Anticoagulation Education for Providers

The National Patient Safety Goals require that we provide education regarding anticoagulant therapy to prescribers, staff, residents, and families. The education should include the following elements:
- The importance of follow-up monitoring
- Compliance
- Drug-food interactions
- The potential for adverse drug reactions and interactions

Floyd meets this requirement by providing the following excerpts from the ACCP Guidelines.

Antithrombotic and Thrombolytic Therapy 8th ED: ACCP Guidelines
Pharmacology and Management of the Vitamin K Antagonists
American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
Jack Ansell, MD

Selected Excerpts:

2.3 Frequency of Monitoring
In hospitalized patients, PT monitoring is usually performed daily, starting after the second or third dose until the TTR has been achieved and maintained for at least 2 consecutive days; then two or three times weekly for 1 to 2 weeks; then less often, depending on the stability of INR results. In outpatients starting warfarin therapy, initial monitoring may be reduced to every few days until a stable dose response has been achieved. When the INR response is stable, the frequency of testing can be reduced to intervals as long as every 4 weeks, although evidence suggests that testing more frequently than every 4 weeks will lead to greater TTR. If adjustments to the dose are required, then the cycle of more frequent monitoring should be repeated until a stable dose response can again be achieved.

The optimal frequency of long-term INR monitoring is influenced by patient compliance, transient fluctuations in the severity of comorbid conditions, the addition or discontinuation of other medications, changes in diet, the quality of dose-adjustment decisions, and whether the patient has demonstrated a stable dose response. Some investigators have attempted to develop predictive models with the goal of reducing the frequency of testing without sacrificing quality.
Recommendations
2.3.1. In patients beginning VKA therapy, we suggest that INR monitoring be started after the initial two or three doses of oral anticoagulation therapy (Grade 2C).
2.3.2. For patients who are receiving a stable dose of oral anticoagulants, we suggest monitoring at an interval of no longer than every 4 weeks (Grade 2C).

Recommendations
4.1 Optimal Management of VKA Therapy
4.1.1. For health-care providers who manage oral anticoagulation therapy, we recommend that they do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions as occurs in an anticoagulation management service (AMS) [Grade 1B].

1.1.2 Environmental Factors and Drug Interactions
Environmental factors such as drugs, diet, and various disease states can alter the pharmacokinetics of warfarin. Consequently, the INR should be measured more frequently than the usual 4-week interval when virtually any drug, dietary supplement, or herbal medicine is added or withdrawn from the regimen of a patient treated with warfarin. Drugs such as cholestyramine can reduce the anticoagulant effect of warfarin by reducing its absorption. Other drugs potentiate the anticoagulant effect of warfarin by inhibiting its clearance, whereas some drugs may inhibit the anticoagulant effect by enhancing its clearance. These latter effects may be through stereoselective or nonselective pathways. (Stereoselective interactions may affect the oxidative metabolism of either the S enantiomer or R enantiomer of warfarin.) Table 2 provides a comprehensive list of drugs that potentiate, inhibit, or have no effect on the anticoagulant effect of warfarin.[] A major problem with the literature on this topic is that many reports are single case studies and not well documented. Thus, the drugs categorized in Table 2 are listed by their probability of causation based on the quality of documentation as assessed by Holbrook et al in their systematic review.

Table 2 -- Drug, Food, and Dietary Supplement Interactions With Warfarin by Level of Supporting Evidence and Direction of Interaction (Section 1.1.2)[*]

Level of Causation	Antiinfectives	Cardiovascular	Analgesics, Antiinflammatories, and Immunologics	CNS Drugs	GI Drugs and Food	Herbal Supplements	Other Drugs
Potentiation							
Highly probable	Ciprofloxacin Cotrimoxazole Erythromycin Fluconazole Isoniazid Metronidazole Miconazole Oral Gel Miconazole Vag Supp Voriconazole	Amiodarone Clofibrate Diltiazem Fenofibrate Propafenone Propranolol Sulfinpyrazone (biphasic with later inhibition)	Phenylbutazone Piroxicam	Alcohol (if concomitant liver disease) Citalopram Entacapone Sertraline	Cimetidine Fish oil Mango Omeprazole	Boldo-funugreek Quilinggao	Anabolic steroids Zileuton
Probable	Amoxicillin / clavulanate Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir Tetracycline	Aspirin Fluvastatin Quinidine Ropinirole Simvastatin	Acetaminophen Aspirin Celecoxib Dextropropoxphene Interferon Tramadol	Disulfiram Chloral hydrate Fluvoxamine Phenytoin (biphasic with later inhibition)	Grapefruit	Danshen Don quai Lycium Barbarum I PC-SPES	Fluorouracil Gemcitabine Levamisole / fluorouracil Paclitaxel Tamoxifen Tolterodine
Possible	Amoxicillin Amoxicillin/tranexamic rinse Chloramphenicol Gatifloxacin Miconazole Topical Gel Nalidixic Acid Norfloxacin Ofloxacin Saquinavir Terbinafine	Amiodarone-induced toxicosis Disopyramide Gemfibrozil Metolazone	Celecoxib Indomethacin Leflunomide Propoxphene Rofecoxib Sulindac Tolmetin Topical salicylates	Felbamate	Orlistat	Danshen/methyl salicylates	Acarbose Cyclophosphamide / methotrexate / fluorouracil Curbicin Danazol Ifosphamide Trastuzumab
Highly improbable	Cefamandol Cefazolin Sulfisoxazole	Bezafibrate Heparin	Levamisole Methylprednisolone Nabumetone	Fluoxetine/diazepam Quetiapine			Etoposide / carboplatin Levonorgestrel
Inhibition							
Highly probable	Griseofulvin Nafcillin Ribavirin Rifampin	Chlestyramine	Mesalamine	Barbiturates Carbamazepine	High vitamin k content foods / enteral feeds Avocado (large amounts)		Mercaptopurine
Probable	Dicloxacillin Ritonavir	Bosentan	Azathioprine	Chloradiazeposide	Soy milk Sucralfate	Ginseng	Chelation therapy Influenza vaccine Multivitamin supplement Raloxifene HCL

Level of Causation	Antiinfectives	Cardiovascular	Analgesics, Antiinflammatories, and Immunologics	CNS Drugs	GI Drugs and Food	Herbal Supplements	Other Drugs
Possible	Terbinafine	Telmisartan	Sulfasalazine		Sushi containing seaweed		Cyclosporine Etretinate Ubidicaremone
Highly improbable	Cloxacillin Natcillin / dicloxacillin Teicoplanin	Furosemide		Propofol		Green tea	

* Data from Holbrook et al[54] with permission.

3.0 Adverse Events and Their Management

3.1 Definition of Major and Minor Hemorrhage

Precise estimates of hemorrhagic event rates are complicated by the inconsistency among classification schemes in clinical research studies.[137] Fihn et al[137] proposed the following three categories of bleeding: (1) minor (reported, but not requiring additional testing, referrals, or visits); (2) major (requiring treatment, medical evaluation, or at least 2 U blood); and (3) life threatening (leading to cardiac arrest, surgical/angiographic intervention, or irreversible sequelae). Most other investigators, however, divide adverse events into minor and major categories, with major events including fatal or life-threatening bleeds (*eg*, intracranial or retroperitoneal) or bleeding with a defined drop in hemoglobin, leading to transfusion of a specified number of units of blood and/or hospitalization. The reader should be aware of these differences when interpreting the results from clinical studies. The reader is referred to the "Hemorrhage Complications" chapter in this supplement for an indepth discussion of hemorrhagic adverse events with anticoagulant therapy.

3.2: Factors Predictive of Adverse Events

3.2.1 Intensity of Treatment

The most important factor influencing the risk of bleeding is the intensity of anticoagulant therapy. The relationship between bleeding and the level of INR has been reported to rise steeply as the INR increases >5.0. The optimal target range for each indication and the lowest effective range are discussed specifically in other articles in this supplement pertaining to each indication.

3.2.2 TTR

The relationship between the intensity of treatment and the risk of an adverse event has been evaluated by examining the frequency of an event as a function of the TTR. A strong relationship between TTR and bleeding or thromboembolic rates has been observed across a large number of studies, with different patient populations, different target ranges, different scales for measuring intensity of anticoagulation (*ie*, PT, PT ratio, and INR), different methods of measuring TTR, and different models of dose management . . . The percentage of INRs or TTR highly depends on the quality of dose management as reflected in studies that report TTR. Poor quality of dose management results in a high rate of low INRs during the first 3 months of treatment following an acute DVT, which in turn, predicts for a higher rate of subsequent recurrence. The quality of dose management is reflected by studies where dose management is provided in a usual care (UC) setting, by an anticoagulation management service (AMS), by PST or patient self-management (PSM), or in the setting of a randomized trial.

3.2.3 Patient Characteristics

Several patient characteristics are associated with higher odds of bleeding during anticoagulation therapy. The patient factor most consistently predictive of major bleeding is a history of bleeding (especially GI bleeding). Other factors associated with a higher risk of bleeding include a history of stroke and the presence of a serious comorbid condition, such as renal insufficiency, anemia, or hypertension.

The relationship between older age and anticoagulant-associated bleeding has been controversial. Many older reports indicate that older individuals do not have an increased risk for bleeding, whereas other reports have described such an association. The discrepancy may be explained partly by the wide range in the mean age of the patients enrolled in the various studies, the relative lack of representation in most studies of patients over 80 years of age, and the selection and survivorship biases in noninception cohort studies. When investigators attempt to separate the effect of age from comorbid conditions associated with age, some have concluded that age in and of itself is not a major independent risk factor, whereas others have found it to be an independent risk factor, even after controlling for the intensity of the anticoagulant effect. Some studies have suggested that older patients who have high-quality anticoagulation management, such as that provided by an AMS, have the same risk of bleeding as their younger counterparts. Last, the location of major bleeding may be a factor, and reasonable evidence suggests a real increase in intracranial hemorrhage in elderly patients. . .