Vitamin K Antagonists [VKAs] and Warfarin

VKAs are a group of substances that reduce blood clotting by reducing the action of vitamin K through the inhibition of vitamin K epoxide reductase (VKORC1). This results in recycling of the inactive vitamin K epoxide back to the active reduced form of vitamin K. VKAs, therefore, block the γ-carboxylation of prothrombin; factor VII, IX, and X residues; as well as proteins C and S. They also affect protein Z. Anticoagulation is therefore dependent on the half-life of the coagulation factor/natural anticoagulant involved. The short half-life of protein C and factor VIIa can subsequently lead to a transient hypercoagulable state observed with the initiation of VKAs and explains the need to start patients with VTE on a heparin until a full depletion of the procoagulant factors is reached in 5–7 days [57].

Mutations of the gene coding for (VKORC1) can give rise to warfarin resistance.

VKAs include coumarins (4-hydroxycoumarins) which include warfarin, acenocoumarol, phenprocoumon, and dicoumarol as well as indandiones which include phenindione.

Warfarin

Historic Background

Warfarin is the most widely used anticoagulant in the world. It was estimated that in 2006 at least 1% of the population and 8% of the people over 80 years of age were using the medication [58].

In the late 1920s, it was noticed that previously healthy cattle in the Canadian Prairies and northern USA, grazing on sweet clover hay, began dying of internal bleeding with no obvious precipitating cause. Such damp hay was infected by molds and contained a hemorrhagic substance. Roderick, a local veterinarian, demonstrated that the acquired coagulation disorder was caused by what he called a "plasma prothrombin defect" [59]. The toxic agent was identified at the University of Wisconsin as bishydroxycoumarin [60] and its structurally similar agent warfarin (Wisconsin Alumni Research Foundation – adding ARIN from coumarin) was promoted as rodenticide [59].

Bioavailability and Half-Life

Warfarin is a racemic mixture of R and S isomers; it is usually administered as sodium salt with 100% bioavailability and a half-life of 36 h. Warfarin and its derivatives have a small therapeutic window.

Formulation

Warfarin is available as warfarin sodium in the following strength: 1, 2, 2.5, 3, 4, 5, 6, and 10 mg tablets.

Dose and Administration

Treatment is usually initiated with a loading dose of 5–10 mg and adjustments are made based on the prothrombin time (expressed in INR) at about 1 week. An average maintenance dose of 5–7 mg orally daily targeting an INR of 2–3 is used for the treatment and prophylaxis of VTE and atrial fibrillation. A target INR of 2.5–3.5 is used for patients with artificial valves and those who need more intense anticoagulation.

Since the medication is dependent on VKORC1 and is metabolized through P450 CYP2C9 [61], inherited polymorphism may have a significant impact on the dose of the medication. This led to the consideration of patient-specific genotype for the adjustment of warfarin therapy [62]. Wells and coworkers also highlighted the role of CYP4F2 [63].

It is usually recommended to administer the drug at bed-time to be ingested with water and away from food to avoid drug-food interactions. Hepatic disease and thyroid dysfunction may also significantly affect the action of warfarin.

The following nomogram could guide the adjustment of INR for patients on warfarin [64].

Target 2.0–3.0 and No Bleeding

Measured INR	Dosage adjustment	Next INR
<1.5	Consider extra dose, increase weekly dose by 10–20%	4–7 days
1.5–1.9	Increase weekly dose by 5–10%	7–14 days
2.0–3.0	**No change**	**See follow-up algorithm (below)**
3.1–3.5	Decrease weekly dose by 5–10%	7–14 days
3.6–4.0	Decrease weekly dose by 10–20%	7–14 days
4.1–4.9	Hold 0–2 day(s) and decrease weekly dose by 20%	4–7 days

Target INR 2.5–3.5 and No Bleeding

Measured INR	Dosage adjustment	Next INR
<1.5	Consider extra dose, increase weekly dose by 10–20%	4–7 days
1.5–2.4	Increase weekly dose by 5–10%	7–14 days
2.5–3.5	**No change**	**See follow-up algorithm (below)**
3.6–4.0	Decrease weekly dose by 5–10%	7–14 days
4.1–4.5	Consider holding 1 dose, Decrease weekly dose by 10%	7–14 days
4.6–4.9	Hold 0–2 day(s) and decrease weekly dose by 10–20%	4–7 days

Follow-Up Algorithm

Number of consecutive INRs in range	Repeat INR
1	4–7 days
2	14 days
3	21 days
4	28 days

For Target 2–3

- If INR 1.8–1.9, consider no dosage change, and repeat INR in 7–14 days.
- ∗If INR 2.0–2.1, or 2.8–3.0, consider repeating INR in 14 days regardless of number of consecutive in range INRs.
- If INR 3.1–3.2, consider no dose change, and repeat INR in 7–14 days.

For Target 2.5–3.5

- If recent mechanical heart valve within 6–8 weeks, consider bridging therapy with therapeutic dose low-molecular-weight heparin.
- If INR 2.3–2.4, consider no dose change, and repeat INR in 7–14 days.
- If INR 2.5–2.6 or 3.3–3.4, consider repeating INR in 14 days, regardless of number of consecutive in-range INRs.
- If INR 3.6–3.7, consider no dose change, and repeat INR in 7–14 days.

Warfarin Resistance

Two types of warfarin resistance have been described:

(a) "Functional" resistance is defined as progression or recurrence of thrombosis despite being on therapeutic range of anticoagulation from the laboratory perspective and is often seen in patients with cancer mandating the switch to alternate anticoagulation [65].
(b) "True" warfarin resistance is rare (< 0.1%) and is defined as warfarin requirements greater than 70 mg per week to maintain the international normalized ratio (INR) in the target therapeutic range [66].

It is usually related to VKORC1 or CYP3C9 mutations or resulting from a gross drug-drug interaction and necessitates the consideration of alternate anticoagulant.

Warfarin Interactions

Food, Food Supplement, and Herbal Interactions

VKAs interact with food containing vitamin K (reducing its actions) [67, 68]; therefore, the intake of foods rich in vitamin K (an average consumption of ½ cup/day) should be about the same each day. If patients want to consume more, the daily amount needs to be consistent.

Examples of food servings rich in vitamin K are illustrated in Fig. 1.7:

Other Interactions

Alcoholic beverages: Alcohol can affect warfarin dose and should be avoided.

Dietary supplements and herbal medications: Many dietary supplements (arnica, bilberry, butchers broom, cat's claw, St John's wort, feverfew, Dong quai, garlic, ginger, ginkgo, and others) can alter the INR/PT. The safest policy for individuals on warfarin is to avoid all dietary supplements. This includes any vitamin/mineral supplements that list vitamin K on the label. If they are taken regularly on a daily basis, they pose less of a problem than if taken off and on.

Vitamin E supplements**:** Vitamin E intake above 1000 International Units (IU) per day may increase the risk of excess bleeding. Research suggests that doses up to 800 IU may be safe for individuals on warfarin, but the evidence is not conclusive [69, 70].

Drug Interactions [69–73]

CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. The more potent warfarin S-enantiomer (60% of the overall anticoagulation response) is metabolized by CYP2C9, while the R-enantiomer is metabolized by CYP1A2 and 3A4.

- Inhibitors of CYP2C9, 1A2, and/or 3A4 have the potential to increase the effect (increase INR) of warfarin by increasing the exposure of warfarin.
- Inducers of CYP2C9, 1A2, and/or 3A4 have the potential to decrease the effect (decrease NR) of warfarin by decreasing the exposure of warfarin.

Coumarins may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

Food serving	Size	Vitamin K (mcg/serving size)
Broccoli, cooked	1 cup	220
Brussels sprouts, cooked	1 cup	219
Collard, cooked	½ cup	418
Parsley, raw	¼ cup	246
Swiss chard, cooked	½ cup	287
Turnip greens, cooked	½ cup	265

Fig. 1.7 Illustrates the content of vitamin K in common food servings [67, 68]

It has been reported that concomitant administration of warfarin and ticlopidine may be associated with cholestatic hepatitis. Figure 1.8 - Established or Potential Drug-Drug Interactions with VKA.

A detailed list of drug interactions could be reviewed in references [70–73].

Contraindications

1. As with all anticoagulants, VKAs are contraindicated with active bleeding or in patients with increased risk of bleeding, e.g., low platelets, severe liver disease, and uncontrolled hypertension. For patients undergoing surgery or invasive procedures, a bridging approach should be considered (Discussed in detail Chap. 12).

Name	Effect	Clinical comment
Nonsteroidal anti-inflammatory drugs (NSAIDs)	May affect prothrombin time May inhibit platelet aggregation May increase risk of gastrointestinal bleeding, peptic ulceration and/or perforation May increase bleeding risk	Close monitoring of patients receiving nonsteroidal anti-inflammatory agents (NSAIDs) is recommended to be certain that no change in anticoagulation dosage is required. Bleeding risk is increased when these drugs are used concomitantly with warfarin. Adjust dosage accordingly or discontinue if necessary. Consult the labeling of all concurrently used drugs to obtain further information about interactions with warfarin or adverse reactions pertaining to bleeding.
Anticoagulants Platelet anti-aggregants Thrombolytics Serotonin reuptake inhibitors	May increase bleeding risk	Bleeding risk is increased when these drugs are used concomitantly with warfarin. Closely monitor patients receiving any such class of drug with warfarin. Adjust dosage accordingly or discontinue if necessary.
Antibiotics and antifungals	May change international normalized ratio (INR)	There have been reports of changes in INR in patients taking warfarin and antibiotics or antifungals, but clinical pharmacokinetic studies have not shown consistent effects of these agents on plasma concentrations of warfarin. Coadministration with warfarin should be avoided or closely monitor INR when starting or stopping any antibiotic or antifungal in patients taking warfarin.

Fig. 1.8 Established and potential drug group interactions with VKA and their effect on INR

2. Warfarin should not be given to people with heparin-induced thrombocytopenia until platelet count has improved or normalized [70].
3. Warfarin is usually best avoided in people with protein C or protein S deficiency without proper bridging as these thrombophilic conditions increase the risk of skin necrosis, which is a rare but serious side effect associated with warfarin [74].
4. Pregnancy: Warfarin is contraindicated in pregnancy as it passes the placental barrier and may cause fetal bleeding. It is commonly associated with poor outcome and is also teratogenic, resulting in a constellation of abnormalities known as fetal warfarin syndrome (FWS). The incidence of birth defects appears to be around 5%, although higher figures (up to 30%) have been reported in some studies [54]. Depending on when exposure occurs during pregnancy, two distinct combinations of congenital abnormalities can arise [75]. It should be definitely avoided in the first trimester.

Warfarin administration in the second and third trimesters is much less commonly associated with birth defects and, when they do occur, is considerably different from FWS.

According to the American College of Chest Physicians (ACCP), warfarin may be used in lactating women who wish to breast-feed [56]. Data does not suggest that warfarin crosses into the breast milk [75].

Adverse Events

1. Bleeding: The risk of severe bleeding is typically at 1–3% per year [76]. Bleeding can occur from many sources with intracranial bleeds and gastrointestinal ones being the most serious [77].

   Risk of bleeding is increased if the INR is out of the therapeutic range [78]. This risk increases greatly once the INR exceeds 4.5 [79].

   The risks of bleeding are increased further when warfarin is combined with antiplatelet drugs such as clopidogrel, aspirin, or nonsteroidal anti-inflammatory drugs [80].

   The bleeding risk prediction can be calculated using one of the following scoring systems:

   - HAS-BLED SCORE [81]: With a maximum score of 9

	Condition	
H	Hypertension (systolic blood pressure > 160 mmHg)	1
A	Abnormal renal function (defined as the presence of chronic dialysis or renal transplantation or serum creatinine 200 μmol/L (>~2.3 mg/dL))	1
	Abnormal liver function (defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2× upper limit of normal, in association with AST/ALT/ALP >3x upper limit normal)	1
S	Stroke (previous history of stroke)	1
B	Bleeding (major bleeding history (anemia or predisposition to bleeding))	1
L	Labile INRs (refers to unstable/high INRs or poor time in therapeutic range (e.g., <60%))	1
E	Elderly (age >/= 65)	1
D	Drug therapy (concomitant therapy such as antiplatelet agents, NSAIDs)	1
	Alcohol intake (consuming 8 or more alcoholic drinks per week)	1
	Total	9

- The scoring system translates into percentage of bleeding/Year:

HAS-BLED score	Bleeds % per Year
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50
Any score	1.56

HEMORR2HAGES is another scoring system used to stratify the risk of bleeding in patients on warfarin. The ATRIA score uses a weighted additive scale of clinical findings for better bleeding risk stratification [82].

2. Warfarin necrosis is a rare but serious and often life-threatening complication resulting from treatment with warfarin and commonly occurs shortly after commencing treatment in patients with a deficiency of protein C. As warfarin initially decreases protein C levels faster than the coagulation factors, it can paradoxically induce a transient hypercoagulable state leading to massive thrombosis with skin necrosis and gangrene of limbs. Its natural counterpart, purpura fulminans, occurs in children who are homozygous for certain protein C mutations [83].
3. Calcification: Several studies have alluded to vascular calcification as a complication of prolonged warfarin use [84].
4. Osteoporosis is a controversial side effect. A retrospective study on 14,564 Medicare patients receiving warfarin for more than 1 year, showed that its use was linked with an increased risk of osteoporosis-related fracture in men. There was no association in women. The mechanism entails interaction with bone proteins [85].
5. Purple toe syndrome is another rare complication occurring during the first few weeks of warfarin therapy and is thought to result from cholesterol embolization of the blood vessels in the skin of the toes or plantar surface of the foot. It may require discontinuation of the therapy [86].

Bridging of Anticoagulation See Chap. 12.

Overdose and Reversal See Chap. 13.