in the cancer patient. Bleeding was also a more frequent reason for stopping anticoagulation in patients with malignancy than in other patients. Higher rates of major bleeding were found to be associated with more advanced malignant disease (89). There was also a trend towards more venous thrombotic recurrences in patients with malignancy and the majority of these patients died during follow-up. Safer and more effective anticoagulant therapy is needed for this challenging group of patients. Besides the higher risk of bleeding complications, cancer patients treated with VKA are also affected by a higher rate of recurrent thrombotic events (87, 89). For all these reasons and after the evidence provided by specific randomized trials (91), it is currently recommended to use low-molecular-weight heparin (LMWH) instead of VKAs at least during the first three months after a VTE in patients with cancer (92).

Co-medication

Co-medication may have important effects on anticoagulation with VKAs (for a review see [93]). Co-medication is especially associated with a higher bleeding risk in elderly patients (54, 94). Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase (COX)-2 inhibitors, of frequent use in older adults treated with VKAs, are a strong risk factor for upper gastrointestinal haemorrhage (95). The concomitant use of aspirin, or other antiplatelet drugs, in anticoagulated patients has also been particularly highlighted as a significant risk factor for bleeding complications (67). A recent case-control study in a cohort of new users of coumarins found that patients who also took clopidogrel or aspirin on top of VKAs had a significantly increased risk of hospitalisation because of major bleeding, mainly upper gastrointestinal bleedings (96). A systematic review and meta-analysis of randomized controlled trials concluded that the current practice of using combined aspirin-VKA therapy gives no advantage, except in patients with a mechanical heart valve, given the questionable benefits in reducing thromboembolic events and the increased risk of major bleeding (97). Accordingly, the addition of aspirin to warfarin in patients treated for AF who also have stable vascular disease is discouraged since adding aspirin does not seem to prevent stroke or other vascular events but increases the risk of bleeding (98).

Table 1 summarises the factors that may affect the quality of treatment and the risk of bleeding complications in patients on chronic treatment with VKAs.

Hospitalisation

A retrospective chart review study at Brigham and Women's Hospital (Boston, MA, USA) indicated that VKA-associated bleeding increases among hospitalised patients over time when

Table 2: Characteristics of studies evaluating clinical prediction rules (CPR) for bleeding.

Study author, year (reference)	1 – Design 2 – N. of patients 3 – Indication of treatment	Name and elements of CPR	1 – Definition of major bleeding 2 – Event adjudication	Patients N (%) in risk categories	Major bleeding N (%) in risk categories	Duration of follow-up
Landefeld, 1989 (102)	1 – prospective Inception cohort 2 – Test = 375 Validation = 187 3 – Mixed	Outpatient Bleeding Risk Index (OBRI) age >65, history of stroke, history of GI bleeding, serious comorbidity (recent MI, renal insufficiency, severe anemia), atrial fibrillation (1 point assigned for each predictor: high risk: >3 points)	1 – fatal, life-threatening, potentially life-threatening, led to severe blood loss, led to surgical treatment or led to moderate blood loss that was acute or subacute and was not explained by trauma or surgery. 2 – not described	Low = 57 (31) Intermediate = 107 (58) High = 20 (11)	Low = 1 (2) Intermediate = 18 (17) High = 13 (63)	18 mo. (mean)
Beyth, 1998 (103)	1 – prospective Inception cohort 2 – Test = 565 Validation = 264 3 – mixed	modified OBRI-(mOBRI) Age >65, History of stroke History of GI bleeding Recent MI, Hct <30% Cr >1.5 mg/dl, diabetes mellitus (1 point assigned for each predictor: High risk >3 points)	1 – Overt bleeding leading to a loss of at least 2.0 units in 7 days or less, or life-threatening 2 – Blinded	Low = 80 (30) Intermediate = 166 (63) High = 18 (7)	Low = 2 (3) Intermediate = 20 (12) High = 10 (53)	48 mo.
Kuijer, 1999 (104)	1 – post-hoc analysis of RCT -Columbus Study- 2 – Test = 241 Validation = 780 3 – VTE	SBRPS: Age (>60), sex, malignancy, body surface area (>2 m ²) coumarin type (long vs. short acting) (score = [1.6 x age] + [1.3x sex] + [2.2 x malignancy] + [2.4 x body surface area] + [1.3 x coumarin type]) Simplified score = [1.6 x age] + [1.3x sex] + [2.2 x malignancy] High risk score >3	1 – 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. 2 Blinded to allocation	Low = 170 (22) Intermediate = 460 (59) High = 150 (19)	Low = 1 (0.5) Intermediate = 8 (1.7) High = 10 (7)	3 mo.
Wells, 2003 (108)	1-Prospective 1-Validation=222 3-VTE	MOBRI	1 – Loss of 2 units of blood in a 7-day period or bleeding that was otherwise life threatening. 2 – Blinded	Low= 128 (57.6) Intermediate= 92 (41) High = 2 (1)	Low = 0 Intermediate = 18 (5) High = 0	18 mo.
Aspinall, 2005 (109)	1 – Inception cohort Prospective in pharmacist run anti-coagulation clinic 2 – Validation = 1269 3 – Mixed	MOBRI	1 – Hemodynamic instability, necessity of a transfusion, intracranial hemorrhage, or deaths (e.g. a GI bleed in a hypotensive patient, subdural hematoma) 2 – not described	Low = 130 (10.2) Intermediate = 943 (74) High = 196 (15.4)	Low = 2 (1.5) Intermediate = 18 (2) High = 22 (11.2)	12 mo.
Gage, 2006 (105)	1 – retrospective chart review of National Registry of Atrial Fibrillation data set 2 – Validation = 1604 3 – Atrial fibrillation	1 – HEMORR2HAGES: Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75 years), Reduced platelet count or function, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, and Stroke (1 point each). previous hemorrhages (2 points) High risk ≥4	1 – ICD-9CM codes for bleed in any location 2 – not described	Low = 717 (45) Intermediate = 694 (43) High = 193 (19)	Low = 15 (2) Intermediate = 35 (5) High = 17 (9)	3138 patient-year

Table 2: Continued

Study author, year (reference)	1 – Design 2 – N. of patients 3 – Indication of treatment	Name and elements of CPR	1 – Definition of major bleeding 2 – Event adjudication	Patients N (%) in risk categories	Major bleeding N (%) in risk categories	Duration of follow-up
Shireman, 2006 (106)	1 – retrospective chart review of National Registry of Atrial Fibrillation and Medicare data set 2 – Test = 19875 Validation = 6511 3 – Atrial fibrillation	age >70 years; gender; remote bleeding; recent (ie, during index hospitalization) bleeding; alcohol/drug abuse; diabetes; anemia; and antiplatelet drug use. High risk >2 Name of CPR not specified	1 – Hospitalization for “major acute bleeding” (including GI hemorrhage or intracranial hemorrhage) 2 – not described	Low = 3889 Intermediate = 2400 High = 222	Low = 35 (0.9) Intermediate = 48 (2) High = 12 (5.4)	3 mo.
Ruiz-Gimenez, 2008 (107)	1 – prospective multicenter registry RIETE of symptomatic acute VTE 2 – Test = 13057 validation = 6572 3 – VTE	age >75 years, recent bleeding, cancer, creatinine levels >1.2 mg/dl, anemia, or pulmonary embolism at baseline (2 points to recent bleeding, 1.5 to abnormal creatinine levels or anemia, 1 point to the remaining variables). High risk >4 points Name of CPR not specified	1 – overt, requiring a transfusion of 2 or more units of blood, retroperitoneal, spinal, intracranial, fatal 2 – not described	Low = 1340 (21) Intermediate = 4891 (74) High = 341 (5.2)	Low = 1 (0.07) Intermediate = 137 (2.8) High = 21 (6.12)	3 mo.

two different periods were considered (99). The proportion of patients with major and intracranial bleeding increased from 20.2% and 1.9%, respectively, from 1995 to 1998, to 33.3% and 7.8%, respectively, from 1998 to 2002. This may be attributed to improved imaging techniques and also increased use of combined anticoagulant regimens as 81% of subjects also received drugs such as antiplatelet agents or other anticoagulants or NSAIDs or warfarin potentiators (99). In addition, appropriate anticoagulation is difficult to achieve in hospitalised patients and there are many medication errors in anticoagulated patients as shown by a retrospective chart review at Brigham and Women’s Hospital from 1999 to 2003 (100). There were 1.67 medication errors for every 1,000 patients treated with anticoagulants, including warfarin. Also, excessive anticoagulation is associated with increased mortality in hospitalised patients with bleeding complications as shown by prospective cohort study of 101 patients admitted with major bleeding during anticoagulation with warfarin, unfractionated heparin or LMWH.

Excessive warfarin therapy was associated with increased 60-days mortality (101).

Clinical prediction rules for bleeding

Treatment- and person-associated factors have been combined in clinical prediction rules in the attempt to identify those patients at a higher risk for bleeding during anticoagulation. These prediction rules could help physicians stratify patients into categories of risk and thus the risk/benefit ratio of VKAs could be evaluated not only upon starting but also when prolonging such treatment.

So far several distinctive clinical prediction rules have been proposed (102–107). The characteristics of the studies with the

different elements of the five clinical prediction rules are reported in Table 2. Among these scores, the modified Outpatient Bleeding Risk Index (mOBRI) has been the most extensively validated in different indications for VKAs in studies with a follow-up between 12 and 48 months (103, 108, 109). However, none of these studies except one (103) had a blinded outcome assessment of bleeding, and different classifications of major bleeding were adopted in different studies. The setting of the anticoagulation control was clearly indicated by Beyth et al. (primary physician) and the study by Aspinall et al. (pharmacist-run anticoagulation clinic).

The score proposed by Kuijter et al. (SBRPS) (104) was based on a post-hoc analysis of a randomised trial of acute treatment of VTE with LMWH (Columbus study) with a follow-up of only three months and with a different classification of bleeding when compared with other studies. This score was derived from selected patients enrolled in a randomised clinical trial with low bleeding rates, and therefore its generalisability to routine clinical practice is limited.

Gage et al. (105) and Shireman et al. (106) conducted a retrospective chart review of the National Registry of Atrial Fibrillation gathered in the USA by five quality improvement organisations. Gage et al. combined the elements of previous scores (OBRI, SBRPS) in a single clinical prediction rule. The classification of bleeding was based on ICD-9CM codes in both studies, and no blinded outcome assessment was conducted. No indication of the setting of anticoagulation control was provided and follow-up was only 90 days in the study by Shireman et al. The validity of these scores is limited by the use of retrospective databases with no inception cohorts. In fact the retrospective design implies potential loss of patients with complications in early phase of treatment.

Dahri et al. (110) conducted a systematic review and a performance analysis of four different prediction rules (103–106). The results of this review showed that the methodological quality of all available studies was poor and none of the clinical prediction rules were associated with sufficiently large or small likelihood ratios for the prediction of major bleeding or its absence.

More recently, the RIETE investigators (107) have derived and validated a score in 19,274 patients to predict the risk of major bleeding within three months of anticoagulant therapy for venous thromboembolism (Table 1). The likelihood ratio test was: 0.14 (95% CI: 0.07–0.27) for patients at low risk and 2.96 (95% CI: 2.18–4.02) for those at high risk. In the validation sample the incidence of major bleeding was: 0.1%, 2.8%, and 6.2%, respectively, in low, intermediate and high risk. No blinded outcome assessment was conducted, the follow-up was only 90 days and the rate of patients at a high risk was low.

So far no trials evaluating the impact of these scores on patients outcomes are available and none of the proposed clinical prediction rule can be recommended for widespread clinical use. Several reasons could explain the lack of and difficulties in devising an accurate clinical prediction rule. Some factors related to bleeding risk have not been included in the different scores, such as quality of anticoagulation control, compliance, co-medications such as NSAIDs, presence of occult sites of bleeding, history of poorly controlled anticoagulation therapy. These factors are generally unavailable at the start of treatment and they may also change during treatment especially in case of long-term treatment. Thus periodic assessment of the bleeding risk could be needed. Moreover in the HEMORR2HAGES score (105) some factors such as platelet function and CYP2C9 single nucleotide polymorphism are not easily available. Age is an element considered in all proposed scores, however, an advanced age was considered only in the scores by Gage et al. and Shireman et al. (> 70 and > 75 years, respectively) in AF patients (105, 106). Only the mOBRI has been validated in patients with mixed indication for VKAs, although the patient samples were small. The other scores have been validated in AF or VTE and therefore not easily applicable to other populations.

Although no reliable tool is available to assess bleeding risk during anticoagulation, known risk factors for increased risk of bleeding should be taken into account on an individual basis when starting anticoagulation. Further research efforts are needed to establish an accurate clinical prediction rule.

Pre-warfarin initiation genetic testing

Pre-warfarin initiation genetic testing has emerged as the key current, controversial issue related to the risk of bleeding on warfarin. In 2007 the FDA issued a black box warning which updated the product label of warfarin by advising physicians to consider CYP2C9 and VKORC1 genetic tests to improve their initial estimate of warfarin dose (111). Pharmacogenomics in which genetics explains individual differences in drug responses has the potential to provide individually tailored warfarin dosing (112). As a result it could reduce the risk of bleeding by increasing dosing accuracy, shortening the time to achieve a therapeutic range and identifying those individuals who may require more frequent monitoring (113).

Current pharmacogenomics tests detect CYP2C9*2 (430C>T), CYP2C9*3 (1075A>C) and VKORC1 (-1693G>A) by polymerase chain reaction (PCR) amplification of selected DNA fragments. These tests can be performed using cheek swabs or blood samples with a typical 24– to 48-hour turnaround time for test results. Rapid one-hour tests have also been developed.

Retrospective studies or cross-sectional studies showing that genetic polymorphisms affect warfarin dosing may have excluded individuals who stop warfarin early because of adverse effects or those who have difficulty attaining a therapeutic maintenance dose (113). Four prospective studies have evaluated genotype guided algorithms and two reviews of these studies have been conducted (114–119). More recently, Kangelaris et al. (120) have conducted a systematic review with the aim to investigate the safety and efficacy of genotype-guided dosing of warfarin in reducing serious bleeding events and over-anticoagulation. Only three randomised clinical trials were included in the meta-analysis comparing pharmacogenetic dosing of warfarin with a standard dose control algorithm in adult patients (n = 423; 97% Caucasians) starting warfarin for the first time (114, 121, 122). These three studies were single center with follow-up ranging from 22 to 46 days with different dosing models for the pharmacogenetic and control dosing arms, and significant variability of design quality, intervention and outcome measures. Only one study incorporated both CYP2C9 and VKORC1 variants (114), while two studies only considered CYP2C9 variants (121, 122). Two of the pharmacogenetics algorithms were previously validated and adjusted for covariates of age, sex and weight (114, 121). Computer-assisted dosing with DAWNAC computer algorithm was employed in one study (122). Study quality was adequate for only two studies (114, 121). None of the studies was powered to show a difference in major bleeding and the pooled risk ratio of major bleeding between pharmacogenetics and control was 0.69 with 95% CI: 0.16–2.9 which did not reach statistical significance. The results of this systematic review indicate that it is still uncertain whether pharmacogenetic dosing is safer and more effective than the standard strategy with careful INR monitoring.

Moreover, pharmacogenomic testing will add to the costs associated with warfarin therapy; however, these additional costs could be offset by reducing the expenses associated with adverse events such as bleeding and strokes. Eckman et al. (123) have recently conducted a the cost-effectiveness analysis of genotype-guided dosing versus standard induction of warfarin therapy for patients with non-valvular AF in the USA. On the basis of current data and cost of testing (about \$400), there is only a 10% chance that genotype-guided dosing is likely to be cost-effective (that is, <\$50,000 per QALY). Sensitivity analyses revealed that for genetic testing to cost less than \$50,000 per QALY, it would have to be restricted to patients at high risk for haemorrhage or meet the following optimistic criteria: prevent greater than 32% of major bleeding events, be available within 24 hours, and cost less than \$200. At its current cost, routine genotyping before warfarin dosing is not economically attractive.

At the moment no widely accepted pharmacogenetic algorithm for warfarin initiation is available and new models are being developed and validated. The most comprehensive and

widely available algorithm has been recently validated by the International Warfarin Pharmacogenetics Consortium (124) and will be used in the largest randomised ongoing trial. Several randomised clinical trials comparing pharmacogenetic warfarin dosing to a control-dosing algorithm among patients starting warfarin therapy are currently ongoing or just completed in a large number of patients (> 2,500). These studies should clarify the clinical role of genetic testing in warfarin management. Future perspectives

This issue is even more pressing when we consider the newer oral anticoagulants which can be administered in fixed doses

without monitoring. The rate of bleeding complications is low in clinical trials evaluating these drugs in highly selected populations. However, in routine clinical practice the risk of bleeding of the new oral anticoagulants is likely to be influenced by some, if not all, person- and treatment-related factors which affect the bleeding risk with VKAs. The new drugs do not require monitoring for the low intra- and inter-individual variability of their effect. This paramount advantage could be a disadvantage when considering the bleeding risk in the individual patient, as treatment-related factors affecting bleeding, such as intensity and quality of anticoagulation may be difficult to evaluate.

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