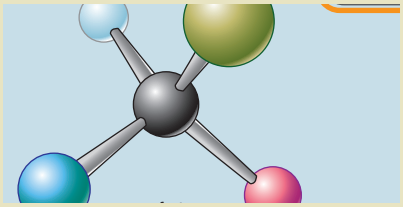
abstract



Warfarin reduces the risk of thrombotic complications in a wide range of patients and appears to be particularly effective in older adults. Warfarin initiation should be undertaken with care in the older adults because they are likely to require smaller maintenance doses to achieve the same target international normalized ratio (INR). Inappropriate prescribing of medications among older adults increases the risk of drug interactions that may alter warfarin anticoagulation. Such interactions should be anticipated and monitored to ensure that over- or under-anticoagulation do not persist. A range of strategies are available to follow warfarin therapy in the outpatient setting to ensure safe and effective anticoagulation.

Key words: *warfarin, anticoagulation, vitamin K, atrial fibrillation*

Warfarin Anticoagulation in Older Adults: A Review of Outpatient Initiation and Monitoring

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Introduction

Warfarin anticoagulation is challenging. Its clinical efficacy is dependent on maintaining anticoagulation within a narrow therapeutic window; its dose response is variable and influenced by other drugs and diet; and supratherapeutic anticoagulation carries a significant risk of bleeding, which can be fatal. Despite these challenges, the number of aging individuals who are candidates for warfarin therapy is increasing, due in large part to the increased prevalence of atrial fibrillation with increasing age.[1] Atrial fibrillation affects approximately 10% of individuals ≥ 80 years of age.[2] Warfarin therapy reduces the risk of stroke in a broad subset of patients with atrial fibrillation by 68%,[3] and the benefit of anticoagulation is greatest among patients greater than 75.[4,5] Despite this evidence, warfarin use in patients > 80 years remains low at 12–24%, even after adjusting for contraindications to anticoagulation (Table 1).[6,7] Risk of hemorrhage and erratic control are frequently cited reasons for physicians not prescribing anticoagulants to geriatric patients.[8] Optimal anticoagulation control in the older population, as with any patient group, is facilitated by physician appreciation of the challenges and evidence in support of oral anticoagulant therapy. This review will focus specifically on initiating and monitoring warfarin therapy in the outpatient setting.

Pharmacology and Monitoring

Warfarin, along with other Coumarin derivatives, produces its anticoagulant effect through a reduction in the vitamin K-dependent coagulation factors II, VII, IX, and X (Figure 1). The prothrombin time (PT) test, which reflects warfarin's reduction of factors II, VII, and X at a rate proportional to their respective half-lives, is used to monitor warfarin anticoagulation. During the first several days of warfarin therapy, the PT reflects mainly a reduction of factor VII with its half-life of only six hours. Since 1982, the international normalized ratio (INR) has been used to standardize the reporting of PT results and to account for variability in local thromboplastin reagents used in the test. Therapeutic anticoagulation is achieved by titrating the dose of warfarin to reach a target INR range, which for most indications is between 2.0 and 3.0 (Table 2).

Table 1: Common Reasons why Warfarin Is Underprescribed in Older Adults

Risk perception of erratic INR control
Risk perception of anticoagulation-associated bleeding
Concern for potential drug interactions
Need for frequent INR monitoring
Emphasis on other medical comorbidities in older adults

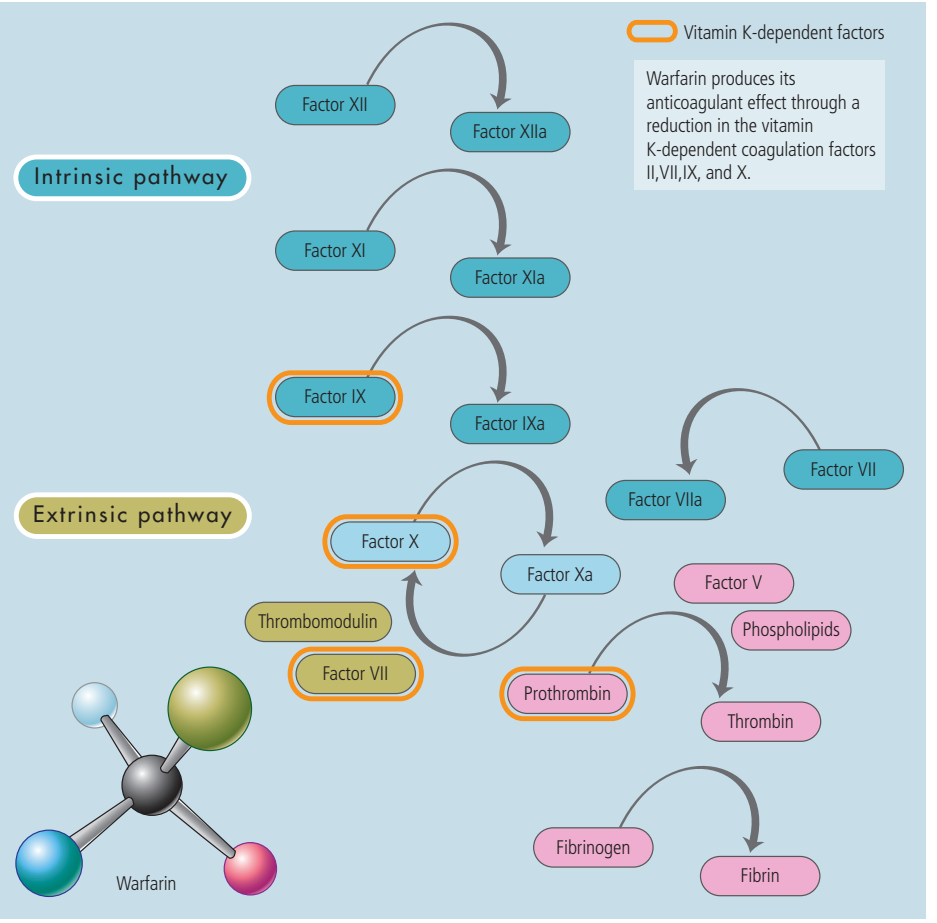
Initiation and Maintenance Dosing

The effect of warfarin on the PT is seen within the first two to three days of therapy; however, onset of therapeutic anticoagulation is delayed for several days while factors II and X decline at a rate proportionate to their half-lives.[9] This disassociation between the INR and true anticoagulation early in therapy may account for early recurrences of thrombosis in patients treated for acute deep vein thrombosis who do not receive heparin.[10] The urgency with which anticoagulation is required determines the strategy for warfarin initiation. When a rapid anticoagulant effect is desired—for example, after acute venous thromboembolism—heparin should be administered concurrently with warfarin and discontinued only once the INR has remained therapeutic for at least two consecutive days.[10] Concurrent treatment with heparin is also recommended in patients with known protein C deficiency or other thrombophilic states to protect against the possibility of an early hypercoagulable state caused by warfarin's reduction of vitamin K-dependent coagulation inhibitors. However, in most outpatient scenarios, such as chronic atrial fibrillation, warfarin can be initiated without heparin at the anticipated maintenance dose. The safety of this strategy has been established in many large randomized trials involving patients with atrial fibrillation.[11]

When starting warfarin, a large loading dose (>10 mg) should not be used. Whether lower loading doses (for example, 10 mg) hasten anticoagulation remains controversial.[9,12,13] The Seventh American College of Chest Physicians Consensus Conference on Antithrombotic and Thrombolytic Therapy recommends initiating warfarin at a dose of 5 mg in older adults.[14] However, an argument for lower initial dosing could be made based on the observation that median daily doses of warfarin are less than 5 mg per day in older adults.[15]

Until recently, there was little published evidence specifically addressing warfarin dose requirements in the geriatric population. A recent prospective cohort study[15] examined trends in warfarin maintenance dosing among 4,616 patients with a target INR of 2.0–3.0 who were monitored within an ambulatory setting. The mean age of the cohort was 72; a total of 1,127 patients were >80 years old. Sixty-two percent received warfarin for stroke prevention in the setting of atrial fibrillation. In this study, as in others, important relationships were observed between reduced warfarin dosing requirements and increasing age, female gender, and amiodarone use. For each additional year of age, the average weekly warfarin dose decreased by 0.4 mg (P<0.001). At any given age, the mean weekly warfarin dose for women was 4.5 mg lower than that of men (P<0.001). The mean weekly warfarin dose among those also prescribed amiodarone was 7.3 mg less than those not using amiodarone (P<0.001). The often recommended 5 mg initiation dose exceeded the maintenance dose requirement in 82% of women >70 and 65% of men >70 in this cohort. These observations suggest that most older patients are best started on a warfarin dose that reflects their age and gender (Table 3) rather than an arbitrary dose that may exceed what they are likely to require over the long term.

Figure 1:
Warfarin's Effect on the Coagulation Cascade



Warfarin impairs the hepatic enzymes vitamin K-epoxide reductase and vitamin K reductase, which are required for the "recycling" of oxidized vitamin K into reduced vitamin K. In the presence of warfarin, dysfunctional coagulation factors II (prothrombin), VII, IX, and X are produced and released into the circulation.

INR Monitoring

The frequency of INR monitoring is highly individualized and is determined in large part by a patient's evolving dose-response relationship with warfarin. However, when initiating warfarin therapy in the outpatient setting, most clinicians monitor the INR two to three times weekly for the first one to two weeks,

Table 2: Recommended Therapeutic Ranges of the International Normalized Ratio (INR) for Common Indications for Warfarin Anticoagulation

Indication	INR range
Prophylaxis of venous thrombosis (high risk surgery)	2.0–3.0
Treatment of venous thrombosis	
Treatment of pulmonary embolism	
Prevention of systemic embolism	
Tissue heart valves	
AMI (to prevent systemic embolism)	
Valvular heart disease	
Atrial fibrillation	
Bileaflet mechanical valve in aortic position	
Mechanical prosthetic valves (high risk)	2.5–3.5
Prophylaxis of recurrent myocardial infarction	

Source: Adapted from Ansell J et al., 2004.[14]

and then less often, depending on whether a stable warfarin dose has been established. A common error seen during warfarin initiation is excessively frequent INR monitoring and subsequent dose changes. Table 4 presents a recommended frequency of INR measurement. Once the INR is stable, the frequency of INR measurement can be reduced to longer intervals, as long as every four weeks. In the long term, the frequency of INR measurement is influenced by a number of factors including patient compliance, previous dose adjustments, and changes in medical status, medications, and diet. More frequent INR monitoring should follow any warfarin dosage change, and after the introduction of any new medication, until it is clear that the INR has not been influenced.

Variability in the Dose Response of Warfarin

Fluctuations in vitamin K intake, impaired vitamin K absorption, and interference with the bacterial synthesis of vitamin K through antibiotic use have the potential to create instability in the warfarin dose-response relationship.[16,17]

A large number of medications are known to potentiate the anticoagulant effect of warfarin. Warfarin is a racemic mixture of R and S enantiomers. Inhibition of the metabolism of s-warfarin by drug competition for the cytochrome P450 isozyme CYP2C9 is the most potent mechanism by which warfarin anticoagulation is potentiated. Amiodarone is a potent inhibitor of the metabolic clearance of both R and S isomers and thus strongly potentiates warfarin anticoagulation. Table 5 lists medications most consistently reported to potentiate warfarin anticoagulation. Drugs that enhance hepatic clearance such as barbiturates, rifampin, and carbamazepine inhibit the anticoagulant effect of warfarin, thereby increasing warfarin dose requirements.

The increased sensitivity of older patients to warfarin is likely multifactorial. Reduced dietary vitamin K intake and absorption leading to diminished coagulation factor synthesis, and polypharmacy resulting in drug interactions which potentiate the therapeutic effect of warfarin are likely to contribute. Pharmacokinetic changes including warfarin absorption, bioavailability, and volume of distribution are largely unchanged in the older adult.[18]

Management of Nontherapeutic INRs

Patients with an INR below the therapeutic range can be managed by either adjusting the warfarin dose, typically by 5–20% of the cumulative weekly dose, or through a one-time larger dose followed by a return to the daily maintenance dose. Unfortunately, there is little evidence to demonstrate the superiority of one approach over the other. Despite the lack of evidence, practical suggestions can be made. If it is likely that the INR fell as a result of a transient problem, such as inadvertent dosage omission, increasing the dose for one or two days followed by a return to the previous dose will likely suffice. If the fall is due to a more persistent factor, such as a new medication, the dose should be increased and the INR re-evaluated in five to seven days.

Management of supratherapeutic INRs can be accomplished with more frequent monitoring without a dosage change, holding warfarin for a day or more followed by a return to warfarin at a lower weekly dose, or with the administration of vitamin K. Asymptomatic elevation of the INR is a common and important clinical problem; a strong relationship exists between the degree of INR elevation and the risk of hemorrhage. Serious warfarin-associated bleeding usually occurs from the gastrointestinal or genitourinary system[19]; the risk of such bleeding may as much as double for each one-point increase in the INR.[20] The

Table 3: Median Warfarin Dose Requirements among Patients Taking Warfarin for Atrial Fibrillation

	Median Warfarin Dose (mg)	
Age (yr)	Men	Women
50–59	5.4	5.0
60–69	4.6	4.0
70–79	4.3	3.5
80–89	3.9	3.2
≥ 90	3.6	3.0

Source: Adapted from Garcia D, et al., 2005.[15]

choice of strategy is influenced by the patient's risk of bleeding, medical comorbidities, and the patient's sensitivity to warfarin dose adjustments. Hylek *et al.* found that among patients with an INR >6.0 who were managed by withholding two doses of warfarin therapy the INR reduced more slowly in the setting of lower maintenance doses, older age, higher initial INR, decompensated congestive heart failure, and active cancer.[21] Given the relatively slow decline in the INR by withholding warfarin alone, parenteral vitamin K may be used in some cases to more rapidly correct the INR.

Two double-blind, placebo-controlled RCTs have demonstrated that administering oral vitamin K therapy reduces the INR more promptly than withholding warfarin alone.[22,23] In a placebo-controlled RCT of 1 mg of oral vitamin K for asymptomatic INR elevation, a lower bleeding rate over the three-month follow-up period was observed among patients randomly assigned to vitamin K (4% vs. 15%, P=0.05).[23] RCT evidence also supports the equivalence of oral vitamin K to the intravenous route,[24] and its superiority to subcutaneous vitamin K injection[25] in the correction of asymptomatic INR elevation. Although no tablet form of vitamin K is currently available in Canada, the intravenous formulation can be given orally (either undiluted or after mixing with orange juice to mask its unpleasant taste). A recent systematic review of oral vitamin K concluded that 1 mg of oral vitamin K therapy is an appropriate option for INRs between 4.5 and 10, with limited risk of inducing subtherapeutic anticoagulation.[26]

For patients with supratherapeutic INRs and active bleeding, rapid reversal of anticoagulation is required and can be managed with the use of intravenous vitamin K, fresh frozen plasma, prothrombin concentrates, or recombinant factor VIIa.[27]

Periprocedure Management of Warfarin Therapy

Several options are available for the management of warfarin anticoagulation in anticipation of a planned invasive procedure, including a) reversal of warfarin anticoagulation or b) continuing anticoagulation with unfractionated or low molecular weight heparin at prophylactic or therapeutic doses. A recent review[28] summarizes management options for a range of surgical procedures including cataract surgery, pacemaker insertion, and GI endoscopy. In many cases, warfarin may not need to be stopped prior to minimally invasive procedures. For example, studies examining warfarin management in preparation for dental

Table 4: Warfarin Initiation Scenario

An 87-year-old woman presents with new onset atrial fibrillation. She is treated with amiodarone and advised to initiate warfarin. Her cardiologist prescribes a 7.5 mg warfarin dose for two days followed by 5 mg on the third day with an INR on the day of the second 7.5 mg warfarin dose. She is advised to attend your office one week after initiation. However, she calls you for advice.

Problems

1) The prescribed initiation dose is likely to be well in excess of the chronic maintenance dose, which will be reduced due to the patient's age, gender, and concurrent amiodarone use.

2) Assessing the INR on the second day of warfarin therapy is unhelpful since the INR will not yet have responded. Increasing the dose based on a subtherapeutic INR is inappropriate in this setting. Although possible, the likelihood of detecting a marked prolongation of the INR on this day is also very low.

Solution

Although the patient has taken a 7.5 mg warfarin dose you suggest that she disregard the cardiologist's advice and take a 3 mg dose alternating with a 4 mg dose and have her INR measured on day five of therapy. The INR on that occasion is 2.7; an additional INR performed one week later is 2.6. The patient has achieved stable anticoagulation with only two INR determinations and could be monitored as infrequently as every second week and up to every four weeks once a stable dose relationship is achieved.

Table 5: Common Drugs that May Increase the International Normalized Ratio (INR) by Potentiating the Anticoagulant Effect of Warfarin

Analgesics and anti-inflammatory drugs: acetaminophen, fenoprofen, piroxicam, tramadol
Antibiotics: cephalosporins (cefotetan, ceftriaxone), tetracyclines (doxycycline, tetracycline), macrolides (azithromycin, clarithromycin, erythromycin), quinolones (ciprofloxacin, levofloxacin, norfloxacin, ofloxacin), sulfonamides (trimethroprim-sulfamethoxazole), others (metronidazole)
Central nervous system: alcohol, anticonvulsants (phenytoin, valproate), SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline)
Cardiac: amiodarone, propranolol, quinidine
Endocrine: gemfibrozil, lovastatin, levothyroxine, simvastatin
Gastrointestinal: cimetidine, cisapride, omeprazole
Other: allopurinol, pentoxifylline, tamoxifen

procedures have found no difference in postprocedure bleeding at low or higher INR levels.[29,30] Similarly, many surgeons are comfortable continuing warfarin around the time of cataract surgery, unless retrobulbar anesthesia is planned.[31]

A comprehensive review of warfarin bridging therapy is beyond the scope of this review; however, most large bridging clinics divide patients into three groups. In general, patients with low risk of thrombosis or very high risk of bleeding simply have their warfarin withheld in the periprocedure time period, with warfarin reintroduced when hemostasis is assured. Meanwhile, patients with a moderate risk of thrombosis may receive prophylactic dose low molecular weight heparin and those at high risk of thrombosis will usually receive low molecular weight heparin at a therapeutic dose with the immediate preoperative dose given more than 24 hours prior to the procedure.

Conclusion

Warfarin is likely to remain the only widely available oral anticoagulant agent for the foreseeable future and is currently the mainstay of anticoagulant therapy. Warfarin reduces the risk of thrombotic complications in a wide range of patients and appears particularly efficacious in the older adult for stroke prevention in the setting of atrial fibrillation. Warfarin initiation should be undertaken with care in older adults because they are likely to require smaller maintenance doses to achieve the same target INR. Older patients may be taking additional medications with the potential to interfere with the anticoagulant effect of warfarin; such interactions should be anticipated and monitored to ensure that over- or under-anticoagulation, with their attendant risks of bleeding or thrombosis, do not persist.

The authors have no commercial associations of relevance to the content of this article. Dr. Crowther holds a Canadian Institutes of Health Research Scholarship.

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