2 Warfarin

Gregory C. Hadlock, Allison E. Burnett, and Edith A. Nutescu

Clinical Vignette

AG is a 63-year-old woman presenting to the emergency department with a 4-day history of shortness of breath. 3 weeks prior to the onset of her symptoms, she had a left tibia fracture and has been largely immobile since. She has a past medical history of type 2 diabetes mellitus, hypertension, and stage 4 chronic kidney disease (CKD), with a baseline serum creatinine of 2.9 mg/dL. She is up-to-date on her cancer screenings, including for breast, colon, and cervical cancers, which all have been negative. A computed tomography angiogram of the chest revealed bilateral pulmonary emboli. The patient was initiated on therapeutic anticoagulation with a heparin infusion and bridged to warfarin for a 3-month treatment duration.

Introduction

Until recently, vitamin K antagonists, such as warfarin, were the only oral anticoagulants available for long-term or extended anticoagulation. Although very effective for prevention and treatment of venous and arterial thromboembolism, warfarin has a narrow therapeutic index; has many drug, disease, and dietary interactions; and requires frequent monitoring and dose adjustments [1–4]. These drawbacks have historically resulted in under treatment of patients that warrant anticoagulation therapy [5]. While direct oral anticoagulants (DOACs) have significantly changed approaches to anticoagulation therapy, are more convenient, and are easier to use, warfarin will continue to be a mainstay of therapy for many patients. Thus, clinicians must possess familiarity with this still widely used medication. In this chapter, we will discuss the pharmacology,

G. C. Hadlock
Inpatient Pharmacy Department, University of New Mexico Hospital, Albuquerque, NM, USA
e-mail: ghadlock@salud.unm.edu

A. E. Burnett (✉)
University of New Mexico College of Pharmacy, Albuquerque, NM, USA
e-mail: aburnett@salud.unm.edu

E. A. Nutescu
Department of Pharmacy Systems, Outcomes and Policy, Center for Pharmacoepidemiology and Pharmacoeconomic Research, The University of Illinois at Chicago College of Pharmacy, Chicago, IL, USA
e-mail: enutescu@uic.edu

J. F. Lau et al. (eds.), *Anticoagulation Therapy*, https://doi.org/10.1007/978-3-319-73709-6_2

clinical utility, and practical management aspects that promote optimized safety and efficacy of warfarin therapy.

Pharmacology

Mechanism of Action

Warfarin is an oral anticoagulant that acts as a vitamin K antagonist. Vitamin K is an essential cofactor in the γ-carboxylation of several glutamic acid residues in the hepatically produced vitamin K-dependent procoagulant factors II, VII, IX, and X, as well as the anticoagulant proteins C and S. Warfarin interferes with the hepatic recycling of vitamin K by inhibiting vitamin K epoxide reductase (VKOR), the enzyme that converts vitamin K epoxide to vitamin K. The accumulation of vitamin K epoxide reduces the effective concentration of vitamin K and reduces the synthesis of functional coagulation factors. Concentrations of functional clotting factors II, VII, IX, and X are diminished gradually at rates corresponding to their elimination half-lives (Table 2.1). As it has no effect on preexisting functional circulating clotting factors, the onset of the anticoagulant effect of warfarin is delayed. It takes approximately 5–7 days to reach a steady state of anticoagulation after warfarin therapy is initiated or after dosing changes. Protein C and its cofactor protein S are also vitamin K dependent, and these proteins are depleted by warfarin at rates dependent on their elimination half-lives. Due to its shorter half-life, protein C activity falls more rapidly than the procoagulant clotting factors II, IX, and X, which can lead to a paradoxical hypercoagulable state during the first few days of warfarin therapy. This can be managed through avoidance of excessive "loading" doses of warfarin (e.g., >10 mg) which may cause protein C to fall too precipitously and/or use of overlapping parenteral therapy during the first 5–7 days of warfarin initiation [1, 3, 6].

Table 2.1 Elimination half-lives of vitamin K-dependent clotting factors

Clotting factor	Half-life (h)
II (prothrombin)	42–72
VII	4–6
IX	21–30
X	27–48
Protein C	9
Protein S	60

Warfarin is administered orally as a racemic mixture of stereoisomers (*R* and *S* enantiomers), each with distinctive metabolic pathways, half-lives, and potencies. The S isomer is three to five times more potent than the R isomer, has a longer elimination half-life, and is primarily metabolized by cytochrome P450 (CYP) 2C9. The R isomer is metabolized primarily by CYP1A2 and CYP3A4. Many drugs, herbal, and nutritional products interact with warfarin by stereoselectively inhibiting the metabolism of either the R isomer or the S isomer (Table 2.2 and Table 2.3). Differences in metabolism, along with disease- and/or drug-induced alterations in metabolism, account for much of the variation in an individual's initial response to, and maintenance requirement for, warfarin. Genetic expression of CYP2C9 influences the rate of metabolism of warfarin and thus impacts dosing requirements to meet a particular therapeutic end point [7]. Variability in genetic expression of VKORC1 (the gene that encodes subunit 1 of the vitamin K epoxide reductase complex) also influences dosing requirements in patients taking warfarin [7]. Genetic testing for CYP2C9 genotype and VKORC1 haplotype can be incorporated with clinical and demographic information to predict warfarin dose requirements in individual patients, using dosing algorithms that have been developed and investigated. A practical example is available online at www.warfarindosing.org [8]. The prevalence of these polymorphisms varies in different populations. Current evidence does not support routine use of genetic information to guide warfarin dosing as it has not been shown to provide significant benefit above and beyond use of clinical information and dosing nomograms [9].

Pharmacokinetics

Absorption

Warfarin has almost 100% oral bioavailability and is rapidly absorbed in the upper gastrointestinal tract (GI). Peak plasma concentrations of warfarin occur in 90 min [10, 11].

Table 2.2 Clinically significant warfarin drug interactions[a]

Increase anticoagulation effect (↑ INR)	Decrease anticoagulation effect (↓ INR)	Increase bleeding risk
Alcohol binge	Azathioprine	Abciximab
Allopurinol	Barbiturates	Argatroban
Amiodarone	Carbamazepine	Aspirin
Azithromycin	Cholestyramine	Bivalirudin
Bactrim	Dicloxacillin	Clopidogrel
Ciprofloxacin	Griseofulvin	Dalteparin
Citalopram	Nafcillin	Danaparoid
Clarithromycin	Phenytoin	Dipyridamole
Clofibrate	Primidone	DOACs
Danazol	Rifampin	Enoxaparin
Disulfiram	Rifabutin	Eptifibatide
Doxycycline	Sucralfate	Fondaparinux
Erythromycin	Vitamin K	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Fenofibrate		Prasugrel
Fluconazole		Ticagrelor
Fluorouracil		Ticlopidine
Fluoxetine		Tirofiban
Fluvoxamine		Unfractionated heparin
Gemfibrozil		
Isoniazid		
Itraconazole		
Levofloxacin		
Lovastatin		
Metronidazole		
Miconazole		
Neomycin		
Omeprazole		
Phenylbutazone		
Piroxicam		
Propafenone		
Sertraline		
Simvastatin		
Sulfamethoxazole		
Sulfinpyrazone		
Tamoxifen		
Testosterone		
Tetracycline		
Vitamin E		
Voriconazole		
Zafirlukast		

INR international normalized ratio
[a]List is not exhaustive

Distribution

Warfarin is approximately 99% bound to the plasma protein albumin, which leads to its relatively low volume of distribution (Vd) of 0.14 L/kg [11]. Also, because of its extensive protein binding, warfarin exhibits nonlinear pharmacokinetics, and small adjustments in dose can lead to large changes in anticoagulant response [1].

Table 2.3 Potential warfarin interactions with herbal and nutritional products[a]

Increased anticoagulation effect (increase bleeding risk or ↑ INR)		Decreased anticoagulation effect (↓ INR)
Amica flower	Ginkgo	Coenzyme Q_{10}
Angelica root	Horse chestnut	Ginseng
Anise	Licorice root	Green tea
Asafoetida	Lovage root	St. John's wort
Bogbean	Meadowsweet	
Borage seed oil	Onion	
Bromelain	Papain	
Capsicum	Parsley	
Celery	Passionflower herb	
Chamomile	Poplar	
Clove	Quassia	
Danshen	Red clover	
Devil's claw	Rue	
Dong quai	Sweet clover	
Fenugreek	Turmeric	
Feverfew	Vitamin E	
Garlic	Willow bark	
Ginger		

INR international normalized ratio
[a]List is not exhaustive

Metabolism

Racemic warfarin has an average plasma half-life of ~40 h (range of 15–60 h). Warfarin is extensively metabolized in the liver via several isoenzymes including CYP 1A2, 3A4, 2C9, 2C19, 2C8, and 2C18. Due to genetic variations in these isoenzymes, hepatic metabolism of warfarin varies greatly among patients, leading to potentially large interpatient differences in dose requirements [1, 3, 4, 10, 11].

Elimination

Warfarin and its metabolites are primarily excreted in the urine [3, 10, 11]. Renal impairment has no direct impact on warfarin pharmacodynamics since these metabolites have little or no anticoagulant activity. However, renal impairment may diminish the function of CYP2C9, leading to accumulation of warfarin, thus enhancing its effect [10].

Pharmacodynamics

Warfarin's *anticoagulant* effect is related to plasma depletion of vitamin K-dependent coagulation factors and manifests as an elevation in the international normalized ratio (INR) which is exquisitely sensitive to reductions in factor VII. The *antithrombotic* effect of warfarin relies on significant depletion of prothrombin (factor II) and factor X in the plasma that is delayed for at least 5–7 days after warfarin initiation due the long half-life of prothrombin and factor X. It is important to recognize that patients may achieve a therapeutic INR within the first few days of therapy (due to rapid depletion of factor VII that usually occurs in the setting of excessive warfarin doses) and appear to be anticoagulated but may still be at risk for propagation or recurrence of an acute thrombus since prothrombin and factor X levels are still close to normal. This provides rationale for continuing overlapping parenteral therapy for a full 5 days, even if a therapeutic INR is attained prior to day 5, in patients with an acute event [1, 3, 10]. Rapid increases in INR during the first few days of therapy warrant warfarin dose reductions to prevent supratherapeutic INR values early in warfarin therapy. Through its antithrombotic effects, warfarin reduces the likelihood of thrombus propagation in acute VTE and lowers the risk of thromboembolism in other indications associated with thrombosis, such as atrial fibrillation [1].

Clinical Utility

As the only oral anticoagulant for over 60 years, warfarin is widely used in the treatment and prevention of thromboembolic events across a broad range of disease states and conditions. In the past decade, the advent of direct oral anticoagulants (DOACs), including the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, and the direct thrombin inhibitor (DTI), dabigatran, has ushered in a new era of oral anticoagulant options for patients and clinicians. While research and experience with warfarin exceed that with DOACs, the advent of these non-vitamin K antagonist therapies is significantly and rapidly changing the therapeutic landscape and leading to a decline in warfarin use [12, 13]. Several large randomized controlled trials and meta-analyses have shown DOACs to be equally effective to warfarin, with significantly better safety profiles, in both non-valvular atrial fibrillation

(NVAF) and treatment of venous thromboembolism (VTE) [14, 15]. Importantly, these results have been confirmed in several phase IV, real-world analyses [16–23]. Based on these findings, DOACs have been placed on equal or better footing than warfarin in several national and international societal guidelines for NVAF [24, 25] and are preferred for treatment of VTE [26]. Additionally, DOACs are more convenient, are easier to use, and provide greater patient satisfaction [27–29]. Table 2.4 provides a comparison of the characteristics of warfarin and DOACs.

It is important to note that not all patients are eligible for treatment with a DOAC [30]. Additionally, warfarin has been extensively used for numerous clinical indications since its approval in the 1950s, providing a significant advantage of patient and clinician familiarity and experience. Thus, in many populations, warfarin will likely continue to serve an important role [4]. Table 2.5 lists characteristics of patients who are not optimal DOAC candidates and should likely be managed with warfarin therapy.

Practical Management

Regardless of the setting where an anticoagulation patient is to be managed, best practices suggest that it should be done "in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up and patient communication of results and dosing decisions" [2]. Structured anticoagulation therapy management services (e.g., anticoagulation clinics) have been demonstrated to improve the efficacy and safety of warfarin therapy, and consideration for patient referral is recommended [33].

Patient Engagement and Education

Patient education is a vital component of warfarin therapy. Improved outcomes have been reported when patients take responsibility for, understand, and adhere to an anticoagulation plan of care [1, 2, 34]. National regulatory bodies, such as the Joint Commission, have mandated patient

Table 2.4 Comparison of oral anticoagulant pharmacokinetics and pharmacodynamics

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target(s)	IIa, VIIa, IXa, Xa	IIa	Xa	Xa	Xa
Prodrug	No	Yes	No	No	No
Bioavailability (%)	80–100	6.5 (pH dependent)	80	50	62
Volume of distribution (L)	10	50–70	50	23	> 300
Peak effect	4–5 days	1.5–3 h	2–4 h	1–3 h	1–2 h
Half-life[a]	40 h	12–17 h	5–9 h	9–14 h	10–14 h
Renal elimination	None	80%	33%	25%	35–50%
Protein binding (%)	> 99	35	90	87	55
Dialyzable	No	Yes	No	No	Possible
Drug interactions	Numerous	P-gp	CYP3A4, P-gp	CYP3A4, P-gp	P-gp
Routine coagulation monitoring	Yes	No	No	No	No
Antidote	Vitamin K	Idarucizumab	No	No	No
Lab measure	INR	aPTT* TT, dTT, ECT*	PT* Anti-Xa*	Anti-Xa*	Anti-Xa*
Dietary interactions/ considerations	Numerous	None	Take treatment doses with food	None	None

*For qualitative assessment only as these measures have not been correlated with pharmacodynamic effect

P-gp P-glycoprotein, *INR* international normalized ratio, *aPTT*, activated partial thromboplastin time, *TT* thrombin time, *dTT* dilute thrombin time, *ECT* ecarin clotting time, *PT* prothrombin time

aIn patients with normal renal function

Table 2.5 Patients that should be considered for warfarin therapy rather than a DOAC [4]

Characteristic	Comment/rationale
Suboptimal adherence	Compared to DOACs, warfarin has a long half-life (~40 h vs. ~12 h), and missed doses will result in less dramatic fluctuations in anticoagulant levels and increased risk for adverse events
Significant DOAC drug interactions	Warfarin drug interactions may be managed via increased frequency of INR monitoring and dose adjustment. With DOACs, there is no routine, readily available laboratory assay to aid in monitoring for accumulation or underexposure in the setting of possible drug interactions
Reduced renal or hepatic function	The DOACs are all at least partially reliant on renal elimination. In patients with severe renal impairment, warfarin would be the preferred oral anticoagulant until more data is available. Among patients with significant hepatic impairment, anticoagulant status and drug accumulation may be more readily assessed for warfarin (via INR testing) compared to DOACs
Financial constraints	Because it is available in generic form, warfarin (and its associated monitoring) may have less financial impact on patients compared to DOACs. All patients should be evaluated for longitudinal access to needed medications for the duration of therapy prior to prescribing
Mechanical cardiac valve	Based on negative results of the RE-ALIGN trial [31], which was terminated early due to an increased risk of thromboembolic and bleeding events in patients receiving dabigatran when compared to warfarin, patients with mechanical cardiac valves should be managed with warfarin therapy
Indication for anticoagulation or patient population in which DOACs have not been adequately studied	These include, but are not limited to: • Antiphospholipid antibody syndrome (APS) • Cancer-associated VTE • Extremes of weight (< 50 or >120 kg) • Indications other than NVAF or VTE • Require concomitant dual antiplatelet therapy • Pregnancy • Breastfeeding • Pediatrics Until more data is available, the above patient populations should receive conventional anticoagulant therapies, such as warfarin or LMWH, whenever possible
Express a preference for warfarin over a DOAC	• With multiple oral anticoagulant options now available, it is imperative to employ a shared decision-making approach with patients, families, and caregivers. • Some patients may prefer warfarin therapy and associated routine monitoring • Additionally, some patients may express concern over lack of an antidote for factor Xa inhibitors such as apixaban, edoxaban, and rivaroxaban • While evidence suggests an advantage for DOACs over warfarin in bleeding outcomes and mortality despite no antidote [32], patient preference must be considered in order to optimize adherence

DOAC direct oral anticoagulant, *INR* international normalized ratio, *VTE* venous thromboembolism, *NVAF* non-valvular atrial fibrillation

and family education prior to discharge from the hospital on key elements of warfarin therapy including, but not limited to, the importance of follow-up monitoring, compliance, interactions, and management of potential adverse events [35]. Effective methods of anticoagulation education for patients and caregivers include face-to-face interaction with a trained professional, group training sessions, audiovisual resources, and/or the use of written materials. Several web resources are available for warfarin education, including the video "Staying Active and Healthy with Blood Thinners" from the Agency for Healthcare Research and Quality (AHRQ) (Available at https://www.ahrq.gov/patients-consumers/diagnosis treatment/treatments/btpills/stayactive.html) [36].

Education provided to patients should be delivered at an appropriate health literacy and reading level and in the patient's preferred language. The use of the "teach back" method with open-ended questions aids in assessing the patient degree of understanding and should be routinely employed. Key elements should be discussed upon initiation of therapy, with reinforcement of education at each clinic visit [37] (Table 2.6).

Table 2.6 Key elements of warfarin patient education

• Identification of generic and brand names of warfarin
• Reasons they need anticoagulation therapy
• Expected duration of therapy
• Dosing and administration
• Visual recognition of warfarin tablet strength and color
• What to do if a dose is missed
• Importance of INR monitoring and compliance with medications and appointments
• Recognition of signs and symptoms of bleeding and thromboembolism
• What to do if bleeding or thromboembolism occurs
• Recognition of signs and symptoms of disease states that influence warfarin dosing requirements
• Potential for interactions with prescription and over-the-counter medications and natural/herbal products
• Dietary considerations and use of alcohol
• Avoidance of pregnancy
• Significance of informing other healthcare providers that warfarin has been prescribed
• Importance of obtaining and wearing a medical alert bracelet or necklace stating they are on anticoagulation therapy
• When, where, and with whom follow-up will be provided

INR international normalized ratio

Dosing: Initiation

When initiating warfarin therapy, it is challenging to predict the precise maintenance dose a patient will eventually require. The dose response to warfarin is influenced by several factors, including inherent patient characteristics, such as age and genetics, as well as drug/diet/disease state interactions and clinical status (Table 2.7). These should all be factored into decisions about what warfarin dose to administer.

Before initiating therapy, patients should be assessed for any contraindications to anticoagulation therapy (Table 2.8) and risk factors for major bleeding (Table 2.9). Clinicians should conduct a thorough medication history including the use of prescription and nonprescription drugs and any herbal supplements to detect interactions that may affect warfarin dosing requirements (Tables 2.2 and 2.3). A brief review of the vitamin K content of foods and the importance of maintaining a stable intake of vitamin K from week to week should be included in the initial patient visit with reinforcement during subsequent patient visits (Table 2.10).

Because warfarin does not follow linear kinetics, small dose adjustments can lead to large changes in anticoagulant response [3, 10]. Therefore, warfarin dose must be determined by frequent clinical and laboratory monitoring, and adjustments should be guided by dosing nomograms [38–41]. An example of a flexible dosing nomogram that allows for initiation of warfarin 5 or 10 mg is shown in Table 2.11. Although there are conflicting data regarding the optimal warfarin induction regimen, when the patient's genotype is not known, most patients can start with 5 mg daily, and subsequent doses are determined based on INR response. Younger (<55 years) and otherwise healthy patients may safely use higher warfarin initiation doses (e.g., 7.5 or 10 mg). Conversely, more conservative initiation doses (e.g., <5 mg) should be used in patients likely to be more warfarin sensitive, including elderly patients (≥75 years); patients with heart failure, liver disease, or poor nutritional status; and patients who are taking interacting prescription and herbal or over-the-counter medications (Tables 2.2 and 2.3) or are at high risk of bleeding [1, 2, 10]. Loading doses of warfarin (e.g., ≥15 mg) should be avoided, as they may provide a false impression that a therapeutic INR has been achieved in 2–3 days as well as lead to potential future overdosing [2, 4].

Dosing: Maintenance

When a patient's INR is out of range, an adjustment in warfarin dosing may be necessary. Table 2.12 describes suggested approaches to warfarin dosing adjustments for both regular-intensity (INR goal 2–3) and high-intensity (INR goal 2.5–3.5) maintenance therapy. Typically, dosing adjustments of 5–20% of the total daily dose (or the total weekly dose) are appropriate to reach the therapeutic range [1, 2, 10, 44]. Because warfarin does not follow linear kinetics, small

Table 2.7 Warfarin interactions with disease states and clinical conditions

Clinical condition	Effect on warfarin therapy
Advanced age	• Increased sensitivity to warfarin due to reduced vitamin K stores and/or lower plasma concentrations of vitamin K-dependent clotting factors (with decreasing hepatic function over time)
Pregnancy	• Teratogenic; avoid exposure during pregnancy whenever possible
Breastfeeding	• Not excreted in breast milk; can be used postpartum by nursing mothers
Alcohol	• Acute ingestion: Inhibits warfarin metabolism, with acute elevation in INR
	• Chronic ingestion: Induces warfarin metabolism, with higher dose requirements
Hepatic impairment	• May induce coagulopathy by decreased production of clotting factors, with baseline elevation in INR
	• May reduce clearance of warfarin
Renal impairment	• Reduced activity of CYP2C9, with lower warfarin dose requirements
Heart failure	• Reduced warfarin metabolism due to concomitant congestive hepatopathy
Cardiac valve replacement	• Enhanced sensitivity to warfarin postoperatively due to hypoalbuminemia, lower oral intake, decreased physical activity, and reduced clotting factor concentrations after cardiopulmonary bypass
Nutritional status	• Changes in dietary vitamin K intake (intentional or as the result of disease, surgery, etc.) alter response to warfarin
	• Reduced levels of serum albumin will potentiate warfarin effect
Use of tube feedings	• Decreased sensitivity to warfarin, possibly caused by warfarin binding to feeding tube, changes in absorption, or vitamin K content of nutritional supplements
Thyroid disease	• Hypothyroidism: Decreased catabolism of clotting factors requiring increased dosing requirements
	• Hyperthyroidism: Increased catabolism of clotting factors causing increased sensitivity to warfarin
Tobacco use	• Smoking: May induce CYP1A2, increasing warfarin dosing requirements
	• Chewing tobacco: May contain vitamin K, increasing warfarin dosing requirements
Fever/active infection	• Increased catabolism of clotting factors, causing acute increase in INR
Diarrhea	• Reduction in secretion of vitamin K by gut flora, as well as increased flushing of vitamin K from gut, causing acute increase in INR
Malignancy	• Increased sensitivity to warfarin by multiple factors (drug interactions, altered absorption, etc.)

INR international normalized ratio

Table 2.8 Contraindications to warfarin [1, 2]

General
Active bleeding
Hemophilia or other hemorrhagic tendencies
Severe liver disease with elevated baseline INR
Severe thrombocytopenia (platelet count <20 × 10^3/mm^3 [20 × 10^9/L])
Malignant hypertension
Inability to meticulously supervise and monitor treatment
Hypersensitivity to warfarin
Pregnancy
History of purple toe syndrome
Inability to obtain follow-up INR measurements
Inappropriate medication use or lifestyle behaviors

INR international normalized ratio

dose adjustments can lead to large INR changes; thus large dose adjustments (i.e., >20% of the total weekly dose) are not recommended. Maintenance dosing guidelines should only be applied to patients who have reached a steady-state dose and are not still in the initiation phase of therapy (Table 2.12).

Administration

Warfarin should be administered orally once a day at approximately the same time each day. In clinical practice, patients are often encouraged to take their dose later in the day so as to facilitate implementation of needed dose changes identified at daytime clinic visits. Warfarin may be crushed and given via feeding tubes [11]. However, bioavailability of warfarin given via this route will be significantly diminished and will require a dose increase.

Table 2.9 Risk factors for major bleeding while on warfarin therapy [42]

Anticoagulation intensity (e.g., INR > 5, aPTT >120 s)
Initiation of therapy (first few days and weeks)
Unstable anticoagulation response
Age > 65 years
Concurrent antiplatelet drug use
Concurrent nonsteroidal anti-inflammatory drug use
History of gastrointestinal bleeding
Recent surgery or trauma
High risk for fall/trauma
Heavy alcohol use
Renal failure
Hepatic impairment
Cerebrovascular disease
Malignancy

aPTT activated partial thromboplastin time, *INR* international normalized ratio

Monitoring

Before the initiation of any antithrombotic therapy, including warfarin, an assessment of baseline coagulation status is necessary. The clinician should obtain a baseline platelet count, hemoglobin (Hgb), and/or hematocrit (Hct), as well as evaluate the integrity of the extrinsic and intrinsic coagulation pathways with the prothrombin time (PT) and the activated partial thromboplastin time (aPTT).

Because warfarin has a narrow therapeutic index and significant inter- and intrapatient variability, it requires frequent laboratory monitoring to ensure optimal outcomes and minimize complications. The PT, which measures the biological activity of factors II, VII, and X, was initially the most frequently used test to monitor warfarin's anticoagulant effect. However, wide variation in sensitivity among commercially

Table 2.10 Vitamin K content of select foods[a]

Very high (>200 mcg)	High (100–200 mcg)	Medium (50–100 mcg)	Low (<50 mcg)
Brussels sprouts	Basil	Apple, green	Apple, red
Chickpea	Broccoli	Asparagus	Avocado
Collard greens	Canola oil	Cabbage	Beans
Coriander	Chive	Cauliflower	Breads and grains
Endive	Coleslaw	Mayonnaise	Carrot
Kale	Cucumber (unpeeled)	Pistachios	Celery
Lettuce, red leaf	Green onion/scallion	Squash, summer	Cereal
Parsley	Lettuce, butterhead		Coffee
Spinach	Mustard greens		Corn
Swiss chard	Soybean oil		Cucumber (peeled)
Tea, black			Dairy products
Tea, green			Eggs
Turnip greens			Fruit (varies)
Watercress			Lettuce, iceberg
			Meats, fish, poultry
			Pasta
			Peanuts
			Peas
			Potato
			Rice
			Tomato

[a]Approximate amount of vitamin K per 100 g (3.5 oz) serving

Table 2.11 Flexible warfarin initiation dosing nomogram [43]

Day	INR	10 mg initiation dose	5 mg initiation dose
1		10 mg	5 mg
2	<1.5	7.5–10 mg	5 mg
	1.5–1.9	2.5 mg	2.5 mg
	2.0–2.5	1.0–2.5 mg	1–2.5 mg
	>2.5	0	0
3	<1.5	5–10 mg	5–10 mg
	1.5–1.9	2.5–5 mg	2.5–5 mg
	2.0–2.5	0–2.5 mg	0–2.5 mg
	2.5–3.0	0–2.5 mg	0–2.5 mg
	>3.0	0	0
4	<1.5	10 mg	10 mg
	1.5–1.9	5–7.5 mg	5–7.5 mg
	2.0–3.0	0–5 mg	0–5 mg
	>3.0	0	0
5	<1.5	10 mg	10 mg
	1.5–1.9	7.5–10 mg	7.5–10 mg
	2.0–3.0	0–5 mg	0–5 mg
	>3.0	0	0
6	<1.5	7.5–12.5 mg	7.5–12.5 mg
	1.5–1.9	5–10 mg	5–10 mg
	2.0–3.0	0–7.5 mg	0–7.5 mg
	>3.0	0	0

INR international normalized ratio

available thromboplastin reagents was found to provide significantly different PT results across reference laboratories, potentially leading to inappropriate dosing decisions [1, 2, 10]. In the early 1980s, the World Health Organization (WHO) developed a system to standardize PT results. All commercially available thromboplastins are compared with an international reference thromboplastin and then assigned an International Sensitivity Index (ISI). This value is used to mathematically convert PT results to the international normalized ratio (INR) by exponentially multiplying the PT ratio to the power of the ISI of the thromboplastin being used in the laboratory to measure the test (INR = $[\text{PT patient}/\text{PT mean normal}]^{\text{ISI}}$), with the ISI of the international reference thromboplastin being 1.0. Thus, the INR has become the internationally recognized standard for monitoring warfarin therapy.

The goal or target INR for each patient is based on the indication for warfarin therapy [2, 10]. The therapeutic INR range was first developed empirically but has since been confirmed by a number of large prospective trials [10]. Standard-intensity warfarin therapy is defined as a goal INR of 2.5 (range, 2.0–3.0) and is appropriate for most clinical situations that require prevention and/or treatment of thromboembolic disease. High-intensity warfarin therapy is used in mechanical valve replacement and certain situations of thromboembolic recurrence, despite adequate anticoagulation, and is defined by a goal INR of 3.0 (range, 2.5–3.5) [2, 10].

After initiating warfarin therapy, the INR should be monitored at least every 2–3 days during the first week of therapy. Once a stable response to therapy is achieved, INR monitoring may be performed less frequently, once a week for the first 1–2 weeks, then every 2 weeks, and eventually monthly thereafter. Very stable patients may have their monitoring extended up to every 12 weeks. Highly motivated and well-trained patients may be good candidates for self-testing or self-management by using a point-of-care INR testing device approved for home use [2, 10].

At each encounter, the patient should be interviewed by use of open-ended questions about any factors that may impact the INR including general health status, use of interacting medications, adherence to therapy, dietary variances, and any issues with bleeding or clotting. Warfarin dose adjustments should take into account not only the INR result but also patient-related factors that influence the result.

Transitioning Between Warfarin and Other Anticoagulants

If a transition *from* warfarin to a DOAC or parenteral anticoagulant is indicated, we suggest stopping warfarin, trending the INR, and initiating the new anticoagulant once the INR is <2.5 and trending down [30].

If transitioning *to warfarin* from a DOAC or parenteral anticoagulant, consideration of the patient's underlying thromboembolic risk

Table 2.12 Warfarin maintenance dosing nomogram

Goal INR 2–3	Adjustment	Goal INR 2.5–3.5
INR < 1.5	• Increase maintenance dose by 10–20% • Consider a booster dose of 1.5–2x daily maintenance dose • Consider resumption of prior maintenance dose if factor causing decreased INR is considered transient (e.g., missed warfarin dose(s))	INR < 2.0
INR 1.5–1.8	• Increase maintenance dose by 5–15% • Consider a booster dose of 1.5–2x daily maintenance dose • Consider resumption of prior maintenance dose if factor causing decreased INR is considered transient (e.g., missed warfarin dose(s))	INR 2.0–2.3
INR 1.8–1.9	• No dosage adjustment may be necessary if the last two INRs were in range, if there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician, the INR does not represent an increased risk of thromboembolism for the patient • If dosage adjustment needed, increase by 5–10% • Consider a booster dose of 1.5–2x daily maintenance dose • Consider resumption of prior maintenance dose if factor causing decreased INR is considered transient (e.g., missed warfarin dose(s))	INR 2.3–2.4
INR 2.0–3.0	Desired range—No adjustment needed	INR 2.5–3.5
INR 3.1–3.2	• No dosage adjustment may necessary if the last two INRs were in range, if there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician, the INR does not represent an increased risk of hemorrhage for the patient • If dosage adjustment needed, decrease by 5–10% • Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion)	INR 3.6–3.7
INR 3.3–3.4	• Decrease maintenance dose by 5–10% • Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion)	INR 3.8–3.9
INR 3.5–3.9	• Consider holding one dose • Decrease maintenance dose by 5–15% • Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion)	INR 4.0–4.4
INR ≥ 4.0 but <9 and no bleeding	• Hold until INR < upper limit of therapeutic range • Decrease maintenance dose by 5–20% • Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion) • If patient considered to be at significant risk for bleeding, may consider low dose vitamin K 1–2.5 mg orally	INR ≥ 4.5 but <9 and no bleeding
INR ≥ 9 and no bleeding	• Hold until INR < upper limit of therapeutic range • Administer vitamin K 2.5–5 mg orally • Decrease maintenance dose by 5–20% • Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion)	INR ≥ 9 and no bleeding

INR international normalized ratio

should be undertaken. If the patient has an acute thrombotic event, the DOAC should be overlapped with the warfarin for at least 3 days and until the INR is >2. As the DOACs will impact the INR, it is important in patients transitioning from a DOAC to have their INR measured just prior to the next DOAC dose to minimize this lab interference [4]. Rapid-acting parenteral anticoagulants, such as LMWH, should be overlapped with warfarin for a minimum of 5 days and until the INR is >2. If the patient does not have an acute thrombotic event, it is reasonable to simply stop the DOAC or parenteral anticoagulant and initiate warfarin at a dose appropriate for the patient's clinical characteristics and current clinical status.

Management of Warfarin Around Elective Procedures

With perioperative warfarin management, the first question should be "Does the patient require interruption of warfarin therapy?" Minimally invasive procedures, such as minor dental procedures, cataract surgery, chest tube removal, catheter ablation, minor dermatologic procedures, etc., do not warrant interruption of warfarin therapy [4, 45, 46]. For more invasive procedures, it may be necessary to temporarily interrupt long-acting warfarin therapy to mitigate bleeding risk. Based primarily on expert opinion, it became common over the last two decades to employ a "bridging strategy" for patients requiring temporary warfarin interruption for a procedure. This is accomplished via suspending the warfarin for a number of days prior to the procedure to allow offset of anticoagulant effect and then utilizing a shorter-acting anticoagulant (most commonly LMWH) prior to and after the procedure to minimize the time the patient has subtherapeutic levels of anticoagulation. However, more recent evidence, both retrospective and prospective, has found that bridging is associated with a higher risk of major bleeding and does not significantly reduce thromboembolic events [47–49]. Thus, there is a paradigm shift away from bridging practices except for those patients at highest thromboembolic risk [50]. This may include patients with a thromboembolic event within the past 3 months, mechanical cardiac valve(s), known strong thrombophilia (e.g., antiphospholipid antibody syndrome), history of recurrent thromboembolic events, or history of a thromboembolic event during warfarin interruption. Warfarin bridging is not recommended for patients who are not at high thromboembolic risk [4, 45, 46, 50]. If patient is deemed to be at high risk for a thromboembolic event, this must be carefully weighed against their individual risk of bleeding as well as the bleed risk of the procedure itself. If the bleed risk outweighs the thromboembolic risk, it may be reasonable to forego bridging. For patients at high thromboembolic risk in whom a bridging strategy is to be employed around an elective procedure, it should be done in a standardized manner. For example, warfarin should be interrupted 4–5 days before the procedure but possibly for fewer days (i.e., 2–3 days) for less invasive procedures where some residual anticoagulant activity is acceptable. LMWH at a therapeutic dose should be started 2–3 days before the procedure and stopped ≥24 h before the start of surgery. The day prior to surgery, an INR should be checked to ensure it is at goal for the procedure. If the INR is above goal for the procedure, low-dose oral vitamin K 1–2.5 mg may be administered (see reversal section below for more information). If the patient is hemodynamically stable, and no further invasive procedures are anticipated, warfarin should be resumed the evening of the procedure. LMWH should be started no sooner than 24 h postoperatively for low bleed risk procedures and 48–72 h for high bleed risk procedures and continued until INR is therapeutic [4, 46]. A step-up approach wherein prophylactic dose LMWH is employed for 24–48 h prior to increasing to therapeutic dose LMWH is a reasonable approach to minimize risk for postoperative deep vein thrombosis (DVT) [49].

For management of warfarin around urgent or emergent procedures, see reversal section below.

Adverse Effects

Skin Necrosis

Warfarin-induced skin necrosis is an extremely rare but serious adverse effect that occurs in <0.1% of patients treated with warfarin [51]. It presents as an eggplant-colored skin lesion or a maculopapular rash within the first week of warfarin therapy and usually manifests in fatty areas such as the abdomen, buttocks, and breasts. The lesions may progress to frank necrosis with blackening and eschar as a result of microvascular thromboses within subcutaneous fat. Patients who receive large loading doses of warfarin or have protein C or S deficiency are at the highest risk of developing this complication [52]. In these patients, rapid depletion of protein C before depletion of vitamin K-dependent clotting factors during early warfarin therapy can result in an imbalance between procoagulant and anticoagulant activity, leading to initial hypercoagulability and thrombosis. Adequate heparinization during initiation of warfarin and/or avoidance of large loading doses can prevent the development of an early hypercoagulable state.

In patients who develop skin necrosis, warfarin therapy should be discontinued immediately. However, subsequent treatment with warfarin is not necessarily contraindicated if it is required for treatment or prevention of thromboembolic disease and there are no other viable options. In patients with protein C or protein S deficiency and a history of skin necrosis who are not candidates for alternative anticoagulants, warfarin therapy may be reinitiated at low dosages as long as therapeutic heparinization has been achieved. Heparin therapy should be maintained until the INR has been within the therapeutic range for at least 72 h [51, 52].

Purple Toe Syndrome

Purple toe syndrome is another rare side effect of warfarin. Patients typically present 1–2 months after warfarin initiation with a purplish, painful discoloration of their toes that blanches with pressure and fades with elevation. The pathophysiology of this syndrome has been related to cholesterol microembolization from atherosclerotic plaques, leading to arterial obstruction. Because cholesterol microembolization has been associated with renal failure and death, warfarin therapy should be discontinued in patients who develop purple toe syndrome, and an alternative anticoagulant should be initiated [53].

Other Adverse Effects

Other side effects of warfarin that have been reported include alopecia, calciphylaxis, and hypersensitivity reactions [11]. Alternative anticoagulant options should be considered in cases of calciphylaxis as warfarin is thought to increase the risk of this life-threatening skin complication of end-stage renal disease. Occasionally, patients have an allergy to the color dye in warfarin tablets. In these instances, if no other anticoagulant options are viable, white, dye-free 10 mg warfarin tablets may be used in appropriate dosing fractions (e.g., ½ tablet for 5 mg dose).

Bleeding

Similar to other anticoagulants, the primary side effect of warfarin is bleeding [42]. The incidence of warfarin-related bleeding appears to be highest during the first few weeks of therapy and ranges from 1% to 10% annually, with the gastrointestinal tract being the most common site of bleeding [54]. Intracranial hemorrhage (ICH) is the most concerning bleeding complication as it is associated with high morbidity and mortality [55]. It is important to counsel patients that warfarin will increase their likelihood of bruising, longer bleeding from cuts, increased menstrual flow, and occasional nosebleeds. Serious bleeding requires evaluation by a medical provider for potential intervention and to assess whether the bleeding is due to their warfarin therapy or another cause (e.g., cancer, injury, etc.). Signs and symptoms of serious bleeding that warrant medical attention include hematemesis, black and tarry stools, bright red blood in the stool or urine, altered mental status, severe headache, bleeding that will not stop, and head injury. While there are myriad risk factors for bleeding (see Table 2.7), the strongest risk factor for bleeding is the intensity of anticoagulation [1, 42]. A number of clinical tools have been developed to estimate a patient's bleeding risk, including the commonly used HAS-BLED score [56, 57]. Bleeding risk scores should never be used as the sole reason to avoid use of anticoagulation therapy. Conversely, such clinical tools should be routinely employed to identify, modify, and/or remove any factors that might contribute to anticoagulant-associated bleeding (e.g., concomitant antiplatelet therapy that may not be necessary). Growing evidence suggests that after patient experiences a significant bleed, the benefit of resuming anticoagulant therapy and avoidance of thromboembolic events far outweighs the risk of recurrent bleed. Thus, most patients should have their therapy reinitiated. The timing of resumption is less clear and depends on the location of the bleed and underlying indication for anticoagulation. In most instances, resuming sometime between 14 and 30 days is reasonable but may differ based on the clinical situation and patient preferences [58]. The risk versus benefit of anticoagulation therapy must be regularly assessed in an ongoing manner via a shared decision-making process between the clinician and the patient or caregiver.

Reversal

There may be clinical situations that require warfarin reversal, such as severe INR derangements, need for urgent or emergent procedures, or significant bleeding events [42]. Reversal of warfarin may be achieved by withholding warfarin, administration of the antidote vitamin K, repletion of functional clotting factors with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC), or some combination of these approaches [10, 11, 59, 60]. The reversal strategy employed should be based on both the severity of the patient's clinical status and the rapidity with which reversal needs to occur. Warfarin reversal should be performed judiciously and only in certain clinical situations, as normalization of the patient's underlying coagulation status may predispose them to thromboembolic events.

INR Derangements in Asymptomatic Patients

INR < 9

The 30-day risk of bleeding in patients with an INR between 5 and 9 is low (0.96%), and use of vitamin K is not common practice in the United States [61]. While administration of low-dose oral vitamin K 1.25 mg in asymptomatic (i.e., non-bleeding) patients with an INR between 5 and 9 has been shown to lower the INR more quickly than simply withholding warfarin, it is not associated with a decreased risk of major bleeding [60, 62]. Thus, in patients with an INR ≤ 9 with no active bleeding or imminent risk of bleeding, it is recommended to withhold warfarin until the INR decreases to within therapeutic range, reduce the weekly dose or address causative factors for the INR derangement, and employ more frequent monitoring until INR stability is regained. The time required for INR to return to the therapeutic range after warfarin is withheld depends on several patient characteristics. Advanced age, lower warfarin maintenance dose requirements, and higher INR are associated with increased time for INR correction. Other factors that can prolong the time for INR to return to the therapeutic range include decompensated heart failure, active malignancy, and recent use of medications known to potentiate warfarin. To shorten the time of INR correction to within the therapeutic range, an alternative approach is to withhold warfarin and administer a small dose of oral vitamin K (1–2.5 mg), which will correct over-anticoagulation in 24–48 h without causing prolonged resistance to warfarin therapy, a problem commonly seen with larger (e.g., 10 mg) doses of vitamin K [10, 59, 60].

INR > 9

In asymptomatic patients with an INR > 9, warfarin should be withheld for one to two doses along with investigation for cause of the derangement, administration of a higher dose of oral vitamin K (2.5–5 mg), and more frequent INR monitoring [10, 60], as these patients may be at higher risk for bleeding over 30 days [61].

Bleeding Events

Nonmajor Bleeding

Patients who experience a non-life-threatening bleeding event, such as bleeding into the oral cavity, should have their warfarin therapy temporarily held and be given low-dose IV vitamin K 1–2.5 mg, followed by monitoring for adequate response to interventions and hemostasis (Fig. 2.1).

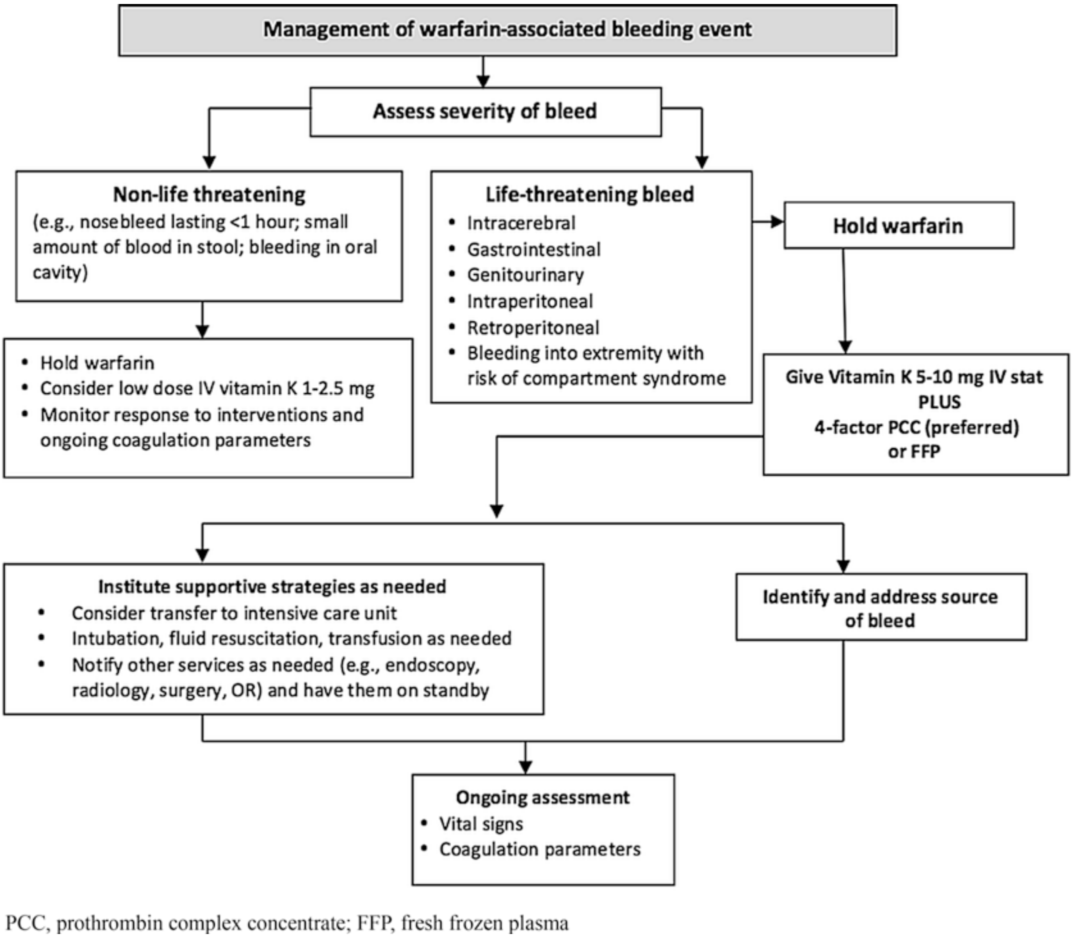

Fig. 2.1 Management of warfarin-associated bleeding event. *PCC* prothrombin complex concentrate, *FFP* fresh frozen plasma

Major Bleeding

Major bleeding may be life- or limb-threatening and often occurs in non-compressible areas such as the gastrointestinal tract, retroperitoneal space, or in the head. The 30-day mortality rate for major bleeding in warfarin patients is approximately 10%. Intracranial hemorrhage is the most concerning type of bleed, with a 30-day mortality rate of approximately 50%. Warfarin patients who experience a major bleed, regardless of their INR, require prompt and assertive intervention strategies. While there is no robust evidence toward better outcomes with rapid INR normalization, every attempt should be made to correct the coagulopathy as quickly as possible. Patients should have their warfarin held, receive 5–10 mg of vitamin K intravenously, and have their clotting factors aggressively replaced [10, 60]. Vitamin K will provide sustained reversal and avoid a rebound hypocoagulable state. Due to the delayed onset of intravenous vitamin K, rapid reversal of the INR is achieved through administration of either prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) [10, 11, 59, 60].

The PCC product that is available in the United States for warfarin reversal is the four-factor product, Kcentra®. It contains the vitamin K-dependent clotting factors II, VII, IX, and X, as well as small amounts of Proteins C and S and heparin to mitigate thrombotic potential. PCC is preferred over FFP in most clinical situations as it has numerous advantages [59]. FFP must be cross-matched to the patient to ensure ABO compatibility and must be thawed prior to administration, both of which can delay therapy. The biggest drawback of FFP is potential for volume overload. For effective INR reversal in the setting of a major bleed, it should be dosed at 15–30 mL/kg, which can often equate to more than a liter of fluid [4, 59]. In patients that need volume resuscitation, such as major gastrointestinal hemorrhage, this may be desirable. However, in other patients who are unable to tolerate large volumes, this may lead to adverse events such as pulmonary edema and sometimes transfusion-related acute lung injury (TRALI). PCC contains 25 times the amount of clotting factors of FFP [63]. Thus, an equivalent amount of clotting factors can be given in 40 mL of PCC as compared to 1000 mL of FFP. Also, PCC does not requiring thawing or cross-matching. Recent meta-analyses have shown that PCC provides more rapid reduction in the INR, reduced mortality, and less volume overload and is no more prothrombotic than FFP [64, 65].

Importantly, PCC has variable dosing methods, including those based on INR, target INR, bodyweight, and fixed dosages, with no one method showing superiority over the others [66]. Recombinant factor VII has also been used for warfarin reversal [11, 59, 60]. However, its safety and efficacy in restoring hemostasis is not well-defined [67] and should not be used first-line.

Urgent or Emergent Procedures

For warfarin patients who require urgent or emergent procedures, the reversal strategy depends on how quickly and how much the patient needs to be reversed.

- For procedures that need to occur within the next 6–8 h and cannot be delayed, PCC is preferred.
- For procedures that need to occur within the next 24 h, it is recommended to give IV vitamin K 0.5–2.5 mg.
- For procedures that are anticipated to occur between 24 and 72 h, the use of oral vitamin K 0.5–2.5 mg is recommended.
- For procedures that are to occur at >72 h, simply withholding warfarin and trending the INR are appropriate.

Special Considerations

Pregnancy

Warfarin freely crosses the placenta, and exposure during pregnancy is associated with fetal anomalies and late fetal loss in up to 10% of cases [68–70]. Women of childbearing potential who require long-term warfarin therapy should be instructed to use an effective form of contraception or undergo frequent pregnancy testing if attempting conception [71]. When anticoagulation is required during pregnancy, the safety and efficacy for both the mother and the fetus must be considered. Neither unfractionated (UFH) nor LMWH cross the placenta and are considered safe for the fetus. Guidelines from the American College of Chest Physicians [71] recommend LMWH over warfarin throughout all stages of pregnancy for women requiring anticoagulation for VTE treatment. Pregnant women with mechanical cardiac valves are at exceptionally high risk for thromboembolic events. Unfortunately, optimal anticoagulation therapy for mechanical valves during pregnancy, particularly during the first trimester, remains controversial. Warfarin affords the most protection for the mother against thromboembolic events (2–4% compared to 9–12% for LMWH and up to 33% for subcutaneous unfractionated heparin) in the setting of mechanical cardiac valves [68, 72]. However, this must be balanced against warfarin-associated fetal complications. The risk appears to be greatest during the first trimester and among women whose warfarin dosing requirement is ≥5 mg daily [68, 70, 73]. As such, anticoagulation for mechanical valves during pregnancy is a highly individualized choice. Pregnant patients with mechanical valves should be counseled regarding the risks of warfarin therapy, especially during the first trimester and at term [71]. National and international guidelines suggest it reasonable to continue warfarin during the first trimester if the daily dose requirement is ≤5 mg and there has been full disclosure of the risks and benefits through a shared decision-making process with the patient. For women whose warfarin requirement is >5 mg daily or place a higher value on avoiding embryopathies than avoiding valve thrombosis, anticoagulation with LMWH or UFH during the first trimester may be employed with the cognizance of a possible increased risk of thromboembolic complications with these agents. When used, LMWH should be administered twice daily with close monitoring to ensure adequate levels of anticoagulation. Unfractionated heparin should be administered intravenously via continuous infusion, as the subcutaneous route in pregnant women with mechanical valves is associated with a very high incidence of valve thrombosis. As with LMWH, close monitoring for adequate levels of anticoagulation is imperative. For the second and third trimesters, it is recommended to utilize warfarin, if the patient is amenable, along with low-dose concomitant aspirin 81 mg daily. At the 36th week of gestation, the patient should be transitioned from warfarin to LMWH or UFH in anticipation of delivery [74, 75].

Breastfeeding

Warfarin is not detectable in breast milk from lactating patients treated with warfarin and is thus a viable option in breastfeeding mothers [11, 76].

Pediatric Patients

Thromboembolic events in pediatric patients occur less frequently than in adults. Consequently, much of the anticoagulation clinical management practices in pediatric patients are based off adult evidence and recommendations [77]. Warfarin therapy is a commonly used long-term anticoagulant in children and can be successfully managed using INR goals similarly as with adults [77, 78]. Furthermore, warfarin is currently the only oral anticoagulant FDA-approved for use in pediatric patients; however, several clinical trials of DOACs in pediatric populations are currently underway [79, 80].

While the management of warfarin is similarly performed with INR monitoring and goals as with adults [77], warfarin use in pediatric patients can be more challenging [81]. In pediatric patients, warfarin is initiated using weight-based dosing (e.g., 0.2 mg/kg/day) and requires more frequent monitoring and dose adjustments than in adults. For instance, in neonates, plasma levels of vitamin K-dependent coagulation factors are much lower than in adults. Further, infant formula is often supplemented with vitamin K, but breast milk has very low levels of vitamin K, and consequently the primary source of nutrition in neonates and infants will dramatically affect their warfarin sensitivity [77]. Additionally, as a child ages, their hemostatic system changes and subsequently may alter their warfarin requirements, with infants generally requiring more warfarin than older pediatric patients to achieve their INR goal [11, 78].

Conclusion

Although the therapeutic landscape of anticoagulation is rapidly changing with the advent of the DOACs, warfarin will continue to be a mainstay of therapy for many patient populations and in numerous clinical indications. Optimized safety and efficacy depends on active participation of knowledgeable patients as well as clinician familiarity with the unique, and sometimes challenging, pharmacokinetics, pharmacodynamics, and practical management aspects of warfarin.

Key Points

- Due to the hypercoagulable state during the first few days of warfarin therapy, along with delayed antithrombotic effect, patients with acute thrombosis should receive a rapid-acting anticoagulant (heparin, low-molecular-weight heparin (LMWH), or fondaparinux) while transitioning to warfarin therapy [1, 6, 10].
- Warfarin is metabolized by multiple hepatic cytochrome P450 isoenzymes and has many clinically significant drug-drug interactions that may warrant dose adjustment or increased frequency

of monitoring to avoid adverse events (Tables 2.2 and 2.3).

- Warfarin is prone to numerous clinically significant drug-drug and drug-food interactions, and patients on warfarin should be questioned at every encounter to assess for any potential interactions with foods, drugs, herbal products, and nutritional supplements. More frequent monitoring should be instituted when interacting medications are changed to avoid clinically significant hemorrhagic or thromboembolic complications.
- Patients on warfarin may experience changes in the INR due to fluctuating intake of dietary vitamin K (Table 2.10). However, patients should be instructed to maintain a consistent diet rather than strictly avoiding vitamin K-rich foods.
- Most patients may be initiated on a dose of warfarin 5 mg daily with frequent monitoring and dose adjustment until their response to warfarin is known. Small dosage adjustments (5–20%) should be made, if indicated, recognizing that the full effect of any dose adjustment will not be seen for 2–3 days.
- Vitamin K is the antidote for warfarin. It should be given either orally (PO) or intravenously (IV), depending on the clinical situation. Both routes are equally effective in reversing warfarin, but the IV route provides more rapid reversal.
- All warfarin patients with major bleeding should receive IV vitamin K 5–10 mg.
- PCC is preferred over FFP for factor replenishment in warfarin-associated major hemorrhage.

Self-Assessment Questions

1. A 73-year-old woman with a past medial history of heart failure presents with new onset atrial fibrillation. Her renal function and drug interactions preclude her from being a good DOAC candidate, and she is initiated on warfarin 5 mg PO every evening. Which of the following is the most appropriate counseling point regarding her dietary intake?
   (a) She does not have to avoid healthy foods, such as leafy green vegetables, but rather should strive to maintain consistency in her diet.
   (b) She should avoid leafy green vegetables, such as spinach, as this will antagonize the warfarin and make it difficult to keep her INR in the therapeutic range.
   (c) She should take her warfarin with food to promote absorption.
   (d) She should take warfarin on an empty stomach to promote absorption.
2. A 75-year-old woman with a history of heart failure and atrial fibrillation on chronic warfarin therapy presents to the emergency department with a chief complaint of significant blood in her stools and fatigue. She is hypotensive (BP 83/50) and has decreased mental status. Her hemoglobin is 4.6 g/dL, down from 11.2 g/dL at last visit. Her INR is 3.3.

   What is the most appropriate action at this time in regard to managing her anticoagulation?
   (a) Withhold any anticoagulation, administer vitamin K 2.5 mg PO, and have her follow up at the anticoagulation clinic.
   (b) Withhold any anticoagulation and administer FFP 6–8 units.
   (c) Withhold any anticoagulation, and administer IV vitamin K 10 mg stat along with PCC.
   (d) Withhold warfarin, trend the INR, and resume once it is in the therapeutic range.
3. A 68-year-old man is diagnosed with bilateral pulmonary emboli 1 week after he underwent a total knee arthroplasty. His past medical history is significant for a gastrointestinal bleed 4 months ago, cirrhosis, heart failure, and hypertension. His baseline INR is 1.4 and his renal function is normal. His insurance will not cover a DOAC, and the decision is made to start warfarin. What would be the most appropriate starting dose of warfarin?

(a) 10 mg PO daily as he may be warfarin resistant.
(b) 5 mg PO daily as he should not be warfarin sensitive.
(c) 2.5 mg PO daily as he may be warfarin sensitive.
(d) His risk for bleeding precludes the use of anticoagulation.

4. How long should enoxaparin be overlapped with his warfarin therapy during warfarin initiation?
   (a) Until the INR is >2.
   (b) For a minimum of 5 days and until the INR is within the target range.
   (c) Enoxaparin bridging is not indicated in this patient.
   (d) For 3 days or until the INR is >2.
5. Which of the following patients would require warfarin therapy rather than a DOAC?
   (a) A 77-year-old woman with a past medical history of hypertension, hyperlipidemia, mechanical aortic valve, and atrial fibrillation
   (b) A 35-year-old man with an upper extremity DVT secondary to his hemodialysis catheter
   (c) Neither
   (d) Both

Self-Assessment Answers

1. (a) She does not have to avoid healthy foods, such as leafy green vegetables, but rather should strive to maintain consistency in her diet.

   Because warfarin inhibits vitamin K-dependent factor development, it is important to maintain a consistent level of dietary vitamin K every day to reduce fluctuations in INR levels. Patients should not be counseled to avoid dietary vitamin K, but rather they should be counseled to keep the dietary vitamin K intake relatively consistent.
2. (c) Withhold any anticoagulation, and administer IV vitamin K 10 mg stat along with PCC.

   Given her acute drop in hemoglobin, altered mental status, and bloody stools, she likely requires rapid reversal of warfarin's effect. This is best achieved with IV vitamin K as well as PCCs. Oral vitamin K will not achieve a sufficiently rapid effect. FFP may rapidly reverse her INR, but the high volume required for administration puts her at risk for a heart failure exacerbation.
3. (c) 2.5 mg PO daily as he may be warfarin sensitive

   Given his known cirrhosis comorbidity and prior gastrointestinal bleed, initiation of low-dose warfarin is most appropriate to avoid INR levels above the therapeutic range.
4. (b) For a minimum of 5 days and until the INR is within the target range

   Due to the half-life of various factors (II, VII, IX, and X) along with protein C and protein S, enoxaparin should be overlapped with warfarin for a minimum of 5 days and until the INR is within the target range.
5. (d) Both

   Warfarin is preferred of DOAC therapy in any patient with a mechanical cardiac valve replacement due to high rates of valve thrombosis with DOAC therapy. Patients on hemodialysis are generally not good DOAC candidates because each of the DOAC medications is partially excreted by the kidneys.

References

1. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e44S–88S.
2. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S–84S.
3. Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Erratum to: pharmacology of anticoagulants used in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016; 42(2):296–311.
4. Witt DM, Clark NP, Kaatz S, Schnurr T, Ansell JE. Guidance for the practical management of warfa-