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Pharmacology and Management of the Vitamin K Antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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Pharmacology and Management of the Vitamin K Antagonists*

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This article concerning the pharmacokinetics and pharmacodynamics of vitamin K antagonists (VKAs) is part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). It describes the antithrombotic effect of the VKAs, the monitoring of anticoagulation intensity, and the clinical applications of VKA therapy and provides specific management recommendations. Grade 1 recommendations are strong and indicate that the benefits do or do not outweigh the risks, burdens, and costs. Grade 2 recommendations suggest that the individual patient's values may lead to different choices. (For a full understanding of the grading, see the "Grades of Recommendation" chapter by Guyatt et al, *CHEST* 2008; 133:123S–131S.)

Among the key recommendations in this article are the following: for dosing of VKAs, we recommend the initiation of oral anticoagulation therapy, with doses between 5 mg and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the international normalized ratio (INR) response (Grade 1B); we suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial (Grade 2C); and in elderly and other patient subgroups who are debilitated or malnourished, we recommend a starting dose of ≤ 5 mg (Grade 1C). The article also includes several specific recommendations for the management of patients with nontherapeutic INRs, with INRs above the therapeutic range, and with bleeding whether the INR is therapeutic or elevated. For the use of vitamin K to reverse a mildly elevated INR, we recommend oral rather than subcutaneous administration (Grade 1A). For patients with life-threatening bleeding or intracranial hemorrhage, we recommend the use of prothrombin complex concentrates or recombinant factor VIIa to immediately reverse the INR (Grade 1C). For most patients who have a lupus inhibitor, we recommend a therapeutic target INR of 2.5 (range, 2.0 to 3.0) [Grade 1A]. We recommend that physicians who manage oral anticoagulation therapy do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dose adjustments [Grade 1B]. In patients who are suitably selected and trained, patient self-testing or patient self-management of dosing are effective alternative treatment models that result in improved quality of anticoagulation management, with greater time in the therapeutic range and fewer adverse events. Patient self-monitoring or self-management, however, is a choice made by patients and physicians that depends on many factors. We suggest that such therapeutic management be implemented where suitable (Grade 2B). ***(CHEST 2008; 133:160S–198S)***

Key words: anticoagulation; pharmacogenetics; pharmacology; quality of care; vitamin K antagonists; warfarin

Abbreviations: AMS = anticoagulation management service; CHF = congestive heart failure; CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; INR = international normalized ratio; ISI = international sensitivity index; NSAID = nonsteroidal antiinflammatory drug; OR = odds ratio; PCC = prothrombin complex concentrate; POC = point of care; PSM = patient self-management; PST = patient self-testing; PT = prothrombin time; SNP = single nucleotide polymorphism; TTR = time in the therapeutic range; UC = usual care; VKA = vitamin K antagonist; VKOR = vitamin K oxide reductase; WHO = World Health Organization

Summary of Recommendations

2.1 Initiation and Maintenance Dosing

2.1.1. In patients beginning vitamin K antagonist (VKA) therapy, we recommend the initiation of oral anticoagulation with doses between 5 mg and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the international normalized ratio (INR) response (Grade 1B)**. At the present time, for patients beginning VKA therapy without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing** (Grade 2C)**.**

2.2 Initiation of Anticoagulation in Elderly or Other Populations

2.2.1. In elderly patients or patients who are debilitated, are malnourished, have congestive heart failure (CHF), have liver disease, have had recent major surgery, or are taking medications known to increase sensitivity to warfarin (*eg*, amiodarone), we recommend the use of a starting dose of ≤ 5 mg (Grade 1C) **with subsequent dosing based on the INR response**.

2.3 Frequency of Monitoring

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)**.**

2.4 Management of Nontherapeutic INRs

2.4.1. For patients with INRs above the therapeutic range but < 5.0 and with no significant bleeding, we recommend lowering the dose or omitting a dose, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level. If only minimally above therapeutic range or associated with a transient causative factor, no dose reduction may be required (all Grade 1C)**.**

2.4.2. For patients with INRs of ≥ 5.0 but < 9.0 and no significant bleeding, we recommend omitting the next one or two doses, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level (Grade 1C)**. Alternatively, we suggest omitting a dose and administering vitamin K (1 to 2.5 mg) orally, particularly if the patient is at increased risk of bleeding** (Grade 2A)**. If more rapid reversal is required because the patient requires urgent surgery, we suggest vitamin K (≤ 5 mg) orally, with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, we suggest additional vitamin K (1 to 2 mg) orally** (Grade 2C)**.**

2.4.3. For patients with INRs ≥ 9.0 and no significant bleeding, we recommend holding warfarin therapy and administering a higher dose of vitamin K (2.5 to 5 mg) orally, with the expectation that the INR will be reduced substantially in 24 to 48 h (Grade 1B)**. Clinicians should monitor the INR more frequently, administer additional vitamin K if necessary, and resume therapy at an appropriately adjusted dose when the INR reaches the therapeutic range.**

2.4.4. In patients with serious bleeding and elevated INR, regardless of the magnitude of the elevation, we recommend holding warfarin therapy and giving vitamin K (10 mg) by slow IV infusion supplemented with fresh frozen plasma, prothrombin complex concentrate (PCC), or recombinant factor VIIa, depending on the urgency of the situation. We recommend repeating vitamin K administration every 12 h for persistent INR elevation (all Grade 1C)**.**

2.4.5. In patients with life-threatening bleeding (*eg*, intracranial hemorrhage) and elevated INR, regardless of the magnitude of the elevation, we recommend holding warfarin therapy and administering fresh frozen plasma, PCC, or recombinant factor VIIa supplemented with vitamin K, 10 mg by slow IV infusion, repeated, if necessary, depending on the INR (Grade 1C)**.**

2.4.6. In patients with mild to moderately elevated INRs without major bleeding, we recommend that when vitamin K is to be given, it be administered orally rather than subcutaneously (Grade 1A)**.**

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2.5 Management of Variable INRs

2.5.1. For patients receiving long-term warfarin therapy with a variable INR response not attributable to any of the usual known causes for instability, we suggest a trial of daily low-dose oral vitamin K (100 to 200 μg), with close monitoring of the INR and warfarin dose adjustment to counter an initial lowering of the INR in response to vitamin K (Grade 2B)**.**

2.7 Management of INRs in the Antiphospholipid Syndrome

2.7.1. In patients who have a lupus inhibitor, who have no additional risk factors, and who have no lack of response to therapy, we recommend a therapeutic target INR of 2.5 (INR range, 2.0 to 3.0) [Grade 1A]**. In patients who have recurrent thromboembolic events with a therapeutic INR or other additional risk factors for thromboembolic events, we suggest a target INR of 3.0 (INR range, 2.5 to 3.5)** [Grade 2C]**.**

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]**.**

4.3 Patient Self-Testing and Patient Self-Management

4.3.1. Patient self-management (PSM) is a choice made by patients and health-care providers that depends on many factors. In patients who are suitably selected and trained, patient self-testing or PSM is an effective alternative treatment model. We suggest that such therapeutic management be implemented where suitable (Grade 2B)**.**

The coumarins or vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulant therapy for more than 60 years. Their effectiveness has been established by well-designed clinical trials for the primary and secondary prevention of venous thromboembolism, for the prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, as an adjunct in the prophylaxis of systemic embolism after myocardial infarction, and for reducing the risk of recurrent myocardial infarction. VKAs are challenging to use in clinical practice for the following reasons: (1) they have a narrow therapeutic window; (2) they exhibit considerable variability in dose response among patients due to genetic and other factors; (3) they are subject to interactions with drugs and diet; (4) their laboratory control is difficult to standardize; and (5) maintenance of a therapeutic level of anticoagulation requires a good understanding of the pharmacokinetics and pharmacodynamics of warfarin and good patient communication. Because warfarin is the most commonly used VKA worldwide, we will use it interchangeably with VKA throughout this article.

1.0 Pharmacology and Monitoring of VKAs

The VKAs produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide), thereby modulating the γ-carboxylation of glutamate residues (Gla) on the N-terminal regions of vitamin K-dependent proteins[1–7] (Fig 1). The vitamin K-dependent coagulation factors II, VII, IX, and X require γ-carboxylation for their procoagulant activity, and treatment with VKAs results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity.[8,9] Carboxylation is required for a calcium-dependent conformational change in coagulation proteins[10–12] that promotes binding to cofactors on phospholipid surfaces. In addition, the VKAs inhibit carboxylation of the regulatory anticoagulant proteins C, S, and Z and thereby have the potential to be procoagulant.[13] Under most circumstances, however, the anticoagulant effect of the VKAs is dominant. Carboxylation requires the reduced form of vitamin K (VKH_2), a γ-glutamyl carboxylase, molecular oxygen, and carbon dioxide.[1] Vitamin K epoxide can be reused by reduction to VKH_2. The oxidation-reduction reaction involves a reductase pair. The first, vitamin K epoxide reductase, is sensitive to VKA, whereas vitamin K reductase is less sensitive.[1–3] Therefore, the anticoagulant effect of the VKAs can be overcome by low doses of vitamin K (phytonadione) [Fig 1]. Patients treated with large doses of vitamin K can become resistant to warfarin for up to 1 week or more because the vitamin K accumulating in the liver is available to the VKA-insensitive reductase.

The VKAs also interfere with the carboxylation of Gla proteins that are synthesized in bone.[14–17] Although these effects contribute to fetal bone abnormalities when mothers are treated with a VKA during pregnancy,[18,19] it is unclear how they might affect children. Two uncontrolled cohort studies described

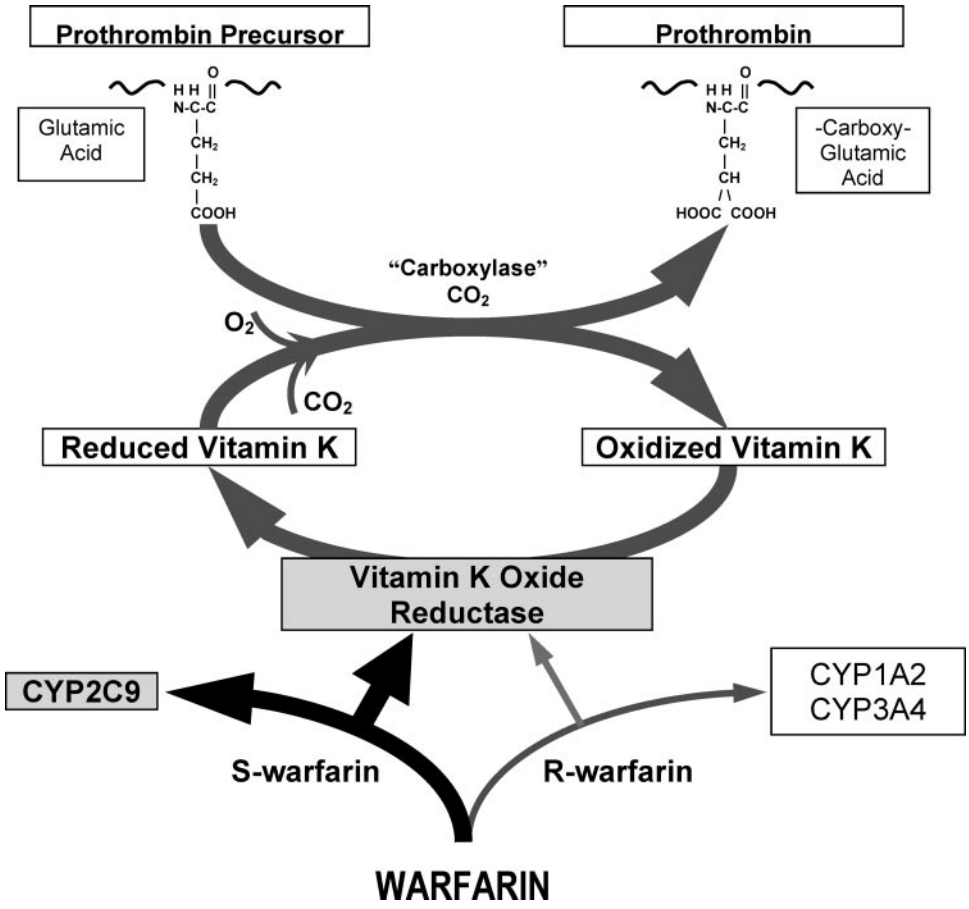

FIGURE 1. Vitamin K_1 is reduced to vitamin KH_2. The major warfarin-sensitive enzyme in this reaction is the vitamin K oxide reductase mainly inhibited by the S enantiomer of warfarin. S-warfarin is metabolized by the p450 cytochrome enzyme, CYP2C9.

reduced bone density in children on warfarin for > 1 year, but the role of the underlying disorders in reducing bone density remains unclear.[20]

1.1 Pharmacokinetics and Pharmacodynamics of Warfarin

Warfarin is the most common VKA in clinical use. It is a racemic mixture of two optically active isomers, the R and S enantiomers. Warfarin is highly water soluble, rapidly absorbed from the GI tract, has high bioavailability,[21,22] and reaches maximal blood concentrations about 90 min after oral administration.[21,23] Racemic warfarin has a half-life of 36 to 42 h[24] (R-warfarin, 45 h; S-warfarin, 29 h); circulates bound to plasma proteins (mainly albumin); and accumulates in the liver, where the two enantiomers are metabolically transformed by different pathways (Fig 1).[24] The S enantiomer of warfarin (2.7 to 3.8 times more potent than the R enantiomer) is metabolized primarily by the CYP2C9 enzyme of the cytochrome P450 system.[25] The less potent R enantiomer is metabolized primarily by two cytochrome enzymes, 1A2 and 3A4. The relationship between the dose of warfarin and the response is modified by genetic and environmental factors that can influence the absorption of warfarin, its pharmacokinetics, and its pharmacodynamics.

Like warfarin, acenocoumarol and phenprocoumon also exist as optical isomers but with different stereochemical characteristics. R-acenocoumarol has an elimination half-life of 9 h; is primarily metabolized by CYP2C9 and CYP2C19; and is more potent than S-acenocoumarol due to faster clearance of S-acenocoumarol, which has an elimination half-life of 0.5 h and is primarily metabolized by CYP2C9.[26] Phenprocoumon is a much longer-acting agent, with both the R- and the S-isomers having elimination half-lives of 5.5 days. Both are metabolized by CYP2C9, and S-phenprocoumon is 1.5 to 2.5 times more potent than R-phenprocoumon.[27]

Superwarfarin rodenticides are commonly used in the United States, and most contain brodifacoum, a

4-hydroxycoumarin with high lipid solubility and an elimination half-life of 24 days.[28] In cases of accidental or intentional brodifacoum poisoning, the principal treatment is vitamin K, with repeated doses given anywhere from daily to every few days to counteract the long half-life of brodifacoum.[28,29] For patients who are actively bleeding, immediate reversal can be achieved with factor concentrates, such as prothrombin complex concentrates (PCCs) or recombinant factor VIIa along with repeated daily administration of vitamin K.[30]

1.1.1 Genetic Factors

There are a number of mutations in the gene coding for the cytochrome P450 2C9 hepatic microsomal enzyme, which is responsible for the oxidative metabolism of the more potent warfarin S enantiomer,[24,31–35] and these mutations will alter the pharmacokinetics of warfarin. The most common and best documented alleles, designated 2C9*2 or 2C9*3 to differentiate it from the wild type, 2C9*1, are associated with an impaired ability to metabolize S-warfarin, resulting in an increased S-warfarin elimination half-life. Mutations in this gene are independently responsible for the reduced warfarin requirements seen in individuals with one or more combinations of these polymorphisms (Table 1).[32,36,37] Several investigations[32,37,38] have shown that these mutations, as well as others,[34,39,40] also are associated with an increase in adverse clinical outcomes that also occur with the use of acenocoumarol but not with phenprocoumon.[41,42]

The target for warfarin's inhibitory effect on the vitamin K cycle is the vitamin K oxide reductase (VKOR) enzyme first described in 1974.[43] The gene coding for the VKOR protein was recently identified and found to be located on the short arm of chromosome 16.[44,45] The gene encodes for several isoforms of the protein that collectively are termed the VKOR complex 1 (VKORC1). Subsequently, mutations in this gene have been identified, leading to enzymes with varying sensitivities to inhibition by warfarin,[45,46–50] thereby affecting the pharmacodynamics of warfarin. These mutations are likely to be the cause of hereditary warfarin resistance in some individuals.[50] The mutations occur with differing frequencies in various ethnic populations and account, in part, for the difference in warfarin doses required to maintain a therapeutic international normalized ratio (INR)[35,46–48,51] (Table 1).

Another genetic mutation that affects the pharmacodynamics of warfarin is in the factor IX propeptide. It causes selective reduction in factor IX during treatment with coumarin drugs without excessive prolongation of the prothrombin time (PT).[33] Factor IX activity decreases to about 1 to 3% of normal, whereas levels of other vitamin K-dependent coagulation factors decrease to 30 to 40% of normal. Two distinct missense mutations involving the propeptide coding region have been described. They are estimated to occur in $< 1.5\%$ of the population and are expressed as selectively increased sensitivity to the VKA-mediated reduction of factor IX activity.[52] This selective marked reduction in factor IX activity has been reported[33,52] to increase the risk of bleeding during anticoagulant therapy, and management of such rare patients can be difficult.[53]

Table 1—*Observed Frequency of CYP2C9 and VKORC* Variants Among Various Ethnic Groups (Section 1.1.1)*

CYP2C9 genetic alleles† point mutation	CYP2C9*1 Arg_{144}/IIc_{359}, %	CYP2C9*2 Cys_{144}/IIc_{359}, %	CYP2C9*3 Arg_{144}/Leu_{351}, %	CYP2C9*4 Arg_{144}/Thr_{359}, %	CYP2C9*5 Arg_{144}/Glu_{360}, %
Ethnic group					
White	79–86	8–19.1	6–10	ND	ND
Indigenous Canadian	91	3	6	ND	ND
African American	98.5	1–3.6	0.5–1.5	ND	2.3
Asian	95–98.3	0	1.7–5	0–1.6%	0
VKORC genetic					
Haplotype	H1 CCGATCTCTG	H7 TCGGTCCGCA			
Sequence‡	H2 CCGAGCTCTG	H8 TAGGTCCGCA			
		H9 TACGTTCGCG			
Ethnic group, %					
European	37	58			
African	14	49			
Asian	89	10			

*CYP2C9 and VKORC data from Wittkowsky[32] and Rieder et al.[47] ND = not determined.

†CYP2C9*2, *3, *4, and *5 represent genetic polymorphisms of the wild-type enzyme, CYP2C9*1.

‡H1 and H2 represent warfarin-sensitive haplotype. H7, H8, and H9 represent warfarin-resistant haplotype.

1.1.2 Environmental Factors and Drug Interactions

Environmental factors such as drugs, diet, and various disease states can alter the pharmacokinetics of warfarin.[54] 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.[55] These latter effects may be through stereoselective or nonselective pathways.[56,57] (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.[54] 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[54] in their systematic review.

The inhibition of S-warfarin metabolism is more important clinically because this enantiomer is five times more potent than the R enantiomer as a VKA.[56,57] Phenylbutazone,[58] sulfinpyrazone,[59] metronidazole,[60] and trimethoprim-sulfamethoxazole[61] inhibit the clearance of S-warfarin, and each potentiates the effect of warfarin on the PT. In contrast, drugs such as cimetidine and omeprazole, which inhibit the clearance of the R-isomer, potentiate the PT only modestly in patients who have been treated with warfarin.[57,60,62] Amiodarone is a potent inhibitor of the metabolic clearance of both the S enantiomer and the R enantiomer and potentiates warfarin anticoagulation.[63] The anticoagulant effect is inhibited by drugs like barbiturates, rifampin, azathioprine, and carbamazepine, which increase hepatic clearance. Long-term alcohol consumption has a similar potential to increase the clearance of warfarin, but ingestion of even relatively large amounts of wine had little influence on the PT in normal volunteers who were given warfarin.[64] The effect of enzyme induction on warfarin therapy has been discussed in more detail in a critical review.[65]

Drugs also may influence the pharmacodynamics of warfarin by inhibiting the synthesis of or increasing the clearance of vitamin K-dependent coagulation factors or by interfering with other pathways of hemostasis. The anticoagulant effect of warfarin is augmented by second-generation and third-generation cephalosporins, which inhibit the cyclic interconversion of vitamin K[66,67]; by thyroxine, which increases the metabolism of coagulation factors[68]; and by clofibrate through an unknown mechanism.[69] Doses of salicylates of > 1.5 g/d[70] may augment the anticoagulant effect of warfarin. The commonly held view that acetaminophen does not significantly augment warfarin's effect has been challenged. Thus, a potentiating effect of acetaminophen has been reported when large doses are used over prolonged periods.[71,72] Although the potentiating effect may be minimal and inconsistent in some cases, large doses of acetaminophen have been shown to prolong the INR in a recent randomized, blinded trial.[73] Acetaminophen's mechanism of warfarin potentiation is possibly by inhibition of VKOR by a toxic metabolite of the drug,[74] although the accumulation of this metabolite may vary among individuals, thus accounting for a variable potentiating effect.[75] Heparin potentiates the anticoagulant effect of warfarin but in therapeutic doses produces only a slight prolongation of the PT. The mechanisms by which erythromycin[76] and some anabolic steroids[77] potentiate the anticoagulant effect of warfarin are unknown. Sulfonamides and several broad-spectrum antibiotic compounds may augment the anticoagulant effect of warfarin in patients consuming diets that are deficient in vitamin K by eliminating bacterial flora and aggravating vitamin K deficiency.[78]

Aspirin,[79] nonsteroidal antiinflammatory drugs (NSAIDs),[80,81] penicillins in high doses,[82,83] and moxalactam[67] increase the risk of warfarin-associated bleeding by inhibiting platelet function. Of these drugs, aspirin is the most important because of its widespread use and prolonged effect.[84,85] Aspirin and NSAIDs also can produce gastric erosions that increase the risk of upper GI bleeding. This effect can occur even with cyclooxygenase-2 inhibitors, which were originally believed to be less likely to predispose to gastric bleeding than NSAIDs.[81] In one case-controlled analysis of 98,821 subjects on warfarin identified in linked databases, celecoxib and rofecoxib were associated with a 1.7-fold or 2.4-fold risk of GI hemorrhage, respectively.[81] The risk of clinically important bleeding is heightened when high doses of aspirin are taken during high-intensity warfarin therapy (INR range, 3.0 to 4.5).[79,86] However, low doses of aspirin (*ie*, 75 to 100 mg daily) combined with moderate-intensity and low-intensity warfarin anticoagulation therapy also are associated with increased rates of bleeding.[87,88]

Nutritional supplements and herbal products are particularly problematic in that warfarin-treated patients often fail to inform physicians that they are using such products, and physicians rarely ask. In one survey of 1,200 subjects from four large anticoagulation clinics, one third used dietary supplements, and one third indicated that their provider failed to discuss potential interactions with them.[89] There is

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 l 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
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.

also little or no standardization of the content of such products, especially herbal remedies, and reports of interactions often are anecdotal or single-case studies without good substantiation.[90–93] Of the higher-quality studies, ginkgo and ginger were shown not to have an effect on warfarin in healthy subjects in a randomized, open-label, crossover study,[94] and coenzyme Q_{10} (and ginkgo) were shown not to have an effect in a randomized, double-blind, crossover study.[95] Ginseng was shown to reduce the effect of warfarin in a randomized, placebo-controlled trial.[96] Not surprisingly, products with a high content of vitamin K, such as green tea, were shown to reduce the anticoagulant effect of warfarin.[54]

Subjects receiving long-term warfarin therapy are sensitive to fluctuating levels of dietary vitamin K,[97,98] which is derived predominantly from phylloquinones in plant material.[98] Sadowski et al[99] have listed the phylloquinone content of a wide range of foodstuffs, which also can be found on the Internet (http://ods.od.nih.gov/factsheets/cc/coumadin1.pdf). Phylloquinones act through the warfarin-insensitive pathway.[100] Important fluctuations in vitamin K intake can occur in both healthy and sick subjects.[101] An increased intake of dietary vitamin K that is sufficient to reduce the anticoagulant response to warfarin[97] occurs in patients consuming green vegetables or vitamin K-containing supplements, while following weight-reduction diets, and in patients who have been treated with vitamin K supplements. Reduced dietary vitamin K intake potentiates the effect of warfarin in sick patients who have been treated with antibiotics and IV fluids without vitamin K supplementation and in patients who have states of fat malabsorption.

Hepatic dysfunction potentiates the response to warfarin through the impaired synthesis of coagulation factors. Hypermetabolic states produced by fever or hyperthyroidism increase warfarin responsiveness, probably by increasing the catabolism of vitamin K-dependent coagulation factors.[68,102]

1.2 The Antithrombotic Effect of VKAs

The antithrombotic effect of VKAs has conventionally been attributed to their anticoagulant effect, which in turn is mediated by the reduction of four vitamin K-dependent coagulation factors. Evidence suggests, however, that the anticoagulant and antithrombotic effects can be dissociated and that the reduction of prothrombin and possibly factor X are more important than the reduction of factors VII and IX for the antithrombotic effect. This evidence is indirect and has been derived from the following observations. First, the experiments of Wessler and Gitel[103] more than 40 years ago using a stasis model of thrombosis in rabbits showed that the antithrombotic effect of warfarin requires 6 days of treatment, whereas an anticoagulant effect develops in 2 days. The antithrombotic effect of warfarin requires the reduction of prothrombin (factor II), which has a relatively long half-life of about 60 to 72 h compared with 6 to 24 h for other vitamin K-dependent factors that are responsible for the more rapid anticoagulant effect. Second, in a rabbit model of tissue factor-induced intravascular coagulation,[104] the protective effect of warfarin was mainly a result of lowering prothrombin levels. Third, Patel and associates[105] demonstrated that clots formed from umbilical cord plasma containing about half the prothrombin concentration of plasma from adult control subjects generated significantly less fibrinopeptide A than clots formed from maternal plasma. The view that warfarin exerts its antithrombotic effect by reducing prothrombin levels is consistent with observations that clot-bound thrombin is an important mediator of clot growth[106] and that reduction in prothrombin levels decreases the amount of thrombin generated and bound to fibrin, thereby reducing thrombogenicity.[105]

The suggestion that the antithrombotic effect of warfarin is reflected in lower levels of prothrombin forms the basis for overlapping the administration of heparin with warfarin until the PT or INR is prolonged into the therapeutic range during the treatment of patients with thrombosis. Because the half-life of prothrombin is about 60 to 72 h, at least 4 days of overlap is necessary. Furthermore, the levels of native prothrombin antigen during warfarin therapy more closely reflect antithrombotic activity than the PT.[107]

1.3 Monitoring Anticoagulation Intensity

The PT test[108] is the most common test used to monitor VKA therapy. The PT responds to a reduction of three of the four vitamin K-dependent procoagulant clotting factors (*ie*, II, VII, X) that are reduced by warfarin at a rate proportional to their respective half-lives. Thus, during the first few days of warfarin therapy, the PT reflects mainly a reduction of factor VII, the half-life of which is approximately 6 h. Subsequently, the reduction of factors X and II contributes to prolongation of the PT. The PT assay is performed by adding calcium and thromboplastin to citrated plasma. Thromboplastins vary in responsiveness to a reduction of the vitamin K-dependent coagulation factors. An unresponsive thromboplastin produces less prolongation of the PT for a given reduction in vitamin K-dependent clotting factors than a responsive one. The responsiveness of a thromboplastin can be measured by assessing its international sensitivity index (ISI) [see below]. Highly sensitive thromboplastins (ISI, approx-

imately 1.0) that comprise human tissue factor produced by recombinant technology and defined phospholipid preparations are now available. Poller[109] and Kirkwood,[110] have reviewed the history of standardization of the PT, and more detailed discussions can be found in prior editions of this article.[111]

PT monitoring of warfarin treatment is not standardized when expressed in seconds, as a simple ratio of the patient's plasma value to that of plasma from a healthy control subject, or as a percentage of diluted normal plasma. A calibration model,[110] which was adopted in 1982, is now used to standardize reporting by converting the PT ratio measured with the local thromboplastin into an INR, calculated as follows:

$$\text{INR} = (\text{patient PT/mean normal PT})^{\text{ISI}}$$

or

$$\log \text{INR} = \text{ISI} (\log \text{observed PT ratio})$$

where ISI denotes the ISI of the thromboplastin used at the local laboratory to perform the PT measurement. The ISI reflects the responsiveness of a given thromboplastin to the reduction of the vitamin K-dependent coagulation factors compared with the primary World Health Organization (WHO) international reference preparations so that the more responsive the reagent, the lower the ISI value.[109,110] As the INR standard of reporting was widely adopted, a number of problems surfaced, which are listed in Table 3 and reviewed briefly below.

The INR is based on ISI values derived from the plasma of patients who had received stable anticoagulant doses for at least 6 weeks.[112] As a result, the INR is less reliable early in the course of warfarin therapy, particularly when results are obtained from different laboratories. Even under these conditions, however, the INR is more reliable than the unconverted PT ratio[113] and is thus recommended during both the initiation and maintenance of warfarin treatment. The validity of the INR in other conditions of impaired coagulation has not been fully evaluated. Although the INR may be no worse a measure of impaired coagulation in liver disease than the PT in raw seconds or the unconverted PT ratio,[114,115] there is evidence that the PT reported in percent activity based on a dilution curve of normal plasma is a more accurate reflection of liver-induced coagulation impairment.[116,117]

The INR accuracy can be influenced by reagents of different sensitivities[118] and by the automated clot detectors now used in most laboratories.[119–126] In general, the College of American Pathologists has recommended[127] that laboratories use thromboplastin reagents that are at least moderately responsive (*ie*, ISI, < 1.7) and reagent/instrument combinations for which the ISI has been established and validated.

Table 3—*Potential Problems With the INR (Causes of Erroneous INR) [Section 1.3]

Problems	Description
Incorrect PTR from erroneous PT determination due to pretest variables (sampling and blood collection problems)	Trisodium citrate concentration, storage time, storage temperature, evacuated tube effects, inadequate sample, variations in manual technique
Incorrect normal value	From nonuse of MNPT, error in MNPT due to: (1) unrepresentative selection; (2) technical faults (see above); (3) nonuse of geometric mean
Incorrect ISI of local thromboplastin reagent/test system from lack of reliability of the ISI result provided by the manufacturer	Incorrect choice of IRP; poor distribution of coumarin test samples across treatment range; inadequate numbers of test samples in ISI calibration; incorrect transformation of PTR of test plasmas to INR
Drift of ISI since original calibration	
Instrument (coagulometer) effects on INR at local site	
Lupus anticoagulant effects on some thromboplastin reagents	
Lack of reliability of the INR system when used at the onset of warfarin therapy and for screening for a coagulopathy in patients with liver disease	
Relative lack of reliability of INR > 4.5, as these values are excluded from ISI calibrations	

*IRP = international reference preparation; MNPT = mean normal PT; PTR = prothrombin time ratio.

ISI values provided by the manufacturers of thromboplastin reagents are not invariably correct when applied locally,[128–130] and this adversely affects the reliability of measurements. Local calibrations can be performed using plasma samples with certified PT values to determine the instrument-specific ISI. The mean normal plasma PT is not interchangeable with a laboratory control PT.[131] Therefore, the use of other than a properly defined mean normal PT can yield erroneous INR calculations, particularly when less responsive reagents are used. The mean normal PT should be determined with each new batch of thromboplastin with the same instrument used to assay the PT.[131]

The concentration of citrate that is used to anticoagulate plasma may affect the INR.[132,133] In general, higher citrate concentrations (3.8%) lead to higher INR values,[132] and underfilling the blood collection tube spuriously prolongs the PT because

excess citrate is present. Using collection tubes containing 3.2% concentrations of citrate for blood coagulation studies and adequately filling them can reduce this problem.

1.4 Optimal Therapeutic Range

The optimal target range for the INR is likely not to be the same for all indications. It is likely to be influenced not only by the indication for its use, but also by patient characteristics. Thus, in patients who are at very high risk of bleeding, it might be prudent to sacrifice some efficacy for safety. Bleeding, the major complication of oral anticoagulant therapy, is closely related to the intensity of anticoagulation.[134–139] Accordingly, there has been interest in establishing the lowest effective therapeutic range.[139–148] Universal agreement has not been reached on the optimal range for the various indications because data on the topic are incomplete. For example, European experts tend to recommend higher ranges for patients with mechanical heart valves than do North American experts.[146,149–151]

Investigators have used various methodologic approaches to establish the most appropriate range for different indications, as follows: (1) randomized trials in which patients are assigned to two different target ranges[142–145,152,153]; (2) indirect comparisons of results of randomized trials comparing patients treated with different intensities of anticoagulants or to those treated with another antithrombotic agent (usually aspirin)[154–157]; (3) subgroup analyses of observational studies (including within treatment groups of randomized trials) relating the observed INR or time spent in an INR range at the time of the outcome to either a bleeding event or a thromboembolic event[137–140,158,159]; and (4) case-control studies in which the INR levels at the time of an event are recorded and compared with INR levels in appropriately selected control subjects.[141] All of these designs have limitations, but a randomized trial that compares two target INR ranges provides results that are closest to the truth because if appropriately designed, it minimizes bias.[160]

Four randomized studies[142–145] have compared a moderate-intensity INR (approximately 2.0 to 3.0) to higher-intensity adjusted dose oral anticoagulation, and all reported that the moderate intensity reduced the risk of clinically important bleeding without reducing efficacy. In two of these studies, one in patients with venous thromboembolism[142] and the other in patients with tissue heart valves,[143] patients assigned to an INR intensity of 2.0 to 3.0 experienced less bleeding without apparent loss of efficacy than those who were assigned to an INR of 3.0 to 4.5. The results of these trials influenced the decision to lower the target INR range in North America to 2.0 to 3.0 for these and other indications.[150,151] Recently, a randomized trial demonstrated that an INR of < 2.0 (INR target, 1.5 to 2.0)[152] reduced the recurrence of venous thrombosis after an initial 3 to 6 months of standard treatment when compared to placebo. A subsequent clinical trial,[153] however, found that maintaining an INR intensity of 2.0 to 3.0 in the same setting was more effective than a lower intensity of 1.5 to 2.0 and was not associated with a greater risk of bleeding.

Fixed minidose warfarin (1 mg daily) has been evaluated in a number of clinical settings. A small randomized trial[161] reported the finding that fixed minidose warfarin (*ie*, 1 mg daily) was effective in preventing subclavian vein thrombosis in patients with malignancy who had indwelling catheters. Subsequently, two prospective cohort studies[162,163] reported a reduced incidence of catheter thrombosis compared to historical controls in patients treated with 1 mg warfarin. In contrast, two larger randomized studies failed to support the effectiveness of warfarin.[164,165] Heaton et al[165] randomized 88 patients and objectively documented thrombosis in 18% of the warfarin group vs 12% of the placebo group. Couban et al[164] randomized 255 patients and reported a 5% rate of symptomatic deep vein thrombosis (DVT) in the warfarin-treated group vs 4% in the placebo group. Investigators have reported similar findings of the ineffectiveness or reduced effectiveness of fixed minidose warfarin compared to dose-adjusted warfarin (INR, 2.0 to 3.0). Three of these studies[164–170] evaluated its efficacy following major orthopedic surgery, and one each evaluated its efficacy in patients with indwelling catheters,[164] atrial fibrillation,[169] or acute myocardial infarction.[170] Therefore, therapy with fixed minidose warfarin is either ineffective or much less effective than that with dose-adjusted warfarin in moderate-to-high-risk situations.

Oral anticoagulants are effective in preventing stroke[171–175] and prolonging survival in patients with atrial fibrillation.[176] Although moderate-intensity warfarin therapy (INR, 2.0 to 3.0) has not been directly compared with higher-intensity regimens in atrial fibrillation, the recommendation of a target INR of 2.0 to 3.0 is supported by the following evidence: (1) indirect comparison of several randomized trials[155–157,177,178] showed that moderate-intensity warfarin regimen (INR, 2.0 to 3.0) resulted in a similar risk reduction as higher-intensity regimens; (2) a randomized trial[179] reported that adjusted-dose warfarin therapy (INR, 2.0 to 3.0) was more effective than the combination of fixed-dose warfarin (3 mg) and aspirin; and (3) a subgroup analysis of one prospective study,[140,159] the results of one case-control study,[141] one prospective cohort study,[180] and two prospective registries[181,182]

showed that the efficacy of oral anticoagulant agents is reduced when the INR falls to < 2.0.

In contrast to studies in the primary and secondary prevention of venous thrombosis and in the prevention of systemic embolism in patients with atrial fibrillation, warfarin at an INR of 2.0 to 3.0 has not been compared to a higher target INR in patients with acute myocardial infarction except when the oral anticoagulant was combined with aspirin. Two randomized trials[183,184] reported that a higher-intensity warfarin regimen (INR, 3.0 to 4.0) is more effective than aspirin alone in preventing recurrent infarction, stroke, or death and is as effective and at least as safe as the combination of aspirin and a moderate-intensity anticoagulant regimen (INR, 2.0 to 2.5) following an episode of acute coronary syndrome. In contrast, the combination of aspirin and moderate-intensity anticoagulation (INR, 2.0 to 3.0) is more effective than aspirin alone following an episode of acute coronary syndrome, albeit, at a significantly greater risk of major bleeding.[85] The combination of a lower-intensity anticoagulant regimen (INR, 1.5 to 2.5) and aspirin has been shown to be no more effective than aspirin alone.[185,186] These secondary prevention studies contrast with those reported in the primary prevention of myocardial infarction in which low-intensity warfarin therapy (INR, 1.3 to 1.8) either used alone or in combination with aspirin was effective in high-risk men.[88]

In conclusion, a single therapeutic range for VKAs may not be optimal for all indications. However, a moderate-intensity INR (2.0 to 3.0) is effective for most indications. The possible exception is the primary prevention of myocardial infarction in high-risk patients in which a lower INR is preferable. In addition, a lower INR range (1.5 to 2.0) is effective in patients with venous thrombosis who have received 6 months of full-dose treatment (INR, 2.0 to 3.0), although the lower intensity is less effective than the higher intensity. Fixed-dose warfarin therapy has a reduced efficacy or none at all. The optimal intensity for patients with prosthetic heart valves remains uncertain, although there is evidence that such patients do not require the very-high-intensity regimens that have been used in the past. Although defining an appropriate range is an important step in improving patient outcomes, it is only the first of two steps. The second is ensuring that the targeted range is achieved promptly and maintained. In general, success in achieving this second goal has been suboptimal. It is better when the INR is controlled by experienced personnel in anticoagulant clinics and by using computer-assisted dosage adjustment.[187] Clinicians can find specific recommendations regarding the optimal intensity of therapy for each of these indications in the articles in this supplement that deal with each indication.

2.0 Dose Management of VKA Therapy

Using the correct intensity of a coumarin anticoagulant and maintaining the patient in the therapeutic range are two important determinants of its therapeutic effectiveness and safety. High-quality dose management is needed to achieve and maintain the INR in the therapeutic range. The ability of the health-care provider to make appropriate dosage and follow-up decisions can have a major impact on therapeutic effectiveness. The comprehensive management of the VKAs requires a knowledgeable health-care provider, an organized system of follow-up, reliable PT monitoring, and good patient communication and education.[187–189]

The following discussion addresses a number of management issues pertaining to the use of VKAs. A systematic review of the literature was performed based on predefined criteria for the population at risk, the intervention or exposure evaluated, the outcomes assessed, and the methodology of the trials evaluated (Table 4).

2.1 Initiation and Maintenance Dosing

Following the administration of warfarin, an initial effect on the INR usually occurs within the first 2 or 3 days, depending on the dose administered, and an antithrombotic effect occurs within the next several days.[190,191] Heparin or low-molecular-weight heparin should be administered concurrently when a rapid anticoagulant effect is required, and its administration should be overlapped with warfarin until the INR has been in the therapeutic range for at least 2 days to allow for further reduction of factors X and II. A loading dose (*ie*, > 10 mg) of warfarin is not recommended. A number of randomized studies have supported the use of a lower initiation dose. Harrison et al[190] and Crowther et al[192] found that in hospitalized, predominantly elderly patients, commencing with an average maintenance dose of 5 mg warfarin usually results in an INR of > 2.0 in 4 or 5 days with less excessive anticoagulation compared to that with an initial 10-mg dose. Kovacs et al,[193] however, found that in outpatients who had been treated for venous thromboembolism, an initial 10-mg dose for the first 2 days of therapy compared to a 5-mg dose resulted in a more rapid achievement of a therapeutic INR (1.4 days earlier) without a difference in rates of excessive anticoagulation. This study,[193] however, included fewer patients over 75 years of age than did the study of hospitalized patients.[192] Thus, there is room for flexibility in selecting a starting dose of warfarin. Some clinicians prefer to use a large starting dose (*eg*, 7.5 to 10 mg), whereas a starting dose of ≤ 5 mg might be appropriate in elderly patients; in patients with impaired nutrition, liver dis-

Table 4—*Question Definition and Eligibility Criteria for Managing Oral Anticoagulant Therapy for Which Recommendations Are Being Proposed (Section 2.0)**

Section	Population	Intervention or Exposure	Outcomes	Methodology	Exclusion Criteria
2.1.1	Patients taking VKA	Initial dosing of VKA	Time to achieve therapeutic range; rates of supratherapeutic or subtherapeutic INR	RCT	< 25 patients
2.1.2	Elderly patients taking VKA	Initial dosing of VKA	Time to achieve therapeutic range; rates of supratherapeutic or subtherapeutic INR	RCT; prospective cohort; observational	< 25 patients
2.1.3	Patients taking VKA	Frequency of INR monitoring (higher vs lower frequency)	TTR; rates of hemorrhage or thromboembolism	RCT; prospective cohort; observational	None
2.1.4	Patients taking VKA with nontherapeutic INR without bleeding	Dose management; use of vitamin K to correct INR	Time to return to therapeutic INR; hemorrhage or thromboembolism	RCT; prospective cohorts; observational	Reports before 1995
2.1.4	Patients taking VKA with any INR and active bleeding or need for emergent reversal of INR	Dose management; use of vitamin K, FFP, PCCs, rVIIa to reverse INR or bleeding	Time to return to therapeutic INR; hemorrhage or thromboembolism	RCT; prospective cohorts; observational	None
2.1.5	Patients taking VKA with unstable or variable INR over time	Dose management; use of vitamin K to stabilize INR	Stability of INR within therapeutic range	RCT; prospective cohorts	None
2.1.7	Patients with antiphospholipid syndrome and taking VKA	INR therapeutic range	Hemorrhage or thromboembolism	RCT; prospective cohort; observational; registries	None
2.3.1	Patients taking VKA	UC vs AMS care	TTR; hemorrhage or thromboembolism	RCT; prospective cohort; observational	< 100 patients; use of PT rather than INR
2.3.3	Patients taking VKA	Use of POC monitor at home to measure INR and/or to adjust VKA dose compared to UC or AMS	TTR; hemorrhage or thromboembolism	RCT; prospective cohort; observational	< 50 patients

*FFP = fresh frozen plasma; rVIIa = recombinant factor VIIa; RCT = randomized controlled trial.

ease, or congestive heart failure (CHF); and in patients who are at high risk of bleeding. An initial dose of 2 to 3 mg is appropriate for patients who have undergone heart valve replacement.[194,195]

In the past few years, studies have shown that pharmacogenetics plays an important role in the pharmacokinetic and pharmacodynamic behavior of warfarin. Single nucleotide polymorphisms (SNPs) in the gene coding for CYP2C9, the principal enzyme responsible for metabolizing the S enantiomer of warfarin, will significantly alter the rate of metabolism (*ie*, half-life) of warfarin, affecting both the rapidity of initial effect and the dose required to maintain a therapeutic INR. Similarly, various mutations in the gene coding for the VKORC1 enzyme will lead to a protein that is either sensitive or resistant to warfarin inhibition and, thus, affect the initial dose required to achieve a therapeutic INR as well as the dose required to maintain a therapeutic INR. In a retrospective, observational analysis, Joffe et al[196] found that CYP2C9 polymorphisms independently predicted low warfarin requirements after adjusting for body mass index, age, acetaminophen use, and race (odds ratio [OR], 24.8; 95% confidence interval [CI], 3.83 to 160.78). Gage et al[197] developed a dosing algorithm based on CYP2C9 polymorphisms along with clinical and demographic factors in 369 patients on stable warfarin therapy. Older age, low body surface area, and the presence of CYP2C9*2 or CYP2C9*3 alleles were strongly associated with lower warfarin dose requirements ($p < 0.001$). The maintenance dose decreased by 8% per decade of age, by 13% per SD in body surface area, by 19% per CYP2C9*2 allele, and by 30% per CYP2C9*3 allele. These factors, along with gender, accounted for 39% of the variance

in the maintenance dose of warfarin. Sconce et al[49] similarly found that age, height, and CYP2C9 genotype significantly contributed to S-warfarin clearance in 297 patients on stable anticoagulation. The mean daily warfarin dose was highest in those who were homozygous for the CYP2C9 wild type compared to the CYP2C9*2 and CYP2C9*3 alleles. The impact of these mutations in CYP2C9 also affects acenocoumarol, although to a lesser degree because the anticoagulation potencies of the R and S enantiomers are comparable.[198]

Genetic mutations in the gene coding for the VKORC1 often involve several mutations, leading to various haplotypes that cause greater resistance to warfarin therapy. Harrington et al[50] found a warfarin-resistant individual who had high serum warfarin concentrations and a 196G > A transition, predicting a Val66Met substitution in VKORC1. In a study of 147 patients, D'Andrea et al[46] found that patients with a 1173CC genotype required a higher mean maintenance dose than those with a CT or TT genotype, as did Quteineh et al,[199] who found that a 1173 C > T polymorphism was significantly associated with the risk of anticoagulation overdose. By identifying a number of noncoding SNPs, Rieder et al[47] were able to infer that five major haplotypes are associated with different dose requirements for maintaining a therapeutic INR. The maintenance dose ranged from a low of 2.7 mg warfarin per day for the sensitive haplotypes up to 6.2 mg per day for the resistant haplotypes. Asian Americans had the higher proportion of sensitive haplotypes, whereas African Americans more frequently exhibited the resistant haplotypes (Table 1). Sconce et al[49] found that a combination of CYP2C9 and VKORC1 genotypes plus height produced the best predictive model for estimating warfarin dose, whereas Vecsler et al[200] reported that CYP2C9 and VKORC1 genotypes together with age and body weight could explain as much as 63% of the dose variance, and Herman et al[35] could explain 60% of dose variability due to CYP2C9 and VKORC1 polymorphisms, age, and body surface area.

These findings are significant not only because they may predict initial and maintenance warfarin dosing requirements, but also because certain genotypes have been associated with adverse events. Thus, Higashi et al[38] studied 185 patients, 58 with at least one variant genotype of CYP2C9, and found in those with variant genotypes an increased risk of having INRs above range (hazard ratio [HR], 1.40; 95% CI, 1.03 to 1.90) and a significant risk of a serious or life-threatening bleeding event (HR, 2.39; 95% CI 1.18 to 4.86). The latter hazard estimate was based on a few events in a very small number of patients with the variant genotypes. Joffe et al,[196] also studying CYP2C9 SNPs, found an upward trend in rates of an INR > 6.0 or of bleeding in patients who were categorized as heterozygotes or compound hetero/homozygotes compared to wild types, as did Veenstra et al.[34] A similar increased risk of bleeding was seen in patients with these polymorphisms who were taking acenocoumarol but not phenprocoumon.[41]

The ability to determine mutations in the genes coding for these two proteins will likely influence future dosing patterns (*eg*, algorithms), but just how much value they will add to conscientious monitoring of the INR and dose management remains to be determined.[201] To date, only pilot trials of genetic-based dosing have been performed with mixed results. Hillman et al[202] randomized 38 patients to standard vs genetic-based dosing and showed a nonstatistical decrease in adverse events (6 of 20 in the standard group vs 2 of 18 in the genetic-based dosing group). All patients were dosed based on an algorithm taking into account mutations in CYP2C9. Voora et al[203] dosed a single cohort of 48 orthopedic patients according to their CYP2C9 genotype in addition to age, weight, height, gender, race, and use of simvastatin or amiodarone. Although patients with a CYP2C9 variant promptly achieved a stable dose, they continued to be at higher risk of an INR > 4.0 than patients with a normal genotype. The use of genetic testing before initiating warfarin therapy is impractical in most centers because it is not available in a timely manner. The future role of genetic testing in assisting dose prediction only can be determined by appropriately designed randomized trials.

After 4 to 5 days of concomitant warfarin and heparin therapy, heparin is discontinued when the INR has been in the therapeutic range on two measurements approximately 24 h apart. This delay in discontinuing heparin allows factors X and II to be reduced to their plateau levels. If treatment initiation is not urgent (*eg*, in chronic stable atrial fibrillation), warfarin administration, without concurrent heparin administration, can be commenced out of hospital with an anticipated maintenance dose of 4 to 5 mg/d. In patients with a known protein C deficiency or another thrombophilic state, it would be prudent to begin heparin therapy before or at the same time as starting warfarin therapy to protect against a possible early hypercoagulable state caused by a warfarin-mediated reduction in the vitamin K-dependent coagulation inhibitors.[204]

Because dose requirements often change during maintenance therapy, physicians use various strategies to ensure that dosing instructions are simple and clear for the patient. Some providers prefer to use a fixed tablet strength of warfarin and to use alternate dose amounts (tablets or fraction of tablets) per day. Others prefer a uniform daily amount that might require the patient to have different tablet strengths. Both methods achieve similar outcomes, although the former practice may be more confusing for the patient.[205,206]

Recommendation

2.1.1. In patients beginning VKA therapy, we recommend the initiation of oral anticoagulation, with doses between 5 and 10 mg for the first 1 or 2 days for most individuals and subsequent dosing based on the INR response (Grade 1B)**. At the present time, for patients beginning VKA therapy, without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing** (Grade 2C)**.**

2.2 Initiation of Anticoagulation in the Elderly

The dose required to maintain a therapeutic range for patients over 60 years of age decreases with increasing age,[195,207–209] possibly because of a reduction in the clearance of warfarin with age.[210,211] Gender also influences dose, with women requiring less warfarin to maintain a therapeutic INR than men at an equivalent age.[195] In a prospective cohort study of elderly patients who were given three initial doses of 4 mg, Siguret et al[212] were able to accurately predict the maintenance dose based on the INR on the third day in 73% of patients, and within 1 mg of the maintenance dose in 95% of patients; no patient had an INR > 4.0. Therefore, in elderly patients, the initial dose of warfarin should not be > 5 mg,[213] and in some cases (*ie*, in patients with a high risk of bleeding; in those who are undernourished, have congestive heart failure (CHF), or have liver disease; or in those who have undergone heart valve replacement surgery), it should be less.[195,213] Other factors that may influence the response to anticoagulation in elderly patients include the potential for a greater number of other medical conditions and/or concurrent drug use.[207] Consequently, it is advisable to monitor older patients more frequently in order to maximize their time in the therapeutic range (TTR).[214]

Recommendation

2.2.1. In elderly patients or in patients who are debilitated, malnourished, have CHF, have liver disease, have had recent major surgery, or are taking medications known to increase the sensitivity to warfarin (*eg*, amiodarone), we recommend the use of a starting dose of ≤ 5 mg (Grade 1C) **with subsequent dosing based on the INR response.**

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[215,216] 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[217,218] have attempted to develop predictive models with the goal of reducing the frequency of testing without sacrificing quality. Pengo et al[218] randomized 124 patients with prosthetic mechanical heart valves who were on stable therapy for at least 6 months to INR monitoring either at 6-week or at 4-week intervals. They found no difference in time in, above, or below range between the groups; however, the actual interval of monitoring was 24.9 days in the 6-week group and 22.5 days in the 4-week group ($p < 0.0003$). Other clinical trials[215,216] have suggested that during long-term treatment, the TTR and, presumably, fewer adverse events can be maximized by more frequent testing. This finding is particularly true in studies using patient self-testing (PST) in which access to testing is virtually unlimited. Horstkotte et al[215] addressed this issue in 200 patients with mechanical cardiac valves and found that the percentage of INRs within the target range increased from 48% when monitoring was performed at an average interval of 24 days to 89% when monitoring was performed at an average of every 4 days by home PST using a point-of-care (POC) monitor. In a recent study of $> 4{,}000$ patients with chronic atrial fibrillation and $> 250{,}000$ INRs, Shalev et al[219] found a greater time in range as the testing interval decreased from every 5 weeks to every 3 weeks (41 to 48%, $p < 0.0005$), and the investigators suggested that patients should be monitored no longer than every 4 weeks. More frequent monitoring may be advisable for patients who exhibit an unstable dose response.

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).

2.4 Management of Nontherapeutic INRs With or Without Bleeding

Fluctuations in INR may occur because of any one or more of the following conditions: (1) inaccuracy in INR testing; (2) changes in vitamin K intake; (3) changes in vitamin K or warfarin absorption; (4) changes in warfarin metabolism; (5) changes in vitamin K-dependent coagulation factor synthesis or metabolism; (6) other effects of concomitant drug use; or (7) patient noncompliance. The management of patients whose INR is outside the therapeutic range is controversial because many of the various options have not been compared.

When the INR is nontherapeutic, there are many options for dose adjustments. Patients whose INR is just outside the therapeutic range can be managed by either adjusting the dose up or down in increments of 5 to 20% based on the cumulative weekly dose of warfarin or by more frequent monitoring, the latter with the expectation that the INR will return to therapeutic levels without a dosage change. Because the absolute daily risk of bleeding is low even when the INR is excessively prolonged, many physicians manage patients with minimally elevated INRs by more frequent monitoring without a dose change[220] or for higher INR values between 4.0 and 10.0, by stopping warfarin for 1 day or more, reducing the weekly dose, and monitoring more frequently.[221,222] Hylek et al[223] reported that when two doses of warfarin were withheld in patients whose INR was > 6.0, the INR returned more slowly if their maintenance dose was lower, they were of older age, they had a higher initial INR, they had decompensated CHF, or they had active cancer. Among 562 patients with an INR between 6.0 and 10.0, the subsequent INR measurement after withholding two doses of warfarin was < 4.0 in 67% of patients and < 2.0 in 12% of patients. Garcia et al[222] assessed the management of 979 patients who presented with an INR between 5.0 and 9.0. Vitamin K was used in only 8.7% of the episodes of elevated INR values, and major bleeding occurred in 1% of all patients in the following 30 days. If the patient is at intrinsically high risk of bleeding or if bleeding has already developed, patients also can be managed by omitting one or more doses, by more frequent monitoring, and by actively intervening to lower the INR more rapidly. The interventions include administering vitamin K and/or infusing fresh frozen plasma,[224] prothrombin concentrates,[225] or recombinant factor VIIa.[226–230] The choice of approach is based largely on the potential risk of bleeding, the presence of active bleeding, and the level of the INR. Crowther et al[231] compared either stopping warfarin or administering oral vitamin K in a randomized trial of patients with an INR of between 4.5 and 10. Those not treated with vitamin K experienced a higher rate of minor bleeding in the following 3 months compared to those who were treated with vitamin K (4% vs 17%, respectively; $p = 0.05$). Ageno et al[232] randomized 59 mechanical heart valve patients with an INR between 6.0 and 12.0 to either 1 mg of oral vitamin K or to no treatment. Although no major bleeding occurred in either group in this small study, 1 mg of oral vitamin K more commonly returned a prolonged INR value to the therapeutic or near-therapeutic range within 1 day than in the no-treatment group (mean INR in 24 h, 2.99 vs 5.23, respectively). Three patients in the vitamin K group had an INR of < 1.8 compared to zero in the control group. Finally, Gunther et al[233] managed 75 episodes of an INR > 10, treating 51 episodes with low-dose vitamin K (2 mg) compared with 24 episodes with no treatment. There were no major bleeds in the treated patients vs three clinically important bleeds in the nontreated patients.

The response to vitamin K administered subcutaneously is less predictable than to oral vitamin K and is sometimes delayed.[234–236] Some studies[236–240] have confirmed earlier reports that oral administration is predictably effective and has the advantages of safety and convenience over parenteral routes. If a decision is made to use vitamin K, it should be administered in a dose that will quickly lower the INR into a safe, but not subtherapeutic range without causing resistance once warfarin is reinstated[241] or without exposing the patient to the risk of anaphylaxis.[242] High doses of vitamin K, though effective, may lower the INR more than is necessary and may lead to warfarin resistance for 1 week or more. Low doses of vitamin K and slow infusion rates are recommended, but there is no definitive evidence that anaphylaxis can be avoided by using low doses or slow infusion rates.[243] A dose range of 1.0 to 2.5 mg is effective when the INR is between 5.0 and 9.0, but larger doses (*ie*, 2.5 to 5 mg) are required to correct INRs of > 9.0. Vitamin K also can be administered by slow IV infusion when there is a greater urgency to reverse anticoagulation[234,244] or an impairment in vitamin K absorption. IV injection may be associated with anaphylactic reactions,[242,243] although such reactions have occurred with non-IV routes of administration.[243]

For life-threatening bleeding, immediate correction of the INR is mandatory. Although fresh frozen plasma can be given in this situation, immediate and

full correction can only be achieved by the use of factor concentrates[225] because the amount of fresh frozen plasma required to fully correct the INR is considerable[245] and may take hours to infuse. Yasaka et al[246] found that a dose of 500 IU of PCC was optimal for rapid reversal for an INR of < 5.0 but that higher doses might be needed for more elevated INRs. Although not currently approved for this indication, recombinant factor VIIa has been shown to be effective in reversing therapeutic INRs to normal at varying doses (10 μg/kg to maximum cumulative dose of 400 μg/kg) in healthy volunteers[230] and to reversing supratherapeutic INRs and/or bleeding in patients on warfarin,[226] again at varying doses (15 to 90 μg/kg). In a prospective observational study of 16 patients with major bleeding on warfarin, Dager et al[247] found that a dose of approximately 16 μg/kg was adequate for rapid reversal of the INR and to achieve a desirable hemostatic effect in 14 patients. Recombinant factor VIIa has a short half-life, and vitamin K should be administered simultaneously to stimulate factor production. Recombinant factor VIIa also has been associated with an increased risk of thromboembolic events,[248] as have some PCCs.[249] Thus, one must take this potential adverse effect into consideration when using such agents. Finally, the use of PCCs or recombinant factor VIIa may vary depending on the availability of such products in one's institution. Table 5 outlines the recommendations for managing patients who are receiving coumarin anticoagulants who need their INR lowered because of actual or potential bleeding.

For patients with subtherapeutic INRs during long-term therapy, no specific studies have examined the optimal method of correction. Because the average daily risk of thrombosis for most indications is quite small, except in exceptional circumstances, most patients do not need to be covered with a rapidly acting anticoagulant, such as heparin or low-molecular-weight heparin. Rather, the weekly cumulative dose of warfarin is usually increased by 10 to 20%, and more frequent monitoring is instituted until the INR is stable. In some cases, patients may be given a one-time larger dose followed by more frequent monitoring with or without a change in the cumulative weekly dose.

Recommendations

2.4.1. For patients with INRs above the therapeutic range but < 5.0 and with no significant bleeding, we recommend lowering the dose or omitting a dose, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level. If only minimally above therapeutic range or associated with a transient causative factor, no dose reduction may be required (all Grade 1C)**.**

2.4.2. For patients with INRs ≥ 5.0 but < 9.0 and no significant bleeding, we recommend omitting the next one or two doses, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level (Grade 1C)**. Alternatively, we suggest omitting a dose and administering vita-**

Table 5—*Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving VKAs (Section 2.4)**

Condition†	Intervention
INR more than therapeutic range but < 5.0; no significant bleeding	Lower dose or omit dose; monitor more frequently and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required **(Grade 1C).**
INR ≥ 5.0, but < 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (1–2.5 mg po), particularly if at increased risk of bleeding **(Grade 1C)**. If more rapid reversal is required because the patient requires urgent surgery, vitamin K (≤ 5 mg po) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K (1–2 mg po) can be given **(Grade 2C).**
INR ≥ 9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg po) with the expectation that the INR will be reduced substantially in 24–48 h **(Grade 1B)**. Monitor more frequently and use additional vitamin K if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic.
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion), supplemented with FFP, PCC, or rVIIa, depending on the urgency of the situation; vitamin K can be repeated q12h **(Grade 1C).**
Life-threatening bleeding	Hold warfarin therapy and give FFP, PCC, or rVIIa supplemented with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR **(Grade 1C).**
Administration of vitamin K	In patients with mild to moderately elevated INRs without major bleeding, give vitamin K orally rather than subcutaneously **(Grade 1A).**

*See Table 4 for other abbreviations.

†If continuing warfarin therapy is indicated after high doses of vitamin K_1, then heparin or low-molecular-weight heparin can be given until the effects of vitamin K_1 have been reversed, and the patient becomes responsive to warfarin therapy. It should be noted that INR values > 4.5 are less reliable than values in or near the therapeutic range. Thus, these guidelines represent an approximate guide for high INRs.

min K (1 to 2.5 mg) orally, particularly if the patient is at increased risk of bleeding (Grade 2A)**. If more rapid reversal is required because the patient requires urgent surgery, we suggest vitamin K (≤ 5 mg) orally with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, we suggest additional vitamin K (1 to 2 mg) orally** (Grade 2C)**.**

2.4.3. For patients with INRs ≥ 9.0 and no significant bleeding, we recommend holding warfarin therapy and administering a higher dose of vitamin K (2.5 to 5 mg) orally, with the expectation that the INR will be reduced substantially in 24 to 48 h (Grade 1B)**. Clinicians should monitor the INR more frequently, administer additional vitamin K if necessary, and resume therapy at an appropriately adjusted dose when the INR reaches the therapeutic range.**

2.4.4. In patients with serious bleeding and elevated INR, regardless of the magnitude of the elevation, we recommend holding warfarin therapy and giving vitamin K (10 mg) by slow IV infusion supplemented with fresh frozen plasma, PCC, or recombinant factor VIIa, depending on the urgency of the situation. We recommend repeating vitamin K administration every 12 h for persistent INR elevation (all Grade 1C)**.**

2.4.5. In patients with life-threatening bleeding (*eg*, intracranial hemorrhage) and elevated INR, regardless of the magnitude of the elevation, we recommend holding warfarin therapy and administering fresh frozen plasma, PCC, or recombinant factor VIIa supplemented with vitamin K (10 mg) by slow IV infusion, repeated, if necessary, depending on the INR (Grade 1C)**.**

2.4.6. In patients with mild to moderately elevated INRs without major bleeding, we recommend that when vitamin K is to be given, it be administered orally rather than subcutaneously (Grade 1A)**.**

2.5 Management of Variable INRs

Although it has long been known that changes in dietary vitamin K intake may influence the stability of the INR in patients on warfarin, only recently have trials been conducted to assess the impact that vitamin K can have on therapeutic stability. In 1993, Sorano et al[250] showed that by stabilizing the intake of dietary vitamin K, more stable anticoagulation can be achieved. By comparing the daily vitamin K intake in 26 unstable patients with 26 stable control patients, Sconce et al[251] showed that the unstable patients had poorer intake of vitamin K. Kurnik et al[252] showed that in vitamin K-depleted patients, very small amounts of vitamin K-containing vitamins will influence the INR to a greater extent than in those with an adequate vitamin K status. In a study of 12 healthy volunteers on oral anticoagulation, Schurgers et al,[253] found that a daily dose of vitamin K of at least 150 μg was needed to alter the INR response. Reese et al[254] used a retrospective analysis to assess the effect of a daily dose of 100 μg of vitamin K_1 in nine unstable patients. These patients experienced an increase in percent INRs (range, 32 to 57%) in response to the daily vitamin K. In a prospective, open-label, crossover study, Ford et al[255] found that five of nine patients improved their stability with low-dose administration of vitamin K. As expected, the INR initially decreased in patients given vitamin K, and an increased dose of warfarin was needed to reestablish an INR in the therapeutic range, which took 2 to 35 days to achieve. Thus, patients must be monitored carefully if this intervention is tried. Finally, Sconce et al[256] conducted the first randomized, blinded trial in 70 unstable patients over a 6-month period. Vitamin K supplementation resulted in a significantly greater decrease in SD of the INR than with placebo (-0.24 ± 0.14 vs -0.11 ± 0.18; $p < 0.001$) and a significantly greater increase in percentage of time within target INR range ($28\% \pm 20\%$ vs $15 \pm 20\%$; $p < 0.01$). In these last two studies, variable INR was defined as requiring a minimum of three warfarin dose changes or three INRs outside of the therapeutic range in the preceding 6 months[255] or an INR SD > 0.5 with at least three warfarin dose changes during the previous 6 months.[256] In determining whether a patient with a variable INR response is suitable for supplemental vitamin K, one must be certain to exclude the known multiple causes of INR variability, and this requirement was also part of the two definitions above.

Recommendation

2.5.1. For patients receiving long-term warfarin therapy with a variable INR response not attributable to any of the usual known causes for instability, we suggest a trial of daily low-dose oral vitamin K (100 to 200 μg), with close monitoring of the INR and warfarin dose adjustment to counter an initial lowering of the INR in response to vitamin K (Grade 2B)**.**

2.6 Management of Oral Anticoagulation During Invasive Procedures

Clinicians often are required to decide how to manage patients who are receiving long-term anticoagulant therapy and require an invasive procedure.[257,258] Because of the complexity of this decision, the "Peri-

operative Management" chapter in this supplement is devoted to this topic (in conjunction with managing antiplatelet therapy during invasive procedures), assessing the literature and arriving at consensus recommendations.

2.7 Management of INRs in the Antiphospholipid Syndrome

Patients who have a lupus anticoagulant or anticardiolipin/β-2-glycoprotein 1 antibodies have an increased risk of thrombosis. Evidence from older observational studies[259,260] suggested that clinical outcomes are improved when the therapeutic range for such patients treated with warfarin was closer to 2.5 to 3.5 rather than 2.0 to 3.0. One potential explanation for the requirement of a higher INR is based on the observation that lupus anticoagulants are able to prolong the INR.[261] Although lupus anticoagulants typically cause prolongation of the activated partial thromboplastin time, they also may cause mild prolongation of the INR or, in the presence of specific antibodies to prothrombin, more marked prolongation of the INR. The degree of prolongation of the INR induced by lupus anticoagulants appears to depend on the reagent used.[262–264] One study[262] found that simultaneous INR values from the same sample of blood from patients who have a lupus anticoagulant and were receiving oral anticoagulants differed from 0.4 to 6.5 between reagents. Two studies[262,265] demonstrated that the standardization of INR values using either calibrated reference plasmas or locally assigned analyzer-specific ISI values can significantly reduce this variability. These latter techniques appear to enable oral anticoagulants to be reliably monitored using the INR system for some reagents but not all. Other techniques for monitoring oral anticoagulant therapy for patients with lupus anticoagulants include the measurement of prothrombin activity and native prothrombin concentration and the prothrombin and proconvertin test.[262,266–269] The validity and reliability of these latter tests have not been rigorously evaluated in controlled clinical trials for patients with lupus anticoagulants.

In a randomized controlled trial of 114 patients with antiphospholipid syndrome who had been treated with warfarin, Crowther et al[270] assigned patients to an INR of either 3.1 to 4.0 or 2.0 to 3.0. They found no difference in recurrent thromboembolism between the two groups (10.7% vs 3.4%; HR, 3.1; 95% CI, 0.6 to 15.0 high intensity vs conventional treatment), although 75% of all patients who had a recurrence were at subtherapeutic levels (INR < 2.0) or not receiving warfarin. The high-intensity group had significantly more men and a trend toward more patients with underlying lupus or arterial disease. There was no difference in major bleeding. In a similar study, Finazzi et al[271] randomized 109 patients with antiphospholipid syndrome to an INR of 3.0 to 4.5 vs conventional treatment (INR range, 2.0 to 3.0) with median follow-up of 3.6 years. Recurrent thrombosis occurred in 11.5% in the high-intensity group vs 5.5% in the conventional group (HR, 1.97%; 95% CI, 0.49 to 7.89). There was no significant difference in major bleeding (27.8% vs 14.6%; HR, 2.18; 95% CI, 0.92 to 5.15). Other investigators have reported similar outcomes in an 8-year follow-up study[272] and in a retrospective cohort study.[273]

Recommendation

2.7.1. In patients who have a lupus inhibitor and who have no additional risk factors and no lack of response to therapy, we recommend a therapeutic target INR of 2.5 (INR range, 2.0 to 3.0) (Grade 1A)**. In patients who have recurrent thromboembolic events with a therapeutic INR, we suggest a target INR of 3.0 (INR range, 2.5 to 3.5)** [Grade 2C]**.**

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.[136–145,274–277] The relationship between bleed-

ing and the level of INR has been reported to rise steeply as the INR increases > 5.0.[138,139,274,276] 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.[189,277,278] A strong relationship between TTR and bleeding or thromboembolic rates has been observed across a large number of studies,[138,171–173,189,274,276–281] 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. In a large, retrospective analysis of patients with mechanical heart valves, Cannegieter et al[138] reported a strong relationship between TTR and major bleeds or thromboembolism for INRs above or below the therapeutic range. A similar relationship has been demonstrated for other groups of patients.[141,274] 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.[189,282] 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. Table 6[172–175,283–308] summarizes data from a range of studies reporting TTR, with results grouped according to the model of dose management. Historically, many studies have failed to measure or report the quality of anticoagulation management as reflected by TTR.[309] We believe that this is a deficiency that can lead to the erroneous interpretation of results, and we urge investigators to measure and report TTR in their studies.

TTR can be determined by a variety of methods, and, therefore, comparisons between studies may be difficult.[310] TTR is most commonly expressed by one of three methods: (1) as the fraction of INR values that are within therapeutic range (*eg*, the number of INRs in range divided by the total number of INR tests); (2) as the "cross-section of the files" methodology, which assesses the fraction of patients (*ie*, INRs) in range at one point in time compared to the total number of patients who had an INR at that point in time; or (3) the linear interpolation method of Rosendaal et al,[311] which assumes that a linear relationship exists between two INR values and allocates a specific INR value to each day between tests for each patient. Each approach has its advantages and disadvantages.[310] Furthermore, the results of all of these methods depend on whether an exact or an expanded therapeutic range is used,[312] whether warfarin-naïve patients (those just beginning therapy) are included or only patients already on established therapy,[313,314] whether INRs obtained during invasive procedures when warfarin therapy might be interrupted are included, and whether different oral anticoagulant preparations (*eg*, warfarin, phenprocoumon, or acenocoumarol) are included.[314–316] Because clinical outcome studies comparing one methodology over another and their correlation with adverse events have not been done, no one method can be recommended, and the reader should be aware of these differences.

3.2.3 Patient Characteristics

Several patient characteristics are associated with higher odds of bleeding during anticoagulation therapy.[134,135,140,144,275,277,317–324] The patient factor most consistently predictive of major bleeding is a history of bleeding (especially GI bleeding).[140,144,277] 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.[134,135,140,144,277,317–324]

The relationship between older age and anticoagulant-associated bleeding has been controversial. Many older reports[137,208,277,278,322–332] indicate that older individuals do not have an increased risk for bleeding, whereas other reports[139,140,179,275,276,318,333–335] 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,[137,207,323,336] whereas others have found it to be an independent risk factor,[136,139] even after controlling for the intensity of the anticoagulant effect. Some studies have suggested[214,337] 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[137,139,338,339] suggests a real increase in intracranial hemorrhage in elderly patients. A recent meta-

Table 6—*TTR Achieved Under Different Models of Anticoagulation Management and With Different Testing Frequencies

Study, yr	Study Design	No. of Patients/Total	Predominant Model of Management	TTR, %	Above Range, %	Below Range, %	Frequency of Monitoring	Method of Determining TTR	Major Diagnosis
RCT, prospective cohort, and crossover studies assessing the model of anticoagulation management†									
Beyth et al,[283] 2000	RCT	162/325	UC	32	16	51		Days in range	Mixed
Horstkotte et al,[284] 1996	RCT	75/150	UC	59			19 d‡	% in range	Mixed
Sawicki,[285] 1999	RCT	89/179	UC	34	16	50		% in range	Valves
Kortke and Korfer,[286] 2001	RCT		UC	60.5	3.7	35.8		% in range	Valves
Matchar et al,[287] 2002	RCT	118/262	UC	52.3				Days in range	AF
Wilson et al,[288] 2003	RCT	106/221	UC	76‡				Days in range	AF
Gadisseur et al,[289] 2003	RCT	221/320	UC	63.5–67.9				Days in range	AF/valves
Palareti et al,[140] 1996	Prospective cohort	2745	AMS	68	6	26	15 d‡	Days in range	Mixed
Cromheecke et al,[290] 2000	Crossover	50	AMS	49				Days in range	Mixed
Watzke et al,[291] 2000	RCT	53/102	AMS (high intensity)	80.1				% in range	Mixed
			AMS (standard intensity)	68.9					
Matchar et al,[287] 2002	RCT	144/262	AMS	55.6				Days in range	Mixed
Wilson et al,[288] 2003	RCT	112/221	AMS	82				Days in range	AF
Abdelhafiz and Wheeldon,[292] 2004	Prospective cohort	402	AMS	66				Days in range	Mixed
Menendez-Jandula et al,[293] 2005	RCT	369/737	AMS	55.6				% in range	Mixed
Fitzmaurice et al,[294] 2002	RCT	280/617	AMS	68				Days in range	Mixed
Beyth et al,[283] 2000	RCT	163/325	PST	56	14	30		Days in range	Mixed
Horstkotte et al[284], 1996	RCT	75/150	PSM	92			4 d‡	% in range	Mixed
Sawicki,[285] 1999	RCT	90/179	PSM	57	10	33		% in range	Valves
Kulinna et al,[295] 1999	Prospective cohort	100	PSM	85.6				% in range	Mixed
Heidinger et al,[296] 2000	Prospective cohort	1,375	PSM	69				% in range	Mixed
Cromheecke et al,[290] 2000	Crossover	50	PSM	55				Days in range	Mixed
Watzke et al,[291] 2000	RCT	49/102	PSM (high intensity)	86.2				% in range	Mixed
			PSM (standard intensity)	82.2					
Kortke and Korfer,[286] 2001	RCT		PSM	78.3	2.9	18.8		% in range	Valves
Gadisseur et al,[289] 2003	RCT	52/320	PST	66.9				Days in range	Mixed
Gadisseur et al,[289] 2003	RCT	47/320	PSM	68.6				Days in range	AF/valves
Menendez-Jandula et al,[293] 2005	RCT	368/737	PSM	58.6				% in range	AF
Fitzmaurice et al,[297] 2005	RCT	337/617		70				Days in range	Mixed
RCT of VKA effectiveness for various indications§									
Smith et al,[298] 1990	RCT		HQDM	64–68	2–4	28–34		% in range and cross-section of files	DVT/PE
BAATAF,[172] 1990	RCT		HQDM	83	9	8	Every 3 wk	Days in range	
SPAF I,[174] 1991	RCT		HQDM	71	5	23	At least once/mo	% in range	AF
Connolly et al,[281] 1991	RCT		HQDM	44	16	40	Every 3 wk	Days in range	AF
Ezekowitz et al,[173] 1992	RCT		HQDM	56	15	29	Monthly	% in range	AF
EAFT,[175] 1993	RCT		HQDM	59	9	32	Every 5 wk	% in range	AF

Table 6—*Continued*

Study, yr	Study Design	No. of Patients/Total	Predominant Model of Management	TTR, %	Above Range, %	Below Range, %	Frequency of Monitoring	Method of Determining TTR	Major Diagnosis
ASPECT,[299] 1994	RCT		HQDM	6,274	6,920	29		%	After MI
SPAF II,[300] 1994	RCT		HQDM	74	5	21	At least once/mo	% in range	AF
SPAF III,[179] 1996	RCT		HQDM	61	14	25	At least once/mo	% in range	AF
Hellemons et al,[301] 1999	RCT		HQDM	48	24	28	Every 2–6	% in range	AF
Hutten et al,[302] 1999	RCT		HQDM	61				Days in range	AF
Gulløv et al,[169] 1998	RCT		HQDM	73	9	18	Not > q 4	Days in range	AF
Hurlen et al,[184] 2002	RCT		HQDM (high dose)	42	4	34		% in range	ACS
			HQDM (low dose)	47	30	23			
Butchart et al,[303] 2002	Prospective cohort			75.5	12.5	12		% in range	Valves
van Es et al,[183] 2002	RCT		HQDM (high dose)	~ 48	~ 17	~ 35			DVT/PE
			HQDM (low dose)	~ 40	~ 40	~ 20			
Kearon et al,[153] 2003	RCT		HQDM	69	11	20	26 d	Days in range	AF
Chimowitz et al,[304] 2005	RCT		HQDM	63.1	17.4	22.7		Days in range	CNS ischemia
ACTIVE,[305] 2006	RCT		HQDM	63.8	15.4	20.8	Monthly	% in range	AF
SPORTIF III,[306] 2003	RCT		HQDM	66	NA	NA	Monthly	Days in range	AF
SPORTIF V,[307] 2005	RCT		HQDM	68	12	20	Monthly	Days in range	AF
Fiessinger et al,[308] 2005	RCT		HQDM	61				Days in range	DVT

*ACS = acute coronary syndrome; AF = atrial fibrillation; HQDM = high-quality dose management; MI = myocardial infarct; PE = pulmonary embolus. See Table 4 for abbreviation not used in the text.

†Studies include those from 1990 or later that were prospective and where TTR and model of anticoagulation management were indicated.

‡Studies of VKA efficacy in various conditions are RCTs where TTR was indicated. The model of management is considered to be the equivalent of an AMS or HQDM.

§Used expanded therapeutic range.

analysis of six trials with more than 1,900 patients with atrial fibrillation found a rate of major hemorrhage of 1.8 per 100 patient-years in those under 75 years of age, rising to 3.2 per 100 patient-years in those 75 years of age and older.[340] Assessing more than 4,200 patients from the Leiden Anticoagulation Clinic, Torn et al[341] found a similar increase with age, rising from 1.5 per 100 patient-years in those under 60 years of age to 4.2 per 100 patient-years in those over 80 years of age (HR, 2.7; 95% CI, 1.7 to 4.4). Finally, Fang et al[339] compared the hemorrhagic rates of more than 13,500 patients with atrial fibrillation who were receiving warfarin with those who were not. In the cohort treated with warfarin (15,300 patient-years), bleeding rates increased at a rate of 1.2 (95% CI, 1.0 to 1.4) per older age group compared to an increase of 1.5 (95% CI, 1.3 to 1.8) in those not treated with warfarin. Similarly, they found a significant increase in intracranial hemorrhage rate in both groups of patients over 80 years of age (OR, 1.8; 95% CI, 1.1 to 3.1 for treated patients vs OR, 4.7; 95% CI, 2.4 to 9.2 for those not treated). Thus, older patients with atrial fibrillation, irrespective of whether they are on anticoagulants, have an increased risk of major hemorrhage. Whether this finding is true for patients with other indications for anticoagulation is unknown.

Based on these findings, individuals who are otherwise good candidates for anticoagulation therapy should not have it withheld because of their age. However, elderly patients should be monitored carefully, and perhaps more frequently, in order to maximize their TTR and to reduce the number of adverse events.

3.3 Frequency of Hemorrhage

The rate of hemorrhagic events must be interpreted in the context of the characteristics of the group studied. Factors that influence the rate of bleeding include the following: the target INR range; whether patients are mostly new to therapy or are participating in established long-term therapy; whether an INR or PT is used to manage therapy; the indication for anticoagulation; the type of VKA used; patient-specific risk factors, including concomitant antiplatelet therapy; and the quality of dose management. It is also not appropriate to extrapolate the rates of adverse events from randomized controlled trials to everyday practice because high-risk patients may be excluded from clinical trials, and monitoring and management of anticoagulation often are more coordinated in clinical trials than in clinical practice. The frequency of hemorrhage associated with oral anticoagulant therapy is reviewed in detail in the "Hemorrhagic Complications" chapter in this supplement.

3.4 Nonhemorrhagic Adverse Events

Other than hemorrhage, the most important side effects of warfarin are acute thrombotic complications, such as skin necrosis and limb gangrene. These uncommon complications are usually observed on the third to eighth day of therapy[342,343] and are caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat (in the case of skin necrosis) and massive outflow obstruction of the venous circulation of the limb (in the case of limb gangrene). The pathogenesis of these complications and the reason for the localization of the lesions are not well-understood. An association between warfarin-induced skin necrosis and protein C deficiency[344–346] and, less commonly, protein S deficiency[347] has been reported, but this complication also occurs in nondeficient individuals. A pathogenic role for protein C deficiency is supported by the similarity of the lesions to those seen in neonatal purpura fulminans that complicate homozygous protein C deficiency. A variant of this syndrome also attributed to a severe, warfarin-induced depletion of protein C is the occurrence of venous limb gangrene during warfarin treatment of cancer-associated DVT[348] and in some patients with heparin-induced thrombocytopenia started on warfarin after withdrawal of heparin.[349,350] The management of patients with warfarin-induced skin necrosis who require lifelong anticoagulant therapy is problematic. Therapy with warfarin is considered to be contraindicated, and long-term heparin therapy is inconvenient and associated with osteoporosis. A reasonable approach in such patients is to restart warfarin therapy at a low dose (*eg*, 2 mg), under the coverage of therapeutic doses of heparin, and to gradually increase the warfarin dose over 1 or more weeks. This approach should avoid an abrupt fall in protein C levels before there is a reduction in the levels of factors II, IX, and X, and it has been reported to not be associated with the recurrence of skin necrosis in a number of case reports.[345,346,350]

3.5 Management of Adverse Events

For the management of major bleeding in patients on VKA therapy, the reader is referred to the discussion under the section, Management of Nontherapeutic INRs With or Without Bleeding.

3.5.1 Alternative Treatment for the Patient Who Bleeds During Warfarin Therapy

The short-term management of patients who bleed with an excessively prolonged INR has been discussed above. The long-term management of patients who have unexplained or recurrent bleeding but who require ongoing protection against systemic embolism (*eg*, patients with mechanical heart valves

or with atrial fibrillation and other risk factors) is problematic. Clinicians can consider the following two options: (1) attempt to identify and reverse the cause of bleeding and (2) examine the possibility of lowering the intensity of the anticoagulant effect. Every effort should be made to treat the cause of bleeding (*eg*, the use of aggressive antiulcer therapy) if it is potentially reversible or to use an antiplatelet agent for selected indications (see the "Antiplatelet Drugs" chapter in this supplement).

The risk of bleeding is strongly related to the intensity of the anticoagulant effect. Therefore, in patients who continue to bleed, the INR should be maintained at the lower limit of the therapeutic range (*ie*, 2.0). Laboratory control of treatment should be optimized by performing frequent INR measurements and by ensuring that a moderately responsive thromboplastin (ISI, < 1.7) is used.[127] For patients with mechanical prosthetic valves (and a persisting risk of increased bleeding), it would be reasonable to aim for an INR of 2.0 to 2.5. Alternatively, in selected patients, one may consider valve replacement with a bioprosthetic valve. For patients with atrial fibrillation (and a persisting risk of increased bleeding), the anticoagulant intensity can be reduced to an INR of 1.5 to 2.0 with the expectation that efficacy will be reduced but not abolished.[141] Alternatively, aspirin can be used to replace warfarin in patients with atrial fibrillation but, again, with the expectation of reduced efficacy. The decision to lower the intensity of therapy to avoid bleeding should be discussed with the patient to understand the patient's preference and values with regard to the risk of thrombosis with lower-intensity therapy and the risk of bleeding with standard therapeutic intensity.

3.5.2 Diagnostic Evaluation of Bleeding

When bleeding occurs, especially from the GI or urinary tract, the presence of an underlying occult lesion should be considered. A number of descriptive studies[351–353] have reported on the probability of finding such a lesion. Coon and Willis[351] identified occult lesions that were responsible for bleeding in 11% of 292 patients with hemorrhage. Jaffin et al[352] found a 12% prevalence of positive stool occult blood test results in 175 patients receiving warfarin or heparin compared with 3% in 74 control subjects. There was no difference between the mean PT or activated partial thromboplastin time in patients with positive and negative test results. In the 16 patients with positive stool occult blood test results, 15 had a lesion that had not been previously suspected, and 4 patients had neoplastic disease. Landefeld et al[136] found that 14 of 41 patients with GI bleeding had important remediable lesions of which two were malignant. This limited information supports the need to investigate patients with occult GI bleeding, as it may herald the presence of an underlying malignancy.

In a randomized controlled study, Culclasure et al[354] found microscopic hematuria in 3.2% of patients (n = 243) receiving oral anticoagulation therapy compared to 4.8% in the control group (n = 258) not receiving anticoagulant therapy. There was no difference in the rate of hematuria with therapeutic or high INRs. Following a second episode of hematuria, 43 patients (patients receiving anticoagulation therapy, n = 32; control patients, n = 11) were investigated. Of these patients, 27 receiving anticoagulation therapy (84%) and 8 controls (73%) were found to have significant underlying disease, with three cancers found in the combined group (7%). These findings are in contrast to the results of other case series[355–357] that have reported a higher incidence of underlying lesions in patients who develop hematuria while receiving anticoagulant therapy.

4.0 Models of Anticoagulation Management

The effectiveness and safety of VKAs critically depend on maintaining the INR in the therapeutic range. This objective is facilitated by aiming for an INR that is in the middle of the INR range (*ie*, a goal of 2.5 for a designated range of 2.0 to 3.0 and a goal of 3.0 for a designated range of 2.5 to 3.5).[358] Approaches to improve anticoagulant control include the use of (1) AMS (*ie*, anticoagulation clinics) to manage therapy, (2) POC INR testing that allows PST and PSM of dose adjustments, and (3) computer software programs to aid in dose adjustment.

4.1 Optimal Management of VKA Therapy

The results of many nonrandomized, retrospective studies have reported better outcomes in patients when anticoagulant therapy is managed by an AMS or ACC than by their personal physicians (*ie*, UC). Four such studies of UC have reported major hemorrhagic rates ranging from 2.8 to 8.1% per patient-year of therapy.[317,320,335,359] Rates of thromboembolism were not reported except in two studies in which the event rates were 6.2% and 8.1% per patient-year (Table 7). Similarly, retrospective and prospective cohort studies[138,140,159,276,292,360] of care provided by an AMS reported rates of major hemorrhage or thrombosis ranging from 1.4 to 3.3% and 0.7 to 6.3% per patient-year of therapy, respectively (Table 7). Three retrospective comparative studies[319,361,362] using a before-and-after design of patients managed by UC or an AMS reported signifi-

Table 7—*Retrospective and Prospective Trials of UC or AMS Management Reporting Major Hemorrhage/Thromboembolism**

Study, yr	Type of Patient	Indication	Intervention	Patients Analyzed, No.	Follow-up, Patient-yr	Major Hemorrhage, % RR (95% CI)	Recurrent TE, % RR (95% CI)	Comment
UC: retrospective trials								
Gitter et al,[320] 1995	Noninception cohort	Mixed	UC	261	221	8.1	8.1	
Beyth et al,[317] 1998	Inception cohort	Mixed	UC	264	440	5.0	NA	
Steffensen et al,[335] 1997	Inception cohort	Mixed	UC	682	756	6.0	NA	
Willey et al,[359] 2004	Inception cohort	VTE	UC	2,090	1,441	2.8	6.2	
Total				3,297	2,858	4.4	6.4	
AMS: retrospective trials								
van der Meer et al,[276] 1993	Noninception cohort	Mixed	AMS	6,814	6,085	3.3	NA	
Cannegeiter et al,[138] 1995	Noninception cohort	MHV	AMS	1,608	6,475	2.5	0.7	
Veeger et al,[360] 2005	Inception cohort	VTE	AMS	2,304	1,441	2.8	6.3	
Total				10,726	14,001	2.9	1.7	
AMS: prospective								
Palareti et al,[140,159] 1996	Inception cohort	Mixed	AMS	2,745	2,011	1.4	3.5	
Abdelhafiz and Wheeldon,[292] 2004	Inception cohort	AF	AMS	402	636	1.7	1.5	
Total				3,147	2,647	1.5	3.0	
UC vs AMS: retrospective trials								
Cortelazzo et al,[319] 1993	NA	MHV	UC	271	677	4.7	6.6	
	NA	MHV	AMS	271	669	1	0.6	
						($p < 0.01$)	($p < 0.01$)	
						0.21 (0.09–0.52)	0.09 (0.03–0.29)	
Chiquette et al,[361] 1998	NA	Mixed	UC	142	102	3.9	11.8	Cost savings of AMS vs UC of $1,621/patient-yr
	NA	Mixed	AMS	82	199	1.6	3.3	
						($p < 0.5$)	($p < 0.05$)	
						0.41 (0.08–2.22)	0.28 (0.08–0.99)	
Witt et al,[362] 2005	NA	Mixed	UC	3,322	1,661	2.2	3.0	
	NA	Mixed	AMS	3,323	1,661	2.1	1.2	
						($p = NS$)	($p < 0.05$)	
						0.95 (0.57,1.60)	0.40 (0.22,0.71)	
UC vs AMS: randomized trials								
Matcher et al[287] 2002	Inception cohort	AF	UC	190	NA	1.6	7.4	
	Inception cohort	AF	AMS	173	NA	1.7	5.2	Randomized managed care practices to have access to AMS rather than patients
						1.10 (0.22–5.37)	0.71 (0.31–1.59)	
Wilson et al,[288] 2003	Inception cohort	Mixed	UC	106	109	0.9	1.8	
	Inception cohort	Mixed	AMS	112	112	1.8	0.9	Time in range + 0.2 U: UC 76% vs AMS 82% ($p = 0.034$); was not powered to detect difference in bleed or TE
						1.95 (0.18–21.16)	0.63 (0.44–0.92)	

*MHV = mechanical heart valve; NA = not applicable; NS = not significant; VTE = venous thromboembolism; RR = relative risk; TE = thromboembolism.

cant improvements in outcomes of hemorrhage or thrombosis with AMS-directed care (Table 7). In contrast, however, two prospective, randomized controlled trials[287,288] comparing UC with the care of an AMS failed to show a significant difference in major hemorrhage or thromboembolism (Table 7). The study by Matchar et al[287] also failed to show a significant improvement in TTR between the two models of care, although the AMS performed modestly better than UC. Wilson et al[288] observed a significant improvement in TTR in the AMS group compared to the UC group (82% vs 76%, respectively; $p = 0.034$). They also noted more high-risk INRs in the UC group vs the AMS group (40% vs 30%; $p = 0.005$). This latter study had a major limitation in that all patients were initially managed in an AMS for 3 months until they were stable and then were observed only for 3 months after randomization to either receive UC or to continue care by the AMS. The other study[287] suffered from a high turnover of patients, the possibility of selection bias of those patients referred to the AMS, the open nature of the study, and targeted ranges that were sometimes outside of recommended guidelines.

Finally, in a systematic review of 67 studies representing more than 50,000 patients managed by anticoagulation clinics (68%), clinical trials (7%), or community practices (24%), van Walraven et al[363] found that the practice setting had the greatest effect on anticoagulation control. TTR (days) varied from 56.7% in community practices to 66.4% for randomized trials. Compared to randomized trials the absolute reduction of TTR for community practices was −12.2% (95% CI −19.5% to −4.8%). The difference between community practices and anticoagulation clinics was −8.3% (95% CI −4.4% to −12.1%). Although the literature comparing UC and AMS is not as robust as one would like, and there is great heterogeneity between studies, the results are almost always consistent, indicating that care provided by an AMS results in better outcomes or more stable therapy than UC.

Recommendation

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 AMS (Grade 1B)**.**

4.2 POC INR Testing

Technological advances in POC PT measurement offer the potential for both simplifying and improving oral anticoagulation management in the professional setting as well as at home. POC monitors measure a thromboplastin-mediated clotting time from a fingerstick sample of capillary whole blood or from unanticoagulated venous whole blood.[364] The result is then converted to a plasma PT equivalent by a microprocessor and is expressed as a PT or an INR. Each manufacturer typically establishes the conversion formula by simultaneously comparing fingerstick or venous whole blood results with an established laboratory method and reagent that is traceable to the international reference thromboplastin.

Numerous studies[365–385] have reported on the accuracy and precision of these instruments, on the ability of both adult and child patients to obtain an INR, and on their general suitability for monitoring anticoagulant therapy. However, limitations to their accuracy and precision also have been documented. Problems identified with POC instruments include greater differences compared to a standard plasma-based methodology as INRs increase above the therapeutic range,[383,384] incorrect calibration of the ISI of the POC instruments,[385] the inability to calculate a mean normal PT,[386] and inaccuracies in INR determination in patients with antiphospholipid antibodies with certain instruments.[387] A major problem of comparative studies is that a similar lack of correlation of INR results exists when anticoagulated plasmas are simultaneously compared using different instrument/thromboplastin combinations.[120–126] These differences may be clinically important in that they may lead to different dosing decisions.[119–125] Kaatz et al[388] compared two POC monitors and four clinical laboratories against a secondary reference thromboplastin preparation. They found that laboratories using a more sensitive thromboplastin showed close agreement with the standard, whereas laboratories using an insensitive thromboplastin showed poor agreement. The two monitors fell between these two extremes.

Steps are still needed to ensure the conformity of POC PT monitors to the WHO INR PT standardization scheme, but the WHO ISI calibration procedure is not practicable using the monitors. Simpler procedures for ISI calibration of POC monitors have recently been tested in a number of multicenter sites by the European Concerted Action on Anticoagulation and the UK National External Quality Assessment Schemes. By using lyophilized plasma calibrants with independently certified INRs, Poller et al[389–391] have shown that verification or recalibration of the ISI of the instrument is possible. However, to obtain reliable ISI values for the two instruments tested, they had to develop different ISI calibration methods. It is likely, therefore, that different types of POC monitor systems will require different ISI calibration methods. In a study of proficiency testing

of three POC monitors over 6 years in more than 10 centers, Kitchen et al[392] found in each survey that INR results in 10 to 11% of the centers were > 15% different from results in other centers using the same monitors. This finding is compared to a 12% difference for hospitals using conventional INR techniques. Thus, as previously discussed, INR results from different instrument and reagent combinations, whether POC or conventional instruments, are not always equivalent. Although regular proficiency testing has been the standard for conventional laboratories and techniques, such testing is difficult at best and may not be possible with all POC instruments. Where possible, we suggest that personnel using POC office-based testing participate in proficiency schemes available through professional or national quality assurance organizations.

4.3 PST and PSM

PST or PSM using a POC instrument represents another model of care with the potential for improved outcomes as well as for greater convenience.[393] PSM is not a new concept,[394] but it only became practical with the advent of POC instruments. Self-testing provides a convenient opportunity for increased frequency of testing when deemed necessary. The use of the same instrument provides a degree of consistency in instrumentation, and self-testing provides the potential for greater knowledge and awareness of therapy, possibly leading to improved compliance. Several systematic reviews or metaanalyses have been conducted in the past few years using different criteria for review, each showing improvements in either or both the quality of anticoagulation control (TTR) or adverse events.[395–397] In the most comprehensive metaanalysis, Heneghan et al[397] pooled estimates from 14 randomized trials of PST showing a significant reduction in thromboembolic events (OR, 0.45; 95% CI, 0.30 to 0.68), all-cause mortality (OR, 0.61; 95% CI, 0.38 to 0.98), and major hemorrhage (OR, 0.65; 95% CI, 0.42 to 0.99) vs the comparator. For PST and PSM combined, there were significant reductions in thromboembolic events (OR, 0.27; 95% CI, 0.12 to 0.59) and death (OR, 0.37; 95% CI, 0.16 to 0.85) but not major hemorrhage (OR, 0.93; 95% CI, 0.42 to 2.05). Table 8 summarizes the most pertinent prospective studies (randomized controlled trials) in which 50 or more patients were studied and clinical outcomes were reported as TTR, adverse events, or both.[283–286,289,291,293,294,398–403] Both PST and PSM studies are included. Because the potential benefit of self-monitoring, either TTR or number of adverse events depends greatly on the quality of management of the comparator group, it is essential to characterize the control group, as in Table 8, according to whether the comparator arm is a UC model of management or an AMS. It should be noted that the difference between groups for TTR is considerably less marked when compared to an AMS as compared to UC, as one might expect given the previous discussion of the quality of anticoagulation control demonstrated in a UC model of management.

None of these PST studies were adequately designed to clearly answer the important questions of what might account for better therapeutic control. The major variables not adequately controlled for include the level of patient education, compliance, the frequency of monitoring, and the consistency of reagent and instrumentation use. Further studies are needed to define the importance of these variables; such studies are ongoing.[404] PST and PSM also require special patient training to implement,[405,406] and this mode of therapy may not be suitable for all patients. It is impractical to apply uniform proficiency testing to PST, but health-care providers should assess patient and equipment performance periodically (*eg*, once or twice per year) using duplicate testing on both the patient's instrument and an office-based instrument. As a consequence of potentially improving outcomes and avoiding adverse events, some investigators[407–409] have also shown a significant cost savings for PSM as well as an improvement in quality of life.[408]

Recommendation

4.3.1. PSM is a choice made by patients and health-care providers that depends on many factors. In patients who are suitably selected and trained, PST or PSM is an effective alternative treatment model. We suggest that such therapeutic management be implemented where suitable (Grade 2B)**.**

4.4 Data Management and Computerized Dosing

An obstacle to the safety and effectiveness of warfarin therapy is the poor quality of dose management as currently practiced.[410,411] Data from clinical trials and observational studies on the success of achieving TTR have indicated a wide range of success (Table 6), from a low of 33% for a UC model to 90% for PSM. Computer assistance through dedicated programs may improve dose management and TTR. Although programs differ, they typically calculate whether a dose adjustment is necessary from a user-defined table of trend rules for each therapeutic range. If it recommends dose adjustment, the current INR is compared to the target INR, and the difference in INR is used in a proprietary equation to calculate the new dose. The time to the next test also is set by the program using a set of variables comparing the current INR, the interval from the last test, the number of

Table 8—*Randomized Trials of PST or PSM Compared to UC or AMS

Author, yr	Study Design	Intervention	No. of Patients	Study Duration, mo	TTR, % INRs or Time in Range	Major Hemorrhage	Thromboembolism	Comment
PST vs UC								
Beyth et al,[283] 2000	RCT	PST/AMS†; UC	163 162	6	56 32 p < 0.001	12% 5.6 p = 0.049	8.6% 13 p = 0.2	Mixed indications
PST vs AMS								
White et al,[398] 1989	RCT	PST/AMS†; AMS	23 24	2	93 75 p = 0.003	0	0	Mixed indications
Gadisseur et al,[289] 2003	RCT	PST/AMS†; AMS	52 60	6	63.9 61.3 p = 0.14	0; 1 event	0	Mixed indications; differences in TTR were noted; between acenocoumarol group and phenprocoumon group
Kaatz et al,[399] 2001	RCT	PST/AMS†; AMS			63 65 p = NS			
PSM vs UC								
Horstkotte et al,[284] 1996	RCT	PSM UC	75 75	18	92.4 58.8			Cardiac valve indication
Sawicki,[285] 1999	RCT	PSM UC	83 82	3	57 33.8 p = 0.006	1 event 1 event	1 event 2 events	Mixed indications; At 6 mo TTR between groups; was NS (p = 0.22)
Fitzmaurice et al,[294] 2002	RCT	PSM UC	23 26	6	74 77 p = NS	0 1 event	0; 0	Mixed indications
Kortke and Korfer,[286] 2001	RCT	PSM UC	305 295	24	78.3 60.5 p ≤ 0.001	1.7% 2.6% p = NS	1.2% 2.1% p = NS	Cardiac valve indication; overall adverse event rate; significant (p = 0.042)
Sidhu and O'Kane,[400] 2001	RCT	PSM UC	34 48	24	76.5 63.8 p < 0.0001	1 event 0	1 event 0	Cardiac valve indication
Gadisseur et al,[289] 2003	RCT	PSM AMS	47 52	6	66.3 63.9 p = 0.14	1 event 1 event	0 0	Mixed indication; one episode of traumatic bleeds in each group
Sunderji et al,[401] 2004	RCT	PSM UC	69 70	8	71.8 63.2			
Voller et al,[402] 2005	RCT	PSM UC	101 101	5	67.8 58.5 p = 0.0061	2 events 0	0 1 event	Indications: atrial fibrillation: study stopped early because of poor enrollment
PSM vs AMS								
Watzke et al,[291] 2000	RCT	PSM AMS	49 53		84.5 73.8	1 event 0	1 event 0	Mixed indications
Khan et al,[403] 2004	RCT	PSM AMS	40 39	6	71.1 70.4			
Menendez-Jandula et al,[293] 2005	RCT	PSM AMS	368 369	12	58.6 55.6 p = NS	4 events 7 events	4 events 20 events	Mixed indications; overall adverse event rate 2.2% in PSM vs 7.3% in AMS (95% CI 1.7–8.5)

*See Tables 4 and 7 for abbreviations not used in the text.
†An AMS performed the dose adjustments for the PST patients.

previous changes, and the number of previous INR values within the target range.

A number of early studies[412–414] evaluated computer programs to improve warfarin dosing. The first randomized study in 1993[415] showed that three contemporary computer programs all performed as well as an experienced medical staff of an AMS in achieving a target INR of 2.0 to 3.0, but the computer achieved significantly better control when more intensive therapy was required (*ie*, INR range, 3.0 to 4.5). In another randomized study[416] of 101 patients who had received long-term anticoagulation therapy in the setting of prosthetic cardiac valves, computerized warfarin adjustments proved comparable to manual regulation in the percentage of INR values maintained within the therapeutic range but required 50% fewer dose adjustments. The first multicenter randomized trial of one computerized dosage program in 1998[417] showed a 22% overall improvement of control with the program compared to the performance by the medical staff. The computer program gave significantly better INR control than experienced medical staff for all 285 patients and all target INR ranges. A slight improvement in TTR also was obtained by Italian investigators[418] using a different management program in more than 1,200 randomized patients from five centers. A total of 71.2% of patients were in range with computer dosing, and 68.2% were in range by manual dosing in the maintenance phase; 51.9% vs 48.1%, respectively, were in range in the first 3 months of the induction period.[418] In both of these studies, the computer did not share the natural overcaution of medical staff in dosing patients at a higher INR range.

Computerized dose management also has been shown to be at least as effective as physician dosing for the initiation of anticoagulation therapy as well as for the long-term management of therapy.[418,419] Computerized dosing programs have limitations in that requirements for information on previous dose levels vary with the individual programs, and some programs are unable to manage dosing during the induction phase.

Improved safety and efficacy from the use of computer programs over conventional medical staff (manual) dosing has, however, not yet been established. Such a study is currently in progress by the European Concerted Action on Anticoagulation, randomizing patients between computer dose management vs manual control using two software programs (DAWN AC, 4S Information Sys, Cumbria, United Kingdom, and PARMA, Instrumentation Laboratories, Milan, Italy). Nor can it be assumed that all computer programs will be equally successful. New programs will require independent validation by large randomized controlled studies to determine the extent of their ability to accurately predict dosage control.

Computerized dose management (with specific software programs) is another option that has been shown to be at least equivalent to physician-managed dosing when large populations of patients are being managed. Similar to PSM, we think that computerized dose management is a physician preference based on a number of factors, such as panel size and ancillary help, and we have no recommendation.

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Conflict of Interest Disclosures

Dr. Ansell discloses that he has received consultant fees from Bristol-Myers Squibb, Roche Diagnostics, and International Technidyne Corporation. He is also on the speakers bureau for Roche Diagnostic Corporation and Sanofi-Aventis, and is the past president of the Anticoagulation Forum.

Dr. Hirsh discloses that he has received partial support for writing two books, one on fondaparinux and one on low-molecular-weight heparin.

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Dr. Palareti discloses that he serves on the speakers bureau of Sanofi-Aventis, GlaxoSmithKline, Instrumentation Laboratory of Roche Diagnostics, and Dade-Behring. He is a member of the Executive Committee of the Italian Federation of Anticoagulation Clinics and the Italian Society of Hematology and Thrombosis (ISTH), and is Co-chair of the Subcommittee on Control of Anticoagulation of the ISTH.

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