

Current strategies to minimize the bleeding risk of warfarin

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Abstract: For many decades, the vitamin K antagonist warfarin has been the mainstay of treatment for various conditions that require anticoagulation, including atrial fibrillation. Although the efficacy of warfarin in both prevention and treatment of thrombosis has been demonstrated in numerous randomized clinical studies, one of the major concerns that remains is the risk of bleeding. Although the net benefit of warfarin has been demonstrated in large clinical trials, physicians and patients alike are often reluctant to use warfarin because of the bleeding risk. Bleeding in patients on warfarin is generally minor requiring no intervention, but the development of a major bleeding complication is associated with significant morbidity and can even be fatal. Numerous risk factors that increase the probability of having a hemorrhage while on warfarin have been identified, and bleeding risk scores have been developed. Various strategies to reduce bleeding risks have been developed and have become more important, since the use of warfarin and other anticoagulants continues to increase. This paper provides a concise review of bleeding risk factors, while outlining recommendations both physician and patients can incorporate to help reduce the risk of bleeding.

Keywords: hemorrhage, warfarin, thrombosis, anticoagulants, dabigatran, vitamin K antagonist

Introduction

Warfarin, the most commonly used anticoagulant in North America, is a vitamin K antagonist that is demonstrated to be efficacious in the prevention of thrombosis and thromboembolism. Its use dates back to the 1950s, when it was approved as an anticoagulant in the United States.¹ Current indications for its use include the prevention of thrombosis in patients either at risk for or with a history of thrombotic events. Such patients include those with thrombophilias, prosthetic heart valves, presence of deep venous thrombosis or pulmonary embolism, and in patients with atrial fibrillation at risk for thromboembolism.^{1,2} A large subset of patients taking this medication are those with atrial fibrillation and current projections show that in 2020 more than 7.5 million people in the United States will be diagnosed with atrial fibrillation. Therefore, the utilization of warfarin will expand within the near future.³

Although warfarin conveys a clear net benefit and its anticoagulant effects can be easily measured by the international normalized ratio (INR), inherent to its use is the risk of life-threatening hemorrhage. This is a common concern for physicians and patients alike upon prescribing this medication. Since its introduction as an approved anticoagulant, many studies have evaluated its bleeding risk.¹⁻¹⁰ This review will summarize

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the risk of bleeding with warfarin and discuss methods for estimating and mitigating risk of bleeding in an individual patient (Table 1).

Bleeding incidence

Numerous studies have shown that the incidence of major bleeding in patients on warfarin ranges from 0.4%–7.2% per year.^{1,4} Minor bleeding rates can be as high as 15.4% per year.⁴ This wide range is thought to be a result of the numerous patient-specific factors that can alter metabolism.¹ In addition, earlier studies often had different definitions for major bleeding events.⁴ More recent studies have been more consistent and usually define major bleeding as fatal

hemorrhage, bleeding requiring hospitalization, bleeding requiring two or more transfusions of packed red blood cells, and bleeding at critical sites, including intracranial and retroperitoneal. Patients with major bleeds have a several-fold increase in death for up to one year following the incident.²

Many of the current studies evaluating the incidence of bleeding in patients on warfarin have evaluated large cohorts of patients with atrial fibrillation (Table 2).^{4–10} The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial studied more than 4,000 patients in evaluation of rate versus rhythm approaches in controlling atrial fibrillation, yet found that the annual risk of major bleeding was approximately 2% per year, with minor bleeding incidents occurring in more than 18% of enrolled patients. The study reported that the majority of patients were supratherapeutic at time of hemorrhage.⁴ In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, patients were randomized to warfarin or the factor Xa inhibitor rivaroxaban. In patients randomized to warfarin, more than 14% had at least one incident of a bleeding event.⁵ The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) cohort of more than 11,000 patients also showed that those on warfarin therapy have a higher rate of bleeding, especially that of intracranial bleeds in which 59 patients suffered an intracranial hemorrhage in the warfarin cohort, compared to 29 without anticoagulation. Intracranial sites are of extreme concern as treatment options can be very limited.⁶

Smaller studies have evaluated bleeding risk in other patient populations.^{7–13} In a group of 820 patients on warfarin, of which 47% had a diagnosis of venous thromboembolism, investigators found that major bleeding events occurred at a rate of 6.5% per year, with 87 patients having a major bleeding event.⁷ Similarly, Wells et al found that in a cohort of 222 patients with either pulmonary embolism or venous thromboembolism, 4.5% had a major bleed within an 18.5 month mean follow-up period.⁸ Kuijer et al, in a cohort of 241 patients, found that almost 4% of patients had a major bleeding event within the first 3 months of starting therapy for venous thromboembolism.⁹

Bleeding risk factors

An important risk factor of bleeding during warfarin therapy that is often neglected is the time period in which patients first initiate therapy. The first 90 days are the most variable in regard to the level of anticoagulation as the INR

Table 1 Selected risk factors that increase bleeding risk with recommendations

Risk factor	Recommendations
First 90 days of treatment	<ul style="list-style-type: none"> • Increase frequency of INR monitoring
Intensity of anticoagulation	<ul style="list-style-type: none"> • Not recommended to reduce INR goal • Discontinue concurrent aspirin therapy in patients with stable coronary artery disease
Older age	<ul style="list-style-type: none"> • Decrease starting dose of warfarin • Increase frequency of INR monitoring
Comorbidities (renal and hepatic dysfunction, diabetes mellitus, hypertension)	<ul style="list-style-type: none"> • Control comorbid conditions with medical therapies
Hospitalized patients	<ul style="list-style-type: none"> • Increase frequency of INR monitoring both during hospitalization and in short-term period after discharge
Lack of knowledge and compliance	<ul style="list-style-type: none"> • Continually educate patient about diagnosis and rationale for warfarin therapy • Maintain a team approach • Recommend patients to obtain a primary care physician and involve primary care physician in care
INR monitoring variability between different medical centers	<ul style="list-style-type: none"> • Ensure appropriate frequency of INR monitoring
Diet and medication changes	<ul style="list-style-type: none"> • Advise patients to keep consistent diet • Recognize medications that can alter warfarin metabolism and increase frequency of INR monitoring during this period
Genetic variations	<ul style="list-style-type: none"> • Not recommended to test for such variations
Periprocedural and operative settings	<ul style="list-style-type: none"> • Ensure discontinuation of warfarin 5 days prior to procedure with bridging therapy, if needed • Educate patient regarding rationale for transient discontinuation of warfarin therapy

Abbreviation: INR, international normalized ratio.

Table 2 Selected trials of major hemorrhage in patients on warfarin therapy

Study/trial	Population	Outcome	Authors' conclusion
AFFIRM ⁴	4,060 patients in a trial comparing rate versus rhythm approach in management of atrial fibrillation; average follow-up of 3.5 years	Major bleeding occurred in 260 patients (6.4%) with annual incidence of approximately 2% per year; non-CNS sites occurred in 203 of patients (7.3%), while CNS hemorrhages occurred in 59 patients (2.1%); minor bleeding occurred in 738 patients (18.2%)	Risk factors for bleeding need to be identified and used to plan therapy
ROCKET-AF ⁵	14,264 patients with nonvalvular atrial fibrillation randomized to receive either warfarin or rivaroxaban; 7,133 patients on warfarin (50.0%), with median study follow-up period 707 days	Minor and major bleeding occurred in 1,449 total patients (14.5%) on warfarin; rate of major bleeding, 3.4%, intracranial hemorrhage, 0.7%, and gastrointestinal bleed, 2.2%	Bleeding remains most worrisome complication of anticoagulation therapy
ATRIA ⁶	Cohort of 11,526 patients with nonvalvular atrial fibrillation, of which 6,320 were on warfarin compared to 5,089 without anticoagulation; median follow-up period of 2.20 years (25; 341 person-years)	59 versus 29 incidents of intracranial hemorrhage and 118 versus 119 incidents of gastrointestinal bleeding in patients on warfarin therapy compared to patients on no therapy, respectively	Warfarin associated with an almost two-fold adjusted increased risk of intracranial hemorrhage compared with no warfarin therapy and no significant increase in nonintracranial hemorrhage
RE-LY ¹⁰	18,113 patients with atrial fibrillation randomly assigned to either warfarin (6,076 patients) or dabigatran therapy; mean follow-up period 2.0 years	Rate of major bleeding 3.4% per year and hemorrhagic stroke 0.38% in warfarin group	Major hemorrhage remains complication of warfarin therapy
Multiple trials ¹¹	Analysis of data from five randomized controlled trials, including Atrial Fibrillation, Aspirin, Anticoagulation Study; Boston Area Anticoagulation Trial for Atrial Fibrillation Study; Canadian Atrial Fibrillation Anticoagulation Study; Stroke Prevention in Atrial Fibrillation Study; and Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Study; evaluated 1,889 patient-years receiving warfarin	Annual rate of major hemorrhage 1.3% in patients receiving warfarin compared to 1.0% in the control group and 1.0% in the aspirin group	Increased risk of bleeding in patients on warfarin compared to no therapy or aspirin therapy
ACTIVE W ¹²	Patients randomized to receive either aspirin–clopidogrel combination (3,335 patients) or warfarin (3,371 patients); mean follow-up 1.3 years	101 patients (2.42% annual risk) versus 93 (2.21% annual risk) with major hemorrhage and 568 patients (13.58% annual risk) versus 481 patients (11.45% annual risk) in patients on warfarin compared to those on aspirin–clopidogrel combination; intracranial bleeds more common in patients on warfarin	Bleeding risk increased in patients receiving warfarin
SPORT IF ¹³	3,922 patients randomized to receive either warfarin (1,962 patients) or ximelagatran; mean follow-up 20 months	Hemorrhagic stroke occurred in two patients in warfarin subset (0.06% per year) and seven patients developed subdural hematoma; major extracerebral bleeding occurred in 84 patients on warfarin (3.1% per year)	Bleeding risk, especially in extracranial sites, remains substantial in patients receiving warfarin
Kuijjer et al ⁹	Bleeding score constructed based on cohort of 241 patients; mean follow-up 3 months	Major bleeding complications occurred in nine patients (3.7%), of which seven occurred in the high-risk group	Bleeding complications are important to consider in patients undergoing warfarin therapy
Wells et al ⁸	Outpatient Bleeding Risk Index accuracy verified in 222 patients with deep venous thrombosis or pulmonary embolism; mean follow-up 18.5 months	Total of 4.5% of patients had episode of major bleeding; risk of major hemorrhage per 100 person-years 0% in low-risk group and 4.3% in moderate-risk group	Bleeding complications can occur in patients on warfarin and Outpatient Bleeding Risk Index can be applied to populations treated for deep venous thrombosis and pulmonary embolism

Abbreviations: CNS, central nervous system; AFFIRM, Atrial Fibrillation Follow-Up Investigation of Rhythm Management; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ACTIVE W, Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; SPORT IF, Stroke Prevention using Oral Thrombin Inhibitor in atrial Fibrillation.

can be labile, attributing to this risk.^{2,14,15} As well, the dose of warfarin therapy can have markedly different effects on individuals, making it a difficult medication to prescribe.^{14,15} Patients can have alternating medication doses, which is reflective of the difficulty in initiating therapy.^{2,3,14} Douketis et al¹⁶ found that major bleeding events occur more frequently within 3 months of starting therapy. In their study, 28 incidents of major bleeding events occurred within a 3-month period; 13 occurred within the first 7 days and 21 within the first 3 weeks.¹⁶ A similar result was seen by Landefeld et al.¹⁷ In their retrospective analysis of 565 records of patients with either atrial fibrillation, venous thrombosis, or prosthetic valves beginning therapy, within the first 30 days following initiation, patients were found to have a 10-fold higher risk of bleeding than the remaining 11 months of the study. Three percent of patients had major bleeding events during this period, compared to 0.3% in the remaining 11 months.¹⁷ A meta-analysis of 29 randomized controlled trials and four prospective cohort studies showed that intracranial hemorrhage within the first 3 months of therapy is of concern. In this analysis, 1.48% of patients had an intracranial hemorrhage within the first 3 months, with 0.65 per 100-patient years following.¹⁸ Conversely, a review of a registry of 5,477 patients found that the risk of ischemic stroke within the first 30 days of a diagnosis of atrial fibrillation is significantly higher than later on in the disease process.¹⁹ Another study of more than 125,000 found that the rate of hemorrhage was almost 12% within the first 30 days of treatment, compared to almost 4% overall.²⁰ Although the bleeding risk remains elevated, physicians need to understand that the risk of adverse events from the thrombophilic condition exists. Therefore, it is important to first understand whether anticoagulation will be of benefit to each individual patient and, if so, more vigilant monitoring of the INR during the first 30 to 90 days of therapy is of utmost importance to avoid possible preventable bleeding events.^{2,3,14–20}

Another risk factor that can increase one's risk of bleeding is the intensity of anticoagulation. Studies have shown that with higher intensities of anticoagulation measured by the INR, patients are at increased risk of hemorrhage.^{2,21–23} In a study of 435 patients followed for more than 7 years that developed intracranial hemorrhage, the 3-month mortality in those patients on warfarin therapy was more than 50%, compared to approximately 25% in patients not on warfarin.²¹ Japanese guidelines recommend a lower intensity of anticoagulation with an INR range of 1.6 to 2.6 in elderly patients because of the association between anticoagulation intensity and bleeding risk.²² A case control study at an

academic medical center of 170 patients also found that INR levels greater than 2.0 can be associated with an increased risk of hemorrhage. This study demonstrated that in patients with atrial fibrillation, the risk of stroke sharply increased when the mean INR was below 2.0. It is important to understand the therapeutic purpose of anticoagulation and that subtherapeutic levels, although associated with lower incidents of bleeding, may deviate from accomplishing the ultimate purpose of anticoagulation therapy.²³ Experts have suggested that warfarin is underutilized in patients secondary to the perceived bleeding risk.²⁴ Other studies show that although increased intensity can result in a higher risk of bleeding, the incidence is not excessive. Pooled data from five randomized controlled trials demonstrated that major hemorrhage in patients on warfarin was 1.3% compared to 1.0% in both the control and aspirin groups.¹¹ Similarly, other studies found that anticoagulation therapy is superior to aspirin–clopidogrel combinations in preventing recurrent thromboembolic events.^{12,25,26} Although increased intensity of anticoagulation can theoretically increase bleeding risk, the reduction of INR goals would not be recommended in most populations as the anticoagulation effects of warfarin will not be as efficacious. Instead, strategies to decrease bleeding risk include discontinuation of antiplatelet agents, such as aspirin, in patients with stable coronary artery disease.²⁶

Numerous patient inherent characteristics that have been associated with increased bleeding risk include increasing age, presence of hypertension, diabetes, anemia, congestive heart failure, female sex, and history of stroke or transient ischemic attack.^{2,4,11,14,15,23,24,26} One study showed that the relative risk of intracranial hemorrhage in patients greater than 80 years of age compared to patients 70–80 years is 2.5.² Conversely, increasing age is associated with a higher risk of morbidity and mortality from the underlying coagulopathic process.⁵ Other studies demonstrated similar findings that the morbidity and mortality from an underlying coagulopathic disorder, especially atrial fibrillation, increases with age.^{11,15} Therefore, age should not be used solely as a contraindication to warfarin therapy. Elderly patients should be initiated on lower doses of warfarin to attain a therapeutic level, as the common starting dose of 5 mg may be too high. More frequent INR testing should be employed in this population.¹⁴

Patients with renal and hepatic disease, diabetes mellitus, heart failure, and hypertension have an increased risk of bleeding on warfarin therapy.^{4,11,14,26} One study found that adequate control of blood pressure in hypertensive patients was associated with a 38% decrease in major vascular events and 34% decrease in hemorrhagic stroke.²⁶

Hospitalized patients, especially those with sepsis and other such hypermetabolic states, have varied response to warfarin therapy.¹⁴ It is important to understand these risk factors and provide appropriate treatment to lessen its potential increase in bleeding risk. Those patients should also undergo more frequent INR testing to ensure that the level of anticoagulation remains therapeutic.

Risk factors that can easily be amended, if appropriately identified, include lack of patient knowledge and compliance.^{14,27,28} The issue of noncompliance is prevalent in both the young and elderly populations.¹⁴ One study found that younger patients may actually be slightly more noncompliant. The mean age of noncompliant patients was 54 years, compared to that of 69 years of those found to be compliant. This study indicated that lack of compliance can be a result of the lack of a primary care physician, a feeling of dissatisfaction about the medical condition, and a lack of understanding of the underlying medical condition.²⁷ A similar pilot study examined patients' knowledge following initiation of anticoagulation therapy for atrial fibrillation. Fewer than half of all patients were able to name atrial fibrillation as their diagnosis. Approximately one-half of patients were aware of the possibility of thromboembolic events with this diagnosis, which improved to 70% following formal teaching. Only 21% of patients understood that anticoagulation therapy helps to prevent strokes, improving to only 27% with formal teaching.²⁸ Therefore, formal education by both a cardiologist and primary care physician is important, and emphasis on the importance of warfarin therapy will help to avoid lack of compliance and medication errors. Patients are strongly encouraged to have a primary care physician to participate in management of warfarin therapy.

Variations in INR monitoring protocols exist between different medical centers. This can result in nontherapeutic levels of warfarin, further increasing the bleeding risk.^{15,29} One large study of 526 INR monitoring sites and 3,371 patients found that the time in therapeutic range averaged 65%.²⁹ Another study had a time in therapeutic range of 58% in a cohort of 472 patients.¹⁵ Others report incidences as low as 29%.²⁹ As a physician, it is important to ensure that adequate INR monitoring occurs. It is important to understand the variation in INR that can result with warfarin therapy and be aggressive in ensuring that supratherapeutic levels are not potentiating bleeding incidents.

Diet and medication changes are two other factors that can increase the risk of bleeding.^{1,14} Many common medications, including acetaminophen, antibiotics, antidepressants, fenofibrate, nonsteroidal anti-inflammatory drugs, and

proton-pump inhibitors can alter the metabolism of warfarin. Alcohol can also affect its metabolism. There is limited data suggesting that the influenza vaccination can cause changes in the INR as well.¹ Therefore, it is important to understand these medication changes and closely monitor the INR if such changes occur. To the same effect, a patient should not be discouraged to change consumption habits of green, leafy vegetables; instead, a patient should be told to keep a somewhat consistent diet.

Multiple genetic variations affect warfarin metabolism.^{2,14,30–32} More than 30 genes have been associated with its metabolism.¹⁴ Polymorphisms of the cytochrome P450 2c9 enzyme decrease metabolism of warfarin, increasing risk of bleeding. Variations of the vitamin K epoxide reductase complex subunit 1 gene and the VKORC1 enzyme can alter metabolism as well.^{2,14} A retrospective study of 185 patients found that more than 30% had at least one variant in the cytochrome P450 2c9 allele, increasing risk for supratherapeutic INRs.³⁰ Another study of 297 patients found that initial variability in the INR response to warfarin is more strongly associated with genetic variability, yet the ultimate influence of this variability is not of clinical significance in patients with stable INR values.³¹ Race and ethnicity have also been thought to affect metabolism of the drug, yet data remains somewhat limited.³⁰ The clinical significance of these variants is controversial, as ultimately each individual patient will ultimately develop their own warfarin-dosing regimen.^{30,31} Testing for such genetic alterations should not routinely be performed.

Risk assessment

Different scoring systems have been developed that incorporate many of the risk factors discussed (Table 3). Each scoring system adds certain points per patient characteristic, and the total score can estimate bleeding risk. Many risk factors are similar between scoring systems, including older age, hypertension, diabetes, anemia, history of bleeding, and alcohol and drug use.^{7,24,33–35,37} One system incorporates the Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke/thromboembolism (CHADS₂) scoring system that is used to assess risk of thromboembolic events in patients with atrial fibrillation. Interestingly, just as the risk of a thromboembolic event increases with CHADS₂ score, so does the risk of major bleeding.³⁴ Two of the most commonly used systems include the 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

Table 3 Bleeding risk schemata in patients on warfarin therapy

Study	Population	Risk factors	Scoring equation	Score results
National Registry of Atrial Fibrillation combined with Medicare Part A claims ³²	Retrospective cohort of patients at least 65 years of age; 26,345 study subjects	<ul style="list-style-type: none"> • Age • Sex • History bleeding • Alcohol/drug abuse • Diabetes • Anemia 	$0.49 X_{Age70} + 0.32 X_{Female} + 0.58 X_{Renal\ bleed} + 0.62 X_{Recent\ bleed} + 0.71 X_{Alcohol\ drug\ abuse} + 0.27 X_{Diabetes} + 0.86 X_{Anemia} + 0.32 X_{Aspirin\ bleed}$ <p>(x = 1 if factor present; x = 0 if factor not present)</p>	Low risk, ≤ 1.07 ; moderate risk, 1.08–2.18; high risk, ≥ 2.19 .
HEMORR2HAGES ³⁷	National Registry of Atrial Fibrillation database, including 3,932 patients	<ul style="list-style-type: none"> • Antiplatelet medication usage • Hepatic or renal disease • Ethanol abuse • Malignancy • Age • Decreased platelet count or function • Rebleeding risk • Hypertension • Anemia • Genetic factors • Fall risk or neuropsychiatric disease • Stroke 	2 points for prior bleed, plus 1 point for each of following: hepatic or renal disease; ethanol abuse; malignancy; age >75 years; reduced platelet count or function; hypertension (uncontrolled); anemia; genetic factors; excessive fall risk; stroke	Rates of bleeding (per 100 patient years): 0 points, 1.9; 1 point, 2.5; 2 points, 5.3; 3 points, 8.4; 4 points, 10.4; 5 points, 12.3.
CHADS ₂ score ³³	Subgroup analysis, including 18,112 patients	<ul style="list-style-type: none"> • Congestive heart failure • Hypertension • Age • Diabetes • Stroke/transient ischemic attack 	1 point for history of congestive heart failure, hypertension, age >75 years, and diabetes mellitus and 2 points for history of stroke/transient ischemic attack	Annual rates of major bleeding: 0–1 point, 2.26%; 2 points, 3.11%; 3–6 points, 4.42%. Annual rates of intracranial hemorrhage: 0–1 point, 0.31%; 2 points, 0.40%; 3–6 points, 0.61%.
Outpatient Bleeding Risk Index ⁸	Retrospective cohort of 556 patients	<ul style="list-style-type: none"> • Age • History of gastrointestinal bleeding • History of stroke • Recent myocardial infarction • Anemia • Renal dysfunction • Diabetes mellitus 	1 point for age greater than 65 years, history stroke, and history of gastrointestinal bleed, and 1 point total for presence of comorbid conditions including recent myocardial infarction; hematocrit <30%; creatinine greater than 1.5 mg/dL; or diabetes mellitus	Estimated risk for major bleed based on points in 3-month period: 0 points (low risk), 2%; 1–2 points (intermediate risk), 5%; 3–4 points (high risk), 23%. Estimated risk for major bleed based on points in 12-month period: 0 points (low risk), 3%; 1–2 points (intermediate risk), 12%; 3–4 points (high risk), 48%.
Anticoagulation and Risk Factors in Atrial Fibrillation database ³⁴	Cohort of 9,186 patients, including 32,888 person-years of follow-up on warfarin	<ul style="list-style-type: none"> • Anemia • Renal disease • Age • History bleeding • Hypertension 	3 points each for anemia and severe renal disease; 2 points for age 75 years or older; and 1 point each for history of bleeding and hypertension	Major hemorrhage rates per year: 0–3 points (low risk), 0.8%; 4 points (intermediate risk), 2.6%; 5–10 points (high risk), 5.8%.

HAS-BLED ^{35,36}	Cohort of 3,978 patients from Euro Heart Survey on Atrial Fibrillation	<ul style="list-style-type: none"> • Hypertension • Renal and liver dysfunction • Stroke • Bleeding • Labile INR • Elderly • Drug or alcohol use 	1 point for each of the following: hypertension; abnormal liver function; abnormal renal function; history of stroke, history of bleeding; labile INR; age over 65 years; drug use; alcohol use	Major bleeding per 100 patients: 0 points, 1.13; 1 point, 1.02; 2 points, 1.88; 3 points, 3.74; 4 points, 8.70; 5 points, 12.50.
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Abbreviations: 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; CHADS₂, Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke/thromboembolism; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65), and Drugs/alcohol; INR, international normalized ratio.

(HEMORR2HAGES) and Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65), and Drugs/alcohol (HAS-BLED) schemata, with the HAS-BLED system thought to be the most accurate and easiest to use.^{33,37,38} Patients are assigned points based on the presence of such risk factors, and each point corresponds to a predicted annual risk of major bleeding that is based on the cohort used in the study.³⁶ Similarly, the HEMORR2HAGES scoring system uses the same factors as HAS-BLED with the addition of malignancy, reduced platelet count or function, anemia, genetic factors, and excessive fall risk.³³ Although these scoring systems are based on cohorts of patients with atrial fibrillation, physicians can apply them to all subsets of patients requiring warfarin anticoagulation. This can give the physician and patient a quantitative measure of bleeding risk, which can aid in the decision to initiate warfarin therapy.

Scoring systems have also been developed to assess the potential benefit of anticoagulation therapy (Table 4). For example, in patients with atrial fibrillation, the CHADS₂ or Congestive heart failure, Hypertension, Age (>75), Diabetes mellitus, Stroke/TIA/Thromboembolism, Vascular disease, Age (65–74 years), Sex category (CHA₂DS₂VASc) have been developed to assess stroke risk.^{39–41} Current guidelines recommend anticoagulation in patients with CHADS₂ or CHA₂DS₂VASc scores of greater than 1,

Table 4 Stroke risk scoring schemata in patients with atrial fibrillation

Schemata	Criteria	Risk
CHADS ₂ ³⁸	<ul style="list-style-type: none"> • Congestive heart failure (1 point) • Hypertension (1 point) • Age ≥75 years (1 point) • Diabetes (1 point) • Prior stroke/transient ischemic attack (2 points) 	Annual stroke risk: 0 points, 1.9%; 1 point, 2.8%; 2 points, 4.0%; 3 points, 5.9%; 4 points, 8.5%; 5 points, 12.5%; 6 points, 18.2%.
CHA ₂ DS ₂ VASc ³⁹	<ul style="list-style-type: none"> • Congestive heart failure (1 point) • Hypertension (1 point) • Age ≥75 years (2 points) • Diabetes (1 point) • Prior stroke/transient ischemic attack (2 points) • Vascular disease (1 point) • Age 65–74 years (1 point) • Sex (female) (1 point) 	Annual stroke risk: 0 points, 0%; 1 point, 1.3%; 2 points, 2.2%; 3 points, 3.2%; 4 points, 4.0%; 5 points, 6.7%; 6 points, 9.8%; 7 points, 9.6%; 8 points, 6.7%; 9 points, 15.2%.

Abbreviations: CHADS₂, Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke/thromboembolism; CHA₂DS₂VASc, Congestive heart failure, Hypertension, Age (>75), Diabetes mellitus, Stroke/TIA/Thromboembolism, Vascular disease, Age (65–74 years), Sex category.

while patients with scores of 0 may benefit from aspirin therapy alone.^{41–43} In patients with atrial fibrillation, physicians should utilize these scoring systems to help decide whether the benefits of anticoagulation outweigh the risks of bleeding.

Strategies for managing bleeding risk

Other special situations exist in which patients on warfarin therapy are at a transiently increased risk of bleeding, including during perioperative periods.^{2,44–46} Patients with atrial fibrillation, for instance, may need to undergo atrial ablation procedures. During these procedures, patients are given varying doses of heparin which is monitored with the activated clotting time (ACT). Variations in the ACT, along with potential remnant warfarin anticoagulation, can increase risk of bleeding.^{45,46} Although recent studies suggest that continued anticoagulation in patients undergoing catheter ablation and device implantation procedures may have less bleeding complications with continued anticoagulation on either warfarin or dabigatran, instead of a transient disruption in therapy, further data is needed.^{47,48} Patients undergoing cardiac catheterization, especially for acute cardiac syndromes, may benefit by using a radial approach.²

Patients undergoing surgical intervention can also be at increased risk. In such cases, the American College of Chest Physicians' guidelines suggest that warfarin therapy should be generally stopped 5 days prior to the procedure and, depending on the individual patient, bridging therapy with low-molecular-weight heparin or other heparin products that can be given. Patients can usually resume warfarin therapy 12 to 24 hours following the intervention with lower-molecular-weight bridging therapy until the INR is therapeutic.^{46,49–51} If the bleeding risk of the procedure is felt to be high, including procedures such as craniotomies, spinal surgery, or partial organ removals, consideration should be given to holding anticoagulation until the risk subsides. Generally, those patients with venous thromboembolism that developed within a 3-month period and arterial thrombosis within a 1-month period would require bridging therapy. Patients should be stratified, based on risk.⁵⁰ Atrial fibrillation patients at high risk for thromboembolism with a CHADS2 score of 5 or above should be considered for bridging therapy as well. In those with scores of 3 or 4, consideration should be given to the individual patient and surgical procedure. Patients with mechanical valves, except for those in the aortic region, would need bridging, while

those with bioprosthetic valves would not, unless associated with atrial fibrillation.^{49,50} It is important to proactively plan for such procedures and educate patients on discontinuation of warfarin therapy, if needed.

One other important consideration is the use of warfarin therapy in conjunction with dual antiplatelet therapy, such as aspirin and clopidogrel. Indications for concomitant antiplatelet use includes primary prevention of coronary artery disease, secondary prevention after a diagnosis of coronary artery disease, maintenance therapy following percutaneous coronary interventions, or stroke.⁵¹ Current American College of Cardiology/American Heart Association guidelines suggest reducing the INR goal in this cohort to 2.0–2.5, especially in elderly patients. Strict INR monitoring is highly encouraged, and patients should be educated on the increased bleeding risk.^{52–54} One study that evaluated the risk of traumatic intracranial hemorrhage in patients with mild head trauma suggested that patients on either warfarin or clopidogrel may have increased risk of intracranial hemorrhage, even in absence of clinical signs or symptoms, adding to the increased bleeding risk in patients on combination treatment.⁵⁵

Newer anticoagulants

Anticoagulation continues to be an evolving field. Although warfarin is the mainstay therapy, many other newer anticoagulants have been developed with intent to decrease risk of bleeding. Three trials comparing novel anticoagulants to warfarin include the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), ROCKET-AF, and ARISTOTLE trials, comparing dabigatran, rivaroxaban, and apixaban, respectively.^{5,9,56,57} The RE-LY trial showed that dabigatran was noninferior to warfarin and that the 110 mg dosing was associated with fewer bleeding events.¹⁰ The ROCKET-AF trial showed no significant difference in bleeding incidents, yet there were fewer fatal and intracranial bleeds in patients on rivaroxaban.⁵ Apixaban was found to be superior to warfarin in decreasing bleeding risk in the ARISTOTLE trial.^{56,57} Dabigatran, rivaroxaban, and apixaban are all currently approved for prevention of thromboembolic events in atrial fibrillation, while rivaroxaban is the only medication with an additional indication for venous thrombosis and pulmonary embolism.⁵⁷ Most of the data on the newer anticoagulants come from cohorts of patients with atrial fibrillation with few comorbidities, yet one of the key components to the success of future anticoagulants is the ability to decrease bleeding risk, further emphasizing this concern.

Although these newer anticoagulants have been introduced, warfarin will continue to be used and likely the mainstay therapy. Antidotes have not been developed in cases of bleeding, and the cost of the newer drugs can be significantly higher than the cost of warfarin. Studies have evaluated a cost benefit analysis using dabigatran based on results from the RE-LY trial. Dabigatran was shown to be more cost-effective in populations at high risk of hemorrhage or high risk of stroke unless INR control was excellent. Otherwise, warfarin was more cost-effective in moderate-risk populations.⁵⁸ Similar studies report that the other novel anticoagulants are cost-effective alternates to warfarin, depending on medication pricing and patient predisposition to neurological events.⁵⁹ Studies assessing the newer anticoagulants have not included patients with renal or hepatic dysfunction. As well, indications of newer anticoagulants are not as diverse as are those for warfarin, including prevention of thromboembolic disease in atrial fibrillation, venous thromboembolism, pulmonary embolism, and prosthetic valves.^{5,56,57}

Conclusion

Warfarin therapy is an important medication in the prevention of thrombosis and thromboembolism. Although it is very efficacious, warfarin carries the risk of bleeding. It is important to understand which factors can attribute to this bleeding risk and make an effort to lessen its effects. Each patient should be assessed individually prior to starting warfarin therapy, and therapy should be personalized to that particular patient, with emphasis on monitoring and patient education. Although a bleeding risk will always remain, careful monitoring of the patients can dramatically reduce this risk.

Disclosure

The authors report no conflicts of interest in this work.

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