

# The Pharmacology and Management of the Vitamin K Antagonists

## The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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This article concerning the pharmacokinetics and pharmacodynamics of vitamin K antagonists (VKAs) is part of the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. The article describes the antithrombotic effect of VKAs, the monitoring of anticoagulation intensity, the clinical applications of VKA therapy, and the optimal therapeutic range of VKAs, 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 suggests that individual patient's values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST* 2004; 126:179S-187S). Among the key recommendations in this article are the following: for dosing of VKAs, we suggest the initiation of oral anticoagulation therapy with doses between 5 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 2B). In the elderly and in other patient subgroups with an elevated bleeding risk, we suggest a starting dose at  $\leq 5$  mg (Grade 2C). We recommend basing subsequent doses after the initial two or three doses on the results of INR monitoring (Grade 1C). The article also includes several specific recommendations for the management of patients with INRs above the therapeutic range and for patients requiring invasive procedures. For example, in patients with mild to moderately elevated INRs without major bleeding, we suggest that when vitamin K is to be given it be administered orally rather than subcutaneously (Grade 1A). For the management of patients with a low risk of thromboembolism, we suggest stopping warfarin therapy approximately 4 days before they undergo surgery (Grade 2C). For patients with a high risk of thromboembolism, we suggest stopping warfarin therapy approximately 4 days before sur-

gery, to allow the INR to return to normal, and beginning therapy with full-dose unfractionated heparin or full-dose low-molecular-weight heparin as the INR falls (Grade 2C). In patients undergoing dental procedures, we suggest the use of tranexamic acid mouthwash (Grade 2B) or epsilon amino caproic acid mouthwash without interrupting anticoagulant therapy (Grade 2B) if there is a concern for local bleeding. For most patients who have a lupus inhibitor, we suggest a therapeutic target INR of 2.5 (range, 2.0 to 3.0) [Grade 2B]. In patients with recurrent thromboembolic events with a therapeutic INR or other additional risk factors, we suggest a target INR of 3.0 (range, 2.5 to 3.5) [Grade 2C]. As models of anticoagulation monitoring and management, we recommend that clinicians incorporate patient education, systematic INR testing, tracking, and follow-up, and good communication with patients concerning results and dosing decisions (Grade 1C+). (*CHEST* 2004; 126:204S-233S)

**Key words:** anticoagulation; pharmacology; vitamin K antagonists

**Abbreviations:** ACC = anticoagulation clinic; AMS = anticoagulation management service; INR = international normalized ratio; ISI = international sensitivity index; LMWH = low-molecular-weight heparin; POC = point of care; PSM = patient self-management; PST = patient self-testing; PT = prothrombin time; SC = subcutaneous; subcutaneously; TTR = time in the therapeutic range; UC = usual care; UFH = unfractionated heparin; VKA = vitamin K antagonist; WHO = World Health Organization

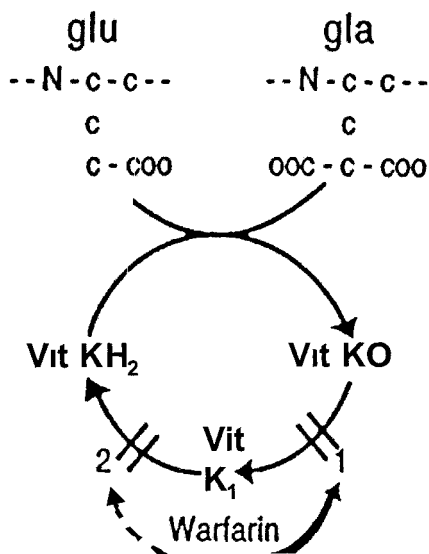
The coumarins or vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulant therapy for > 50 years. Their effectiveness has been established by well-designed clinical trials for the primary and secondary prevention of venous thromboembolism, for the prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, for the primary prevention of acute myocardial infarction in high-risk men, and for the prevention of stroke, recurrent infarction, or death in patients with acute 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 subjects; (3) they are subject to interactions with drugs and diet; (4) they have laboratory control that can be difficult to standardize; and (5) they have problems in dosing as a result of patient nonadherence and miscommunication between the patient and physician. Since warfarin is the most commonly used VKA worldwide, warfarin will be used interchangeably with VKA or coumarin throughout the following discussion.

### 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  $\gamma$ -carboxylation of glutamate residues (Gla) on the N-terminal regions of vitamin K-dependent proteins (Fig 1).<sup>1-6</sup>

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1. KO - reductase - warfarin sensitive
2. K - reductase - relatively warfarin resistant

FIGURE 1. Vitamin K1 is reduced to vitamin KH<sub>2</sub> by two warfarin-sensitive enzymes (KO-reductase to K-reductase), and the nicotinamide adenine dinucleotide-dependent reductase system that is insensitive to warfarin.

The vitamin K coagulation factors II, VII, IX, and X require  $\gamma$ -carboxylation for their procoagulant activity, and treatment with coumarins results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity.<sup>7,8</sup> Carboxylation is required for a calcium-dependent conformational change in coagulation proteins<sup>9-11</sup> that promotes binding to cofactors on phospholipid surfaces. In addition, the VKAs inhibit carboxylation of the regulatory anticoagulant proteins C and S, and thereby have the potential to be procoagulant. However, under most circumstances the anticoagulant effect of the coumarins is dominant. Carboxylation requires the reduced form of vitamin K (vitamin KH<sub>2</sub>), molecular oxygen, and carbon dioxide. The oxidation-reduction reaction between vitamin KH<sub>2</sub> and vitamin K epoxide involves a reductase pair. The first,

vitamin K epoxide reductase, is sensitive to coumarins, whereas vitamin K reductase is less sensitive.<sup>1-3</sup> Therefore, the anticoagulant effect of the coumarins can be overcome by low doses of vitamin K1 (phytonadione) [Fig 1]. Patients treated with large doses of vitamin K1 can become resistant to warfarin for up to 1 week or more because the vitamin K1 accumulating in the liver is available to the coumarin-insensitive reductase.

The coumarins also interfere with the carboxylation of Gla proteins that are synthesized in bone.<sup>12-15</sup> Although these effects contribute to fetal bone abnormalities when mothers are treated with a coumarin during pregnancy,<sup>16,17</sup> there is no evidence that coumarins directly affect bone metabolism when administered to children or adults.

### 1.1 Pharmacokinetics and pharmacodynamics of warfarin

Warfarin is the most common coumarin that is in clinical use. It is a racemic mixture of two optically active isomers, the R and S forms. Warfarin is rapidly absorbed from the GI tract, has high bioavailability,<sup>18,19</sup> and reaches maximal blood concentrations about 90 min after oral administration.<sup>18,20</sup> Warfarin has a half-life of 36 to 42 h,<sup>21</sup> circulates bound to plasma proteins (mainly albumin), and accumulates in the liver, where the two isomers are metabolically transformed by different pathways.<sup>21</sup> 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.

#### 1.1.1 Genetic factors

Genetic factors include the following. (1) There is a common mutation in the gene coding for the cytochrome P450 2C9 hepatic microsomal enzyme that is responsible for the oxidative metabolism of the more potent warfarin S-isomer.<sup>21-24</sup> This mutation is independently responsible for the reduced warfarin requirements seen in individuals with one or more combinations of these polymorphisms (Table 1).<sup>23,25,26</sup> Several investigations<sup>23,26,27</sup> have shown that these mutations are also associated with an increase in adverse clinical outcomes. (2) There is hereditary resistance to warfarin. This occurs in rats as well as in human beings,<sup>28-30</sup> and patients with genetic warfarin resistance require doses that are 5-fold to 20-fold higher than average to achieve an anticoagulant effect. This disorder is attributed to an altered affinity of the warfarin receptor, which results in an increase in the plasma warfarin levels

Table 1—Observed Frequency of CYP2C9 Variants Among Various Ethnic Groups\*

Ethnic Groups	CYP2C9*1	CYP2C9*2	CYP2C9*3	CYP2C9*4	CYP2C9*5
Point mutation	Arg <sub>144</sub> /Ile <sub>359</sub>	Cys <sub>144</sub> /Ile <sub>359</sub>	Arg <sub>144</sub> /Leu <sub>351</sub>	Arg <sub>144</sub> /Thr <sub>359</sub>	Arg <sub>144</sub> /Glu <sub>360</sub>
Whites	79-86%	8-19.1%	6-10%	ND	ND
Indigenous Canadians	91%	3%	6%	ND	ND
African Americans	98.5%	1-3.6%	0.5-1.5%	ND	2.3%
Asians	95-98.3%	0	1.7-5%	0-1.6%	0

\*CYP2C9\*2, CYP2C9\*3, CYP2C9\*4, and CYP2C9\*5 represent genetic polymorphisms of the wild-type enzyme, CYP2C9\*1. ND = not determined. Table reproduced with permission of Wittkowsky.<sup>23</sup>

required to achieve an anticoagulant effect. (3) A mutation in the factor IX propeptide causes selective reduction in factor IX during treatment with coumarin drugs without excessive prolongation of the prothrombin time (PT).<sup>24</sup> Factor IX activity decreases to about 1 to 3% of normal, while 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 coumarin-mediated reduction of factor IX activity. This selective marked reduction in factor IX activity has been reported<sup>24,31</sup> to increase the risk of bleeding during anticoagulant therapy.

### 1.1.2 Environmental factors

Environmental factors such as drugs, diet, and various disease states can alter the pharmacokinetics of warfarin (Table 2). Consequently, the international normalized ratio (INR) should be measured more frequently than the usual 4-week interval when virtually any drug 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. Many other drugs potentiate the anticoagulant effect of warfarin by inhibiting its clearance through stereoselective or nonselective pathways.<sup>32,33</sup> Stereoselective interactions may affect the oxidative metabolism of either the S-isomer or R-isomer of warfarin.<sup>32,33</sup>

The inhibition of S-warfarin metabolism is more important clinically, because this isomer is five times more potent than the R-isomer as a VKA.<sup>32,33</sup> Phenylbutazone,<sup>34</sup> sulfinpyrazone,<sup>35</sup> metronidazole<sup>36</sup> and trimethoprim-sulfamethoxazole<sup>37</sup> 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.<sup>33,36,38</sup> Amiodarone is a potent inhibitor of the metabolic clearance of both the S-isomer and the R-isomer, and potentiates warfarin anticoagulation.<sup>39</sup> The anticoagulant effect is inhibited by drugs like barbiturates, rifampin, 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 has little influence on PT in subjects who have been treated with warfarin.<sup>40</sup> The effect of enzyme induction on warfarin therapy has been discussed in more detail in a critical review (Table 3).<sup>41</sup>

Drugs may also 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,<sup>42,43</sup> by thyroxine, which increases the metabolism of coagulation

**Table 2—Drug and Food Interactions With Warfarin by Level of Supporting Evidence and Direction of Interaction\***

Level of Evidence	Potentialiation	Inhibition	No Effect
I	Alcohol (if concomitant liver disease) amiodarone anabolic steroids, cimetidine,† clofibrate, cotrimoxazole erythromycin, fluconazole, isoniazid (600 mg daily), metronidazole, miconazole, omeprazole, <i>phenylbutazone</i> , piroxicam, propafenone, propranolol,† <i>sulfinpyrazone</i> ( <i>biphasic with later inhibition</i> )	Barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, <i>griseofulvin</i> , nafcillin, rifampin, sucralfate, high vitamin K content foods/enteral feeds, large amounts of avocado	Alcohol, antacids, atenolol, bumetadine, enoxacin, famotidine, fluoxetine, ketorolac, metoprolol, naproxen, nizatidine, psyllium, ranitidine‡
II	Acetaminophen, chloral hydrate, ciprofloxacin, dextropropoxyphene, disulfiram, itraconazole, quinidine, phenytoin (biphasic with later inhibition), tamoxifen, tetracycline, flu vaccine	Dicloxacillin	Ibuprofen, ketoconazole
III	Acetylsalicylic acid, disopyramide, fluorouracil, ifosfamide, ketoprofen, lovastatin, metozalone, moricizine, nalidixic acid, norfloxacin, ofloxacin, propoxyphene, sulindac, tolmetin, topical salicylates	Azathioprine, cyclosporine, etretinate, trazodone	
IV	Cefamandole, cefazolin, gemfibrozil, heparin, indomethacin, sulfisoxazole		Diltiazem tobacco vancomycin

\*Italics indicates those drugs that have supporting level I evidence from both patients and volunteers.

†In a small number of volunteer subjects, an inhibitory drug interaction occurred.

‡Level II evidence of potentiation in patients.

**Table 3—Enzyme-Inducing Drug Interactions With Warfarin\***

Inducing Agent	Isoenzyme Induced†	Expected Onset, d	Anticipated Dosage Adjustments, %	Expected Offset, d
Carbamazepine	CYP3A4	10–35	100‡	42
Barbiturate§	CYP3A	7–30	12.5–25‡	> 42
Phenytoin	Nonspecific	NA	¶	NA
Rifampin	CYP3A4	< 7	100–200‡	21
Griseofulvin¶	Unknown	60	40‡	NA
Nafcillin	NA	< 7	100–400‡	7–28
Dicloxacillin	NA	< 7	2–30‡	NA
Aminoglutethimide#	CYP2B1	14	50–75‡	14
Smoking	CYP1A1, 1A2	NA	‡**	NA
Alcohol	CYP2E1	NA	‡†	
41–54 g‡‡			‡**	
250 g§§				NA

\*NA = not available.

†Information regarding induction of cytochrome-450 isoenzymes is limited. Current literature supports specific isoenzyme induction by the listed agent.

‡An increase in warfarin dosage is anticipated with initiation of the inducing agent.

§Class effect, although time course and extent may vary with the individual barbiturate.

¶A decrease in warfarin dosage is anticipated with initiation of the inducing agent.

¶¶Interaction is more likely with the ultramicrocrystalline formulation of griseofulvin.

#Dose-response relationship, so that 250 mg four times/d showed greater induction than 125 mg four times/d.

\*\*Warfarin clearance increased, but a corresponding change in PT was not reported. See text for further details.

††No change in warfarin dosage appears necessary based on available data.

‡‡Represents ingestion of 41 to 54 g ethanol consumed either as a single dose or daily for 21 days.

§§Represents ingestion of large amounts of ethanol (250 g) consumed daily for more than 3 months.

factors,<sup>44</sup> and by clofibrate, through an unknown mechanism.<sup>45</sup> Doses of salicylates of > 1.5 g per day<sup>46</sup> and acetaminophen<sup>47</sup> may augment the anticoagulant effect of warfarin, possibly by interference with the P450 enzymes.<sup>48</sup> Heparin potentiates the anticoagulant effect of warfarin, but in therapeutic doses produces only a slight prolongation of the PT. The mechanisms by which erythromycin<sup>49</sup> and some anabolic steroids<sup>50</sup> 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.<sup>51</sup>

Drugs such as aspirin,<sup>52</sup> nonsteroidal antiinflammatory drugs,<sup>53</sup> penicillins in high doses,<sup>54,55</sup> and moxalactam<sup>43</sup> increase the risk of warfarin-associated bleeding by inhibiting platelet function. Of these, aspirin is the most important because of its widespread use and prolonged effect.<sup>56</sup> Aspirin and nonsteroidal antiinflammatory drugs can also produce gastric erosions that increase the risk of upper GI bleeding. The risk of clinically important bleeding is heightened when high doses of aspirin are taken during high-intensity warfarin therapy (INR, 3.0 to 4.5).<sup>52,57</sup> However, low doses of aspirin (*ie*, 75 to 100 mg daily) combined with moderate-intensity and low-intensity warfarin anticoagulation therapy are also associated with increased rates of bleeding.<sup>58,59</sup>

Wells et al<sup>60</sup> analyzed reports of possible interaction between warfarin and drugs or foods. There was evidence from observational studies of interaction in 39 of the 81

different drugs and foods appraised. Of these, 17 potentiated the warfarin effect, 10 inhibited it, and 12 produced no effect. Many other drugs have been reported either to interact with oral anticoagulants or to alter the PT response to warfarin.<sup>61,62</sup> The importance of postmarketing surveillance with newer drugs is highlighted by an experience<sup>63</sup> with celecoxib, a drug that showed no interactions in phase 2 studies but was subsequently suspected of potentiating the effect of warfarin in several case reports. This review also drew attention to potential interactions with over-the-counter herbal medicines.

Subjects receiving long-term warfarin therapy are sensitive to fluctuating levels of dietary vitamin K,<sup>64,65</sup> which is derived predominantly from phyloquinones in plant material.<sup>65</sup> The phyloquinone content of a wide range of foodstuffs has been listed by Sadowski and associates.<sup>66</sup> Phyloquinones act through the warfarin-insensitive pathway.<sup>67</sup> Important fluctuations in vitamin K intake can occur in both healthy and sick subjects.<sup>68</sup> An increased intake of dietary vitamin K that is sufficient to reduce the anticoagulant response to warfarin<sup>64</sup> 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 K1 intake potentiates the effect of warfarin in sick patients who have been treated with antibiotics and IV fluids without vitamin K supplementation, and 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 hyperthyroid-

ism increase warfarin responsiveness, probably by increasing the catabolism of vitamin K-dependent coagulation factors.<sup>44,69</sup>

## 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. More recent evidence, however, suggests 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<sup>70</sup> over 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 the protective effect of warfarin was mainly a result of lowering prothrombin levels.<sup>71</sup> Third, Patel and associates<sup>72</sup> 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,<sup>73</sup> and that reduction in prothrombin levels decreases the amount of thrombin generated and bound to fibrin, thereby reducing thrombogenicity.<sup>72</sup>

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. Since 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.<sup>74</sup>

## 1.3 Monitoring anticoagulation intensity

The PT test<sup>75</sup> 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, and 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, approximately 1.0) that are composed of human tissue factor produced by recombinant technology and defined phospholipid preparations are now available. The history of standardization of the PT has been reviewed by Poller<sup>76</sup> and by Kirkwood,<sup>77</sup> and more detailed discussions can be found in prior editions of this article.<sup>78</sup>

PT monitoring of warfarin treatment is not standardized when expressed in seconds or as a simple ratio of the patient's plasma value to that of plasma from a healthy control subject. A calibration model,<sup>77</sup> 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:

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

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 to the primary World Health Organization (WHO) international reference preparations, so that the more responsive the reagent, the lower the ISI value.<sup>76,77</sup> As the INR standard of reporting was widely adopted, a number of problems surfaced. These are listed in Table 4 and are 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.<sup>79</sup> 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,<sup>80</sup> and is thus recommended during both the initiation and maintenance of warfarin treatment. There is also evidence that the INR is a reliable measure of impaired blood coagulation in patients with liver disease.<sup>81</sup>

The INR accuracy can be influenced by reagents of different sensitivities<sup>82</sup> and also by the automated clot detectors now used in most laboratories.<sup>83-90</sup> In general, the College of American Pathologists has recommended<sup>91</sup> that laboratories should use thromboplastin reagents that are at least moderately responsive (*ie*, ISI, < 1.7) and reagent/instrument combinations for which the ISI has been established.

ISI values provided by the manufacturers of thromboplastin reagents are not invariably correct when applied locally,<sup>92-94</sup> and this adversely affects the reliability of measurements. Local calibrations can be performed using plasma samples with certified PT values to determine the

**Table 4—Potential Problems With the INR (Causes of Erroneous INR)\***

Problems	Description
1. Incorrect PT ratio from erroneous prothrombin time 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
2. 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
3. Drift of ISI since original calibration	
4. Instrument (coagulometer) effects on INR at local site	
5. Lupus anticoagulant effects on some thromboplastin reagents	
6. 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	
7. Relative lack of reliability of INR > 4.5 as these values excluded from ISI calibrations	

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

instrument-specific ISI. The mean normal plasma PT is not interchangeable with a laboratory control PT,<sup>95</sup> however, the use of other than a properly defined mean normal PT can yield erroneous INR calculations, particularly when less responsive reagents are employed. The mean normal PT should be determined with each new batch of thromboplastin with the same instrument used to assay the PT.<sup>95</sup>

The concentration of citrate that is used to anticoagulate plasma affects the INR.<sup>96,97</sup> In general, higher citrate concentrations (3.8%) lead to higher INR values,<sup>96</sup> 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 tubes can reduce this problem.

#### 1.4 Clinical applications of VKA therapy

The clinical effectiveness of VKAs in the treatment of a variety of disease conditions has been established by well-designed clinical trials. VKAs are effective for the primary and secondary prevention of venous thromboembolism, for the prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, for the prevention of acute myocardial infarction in patients with peripheral arterial disease and in men who otherwise are at high risk, and for the prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction. Although effectiveness has not been proven by a randomized trial, VKAs are also indicated for the prevention of systemic embolism in high-risk patients with mitral stenosis.

##### 1.4.1 Optimal therapeutic range

The optimal target range for warfarin is not the same for all indications. Not only is it likely to be influenced 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 most feared and major complication of oral anticoagulant therapy, is closely related to the intensity of anticoagulation.<sup>98–101</sup> Therefore, some studies<sup>102</sup> have focused on establishing the lowest effective therapeutic range. Universal agreement has not been reached on the optimal range for the various indications. For example, in Europe higher ranges are recommended for patients with mechanical heart valves than for patients in North America.<sup>103,104</sup>

In performing studies that are aimed at establishing the most appropriate range for different indications, various methodological approaches have been used. These are as follows: (1) randomized trials in which patients are randomly assigned to two different target ranges<sup>105–110</sup>; (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)<sup>111–114</sup>; (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 thromboembolic event<sup>101–103,115,116</sup>; 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.<sup>104</sup> All of these designs have limitations, but the randomized trial, comparing two target INR ranges, provides results that are closest to the truth, because if appropriately designed, it is free of bias.<sup>117</sup>

Four randomized studies<sup>105–108</sup> 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 significant bleeding without reducing efficacy. In

two of these studies, one in patients with venous thromboembolism<sup>105</sup> and the other in patients with tissue heart valves,<sup>106</sup> 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 in North America to 2.0 to 3.0 for these and other indications. More recently, an INR of < 2.0 (INR target, 1.5 to 2.0) has been reported<sup>109</sup> to be effective in the long-term secondary prevention of venous thrombosis when compared to placebo. Another clinical trial,<sup>110</sup> however, found that an INR intensity of 1.5 to 2.0 was not as effective as an INR of 2.0 to 3.0.

After a small randomized trial<sup>118</sup> reported the unexpected finding that fixed minidose warfarin (*ie*, 1 mg daily) was effective in preventing subclavian vein thrombosis in patients with malignancy who had indwelling catheters, two prospective cohort studies<sup>119,120</sup> provided further support by showing a reduced incidence of catheter thrombosis compared to historical control subjects in patients treated with 1 mg warfarin. However, six other studies<sup>121–126</sup> all reported that a fixed dose of 1 mg warfarin was either much less effective than dose-adjusted warfarin therapy (INR, 2.0 to 3.0) or that the 1-mg dose was ineffective. Three of these studies<sup>121–123</sup> evaluated its efficacy following major orthopedic surgery, and one each evaluated its efficacy in patients with indwelling catheters,<sup>124</sup> atrial fibrillation,<sup>125</sup> or acute myocardial infarction.<sup>126</sup> Therefore, therapy with fixed minidose warfarin should be considered much less effective than that with dose-adjusted warfarin in moderate-to-high risk situations, and in some situations it may not be effective at all. For patients with a low thrombogenic risk, the efficacy of therapy with fixed minidose warfarin remains controversial.

The results of randomized trials have demonstrated the efficacy of oral anticoagulants in preventing stroke in patients with atrial fibrillation.<sup>127–131</sup> 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) on indirect comparison of the several randomized trials,<sup>112–114</sup> a moderate-intensity warfarin regimen (INR, 2.0 to 3.0) showed a similar risk reduction as higher intensity regimens; (2) a randomized trial<sup>132</sup> 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<sup>103,116</sup> and the results of one case control study<sup>104</sup> have indicated 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, an INR of 2.0 to 3.0 has not been evaluated in patients with acute myocardial infarction or in patients with prosthetic heart valves, except when the oral anticoagulant was combined with aspirin. Two randomized trials<sup>133,134</sup> have indicated that a higher intensity regimen (INR, 3.0 to 4.0) is more effective than aspirin, 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 a lower intensity anticoagulant regimen (INR, 1.5 to 2.5) and aspirin has been shown to be no more effective than aspirin alone.<sup>135</sup> 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.<sup>59</sup>

In conclusion, it is clear that one single therapeutic range for coumarins will not be optimal for all indications. However, a moderate-intensity INR (2.0 to 3.0) is effective for most indications. The possible exceptions are acute myocardial infarction, in which a higher INR is likely to be superior, and the primary prevention of myocardial infarction in high-risk patients in which a lower INR is effective. 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, depending on the indication. The optimal intensity for patients with prosthetic heart valves remains uncertain, although there is evidence that they do not require the very high-intensity regimens that have been used in the past. Defining an appropriate range is an important step in improving patient management, but it is only the first of two steps. The second is ensuring that the targeted range is achieved. In general, our success in achieving this second goal has been poor. It is better when the INR is controlled by experienced personnel in anticoagulant clinics and by using computer-assisted dosage adjustment.<sup>136</sup> Specific recommendations regarding the optimal intensity of therapy for each of these indications can be found in the articles in this supplement that deal with each indication.

## 2.0 Management of VKA Therapy

Utilizing the correct intensity of a coumarin anticoagulant and maintaining the patient in the therapeutic range are two of the most important determinants of its therapeutic effectiveness and safety. High-quality dose management is essential to achieve and maintain therapeutic efficacy. Attainment of this goal can be influenced by physiologic and pharmacologic factors such as interacting drugs or illnesses that affect the pharmacokinetics or pharmacodynamics of warfarin, dietary or GI factors that affect the availability of vitamin K1, or physiologic factors that affect the synthetic or metabolic fate of the vitamin K-dependent coagulation factors. Patient-specific factors such as adherence to a therapeutic plan are also important. Last, the ability of the health-care provider to make appropriate dosage and follow-up decisions can have an impact. The comprehensive management of these variables requires a knowledgeable health-care provider, an organized system of follow-up, reliable PT monitoring, and good patient communication and education.<sup>136,137</sup>

The following discussion addresses a number of man-

agement issues pertaining to the use of VKAs. A systematic review of the literature was performed based on pre-defined criteria for the population at risk, the intervention or exposure evaluated, the outcomes assessed, and the methodology of the trials evaluated (Table 5). Based on this information and, when necessary, a consensus of opinion by the authors, recommendations and/or suggestions are proposed and graded according to the conventions defined in this supplement.

## 2.1 Practical dose management

### 2.1.1 Initiation and maintenance dosing

Following the administration of warfarin, an initial effect on the PT usually occurs within the first 2 or 3 days, depending on the dose administered, and an antithrombotic effect occurs within the next several days.<sup>138,139</sup> 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. A loading dose (*ie*, > 20 mg) of warfarin is not recommended. A number of randomized studies have supported the use of a lower initiation dose. Harrison et al<sup>138</sup> and Crowther et al<sup>140</sup> found that in hospitalized patients, commencing with

an average maintenance dose of 5 mg warfarin usually results in an INR of  $\geq 2.0$  in 4 or 5 days with less excessive anticoagulation compared to that with an initial 10-mg dose. Kovacs et al,<sup>141</sup> 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. Thus, there is room for flexibility in selecting a starting dose of warfarin. Some clinicians prefer to use a larger starting dose (*eg*, 7.5 to 10 mg), while a starting dose of < 5 mg might be appropriate in the elderly, in patients with impaired nutrition liver disease, or congestive heart failure, and in patients who are at high risk of bleeding. When the INR has been in the therapeutic range on two measurements approximately 24 h apart, heparin therapy is discontinued. If treatment is not urgent (*eg*, 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 per day. 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 warfarin therapy to protect against a possible early hypercoagu-

**Table 5—Question Definition and Eligibility Criteria for Managing Oral Anticoagulant Therapy\***

Section	Population	Intervention or Exposure	Outcomes	Methodology	Exclusion Criteria
2.1	Patients starting oral anticoagulant therapy	Initial dosing of VKA	Recurrent thromboembolism; major and minor hemorrhages; time to achieve therapeutic INR	RCT	None
2.1.2	Elderly on oral anticoagulants	VKA therapy	Major hemorrhage or thrombosis; anticoagulant response; maintenance dose	RCT and observational	None
2.1.5	Patients receiving oral anticoagulants undergoing invasive procedures	Use of alternative therapies (no therapy, UFH, or LMWH)	Major and minor hemorrhage and thromboembolism	RCT and observational	None
2.2.2	Patients receiving oral anticoagulants	VKA therapy	TTR, quality of anticoagulation	RCT and observational	None
2.2.3	Patients receiving oral anticoagulants and in therapeutic range	VKA therapy	Major hemorrhage or thrombosis	RCT and observational	None
2.2.5	Patients receiving oral anticoagulants and bleeding	Management of bleeding	Hemorrhage or thrombosis	RCT and observational	None
2.3.1	Patients receiving oral anticoagulants	ACC vs routine or UC	Hemorrhage or thrombosis	RCT and observational	None
2.3.2	Patients receiving oral anticoagulants	POC monitoring, PST, PSM, or computerized dose management	TTR, major hemorrhage or thrombosis	RCT and observational	None
2.3.3	Patients receiving oral anticoagulants	Different models of care: ACC vs UC vs PST vs PSM	Cost-effectiveness	RCT, cohort, crossover, and observational	None

\*RCT = randomized controlled trial; TTR = time in therapeutic range; ACC = anticoagulation clinic; UC = usual care; PST = patient self-testing; PSM = patient self-management.

lable state caused by a warfarin-mediated reduction in the vitamin K-dependent coagulation inhibitors.<sup>142</sup>

Because dose requirements often change during maintenance therapy, physicians employ various strategies to make dosing simple and clear for the patient. Some providers prefer to use a fixed tablet strength 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.<sup>143,144</sup>

## Recommendations

2.1.1.1. We suggest the initiation of oral anticoagulation with doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the INR response (**Grade 2B**).

### 2.1.2 Initiation of anticoagulation in the elderly

The dose required to maintain a therapeutic range for patients > 60 years of age decreases with increasing age,<sup>145–147</sup> possibly because of a reduction in the clearance of warfarin with age.<sup>148,149</sup> Therefore, in the elderly the initial dose of warfarin should not be > 5 mg,<sup>150</sup> and in some cases (*ie*, in patients with a high risk of bleeding, and in those who are undernourished or have congestive heart failure or liver disease), it should be less. Other factors that may influence the response to anticoagulation in the elderly include the potential for a greater number of other medical conditions and/or concurrent drug use.<sup>145</sup> Consequently, it is advisable to monitor older patients more frequently in order to maximize their time in the therapeutic range (TTR).<sup>151</sup>

2.1.2.1. In the elderly, and in patients who are debilitated, malnourished, have congestive heart failure, or have liver disease, we suggest the use of a starting dose of ≤ 5 mg (**Grade 2C**).

### 2.1.3 Frequency of monitoring

In hospitalized patients, PT monitoring is usually performed daily starting after the second or third dose until the therapeutic range 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 who have started receiving 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 there is evidence<sup>152,153</sup> to suggest 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 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<sup>154</sup> have attempted to develop predictive models with the goal of reducing the frequency of testing without sacrificing quality. Some clinical trials<sup>152,153</sup> have suggested that during long-term treatment the TTR and, presumably, fewer adverse events can be maximized by more frequent testing. This is particularly true in studies utilizing patient self-testing (PST) in which access to testing is virtually unlimited. Horstkotte et al<sup>152</sup> addressed this issue in 200 patients with mechanical cardiac valves in which they 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 self-testing using a point-of-care (POC) monitor. It is suggested that patients should be monitored no less than every 4 weeks. More frequent monitoring may be advisable in patients who exhibit an unstable dose response.

## Recommendations

2.1.3.1. We suggest that INR monitoring should be started after the initial two or three doses of oral anticoagulation therapy (**Grade 2C**).

2.1.3.2. 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**).

### 2.1.4 Management of nontherapeutic INRs

Fluctuations in INR may occur because of any one or more of the following conditions: inaccuracy in INR testing; changes in vitamin K1 intake; changes in vitamin K1 or warfarin absorption; changes in warfarin metabolism; changes in vitamin K1-dependent coagulation factor synthesis or metabolism; other effects of concomitant drug use; or 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. 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. Since 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,<sup>155</sup> or, for higher INR values between 4.0 and 10.0, by stopping warfarin for a day or more, reducing the weekly dose, and monitoring more frequently.<sup>156</sup> Hylek et al<sup>157</sup> 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, had a higher initial INR, had decompensated congestive heart failure, or 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. 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 the following: administering vitamin K1; and/or infusing fresh-frozen plasma,<sup>158</sup> prothrombin concentrates,<sup>159</sup> or recombinant factor VIIa.<sup>160</sup> The choice of approach is based largely on clinical judgement, the potential risk of bleeding, the presence of active bleeding, and the level of the INR. Crowther et al<sup>161</sup> compared either stopping warfarin or administering oral vitamin K1 in a randomized trial in patients with an INR of between 4.5 and 10. A higher rate of minor bleeding was reported in the following 3 months in those who were not treated with vitamin K1 compared to those who were (4% vs 17%, respectively;  $p = 0.05$ ).

If a decision is made to use vitamin K1, 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<sup>162</sup> or without exposing the patient to the risk of anaphylaxis. High doses of vitamin K1, though effective, may lower the INR more than is necessary and may lead to warfarin resistance for a week or more. IV injection may be associated with anaphylactic reactions,<sup>163,164</sup> although such reactions have even been described with non-IV routes of administration.<sup>164</sup> Low doses of vitamin K1 and slow infusion rates are recommended, but there is no definitive evidence that this serious, but rare, complication can be avoided by using low doses or slow infusion rates.<sup>164</sup> The response to vitamin K1 administered subcutaneously (SC) is less predictable compared to oral vitamin K1 and is sometimes delayed.<sup>165–167</sup> Some studies<sup>167–171</sup> have confirmed earlier reports that oral administration is predictably effective, and has the

advantages of safety and convenience over parenteral routes. 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*, 5 mg), are required to correct INRs of > 9.0. Vitamin K1 also can be administered by slow IV infusion when there is a greater urgency to reverse anticoagulation.<sup>165,172</sup> Table 6 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, there are no specific studies examining the optimal method of correction. Since the average daily risk of thrombosis for most indications is quite small, patients do not generally need to be covered with a rapidly acting anticoagulant such as heparin or low-molecular-weight heparin (LMWH). 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

2.1.4.1. For patients with INRs above the therapeutic range, but < 5.0 and with no significant bleeding, lower the dose or omit the dose, monitor more frequently, and resume therapy at a lower dose when the INR is at a therapeutic level. If only minimally above therapeutic range, no dose reduction may be required (all **Grade 2C**).

2.1.4.2. For patients with INRs of  $\geq 5.0$  but < 9.0 and no significant bleeding, omit the next one or two doses, monitor more frequently, and resume therapy at lower dose when the INR is at a therapeutic level. Alternatively, omit a dose and administer vitamin K1 (1 to 2.5 mg) orally,

**Table 6—Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving VKAs\***

Condition	Description
INR above 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 ( <b>Grade 2C</b> )
INR $\geq 5.0$ but < 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently and resume at lower dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K1 ( $\leq 5$ mg orally), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 (2 to 4 mg orally) 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 K1 (1 to 2 mg orally) can be given ( <b>Grade 2C</b> )
INR $\geq 9.0$ ; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K1 (5–10 mg orally) with the expectation that the INR will be reduced substantially in 24–48 h. Monitor more frequently and use additional vitamin K1 if necessary. Resume therapy at lower dose when INR therapeutic ( <b>Grade 2C</b> )
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K1 (10 mg by slow IV infusion), supplemented with fresh plasma or prothrombin complex concentrate, depending on the urgency of the situation; recombinant factor VIIa may be considered as alternative to prothrombin complex concentrate; vitamin K1 can be repeated every 12 h ( <b>Grade 1C</b> )
Life-threatening bleeding	Hold warfarin therapy and give prothrombin complex concentrate supplemented with vitamin K1 (10 mg by slow IV infusion); recombinant factor VIIa may be considered as alternative to prothrombin complex concentrate; repeat if necessary, depending on INR ( <b>Grade 1C</b> )

\*If continuing warfarin therapy is indicated after high doses of vitamin K1, then heparin or LMWH can be given until the effects of vitamin K1 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.

particularly if the patient is at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 ( $\leq 5$  mg) orally 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 K1 (1 to 2 mg) orally can be given (all **Grade 2C**).

2.1.4.3. For patients with INRs of  $\geq 9.0$  and no significant bleeding, hold warfarin therapy and administer a higher dose of vitamin K1 (5 to 10 mg) orally with the expectation that the INR will be reduced substantially in 24 to 48 h. Monitor levels more frequently and use additional vitamin K1 if necessary. Resume therapy at a lower dose when INR reaches therapeutic levels (all **Grade 2C**).

2.1.4.4. In patients with serious bleeding and elevated INRs, we recommend holding warfarin therapy and giving vitamin K1 (10 mg) by slow IV infusion supplemented with fresh plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation. Vitamin K1 administration can be repeated every 12 h (all **Grade 1C**).

2.1.4.5. In patients with life-threatening bleeding and elevated INRs, we recommend holding warfarin therapy and administering prothrombin complex concentrate or recombinant factor VIIa supplemented with vitamin K1, 10 mg by slow IV infusion. Repeat this, if necessary, depending on the INR (**Grade 1C**).

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

### 2.1.5 Management of oral anticoagulation during invasive procedures

Clinicians are often required to decide how to manage patients who are receiving long-term anticoagulant therapy who require an invasive procedure.<sup>173</sup> The decision is based on the perceived risks of continuing or stopping anticoagulant therapy and on the cost of alternative options such as hospitalization for heparin therapy perioperatively. The principal concern is the risk of thrombosis when antithrombotic therapy is discontinued. Estimating the daily risk of a thromboembolism while the patient is not receiving anticoagulation therapy is difficult because data on the subject are sparse. The reported risk of not using preoperative anticoagulants for patients with mechanical heart valves varies from very low<sup>174,175</sup> to unacceptably high.<sup>176,177</sup> Table 7 summarizes the estimated risk for the most common indications based on the available literature.<sup>178</sup> The following approaches can be used: stop warfarin therapy preoperatively and perform the procedure when the INR has returned to safe levels; administer full-dose anticoagulation with IV unfractionated heparin (UFH); administer full-dose anticoagulation with LMWH; or administer prophylactic doses of UFH or LMWH. The effects of high-dose, IV UFH can be readily reversed by discontinuing treatment before a procedure, but its major drawback is the complexity and cost associated with IV

**Table 7—Annualized Risk of Thrombotic Complications in the Absence of Anticoagulant Therapy for Selected Conditions<sup>179</sup>**

Condition	Annualized Thrombosis Risk, %
Lone atrial fibrillation	1
Average risk atrial fibrillation	5
High-risk atrial fibrillation	12
Dual-leaflet (St. Jude) aortic valve prosthesis	10–12
Single-leaflet (Bjork-Shiley) aortic valve prosthesis	23
Dual-leaflet (St. Jude) mitral valve prosthesis	22
Multiple St. Jude prostheses	91

therapy and hospitalization. LMWH can be administered at home to avoid the expense and inconvenience of hospitalization. Several analyses of prospective cohort studies have indicated that LMWH is a suitable and less costly alternative,<sup>179–191</sup> and that it provides therapeutic levels more rapidly and consistently than UFH.<sup>182–192</sup> Although it is not possible to draw firm conclusions on the value of different management strategies, and we must rely on observational studies or risks extrapolated from other clinical scenarios, LMWH therapy appears to be at least as effective, if not more effective, and less costly than UFH therapy.

A recent review<sup>176</sup> on the subject summarizes the options and outcomes for a range of surgical procedures, including cataract surgery, cutaneous surgery, pacemaker and defibrillator procedures, cardiac catheterization, genitourinary surgery, GI endoscopy, and others. With each of the following options, the length of time for warfarin dosage reduction and for the duration of heparin or LMWH use preoperatively can be shortened by administering vitamin K1 24 to 48 h before surgery to reverse the warfarin effect. Table 8 outlines the recommendations for managing patients who are receiving coumarin anticoagulants and require an invasive procedure.

Dental procedures represent a particularly common intervention for patients receiving anticoagulants. A comprehensive review<sup>177</sup> of > 700 case reports indicated in 1998 that in most cases no change in the intensity of anticoagulation therapy is needed. More recent studies<sup>193,194</sup> have reported no difference between the incidence of postprocedure bleeding at low or higher levels of the INR. If there is a need to limit local bleeding, tranexamic acid mouthwash or epsilon amino caproic acid mouthwash has been used successfully without interrupting anticoagulant therapy.<sup>195,196</sup>

### Recommendations

2.1.5.1 For patients with a low risk of thromboembolism, stop warfarin therapy approximately 4 days before they undergo surgery, allow the INR to return to near-normal values, briefly use postoperative prophylaxis (if the intervention increases the risk of thrombosis) with low-dose UFH (5,000 U SC) or a prophylactic dose of LMWH, and simultaneously begin warfarin therapy. Alternatively,

**Table 8—Recommendations for Managing Anticoagulation Therapy in Patients Requiring Invasive Procedures (all Grade 2C)**

Condition	Description
Low risk of thromboembolism*	Stop warfarin therapy approximately 4 d before surgery, allow the INR to return to near normal, briefly use postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH and simultaneously begin warfarin therapy; alternatively, a low dose of UFH or a prophylactic dose of LMWH can also be used preoperatively
Intermediate risk of thromboembolism	Stop warfarin approximately 4 d before surgery, allow the INR to fall, cover the patient beginning 2 d preoperatively with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH and then commence therapy with low-dose UFH (or LMWH) and warfarin postoperatively; some individuals would recommend a higher dose of UFH or a full dose LMWH in this setting
High risk of thromboembolism†	Stop warfarin approximately 4 d before surgery, allow the INR to return to normal; begin therapy with a full dose of UFH or a full dose of LMWH as the INR falls (approximately 2 d preoperatively); UFH can be given as an SC injection as an outpatient, and can then be given as a continuous IV infusion after hospital admission in preparation for surgery and discontinued approximately 5 h before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery; it is also possible to continue with SC UFH or LMWH and to stop therapy 12–24 h before surgery with the expectation that the anticoagulant effect will be very low or have worn off at the time of surgery
Low risk of bleeding	Continue warfarin therapy at a lower dose and operate at an INR of 1.3–1.5, an intensity that has been shown to be safe in randomized trials of gynecologic and orthopedic surgical patients; the dose of warfarin can be lowered 4 or 5 d before surgery; warfarin therapy can then be restarted postoperatively, supplemented with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH if necessary

\*Low risk of thromboembolism includes no recent (> 3 mo) venous thromboembolism, atrial fibrillation without a history of stroke or other risk factors, and bileaflet mechanical cardiac valve in aortic position.

†Examples of a high risk of thromboembolism include recent (< 3 mo) history of venous thromboembolism, mechanical cardiac valve in mitral position, and old model of cardiac valve (ball/cage).

a low dose of UFH or a prophylactic dose of LMWH also can be used preoperatively (all **Grade 2C**).

2.1.5.2. For patients with an intermediate risk of thromboembolism, stop warfarin approximately 4 days before they undergo surgery, allow the INR to fall, cover the patient beginning 2 days preoperatively with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH, and then commence therapy with low-dose UFH (or LMWH) and warfarin therapy postoperatively. (**Grade 2C**).

2.1.5.3. For patients with a high risk of thromboembolism, stop warfarin therapy approximately 4 days before surgery to allow the INR to return to normal at the time of surgery; begin therapy with full-dose UFH or full-dose LMWH as the INR falls (approximately 2 days preoperatively). UFH can be administered as an injection SC as an outpatient and as a continuous IV infusion after hospital admission in preparation for surgery, and can be discontinued approximately 5 h before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery. An alternative is to continue to use SC UFH or LMWH preoperatively and to stop therapy 12 to 24 h before surgery with the expectation that the anticoagulant effect will be very low or have worn off at the time of surgery, then commence full-dose UFH (or LMWH) and warfarin therapy postoperatively (**Grade 2C**). [Editor's note: This text reading "full-dose" has been changed as an erratum to the original printed version of this article.]

2.1.5.4. For patients with a low risk of bleeding, con-

tinue warfarin therapy at a lower dose and operate at an INR of 1.3 to 1.5. The dose of warfarin can be lowered 4 or 5 days before the patient undergoes surgery. Warfarin therapy then can be restarted postoperatively, and supplemented with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH if necessary (**Grade 2C**).

2.1.5.5. In patients undergoing dental procedures with a need to control local bleeding, we suggest tranexamic acid mouthwash (**Grade 2B**) or epsilon amino caproic acid mouthwash without interrupting anticoagulant therapy (**Grade 2B**).

### 2.1.6 Management of INRs in the antiphospholipid syndrome

Patients who have a lupus anticoagulant or antiphospholipid antibodies have an increased risk of thrombosis. Evidence from observational studies<sup>197,198</sup> suggests that clinical outcomes are improved when the therapeutic range for such patients treated with warfarin is 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 PT.<sup>199</sup> Although lupus anticoagulants typically cause prolongation of the activated partial thromboplastin time, they may also cause mild prolongation of the PT or, in the presence of specific antibodies to prothrombin, more marked prolongation of the PT. The degree of prolongation of the PT induced by lupus anticoagulants appears to be dependent on the

reagent used.<sup>200–202</sup> One study<sup>200</sup> found that simultaneous INR values from the same sample of blood from patients who have a lupus anticoagulant and receiving oral anticoagulants differed from 0.4 to 6.5 INR units between reagents. Two studies<sup>203,204</sup> 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.

Crowther et al,<sup>205</sup> in a randomized controlled trial of patients with antiphospholipid syndrome who had been treated with warfarin, assigned patients to an INR of either 2.0 to 3.0 or 3.1 to 4.0. They found no difference in objective end points (*ie*, recurrent thromboembolism) between the two groups of patients, although 75% of all patients who had a recurrence were either 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. Other techniques for monitoring oral anticoagulant therapy for patients with lupus anticoagulants include the measurement of prothrombin activity, native prothrombin concentration, and the prothrombin and proconvertin test.<sup>200,203,206–208</sup> The validity and reliability of these latter tests have not been rigorously evaluated in controlled clinical trials for patients receiving lupus anticoagulants.

## Recommendation

2.1.6.1. In patients who have a lupus inhibitor who have no additional risk factors and no lack of response to therapy, we suggest a therapeutic target INR of 2.5 (INR range, 2.0 to 3.0) [**Grade 2B**]. 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**].

## 2.2 Adverse Events and Their Management

### 2.2.1 Definition of major and minor hemorrhage

Precise estimates of hemorrhagic event rates are complicated by the inconsistency between classification schemes in clinical research studies.<sup>101</sup> Fihn et al<sup>101</sup> proposed the following three categories of bleeding: minor (reported, but not requiring additional testing, referrals, or visits); major (requiring treatment, medical evaluation, or at least 2 U blood); and 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 leading to hospitalization. The reader should be aware of these differences when interpreting the results from clinical studies.

### 2.2.2 Risk factors or determinants for adverse events

**Optimal Intensity of Treatment.** The most important factor influencing the risk of bleeding is the intensity of anticoagulant therapy.<sup>101–108,209–214</sup> As discussed above, the optimal target range for warfarin is not the same for all indications. It is likely to be influenced by the indication for its use and by patient characteristics. In addition to the predictive effect that the targeted INR has on outcome, a number of additional studies have shown what amounts to a steep increase in hemorrhagic events as the INR increases to > 5.0.<sup>102,209,210,213</sup> The optimal target range for each indication and whether or not even lower ranges are effective is discussed specifically in other articles in this supplement pertaining to each indication.

**TTR (Time in therapeutic range).** The relationship between the intensity of treatment and the risk of an adverse event has been evaluated by examining the relationship between the TTR and the frequency of an event.<sup>214,215</sup> A strong relationship between TTR and bleeding or thromboembolic rates has been observed across a large number of studies<sup>102,127–129,210,213,214,216–218</sup> 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, representative study by Cannegieter et al,<sup>102</sup> there was 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.<sup>104,210</sup> Table 9<sup>265–268,323–329</sup> summarizes the data from studies assessing the quality of anticoagulation as reflected by TTR. Many studies fail to measure the quality of anticoagulation management as reflected by TTR. We think this is a deficiency that can lead to the erroneous interpretation of results, and we urge investigators to measure TTR in their studies. TTR can be determined by a variety of methodologies, and, therefore, comparisons between studies may be difficult.<sup>219</sup> The most common methodologies express TTR as the fraction of INR values that are within therapeutic range (*eg*, the number of INRs in the range divided by the number of INR tests), the “cross-section of the files” methodology, which assesses all patients being managed at one point in time by taking the total of those whose INR is in range and dividing it by the total number of patients who had an INR at that point in time, or the linear interpolation method of Rosendaal et al,<sup>220</sup> 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.<sup>219</sup> The results of all of these methods depend on whether an exact or an expanded therapeutic range is used,<sup>221</sup> whether patients just beginning therapy are included or only patients who are already on established therapy are included,<sup>222,223</sup> 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.<sup>223–225</sup> Since clinical outcome studies compar-

**Table 9—TTR Achieved Under Different Models of Anticoagulation Management and With Different Testing Frequencies\***

Study/Year	Predominant Model of Management	PTR vs INR	TTR, † %	Above Range, %	Below Range, %	Frequency of Monitoring	Method of Determining TTR	Major Diagnosis
Garabedian-Ruffalo et al <sup>267/1985</sup>	UC	PTR	64				% in range	Mixed
Gottlieb et al <sup>325/1994</sup>	UC	PTR	50	30	20	Every 25 d ‡	Days in range	Mixed
Holm et al <sup>328/1999</sup>	UC	INR	63	8	29		% in range	Mixed
Beyth et al <sup>300/1997</sup>	UC	INR	33	16	51			Mixed
Horstkotte et al <sup>301/1998</sup>	UC	INR	59			19 d ‡	% in range	Valves
Sawicki et al <sup>304/1999</sup>	UC	INR	34	16	50		% in range	AF/valves
Palareti et al <sup>103/1996</sup>	AMS	INR	68	6	26	15 d ‡	Days in range	Mixed
Cannegieter et al <sup>102/1995</sup>	AMS	INR	61	8	31	18.9 d ‡	Days in range	Valves
Lundstrom and Ryden <sup>326/1989</sup>	AMS	TT	92				% in range	AF
Garabedian-Ruffalo et al <sup>267/1985</sup>	AMS	PTR	86				% in range	Mixed
White et al <sup>306/1989</sup>	AMS	PTR	75				Days in range	Mixed
Ansell et al <sup>305/1995</sup>	AMS	PTR	68	10	22	16 d ‡	% in range	Mixed
Conte et al <sup>265/1986</sup>	AMS	PTR	59	12	29			Mixed
Seabrook et al <sup>266/1990</sup>	AMS	PTR	86	7	7	Once monthly	% in range	Mixed
White et al <sup>306/1989</sup>	PST	PTR	93				Days in range	Mixed
Beyth et al <sup>300/1997</sup>	PST	INR	56	14	30			Mixed
Ansell <sup>305/1995</sup>	PSM	PTR	89	5	6	13.8 d ‡	% in range	Mixed
Horstkotte et al <sup>301/1998</sup>	PSM	INR	92			4 d ‡	% in range	Valves
Sawicki <sup>303/1999</sup>	PSM	INR	57	10	33		% in range	AF/valves
Petersen et al <sup>127/1989</sup>	RCT	INR	73	0.6	26			AF
BAATAF <sup>128/1990</sup>	RCT	PTR	83	9	8	Every 3 wk	Days in range	AF
SPAF I <sup>130/1991</sup>	RCT	PTR	71	5	23	At least once/mo	% in range	AF
SPAF II <sup>327/1994</sup>	RCT	PTR/INR	74	5	21	At least once/mo	% in range	AF
SPAF III <sup>132/1996</sup>	RCT	INR	61	14	25	At least once/mo	% in range	AF
Ezekowitz et al <sup>129/1992</sup>	RCT	PTR	56	15	29	Monthly	% in range	AF
Connolly et al <sup>215/1991</sup>	RCT	INR	44	16	40	Every 3 wk	Days in range	AF
Gullov et al <sup>125/1999</sup>	RCT	INR	73	9	18	Not > q 4 wk	Days in range	AF
EAF <sup>131/1993</sup>	RCT	INR	59	9	32	Every 5 wk	% in range	AF
Hellemons et al <sup>323/1999</sup>	RCT	INR	48	24	28	Every 2–6 wk	% in range	AF
Hutten et al <sup>324/1999</sup>	RCT	INR	61				Days in range	DVT/PE
Kearon et al <sup>110/2003</sup>	RCT	INR	69	11	20	26 d	Days in range	DVT/PE
Smith et al <sup>329/1990</sup>	RCT	INR	64–68	2–4	28–34		% in range and cross Section of files	ACS
van Es et al <sup>133/2002</sup>	RCT (high dose)	INR	~48	~17	~35			ACS
	RCT (low dose)	INR	~40	~40	~20			ACS
Hurlen et al <sup>134/2002</sup>	RCT (high dose)	INR	42	4	34		% in range	ACS
	RCT (low dose)	INR	47	30	23		% in range	ACS

\*PTR = prothrombin time ratio; TT = thrombotest; Mixed = mixed indications for anticoagulation; valves = cardiac prosthetic valve; AF = atrial fibrillation; % in range = proportion of PT tests in therapeutic range divided by the total No. of tests; days in range = estimated No. of days in therapeutic range, are determined by various methodologies; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; SPAF = Stroke Prevention in Atrial Fibrillation; EAFT = European Atrial Fibrillation Trial.

†Values represents mean or median percent of PTs or days in range.

‡Studies that documented the achieved frequency of monitoring as opposed to the stated goal for the monitoring interval.

ing one methodology over another and their correlation with adverse events have not been done, no specific method can be recommended, and the reader should be aware of these differences.

#### Patient Characteristics:

Several patient characteristics have been shown to be associated with higher odds of bleeding during anticoagulation therapy.<sup>98,99,103,107,211,214,226–233</sup> The patient factor

that most consistently has been demonstrated to be predictive of major bleeding is a history of bleeding (especially GI bleeding).<sup>103,107,214</sup> Other factors that have been shown to be associated include a history of stroke and the presence of a serious comorbid condition such as renal insufficiency, anemia, or hypertension.<sup>98,99,103,107,214,226–233</sup>

The relationship between older age and anticoagulant-associated bleeding is controversial. Several reports<sup>101,146,214,216,231–241</sup> have indicated that older individuals are not at increased risk for bleeding, while others<sup>103,132,209,211,213,227,243–246</sup> have described such an association. The discrepancy may be partly explained 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 > 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,<sup>101,145,232,247</sup> while others have found it to be an independent risk factor,<sup>209,212</sup> even after controlling for the intensity of the anticoagulant effect. It has also been suggested<sup>151</sup> that older patients who have high-quality anticoagulation management, such as that provided by an anticoagulation clinic (ACC), have the same risk of bleeding as their younger counterparts. Last, the location of major bleeding may be a factor, and there is reasonable evidence<sup>101,209</sup> to suggest that there is a real increase in intracranial hemorrhage in the elderly. 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 more frequently in order to maximize their TTR and to reduce the number of adverse events.

### 2.2.3 Frequency of hemorrhage

The frequency of hemorrhage associated with oral anticoagulant therapy is reviewed in detail in the chapter by Levine et al in this supplement (see page 000). 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; the indication for anticoagulation; the type of VKA used; and the quality of dose management. Furthermore, it may not be 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 is more coordinated than in clinical practice.

### 2.2.4 Nonhemorrhagic adverse events

Other than hemorrhage, the most important side effect of warfarin is skin necrosis. This uncommon complication is usually observed on the third to eighth day of therapy,<sup>248,249</sup> and is caused by extensive thrombosis of the venules and capillaries within the SC fat. The pathogenesis

of this complication and the reason for the localization of the lesions are not well-understood. An association between warfarin-induced skin necrosis and protein C deficiency<sup>250–252</sup> and, less commonly, protein S deficiency,<sup>253</sup> 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 complicates 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 deep venous thrombosis.<sup>254</sup> 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 is 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 increase the warfarin dosage gradually over several 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 shown to protect against the recurrence of skin necrosis in a number of case reports.<sup>251,252</sup>

### 2.2.5 Management of adverse events

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. The following two options can be considered: (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.

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.<sup>255</sup> 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.<sup>104</sup> Alternatively, aspirin can be used to

replace warfarin in patients with atrial fibrillation, but also 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.

#### Diagnostic Evaluation of Bleeding:

When bleeding occurs, especially from the GI or urinary tract, a serious, the presence of an underlying occult lesion should be considered. A number of descriptive studies<sup>242,256,257</sup> have indicated the probability of finding such a lesion. Coon and Willis<sup>242</sup> identified occult lesions that were responsible for bleeding in 11% of 292 patients with hemorrhage. Jaffin et al<sup>256</sup> 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 patients with positive stool occult blood test results, 15 of 16 patients had a lesion that had not been previously suspected, and 4 patients had neoplastic disease. Landefeld et al<sup>212</sup> 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, since, if found, there may be a 5 to 25% chance of finding a malignant source.

In a randomized controlled study, Culclasure et al<sup>258</sup> found microscopic hematuria in 3.2% of patients receiving oral anticoagulation therapy compared to 4.8% in the control group not receiving anticoagulation 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, 32; control patients, 11) were investigated. Of these patients, 27 of those receiving anticoagulation therapy (84%) and 8 of the control patients (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<sup>259–261</sup> that have reported a much higher incidence of underlying lesions in patients who develop hematuria while receiving anticoagulant therapy.

### 2.3 Models of anticoagulation management

The effectiveness and safety of VKAs are critically dependent 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).<sup>262</sup> Approaches to improve anticoagulant control include the use of (1) anticoagulation management services (AMSs) [*ie*, ACCs] to manage therapy, (2) POC PT testing that allows PST and patient self-management (PSM) of dose adjustments, and (3) computer software programs to aid in dose adjustment.

#### 2.3.1 Usual care vs AMSs

The results of many nonrandomized studies have reported better outcomes when anticoagulation therapy is managed by an AMS or ACC compared to patients managed by their personal physicians (*ie*, usual care [UC]). In contrast, two randomized controlled trials<sup>263,264</sup> comparing UC with the care of an AMS failed to show a significant improvement in TTR between the two models of care, although in both studies the AMS performed modestly better than UC. Both studies had important limitations. In one study,<sup>264</sup> published as an abstract, all patients were initially managed in an AMS for 3 months until they were stable, and then they were observed for only 3 months after randomization to either receive UC or to continue care by the AMS. The other study<sup>263</sup> 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. Tables 10 to 12 summarize the results of studies assessing the frequency of hemorrhage or thrombosis based on the model of care and provide information about baseline risks in the various settings. These studies were selected based on the following criteria: published in 1980 or later; providing sufficient information to classify the model of care as either UC or an AMS; defining the criteria for major hemorrhage; identifying the rate of major hemorrhage; and providing information to determine the number of patient-years of therapy for comparative purposes, including at least 200 patients and having > 80% follow-up. Table 10 summarizes four large retrospective observational studies on UC.<sup>211,226,229,245</sup> The results indicated a rate of major hemorrhage of approximately 6% per patient-year of therapy. Table 11 summarizes the results achieved with an AMS from mostly retrospective observational analyses.<sup>101,102,103,116,213,214,216,231–233</sup> A majority of the earlier studies used a PT ratio to monitor therapy, thereby potentially providing more intense therapy. Higher rates of bleeding were noted in these earlier studies compared to the last three, which employed an INR to monitor therapy. Table 12 summarizes three studies<sup>229,263,269</sup> in which investigators used clinical outcomes to compare two models of care in a single setting. Two of these studies used a before-and-after design, and one study was a prospective randomized trial.<sup>263</sup> The randomized trial<sup>263</sup> was underpowered to detect a reduction in the incidence of major hemorrhage or thromboembolism, although it also failed to show a difference between the quality of anticoagulation control as determined by TTR. The other studies showed a consistent benefit to care provided by an AMS.

Although many studies suggest that the coordinated approach of an ACC is superior to UC, these studies were not randomized. Thus, what constitutes the best approach requires additional rigorous, large-scale, long-term randomized studies, and we are not making a specific recommendation for or against the use of an AMS.

#### Cost-Effectiveness of UC vs AMS:

Because of improved outcomes with fewer hospitalizations and emergency department visits, the management of anticoagulation therapy by an AMS may prove to be

**Table 10—Frequency of Major Hemorrhage/Thromboembolism in Patients Managed Under a UC Model of Management\***

Study/Year	Patients, No.	Patient Years, No.	Years of Data Collection	New or Established Patient	Indications	Hemorrhage†		Recurrent TE†	Definition of Major Bleed
						Major	Fatal‡		
Landefeld and Goldman <sup>211</sup> /1989	565	876	1977–1983	New	Ven & Art	7.4	1.1	NA	Fatal or life-threatening ( <i>ie</i> , surgery, angiography, or irreversible damage); potentially life threatening ( $\geq 3$ -U bleed, hypotension, Hct $\leq 20$ )
Gitter et al <sup>229</sup> /1995	261	221	1987–1989	Established	Ven & Art	8.1	0.45	8.1	$\geq 2$ -U bleed in $\leq 7$ d; life-threatening bleed
Beyth et al <sup>226</sup> /1998	264	440	1986–1993	New	Ven & Art	5.0	0.68	NA	Overt bleeding that led to loss of $\geq 2$ U in $\leq 7$ d or life-threatening bleed
Steffensen et al <sup>245</sup> /1997	682	756	1992–1994	New	Ven & Art	6.0	0.9	NA	Fatal bleeding or bleeding requiring hospitalization

\*Ven & Art = mixed indications in the venous and arterial system; NA = not available; Hct = hematocrit; TE = thromboembolic event.

†Values given as percent per patient year of therapy.

‡Fatal hemorrhagic events also included with major hemorrhage.

more cost-effective, as demonstrated by a number of investigators suggesting a “cost avoidance” of approximately \$1,000 per patient year of therapy.<sup>269–271</sup> These observations need to be validated by randomized studies.

### 2.3.2 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 un-anticoagulated venous whole blood.<sup>272</sup> The result is then converted to a plasma PT equivalent by a microprocessor and is expressed as a PT or 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. Table 13 identifies monitors that have been developed in the last 15 years. Some of these have been approved for professional use only, while others have also been approved for PST at home.<sup>272</sup>

Numerous studies<sup>273–293</sup> have reported on the accuracy and precision of these instruments, on the ability of patients, both adults and children, 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,<sup>291,292</sup> incorrect calibration of the ISI of the POC instruments,<sup>293</sup> and the inability to calculate a mean normal PT.<sup>294</sup> A major problem of comparative studies is the fact that there is a similar lack of correlation of INR results when anticoagulated plasmas are simultaneously compared using different instrument/thromboplastin combinations.<sup>83–90</sup> These dif-

ferences may be clinically important in that they may lead to different dosing decisions.<sup>82–89</sup> Kaatz et al<sup>295</sup> 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. By using lyophilized plasma calibrants with independently certified INRs, Poller and colleagues<sup>296–298</sup> 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.

PST and PSM. PST or PSM using a POC instrument represents another model of care with the potential for improved outcomes as well as greater convenience.<sup>299</sup> 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. Table 14 summarizes studies in which clinical outcomes, either TTR or the number of adverse events, have been reported.<sup>300–311</sup> Both PST and PSM studies are included. Since the potential benefit of PST, either TTR or number of adverse events, depends

**Table 11—Frequency of Major Hemorrhage/Thromboembolism in Patients Managed Under an AMS\***

Study/Year	Patients, No.	Patient Years, No.	Years of Data Collection	New or Established Patient	Indications	Target	Hemorrhage†		Recent TE‡	Definition of Major Bleed
							Major	Fatal‡		
Forfar <sup>24</sup> /1982	541	1,362	1970–1978	N and E	Ven & Art	PTR 1.8–2.6	4.2	0.14	NA	Significant bleed requiring medical advice (excluding bruises and epistaxis)
Petty et al <sup>22</sup> /1988	310	385	1977–1980	N and E	Ven & Art	NA	7.3	0.77	NA	Life-threatening bleed (GI, intracranial, subdural, or death); discontinuing therapy
Film et al <sup>101</sup> /1993	928	1,950	NA	N	Ven & Art	PTR 1.3–1.5 PTR 1.5–1.8	1.7	0.2	7.5	Fatal or life-threatening bleed (CPR, surgery angiography, irreversible damage, hypotension, Hct < 20, ≥ 3-U bleed)
van der Meer et al <sup>21</sup> /1993	6,814	6,085	1988	N and E	Ven & Art	INR 2.4–5.3	3.3	0.64	NA	Fatal bleed; intracranial bleed; transfusion, or surgery; all muscle and joint bleeds
Cannegieter et al <sup>102</sup> /1995	1,608	6,475	1985–1987	N and E	Mech Valves	INR 3.6–4.8	2.5	0.33	0.7	Fatal or bleed leading to hospitalization
Palareti and colleagues <sup>103,116</sup> /1996	2,745	2,011	1993–1995	N	Ven & Art	INR 2.0–3.0 INR 2.5–4.5	1.4	0.24	3.5	Fatal bleed; intracranial bleed; ocular bleed with blindness; joint, retroperitoneal bleed; surgery or angiography, > 2 g bleed; transfusion ≥ 2 U

\*TE = thromboembolism; N = new; E = established; CPR = cardiopulmonary resuscitation. See Tables 3 and 9 for abbreviations not used in text.

†Values expressed as percent per patient year of therapy.

‡Fatal hemorrhagic events also included with major hemorrhage.

**Table 12—Frequency of Major Hemorrhage/Thromboembolism in Patients Managed Under UC vs AMS\***

Study/Year	Model of Care	Patients, No.	Patient Years, No.	Years of Data Collection	Indications	Target	Hemorrhage†			Recurrent TE‡	Combined Hemorrhage/TE†	Cost Savings†
							Maj	Fatal‡	Fatal‡			
Cortelazzo et al <sup>22</sup> /1993	UC AMS	271 271	677 669	1982–present 1987–1990	Mech Valves Mech Valves	25–35%§ INR 3.0–4.5	4.7 1.0	0 0	0 0	6.6 0.6	11.3 1.6	
Chiquette et al <sup>26</sup> /1998	AMS UC	82 142	199 102	1977–1986 1991–1992	Ven & Art Ven & Art	NA NA	2.0 3.9	NA 0.9	NA 11.8	3.5 11.8	5.5 15.7	
Matchar et al <sup>23</sup> /2002	AMS UC	176 190	123 190	1992–1994 ~1998–2000	Ven & Art AF	NA INR 2.0–3.0	1.6¶ 1.6¶	0 0	0 0	3. 4.2¶	4.9 5.8¶	\$1,621
	AMS	173	173	~1998–2000	AF	INR 2.0–3.0	1.7¶	0	0	3.5¶	5.2¶	

\*Mech = mechanical. See Tables 3, 9, and 10 for abbreviations not used in the text.

†Rates expressed as percent per patient year of therapy.

‡Fatal hemorrhagic events included with major hemorrhage.

§Prothrombin activity.

¶Two TE events fatal.

¶¶Values given as number of events/patients studied, not per patient year of therapy.

**Table 13—Capillary Whole-Blood (Point-of-Care) PT Instruments\***

Instrument	Clot Detection Methodology	Type of Sample	Home Use Approval†
ProTIME Monitor 1000‡§	Clot initiation: thromboplastin	Capillary WB	No
Coumatrak†	Clot detection: cessation of blood flow through capillary channel	Venous WB	
Model 512 Coagulation Monitor‡¶			
CoaguChek Plus‡#			
CoaguChek Pro‡#			
CoaguChek Pro/DM‡#			
CoaguChek#	Clot initiation: thromboplastin	Capillary WB	Yes
CoaguChek S#	Clot detection: cessation of movement of iron particles	Venous WB	
Thrombolytic Assessment System@		Plasma	
Rapidpoint Coag**			
ProTIME Monitor‡‡	Clot initiation: thromboplastin	Capillary WB	Yes
Hemochron Jr‡‡	Clot detection: cessation of blood flow through capillary channel	Venous WB	
Avosure Pro+§§	Clot initiation: thromboplastin	Capillary WB	Yes
Avosure Pro§§	Clot detection: thrombin generations detected by fluorescent thrombin probe	Venous WB	
Avosure PT§§		Plasma	
Harmony	Clot initiation: thromboplastin	Capillary WB	Yes
	Clot detection: cessation of blood flow through capillary channel	Venous WB	
INRatio¶¶	Clot initiation: thromboplastin	Capillary WB	Yes
	Clot detection: change in electrical impedance in sample	Venous WB	

\*WB = whole blood.

†Approved for home use in the United States.

‡Based on the original Biotrack model (Protime Monitor 1000) and are licensed under different names. The latest versions available are the CoaguChek Pro and Pro/DM (as models evolved, they acquired added capabilities). Earlier models are no longer available.

§Biotrack, Mountain View, CA.

||Dupont Pharma, Wilmington, DE.

¶Ciba Corning, East Walpole, MA.

#Roche Diagnostics, Basel Switzerland.

@PharmaNetis, Morrisville, NC.

\*\*Bayer Diagnostics, Tarrytown, NY.

‡‡ITC, Edison, NJ.

§§Avosure instruments removed from market when manufacturer (Avocet, Inc) ceased operations in 2001.

||||Lifescan, Milpitas, CA; no longer available.

¶¶Hemosense, Milpitas, CA.

greatly on the quality of management of the comparator group, the studies in Table 14 are grouped according to whether the comparator arm was 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 vs UC. 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 that were 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 parameters. As a consequence of potentially improving outcomes and avoiding adverse events, some investigators<sup>312</sup> also have shown a significant cost savings for PSM.

PST and PSM require special patient training to implement, and this mode of therapy may not be suitable for all patients. Although PST appears to provide greater TTR or improved clinical outcomes compared to UC, the differences are less marked compared to care provided by an

AMS, and a definitive recommendation cannot yet be made as to the overall value of PST or PSM compared to a systematic approach to anticoagulation therapy management.

POC INR monitoring by the patient at home is a new option for patient monitoring that, in properly selected and trained patients, has been shown to improve TTR and clinical outcomes compared to usual anticoagulation therapy management. However, the utilization of patient self-monitoring is a choice made by patients and physicians that depends on many factors. We have no specific recommendation but leave the choice to the physician and patient based on their individual preferences and needs.

### 2.3.3 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.<sup>313,314</sup> Data from clinical trials and obser-

**Table 14—Studies of PST and PSM of Oral Anticoagulation Stratified by Whether the Comparator Group is Routine Medical Care or an AMS Model of Care\***

Study/Year/Type	Study Groups	TTR	Adverse Events
Beyth <sup>300</sup> /2000/RCT	PST† vs UC	56% vs 32%	14% vs 25%
Horstkotte et al <sup>301</sup> /1998/RCT	PSM vs UC	92% vs 59%	5.4% vs 4.5%
Hasenkam et al <sup>302</sup> /1997/Cohort	PSM vs UC	77% vs 59%	No AEs
Sawicki <sup>303</sup> /1999/RCT	PSM vs UC	57% vs 34%	3 vs 1
Kortke and Kofer <sup>304</sup> /2001/RCT	PSM vs UC	78% vs 61%	2.9% vs 4.7%
Preiss et al <sup>305</sup> /2001/Sequential Cohort	PSM vs UC	74% vs 63%	3.28% vs 4.67%
White et al <sup>306</sup> /1989/RCT	PST† vs AMS	87% vs 68%	No AEs
Kaatz et al <sup>307</sup> /2001/RCT	PST† vs AMS	63% vs 65%	NA
Gadisseur et al <sup>311</sup> /2001/Cohort	PST vs AMS	70% vs 69%	NA
Ansell et al <sup>308</sup> /1995/Cohort	PSM vs AMS	88% vs 66%	No AEs
Watzke et al <sup>309</sup> /2000/RCT	PSM vs AMS	86% vs 80%	2 vs 0
Cromheecke et al <sup>310</sup> /2000/Crossover	PSM vs AMS	55% vs 49%	No AEs
Gadisseur et al <sup>311</sup> /2001/Cohort	PSM vs AMS	71% vs 69%	NA

\*AE = adverse event. See Tables 3 and 5 for abbreviations not used in the text.

†Dose management for PST group performed by an anticoagulation management service.

ventional studies on the success of achieving TTR have indicated a wide range of success in achieving TTR (Table 9), from a low of 33% for a UC model to 90% for PSM. Computer assistance by the use of 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 dose is also set by the program using a set of variables comparing the current INR, the interval from the last test, the number of previous changes, and the number of previous INR values within the target range.

A number of early studies<sup>315–317</sup> evaluated computer programs to improve warfarin dosing. The first randomized study in 1993<sup>318</sup> 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, 3.0 to 4.5). In another randomized study,<sup>319</sup> of 101 patients who had received long-term anticoagulation therapy with 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<sup>320</sup> 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<sup>321</sup> using a different management program in > 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, and 51.9% vs 48.1%,

respectively, were in range in the first 3 months of the induction period.<sup>321</sup> In both of these studies, the natural overcaution of medical staff in dosing patients at a higher INR range was not shared by the computer.

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 the long-term management of therapy.<sup>321,322</sup> 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.

Clinical benefit 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 patient self-monitoring, we think that this is a physician preference based on a number of factors such as panel size and ancillary help, and we have no recommendation.

## SUMMARY OF RECOMMENDATIONS

### 2.1.1 The Appropriate Dose for Initiation of Oral Anticoagulants

2.1.1.1. We suggest the initiation of oral anticoagulation therapy with doses between 5 and 10 mg for the first 1 or

2 days for most individuals, with subsequent dosing based on the INR response (**Grade 2B**).

### **2.1.2 Anticoagulation in the Elderly**

2.1.2.1. In the elderly, for patients who are debilitated, malnourished, have congestive heart failure, or have liver disease we suggest the use of a starting dose of  $\leq 5$  mg (**Grade 2C**).

### **2.1.3 Frequency of Monitoring Oral Anticoagulation Therapy**

2.1.3.1. We suggest starting INR monitoring after the initial two or three doses of oral anticoagulation therapy (**Grade 2C**).

2.1.3.3. 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**).

### **2.1.4 Management of Dosing When the INR Is Nontherapeutic**

2.1.4.1. For patients with INRs above the therapeutic range but  $< 5.0$  who have no significant bleeding, lower the dose or omit the dose, monitor more frequently, and resume therapy at a lower dose when the INR is in the therapeutic range. If only minimally above the therapeutic range, no dose reduction may be required (all **Grade 2C**).

2.1.4.2. For patients with INRs of  $\geq 5.0$  but  $< 9.0$  who have no significant bleeding, omit the next one or two doses, monitor more frequently, and resume therapy at a lower dose when the INR is in the therapeutic range. Alternatively, omit a dose and administer vitamin K1 (1 to 2.5 mg orally), particularly if the patient is at an increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 ( $\leq 5$  mg orally) 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 K1 (1 to 2 mg orally) can be given (all **Grade 2C**).

2.1.4.3. For patients with INRs of  $\geq 9.0$  who have no significant bleeding, hold warfarin therapy and administer a higher dose of vitamin K1 (5 to 10 mg orally) with the expectation that the INR will be reduced substantially in 24 to 48 h. Monitor the patient more frequently and use additional vitamin K1 if necessary. Resume therapy at a lower dose when INR is in the therapeutic range (all **Grade 2C**).

2.1.4.4. In patients with serious bleeding and elevated INRs, we recommend holding warfarin therapy and administering vitamin K1 (10 mg by slow IV infusion), supplemented with fresh plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation. Vitamin K1 administration can be repeated every 12 h (all **Grade 1C**).

2.1.4.5. In patients with life-threatening bleeding and elevated INRs, we recommend holding warfarin therapy

and administering prothrombin complex concentrate or recombinant factor VIIa supplemented with vitamin K1 (10 mg by slow IV infusion). Repeat the procedure if necessary, depending on INR (**Grade 1C**).

2.1.4.6. In patients with mild to moderately elevated INRs who have no major bleeding, we suggest that vitamin K be administered orally rather than SC (**Grade 1A**).

### **2.1.5 Management of Dosing When an Invasive Procedure Is Required**

2.1.5.1. For patients with a low risk of thromboembolism, stop warfarin therapy approximately 4 days before surgery, allow the INR to return to near-normal values, briefly use postoperative prophylaxis (if the intervention increases the risk of thrombosis) with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH and simultaneously begin warfarin therapy. Alternatively, a low dose of UFH or a prophylactic dose of LMWH also can be administered preoperatively (all **Grade 2C**).

2.1.5.2. For patients with an intermediate risk of thromboembolism, stop warfarin therapy approximately 4 days before surgery, allow the INR to fall, cover the patient beginning 2 days preoperatively with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH and then commence administration of a low dose of UFH (or LMWH) and warfarin postoperatively (**Grade 2C**).

2.1.5.3. For patients with a high risk of thromboembolism, stop warfarin therapy approximately 4 days before surgery to allow the INR to return to normal at the time of surgery, and begin therapy with a full dose of UFH or a full dose of LMWH as the INR falls (approximately 2 days preoperatively). UFH can be administered as an SC injection on an outpatient basis and as a continuous IV infusion after hospital admission in preparation for surgery and should be discontinued approximately 5 h before surgery with the expectation that the anticoagulant effect will have worn off by the time of surgery. An alternative is to continue to use SC UFH or LMWH preoperatively and to stop therapy 12 to 24 h before surgery with the expectation that the anticoagulant effect will be very low or have worn off by the time of surgery, then commence administering a full dose of UFH (or LMWH) and warfarin postoperatively (**Grade 2C**). [Editor's note: This text reading "full dose" has been changed as an erratum to the original printed version of this article.]

2.1.5.4. For patients with low risk of bleeding, continue warfarin therapy at a lower dose and operate at an INR of 1.3 to 1.5. The dose of warfarin can be lowered 4 or 5 days before surgery. Warfarin therapy then can be restarted postoperatively, supplemented with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH, if necessary (**Grade 2C**).

2.1.5.5. In patients who are undergoing dental procedures with a need to control local bleeding, we suggest the use of tranexamic acid mouthwash (**Grade 2B**) or epsilon amino caproic acid mouthwash without interrupting anti-coagulant therapy (**Grade 2B**).

### 2.1.6 Therapeutic Range in the Presence of a Lupus Inhibitor

2.1.6. In patients who have a lupus inhibitor and who have no additional risk factors and have not failed to respond to therapy, we suggest a therapeutic target INR of 2.5 (INR range, 2.0 to 3.0) [Grade 2B]. 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].

### 2.3.1 Models of Anticoagulation Monitoring and Management

2.3.1. 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 dosing decisions (Grade 1C+).

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