Chapter 10

Essential Warfarin Knowledge

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Chapter Outline

Objectives

1. Understand the clotting cascade and important properties of vitamin K dependent clotting factors.
2. Identify indications and contraindications for warfarin therapy.
3. Recognize specific disease, herbal, and drug interactions associated with warfarin therapy.
4. Given a patient case, develop an appropriate treatment plan for patients outside goal INR.
5. Develop a patient specific pre- and post-treatment plan for patients requiring interruption of warfarin therapy.

Despite the vast amount of clinician experience with warfarin, developed at the University of Wisconsin in 1948, safe management of warfarin remains a challenge for usual care environments and practitioners.[1] Given the tremendous number of medications available in the U.S., warfarin remains among thirteen other medications the Institute for Safe Medication Practices considers a high alert medication for 2005.[2] Warfarin is also a frequently prescribed medication in the United States with approximately 21.2 million prescriptions in 2003.[3] Although there have been hopes and near successes for an oral replacement to warfarin, warfarin remains the predominant oral anticoagulant used in North America.[4,5]

Pharmacology

Warfarin reduces clot formation by disrupting the liver's production of functional vitamin K dependent clotting factors II, VII, IX, and X (Figure 10-1). A simplified explanation is that warfarin binds the enzyme vitamin K epoxide reductase (VKOR) in the liver interfering with the regeneration of natural vitamin K[1] from its inactive form, (oxidized) vitamin K 2-3 epoxide.[6] The clotting factors II, VII, IX, and X require gamma-carboxylation of their precursors in order to produce their procoagulant effect. This gamma-carboxylation step, gives the protein the calcium mediated ability to bind negative charged phospholipid surfaces, this being a requirement for the clotting factor's procoagulant activity.[6] Warfarin therefore causes production of partially carboxylated and decarboxylated proteins having reduced pro-

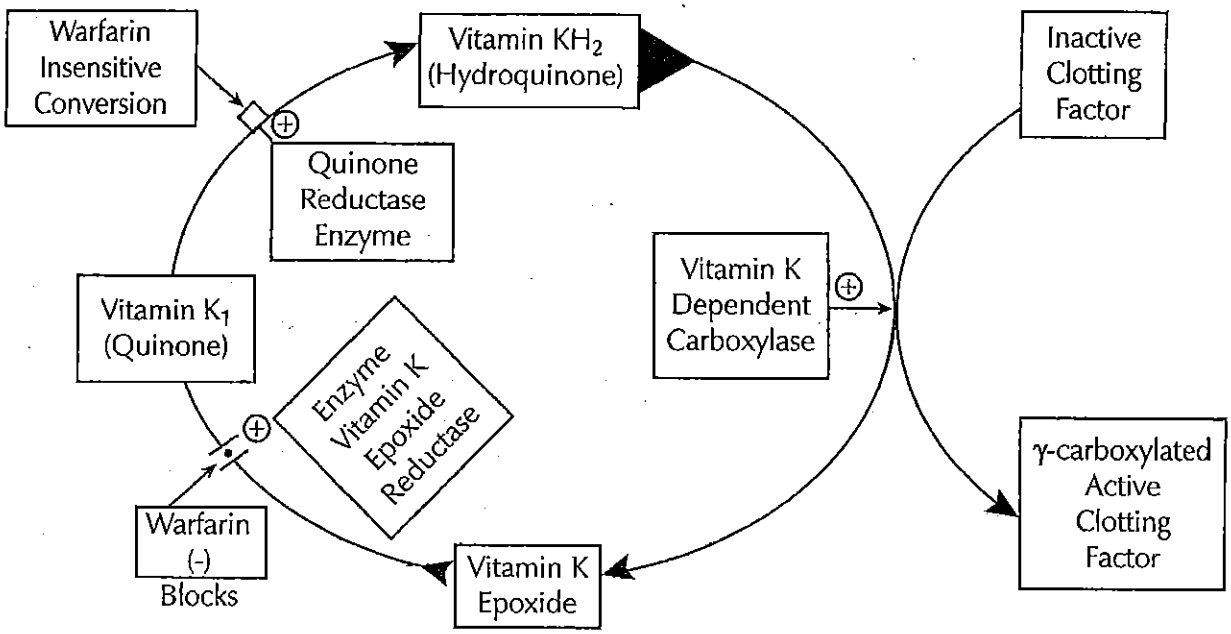


Figure 10-1. Vitamin K cycle. Warfarin blocks the conversion of vitamin K epoxide to vitamin C. CD

coagulant activity.[7-10] Warfarin also interferes with the synthesis of other vitamin K dependent proteins like endogenous anticoagulant proteins C and S as well as other proteins located in bone, cartilage, and other tissues unrelated to coagulation.[11,12]

Important concepts to understand in anticoagulation are intrinsic versus extrinsic clotting factors, clotting factor half-lives, warfarin's inhibition of anticoagulant proteins C and S, and warfarin's delayed onset (Figure 10-2). Warfarin does not inhibit activity of existing clotting factors. Depletion of these factors through normal catabolism and replacement with newly synthesized dysfunctional clotting factors must occur before therapeutic response to warfarin is established. Vitamin K dependent clotting factors differ in degradation half-lives; factor II (prothrombin) 48–120 hours (~60), factor VII 2 to 6 hours (~6), factor IX 18-40 (~25) hours, and factor X 30–70 hours (~35.6) (see Figure 10-2). In theory, response therefore requires approximately 5 days of warfarin and depletion of functional factors II and X to achieve effective anticoagulation.[6] Factor VII is in the extrinsic pathway and inhibition does not provide effective anticoagulation despite causing early INR elevation (Figure 10-2). The half-lives of anticoagulant proteins C and S are approximately 8 and 30 hours. Since warfarin reduces activity of anticoagulant proteins C and S having shorter half-lifes than factors II and X, in theory, a hypercoagulable state may be induced early in therapy.[1] Due to delayed depletion of factors X and II, and earlier reduction of anticoagulant proteins C and S, injectable anticoagulant overlap is often required when immediate anticoagulation is needed. Opinions regarding duration of overlap vary; although many authorities recommend a minimum of 5 days overlap and that the INR be in range and stable before heparin discontinuation.

Pharmacokinetics/ Pharmacodynamics

Warfarin is an equal mixture of two optically active isomers, R- and S-warfarin. The warfarin S isomer is more potent and each isomer is metabolized through different pathways.[13] Warfarin is available in an oral or injectable formulation. The IV formulation is used less frequently; however, this route prevents disruption of stabilized warfarin in hospitalized patients who have lost all enteral routes. Following oral administration with a functional GI tract, maximum plasma concentration occurs in approximately 90 minutes.[13,14] Warfarin's half-life ranges from 36 to 42 hours.[6] Warfarin is extensively bound to plasma proteins 97%–99%, predominantly albumin, and then accumulates in microsomes of the liver.[15] Warfarin dose response among patients is highly variable secondary to inter-patient differences in: metabolism, vitamin K diet, receptor affinity, quantity of vitamin K dependent clotting factors, genetic factors, disease states, binding proteins, laboratory testing, drug interactions, and compliance.[6,16,17]

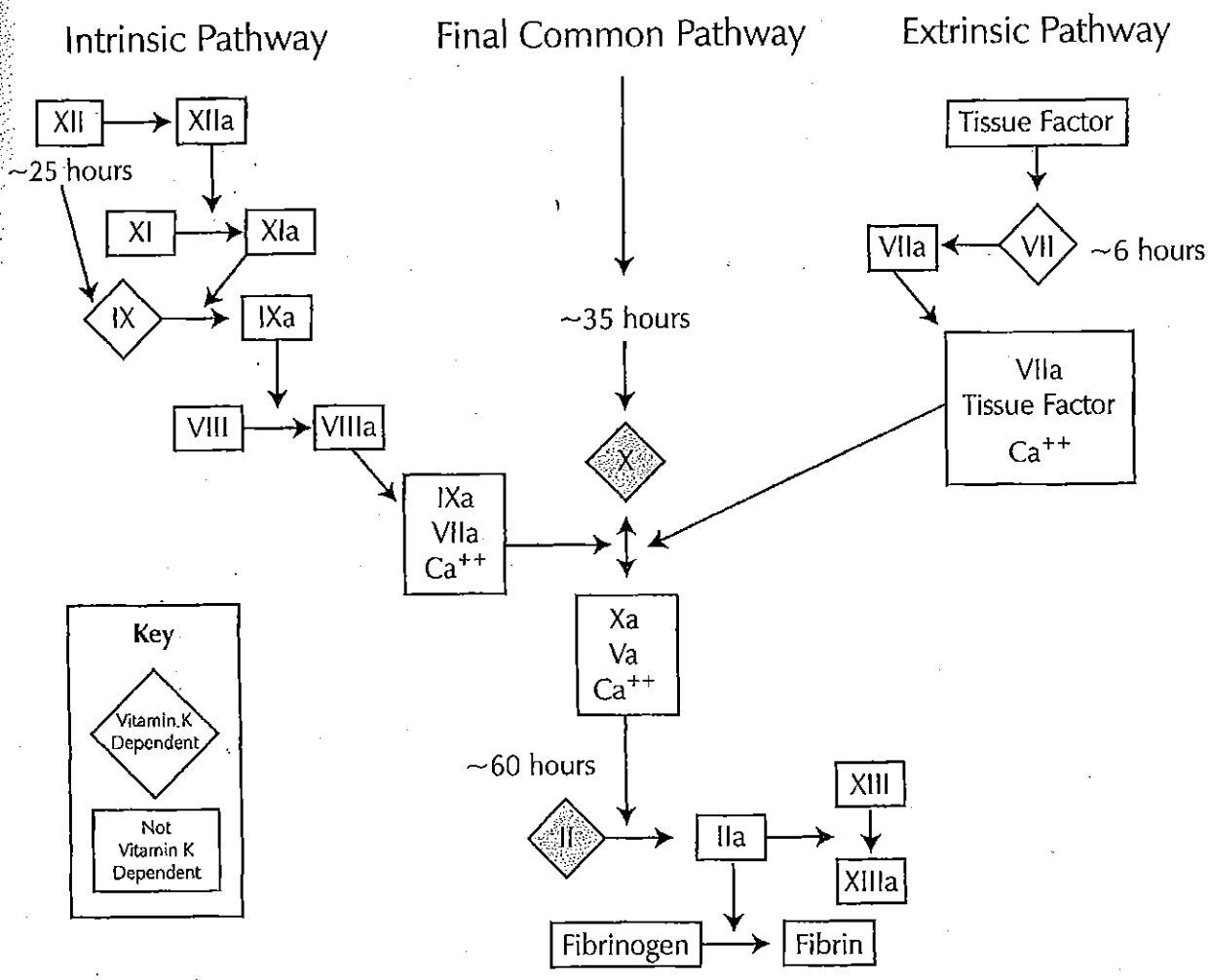


Figure 10-2. Coagulation cascade and vitamin K–dependent clotting factor half-lives. Shaded clotting factors are critical warfarin targets.

Clinical Pearls

Hospital pharmacists managing warfarin will encounter patients who cannot take warfarin enterally. If the INR is in range or close to in range, and the pharmacist and physician agree warfarin is still safe, using IV warfarin can prevent disruption of stabilized patients. This avoids use of other injectable anticoagulants and re-titration of warfarin. These patients often require lower IV doses from baseline despite equal bioavailability of oral warfarin secondary to acute illnesses, medication used to treat the illness, and/or decreased nutritional intake of vitamin K.

Due to the long half-life of warfarin, every dose taken within the last 7 days must be considered when making dosing decisions. However, the inpatient pharmacist will discover the doses taken 2–3 days ago will have the most prominent effect on current day INR and these require careful consideration when making dose adjustments.

Clinical Pearls

Patient and medical staff education on warfarin interactions reduce hospital admissions by improving warfarin management and preventing warfarin misadventures. Hospital admissions secondary to warfarin drug interactions provide an opportunity to educate the prescriber, patient's outpatient pharmacy, and patient on interaction screening. These admissions also require completion of an adverse drug reaction form. These interventions on preventable warfarin adverse drug events help prevent future occurrences.

Interactions involving inhibition of S-warfarin metabolism are more severe and often require pre-emptive warfarin dose adjustments or interchange to safer alternatives. Interactions involving the five times less potent R-isomer can often be managed by daily INR monitoring and often don't cause as dramatic INR elevations.

Clearly determining if a medication, even those known to interact, caused an INR elevation in hospitalized patients is difficult because acute illnesses may also elevate the INR. A good example is a patient receiving metronidazole for *Clostridium difficile* colitis. When an INR bump occurs, is it from the metronidazole, the severe diarrhea, poor vitamin K intake, or all of the above? Often, it is a combination of factors and the presumed "drug interaction" may become less pronounced as the patient recovers from illness.

Drug Interactions

Medication interactions can affect warfarin response in the following ways:

- binding warfarin and reducing GI absorption (cholestyramine).[17,18]
- decrease clotting factor production by inhibiting vitamin K recycling (2nd and 3rd generation cephalosporins).[19-22]
- change metabolism of clotting factors by the liver (thyroxin,[23] methimazole[24]).
- directly increasing or decreasing warfarin metabolism in the liver.

Inhibitors of 2C9 and S-isomer[25] warfarin metabolism include metronidazole,[26] ritonavir,[27] sulfinpyrazone,[28] amiodarone, fluconazole, and trimethoprim-sulfamethoxazole.[29] Inhibitors of 1A2 and 3A4 metabolizers of R-isomer warfarin[27,30] include quinolones,[31-33] omeprazole,[6,26,34] cimetidine,[6,26,34] and macrolides.[35-37] A comprehensive list of warfarin interactions by probability of occurrence are provided in Tables 10-1 and 10-2.[30] R-isomer interactions can also be clinically relevant and require increased monitoring but tend to be less dramatic than S-isomer interactions.[34,38] The *Chest* guidelines suggest increased INR monitoring following virtually any medication/herbal addition or withdrawal.[39,40] Following addition of interacting medications, hospitalized patients should have daily INRs. Some interactions like amiodarone are delayed and take longer before stabilization occurs.

Information regarding interactions between herbals and warfarin is scant. Published reports are often from case reports and experience from clinicians managing anticoagulation clinics. Clinically relevant herbal interactions are listed in Table 10-2.[30] Herbal supplements are not standardized with regard to purity, content, or potency, it is therefore difficult to estimate the degree of interaction with an herbal product. Therefore, it is best to discourage warfarin patients from taking herbal supplements. While medications and herbals may not have metabolism interactions with warfarin, agents altering platelet function increase risk of bleeding. Agents include aspirin, clopidogrel, dipyridamole, nonsteroidal anti-inflammatories (NSAIDs), high-dose penicillin, garlic, ginger, gingko biloba, ginseng, fish oils, vitamin E, and others.[40] Aspirin's effects on bleeding with warfarin has been studied more than others. The extent of increased bleeding correlates with aspirin dose and warfarin intensity; however, aspirin in combination with warfarin always increases bleeding over warfarin alone.[39,40] Aspirin and NSAIDs also increase bleeding by causing gastric erosions. There is little published data regarding the safety of combining warfarin with Plavix® nor do the Chest guidelines discuss this combination, as they do the combination of aspirin 81 mg and warfarin. Most experienced anticoagulation specialists generally feel the combination of Plavix® and warfarin is rarely justified and carries a higher risk of bleeding than combining warfarin and 81 mg aspirin. There are, perhaps, rare circumstances in which the benefits outweigh the risks of increased bleeding. This might include early status post drug eluding stent placement in a patient requiring warfarin for another justified indication. In these circumstances, patients require

Table 10-1. CD

Clinically Significant Interactions with Warfarin by Level of Causation and Drug Group

Level of Causation	Anti-infectives	Cardiovascular Drugs	Analgesics, Anti-inflammatories, and Immunologics	CNS Drugs
Potentiation				
I Highly Probable	Ciprofloxacin Cotrimoxazole Erythromycin Fluconazole Isoniazid (600 mg/d) Metronidazole Miconazole oral gel Miconazole vaginal suppositories Voriconazole	Amiodarone Clofibrate Diltiazem Fenofibrate Propafenone Propranolol Sulfinpyrazone (biphasic with later inhibition)	Phenylbutazone Piroxicam	Alcohol (if concomitant liver disease) Citalopram Entacapone Sertraline
II Probable	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir Tetracycline	Fluvastatin Quinidine Ropinirole Simvastatin	Acetaminophen Acetylsalicylic acid Celecoxib Dextropropoxyphene Interferon Tramadol	Disulfiram Choral hydrate Fluvoxamine Phenytoin (biphasic with later inhibition)
III Possible	Amoxicillin Amoxicillin/tranexamic rinse Chloramphenicol Gatifloxacin Miconazole topical gel193 Nalidixic acid Norfloxacin Ofloxacin Saquinavir Terbinafine	Amiodarone-induced toxicosis Disopyramide Gemfibrozil Metolazone	Celecoxib Indomethacin Leflunomide Propoxyphene Rofecoxib Sulindac Tolmetin Topical salicylates	Felbamate
IV Highly Improbable	Cefamandole Cefazolin Sulfisoxazole	Bezafibrate Heparin	Levamisole Methylprednisolone Nabumetone	Fluoxetine/diazepam Quetiapine
Inhibition				
I Highly Probable	Griseofulvin Nafcillin Ribavirin Rifampin	Cholestyramine	Mesalamine	Barbiturates Carbamazepine
II Probable	Dicloxacillin Ritonavir	Bosentan	Azathioprine	Chlordiazepoxide
III Possible	Terbinafine	Telmisartan	Sulfasalazine	
IV Highly Improbable	Cloxacillin Nafcillin/dicloxacillin Teicoplanin	Furosemide		Propofol

Source: Adapted with permission from reference 30.

Table 10-2.

Clinically Significant Interactions with Warfarin by Level of Causation and Drug Group (Continued)

Level of Causation	GI Drugs and Food	Herbal Supplements	Other Drugs
		Potentiation	
I Highly Probable	Cimetidine Fish oil Mango Omeprazole	Boldo-fenugreek Quilinggao	Anabolic steroids Zileuton
II Probable	Grapefruit juice	Danshen Dong quai Lycium barbarum L PC-SPES	Fluorouracil Gemcitabine Levamisole/fluorouracil Paclitaxel Tamoxifen Tolterodine
III Possible	Cranberry juice Orlistat	Danshen/methyl salicylate	Acarbose CMF (cyclophosphamide/methotrexate/fluorouracil) Curbicin Danazol Ifosphamide Trastuzumab
IV Highly Improbable			Etoposide/carboplatin Levonorgestrel
		Inhibition	
I Highly Probable	High vitamin K content foods/enteral feeds Avocado (large amounts)		Mercaptopurine
II Probable	Soy milk Sucralfate	Ginseng	Chelation therapy Influenza vaccine Multivitamin supplement Raloxifene hydrochloride
III Possible	Sushi containing seaweed		Cyclosporine Etretinate Ubidicarenone
IV Highly Improbable		Green tea	

Abbreviations: CNS, central nervous system; GI, gastrointestinal.
Source: Adapted with permission from reference 30.

Clinical Pearl

Patients who experience acute liver dysfunction (hypotensive episodes, liver metastasis, etc.) while in the hospital will be extremely sensitive to warfarin. Vigilance is necessary when managing warfarin in these patients (daily INRs and warfarin adjustments) and sometimes holding warfarin until liver function recovers is required. Close consultation with the attending physician is advised in these situations.

very close monitoring and additional education with regard to medication interactions.

When deciding whether to combine warfarin with anti-platelet agents, the pharmacist must carefully weigh risks versus benefits for a specific patient.

Warfarin-Disease Interactions

Since the liver is responsible for production and metabolism of clotting factors and metabolism of warfarin, altered warfarin response with hepatic disease is not surprising.[40-45] Liver dysfunction is associated with increased bleeding.[46] A review evaluating 29,000 INRs found risk factors for INR ≥ 6 to include: liver disease, alcoholism, drug interactions, warfarin therapy for less than 6 months, and frequent dosage adjustments.[47]

Clinical Pearl

When practicing inpatient anticoagulation, thyroid status is often not a clinical concern unless it is changing. In other words, stable levothyroxine patients in euthyroid status should be treated like patients without thyroid issues. Hypothyroid patients initiated on levothyroxine or having levothyroxine dose increases may require warfarin dose reduction. Patients undergoing hyperthyroid treatment will likely require warfarin dose increases.

Changes in thyroid function cause changes in clotting factor metabolism, necessitating warfarin dose adjustments.[23,40] Hyperthyroidism increases a patient's sensitivity to warfarin by increased catabolism of clotting factors.[23,48] Hyperthyroidism also increases warfarin's binding affinity, further decreasing clotting factor production and warfarin dose requirement.[49] Increased warfarin sensitivity with hyperthyroidism has been observed in at least five human trials.[23,50-53] Published reports show stabilized warfarin patients who subsequently developed hypothyroidism, had a thyroidectomy, or received iodine ^{131} resulting in hypothyroidism; required a two- to three-fold warfarin dose increase to maintain therapeutic INRs.[54,55]

The mechanism of increased warfarin sensitivity in heart failure is unknown, however, evidence supports lowering warfarin doses, especially during exacerbations. All heart failure patients are not sensitized to warfarin.[47] Sensitization occurs during periods of decompensation or hepatic congestion, possibly due to reduced clotting factor production and plasma volume expansion.[56-58] Seven studies have shown increased sensitivity in heart failure; three of these used increased bleeding to support their conclusion.[56,59-65]

Other disease states have been implicated in difficult warfarin management. Cancer patients are sometimes difficult to manage on warfarin. Factors making these patients difficult to manage include: chemo/warfarin interactions, malnutrition/nausea/vomiting, liver/blood abnormalities, volume changes, and warfarin interruptions due to thrombocytopenia and surgery.[66,67] Fever, commonly present in hospitalized patients, has been shown to reduce metabolism of antipyrine; metabolized through the same pathways as warfarin CYP1A2 and CYP3A4.[25,27,30,68-70] In a small subset of fever patients, increased clotting factor metabolism has also been observed.[48] In practice, many warfarin patients with infections have elevated INRs. Finally, any disease that affects a patient's eating habits or absorption of vitamin K can affect warfarin dosing.

Clinical Pearl

Previously stabilized warfarin patients often have elevated INRs when admitted with decompensated heart failure. This often requires holding or reducing their warfarin dose by about 50% for 1–2 days after admission, but as they diurese and improve, they often require their previous warfarin dose. Pharmacists are often reluctant to resume previous dosing thinking "the dose made them go high" overlooking the acute illness as the cause rather than the dose. As with all warfarin patients, it is important for pharmacists to understand the patient's complete clinical status and not just "treat the numbers."

Genetic Issues Affecting Warfarin Dosing

A few genetic polymorphisms decrease warfarin metabolism. Studies have evaluated CYP450 2C9 gene mutations that encode for the enzyme responsible for metabolism of the more potent S-isomer of warfarin. Specific mutations causing increased warfarin sensitivity or bleeding include CYP2C9-2 and CYP2C9-3, with normal metabolism being homozygous CYP2C9-1.[71-80] A gene encoding the CYP450 2C9 enzyme is found on each chromosome. Patients may be normal (CYP2C9-1/1), polymorphic heterozygous (CYP2C9-1/3, -1/2), polymorphic homozygous (CYP2C9-3/3, -2/2) or have mixed polymorphic alleles (i.e., CYP2C9-2/3). Three larger studies of CYP2C9 polymorphism were Herman et al. n = 188,[73] Kamali et al. n = 121,[76] and Scordo et al. n = 93.[79] The most warfarin-sensitive polymorphism in all three trials was the homozygous 3/3 consistently followed by the 2/3, followed by the 1/3 and 2/2, followed by the least affected 1/2 polymorphism, which still required a 30%–40% lower dose than 1/1.[73,76,79] The incidence of specific types of polymorphisms among general populations were similar across the three studies: CYP2C9-1/1 (58%–63%), CYP2C9-1/2 (16%–25%), CYP2C9-1/3 (12%–17%), CYP2C9-2/3 (1%–6%), CYP2C9-3/3 (1%–3%), and CYP2C9-2/2 (0%–2%).[73,76,79] When ethnic groups were studied individually, the incidence differed for each. The incidence of CYP2C9-2 polymorphism was 20% for whites, 1% for African Americans; however, it has

not been identified in Chinese or Japanese populations.[81] The incidence of the CYP2C9-3 polymorphism was 16.2% for Hispanics, 3.7%–9.2% for whites, 1.7%–2.6% for Asians, and 0.5%–1.25% for African Americans.[81]

Without availability of routine genetic testing, an elevated serum S:R warfarin concentration ratio correlates well with the presence of CYP2C9 polymorphisms. Data from the Herman et al.,[73] Kamali et al.,[76] and Scordo et al.[79] trials show the warfarin S:R concentrations ratios one might expect to find among a sample population: CYP2C9-1/1 (range S:R 0.44–0.63 to 1), CYP2C9-1/2 or 1/3 (range S:R 0.61–0.74 to 1), CYP2C9-2/2 (range S:R 0.8–1.14 to 1), CYP2C9-2/3 (range S:R 0.84–1.47 to 1), and CYP2C9-3/3 (range S:R 2.16–2.65 to 1).[73,76,79] As patients with polymorphisms require lower warfarin doses they often have reduced serum R-isomer concentrations as well. Therefore, an elevated S:R concentration ratio is the distinctive characteristic of probability and may prove to be an inexpensive approach to identify these patients.

Another genetic polymorphism increasing warfarin sensitivity is the vitamin K reductase complex subunit one (VKORC1).[82-86] Warfarin binds the enzyme vitamin K epoxide reductase, the specific protein target being VKORC1 (see Figure 10-1).[87,88] The degree to which these polymorphisms affect warfarin dosing relative to those of the CYP2C9 polymorphisms requires further study as available studies are conflicting, VKORC1 polymorphisms appeared to have a greater impact on dosing by Rieder et al., Wadelius et al., Schalekamp et al., and Bodin et al.[83,86,89,90] However, two studies found CYP2C9 polymorphisms to have a greater impact on warfarin dosing relative to VKORC1 polymorphisms.[82,84] Given multiple variations of these polymorphisms and that both the VKORC1 and CYP2C9 polymorphisms have been identified in the same patient, further study is needed.[90] The study by Reider et al.[83] evaluated the incidence of VKORC1 polymorphisms by specific demographic groups. The specific VKORC1 polymorphisms associated with increased warfarin sensitivity were found in 89%, 37%, and 14% of Asian-Americans, European-Americans, and African Americans, respectively. These findings are consistent with population-based warfarin dosing studies showing Asians often require lower doses, followed by Europeans, who usually require intermediate doses, followed by African descendents requiring larger warfarin doses.[91-94] At least one cause of warfarin resistance is likely associated with mutations of the VKORC1 gene.[95,96] Further investigation is needed to fully understand mutations occurring on VKORC1 gene and their implications on warfarin dosing. In addition to further research on predictors of warfarin sensitivity, more information is needed regarding the development of affordable diagnostic devices that could be selectively used by clinicians to test high-risk patient groups.

Clinical Pearl

The area of pharmacogenomics in relation to warfarin is rapidly evolving. While validated uses of this information to improve direct patient care are not yet available, this may occur in the near future. For example, could genetic genotyping be done on patients to assist in initial warfarin dose selection? Inpatient anticoagulation pharmacists are encouraged to keep up on this cutting edge topic as the information provided is preliminary.

Clinical Pearl

Hospitalized patients often have changes in diet causing fluctuating warfarin requirements and dosing that is distinctly different from their outpatient requirements. Further, enteral and parenteral nutritional supplements containing vitamin K further complicate matters. It is important for pharmacists to follow changes in feeding rates and diets as these influence warfarin dosing.

Diet and Vitamin K

The body converts ingested vitamin K1 into a required cofactor (reduced vitamin K, vitamin KH2 used to synthesize coagulation factors: II, VII, IX, X, and proteins C and S (see Figure 10-1). This production process is not sensitive to warfarin and therefore circumvents warfarin's action of causing a partial vitamin K deficient environment.[97] Consistent vitamin K intake is essential to reduce variability in warfarin dosing.[98,99] For new warfarin patients, dietary consistency is a difficult lifestyle adjustment and suggesting a dietary log in the beginning improves stabilization.[98,100,101] Providing patients a list of foods with a high content of vitamin K is helpful in this task. Available are a number of references that describe the vitamin K content of specific foods.[102,103] Vitamin K is often concentrated in green plant materials such as broccoli; herbals such as green tea; certain oils such as canola; and many hospital nutritional supplements, foods, and

drinks. The message to patients should be to eat the same size and number of servings each week of foods with a high content of vitamin K.

Indications

Given warfarin's long existence, there are many on- and off-label indications supported by clinical trials. Although aspirin is the mainstay for prevention of myocardial infarction (MI), warfarin has generated interesting data. Following MI, patients have a 24% increased DVT risk when not receiving anticoagulation.[104] MI patients occasionally have extended immobility warranting DVT prophylaxis. Warfarin has consistently reduced the risk of pulmonary embolism following MI and less consistently the risk of stroke, recurrent MI, and mortality.[105-107] To quickly summarize, data is best broken down into three evaluated regimens: low intensity (fixed dose 1 and 3 mg or INR < 2), moderate intensity (INR 2–3), and high (INR 2.8–4.8) intensity warfarin. Aspirin plus low-intensity warfarin does not reduce primary outcomes and is associated with a non-statistical increase in bleeding versus aspirin alone.[108-112] Trials comparing aspirin plus moderate-high intensity warfarin show a non-statistically significant reduction of fatal and nonfatal MI versus aspirin alone.[108,113,114] This same regimen showed statistically significant reductions[108,113] and a non-statistically significant reduction[114] favoring combination therapy for the combined endpoint of death, MI, and stroke. Moderate-high intensity warfarin plus aspirin versus aspirin alone has shown an increase risk of bleeding; however, this was often either non-statistically significant increase in major bleeding or a statistically significant increase in minor bleeding.[108,113,114] A review article on warfarin in coronary artery disease showed moderate-high intensity warfarin plus aspirin reduced the combined endpoint of death, MI, and stroke incidence by 54 per 1000 patients at a cost of 16 major bleeds per 1000 patients compared to aspirin alone.[109] The coagulation system remains hyperactive for an extended period following coronary ischemia and MI.[115] There is likely a small population of coronary disease patients who benefit from combination therapy. Patients having atrial fibrillation or possibly those with a significant family history of early coronary disease refractory to usual antiplatelet therapy may benefit from warfarin.

Stroke Prevention in Atrial Fibrillation

Atrial fibrillation (AF) is a growing problem in the United States. Epidemiologic data estimate AF will increase from 2 million in 1995 to over 4 million by 2030.[116] This will have a significant financial and social impact on society due to increased stroke and stroke rehabilitation. U.S. annual incidence of AF induced stroke is approximately 60,000 and growing.[116] Non-valvular AF causes a 5-fold increase stroke risk while valvular AF causes a 17-fold increase in stoke risk (see Table 10-3).[117-122] Strokes resulting from AF are more debilitating than non-cardiogenic strokes. Approximately 71% of first time AF stroke patients either die or have severe permanent neurological impairments.[120] Compounding this problem is underutilization of warfarin providing improved stroke prevention in many patients relative to aspirin. United States data indicate only 20%–44% of AF patients that should receive warfarin actually do.[123-129] Data from a U.S. study site previously involved in an anticoagulation trial for AF, reported 78.8% compliance showing this is a correctable problem.[130] Barriers to appropriate warfarin use in AF include fall risk, inconvenient lab monitoring, interactions, compliance, bleeding risk, and understanding efficacy differences between aspirin and warfarin. Warfarin's superiority over aspirin in moderate to high risk AF has been shown in many studies. Data from two separate meta-analyses have shown the relative risk reduction using warfarin versus aspirin ranges from 36%–46% for all strokes and 46%–52% for ischemic strokes (see Table 10-4).[131-133] Given the variability of stroke rates in AF patients and the apparent reluctance to use warfarin, proper patient selection is important. Patient characteristics with atrial fibrillation and probability of stroke have been evaluated in a number of clinical trials (see Table 10-5).[134-144]

Table 10-3.
Relative Risk of Stroke by Age and Presence of Atrial Fibrillation

STUDY	Mean Age	Stroke Incidence		Relative Risk
		AF	No AF	
Framingham, USA	70 yr	4.1% per year	0.74% per year	5.6
Shibata, Japan	65 yr	5.0% per year	0.90% per year	5.6
Whitehall, UK	60 yr	1.8% per year	0.26% per year	6.9
Reykjavik, Iceland	52 yr	1.6% per year	0.23% per year	7.1

Source: References 120–122.

Table 10-4.

Warfarin vs. Aspirin for Stroke Prophylaxis by Risk Group

Risk Factors	Stroke Incidence with Aspirin	Relative Risk Reduction with Warfarin	NNT♁
Prior Stroke/TIA	10% per year	60% per year	17
High Risk	>4% per year	55% per year	35
Moderate Risk	2%–4% per year	45% per year	75
Low Risk	<2% per year	35% per year	>200

♁ Number treated with warfarin for 1 year instead of aspirin to prevent one stroke

Source: Reference 133.

Table 10-5.

Annual Stroke Rate by the Presence of a Specific Risk Factor

Risk Factor	Percent Range of Annual Stroke Rate	Risk Rating
Prior Stroke/TIA	4%–13% RR 1.9–2.9	High
Women > 75 Years	3.7%–7.1%	High
Systolic BP > 160 mmHg	3.7%–7.1% or RR 2.3	High
Age > 75 Years + History of Hypertension	7.1%	High
Congestive Heart Failure	2.7%–6.8%	High
Age > 75 Years	2.8%	High
History of Hypertension	2.7%–7.6% or RR 1.6–2.2	Moderate-High
Age > 65 Years	2.2%–2.4%	Moderate-High
Diabetes	5.4%–8.6% RR 1.6–1.8	Moderate-High

Source: References 134–144.

Table 10-6.

Antithrombotic Recommendations by Patient and Risk Factor

Patient Type with AF or PAF	Suggested Antithrombotic Without Contraindications	Risk Assessment
Age < 65 years	Aspirin 325 mg daily	No risk factors
Age < 65 years	Warfarin INR 2–3	EF ≤ 35%, history of embolism, hypertension, diabetes, impaired LVH, prior stroke/TIA
Age 65–75	Warfarin INR 2–3 or Aspirin 325 mg daily	No risk factors
Age 65–75	Warfarin INR 2–3	EF ≤ 35%, history of embolism, hypertension, diabetes, impaired LVH, prior stroke/TIA, left atrial enlargement
Age > 75	Warfarin INR 2–3	Without contraindications then regardless

Source: References 141 and 146.

Stroke risk from paroxysmal atrial fibrillation (PAF) or flutter is not much different than chronic AF.[133,135,138,145,146] This is especially true when PAF is accompanied with risk factors such as hypertension, diabetes, mitral stenosis, advanced age, valvular disease, or HF. Sometimes patients are younger and depending on the frequency and duration of irregularity are at lower risk and prophylaxis with aspirin is sufficient. See Table 10-6 for long-term stroke prophylaxis recommendations.

Several strategies exist for cardioversion and how patients are managed is guided by physician/patient preference, time of presentation after onset, and availability of biplane or multiplane transesophageal echocardiography (TEE), and stroke risk factors.[141,146-151] Patients presenting for cardioversion less than 48 hours following onset are considered low risk for left atrial appendage thrombi causing stroke with cardioversion. Patients, however, may not recognize when the AF began and there are other risk factors for stroke to consider. Some studies support early cardioversion in these patients without TEE or prior anticoagulation[144,145] while others enrolling patients with AF less than 72 hours found left atrial thrombi present in 13% of patients, indicating higher than expected risk for stroke.[146] In AF patients presenting less than 48 hours requiring early cardioversion due to hemodynamic instability, cardioversion can be done with or without delay of IV heparin.[141,146] Anticoagulation following cardioversion should be based on patient's stroke risk and certainty of less than 48-hour presentation. If anticoagulation is necessary, warfarin with an INR of 2–3 is recommended for 4 weeks provided patient remains in normal sinus rhythm (NSR).[141,146] AF patients presenting after 48 hours requiring early cardioversion due to hemodynamic instability and without prior anticoagulation (INR 2–3) will require a bolus of IV heparin followed by aPTT-adjusted heparin infusion. These patients also require warfarin INR 2–3 for at least 4 weeks following cardioversion or longer if they revert to atrial fibrillation.[141,146] AF patients presenting after 48 hours or uncertain duration in a stable patient, two options are available. The first being adjusted warfarin INR 2–3 for 3 weeks prior to cardioversion, followed by warfarin INR 2–3 for 4 weeks after cardioversion, assuming NSR is maintained.[141,146] Multiplane TEE allows better visualization of left atrial thrombi predisposing patients to stroke with cardioversion. If high-quality TEE shows no sign of left atrial appendage thrombi, the patient can be placed on IV heparin and cardioverted.[141,146] The presence of left atrial thrombi requires the patient to have 3 weeks of anticoagulation and possibly longer depending on repeat TEE before cardioversion.[141,146] After successful cardioversion, assuming NSR is maintained, patients require warfarin INR 2–3 for 1 month or longer should AF return.[141,146]

DVT Prophylaxis

Warfarin is an effective, inexpensive DVT prophylactic agent at INR 2–3, especially for patients requiring longer durations (i.e., 28–35 days for HIP fracture/replacement or post surgical cancer patients).[152] Slower offset, however, requires earlier coordination for surgical procedures. LMWHs and Xa inhibitors are sometimes cost prohibitive and SC heparin requiring three injections daily for optimal prophylactic effect is uncomfortable. DVT and pulmonary embolism (PE) in hospitalized patients is largely avoidable with prophylaxis, and sometimes these lead to fatality.[153] Surviving DVT patients often have vessel abnormalities causing prolonged symptoms, recurrent DVT, and future increased health costs.[154-158] A hospital's performance on prevention of DVT has the attention of the Joint Commission® and the Agency for Healthcare Research and Quality. Prophylaxis poses only small risk that differs depending on the agent chosen.

Patient risk stratification is important for identifying patients requiring DVT prophylaxis. See Table 10-7 for high-risk patients and DVT incidence by condition. Many inpatient orthopedic procedures, including arthroplasty, require pharmacological VTE prophylaxis regardless of age or risk factors. Warfarin is considered an acceptable

Clinical Pearl

When warfarin is used for DVT prophylaxis, it is typically used in surgical patients requiring longer prophylaxis than routine medical patients. Orthopedics represents an area where warfarin is often used. Why? Orthopedic patients, particularly hip replacement or hip fracture patients, have prolonged DVT risk. The Seventh American College of Chest Physicians Consensus Conference on Antithrombotic Therapy makes a 1A recommendation for extended DVT prophylaxis 28–35 days following hip surgery.[152] Few patients would rather give themselves an injection each day when they could take a pill and have occasional blood draws. Due to delayed warfarin onset, many will bridge high-risk patients (orthopedic surgery with risk factors listed in Table 10-8) with prophylactic doses of heparin or LMWH until the INR is in range.

option for orthopedic surgery DVT prophylaxis.[152] Warfarin's slow onset, even administered the evening before surgery, is unlikely to provide benefit for several days. Studies have shown early anticoagulation, within 12 hours post-op, reduces risk of DVT.[159-167] Initiation of LMWH or fondaparinux before orthopedic surgery or in close proximity 2–6 hours) post operatively is associated with increased bleeding, but this may not apply to SC heparin.[164,165] A review article on DVT prophylaxis duration following various surgeries has been published.[168] Admission types requiring pharmacological DVT prophylaxis with one or no risk factors include: trauma, CHF, bed confinement, critical care, spinal cord injury, and moderate general surgery age 40–60 years. Patients require risk factor assessment as they often have more than one risk factor and each adds cumulative risk for DVT; see Table 10-8 for DVT risk factors.[169] To improve patient safety, institutions may develop a DVT prophylaxis protocol for patient selection.

DVT Treatment

The incidence of DVT and PE is approximately 145 per 100,000 and 69 per 100,000 persons respectively.[170] Complications of untreated DVT include PE, recurrent DVT, subsequent venous valvular dysfunction, residual partial occlusion, and thrombophlebitis.[171,172] The most significant is PE, being the primary cause of death in 100,000 persons/year and a co-morbid contributor of an additional 100,000 deaths.[173] Untreated pulmonary embolism can lead to death, pulmonary hypertension, and right sided heart failure. Goals for treatment include: prevent PE, arrest clot growth, stabilize patients with PE, and prevent recurrent venous thromboembolism (VTE). This requires rapid anticoagulation and on rare occasions a thrombolytic for PE causing hemodynamic compromise. It is important to inquire about recent traumas, surgery, new or changed medications predisposing patients to VTE (i.e., estrogen modifiers) and family history of VTE, as these

Table 10-7.
Risk of DVT From Hospitalization

Risk	Hospitalized Group	Incidence of DVT
Low	Medical patients	10%–20%
Moderate	General surgery Gynecological surgery (major) Neurological Urological surgery (major)	15%–40%
High	HIP or knee (arthroplasty, replacement, fracture) Stroke	20%–60%
Highest	Trauma (major) Spinal cord injury	40%–80%
Variable	Critical care	10%–80%

Source: Reference 152.

Table 10-8.
Cumulative Individual Risk Factors for VTE

Advanced age	Central venous catheter	Acute illness
Contraceptives	COPD/bronchitis/severe pneumonia	Chemotherapy
Immobility	Estrogen replacement	Trauma
Malignancy	Hypercoagulable disease	Heart failure
Obesity	Inflammatory bowel disease	Surgery
Prior VTE	Peripheral vascular disease	Varicose veins
Smoking	Selective estrogen receptor modifiers (SERMS)	Spinal cord injury

Source: Reference 152.

Table 10-9.
Hypercoagulable Conditions

Serum Deficiencies	Gene Mutations	Serum Markers	Other
Antithrombin	Factor V Leiden	⇧ Factor VIII, IX, XI	Activated protein C resistance
Protein C	Prothrombin 20210A	Antiphospholipid antibodies	
Protein S		⇧ Homocysteine	
Plasminogen		⇧ D-dimer after complete anticoagulation course	
		⇧ Lipoprotein (a)	
		⇧ Thrombin-activatable fibrinolysis inhibitor	
		⇧ Thrombin generation > 400 nM after anticoagulation completion	

Source: References 174 and 175.

determine the duration of anticoagulation therapy (idiopathic versus causative insult) and whether patients may benefit from hypercoagulable studies to identify thrombophilias. Approximately 30% of patients with idiopathic DVT or PE have a thrombophilia, especially those presenting younger than 50 years.[174,175] Known hypercoagulable states and at risk serum markers can be found in Table 10-9.

Anticoagulation may be started prior to completion of diagnostic studies in symptomatic patients. Many institutions after baseline labs start a therapeutic dose of an injectable anticoagulant. Using IV heparin versus LMWH or X-a inhibitor during the diagnostic period allows faster offset of action if VTE is ruled out. Once studies confirm VTE, the patient can be started on warfarin. Whether patients continue on IV heparin or are converted to LMWH, Xa-inhibitor, or high dose SC heparin as bridge to therapeutic warfarin is the clinician's choice.[176,177]

Clinical Pearl

Outpatient treatment of VTE is effective and supported by literature as providing significant cost savings and reduced length of stay.[178-186] Pharmacy inpatient anticoagulation services working together with outpatient counterparts can ensure success of this program by providing patient education and follow-up allowing same- or next-day discharge. The financial savings generated by such a program will help justify the need for pharmacists to provide these services.

Recurrent VTE at 2, 5, and 8 years is 17.5%, 25%, and 30% respectively.[170-172,176] Patients with malignancy or hypercoagulable states have a hazard ratio 1.7 and 1.4 for recurrent VTE respectively.[176] Approximately 5% of patients will die as a result of the second VTE event.[187] The duration of anticoagulant therapy should be patient specific and depends on a number of factors including presence of malignancy, idiopathic versus identifiable etiology, first episode versus a recurrent event, and the presence of a known hypercoagulable condition. See Table 10-10 for the recommended duration of anticoagulation based on patient specific criteria. Other considerations in determining duration of treatment may include: elevated D-dimer levels despite usual duration, residual occlusion using compression ultra sonography despite appropriate duration, and elevated (>400 nM) thrombin generation.[176,188-190]

Valvular Heart Disease and Prosthetic Heart Valves

Systemic embolism due to valvular disease has decreased secondary to reduced rheumatic heart disease, improved prosthetic valve technology, improved techniques in valve repair, and increased utilization of anticoagulation.[191] Valvular disease without anticoagulation results in devastating outcomes and these are the most fragile of anticoagulation patients. Without proper anticoagulation, patients are at risk for stroke and may also require valve replacement or repair procedures having survival risks and loss of productivity and quality of life. Therefore, it is important these patients are well managed long-term and during peri-procedural interruptions of anticoagulant therapy. When

Table 10-10.

Recommended Treatment Duration for VTE

DVT/PE Classification and Frequency Group	Suggested Duration of Therapy	Target INR
1st Occurrence–Identified, Modifiable Cause	3 months	2–3
1st Occurrence–with Malignancy	LMWH 3-6 months then warfarin until cancer is resolved	2–3
1st Occurrence–Idiopathic or 1 Thrombophilic Condition	6–12 months	2–3
1st Occurrence–Antiphospholipid Syndrome or ≥ 2 Thrombophilic Conditions	12 months	2–3
Recurrent VTE	Lifetime	2–3
Recurrent VTE + Antiphospholipid Syndrome	Lifetime	2.5–3.5

Source: References 40 and 176.

valvular patients have AF, the risk of systemic emboli increases three to seven times those in normal sinus rhythm.[191] Other risk factors include: heart failure, previous thromboembolism, age (50–69 and ≥70), permanent pacemaker, hypertension, left atrial size ≥ 50 mm, size or severity of valvular lesion, smoking, diabetes, and hyperlipidemia.[191-194] Often, more important is the type and location of the prosthetic heart valve, mechanical valves are more thrombogenic than bioprosthetic valves, yet both are more thrombogenic than native valves.[191-194] Earlier model mechanical valves, like the ball cage, Starr-Edwards, or Bjork-Shiley were highly thrombogenic compared to single tilting disc valves and newer bileaflet valves.[191,192,194] At a goal INR of 2–2.9, incidence of thromboembolism per year was 0.5%, 0.7%, and 2.5% for the bileaflet, tilting disc, and cage ball or cage disc valves, respectively.[195] Prosthetic valves in the mitral position are more thrombogenic than the same valve in the aortic position.[191,192,194] Without anticoagulation, the bileaflet St. Jude valve caused systemic emboli 22% per year in the mitral position versus 12% in the aortic position.[196] Table 10-11 compares the incidence of systemic embolism by valve type and location. Interpret this data carefully as outcomes were extracted from different trials using similar INR ranges with differences in the time patient's spent in range. The same holds true for major bleeding events listed in the final column, these values are best fit estimates.

Patients may receive bioprosthetic or mechanical heart valves; this decision is based on life expectancy and willingness to take life-long warfarin. Bioprosthetic valves have shorter life expectancies (~15 years) but allow patients with no additional risk factors like AF to take aspirin after 3 months of warfarin. Bioprosthetic valves can also be placed in either the aortic or mitral position and are less thrombogenic than mechanical valves. Antithrombotic prophylaxis is the same for the three types of bioprosthetic heart valves; transplanted human, porcine, and pericardial (bovine). Recommendations for anticoagulation are provided in Table 10-12.

Recommendations for antithrombotic therapy in patients with valvular disease, not including prosthetic valves, are covered in Table 10-13. Most patients with valvular disease plus AF require warfarin unless contraindicated. There are other conditions, like septal wall defects, where antithrombotic decisions remain unclear. Exercise caution when labeling treatment failures; adequate doses, therapeutic levels, and dosing compliance must be verified for recent past not just present day. Combination therapy with aspirin is always associated with increased bleeding requiring extra caution when making warfarin dose adjustments. These patients also require additional instruction regarding compliance and changes in medications.

Ischemic Stroke

Stroke prevention with warfarin is limited to patients with AF, hypercoagulable states, or valvular heart disease. Infrequent exceptions may also include septal wall defects or aspirin failures. The majority (85%) of strokes are ischemic and 20% originate within the heart, often secondary to AF.[197] Unfortunately, 30% of ischemic strokes have an unidentifiable origin following a thorough evaluation by neurology and cardiology.[197] While in theory, it seems reasonable to treat patients who present with acute strokes secondary to AF with full dose anticoagulation, randomized trials do not support this practice.[198-204] Other than unquestionable benefits of DVT prophylaxis in acute ischemic

Table 10-11.
Incidence of Systemic Thromboembolism by Valve Type, Location, and INR

Specific Valve Type	Valve Location	Target INR Ranged Desired	Range TE/year	Estimated ❖ Major Bleeding
St. Jude Mechanical Bileaflet	Mitral Position	1.8–2.8	0.4%–6.5%	N/A
		2.5–3.5	3.4%–4.7%	1.2% /year
		2.8–4.5	2.2%–2.9%	0.4%–6.6% /year
	Aortic Position	1.8–2.8	0.7%–3.9%	N/A
		2–3	0.8%–1.9%	4% / year
		2.5–4.5	0.8%–3.0%	2.0%–6.6% /year
Medtronic Hall	Mitral Position	2.0–3.0	N/A	4%/year
		2.5–3.5	2.1%–4.7%	1.2%/year
		3.0–4.5	1.5%	0.4%–6.6% /year
	Aortic Position	2–3	1.3%	4%/ year
		2.5–3.5	N/A	1.2%/year
		3.0–4.5	0.7%	0.4%–6.6%/year
Bjork Shiley Spherical Disc	Mitral Position	2.0–4.5	2.6%	1.6%/year
		3.0–4.0	1.5%	N/A
	Aortic Position	2.0–4.5	1%	1.6%/year
		3.0–4.0	0.4%	N/A
Bjork Shiley Convexo Concave	Mitral Position	3.0–4.0	2.1%	N/A
	Aortic Position	3.0–4.0	0.5%	N/A
Sorin Mono	Mitral Position	2.5–4.0	1.7%	N/A
	Aortic Position	2.5–4.0	0.9%	N/A

❖ Each value/range extrapolated/best fit using multiple trials with varying INR compliance.
Source: References 191 and 192.

stroke, guidelines by the American Heart Association and the American Academy of Neurology do not support full dose anticoagulation immediately following due to increased hemorrhagic progression in the early phase.[205,206] The majority of data for non-cardiogenic stroke, including major intracranial artery stenosis, do not support warfarin over aspirin.[207,208] There are small subsets where warfarin has not been evaluated in well-designed trials; however, appear to benefit from warfarin based on nonrandomized, non-comparator trials. These populations include cervical artery dissection, major carotid stenosis awaiting endarterectomy, antiphospholipid antibody, and prothrombotic disorders.[197] Patients with idiopathic stroke and underlying mobile aortic arch thrombi may also benefit from warfarin.[197]

Antiphospholipid Antibody Syndrome (APS)

The autoimmune disorder APS is defined by the presence of antiphospholipid antibodies in a patient with arterial or venous thrombosis or an adverse outcome during pregnancy.[209,210] Generally speaking, there are two types of antiphospholipid antibodies (APLAs); lupus anticoagulants and anticardiolipin antibodies. Lupus anticoagulants are known to prolong phospholipid-dependent clotting assays.[211-213] APLAs are commonly found in approximately 30%–50% of systemic lupus erythematosus (SLE) patients. This is in contrast to 1%–10% of the general population.[214,215] APLAs are found in 4%–21% of the general population presenting with thrombosis.[216,217] During a 6-year follow-up of APS patients, the incidence of VTE was 29%–55% with nearly half being pulmonary embolism.[218] In a study using stricter criteria for APS diagnosis, the incidence of thrombosis was 32%.[219] In patients less than 50 years presenting with stroke, approximately 50% were found to have APLAs.[220] There are a number of theories why APS patients are predisposed to thrombotic events. These include: increased endothelial cell activation, increased oxidative injury of vascular endothelium, interference with phospholipid-binding proteins involved in regulation of the clotting cascade, increased activa-

Table 10-12.
Antithrombotic Recommendations for Patients with Prosthetic Heart Valves

Prosthetic Heart Valve by Type, Location, and Risk Conditions	Antithrombotic Therapy	Duration	INR
Mechanical Valve (except ball cage) Aortic Position	Warfarin + UF/LMWH bridge 2 in range INRs	Indefinite	2–3
Mechanical Valve Mitral Position	Warfarin + UF/LMWH bridge 2 in range INRs	Indefinite	2.5–3.5
Ball Cage Valve (any position)	Warfarin + aspirin 75–100 mg daily	Indefinite	2.5–3.5
Bioprosthetic Valve–No Risk Factors Aortic Position	Aspirin 80–100 mg daily or ↓	3 months	N/A
	Warfarin + UF/LMWH bridge 2 in range INRs	3 months, then aspirin 75–100 mg	2–3
Bioprosthetic Valve–no risk factors Mitral Position	Warfarin + UF/LMWH bridge 2 in range INRs	3 months, then aspirin 75–100 mg	2–3
High Risk Conditions or Treatment Failures with Prosthetic Heart Valve			
Mechanical Valve (Any Position) + AF, MI, Left Atrial Enlargement, Endocardial Damage, Low EF, Systemic Embolism at Goal INR	Warfarin + aspirin 75–100 mg daily	Indefinite	2.5–3.5
Bioprosthetic Valve (Any Position) with History of Systemic Embolism	Warfarin + UF/LMWH bridge 2 in range INRs	3–12 months	2–3
Bioprosthetic Valve (Any Position) Left Atrial Thrombus at Surgery	Warfarin + UF/LMWH bridge 2 in range INRs	Indeterminate	2–3
Bioprosthetic Valve (Any Position) Atrial Fibrillation	Warfarin + UF/LMWH bridge 2 in range INRs	Indefinite	2–3

Source: References 191, 192, and 194.

tion of platelets, and possibly inhibition of protein C and S activity.[221-223]

The presence of APLAs in and of itself is not an indication for warfarin. It is likely patients with SLE and APLAs have higher risk than patients having only APLAs.[224,225] Based on consensus opinion, asymptomatic APLA positive patients without history of thrombosis may benefit from aspirin 81 mg daily.[226] Based on consensus recommendations, pregnant patients with APLAs and one previous late pregnancy loss or ≥ two early pregnancy losses, warrants treatment with aspirin 81 mg daily and prophylactic doses of LMWH or unfractionated heparin.[227] Initiation of aspirin 81 mg daily should begin during trials of conception and prophylactic doses of LMWH or unfractionated heparin should be started when viable pregnancy is confirmed and continued through late into the final trimester.[228] Treatment recommendations for VTE with APS can be found in Table 10-10.

Dose Management

Secondary to warfarin's delayed onset of action, initiation and management of warfarin often requires management of injectable anticoagulants. For many indications it is important that initiation of warfarin be overlapped or bridged with an injectable anticoagulant. Both should be overlapped for at least 4–5 days and the INR should be in range and stable before discontinuation of injectable anticoagulation.[39,40,176,191] Since warfarin has no action on existing clotting factors, this overlap period allows for depletion of existing clotting factors while the injectable anticoagulant immediately inhibits clotting factors currently present in the circulation. Extended overlap with injectable anticoagulants, in theory could increase a patients risk for bleeding. Given an elevated INR reflects a reduced concentration or quantity of functional clotting factors, continuation or initiation of injectable anticoagulants while therapeutic on warfarin, means inhibiting the activity of an already reduced quantity of functional clotting factors.

In patients taking warfarin prior to admission, it is important to obtain patient's dosing history to know warfarin requirements in a healthy state. The patient's indication for warfarin is also important to

Table 10-13.

Antithrombotic Recommendations for Patients with Valvular Heart Disease

Heart Valve Disease and Risk Conditions	Antithrombotic Therapy	Duration	INR
Mitral Valve Disease in Normal Sinus Rhythm with Left Atrial Diameter < 5.5 cm	No warfarin, possibly aspirin 75–100 mg daily	N/A	N/A
Rheumatic Mitral Valve with AF or History of Systemic Embolism	Warfarin without aspirin	Indefinite	2–3
Mitral Valvuloplasty Procedure No Risk Factors or Events	Warfarin	3 wks prior and 4 wks after	2–3
	Then no warfarin or aspirin	Indefinite	N/A
Mitral Annular Calcification Without Systemic Embolism	No warfarin or aspirin	Indefinite	N/A
Aortic Valve/Aortic Arch Disorders Without Embolism or Indication	No warfarin or aspirin	Indefinite	N/A
Endocarditis and Mechanical Valve Without Contraindications — Aortic	Warfarin + UF/LMWH bridge 2 in range INRs	Indefinite	2–3
Mitral	Warfarin + UF/LMWH bridge 2 in range INRs	Indefinite	2.5–3.5
Nonbacterial Endocarditis and Systemic or Pulmonary Emboli	IV unfractionated heparin	Unspecified	N/A
Endocarditis with Disseminated Cancer or Debilitating Disease with Aseptic Vegetations	IV unfractionated heparin	Unspecified	N/A
High Risk Conditions or Treatment Failures with Valvular Heart Disease			
Rheumatic Mitral Valve with AF or History of Systemic Embolism and Systemic Embolism at Goal INR	Warfarin + aspirin 75–100 mg daily or dipyridamole/clopidogrel	Indefinite	2–3
Mitral Valve Disease in Normal Sinus Rhythm with Left Atrial Diameter >5.5 cm	Warfarin	Indefinite	2–3
Mitral Valvuloplasty with Unexplained TIA or Stroke	Aspirin 50–162 mg daily or dipyridamole/clopidogrel	Indefinite	N/A
Mitral Valvuloplasty with TIA or Systemic Embolism Despite Antiplatelet Therapy	Warfarin	Indefinite	2–3
Mitral Annular Calcification with Non-Calcific Systemic Embolism	Warfarin	Long-term Unspecified	2–3
Aortic Valve/Aortic Arch Disorder with Mobile Aortic Atheromas and Aortic Plaques > 4 mm by TEE	Warfarin	Unspecified	2–3

Source: References 191–194.

Clinical Pearls

Data on how often INRs are required in the inpatient setting is scarce. Considering the instability of patients in high acuity settings, increased probability of medication interactions, and changes in dietary intake of vitamin K, many hospitals often have policies requiring daily INRs and daily warfarin dosing. This ensures patients, at least in theory, are reassessed daily. This type of policy leads to unnecessary INR checks, however, it is likely better than the alternative which is a lack of proper oversight of this high-risk medication.

Many hospitals standardize their warfarin administration time to the evening so dose adjustments can be made the same day as an INR check and to match when most patients take warfarin at home. When designing these systems, it is important to assure enough time has passed, particularly after the first dose of warfarin, before INR is checked. Most hospitals try to assure at least 12 hours have passed.

determine appropriate therapeutic range. Medication changes occur frequently in hospitalized patients therefore medication interaction screening is required daily. Hospitalized patients are also more likely to experience significant changes in dosing requirements secondary to nutritional feedings and changes in clotting factor metabolism or production related to fever, thyroid, liver disease, decompensated heart failure, or other diseases.

There is much debate regarding the most appropriate way to initiate warfarin and dose selection. The benefits of obtaining an early therapeutic INR include: reduced length of stay; reduced exposure to heparin and possibly HIT; reduced expense of LMWH, and reduced heparin monitoring. Risks that must be weighed against these benefits include: overshooting desired INR, risk of bleeding associated with elevated INR, cost and inconvenience of increased monitoring associated with elevated INRs, delayed discharge secondary to elevated INR, and a clouded picture of patient's maintenance dose when loading doses are used. Use of excessive (20-mg) loading doses is not recommended, even 15-mg doses have not been studied in well-designed clinical trials.[40] The Coumadin® package insert recommends initiation of 2–5 mg per day and adjustment based on INR determinations.[229] The initiation dose should take into consideration acuity of the indication and warfarin sensitizers such as age, gender, weight, ethnic background, bleeding risks (i.e., postoperative), nutritional status, presence of interacting medications, and illnesses such as liver disease or heart failure. In contrast to younger patients, older patients require lower doses, more often become supratherapeutic, and take longer to return to the desired INR.[230-236] In addition, elevated INRs are more likely to cause bleeding in older versus younger patients.[237-240] Garcia evaluated 12,202 patients finding a 0.4-mg decrease in weekly maintenance dose for each additional year of age.[241] Furthermore, for any given age, men required 4.5 mg more warfarin per week than women.[241] The study showed a 5-mg daily dose would exceed the average maintenance for 82% of women and 65% of men older than 70 years.[241] Warfarin dose requirements by patient weight didn't correlate as well as gender or age however, patients greater than 234 pounds required larger maintenance doses.[241]

A number of warfarin dosing nomograms have been evaluated. These studies have important differences when interpreting results including: enrollees' age, inpatient versus outpatient, gender mixes, co-morbidities, and controlling for variables known to affect warfarin sensitivity.[242-249] With the exception of the Gedge study,[243] a summary of trial results are found in Table 10-14. The inpatient study by Gedge (Table 10-15) was interesting in that a single 10-mg dose was compared to initiation with two 10-mg doses. Warfarin loading doses are linked to increased, although non-significant, increases in bleeding.[246, 247] These studies however, were not sufficiently powered to detect statistically significant increases in bleeding.[246, 247] Readers are

Clinical Pearl

Inpatient anticoagulation pharmacists need to identify warfarin sensitization factors when initiating and managing warfarin. Factors include, interacting medications, elderly, malnutrition, and disease states such as heart failure. For these reasons, acutely ill patients starting warfarin should be initiated on 5 mg of warfarin or less per day.

referred to these articles to make their own evaluation regarding the nomograms; however, caution is advised regarding the use of initiation doses greater than 5 mg in high bleeding risk patients.

Initiating 7.5 mg of warfarin in an elderly post operative female may result in major bleeding and over-shoot the desired INR delaying discharge. In patients requiring acute anticoagulation, it is sug-

Table 10-14.

Warfarin High Dose vs. Low Dose Initiation Nomograms

Study	Mean Age	INR	10 mg Nomogram	5 mg Nomogram	p value
Harrison[244]	N/A	2–3 @ 36 h	6 (24%)	1 (4%)	N/A
		> 2 @ 36 h	11 (44%)	2 (8%)	0.005
n = 25 10 mg		> 3 @ 36 h	5 (20%)	1 (4%)	N/A
n = 24 5 mg		2–3 @ 60 h	9 (36%)	10 (42%)	N/A
		> 2 @ 60 h	18 (72%)	10 (42%)	N/A
		> 3 @ 60 h	9 (36%)	0 (0%)	0.002
Kovacs[245]	55.5 years	Mean to INR > 1.9	4.2 days	5.6 days	<0.001
		< 2 or >3 @ 1 week	N/A	N/A	N/A
n = 104 10 mg		Total INRs < 2 or >3 in 4 weeks	186	207	>0.2
n = 97 5 mg		2–3 @ day 5	86 (83%)	45 (46%)	<0.001
Crowther[242]	~ 66 years	<2 @ day 3	43%	44%	N/A
		2–3 @ day 3	33%	50%	N/A
n = 21 10 mg		> 3 @ day 3	24%	6%	N/A
n = 31 5 mg		<2 @ day 5	15%	8%	N/A
		2–3 @ day 5	69%	88%	N/A
		> 3 @ day 5	15%	4%	N/A
O'Connell[246]		<2 @ day 2	88%	84%	N/A
		2–3 @ day 2	0%	6%	N/A
n = 40 *9 mg = 72.4 yr		> 3 @ day 2	5%	0%	N/A
n = 33 *≤ 5 mg = 77.3 yr		Time to INR > 2	3 days	3.4 days	0.38
*doses above are means		<2 @ day 4	60%	48%	N/A
		2–3 @ day 4	10%	24%	N/A
		>3 @ day 4	18%	15%	N/A
		≥1 INR @ ≥ 4	21%	28%	0.54
Quiroz[247]	~ 50.5 years	2 INRs > 1.9	5 days	5 days	N/A
		Mean INR @ day 5	2.2	2	N/A
n = 25 10 mg		>2 @ day 3	favored		<0.01
n = 25 5 mg		>2 @ day 4	favored		<0.01
		2–3 @ day 5	56%	52%	> 0.5
		2–3 @ day 10		favored	<0.01
		2–3 @ day 11		favored	<0.01
		2–3 @ day 14		favored	<0.01
		>3 overall	14.5%	3.7%	<0.001

Table 10-15.

Warfarin High Dose vs. Modified High Dose Initiation Nomograms

Study	Age	INR	10 mg × 2 doses	10 mg × 1 doses	p value
Cedge[243] n = 120	65–75 yr n = 30 10 mg × 2 doses	INR > 4.5 in 8 days	20%	3%	< 0.05
	n = 30 10 mg × 1 doses	Time with INR 2–3	2.7 days	3.0 days	0.03
		Time to INR >2	3.8 days	4.6 days	0.03
	> 75 yr n = 30 10 mg × 2 doses	INR > 4.5 in 8 days	37%	3%	< 0.01
		Time with INR 2–3	2.4 days	2.9 days	0.04
	n = 30 10 mg × 1 doses	Time to INR > 2	3.5 days	4.5 days	0.003
	Combined n = 120	Doses held in 8 days	59 held doses	18 held doses	N/A

gested to bridge with injectable anticoagulant rather than use excessive warfarin doses. The clinician should obtain a thorough patient history to identify drug interactions, nutritional status, liver disease or heart failure, herbal use, history of bleeds or thromboembolic events, and patient's previous warfarin dosing history if available.

Laboratory Monitoring

Warfarin intensity was originally reported in prothrombin time (PT), the seconds increasing corresponding to a reduction in factors II, VII, and X. Although warfarin inhibits factor IX production, the PT does not measure factor IX.[40] The PT is obtained by adding calcium and thromboplastin to the patient's serum in a citrated plasma tube.[40, 39] Due to variation in prothrombin time results from different labs using different thromboplastin agents, it became necessary to standardize prothrombin time ratio so a given sample provided reproducible results at different labs. One of these strategies was the INR measurement adjusting for thromboplastin reagent sensitivity as determined by the International Sensitivity Index (ISI). The INR was adopted in 1982 and was the beginning of improvements towards a standardized measurement of warfarin intensity. The INR calculation = (patient prothrombin time/mean prothrombin time)[ISI].

Another improvement for warfarin monitoring was improved sensitivity of thromboplastin reagents. The lower the ISI value the more sensitive the thromboplastin. In 1992 the ISI values were 1.4 to 2.8 for most U.S. laboratories.[250-253] Shortly thereafter, recombinant DNA technology allowed for more sensitive thromboplastin reagents with ISI values of 0.9 to 1.[254] Another variable for INR results is the concentration of citrate used in collection tubes and filling the tube with the proper blood volume.[255, 256] Citrate concentrations generally range from 3.2%–3.8%; a higher concentration caused by under-filling the tube can cause an elevated INR.[255] The likelihood of this problem may be reduced by using 3.2% citrated plasma tubes and insuring appropriate blood volume is collected in the tube.[40] Automated analyzers and their calibration methods can also affect the reliability and reproducibility of INR results, for a more in-depth review the reader is referred to the following citations.[257-266]

It is important to understand INRs for patients with lupus anticoagulant, particularly those with prothrombin antibodies, can be falsely elevated.[211-213, 267, 268] The degree of false elevation varies according to the reagent used.[211, 212, 268] Variation of INR results may be minimized using standardized plasma samples during calibration and using local analyzer specific ISI values.[269] Other methods for monitoring or validation of usual INR results have been investigated for lupus anticoagulant and include: measuring prothrombin activity or native thrombin, prothrombin and proconvertin test, and measuring chromogenic factor X activity.[40, 211, 270]

Clinical Pearl

Nomograms can be used to develop institution protocols/guidelines; however, nomograms do not take into account the rapid changing status of the hospitalized patient. Pharmacists require the ability to deviate from the nomogram when their clinical judgment deems this necessary to assure they are treating the patient, not the numbers.

Management of Non-Therapeutic INRs

Elevations in INR are broadly categorized as those requiring warfarin dose adjustments versus warfarin reversal and elevations complicated by serious bleeding versus those involving life threatening bleeding.[40] Management is very patient- and case-specific, and controversy also exists given the number of available options and lack of well-designed trials comparing these options.[40] These decisions can be further complicated by supply issues with prothrombin-complex concentrates (PCC).

Among the worst bleeding events secondary to warfarin are intracranial hemorrhages (ICH). ICHs are the most fatal of strokes with a mortality rate of 30%–55% and in warfarin patients this increases to 67%.[271-274] The objective is to stop early expansion occurring in approximately 40%, as continuation of bleeding into the hematoma is a predictor of death.[275, 276, 277] ICHs with warfarin are at greater risk for expansion; 50% versus 18%–38% in those without anticoagulation.[275, 276, 278]

Although there is a black box warning for IV vitamin K due to anaphylactic reactions, life threatening bleeding is a justifiable cause to use this route.[40, 279-281] Incidence of IV vitamin K anaphylactic reactions is low and is estimated to be as few as three cases per 10,000 doses.[280,282] Vitamin K by the IV route works in less than 4 hours and is both faster and more potent than SC, IM, or oral routes.[281,283,284] In serious and life-threatening bleeding, it is recommended that vitamin K 10 mg by slow (30 minutes) IV piggyback infusion be supplemented with fresh frozen plasma (FFP) or PCC.[40] In urgent cases and/or where there are supply issues with FFP or PCC, recombinant factor VIIa can be considered as an alternative to PCC.[40] In bleeding patients anticoagulated with warfarin, administration of vitamin K is required to maintain sustained reversal and prevent early re-bleeding.[40,285,286]

Fresh frozen plasma (FFP) contains clotting factors and has been used effectively to augment the affects of IV vitamin K in patients with serious bleeding related to warfarin. FFP is commonly ordered as 2–6 units; however, it may also be dosed at 10–15 mL/kg or more for extreme bleeding cases.[287] Newer alternatives have overcome shortcomings of FFP; however, the cost of these alternatives and supply issues are problematic. A disadvantage of FFP is requirement for thawing and compatibility testing; this can delay initiation without early coordination between the physician, unit, and lab. Another FFP disadvantage is the low concentration and content variability of individual clotting factors.[286, 288, 289] The low concentration of clotting factors in FFP requires large volumes ranging from 800–3500 mL to achieve INRs ≤ 1.4.[288,290-293] For patients with heart failure and other volume-sensitive patients, this may require slower administration and aggressive diuresis. Rare adverse events of FFP include allergic reactions, blood-borne infections, citrate toxicity, and transfusion-related lung injury.[294,295] Nonetheless, FFP when administered with IV vitamin K is effective for management of life threatening bleeding.[40,287,288,290,296] In using this combination, early patient presentation and rapid administration of both improves early reversal of warfarin.[288,290]

Prothrombin-Complex Concentrate (PCC) provides a concentrated supply of vitamin K dependent clotting factors II, VII, IX, and X. PCC does not require compatibility testing or thawing before use.[286,297] Secondary to virus inactivation, PCCs have a lower risk of infection unless available FFPs contain methylene blue or are solvent detergent treated FFPs.[297] There are differing opinions regarding dose of PCCs; the U.K. guidelines for warfarin reversal recommends 50 units/kg.[298] Some studies suggest dose should be based on INR. One study used 25 units/kg for INRs between 2–3.9, 35 units/kg for INRs between 4–5.9, 50 units/kg for INRs > 6.[288,299] Other studies showing successful reversal have used a standard dose of 30 units/kg or even smaller doses such as 500 units were reported effective in elderly patients.[300,301] Dosing differences may partly be explained by varying quantities and type of individual clotting factors in these products. Some contain equal amounts of factors II, VII, IX, and X where others may contain varying quantities II, IX, and X.[297] Package inserts are often helpful in providing detailed information regarding quantities of each factor and dosing. Several trials indicate PCCs more rapidly correct the INR than administration of FFP.[288,302,303] This may be related to the FFP dose or late initiation, slower FFP administration, and varying doses or routes of adjunctive vitamin K. Given these differences, nothing remains crystal clear when selecting an adjunctive agent to IV vitamin K for reversal. Disadvantages of PCCs include: cost, occasional supply issues, DIC development, thrombosis potential in high-risk patients, and lack of standardized dosing.[286,297,304-307]

Recombinant factor VIIa is another adjunctive agent that may be combined with IV vitamin K.

Recombinant VIIa reverses anticoagulation by activating factors IX, X, and II. Concerns whether there are sufficient quantities of these factors in patients receiving warfarin requires further study. Possibly more concerning is the recently published article by O'Connell[308] describing their review of 431 adverse drug events associated with Recombinant VIIa submitted to the FDA March 1999 to December 2004. Of the 431 reports, 185 describe thrombotic events warranting further investiga-

tion, given underreporting of ADRs, and the need to determine the actual occurrence rate.[308] In the Mayer trial 309 combined arteriole and venous thrombotic events were 2%, 6%, 4% and 10% for the placebo, 40 mcg/kg, 80 mcg/kg, and 160 mcg/kg groups, respectively. Recombinant VIIa has been studied in hemorrhagic stroke; however, it is important to note these studies excluded patients with history of thrombosis and those taking warfarin.[309,310] These results, therefore, do not provide support for factor VIIa in warfarin patients with ICH. Sorensen[311] evaluated warfarin patients with CNS bleeds (n = 6) and (n = 1) at risk for ICH. Admission INRs were 2.9 to 4.1 for six patients and greater than 7 for one. All but two patients received IV vitamin-K, 10 mg IV x 4 patients and 1 mg IV x 1 patient. One patient had not received warfarin in the previous 9 days having an INR of 3.6. Three patients received FFP, 2 units each. INRs following above interventions were less than 2.8 for four patients, less than 4 for two patients, and 6.6 for the seventh patient. Six of seven patients underwent neurosurgical drainage of hematomas after receiving a bolus of 10–40 mcg/kg Recombinant VII, for an intended target INR ≤ 1.5. One patient who did not receive vitamin K preoperatively required three bags of FFP to maintain an INR < 2.0 post-operatively. This study indicates recombinant VIIa monotherapy is not sufficient for warfarin patients and must be administered with IV vitamin K given factor VIIa's short half-life of 2.3 hours.[312] Freeman[291] evaluated warfarin patients with acute ICH (n = 7) who required immediate reversal of warfarin. Admission INRs were ≥ 2.9 for six patients and 5.6 for the seventh. All but one received vitamin K; however, three of six patients were given less than the recommended 10-mg dose. Only one vitamin K dose was given IV, two were given SC, and routes on the other three were not stated. Six of seven patients received a mean dose of 7.2 units of FFP. The mean INR prior to recombinant VIIa was 2.7 and decreased to 1.08 after administration of 62 mcg/kg. It is interesting to note the patient presenting with an INR of 5.6 did not reach an INR less than 2 before 18 hours. The reader is referred to other studies investigating the role of recombinant VIIa for patients experiencing serious or life threatening bleeding.[292,313-316] Possible limitations of recombinant VIIa is that it may not completely reverse warfarin effects, especially those with elevated INRs, and also does not appreciably increase the activity level of factors II, IX, and X following administration.[317,291,314] Concerns regarding wide acceptance of recombinant VIIa for warfarin reversal include: limited data of factor VIIa in warfarin patients, emerging risks for thrombosis with added patient experience, and an estimated acquisition cost of $5,714 per dose at 40 mcg/kg in a 70-kg patient.[286,308,318]

Clinical Pearl

Injectable vitamin K can be given orally when doses less than 2.5 mg are desired.

Routine management of moderately elevated INRs requires holding one or more doses and/or small doses of oral vitamin K. Trials show the oral route is less variable, more reliable, and safer than the other routes.[40,279] The daily risk of bleeding secondary to a temporary elevated INR is low and more frequent monitoring is an option.[40]

Elevated INRs less than 5 and without significant bleeding can generally be managed by omitting a single dose and repeating the INR next day. Warfarin can be resumed at a lower dose when the INR is close to or in the desired range. The amount of dose reduction is based on the cause and whether it is reversible, such as a drug interaction, where patients can be switched from ciprofloxacin or sulfamethoxazole to cephalexin for UTI.

INRs greater than 5 but less than 9 and without significant bleeding can be managed by omitting one or two doses guided by daily INRs. Depending on the patient's bleeding risks (i.e., elderly, liver disease, malnourished, CHF) the patient may be given oral vitamin K ≤ 5 mg in addition to one or two held doses. Acutely ill patients are often slower to correct and interactions sometimes involve medications without alternatives.

Patients with elevated INRs ≥ 9 and without significant bleeding should be given vitamin K 5–10 mg orally. This would be expected to drop the INR within 24–48 hours. The warfarin should be placed on hold and resumed based on daily INR determinations.[40] In a hospitalized patient, repeat INRs should be preformed daily to guide subse-

Clinical Pearl

Many inpatient anticoagulation programs develop vitamin K reversal guidelines for their institution. This aids both the pharmacists and the physicians. Another project many departments take on is the development of usage criteria for recombinant factor VIIa to attempt to minimize the thrombotic risk to patients and save institution resources. Figures 5-1 and 5-11 in Chapter 5 are examples of these documents.

quent dosing. In patients with elevated INRs and upcoming procedures, oral vitamin K is useful in reversing many patients within 24–48 hours.[40]

Management of Warfarin for Invasive Procedures

In preparing anticoagulated patients for an invasive surgical procedure, the first step is to identify the patient's risk for thrombotic event without anticoagulation. Patients going for surgical procedures can generally be placed into one of three categories; low, moderate, or high risk for thrombosis. Individual risks are additive; for example, AF with versus without prior stroke or TIA. See Table 10-16 for patient types, risk stratification, and peri-procedural anticoagulation management.[39,40,191,319,320] The decision to use large weight-based doses of SC heparin instead of LMWH seems an acceptable alternative.[39,40] When used for short durations, as in the periprocedural setting, monitoring may not be necessary. At least for short periods in the setting of acute DVT treatment (high risk), weight-based (333 units/kg × 1 dose then 250 units/kg) SC heparin twice daily appears as effective as adjusted IV heparin or weight-based SC LMWH for treatment of VTE.[177,321,322] However, when bridge therapy is required for extended periods in high-risk patients such as those with mechanical heart valves or even short periods in renal dysfunction patients, aPTT monitoring and adjustment of high-dose SC heparin is warranted. Platelet count monitoring is also necessary for HIT.

Another option that has been evaluated to prepare patients for minor to major surgical procedures is lowering the intensity of anticoagulation.[39,40,323] In a small population, this was evaluated in high-risk thromboembolism patients undergoing higher risk bleeding procedures.[323] Other studies have evaluated partial or full-dose anticoag-

Table 10-16.

Risk of Thrombotic Event Without Therapy

Indication for Anticoagulation	Thrombotic Event per Year	Suggested Method for Prophylaxis
Low Risk of Thromboembolism		
Non Valvular AF w/o Risk Factors	5%	D/C aspirin if any 7 days prior* D/C warfarin 4 days prior to procedure Optional prophylactic dose UFH or LMWH 2 days prior to surgery Prophylactic dose UFH or LMWH postoperatively and begin warfarin
BioProsthetic Valve Mitral or Aortic Position*	0.2%–3.3%	
VTE > 3 months	10%	
Bi-leaflet Aortic Valve	10%–12%	
Moderate Risk of Thromboembolism		
AF with Risk Factors or Previous Embolism	12%	D/C aspirin if any 7 days prior D/C warfarin 4 days prior to procedure Prophylactic dose UFH or LMWH 2 days prior to surgery Prophylactic dose UFH or LMWH postoperatively and begin warfarin Optional weight-based IV UFH or SC LMWH postoperatively and begin warfarin
Arterial Embolism in the Last Month	15%	
Recurrent Venous Thromboembolism	15%	
High Risk of Thromboembolism		
Dual-Leaflet (St. Jude) Mechanical Mitral Valve	22%	D/C aspirin if any 7 days prior D/C warfarin 4 days prior to procedure Weight-based SC or IV UFH or SC LMWH started ~ 2 days preoperatively. Continue SC agent ~ 12 h pre-op, Continue IV agent ~ 5 h pre-op As soon as safely possible begin weight-based IV UFH or SC LMWH postoperatively and begin warfarin
Single-Leaflet (Bjork-Shiley) Mechanical Aortic Valve	23%	
VTE < 3 months	40%	
Multiple (St. Jude) Mechanical Valves	91%	

Source: References 39, 40, 191, 319, and 320.

ulation in orthopedic surgical patients to determine the effectiveness of VTE prophylaxis and bleeding incidence.[324-326] Using this method, patients have their dose reduced to half their usual maintenance dose 5–7 days prior to the procedure. A follow-up INR with possible dose adjustment is scheduled a few days prior to the procedure. The goal is to obtain an INR of 1.3 to 2, depending on bleeding risk of the procedure, on the operative day.[39,40,323]

Other encountered procedures include gastrointestinal (GI) procedures. The American Society of Gastrointestinal Endoscopy divided endoscopic procedures into two groups, those at low and high risk for bleeding; see Table 10-17.[327] In their 2002 guidelines for anticoagulated patients, they do not routinely recommend withholding patient's anticoagulation for low risk procedures.[327] Generally, for high-risk procedures anticoagulation can be withheld for short periods similar to management of patients in Table 10-16.[327]

Other procedures identified as low risk for bleeding, and therefore better to continue anticoagulation in patients at high risk for thromboembolisms, include: arthrocentesis, cataract surgery, minor cutaneous and dermatologic procedures, and joint and soft tissue injections.[1,39,40,319,320,323] Anticoagulation may also be reduced to the lower end of the patient's therapeutic range when the risk for bleeding is higher.

Warfarin and Hemorrhage Risk

Factors associated with increased bleeding on warfarin include: age (> 75 years old); warfarin intensity; renal insufficiency or anemia; history of bleeding; hypertension; history of stroke; use of aspirin, NSAIDs, or other medications affecting platelet function or GI irritants; peripheral vascular disease; multiple medications or new interacting medication; and heart failure.[39,40,46,237-240,328-330] Given the very clear association of increased INR and bleeding, anything with the potential to increase INR increases risk of bleeding. Additional bleeding risks may include malnutrition, alcohol intake, herbal use, noncompliance, peptic ulcer disease, and malignancy. Two studies have identified an increased bleeding risk with the first 3 months of warfarin initiation.[328,239] See Table 10-18 for a comparison of bleeding risks by INR and indication.[331-334] A number of studies have shown a steep slope increase in bleeding rates for INRs > 5.[195,237,240,335,336] Warfarin use is a significant predictor of mortality in ICH, specifically the odds ratio of mortality was 1.5, 2, and 3.7 for INRs < 2, 2–3, and > 3, respectively.[274] Warfarin did not appear to adversely affect functional recovery in those that survived relative to control patients.[274]

The effect of age on bleeding events with warfarin remains controversial. Trials controlling for other variables like comorbid conditions, found

Clinical Pearl

Many patients have a comprehensive anticoagulation bridging plan in place prior to elective admissions. Unfortunately, this bridge therapy plan is sometimes overlooked post-procedure. Sometimes, no plan was considered at all pre-procedure. A key role for inpatient anticoagulation pharmacists is to ensure implementation of necessary bridge therapy when planned or when it was not planned yet indicated. For example, anticoagulation pharmacists should carefully evaluate and consider starting injectable anticoagulants post surgery in any patient with a history of mechanical mitral valve replacement.

Table 10-17.
Bleeding Risks Associated with Endoscopic Procedures

Low Bleed-Risk Endoscopic Procedures	High Bleed-Risk Endoscopic Procedures
Upper endoscopy with or without biopsy	Polypectomy
Flexible sigmoidoscopy with or without biopsy	Laser ablation and coagulation
Colonoscopy with or without biopsy	Endoscopic sphincterotomy
Endoscopic retrograde cannulation of the pancreatic duct without sphincterotomy	Percutaneous endoscopic gastrostomy tube placement
Biliary stent insertion without sphincterotomy	Pneumatic or bougie dilation
Endosonography without fine-needle aspiration	Treatment of varices
Push enteroscopy of the small bowel	

Source: Reference 327.

Table 10-18.
Rates of Clinically Significant Bleeding by Intended INR Range

Indication	# Patients Study	Goal INR Range	Bleeding Incidence	p Value
Mechanical Heart Valve with ASA 300 mg/d and Dipyridamole 75 mg bid	n = 99 Altman et al.[331]	2–2.9	6%	<0.02
		3–4.5	24%	
DVT	n = 96 Hull et al.[332]	2–2.5	4.3%	0.015
		3–4.5	22.4%	
Mechanical Heart Valve	n = 247 Saour et al.[333]	1.9–3.6	21.3%	<0.002
		7.4–10.8	42.4%	
Tissue Prosthetic Heart Valve	n = 210 Turpie et al.[334]	2–2.5	5.9%	<0.002
		2.5–4	13.9%	

that age was not an independent risk factor.[337-340] However, two other trials controlling for intensity of anticoagulation and other variables, showed age was an independent risk factor for bleeding.[237, 341]

The inpatient anticoagulation pharmacist is constantly weighing the risk of thrombosis versus bleeding on a daily basis. The pharmacist should always be aware of risk factors the patient carries for bleeding (covered above) due to warfarin, such as:

- age (> 75 years old)
- warfarin intensity (high INR, particularly when > 5)
- renal insufficiency
- history of bleeding
- hypertension
- history of stroke
- concomitant medications (examples: aspirin, ibuprofen, etc.)
- peripheral vascular disease
- heart failure

This must be balanced against the risk of thrombosis for each individual patient. For the venous thromboembolism, Tables 10-8, 10-9, and 10-10 allow the reader to easily identify different risks of embolism a patient may have. Table 10-5 likewise portrays embolism risk factors for atrial fibrillation. This table also shows that some risk factors seem greater than others. Key risk factors for embolism for prosthetic heart valves discussed in the text (Table 10-11) include:

Clinical Pearls

Patient education on bleeding, minor nose bleeds, gum bleeding after brushing, and increased bruising is common for warfarin patients. However, these may also indicate an elevated INR in a patient not used to these experiences while therapeutic on warfarin. Patients require education on how to manage these symptoms and advice on specific symptoms requiring medical attention. Patients prone to minor nose bleeds should be informed of nasal moisturizers that reduce this occurrence. Patients tend to bruise easily on warfarin; however, bruises should not continue to grow after several days.

Red or brown urine or red or black tarry stools are often symptoms of more serious bleeding. These require medical attention and INR check. Patients with hemorrhoids or frequent constipation may have blood on toilet paper. Stool softeners can be helpful in this situation. This, however, should also be evaluated by a physician in patients recently starting warfarin or for those not having this problem previously. Positive stool guiacs and red or black tarry stools can be symptoms of a more serious condition such as malignancy or the result of excessive anticoagulation. Warfarin patients who develop occult GI bleeding have a 5%–25% chance of finding a malignant source with further evaluation.[40] Any bleeding regardless of source that doesn't resolve quickly with minor attention requires medical attention and check of the INR.

Clinical Pearl

The inpatient anticoagulation pharmacist must carefully monitor his or her patients for planned invasive procedures and consult directly with affected physicians to determine goal INR to minimize bleeding risk.

- Mechanical prosthetic valves are higher risk than bioprosthetic valves
- "Old" first-generation mechanical valves like ball and cage valves
- Mitral valves are higher risk than aortic valves
- Atrial fibrillation
- Left atrial enlargement (≥50 mm)
- Poor left ventricular function
- Age > 70 years old
- History of prior embolism

The skilled inpatient anticoagulation pharmacist will automatically and intuitively weigh the above thrombosis and bleeding risk factors before making management decisions on patients. Often, the pharmacist will be more aggressive with therapy (use higher doses of warfarin, bridge with injectable anticoagulants, etc.) when a patient has a high risk of thrombosis and a low risk of bleeding. At other times, the pharmacist may be more cautious (use lower doses or hold warfarin, forgo the use of injectable anticoagulants, etc.) when the risk of bleeding is high and thrombosis risk is low. In this situation, the skilled pharmacist may even consider a temporary, lower target INR range until the risk of bleeding subsides.

Warfarin Adverse Effects

A serious adverse effect other than bleeding is warfarin-induced skin necrosis.[39,40] Warfarin-induced skin necrosis is a rare side effect with an incidence of 0.01 to 0.1%.[342] Warfarin skin necrosis may occur in all ages or sexes of warfarin patients, however, seems more common in middle-aged, obese females.[343] A review of the literature indicates it more commonly involves fatty subcutaneous areas of the body including the thigh, buttocks, and breast, and a number of cases have also involved the penis.[343-346] Warfarin skin necrosis often occurs between the third and eighth day of therapy; however, it has been reported at day 10 also.[40,343-345] Warfarin skin necrosis often begins with pain in the affected area followed by erythematous flush. This progresses into petechial hemorrhages, then into red, blue, and/or black necrotic tissue that may hemorrhage.[343-345] There is likely an association between warfarin skin necrosis and protein C deficiency and to a lesser extent protein S. This is supported by earlier reports involving large initial doses of warfarin without using injectable anticoagulant bridge therapy.[343] Warfarin skin necrosis can occur without protein C or S deficiency, however, these patients are at greater risk.[40] Management of warfarin skin necrosis should include warfarin discontinuation and initiation of an injectable anticoagulant. An estimated 50% of patients will require surgical debridement.[344] Warfarin can later be restarted at low doses (i.e., 2 mg) providing the patient is on full dose injectable anticoagulant. Slow upward titration of warfarin over several weeks is recommended in conjunction with full dose injectable anticoagulation.[40,343]

Purple toe syndrome is another rare complication of warfarin that generally occurs during the third to tenth week of therapy.[347-349] Warfarin may enhance the release of cholesterol microemboli from plaques on vessel walls.[347] Purple toe syndrome often manifests as painful, purple, or mottled discoloration of the toes and sides of feet. Discolorations often blanch with pressure and sometimes fade with elevation of the effected extremity.[348,349] Discontinuation of warfarin is recommended because patients sometimes progress to gangrenous necrosis requiring debridement and/or amputation.[347,349] Some patients have later been restarted on warfarin therapy without reoccurrence however, close monitoring and patient education is required.[348]

Precautions and Contraindications

In practice, falls are often cited as a reason to avoid warfarin in patients with AF. One study evaluated this theory; their findings were that a patient would have to fall 295 times in 1 year for the risks of warfarin to outweigh the benefits.[350] The authors' major risk of concern was a subdural hematoma while on warfarin. The authors concluded that falls did not justify avoidance of warfarin; however, they felt it was important to identify and correct the reason for falls. They stated falls were a major cause of orthopedic fractures in elderly patients and fractures rather than bleeding on warfarin causes significant morbidity. It is estimated that one in ten falls will result in major injury in community dwelling elderly patients.[351] Other factors important in this population include numerous medications, multiple prescribing physicians, best price pharmacy shopping, multiple medical conditions, more frequent illnesses, and frequent changes in nutritional status.

There are conditions where warfarin is considered a relative contraindication and the clinician must weight patient's specific risks versus benefits. These include: senility, alcoholism, pregnancy 2nd or 3rd trimester, patient reliability, psychosis, and availability of laboratory testing and coordination of dose adjustment. Absolute contraindications include: blood dyscrasias prone to bleeding; recent or planned neuro, ocular, or traumatic surgery; malignant hypertension; overt bleeding or active ulcerations of the GI or respiratory tract; current or recent cerebrovascular hemorrhage; pericarditis or pericardial effusions; eclampsia or preeclampsia; spinal puncture; first trimester of pregnancy, specifically weeks 6 through 12 of gestation; and threatened abortion.

Warfarin precautions include recent surgery or trauma; heparin-induced thrombocytopenia, specifically initiation prior to platelet recovery greater than 100,000 or ideally more than 150,000; altered intestinal flora; IM injections; protein C or S deficiency; thrombocytopenia; liver dysfunction; debilitated patients; elderly; and children. The latter four with regard to reduced dosing and increased monitoring.

The limited studies on children taking warfarin indicate these are difficult to manage patients.[352-355] Plausible factors include: complicated medical problems, non-compliance, developing gut flora, corticosteroids, dietary compliance, enteral feedings, and difficult venous access. Children can be divided into three groups less than 1 year, age 1 to 6 years, and 7 to 18 years.[353] Children less than 1 year require larger doses, longer bridge therapy, and take longer to therapeutic INR.[353,356] Children aged 1 to 6 years often require larger doses than their teenage counterparts.[353,356] A child-based warfarin nomogram has been evaluated in two separate trials.[353,356] Children were initiated at a dose of 0.2 mg/kg with subsequent dosing adjusted by nomogram.[353,356] The largest study enrolling 262 infants and children found the average dose for infants and teenagers to be 0.32 mg/kg and 0.09 mg/kg respectively.[353] Corticosteroids were an independent predictor of time outside therapeutic range.[353] Enteral feedings, phenobarbital, and carbamazepine were found to cause increased warfarin dose requirements.[353] Adverse events in children receiving warfarin appear to be similar to the incidence in adults. In newborn and breast-feeding infants being treated with warfarin, consistent vitamin K intake is problematic. Breast milk should be supplemented with 1–2 ounces of infant formula per day due to the low vitamin K content of breast milk.[357] Children receiving long-term warfarin therapy should have periodic bone density scans.[358,359] Although there is not much data guiding practice, bone development is important during childhood and children with mechanical heart valves receive longer durations of warfarin therapy than most other populations. A case control study compared 17 children having received an average 8.2 years of warfarin to 321 random control patients. They found reduced bone density in the lumbar spine measured by Z-score after controlling for age and body size.[358]

Warfarin and Pregnancy

Warfarin patients attempting pregnancy require frequent pregnancy tests.[360] Warfarin is teratogenic, mostly during the first trimester, weeks 6 through 12 being the most critical.[360,361] Unlike heparin and LMWH, warfarin crosses the placenta causing fetal warfarin syndrome (FWS).[360,362] Common characteristics of FWS include: nasal hypoplasia, blindness, retardation, seizures, congenital heart disease, scoliosis, low birth weight, deafness, and death.[362] Warfarin use up to the 6th week of gestation is likely safe.[361] Warfarin during the 2nd and 3rd trimester may also be safe although one study reported neurodevelopmental problems may be more likely in offspring exposed to warfarin during the 2nd and 3rd trimester of pregnancy.[363]

VTE treatment during pregnancy may be done with IV heparin, LMWH, or high dose adjusted SC heparin after an IV bolus. Given the risk of heparin-induced thrombocytopenia, frequent aPTT monitoring, and osteoporosis; LMWH with a category B pregnancy rating should be given higher priority as a treatment alternative.[360] Anticoagulation must be discontinued 24 hours prior to delivery or induction of labor. Pregnancy with prior history of single VTE due to a transient condition no longer present may only require careful monitoring and patient education. If the prior VTE was due to pregnancy or related to estrogen and/or risk factors such as extended immobility or obesity are present, prophylactic anticoagulation (enoxaparin 40 mg SC daily, dalteparin 5000 units SC daily, or heparin 5000 units SC q 8–12 h) up to delivery is appropriate.[360] Recommendations for anticoagulation in other clinical scenarios of pregnancy can be found in Table 10-19. In all pregnant patients with history of prior VTE, elastic compression stockings are recommended during and 4-6 weeks after delivery.[360]

Generic Versus Brand Warfarin

Access to generic medications has saved consumers eight to ten billion dollars.[364] The 1984 Drug Competition and Patent Term Restoration Act, improved patient's access to generic medications and

Table 10-19.

Clinical Scenarios Requiring Anticoagulation During Pregnancy

Patient Type	Recommended Anticoagulation Regimens
No VTE hx with Laboratory-Confirmed Thrombophilia (Listed in Table 10-11)	Prophylactic LMWH (i.e., enoxaparin 40 mg SC daily) UFH 5000 units SC q12h
Single Idiopathic DVT - not currently on anticoagulation	Prophylactic LMWH (i.e., dalteparin 5000 U SC daily) UFH 5000 units SC q12h UFH SC q12h adjusted to anti-Xa 0.1–0.3 U/mL Also during postpartum period for 4–6 weeks
Single Idiopathic DVT with Thrombophilia (Listed in Table 10-11) - not currently on anticoagulation	Intermediated-dose LMWH (enoxaparin 40 mg SC q 12 h or dalteparin 5000 U SC q12h) UFH SC q12h adjusted to anti-Xa 0.1–0.3 U/mL Also during postpartum period for 4–6 weeks
Multiple DVT or Single with Thrombophilia (Listed in Table 10-11) - currently on anticoagulation	Full adjusted dose LMWH Full adjusted dose UFH, to anti-Xa 0.3–0.7 U/mL (after IV bolus, dosing may be adjusted SC bid)
Pregnancy with APLAs and One Previous Late Pregnancy Loss or ≥ Two Early Pregnancy Losses, Preeclampsia, Intrauterine Growth Restriction - not currently on anticoagulation	Aspirin 81 mg po daily plus one from below: Prophylactic LMWH (i.e., dalteparin 5000 U SC daily) UFH 5000 units SC q12h UFH SC q12h adjusted to anti-Xa 0.1–0.3 U/mL D/C aspirin ~ 5 days before delivery D/C LMWH or UFH ~ 24 h before delivery
Pregnancy with Congenital Thrombophilic Deficit and Recurrent Miscarriages, 2nd or 3rd Trimester Loss, Severe or Recurrent Pre-eclampsia, or Abruption - not currently on anticoagulation	Aspirin 81 mg po daily plus one from below: Prophylactic LMWH (i.e., dalteparin 5000 U SC daily) UFH 5000 units SC q 12h UFH SC q12h adjusted to anti-Xa 0.1–0.3 U/mL D/C aspirin ~ 5 days before delivery D/C LMWH or UFH ~ 24 h before delivery Restart proph LMWH or UFH post delivery x 4–6 weeks
Pregnancy with Mechanical Heart Valve	Full dose LMWH adjusted to anti-Xa 1–1.2 U/mL measured 4 hours post injection till or Full adjusted dose UFH, to anti-Xa 0.35–0.7 U/mL (after IV bolus, dosing may be adjusted SC bid) or AFTER 13th week of gestation, either of the above therapies may be converted to warfarin adjusted according to Table 10-14. Halfway through the third trimester patient must be switched back to adjusted UFH or LMWH. High-risk conditions also require addition of aspirin, see Table 10-14.

Source: Reference 360.

cost savings. This act also established a method for determining a generic drug's bioequivalence to a branded product.[364] Generic products are considered bioequivalent after passing a single dose two way crossover study in 24 to 36 healthy subjects. A passing analysis requires peak serum concentration (Cmax) and area under the curve (AUC) to fall within 80%–125% of the branded product with a 90% confidence interval.[365,366] Unlike aminoglycosides, therapeutic warfarin is not determined by serum concentrations but rather INR measurements. Two concerns arise from this. First total concentrations are measured not concentrations of the specific isomers (reminder that the S isomer is more potent than the R isomer). The second is that intraindividual variability has been identified when looking at warfarin plasma concentrations versus anticoagulant response.[367] These are merely obser-

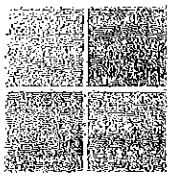
vations and whether there is a clinically important change after switching to generic can only be determined from well designed clinical trials.

The FDA conducts approximately 3,500 inspections per year in manufacturing facilities and brand name manufacturers produce approximately 50% of generic products.[364] Generic warfarin was previously available; however, after litigation was withdrawn in 1992 and then became available again in 1997.[368,369] In addition to Bristol Meyers Squibb Coumadin®, the electronic orange book lists seven AB rated generic warfarins.[370] Given the number of generics, it is difficult to determine the variability if any, one might find with a specific generic. Available data evaluating some of these generics, indicates a clinically significant problem is unlikely and variability is more likely from other causes.

Given warfarin's narrow therapeutic window, increased monitoring following a change in brand is reasonable. However, the FDA in January 1998 regarding narrow therapeutic index generics stated, "It is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class, when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration."[371] In this letter they further stated the "FDA approved product labeling does not recommend that any additional tests need to be performed by the health care provider when a switch occurs from a brand-name drug product to a generic equivalent drug product, from a generic equivalent to a brand-name product drug, or from one generic product to another when both are deemed equivalent to a brand-name drug product."[371] Available data supports allowing patients wanting to switch to generic, the opportunity to do so with temporary increased monitoring. See Table 10-20 for a summary of published clinical trials.[372-375]

Conclusion

Warfarin is an extremely effective anticoagulation medication that has been in use over fifty years. Despite that long track record of efficacy, it remains one of the most inherently dangerous medications used in clinical medicine. Its complicated pharmacodynamic profile and numerous factors make it an excellent target for an inpatient anticoagulation service to manage. Inpatient anticoagulation pharmacists face a daunting, but surmountable, task in mastering the management of this medication. Inpatient pharmacists who learn to manage warfarin well will tremendously improve care to the patients they serve.



Patient Cases

Case 1

MJ is a 56-yo female admitted to the hospital with shortness of breath and chest pain. Her past medical history includes atrial fibrillation, hypertension, and chronic heart failure. Social history includes smoking 1 ppd and she denies ethanol intake. She reports taking the following medications at home: warfarin 5 mg daily, other medications include losartan 50 mg po daily, digoxin 0.25 mg po daily, furosemide 40 mg po daily, conjugated estrogens 0.625 mg po daily, and metoprolol XL 50 mg po daily. She also reports starting doxycycline 100 mg twice daily which was prescribed 6 days ago by her primary care physician for community acquired pneumonia. She denies any signs/symptoms of stroke, thromboembolic complications, or bleeding. She reports eating less than her usual over the past several days since she began feeling sick and nauseous. She has been on her current dose of warfarin for over 6 months with INRs ranging from 2.1–3.3. Her INR on admission was 4.7 (goal 2–3) and has been placed on hold pending a consult from the pharmacy anticoagulation service team. She denies any missed doses of warfarin. You speak with the physician who feels the patient has not improved on the current antibiotics after reviewing chest X-ray, vitals, and lung sounds. It is also noted that the patient has a heart rate of 50. Her serum creatinine is also elevated at 1.4 which her physician feels may be due to reduced fluid intake and possibly worsening heart failure. Blood and sputum cultures were drawn and antibiotics have been changed to levofloxacin 500 mg daily po daily and the doxycycline has been discontinued.

Q: How should the warfarin be managed upon hospital admission?

A: The best course of action is to hold warfarin and draw daily INRs. The elevated INR is likely due to numerous reasons including doxycycline therapy, reduced PO intake, and a possible heart failure exacerbation. Due to the elevation in serum creatinine, use of doxycycline, low heart rate, and poor appetite, you also ask the physician to consider the possibility of digoxin toxicity.

Day 2. The next morning's labs reveal a digoxin level of 2.9 and an INR of 4.1 following one held dose. The physician holds the digoxin, thanks you for your insight, and asks you to continue to manage the anticoagulation.

Table 10-20.

Observations Following Changes Between Branded and Generic Warfarin

Author/Study Design/Brand	Subjects	Outcomes Evaluated	Conclusion
Milligan[368] Prospective, non-blinded, non-randomized observational study Brand 8 months control vs. Barr for 10 months after	n = 182 Mean age 75 y AF: 60% Valve: 13% Stroke/TIA: 11% DVT/PE: 9% Other: > 6%	Bleeding req. med. care	No difference
		Dose changes/Pt days	No difference
		Required INRs/Pt days	No difference
		Thrombotic events	No difference
		INRs in therapeutic range	75.6% vs. 78.4% P = 0.3
Witt[369] Retrospective, uncontrolled, Brand 90 days control vs. Barr for 90 days thereafter	n = 2299 Mean age 69 y AF: 41% Valve: 12% Stroke/TIA: 8% DVT/PE: 27% Other: >12%	# INR tests per patient	3.92 brand vs. 3.89 Barr p < 0.05
		Warfarin dose (mg)	4.54 brand vs. 4.49 Barr p < 0.05
		INRs within therapeutic range	65.9% brand vs. 63.3% Barr p = 0.0002
		INR control after Barr switch change by > 10%	33.1% improved 38.9% worsened
		Complication rate per 100 patient years	NS
		% patients > 1 dose change	NS
Swenson[372] Prospective, non-blinded, non-randomized observational study, Brand 4 weeks vs. Barr/Brand for 8 weeks thereafter	n = 105 Converted to Barr n = 105 Stay Brand Mean age 76–78 y AF: 64%–70%	INR Brand pre/post	2.6/2.8
		INR Brand/Barr post change	2.6/2.7
		Required dose changes	31 Barr/63 Brand
		INR change > 1	10 Barr/14 Brand
Weibert[373] Randomized, prospective, single-blind, multi-center, crossover trial. All 4 weeks Brand then 4 weeks either Brand/Apothecon (Sandoz) then crossover 4 weeks	n = 113 Mean age 70 y AF: 100%	Number INRs < 1.8	Brand: 9 Apothecon: 9
		Number INRs > 3.2	Brand: 9 Apothecon: 10
		Dose change ≥ 20%	Brand: 7 Apothecon: 7
		Significant bleed/thromb	NS
Lee[374] Randomized, prospective, observer-blind, crossover trial. 3 x 28d periods Brand x 28d > Generic 56d Generic x 28d > Brand 56d	n=34 Mean age 52 y Mech valve 100%	Pooled mean INR	2.28 vs. 2.27
		Adverse events	NS
Pereira[375] Randomized, prospective, triple-blind, crossover trial. Brand versus Apo-warfarin	n=7 Mean age 63 y Mech valve 100%	Mean INR results	NS
		INR variation	NS

Q: How should the warfarin be managed at this point?

A: Although the INR has improved, the INR is still > 4. The risks of thrombosis this patient has are history of hypertension and heart failure. Since the patient continues to appear sensitive to warfarin, it would be wise to hold warfarin and continue daily INRs.

Day 3. The next morning's labs reveal an INR of 3 following two held doses. The patient is afebrile, feeling better, and has resumed her previous appetite. She wants to be discharged from the hospital and her physician agrees. He requests from you warfarin discharge instructions, the patient will be discharged on levofloxacin 500 mg po daily, digoxin 0.125 mg po daily, and her previous meds excluding doxycycline.

Q: How should the warfarin be handled at this point?

A: Resume warfarin 5 mg daily po daily and have an INR drawn 2–3 days following discharge.

Case 2

DJ is a 64-yo female admitted to the hospital after 5 days of dizziness spells, pounding in her chest, and new onset chest pain. Her past medical history includes hypertension, unstable angina with no previous heart attack, and chronic heart failure. She reports having familiar episodes of a racing heart in the past but that it has always gone away before now and that it had never made her feel dizzy. Social history includes previous smoker but quit 7 years ago and occasional ethanol ingestion of two drinks four times per week. She reports taking the following medications at home: aspirin 81 mg po daily, lisinopril 20 mg po daily, digoxin 0.125 mg po daily, furosemide 40 mg po daily, KCL 20 mEq po daily, nitroglycerin SL spray prn, and carvedilol 12.5 mg bid. She denies any symptoms of weakness in her arms or legs, headache, visual or hearing disturbances, or other stroke symptoms. EKG reveals no ST segment changes only atrial fibrillation. Her heart rate is 140 beats per minute. Cardiac enzymes are also noted to be negative. The patient is admitted to the telemetry floor and started on a diltiazem drip which resolves the patient's symptoms. Pharmacy is consulted for anticoagulation management in preparation for cardioversion.

Q: What are the acceptable options for anticoagulation to facilitate cardioversion in this patient?

A: Given the duration of atrial fibrillation > 48 hr and that the patient is hemodynamically stable, cardioversion should be postponed. She will require 3 weeks of warfarin INR 2–3 before elective cardioversion. The patient should be started on warfarin 4 mg daily and an INR drawn in 2 days. The patient has two risk factors for stroke due to atrial fibrillation (risk factors of history of hypertension and chronic heart failure) may or may not be started on an injectable anticoagulant as bridge therapy. The aspirin should likely be discontinued due lower bleeding risk, but it would be reasonable to wait until the INR is in range if an injectable anticoagulant is not used (offers some stroke protection).

Although the above strategy was chosen in this case, one other strategy could have been implemented. If high quality TEE was performed and showed no sign of left atrial appendage thrombi, the patient could be placed on IV heparin and cardioverted.

Day 3. The morning labs reveal an INR of 1.6 following two 4-mg doses of warfarin.

Q: How should the warfarin be managed at this point?

A: Continue warfarin 4 mg daily and draw daily INRs if the patient remains hospitalized. The patient may also be discharged on warfarin 4 mg daily having an INR drawn in 2 days and instructions not to take her warfarin until the INR results are returned. The maintenance dose for this patient will likely be around 24 mg/week. Once the patient is therapeutic on warfarin, it may be best to discontinue aspirin if it was continued initially. The aspirin may be resumed once the patient has been converted and the 4 weeks of warfarin after conversion is complete provided the patient does not have a recurrence of atrial fibrillation, which is quite common.

Case 3

AM is a 27-yo female who presents to the emergency department with unexplained shortness of breath, cough, and chest pain × 2 weeks. She teaches physical education and coaches' volleyball and basketball at the local high school. In addition, AM usually runs 3 miles about 3 days per week. She visited her primary care physician 10 days ago complaining of shortness of breath and exercise intolerance. She stated that she had difficulty walking up the stairs. AM is well known to her physician, he has been her physician for 5 years. She admits to being overly concerned about her health sometimes. Her physician could not find obvious causes of her symptoms and thought she was wor-

rying for no reason given her great physical condition. Prior to admission AA was in excellent health and appears very conscious about her health. Her only medication is birth control. She was previously taking ethinyl estradiol (20 mcg)/norethindrone (1 mg) (Loestrin 21 1/20) for 7 years but switched to ethinyl estradiol (35 mcg)/norgestimate (0.18, 0.215, 0.25 mg, Ortho Tri-Cyclen) 3 months ago to help with her acne. Patient appears moderately distressed and anxious. Vital signs: T: 98.9°F, BP: 129/78, HR: 109 bpm, RR: 22/min. Labs are normal except for elevated d-dimer. CBC, PT, PTT baseline labs are also normal. A CT identifies a large PE although the patient appears stable. Due to the patient's age and excellent physical condition hematology is consulted along with pharmacy for anticoagulation management.

Q: How should this patient initially be managed?

A: An excellent strategy would be to start the patient on a heparin drip with an 80 units/kg bolus then followed by an 18 units/kg/hr infusion. An a aPTT should be drawn in 6 hours and adjust per hospital protocol. Administer warfarin 7.5 mg daily and start daily INRs.

Day 3. The INR is 1.7 after two 7.5-mg doses of warfarin and the patient remains therapeutic on IV heparin. The patient just started a new job at the local high school and does not have very many sick days and wishes to go home.

Q: You are asked for advice by the physician who feels the patient is stabilized clinically and feels she is reliable for follow-up as an outpatient. Hematology also reports a hypercoagulable panel found she has a heterozygous Factor V Leiden gene mutation.

A: As long as the patient is hemodynamically stable and appears reliable for education and follow-up the patient can be discharged. Case management will need to confirm the patient or the insurance is willing and able to pay for outpatient LMWH. Ideally, the hospital has LMWH outpatient discharge kits. These usually have a sharps container, instructional video, alcohol swabs, and an educational booklet. Once payment arrangements are confirmed and availability at the local pharmacy is established, patient education and switch to a therapeutically dosed (i.e., enoxaparin 1 mg/kg sc twice daily) LMWH can be made. The IV heparin can be shut off at the time of LMWH administration. It is best if the patient gives this injection herself. This way the patient is observed, and shows she is willing to administer the injections on her own following discharge. The patient should be discharged on warfarin 7.5 mg daily and also LMWH therapy. Overlap should be for 5 days total assuming there have been two therapeutic INRs on warfarin. An INR should be drawn on the second morning following discharge with instructions not to take her warfarin until the INR results are returned. Given the patient's Factor V Leiden gene mutation, she will require warfarin for 6–12 months, even though the birth control pill change may have contributed to the event. Non-hormonal forms of birth control should now be used in this patient to minimize risk of venous thromboembolism and to avoid pregnancy while on warfarin.

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