ANTICOAGULATION WITH WARFARIN: GUIDE FOR FAMILY PHYSICIANS

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ABSTRACT

Background

Family physicians commonly manage patients on warfarin, either for anticoagulation or for comorbid conditions. The article presents a review of the literature to guide (1) indications for anticoagulation and target International Normalised Ratio (INR); (2) anticoagulation monitoring and dose management; (3) periprocedural management of anticoagulation and aspirin therapy and (4) considerations of drug, herb, food and disease interactions with warfarin.

Methods

A PubMed search was conducted in Jun 2005 with a focus on evidence-based consensus guidelines and authoritative reviews. Thirty-five papers were found useful for this review.

Results

The target INR is generally 2 – 3 for most indications, including bioprosthetic heart valves, and 2.5 – 3.5 for mechanical prosthetic valves. A monitoring interval of no longer than every 4 weeks is suggested. With adjustments to the dose, more frequent monitoring should be repeated. Serious embolic complications are more likely to occur in patients whose anticoagulant therapy is interrupted than are bleeding complications when anticoagulant therapy is continued. Most patients can undergo simple dental and dermatological procedures, cataract surgery and diagnostic endoscopy without alteration of anticoagulation or aspirin therapy. Many drugs, herbs, food substances and disease states interact with warfarin to varying degrees.

Conclusion

Anticoagulation can be managed safely by the family physician with careful attention to therapeutic INR and potential interactions. Periprocedural management of anticoagulation is dependent on the location and extent of surgery, the accessibility of the bleeding site to compression, and the patient's risk of thromboembolism.

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INTRODUCTION

Warfarin has been established by well-designed clinical trials for the prevention and treatment of venous or arterial thrombosis and embolism. It is a potentially hazardous drug, causing major bleeding in 1% - 2% of people treated, and intracranial bleeding in about 0.1% - 0.5% during each year of therapy[1].

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It is challenging to use in clinical practice for the following reasons[2,3]:

- It has a narrow therapeutic window.
- There is considerable variability in dose response among subjects.
- It has a slow onset and offset of action.
- It is subject to interactions with drugs, diet, and disease conditions.
- The laboratory control can be difficult to standardise.
- It requires frequent monitoring of anticoagulant effect via the international normalised ratio, constant dose adjustments, patient education, strict compliance, and frequent follow-up.

Family physicians may manage patients on warfarin in various situations:

1. Maintenance of anticoagulation therapy.
2. Management of acute or chronic conditions in patients on warfarin.
3. Request for advice from dentists and surgeons on oral anticoagulation during invasive procedures.

The goal of anticoagulant therapy is to administer the lowest possible dose of anticoagulant to prevent clot formation or expansion. By using the lowest possible required dose of warfarin, the physician can minimise the risk of bleeding while providing the benefits of anticoagulation[4].

The article attempts to set out various guidelines based on current evidence and literature for:

1. Target INR for various indications.
2. Simple regimen for monitoring of INR (International Normalised Ratio) and adjustment of warfarin dose.
3. Periprocedural management of anticoagulation and antiplatelet therapy.
4. Drug, herb, food and disease interactions.

Anticoagulation scenarios that do not involve the family physician in the local context, e.g. initiation of anticoagulation for atrial fibrillation or treatment of acute deep vein thromboses, are outside of the scope of this article. Similarly, the use of other antithrombotics such as LMWH (low molecular weight heparin) is not discussed.

METHODOLOGY

Anticoagulation with warfarin is a wide topic with thousands of articles published. This article focused on evidence-based consensus guidelines and authoritative reviews. Full-text articles were accessed through Ovid, Science Direct, MD Consult and the World Wide Web.

A PubMed search was conducted with the following search strategies during the period 18 – 24 June 2005:

1. Keywords anticoagula* OR warfarin, limited to <Publication Type> Practice Guideline, <Language> English and <Publication Date> from 2000/01/01.
   68 articles were returned. 10 relevant full-text articles were selected and reviewed.
2. Keywords warfarin AND pharmacology, limited to <Publication Type> Review, <Language> English and <Publication Date> from 2005/01/01.
   25 articles were returned. 5 relevant articles were selected. 3 full-text articles were reviewed.
3. Keywords (anticoagula* OR warfarin) restricted to major topic headings AND keywords (perioperati* OR periprocedur*) limited to <Publication Type> Review, <Language> English and <Publication Date> from 2000/01/01.
   36 articles were returned. 13 relevant articles were selected. 7 full-text articles were reviewed.
4. Keywords (antiplatelet OR aspirin) AND (perioperati* OR periprocedur*), limited to <Publication Type> (Practice Guideline OR Review) and <Language> English.
   82 articles were returned. 7 relevant articles were selected. 1 full-text article and 6 abstracts were reviewed.
5. Keywords (antiplatelet OR aspirin) AND (dental surgery OR oral surgery), limited to <Publication Type> (Practice Guideline OR Review) and <Language> English.
   21 articles were returned. 3 relevant articles were selected. 2 full-text articles were reviewed.
6. Keywords (antiplatelet OR aspirin) AND cataract surgery, limited to Publication Type> Review and <Language> English.
   3 articles were returned. 2 relevant articles were selected and their abstracts were reviewed.
7. MeSH term warfarin restricted to major topic heading AND keywords (food OR diet OR dietary OR drug OR drugs OR disease* OR herb* OR supplement*) AND interaction*, limited to <Publication Type> Review and <Language> English.
   75 articles were returned. 21 relevant articles were selected. 10 full-text articles were reviewed.
8. Keywords (food OR diet OR dietary) AND vitamin K AND content, limited to <Language> English.
   71 articles were returned. 7 relevant articles were selected. 4 full-text articles were reviewed.
9. MeSH terms restricted to major topic headings: warfarin AND (family practice OR physicians, family OR primary health care) limited to <Language> English.
   28 articles were returned. 3 relevant articles were selected. 1 full-text article was reviewed.

Thirty-five papers were found useful for this review.

INDICATIONS AND TARGET INR

Grades of Recommendation[5]

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 (see table below).

Table 1. Methodological Strength of Supporting Evidence

Grade	Risk/ Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	RCTs without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodologica flaws)	Strong recommendations; likely to apply to most patients
1C	Clear	Observational studies stronger evidence is available	Intermediate-strength recommendation; may change when
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendations; other alternatives may be equally reasonable

Table 2 shows an evidence-based guideline for anticoagulation with warfarin based on the 2004 Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy.

The referring specialist would have managed the patient for a period of time and might have an individualised target INR based on the effectiveness of anticoagulation and any bleeding complications.

Table 2. Evidence Based Guideline for Anticoagulation with Warfarin

Condition	Target INR	Grade
Coronary artery disease[6]		
o Primary prevention for high-risk patients	1.5	2A
Coronary artery disease[6]		
o Post-myocardial infarction, high-risk, with aspirin, for 3 months	2 – 3	2A
o Post-myocardial infarction, high-risk or low-risk, with aspirin, for 4 years	2 – 3	2B
Atrial fibrillation/flutter, persistent or paroxysmal, with[7]		
o Prior ischaemic stroke	2 – 3	1A
o Transient ischemic attack (TIA)		1A
o Systemic embolism		1A
o Age > 75 years		1A
(For age 65 – 75 years with no other risk factors, either warfarin or aspirin is acceptable;		1A
For age < 65 years with no other risk factors, aspirin is recommended)		1B
o Moderately or severely impaired left ventricular systolic function		1A
o Congestive heart failure		1A
o Hypertension		1A
o Diabetes mellitus		1A
o Mitral stenosis		1C+
Rheumatic mitral valve disease with[8]		
o Atrial fibrillation	2 – 3	1C+
o Previous history of systemic embolism		1C+
o Sinus rhythm with a left atrial diameter > 5.5 cm		2C
Mitral valve prolapse with[8]		
o Systemic embolism or recurrent TIAs despite aspirin therapy	2 – 3	2C
Mitral annular calcification with[8]		
o Previous history of systemic embolism	2 – 3	2C
Bioprosthetic heart valve for[8]		
o First 3 months after valve insertion	2 – 3	1C+
o 3 – 12 months if previous history of systemic embolism		1C
o Indefinite therapy if atrial fibrillation		1C+
Mechanical prosthetic heart valve with[8]		
o St. Jude Medical (St. Paul, MN) bileaflet valve in the aortic position	2 – 3	1A
o CarboMedics bileaflet valve or Medtronic Hall tilting disk mechanical valves in the aortic position, normal left atrium size, and sinus rhythm		1C+
Deep vein thromboses (DVT) / Pulmonary embolism (PE)[9]		
o First episode DVT/ PE with transient risk factor, treat for 3 months	2 – 3	1A
o First episode of idiopathic DVT/ PE, treat for 6 – 12 months, consider indefinite therapy		1A
o First episode DVT/ PE with cancer, LMWH for 3-6 months, consider indefinite anticoagulant therapy or until cancer is resolved		1A / 1C
o First episode DVT/ PE with thrombophilic conditions, treat for 6 – 12 months, consider indefinite therapy		1C+ / 2C
o 2 or more episodes, for indefinite therapy		2A
Atrial fibrillation / flutter, persistent or paroxysmal, with[7]		
o Bioprosthetic heart valve	2.5 – 3.5	1C+
Mechanical prosthetic heart valve with[8]		
o Tilting disk valves and bileaflet mechanical valves in the mitral position		1C+
o Additional risk factors such as AF, myocardial infarction, left atrial enlargement, endocardial damage, and low ejection fraction (with aspirin)		1C+
o Caged ball or caged disk valves (with aspirin)		2A
Coronary artery disease[6]		
o Post-myocardial infarction, high-risk or low-risk, without aspirin, for 4 years	3 – 4	2B

Patients with the above conditions who are not on anticoagulation should be referred for assessment with a view to initiation of warfarin.

Anticoagulation with warfarin is not recommended in the following:

- Chronic stable coronary artery disease without prior myocardial infarction.[6] (Grade 2C)
- Atrial fibrillation in patients age < 65 years with no other risk factors.[7] (Grade 1B recommendation for aspirin)
- Non-cardioembolic stroke or TIA.[10] (Grade 1A recommendation for antiplatelet agent over anticoagulant)
- Chronic limb ischaemia without acute emboli or thrombosis.[11] (Grade 1A)

Pharmacokinetics of Warfarin[2,3,4,12,13]

- Peak concentration: 90 minutes – 8 hours
- Plasma binding: 99% bound to albumin
- Metabolism: Liver primarily
- Excretion: Inactive metabolites excreted in urine and stool
- Half life: 36 – 42 hours
- Peak effect: 36 – 72 hours
- Duration of effect: 2 – 5 days

Anticoagulation Monitoring and Dose Management

Maintenance therapy involves frequent monitoring of INR and adjustment of warfarin dosage to achieve therapeutic efficacy as well as safety.

Frequency of Monitoring

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[2,12].

For patients who are receiving a stable dose of oral anticoagulants, a monitoring interval of no longer than every 4 weeks is suggested[2,12]. There is evidence to suggest that testing more frequently than every 4 weeks will lead to greater time in therapeutic range and, presumably, fewer adverse events[2].

With adjustments to the dose, more frequent monitoring should be repeated until a stable dose response can again be achieved[2].

Dose Management

Dose requirements often change during maintenance therapy and physicians can employ various strategies to make dosing simple and clear for the patient:

1. Use fixed tablet strength and alternate dose amounts (tablets or fraction of tablets) per day.
   - This approach is possible because of warfarin's long half-life. It is a safe and effective way to provide sufficient anticoagulation[4].
   - This may be more confusing for the patient[2]. It may be simplified by alternating on given days of the week rather than on odd or even days[4].
2. Use uniform daily amount that might require the patient to have different tablet strengths.
   - Warfarin tablets used locally are of the following strengths and colours:
     - 1mg (brown)
     - 3mg (blue)
     - 5mg (pink)
   - This can be confusing to elderly patients who are taking several other medications concurrently and who may confuse tablet colors and strengths[4].

Both methods achieve similar outcomes[2].

MANAGEMENT OF NON-THERAPEUTIC INRs

Table 3. Management of Non-Therapeutic INRs[1,2,4,12,14]

Patient's INR	< TR	Within TR (Therapeutic Range)	> TR – < 5.0 No Significant Bleeding	5.0 – < 9.0 No Significant Bleeding	> 9.0 OR Significant Bleeding
Dose Change	Increase cumulative weekly dose by 5 – 20% (may not be necessary if INR minimally depressed)	No change	Omit 1 dose optional Lower cumulative weekly dose by 5 – 20% (may not be necessary if INR minimally raised)	Omit 1 – 2 doses Oral vit K1 – 2.5mg if increased risk of bleeding Lower cumulative weekly dose by 5 – 20% Resume warfarin when INR within TR	Refer A&E
Next INR	4 – 14 days	4 weekly	4 – 14 days	1 – 4 days	

Suggested Follow-up Algorithm

# Consecutive In-range INRs	Repeat INR in
1	4 – 10 days
2	2 weeks
3	3 weeks
4	4 weeks

Remember:

1. Always consider the trend in INRs when making warfarin management decisions.
2. Consider repeating INR the same day or the next day if the observed value is markedly different from the expected value.
3. Unexpected fluctuations of INR in an otherwise stable patient should be investigated.
   Possible causes include:[2,4,12]
   - Change in diet
   - Poor compliance
   - Undisclosed drug use
   - Alcohol consumption
   - Self-medication
   - Laboratory error
4. Change in a patient's clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing[2].

PERIPROCEDURAL MANAGEMENT OF ANTICOAGULATION THERAPY WITH WARFARIN

Patients receiving chronic anticoagulation therapy pose a clinical challenge when therapy needs to be interrupted for surgical or invasive procedures. Maintaining anticoagulation places them at risk for serious bleeding complications, whereas discontinuing anticoagulation puts them at risk of thromboembolic complications[15].

Factors such as the patient's risk of thromboembolic event, the location and extent of surgery and the accessibility of the bleeding site to compression or other physical means of controlling bleeding strongly influence management[15].

Dental Procedures

Patients receiving anticoagulants commonly undergo dental procedures.

For many of these procedures, provided the patient is within therapeutic INR range, alteration of anticoagulation is not necessary. The associated bleeding is usually trivial or can be readily controlled by local measures. 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[2,12,15,16,17,18].

On the other hand, serious embolic complications, including death, were 3 times more likely to occur in patients whose anticoagulant therapy was interrupted than were bleeding complications when anticoagulant therapy was continued[15].

Interruption or modification of warfarin therapy is not indicated for patients undergoing the following dental procedures:[17,18]

1. Fillings
2. Crowns
3. Bridges
4. Root Canal (endodontics)
5. Routine cleaning
6. Deep cleaning*
7. Scaling and polishing
8. Forceps extraction of 1 – 3 teeth

*May require multiple (i.e. staged) procedures in order to decrease bleeding.

All patients undergoing elective dental procedures should have an INR performed within 24 hours before the procedure (preferably on the same day). If the INR is above therapeutic range, consideration should be made to delaying the procedure in consultation with the managing dentist[15,17].

Dermatological Procedures

For local excision of minor lumps and bumps with little bleeding risk, patients can continue on oral anticoagulation if the expected bleeding is trivial or can be readily controlled by local measures[14,15,16,19].

Cataract Surgery

Oral anticoagulation can continue for patients undergoing cataract surgery[15,16]. The risk of clinically important perioperative bleeding is low, as demonstrated in several studies. Though continuing oral anticoagulation throughout the procedure has not been shown to affect long-term visual acuity, the available literature suggests an increase in minor bleeding events, including mild hyphema and subconjunctival hemorrhage[15,16].

Endoscopy

Low-risk procedures can proceed without adjustment of warfarin dosage if the INR is within therapeutic range. Elective procedures should be avoided when the level of anticoagulation is above the therapeutic range[16,20]. Low risk procedures include:[15,20]

- Diagnostic oesophagogastroduodenoscopy (OGD)
- Flexible sigmoidoscopy with or without biopsy
- Diagnostic endoscopic retrograde cholangiopancreatography (ERCP)
- Biliary stent insertion without endoscopic sphincterotomy
- Endosonography (EUS)
- Push enteroscopy

High-risk procedures such as gastric or colonoscopic polypectomy and ERCP with sphincterotomy and others, which do not fall into the above low-risk group, should follow the recommendations for other surgical procedures[15,20].

Other Surgical Procedures

For other surgical procedures, there is little consensus on the appropriate perioperative treatment of patients on long-term warfarin therapy[15,16,21]. No randomised controlled trials have been performed[16].

Generally, after stopping warfarin therapy, it takes approximately 4 days to reduce the INR from a steady value of 2.0 – 3.0 to ≤ 1.5 (at which point surgery can be safely carried out) and approximately 3 – 5 days to reach therapeutic INR after it is restarted (INR 2.0)[15,21]. When necessary, low dose vitamin K (1 – 2.5mg) can be given to reduce the INR more quickly, over 1 – 2 days after stopping warfarin therapy[2,12,15,21]. If a patient received high-dose vitamin K (5 – 10mg) before surgery, it may result in resistance to re-anticoagulation when warfarin is resumed[21].

The following guide is based on literature and current practice[2,12,14,15,21].

<u>Patients with low risk of thromboembolism</u>

1. *Non-valvular AF < 65 years*

   No other risk factors such as DM, hypertension, IHD, CCF, mitral stenosis, prosthetic heart valves or prior thromboembolism.

2. *Venous thromboembolism (VTE) < 65 years, > 3 months*
   No other risk factors such as obesity, active malignancy, serious neurologic disease with extremity paresis, multiple episodes of VTE or known thrombophilic state.
- Stop warfarin 4 days before surgical procedure.
- Use prophylactic doses of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) post-operatively when a surgical procedure increases the risk of thrombosis. Pre-operative use is optional.
- Resume warfarin post-operatively on the day of surgery.

Patients with intermediate, high or very high risk of thromboembolism

(Patients who do not fall into above low risk group)

- Refer the patient to a cardiologist for individualised periprocedural prophylaxis recommendations.
- Stop warfarin 4 days before surgical procedure.
- Periprocedural bridging with low or full dose (dependent on level of risk) of LMWH or UFH both pre- and post-operatively.
- Resume warfarin post-operatively on the day of surgery.

Patients with low risk of bleeding

- Continue warfarin at a lower dose 4 – 5 days before surgical procedure and operate at an INR of 1.3 – 1.5.
- Supplement with a low dose of LMWH or UFH if necessary.
- Resume full dose warfarin post-operatively on the day of surgery.

PERIPROCEDURAL MANAGEMENT OF ASPIRIN AND OTHER ANTIPLATELET THERAPY

Dental Procedures

Patients can continue on antiplatelet therapy for primary care dental procedures as discussed above for warfarin[18,22].

Dermatological Procedures

Patients can continue on antiplatelet therapy for local excision of lumps and bumps[19].

Cataract Surgery

Antiplatelet therapy can continue for patients undergoing cataract surgery[23].

Endoscopy

In the absence of a pre-existing bleeding disorder, endoscopic procedures may be performed on patients taking aspirin and other NSAIDS in standard doses[20]. The data on other drugs affecting platelet function such as ticlodipine and dipyridamole are inadequate to make recommendations[20].

Other Surgical Procedures

Antiplatelet therapy should be stopped 7 – 10 days prior to surgical procedures with a moderate to high risk of bleeding. Aspirin, ticlopidine and clopidogrel irreversibly inhibit platelet function for the 7 – 10 day platelet life span[21].

DRUG, HERB, FOOD & DISEASE INTERACTIONS

The overall quality of the interaction literature remains extremely poor, precluding definitive recommendations regarding the safe co-administration or avoidance of specific drugs and foods in users of warfarin. It is paradoxical that higher quality studies describe minor or no interaction, while clinically important potentiation or inhibition interactions all originate from poor quality reports. However, relatively consistent reporting of interactions between warfarin and certain commonly used drugs and drug families (mainly anti-infective agents, lipid-lowering drugs, NSAIDs including COX-2 selective NSAIDs, selective serotonin reuptake inhibitors, amiodarone, omeprazole, fluorouracil, and cimetidine) is cause for concern[24].

In patients who are starting therapy with one of these medicines, consideration should be given to using an alternative medication with less potential for warfarin interactions (e.g. acetaminophen instead of NSAIDs). More frequent INR testing during the 2 weeks of the onset or discontinuation of treatment with other medications is advisable[24].

A recent comprehensive systematic review by Holbrook et al[24] synthesised the information from 181 reports of interactions involving 120 drugs or foods. No study met the authors' definition of excellent quality. Thirty-three small RCTs were rated fair or good quality, of which 28 involved healthy subjects and 26 concluded a lack of interaction between warfarin and the drug or food studied. Of the reviewed studies, 148 (82%) were rated poor quality and 130 (88%) of these were case reports, of which 125 (96%) were single case reports. Holbrook et al[24] classified the type of interaction (potentiation, inhibition or no interaction), the severity of effect (major, moderate, minor or non-clinical) and the levels of causation (I – highly probable, II – probable, III – possible or IV – highly improbable). It was only the second similar scale systematic review since the first by Wells et al[25] in 1994.

The following table is based in large part on the work of Holbrook et al[24]. The direction of interaction, the severity of effect and the level of causation as determined by their systematic review are indicated. Due to differences in criteria, the drug, herb and food interactions that are compiled from other sources will only be classified according to the direction of interaction (increase INR or bleeding risk, decrease INR or bleeding risk or no effect) with the severity and the level of causation unclassified. Significant revisions have been made to the table, which was first compiled from a review of the literature in 2004 before Holbrook et al's systematic review.

Table 4. Drug, Herb, Food, and Disease Interaction

Medications	Increase INR or Bleeding Risk	Decrease INR or Bleeding Risk	No Effect
Antibiotics, Antifungals & Antivirals[2,24,25]	**Major**		
	Antifungals o Miconazole topical gel (III) (conflicting severity) Macrolides o Azithromycin (II) Penicillins o Amoxycillin (III) o Amoxycillin/clavulanate (II) o Amoxycillin/tranexamic rinse (III) Quinolones o Ofloxacin (III)		Antifungals o Ketoconazole (II) Quinolones o Enoxacin o Gemifloxacin (I) Vancomycin (IV)
	Moderate		
	Antifungals o Miconazole vaginal suppository (I) o Terbinafine (III) (conflicting potentiation & inhibition) Antivirals o Ritonavir (II) (conflicting potentiation & inhibition) o Saquinavir (III) Chloramphenicol (III) Macrolides o Clarithromycin (II) Quinolones o Gatifloxacin (III) o Levofloxacin (II)	Antifungals o Terbinafine (III) (conflicting potentiation & inhibition) Antivirals o Ritonavir (II) (conflicting potentiation & inhibition) o Ribavirin (I) Penicillins o Cloxacillin (IV) Dicloxacillin (II) Teicoplanin (IV)	
	Minor		
	Antifungals o Voriconazole (I)	Penicillins o Nafcillin/dicloxacillin (IV)	
	Non-Clinical		
	Antifungals o Fluconazole (I) o Itraconazole (II) o Miconazole oral gel (I) (conflicting severity) Antitubercular o Isoniazid (I) Cephalosporins o Cefamandole (IV) o Cefazolin (IV) Macrolides o Erythromycin (I) Metronidazole (I) Nalidixic acid (III) Quinolones o Ciprofloxacin (I) o Norfloxacin (III) Sulphonamides o Cotrimoxazole (I) o Sulfisoxazole (IV) Tetracyclines o Tetracycline (II)	Antifungals o Griseofulvin (I) Antitubercular o Rifampin (I) Penicillins o Nafcillin (I)	

Medications	Increase INR or Bleeding Risk	Decrease INR or Bleeding Risk	No Effect
Anti-Inflammatory & Analgesics[2, 24,25]	**Major**		
	NSAIDs o Indomethacin (III) **Moderate** Cox-2 Inhibitors o Celecoxib (II) NSAIDs o Nabumetone (IV) Paracetamol (I) Tramadol (II)		NSAIDs o Diflunisal (I) o Ketorolac (I) o Ibuprofen (II) o Ketoprofen (II) (conflicting potentiation and no effect) o Meloxicam (I) o Naproxen (I)
	Non-Clinical		
	Antiplatelet o Aspirin (II) o Ticlopidine (III) NSAIDs o Phenylbutazone (I) o Piroxicam (I) o Sulindac (III) o Tolmetin (III) Opiod o Dextropropoxyphene (II) o Propoxyphene (III) Topical salicylates (III)	NSAIDs o Etodolac (I)	
	Unclassified		
	NSAIDs o Ketoprofen (conflicting potentiation and no effect)		
Cardiac[2, 24,25]	**Moderate**		
	Amiodarone-induced toxicosis (III)	Bosentan (II) Diuretic o Furosemide (IV)	ACE inhibitor o Moexipril (I) Angiotensin Receptor Blocker o Eprosartan (I) o Losartan (I) Antiarrythmic o Moricizine (I) (conflicting potentiation and no effect) Anticoagulant o Argatroban (I) o Fondaparinux (I) Antiplatelet o Cilostazol (I) o Clopidogrel (I) Beta-Blocker o Atenolol (I) o Metoprolol (I) Calcium Channel Blocker o Diltiazem (conflicting potentiation and no effect) o Felodipine (I) Diuretic o Bumetadine (I) Levosimendan (I)
	Minor		
		Angiotensin Receptor Blocker o Telmisartan (III)	
	Non-Clinical		
	Antiarrythmic o Amiodarone (I) o Disopyramide (III) o Propafenone (I) o Quinidine (II) Antiplatelet o Aspirin (II) Beta-Blocker o Propranolol (I) Calcium Channel Blocker o Diltiazem (I) (conflicting potentiation and no effect) Diuretic o Metolazone (III) Heparin (IV)	Angiotensin Receptor Blocker o Candesartan cilexetil (II)	
	Unclassified		
	Antiarrythmic o Moricizine (I) (conflicting potentiation and no effect)		

Medications	Increase INR or Bleeding Risk	Decrease INR or Bleeding Risk	No Effect
CNS & Psychiatric[2,24,25]	**Major**		
	Fluoxetine/diazepam (IV)	Propofol (IV) Trazodone (I)	SSRI o Fluoxetine (I)
	Moderate		Donepizil hydrochloride (I)
	Felbamate (III) Quetiapine (IV) Ropinirole (II) SSRI o Fluvoxamine (II)		Levetiracetam (I) Metrinfonate (I) Modafinil (I) Nefazodone (I)
	Minor		
	Entacapone (I) SSRI o Citalopram (I) o Sertraline (I)		
	Non-Clinical		
	Alcohol (I) (concomitant liver disease) Chloral hydrate (II) Disulfiram (II) Phenytoin (II) (biphasic with later inhibition)	Barbiturates (I) Benzodiazepines o Chlordiazepoxide (I) Carbamazepine (I) Phenytoin (II) (biphasic with earlier potentiation)	
Endocrine[2,24,25]	**Moderate**		Colesevelam hydrochloride (II)
	Acarbose (III) Fibrates o Bezafibrate (IV) o Fenofibrate (I) o Gemfibrozil (III) HMG CoA Reductase Inhibitors o Fluvastatin (II) Orlistat (III) Troglitazone (II)		HMG CoA Reductase Inhibitors o Atorvastatin (II) Miglitol (I) Nateglinide (I)
	Minor		
	HMG CoA Reductase Inhibitors o Simvastatin (II)		
	Non-Clinical		
	Anabolic steroids (I) Fibrates o Clofibrate (I) HMG CoA Reductase Inhibitors o Lovastatin (III) Sulfinpyrazone (I) (biphasic with later inhibition)	Sulfinpyrazone (I) (biphasic with earlier potentiation) Cholestyramine (I)	
Gastrointestinal[2,24,25]	**Moderate**		Antacids (I)
	Tolterodine (II)		H-2 Blockers o Famotidine (I) o Nizatidine (I) o Ranitidine (I)
	Non-Clinical		Proton Pump Inhibitor o Pantoprazole (I)
	H-2 Blockers o Cimetidine (I) Proton Pump Inhibitor Omeprazole (I)	Sucralfate (I or II)	Psyllium (I)

Medications	Increase INR or Bleeding Risk	Decrease INR or Bleeding Risk	No Effect
Miscellaneous[2, 24,25]	**Major**		Anastrozole (I) Cilomilast (II) Influenza vaccine (II) (conflicting potentiation, inhibition and no effect) Montelukast (I) Sevelamer hydrochloride (I)
	Danazol (III) Etoposide/carboplatin (IV) Fluorouracil (II) Levamisole (IV) Methylprednisolone (IV) Trastuzumab (III)	Mesalamine (I) Sulfasalazine (III)	
	Moderate		
	CMF (cyclophosphamide/methrotrexate /fluorouracil) (III) Gemcitabine (II) Interferon (II) Levamisole/fluorouracil (II) Levonorgestrel (IV) Paclitaxel (II)	Azathioprine (II) Chelation therapy (II) Mercaptopurine (I)	
	Minor		
	Zileuton (I)	Influenza vaccine (II) (conflicting potentiation, inhibition and no effect) Raloxifene hydrochloride (II)	
	Non-Clinical		
	Ifosphamide (III) Leflunomide (III) Tamoxifen (II)	Cyclosporin (III) High vitamin K content enteral feeds (I)	
	Unclassified		
	Influenza vaccine (conflicting potentiation, inhibition and no effect)		
Herbs & Supplements[24,26-30]	**Increase INR orBleeding Risk**	**Decrease INR orBleeding Risk**	**No Effect**
	Major		Coenzyme Q10/gingko biloba (II) Vitamin E (I) (conflicting potentiation and no effect)
	Danshen (II) Danshen/methyl salicylate (III)	Ginseng (II) Vitamin K	
	Moderate		
	Boldo-fenugreek (I) Dong quai (II) Fish oil (I) Licium barbarum L (II) PC-SPES (II) Quilinggao (I)	Coenzyme Q10 (Ubidicarenone) (III) Green tea (IV)	
	Minor		
	Curbicin (III)	Multivitamin supplement containing vitamin K (II)	
	Unclassified		
	Devil's claw Gingko biloba Papain Vitamin E (conflicting potentiation and no effect)	St John's Wort	
	Potential interaction		
	Feverfew Garlic Ginger		

Food[24,31,32,33,34]	Increase INR or Bleeding Risk	Decrease INR or Bleeding Risk	No Effect
	Moderate		
	Beverages o Grapefruit juice (II) Fruits o Mango (I)	Beverages o Green tea (IV) Sushi containing seaweed (III)	Alcohol (I) Olestra (I) Tobacco (IV)
	Minor		
		Beverages Soy milk (II)	
	Non-Clinical		
	Beverages o Cranberry juice (III) o Alcohol (I)(concomitant liver disease)	High vitamin K content foods /enteral feeds (I) Fruits o Avocado (I) (large amounts)	
	Unclassified		
		Dark leafy greens o Choy sum o Kale/ Gai lan o Lettuce o Okra/ Lady's fingers o Pak choy o Mustard greens/ Gai choy o Parsley o Scallions o Spinach o Turnip greens o Watercress Non-leafy vegetables o Asparagus o Beans - Green beans - Green peas - Soy beans o Broccoli o Brussels sprouts o Cabbage o Cauliflower o Cucumber with peel o EndiveFruits o Avocadoes o Blackberries o Blueberries o Papaya o Prunes o Kiwi fruit Nuts o Cashews o Pine nuts Oils o Canola oil o Cottonseed oil o Olive oil o Rapeseed oil o Soybean oil	

Food[24,31,32,33,34]	Increase INR or Bleeding Risk	Decrease INR or Bleeding Risk	No Effect
		Prepared foods o Coleslaw o Margarine o Mayonnaise o Salad dressings o Tofu	
DISEASE STATES[2,35]	**Increase INR or Bleeding Risk**	**Decrease INR or Bleeding Risk**	**No Effect**
	Congestive cardiac failure Febrile illnesses Hepatic dysfunction Hyperthyroidism Hypothyroidism		

CONCLUSIONS

A good body of evidence exists as to the efficacy of warfarin in reducing stroke risk. Guidelines are clear on the therapeutic INR for most conditions.

Studies suggest monitoring at an interval of no longer than 4 weeks. There is little consensus in the literature on optimal dose management strategies.

There is evidence that interruption of anticoagulation is not necessary for simple dental and dermatological procedures, cataract surgery and diagnostic endoscopy. For other surgical procedures, there is little evidence on the most appropriate treatment. There is a lack of well-designed prospective studies that evaluate the efficacy and safety of different perioperative management strategies.

The number of drugs, herbs, supplements and food substances reported to interact with warfarin continues to expand. Many reports are of poor quality and more systematic study of warfarin drug interactions in patients is needed.

TIPS FOR THE BUSY FAMILY PHYSICIAN

1. The target INR for most indications is 2 – 3, including bioprosthetic heart valves, and 2.5 – 3.5 for mechanical prosthetic valves.
2. Monitor INR no longer than 4-weekly. Recheck more frequently with out-of-range INR or with dose adjustment.
3. Consider the trend in INR results when making dose management decisions. Enquire specifically about recent drugs, herbs, supplements and illnesses.
4. Many substances can potentiate or inhibit warfarin's anticoagulant effect. Caution patients not to self-medicate, including supplements and herbs. Advise a diet stable in vitamin K, avoiding large fluctuations.
5. Azoles, macrolides, quinolones, NSAIDs including COX-2 inhibitors, amiodarone, SSRIs, lipid-lowering agents, omeprazole, and fluorouracil consistently potentiate warfarin's anticoagulant effect. Co-administration should be avoided or closely monitored.
6. Most patients can undergo simple dental and dermatological procedures, cataract surgery and diagnostic endoscopy without alteration of anticoagulation or aspirin therapy.

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