



HEALTH NOTES



Pharmacist Involvement
in Anticoagulant Therapy:
How Patients Benefit

CONSUMER EDUCATION AND COMMUNICATION COMMITTEE



Dedicated to building bridges of communication with those Californians whose health depends on proper drug therapy, compliance with a treatment regimen and a healthier lifestyle.

Members

M. Standifer Shreve, *Chair*

Robert Elsner

Hope Tamraz, *Staff*

CALIFORNIA STATE BOARD OF PHARMACY

Members

Tom Nelson, *President*

Sandra Bauer, *Vice President*

Caleb Zia, *Treasurer*

Robert Elsner

Darlene Fujimoto

John D. Jones

Steve Litsey

Rich Mazzoni

M. Standifer Shreve

Holly Strom

Patricia Harris, *Executive Officer*

Introduction

HEALTH NOTES is published by the California State Board of Pharmacy's Consumer Education and Communication Committee to assist California pharmacists and other health care providers to become better informed on subjects of importance to their patients.

This issue of HEALTH NOTES focuses on the pharmacist's role in managing anticoagulation medications that are used to suppress or delay blood clotting and to treat or prevent a number of health conditions including deep vein thrombosis, pulmonary embolism and strokes.

Every year, more than 700,000 Americans suffer strokes. Someone in the United States has a stroke every sixty seconds and someone dies from a stroke every three and a half minutes. It is estimated that two-thirds of strokes, which occur in the United States, are preventable.¹ Strokes are one of the health conditions that can be prevented by treatment with anticoagulant, or "blood thinning" drugs.

Pharmacists and other health care providers can provide a valuable resource to patients who are receiving anticoagulant therapy by:

- educating patients about their medications and the importance of adhering to their anticoagulant therapy;
- assessing and monitoring the treatment of patients receiving anticoagulant therapy;
- increasing medication compliance to a prescribed drug regimen; and,
- improving patient satisfaction with their treatment and helping to enhance their quality of life.

We anticipate that you will find this issue of HEALTH NOTES to be an important reference source in helping you to communicate information about anticoagulant therapy to your patients.



A handwritten signature in blue ink that reads "M. Standifer Shreve".

M. Standifer Shreve
Editor, Health Notes
*Chair, Consumer Education and
Communication Committee*

¹ References are available upon written request to: California State Board of Pharmacy, Attn: Health Notes Anticoagulation References, 400 R Street, Suite 4070, Sacramento, CA, 95814.

Learning Objectives:

After reading this monograph you should be able to:

- Describe the general principles of blood clotting.
- List three risk factors for developing venous thromboembolism.
- Recommend initial loading and maintenance doses for intravenous heparin for the treatment of deep vein thrombosis or pulmonary embolism.
- List two major differences in the pharmacology of low molecular weight heparin versus standard unfractionated heparin.
- Describe the possible indications for warfarin and heparin and explain when one agent is preferred over the other.
- List the important patient counseling points for patients on warfarin and heparin.
- Identify three critical factors that strongly influence the INR response to warfarin treatment.
- Identify four of the most common classes of medications that interact with oral anticoagulants.
- List the types of providers practicing in anticoagulation outpatient clinics.

Glossary

This glossary is provided to assist pharmacists in explaining clotting disorders and anticoagulant drug therapy to their patients.

Activated Partial Thromboplastin Time (aPPT):

A laboratory blood test used to determine the time (in seconds) for clotting to occur. aPPT is widely used to monitor heparin therapy.

Anticoagulant:

A drug or substance that impairs blood coagulation.

Coagulation:

The process of blood clotting.

Deep Vein Thrombosis (DVT):

Formation of blood clots in the deep veins of the legs.

Embolism:

Obstruction of a blood vessel by a blood clot or a foreign substance (e.g., air, fat).

Embolus:

A clot or any other undissolved mass traveling through the blood stream.

INR (International Normalized Ratio):

A standardized interpretation of the prothrombin time (PT) to correct for interlaboratory variability in PT test results.

Prothrombin Time (PT or "protime"):

A laboratory blood test used to determine the time (in seconds) for clotting to occur, and to judge the effect of warfarin, but not heparin.

Pulmonary Embolism (PE):

A condition in which an embolus lodges in a blood vessel in the lungs. May be a complication of deep vein thrombosis.

Thromboembolism:

The blocking of a blood vessel by a blood clot that has become detached from its site of formation.

Thrombosis:

Development of a thrombus or clot within a blood vessel.

Thrombus:

A blood clot that obstructs a blood vessel or a cavity of the heart.

HEALTH NOTES

VOLUME 1, NUMBER 3



Pharmacist Involvement in Anticoagulant Therapy: *How Patients Benefit*

TABLE OF CONTENTS

3	Introduction
4	Learning Objectives
4	Glossary
Part One:	<i>What are Anticoagulant Drugs Used For, and Why?</i>
7	General Principles of Blood Clotting
9	Drug Approaches to the Treatment of Clotting Disorders & Disease States
13	The Importance of Careful Patient Monitoring
Part Two:	<i>The Role of the Pharmacist in Anticoagulant Therapy</i>
17	Patient Education and Counseling
22	Improving Safety with Warfarin Therapy
26	Management of Special Situations
29	Risk Management of Warfarin Therapy
Part Three:	<i>The Importance of a Collaborative Approach: The Anticoagulation Team</i>
33	A Physicians Perspective
34	Roles of Other Health Care Professionals
Part Four:	<i>Establishing Anticoagulation Services</i>
37	Pharmacist Anticoagulation Management Services: Improving Outcomes and Controlling Costs
Part Five:	<i>Establishing Anticoagulation Services</i>
41	Creating a Comprehensive Anticoagulant Care System
47	Specialized Services in a Long Term Care Setting
Appendix	
49	Continuing Education Questions & Exam

Part One:

What are Anticoagulant Drugs Used For, and Why?

General Principles of Blood Clotting



Richard H. White, M.D.
Professor of Medicine
Chief, Division of General Medicine
Medical Director, Anticoagulation Service
UC Davis School of Medicine



The human circulatory system, composed of blood vessels and capillaries, allows nutrients and oxygen to be delivered to the tissues. When a blood vessel is injured, a complex “coagulation system” composed of proenzymes and enzymes is activated, preventing the loss of blood, plasma and life. To prevent the blood from clotting too readily, an equally complex system of protein enzymes, the “fibrinolytic system,” inhibits blood clotting. This wondrous system works perfectly in most humans, with the blood flowing freely and clotting only when there is an injury.

Injury to the wall of a blood vessel causes the release of factors that activate both platelets and plasma proteins, which in turn can lead to the formation of a blood clot, called a “thrombus.” At the same time, counterbalancing mechanisms are activated that inhibit platelet activation and blood coagulation.

A number of factors and disease states can tip the balance of this delicate, finely tuned system to favor either bleeding or spontaneous clotting. Most of the diseases associated with bleeding are inherited and are deficiencies of one of the components in the coagulation system. The best known of these bleeding diseases is Hemophilia A, which is a defect in coagulation factor VIII. Acquired disorders include diseases associated with the destruction of platelets or consumption of coagulation proteins. Acquired disorders associated with clotting are much more common than acquired disorders that lead to bleeding.

Examples of Clotting Disorders

In most cases, a stroke or myocardial infarction is caused by a small thrombus forming in a coronary or cerebral blood vessel. The pathogenesis of these two "thrombotic" diseases is intimately linked with atherosclerosis. Thrombosis generally occurs in an artery narrowed by atherosclerosis, with an acute rupture in the plaque leading to platelet activation, followed by clot formation.

When the left atrium of the heart fibrillates, it fails to contract properly, leading to stasis of blood in the left atrial appendage. This stasis is associated with an increased risk of formation of a blood clot that can dislodge and embolize to the body or brain. This increased risk is the reason that patients with atrial fibrillation (4% of the population over the age of 65 years) have such a high rate of stroke (5-6 strokes per 100 patients per year).

Acute deep venous thrombosis (DVT) and the related condition, pulmonary embolism (PE), are also common. The pathogenesis of clotting in the venous system is quite different from clotting in the arterial circulation. Venous thrombosis is practically unheard of in children, and the risk increases exponentially with age. The reason appears to be that low-grade activation of blood coagulation increases in older individuals, together with relative inactivation of the fibrinolytic pathways. Given the imbalance that occurs with advancing age, anything that promotes clotting, such as venous stasis (surgery, immobilization, bed rest, etc.) or trauma to the veins (fracture of the hip, orthopedic surgery on the hip or knee), can lead to symptomatic venous thrombosis. Risk factors associated with developing venous thrombosis are shown in Table 1.

TABLE 1. RISK FACTORS FOR DEVELOPING VENOUS THROMBOEMBOLISM

- 1) **Age** (risk rises exponentially)
- 2) **Venous Stasis**
 - Immobilization
 - Congestive heart failure
 - Stroke with paralysis
 - Morbid obesity
- 3) **Cancer**
 - Adenocarcinomas
 - Acute myelogenous leukemia
- 4) **Prior venous thromboembolism**
- 5) **Local trauma to veins**
 - Trauma to the leg (e.g., fracture)
 - Pelvic fracture
 - Total hip or knee arthroplasty
- 6) **Medical conditions**
 - Myeloproliferative diseases
 - Paroxysmal nocturnal hemoglobinuria
 - Crohn's disease and Behcets Syndrome
 - Membranous Nephritis
- 7) **Procoagulant disorders - Thrombophilic disorders**
 - Antithrombin III deficiency
 - Protein C deficiency
 - Protein S deficiency
 - Factor V Leiden defect
 - Lupus anticoagulant
 - Hyperhomocysteinemia
- 8) **Foreign objects** (central lines, A-V shunts, etc.)

The signs and symptoms of deep venous thrombosis are nonspecific. There are multiple causes of leg pain and swelling, so a diagnosis of venous thrombosis cannot be made on clinical grounds alone. There must be objective confirmation of the presence of a clot. The best

finding associated with deep venous thrombosis is unilateral calf swelling combined with unilateral thigh swelling. The presence of tenderness along the path of the deep veins in the thigh may also be a clue. However, redness, calf pain, varicosities, and Holman's sign (calf pain with active dorsiflexion) are nonspecific.

Pulmonary embolism can present in many different ways, from acute sudden death to subacute onset of dyspnea. A classic case might present with abrupt onset of shortness of breath, tachypnea, and tachycardia, with no sign of pneumonia, asthma, or myocardial infarction. However, pulmonary embolism may present as pleuritic chest pain or hemoptysis, or it may mimic pneumonia, an anxiety attack, or even costochondritis. Some elderly patients present with fever and pleural effusions. It requires a skilled clinician to appreciate the many faces of pulmonary embolism and proceed with an appropriate work-up in unusual cases.

The diagnoses of deep venous thrombosis and pulmonary embolism require objective confirmation of thrombosis. One new test that is very helpful when determining whether to exclude the possibility of either deep venous thrombosis or pulmonary embolism is an absence of elevated levels of D-dimer, a breakdown product of cross-linked fibrin. Of patients with objectively confirmed deep venous thrombosis or pulmonary embolism, 98% have a D-dimer level greater than 500 mcg/ml. A D-dimer level below 500 mcg/ml in a patient judged to be at moderate or low probability of having deep venous thrombosis essentially rules out the presence of deep venous thrombosis or pulmonary embolism. Kits are available that can determine the presence or absence of an elevated D-dimer level in less than 30 minutes (e.g., SimpliRED®). Unfortunately, many other conditions can lead to activation of clotting and presence of D-dimer (age, pregnancy, infection, surgery, trauma, etc.), so a positive test is not particularly helpful.

The best way to "visualize" a clot is to use real-time ultrasound testing, also called duplex-ultrasound, color-flow ultrasound and compression ultrasound. A technician scans the deep venous system, pressing the veins looking for an area that fails to compress (because of the presence of a clot). Venography is the "gold-standard" test for detecting clots, but because it is invasive and cannot be performed on 15% of patients with suspected deep venous thrombosis, most centers do not routinely do venography anymore.

In some individuals, a blood clot in the pulmonary arteries can be diagnosed using a lung scan combined with a "high index of suspicion," since a particular pattern found on a lung scan is associated with a "high probability" of having pulmonary embolism. However, this pattern occurs in only about 20% of all cases of pulmonary embolism. Other tests used to diagnose pulmonary emboli include pulmonary arteriography, spiral CT scanning, MRI angiography, and "clinical suspicion," combined with a lower extremity real-time ultrasound test showing the presence of venous thrombosis. As in patients with deep venous thrombosis, a pulmonary embolus is extremely unlikely in a patient with a D-dimer level below 500 mcg/ml.

The long-term complications associated with venous thrombosis include recurrent venous thrombosis or pulmonary embolism, incompetence of the valves in the leg veins leading to venous stasis and chronic venous insufficiency, and bleeding during the course of anticoagulant therapy. Rarely, patients may get such extensive clotting in the veins of the leg that venous gangrene develops, resulting in the loss of the leg. A patient with a pulmonary embolism may die suddenly, lose part of a lung with severe infarction, develop pulmonary hypertension or, rarely, develop chronic shortness of breath. Thankfully, most pulmonary emboli resolve without significant sequelae.



Drug Approaches to the Treatment of Clotting Disorders & Disease States



Jeffrey H. King, Pharm.D.
Assistant Director of Pharmacy
Coordinator, Clinical Pharmacy Services
Director, Pharmacy Anticoagulation Service
UC Davis Medical Center, Sacramento, California

Anticoagulants

Heparin and warfarin are used for the management of thromboembolic disorders and the prevention of subsequent recurrence. They play a major role in the prevention of blood clot formation in high risk patients following surgery and in patients with prosthetic heart valves, underlying atrial fibrillation, unstable angina or endogenous clotting disorders.

The initial treatment of thromboembolic diseases such as deep vein thrombosis and pulmonary embolism is typically with intravenous unfractionated heparin, although an occasional patient may receive it by subcutaneous administration. Warfarin therapy should be started simultaneously and overlap for about five days before heparin is discontinued. Patients are then maintained on oral warfarin for six months if there is no prior history of deep vein thrombosis or pulmonary embolism. Oral warfarin should be continued indefinitely if it is a recurrent condition. The recently approved low molecular weight heparins, or heparin “fractions,” are viable alternatives to unfractionated heparin. The use of low molecular weight heparins in a select group of patients with deep vein thrombosis or pulmonary embolism may be an option for treating patients at home. Low molecular weight heparins require less laboratory monitoring than unfractionated heparin, thereby offering the option of a safe and convenient home treatment alternative.

Heparin and warfarin are prime examples of drugs that have narrow “therapeutic windows” and, as a result, a thorough understanding of the pharmacology and dynamics of these drugs is required in order to safely manage patients on this type of therapy. Therapeutic use of heparin or warfarin requires individualization of the dosage based on clinical indication, the patient’s weight, and laboratory response. Subtherapeutic dosing can be associated with dangerous reembozation or with therapeutic failure, while excess dosing can cause potentially fatal bleeding.

Heparin

Standard heparin and low molecular weight heparins are glycosaminoglycans consisting of alternating chains of uronic acids and glucosamine. Unfractionated heparin consists of a mixture of different length polysaccharide chains. The molecular weights of these chains range from 4,000 to 30,000 daltons, with an average weight of 12,000 to 15,000 daltons. The low molecular weight heparins are derived from unfractionated heparin and consist primarily of shorter polysaccharide chains weighing between 4,000 and 6,500 daltons. The smaller and more uniform size of the low molecular weight heparin fragments provides improved pharmacokinetic and pharmacologic properties.

Pharmacology

Heparin, a rapidly acting anticoagulant, is used in clinical situations where immediate anticoagulation is needed, such as deep vein thrombosis or pulmonary embolism. Heparin requires Antithrombin III (ATIII) to enhance its ability to suppress the clotting process. Unfractionated heparin accelerates the inherent ability of ATIII to inactivate the coagulation enzymes: thrombin (IIa), factor Xa, and factor IXa. The primary target of unfractionated heparin is thrombin (IIa). It acts as a template to which both ATIII and thrombin are bound to form a ternary complex, inactivating thrombin. The shorter low molecular weight heparins are physically too small to attach to both ATIII and thrombin. Although they have some inherent effect on thrombin (IIa), their primary target is the inactivation of factor Xa. The decreased antithrombin activity of the low molecular weight heparins significantly decreases the prolongation of the activated partial thromboplastin time (aPTT). Low molecular weight heparins do have an effect on thrombin, but it is less than that of unfractionated heparin. The ratio of anti-Xa activity to anti-IIa activity is often used to compare the different heparin compounds. Unfractionated heparin has an anti-Xa to anti-IIa ratio of 1:1; the low molecular weight heparins have increased anti-Xa activity where anti-Xa to anti-IIa activity ranges from 2:1 to 4:1 (Table 1).

Table 1. Characteristics of Different Heparin Products

	Standard Heparin <i>UFH</i>	Dalteparin <i>(Fragmin®)</i>	Enoxaparin <i>(Lovenox®)</i>	Nadroparin <i>(Fraxiparin®)</i>
Mean Molecular Weight	12,000 - 15,000	5,000	3,500 - 5,500	4,500
Anti-Xa to Anti-IIa Ratio	1:1	2.0 - 4.0:1	2.7 - 3.9:1	1.6 - 3.5:1
Bioavailability % (sc)	22 - 40	87	91	98
Elimination half-life (hrs)	0.5 - 4.0	2.0 - 5.0	2.2 - 6.0	2.2 - 3.5

In experimental models, the low molecular weight heparins produce less microvascular bleeding for an equivalent antithrombotic effect. However, when compared with unfractionated heparin in clinical trials, this potential benefit of less bleeding with low molecular weight heparins has not been consistently demonstrated.

Because heparin is not orally absorbed, it must be administered either subcutaneously or intravenously. The intramuscular route must be avoided because of hematoma formation.

The pharmacokinetics of unfractionated and low molecular weight heparin differ significantly. The larger mixed-length polysaccharides of unfractionated heparin significantly enhance its uptake, or binding, to serum proteins and cells. Unfractionated heparin has a high binding affinity for endothelial cells, macrophages and serum proteins such as von Willebrand factor, fibronectin and platelet factor 4. The binding of unfractionated heparin to these proteins and cells is responsible for its reduced bioavailability at low concentrations and the variability of its anticoagulant response to fixed doses when treating patients. The biologic half-life of unfractionated heparin ranges from 30 minutes to 4 hours and is dose dependent. Lower doses are rapidly taken up by plasma cellular and protein binding sites, decreasing free or available heparin. As the dose of unfractionated heparin is increased, the binding sites become saturated and the half-life becomes longer. One advantage of low molecular weight heparins is their decreased uptake by plasma components, resulting in a longer, nondose-dependent, pharmacologic half-life and as a result, a more uniform response. This allows once or twice daily dosing without the need for laboratory monitoring.

The primary route of elimination of low molecular weight heparin is renal and, therefore, the half-life is prolonged in patients with renal failure. However, information is lacking regarding the types of dosage adjustments which should be made in patients with renal insufficiency and morbid obesity.

Oral Anticoagulation: Warfarin

Warfarin is the most frequently prescribed oral anticoagulant in North America. Warfarin inhibits the formation of the vitamin K-dependent clotting factors II, VII, IX and X. It has excellent and rapid bioavailability and is usually administered orally; an injectable product is also available, however. After initiation of therapy, an appreciable change in INR is usually not seen for 24 to 36 hours. It takes 4 to 5 days to see the antithrombotic effects of warfarin because of the long half-lives of factors II, IX and X (20 to 60 hours), and the full steady state effect of warfarin is usually not achieved until after 10 to 14 days of continuous warfarin dosing.

Because of its narrow therapeutic range, it is extremely important to monitor patients on warfarin closely. Prior to starting a patient on warfarin, the following information should be obtained about (or from) the patient:

- A baseline PT/INR, platelet, liver function and albumin level should be obtained.
- The patient's current and recent medications should be reviewed to assess potential drug interactions.

- The patient's past medical history should be reviewed for disease states that may potentiate warfarin activity, such as congestive heart disease, hypothyroidism, cirrhosis and malignancy.
- Patient education should start soon after the initiation of warfarin therapy and should be a continuous, planned and individualized process during long-term warfarin treatment.

Initial treatment with warfarin can be started with a dosage of 4 to 5 mg per day. Some clinicians like to give a loading dose of 10 mg initially, but there is no evidence that higher initial doses achieve a more rapid anticoagulation goal. The use of large loading doses (20 to 40 mg) is no longer recommended, since this can lead to dangerous over-anticoagulation. Low starting doses are recommended for elderly and/or debilitated patients and for patients with the potential for an increased response to warfarin. Most patients are satisfactorily maintained on warfarin doses of 2 to 10 mg per day. The average dose of warfarin to provide an INR of 2.5 is 4.3 mg per day. Laboratory testing (INR) is often done daily for the first 3 to 5 days, followed by twice weekly, weekly, then monthly in stable patients. Most patients should have repeat INRs drawn within 7 to 14 days after a warfarin dosage change. Adjustments in therapy due to critical values (INR>6) may require sooner follow-up. The intensity of laboratory monitoring depends on the clinical situation, the practitioner's judgment and the patient's reliability.

Table 2. Therapeutic Goals for Warfarin Therapy

INDICATION	INR RANGE	TARGET
Prophylaxis of Venous Thrombosis	2.0 - 3.0	
Treatment of Venous Thrombosis	2.0 - 3.0	2.5
Treatment of Pulmonary Embolism	2.0 - 3.0	2.5
Prevention of Systemic Embolism	2.0 - 2.5	2.5
Tissue Heart Valves *	2.0 - 3.0	2.5
Atrial Fibrillation	2.0 - 3.0	2.5
Mechanical Prosthetic Valves *	2.5 - 3.5	2.5
St. Jude aortic valve *	2.0- 3.0	2.5
Post myocardial Infarction	2.5 - 3.5	

* Recommendations for INR range and targets for patients with mechanical and tissue heart valves depends on valve placement and clinical history. Readers should refer to the "Fifth ACCP Conference on Antithrombotic Therapy," Chest, 114 (5) November 1998 Supplement.

Contraindications to warfarin include pregnancy, alcoholism/drug abuse, unsupervised patients with dementia/psychosis and patients where the risk of serious bleeding outweighs any potential benefits of therapy.

Treatment of Deep Vein Thrombosis and Pulmonary Embolism

For the treatment of deep vein thrombosis or pulmonary embolism, standard heparin is usually administered as an intravenous bolus followed by a continuous intravenous infusion. Most guidelines and nomograms use weight-based dosing with adjustment of the continuous infusion rate to provide a therapeutic range of 1.5 to 3 times the "control aPTT" or approximately 60 to 90 seconds. The loading, or bolus dose at the initiation of heparin therapy usually ranges from 50 to 80 units/kg. This is immediately followed by a continuous infusion of heparin at a concentration of 100 units/ml (25,000 units in 250 ml D5W) at an initial rate of 18 to 21 units/kg/hr. Infusions should be delivered by an accurate infusion device and NOT by gravity. The aPTT should be obtained no sooner than 6 hours after a bolus dose is given, or 4 hours after any change in infusion rate. The infusion rate should be adjusted to provide an aPTT in the therapeutic range (Table 3). Errors in interpreting the aPTT may occur if the blood sample is drawn too soon after the start of an infusion or a dosing change. An aPTT result that is unusually low or high should always be investigated. Close physical measurement of the infused volume should correlate with the infusion rate over a certain amount of time. Accidental changes in infusion rate do occur, and can be caused by hospital staff or patients. Also, unexplainable aPTT results may be due to an incorrectly made heparin infusion solution.

Table 3. Nomogram For Continuous Heparin Dosage Adjustment *

aPTT 40 or less (normal risk)	100 u/kg IVP, Increase drip by 200 u/hr
aPTT 40 or less (high risk)	50 u/kg IVP, Increase drip by 200 u/hr
aPTT 41-60	Increase drip by 100 u/hr
aPTT 61-90	NO CHANGE (Therapeutic level)
aPTT 91-110	Decrease drip by 100 u/hr
aPTT 110-150	DC Drip x 1 hr, Decrease drip by 200 u/hr
aPTT>150	DC Drip, Repeat aPTT 1 hr post stop

* Dose should be calculated using ideal body weight.

Heparin therapy is usually continued for 5 to 7 days. As mentioned previously, concomitant warfarin therapy should be started on the first or second day of heparin therapy. Heparin should not be discontinued until warfarin provides a therapeutic INR of 2 to 3. The absolute minimum length of heparin therapy should be 4 days, but since shorter courses of heparin therapy have been associated with a higher thrombotic recurrence rate, most practitioners treat with heparin for 5 to 7 days. A minimum of 7 days of heparin is probably required for severe proximal ileo-femoral occlusions or severe pulmonary embolism. Warfarin therapy should be continued for a minimum of 3 months for deep venous thrombosis.

Home Treatment of Deep Vein Thrombosis with Low Molecular Weight Heparin

A substantial number of well-designed clinical trials have compared low molecular weight heparins administered once or twice daily subcutaneously, at home, with standard continuous heparin infusions administered in the hospital, for the treatment of deep vein thrombosis. The results have demonstrated equal efficacy and similar rates of adverse events. The predictable dose response seen with low molecular weight heparins enables weight-based dosing without the need for laboratory monitoring. This eliminates multiple laboratory blood draws and the need for interpretation of the coagulation tests. However, the patients in these studies were carefully selected; not all patients with deep vein thrombosis are candidates for home treatment. Patients must be carefully selected to ensure safe and effective therapy. If appropriate precautions are taken, the use of low molecular weight heparins can enable home treatment and result in a significant decrease in the rate of hospitalization. However, appropriate guidelines and structure must be in place to ensure careful patient selection and continuous care in the ambulatory setting before home treatment is considered. This must include patient assessment, patient education, home nursing, and continuous evaluation of the patient's care while at home (Table 4).

Table 4. Patient Criteria for Ambulatory Treatment of Deep Vein Thrombosis

Clinical

Diagnosis of DVT
 Venous thrombosis requiring heparin
 Age > 16 years
 Stable - otherwise able to discharge
 No recent history of bleeding or peptic ulcer disease
 No major surgery (within 2 weeks)
 No nonsteroidal anti-inflammatory drug*
 No history of severe renal dysfunction**
 No morbid obesity
 No history of alcohol or drug abuse
 *ASA no greater than 325 mg daily allowable
 **Calculated creatinine clearance (Cr Cl) <30 ml/minute

Nonclinical

Compliant patient accepting therapy
 Ability to educate
 Telephone at home
 Communication ability
 Proximity to hospital
 Support at home to enable bed rest
 Signed treatment consent

To date, the majority of clinical experience and published data is in the treatment of deep vein thrombosis with either enoxaparin (Lovenox®, Rhone-Poulenc) or dalteparin (Fragmin®, Pharmacia - Upjohn). Enoxaparin is the only FDA-approved product for home treatment of deep vein thrombosis (Table 5).

Table 5. Treatment Protocol

Anticoagulation Therapy: DVT

Low molecular weight heparin - enoxaparin - 1 mg/kg* subcutaneously every 12 hours.
 Warfarin oral therapy (adjusted for INR 2.0-3.0)
 *Studies in obese patients have not been performed.

Laboratory:

Day 1: CBC with platelets, PT/aPTT, INR, Chem 20
 Day 1 through 7: Daily INR or until stable on warfarin
 Day 3 and 7: repeat CBC with platelets, urinalysis, stool guaiac

Conclusion

Heparin and warfarin are currently the preferred drugs for the management of thromboembolic disorders and the prevention of subsequent recurrence. They play a major role in the prevention of blood clot formation in high risk patients following surgery and in patients with prosthetic heart valves, underlying atrial fibrillation, unstable angina or endogenous clotting disorders. The use of these agents requires careful individualization of dosage based on the patient's clinical situation and appropriate laboratory monitoring.

Careful monitoring and patient education are instrumental in assuring appropriate results. Pharmacists who have a thorough understanding of these agents can play a vital role in assuring that these agents are used safely and effectively in their patients.

References available from the author upon request.



The Importance *of* Careful Monitoring



William Dager, Pharm.D., FCSHP
Pharmacist Specialist,
Pharmacokinetics/Anticoagulation, UC Davis
Medical Center, Sacramento
Associate Clinical Professor of Pharmacy,
UCSF School of Pharmacy
Assistant Clinical Professor of Medicine,
UC Davis School of Medicine



Robert Gosselin, CLT
Senior Specialist, Hematology/Hemostasis
UC Davis Medical Center
Sacramento, CA

Introduction

Finding the correct measure for anticoagulant response has been a challenge since the discovery of anticoagulants early this century. Approaches have ranged from traditional methods performed by clinical laboratories to the use of newer technology in portable devices used outside the laboratory. The basic premise of all routine coagulation testing is the time required to form a clot when test plasma or whole blood is exposed to specific activators. Variations in clot detection methods (e.g., photo-optical light scattering, mechanical resistance) and activating reagents can lead to significant differences between methods and the resultant clotting times. Correct collection and handling of blood samples is extremely important to limit analytical errors, which will bias coagulation results. Examples of problems that commonly occur and can bias results include difficulty in drawing the blood sample, underfilled coagulation tubes, diluted samples, delays in anticoagulating blood and/or delays in testing.

PATIENT CARE TIPS

- The INR system is a method designed to normalize the variability in prothrombin time ratios between different thromboplastin reagents.
- When initiating therapy, a longer period of time between the dose and the INR measurement should provide better dose response information.
- INR values within 8 hours of the first dose should be avoided.
- Depending on the thromboplastin used, heparin may or may not affect the INR.
- Diluted samples from the site of a lab draw can provide elevated or misleading results.
- Unexpected values should always be confirmed prior to making any dramatic dosing changes.

Warfarin

The prothrombin time (PT) is used to monitor the effect of warfarin therapy. The prothrombin time is obtained by mixing a sample of the patient's blood with a thromboplastin (activator) and measuring the time it takes to form a clot. The proliferation of different laboratory instruments and clot detection methods and the wide variety of thromboplastin sources (human brains, rabbit brains, human placenta, recombinant tissue factor, monkey brains) have resulted in challenges in standardizing the measurement of clotting times. Different reagent sources differ in their ability to activate the clotting cascade. Subsequently, they differ in their sensitivity to detecting the factor deficiencies induced by oral anticoagulation. These differences may result in varied clotting times. Therefore, a prothrombin time (PT) of 24 seconds in one laboratory may not be equivalent to 24 seconds in another laboratory. In an effort to equalize these differences and standardize these measurements, the International Normalized Ratio (INR) was developed.¹ The INR is a mathematical expression of the prothrombin time and attempts to account for the mechanical and reagent variables noted above.

The INR is expressed as $INR = [PT/mean]^{ISI}$. The "mean" is the mean normal reference interval for that laboratory, and the "ISI" (International Sensitivity Index) is a value generated by the reagent manufacturer, comparing its thromboplastin sensitivity to a World Health Organization standard. Current recommendations include reagent ISI values of 1.0-1.2 and therapeutic INRs for most indications between 2.0-3.0 (exceptions include certain mechanical heart valves or hypercoagulable states where targets may be 2.5-3.5).²

The use of point-of-care (POC) devices for monitoring oral anticoagulation has gained popularity because of their ease of operation, rapid turnaround time and portability which facilitates testing outside the clinical laboratory. Most of these devices utilize a whole blood sample obtained from a finger stick and can usually provide PT and INR results within 2 minutes. Two of these devices, the Prottime® (International Technidyne Corporation, Edison, NJ) and CoaguChek® (Boehringer Mannheim Corporation, Indianapolis, IN) are approved for patient self-testing.

Some prothrombin times may be falsely elevated in the presence of heparin. To neutralize this effect, some testing reagents include polybrene or other heparin-inactivating agents. An unexpected INR value (high or low) should be rechecked prior to any consideration of a significant dose change. Another important consideration when interpreting INR values is the timing of the blood sample in relation to the first dose. Factor VII is the first procoagulant factor that is reduced with oral anticoagulant therapy (after 8 hours). Therefore, INR values measured within the first 8 hours after the first dose frequently are unchanged (or lower) and may provide misleading information regarding the first dose. A longer time interval between the first dose (or any dose) and the INR measurement is always desirable. In patients being treated for lupus anticoagulants and/or antiphospholipid antibodies, monitoring by using chromogenic factor X levels instead of the INR may be necessary since these conditions may falsely elevate the INR with some thromboplastin reagents.³

Heparin

The activated partial thromboplastin time (aPTT) is used to monitor heparin anticoagulation. Heparin, when complexed with antithrombin, enhances antithrombin's ability to inactivate serine proteases, primarily thrombin and factors IXa and Xa. Like the PT, aPTT methods are highly variable due to differences in reagents (activators and phospholipid sources) and mechanical variations in coagulzers. However, unlike the prothrombin time and the INR, there is no current standardization for this test. In an effort to assist clinicians in treating patients with heparin, the College of American Pathology has recommended that each laboratory provide therapeutic intervals for heparin anticoagulation which are specific to that laboratory. This "recommended range" is based on a regression analysis of aPTT to heparin levels (measured by protamine titration or anti-factor Xa levels) in at least 40 patients undergoing heparin treatment.

Therapeutic heparin ranges are based on the correlation between heparin concentration of 0.2-0.4 units/ml (by protamine titration) and/or 0.3-0.7 units/ml (by anti-Xa activity) to corresponding aPTT values.^{4,5} Separate therapeutic intervals are necessary if different sources are used (e.g. porcine versus bovine). Generally, aPTT values between 60 to 90 are targeted for treatment; however, lower values may be desired for prophylaxis. Measurements are usually made 4 to 8 hours after a change in rate for constant IV infusions (8 hours may be preferable if a bolus was administered) and 8 to 12 hours post-dose for the subcutaneous route. Other difficulties associated with heparin anticoagulation include dose-response relationship not being linear and the high variability seen with subcutaneous administration.

There are numerous point-of-care devices which measure whole blood aPTTs, but poor correlation to traditional, plasma-based clinical laboratory methods and difficulty in assessing therapeutic intervals may limit their usefulness. Low molecular weight heparins have relatively low anti-IIa (thrombin) activity and mainly inhibit factor Xa; therefore, little or no change will occur in the aPTT for patients receiving them. If measurement of the activity of these low molecular weight heparins is necessary, then alternative testing methods such as anti-Xa activity must be used.⁵ The drawback to testing anti-Xa activity is that this test is usually performed only at larger hospitals or reference laboratories and is expensive. Since low molecular weight heparins have less variability in dose

response, most patients receiving low molecular weight heparin prophylaxis or treatment (at higher doses) do not require the monitoring of anti-Xa activity. The aPTT can be used to monitor lepirudin (a recombinant natural anticoagulant from leeches) therapy. This agent is possibly useful in patients allergic to heparin or with antithrombin deficiency. A linear relationship between the lepirudin concentration and aPTT exists.

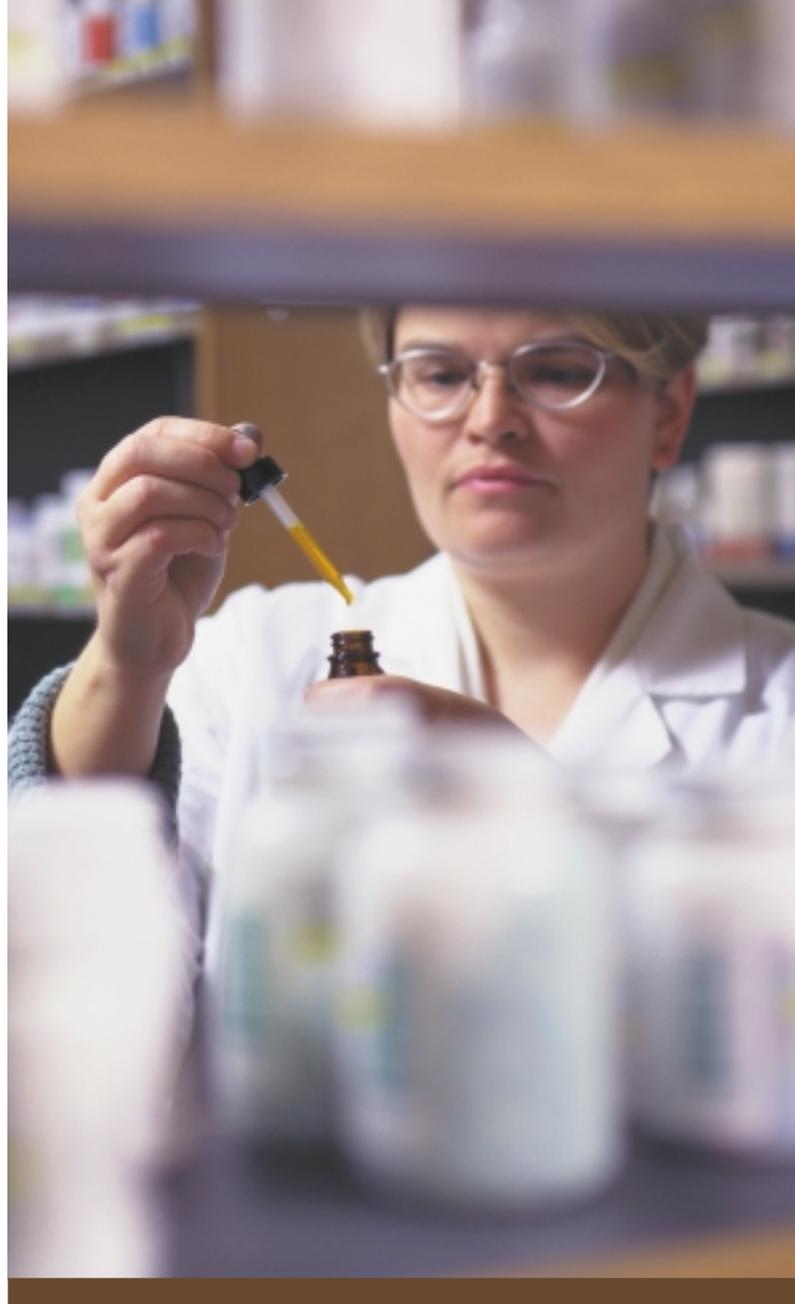
Moderate and high-dose heparin anticoagulation is commonly used in a variety of interventional procedures, including cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), dialysis, continuous venovenous/arteriovenous dialysis, and cardiac catheterization. In these situations, the activated clotting time (ACT) may be used to monitor the anticoagulant response. Much like the aPTT, the ACT also lacks standardization, but there are primarily only 2 types of activators: celite or kaolin. Hypothermia, hemodilution and concomitant therapy (e.g., aprotinin) can all result in variations in these activators' clotting time. All of the aforementioned procedures are guided by activated clotting time (ACT)-driven protocols, where initial dosing may be weight adjusted (e.g., 300 U/kg heparin for cardiopulmonary bypass), but subsequent anticoagulation is based on the activated clotting time result and recommended ranges (e.g., 180 to 200 seconds for extracorporeal membrane oxygenation; >400 seconds for cardiopulmonary bypass).^{6,7} It is important to note that there are specific activated clotting time (ACT) methods for moderate dose anticoagulation used in cardiac catheterization and extracorporeal membrane oxygenation (ECMO), and specific methods for high dose anticoagulation used in cardiopulmonary bypass. More complex monitoring tools, such as thromboelastography, have also been used for monitoring these patients.

Miscellaneous

Selected laboratory tests, such as the hematocrit or platelet count, can help assess the risk or presence of bleeding. For example, an unexplained reduction of the hematocrit may suggest internal blood loss. Occult blood loss in the gastrointestinal tract can be detected by a stool guaiac. Lower platelet counts may indicate a higher bleeding risk when other anticoagulants are also being used. Dramatic drops in the platelet count after initiating heparin therapy may suggest heparin-induced thrombocytopenia (HIT). Liver function studies and serum albumin can be useful in predicting a patient's dose response to anticoagulant therapy.

Looking Ahead

A number of new generation anticoagulants are in clinical use or clinical trials. Examples include direct antithrombins (e.g., hirulog, hirudin), platelet glycoprotein blockers (e.g., IIb/IIIa inhibitors) and snake venom (e.g., aneroD). Thrombolytic therapy (e.g., urokinase, streptokinase, tPA) and alternative therapy associated with heparin-induced thrombocytopenia (e.g., danaproid, lepirudin) also present monitoring issues. New laboratory methods for rapidly measuring platelet function, direct antithrombins, streptokinase antibodies, thrombolytic effect, and other interventional or replacement therapies (e.g., antihemophilic factor III, antithrombin) are currently available or for research use only. Such rapid monitoring methods may facilitate testing in situations where



bleeding is a significant risk or where measuring the efficacy of treatment (thrombolytics, replacement therapy) is desired, but further studies are needed before their widespread use is warranted.

Conclusion

Providing optimal anticoagulation requires careful consideration of each patient's needs, an understanding of the anticoagulants used, their effects and the methods used to measure their effects. Baseline values should always be measured prior to initiating anticoagulant therapy and used as a benchmark to assess the response to therapy or to rule out autoanticoagulation (secondary to liver disease, etc.). Correct understanding of the usefulness and limitations of laboratory results is critical in providing the best possible patient care.

References for this article are available upon written request to: California State Board of Pharmacy, Attn.: Health Notes Anticoagulation References, 400 R Street, Suite 4070, Sacramento, CA 95814.

Part Two:

The Role of the Pharmacist in Anticoagulant Therapy



Diane R. Romac, Pharm.D., FCSHP
Clinical Pharmacist,
UC Davis Medical Center
Assistant Clinical Professor,
UC San Francisco School of Pharmacy
Assistant Clinical Professor,
UC Davis School of Medicine



Patricia L. Poole, Pharm.D., FCSHP
Clinical Pharmacist,
UC Davis Medical Center
Assistant Clinical Professor,
UC San Francisco School of Pharmacy
Assistant Clinical Professor,
UC Davis School of Medicine



Patient Education and Counseling

Why are anticoagulants prescribed?

Warfarin and the heparins are “anticoagulants,” sometimes referred to as “blood thinners.” Anticoagulants are used primarily to prevent clot (thrombus) formation and the extension of existing thrombi. Therapy may be continued for only a few weeks or months, or may be lifelong.

When an immediate anticoagulant effect is required, heparin or low molecular weight heparin should be used, since warfarin does not exert its full therapeutic effect until after several days of therapy. Low molecular weight heparins are also indicated in the short-term prophylaxis of patients undergoing hip or knee replacements or other high-risk surgeries. When an immediate effect is not necessary, such as in patients with chronic atrial fibrillation, warfarin may be initiated as the sole anticoagulant therapy.

A continuous infusion of heparin is commonly used in hospitalized patients with thromboembolism. The use of low molecular weight heparins, administered via the subcutaneous route, has become increasingly common for the home treatment of thromboembolism in some patients. In both of these cases, warfarin therapy may overlap the relatively brief treatment period with heparin (usually 5-7 days) and then should be continued beyond the heparin treatment period to provide long-term anticoagulation therapy. In patients in whom warfarin is contraindicated (e.g., pregnancy), heparin, given subcutaneously, may provide long term anticoagulation therapy.

PATIENT CARE TIPS

- Patients on warfarin should always consult their pharmacists prior to taking ANY new medication, regardless of whether it is a prescription or over-the-counter medication.
- In order to achieve optimal treatment and to prevent adverse effects, thorough patient understanding of anticoagulation therapy is vital.
- Warfarin is one of the most common causes of drug-related admissions to hospitals for medication-related adverse events.
- A consistent, well-balanced diet is the most important dietary factor in maintaining a therapeutic warfarin level.

Anticoagulants are indicated for:

- **Treatment of an existing thrombus such as:**
 - Deep Vein Thrombosis (DVT)
 - Pulmonary Embolism (PE)
- **Prophylaxis against developing a thrombus in situations such as:**
 - High risk for deep vein thrombosis or pulmonary embolism (orthopedic or abdominal surgery, prolonged immobilization)
 - Chronic atrial fibrillation
 - Indwelling intravenous therapy
 - Hypercoagulable states (Protein C deficiency, Protein S deficiency, Antiphospholipid antibody syndrome, Antithrombin III deficiency, Factor V Leiden mutation)
 - Following myocardial infarction in some high-risk patients
 - Prosthetic heart valves
 - Following cerebral vascular embolism to prevent recurrence
 - Recurrent transient ischemic attacks (TIAs)

How to Administer Medications

Approximately one-third of patients who take warfarin and attend anticoagulant clinics have laboratory test results outside of the desired range. Significant fluctuations in a patient's level of anticoagulation are dangerous, increasing the risk of hemorrhage or thromboembolism. Studies have shown that increasing patients' understanding of their anticoagulant therapy results in improved patient compliance, improved therapeutic control, and a decreased number of hospital admissions for bleeding and clotting complications. For these reasons, organized educational programs are a critical component of the therapeutic regimen for patients who take anticoagulant medications.

Patient education may consist of personalized verbal instructions, written information, audio or videotape presentations, or a combination of these modalities. Patients may also benefit from medication compliance aids, such as pill boxes with instructions for use, or medication calendars.

What You Should Tell Patients

Points you should cover when counseling patients regarding their anticoagulation therapy should include the following:

Warfarin

- Why has warfarin been prescribed?
- The dosage that has been prescribed and the color of the tablet.
- Take warfarin on a daily basis at approximately the same time.
- Double check their daily doses, since their dosages may alternate (i.e., by day of the week or every other day).
- Take the medication with a drink of water without regard to meals.
- Never take more medication than is prescribed.
- Keep a record of the doses they take and any doses they miss.
- If they miss a dose, take the dose as soon as they remember it, *if it is on the same day*, but **never** double the dose the day after a dose is missed, **unless directed to do so by their health care provider**.
- Always store medication in the original, labeled prescription container.

ANTICOAGULANT	Heparin	Low Molecular Weight Heparin	Warfarin
<u>Route of Administration:</u>	Intravenous or Subcutaneous	Subcutaneous	Orally (usual) Intravenous (rare)
<u>Usual Clinical Setting:</u>	Short-term or long-term in pregnancy	Short-term	Chronic
<u>Advantages:</u>	1) Inexpensive 2) May be administered via the intravenous or subcutaneous route	1) No lab monitoring 2) Standard dose	1) Inexpensive 2) Administered orally
<u>Disadvantages:</u>	1) Unpredictable kinetics 2) Requires frequent lab monitoring	1) Expensive 2) Must be administered subcutaneously	1) Difficult to regulate 2) Requires laboratory monitoring



- Keep all medication out of the reach of children.
- Consult with their prescribing health care provider prior to any surgery, including oral surgery.
- Avoid hazardous activities that could result in serious lacerations or blunt trauma.
- Minimize alcohol intake.
- Follow a balanced, consistent diet.
- Consult their pharmacist before starting or stopping any new medication, regardless of whether it is a prescription or over-the-counter (OTC) medication.
- Advise women with childbearing potential that warfarin can have adverse effects on fetal development, such as congenital malformation, and emphasize the importance of using an effective (nonhormonal) method of birth control throughout therapy.

Heparin and Low Molecular Weight Heparins

- Why has heparin been prescribed?
- How *much* should be administered and how *often* should it be administered?
- Explain the importance of double checking each dose drawn up in the syringe for accuracy prior to administration by describing:
 - a) the different concentrations of heparin products,
 - b) how to measure the amount to be administered, and
 - c) how to draw up doses.
- Explain how heparin should be administered (subcutaneous injection technique):
 - a) Wash their hands thoroughly prior to handling the medication and syringe.
 - b) Cleanse the injection site with an alcohol swab.
 - c) With one hand, gently pinch a skin fold of the abdomen between the thumb and forefinger. With the other hand, insert the needle straight through the skin deeply and inject the drug.
 - d) Rotate the site of injection daily to either side of the abdomen.
- Describe the proper disposal of syringes and needles (in containers provided or as directed by the health care provider).
- Provide instructions for missed doses—If they miss a dose, they should take it as soon as you remember it, **UNLESS** it is almost time for the next dose.
- Describe the importance of spacing doses evenly and injecting at the same time daily.
- Advise them to consult with their prescribing health care provider prior to any oral surgery.
- Caution them to avoid hazardous activities that could result in serious lacerations or blunt trauma.

Symptoms That Should be Reported Immediately & Who to Call for Problems

Patients should be counseled about when they should seek immediate assistance, either by directly contacting their health care provider, or, if their health care provider is unavailable, by seeking medical attention at an urgent care center or emergency room. Examples include:

- Bleeding from any source that will not stop
- A serious fall, injury or blow to the head
- Blood in the urine or stool
- Bruises of unknown origin
- A fever or illness that does not improve in a reasonable time period
- Pain or swelling in any extremity
- Difficulty breathing
- Unrelieved headache or dizziness

Patients desiring more information or with routine questions should be advised to contact their pharmacists or other health care providers. For more specific questions regarding dosage, patients should be informed to contact the health care providers who monitor their anticoagulation therapy. Patients should also be counseled to always seek the advice of a pharmacist when choosing over-the-counter medications.

Importance of Keeping Medical and Laboratory Appointments

Since maintaining anticoagulation in the desired therapeutic range is vitally dependent on the compliance and understanding of the patient, it is very important to make sure the patient has a good understanding of the need for proper monitoring and follow-up care. With the exception of the low molecular weight heparins, monitoring for effectiveness of anticoagulation therapy is done with various blood tests. Health care providers may also intermittently monitor complete blood counts (CBC), stool tests for occult blood loss and urine tests for hematuria.

Monitoring warfarin

As was described in a previous article, the current standard monitoring test for warfarin is the prothrombin test (also known as the “protime” or “PT”), which is expressed as the INR (International Normalized Ratio). This test measures the degree of anticoagulation (blood thinning) achieved by warfarin. A “normal” INR value for a patient not on warfarin is approximately 1.0. Most patients on warfarin will have a target INR of 2 to 3. Patients with mechanical valves usually have a target INR of 2.5 to 3.5. Each patient is different, however, and it is important for patients to know their target INR range. The INR easily fluctuates and therefore it is extremely important to monitor each patient on a regular basis. Patients may require daily INR testing until a maintenance dose is established, then once or twice weekly for the first month of therapy. After the first month, INR testing is usually indicated every 1 to 4 weeks, depending upon the patient’s response to therapy. When counseling patients on the importance of not missing appointments, it is important to explain that 1) an INR that is too low may indicate that they are at risk for the development of a clot, and 2) an INR that is too high may indicate that they are at increased risk for serious bleeding. It is also important for patients to realize that their warfarin dosages will very likely change based on the results of each test,

and that this could happen frequently, especially when starting on a new dose. For this reason, patients should keep a diary of their INR values and the corresponding warfarin doses. Medications, dietary changes and some clinical conditions can alter a patient's sensitivity to warfarin. Table 1 lists some clinical factors that can affect patient sensitivity to warfarin.

Table 1. Some Clinical Factors that Affect Patient Sensitivity to Warfarin

Clinical Condition	Warfarin Sensitivity INR Result
Alcohol intoxication/binge drinking	Increased
Prolonged fever	Increased
Congestive heart failure exacerbation	Increased
Impaired liver function	Increased
Edema	Decreased
Hyperlipidemia/hypercholesterolemia	Decreased
Hypothyroidism	Decreased

Monitoring Heparin

As described in a previous article, the blood test used to monitor the effectiveness of subcutaneous heparin injections is the “aPTT,” which stands for activated partial thromboplastin time. The timing of the aPTT test in relation to the timing of the subcutaneous injection is important; the test should be performed 6 to 8 hours after the heparin dose is administered. The patient should be advised to let the prescribing health care provider know if any doses were missed or given off schedule, so that the aPTT may be interpreted correctly.

Most patients will have a target aPTT of approximately 55 to 85; however, patient variability exists. Therefore, patients should be advised to learn what their target range is. Hospitalized patients commonly receive an intravenous bolus of heparin, followed by a continuous intravenous infusion. The amounts these patients receive may be based on their body weight. Heparin levels generally approach steady state 6 to 8 hours after an infusion is begun and are assessed by evaluating the effect on the aPTT. The rate of infusion can then be adjusted, based on the initial aPTT result, using a standardized nomogram. The aPTT should be *rechecked* approximately six hours after *any* dosage change. After a maintenance dose is established, the aPTT can be checked once daily.

There is no routine monitoring test for therapeutic efficacy for patients receiving low molecular weight heparin. Doses are standardized and are based on the patient's body weight, as well as the indication for which the patient is receiving anticoagulant therapy. These features (no lab monitoring required and standardized doses) contribute to the popularity of low molecular weight heparins for short-term use, especially in nonhospitalized patients (e.g., for home treatment).

Over-the-Counter (OTC) Drug Use

All patients on warfarin should consult with their pharmacists or health care providers prior to using any over-the-counter (OTC) product. Warfarin interacts with many medications, and many of these interact by more than one mechanism. As a result, the precise effects of these interacting medications on anticoagulant therapy are difficult to predict. Careful blood test monitoring is indicated

when any medication is initiated or withdrawn from the regimen of a stabilized warfarin patient, due to the possible serious consequences of interference with anticoagulant therapy. Stabilization of the warfarin dosage may be particularly difficult if an interacting medication is used *intermittently* rather than *chronically*. This is often the case when patients self-medicate with OTC medications.

Warfarin patients who take over-the-counter vitamin supplements should avoid products that list vitamin K (or phytonadione) as one of the ingredients. These patients should also be cautioned against taking any nonsteroidal anti-inflammatory medications, aspirin or salicylate-containing products without the knowledge of their physicians, since these agents may cause platelet aggregation inhibition and/or gastrointestinal ulceration or hemorrhage.

Dietary Considerations

Foods high in vitamin K may decrease the effect of warfarin. If these foods are eaten only sporadically, this may result in fluctuations of the INR and make it difficult to keep the patient controlled. Eating a well-balanced diet is the best way to avoid significant dietary fluctuations of vitamin K intake. Therefore, patients should not be counseled to avoid foods high in vitamin K, but rather encouraged to incorporate those foods into a well-balanced diet on a regular basis, so that their warfarin dose can be stabilized. For patients who have erratic fluctuations in their INR without identifiable causes, a review of their dietary habits to identify foods with significant quantities of vitamin K may be valuable (Table 2). If a particular food or beverage is identified that proves to be high in vitamin K content, patients should be advised to either incorporate that item into their diets on a regular basis, or minimize its use.

Table 2. Selected Foods with Medium to High Content of Vitamin K

Moderate Vitamin K Content	High Vitamin K Content
Asparagus, 7 spears	Broccoli, 1/2 cup
Avocado, 1 small	Brussels sprouts, 5
Beans, pod, 1 cup	Cabbage, 2/3 cup
Peas, 2/3 cup	Chard, Swiss n/a
Pickle, dill, 1 medium	Collard greens, 1/2 cup
Sauerkraut, 1 cup	Cucumber peel, 1 cup
Soybean, 1/2 cup	Endive, 2 cups
Squash, summer, peel only, n/a	Kale, n/a
	Lettuce: Bib, Heading, Red Leaf, n/a
	Mayonnaise, 7 T
	Mustard greens, 1-1/2 cup
	Oil: Canola, Salad, Soybean, 7 T
	Onion, green, 2/3 cup
	Spinach, 1/2 cup
	Turnip greens, 1-1/2 cups
	Watercress, 3 cups

n/a = not available

If patients are unable to eat for several days due to illness, they should be instructed to contact their physicians, as additional monitoring of the INR may be indicated. See Table 2.

Generic Warfarin

In 1997, Barr Laboratories received FDA approval to manufacture and market a generic version of warfarin in the same doses and colors as DuPont Merck's branded product, Coumadin®. To receive an "AB" rating from the FDA as a bioequivalent generic, the Barr product was required to be within 80-125% of the pharmacokinetic parameters of the brand name product in healthy volunteers. The actual results were well within those limits, with a ratio of AUC¹ of the generic to the brand drug reported to be 99-103%. The FDA sent letters to professional organizations and prescribers stating that drugs deemed bioequivalent (i.e., AB rated) can be expected to have the same degree of safety and efficacy and can be used interchangeably without the need for additional monitoring. While an AB rated generic warfarin is available, there has been disagreement among the experts as to whether these products are interchangeable. *Although experts may disagree about the interchangeability of warfarin products, all will concur that close monitoring and follow-up is critical in all patients who are on medications with a narrow therapeutic index and potentially harmful adverse effects.*

¹ AUC: area under the curve of blood levels plotted against time after administration of each drug.

Suggested Readings and Sources of Information for Health Care Providers

Indications, General Management Review:

1. Hirsh J, Dalen J, Deykin D, Poller L, Bussey H: Oral Anticoagulants—Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range. *Chest* 1995; 108(4):231S-246S.
2. Hyers TM, Hull RD, Weg JG: Antithrombotic Therapy for Venous Thromboembolic Disease. *Chest* 1995; 108(4):335S-351S

Patient Education:

1. Kumar S, Haigh JRM, Rhodes LE, et al: Poor compliance is a major factor in unstable outpatient control of anticoagulant therapy. *Thrombosis and Haemostasis* 1989; 2:729-732.
2. Wyness MA: Evaluation of an educational programme for patients taking warfarin. *Journal of Advanced Nursing*, 1990; 15:1052-1063.
3. Stone S, Holden A, Knapic N, et al: Comparison between videotape and personalized patient education for anticoagulant therapy. *The Journal of Family Practice* 1989; 1:55-57.
4. Roddie A, Pollock A: Correspondence: Therapeutic control of anticoagulation: how important is patient education? *Clin. Lab. Haemat.* 1988; 10:109-112.
5. "A Patient's Guide to Using Coumadin" is a booklet distributed by the DuPont Pharmaceuticals Company to assist in patient education. Free copies of the booklet, as well as medication boxes, video tapes and audiocassettes are available by calling DuPont Pharmaceuticals at 1-800-COUMADIN.

Internet Sites:

1. <http://ipn.intelihealth.com>
(USP Drug Info for the Health Care Professional on



- Anticoagulants - provides a comprehensive review)
2. <http://www.fda.gov>
(FDA website for information on generic substitution)

Dietary Considerations:

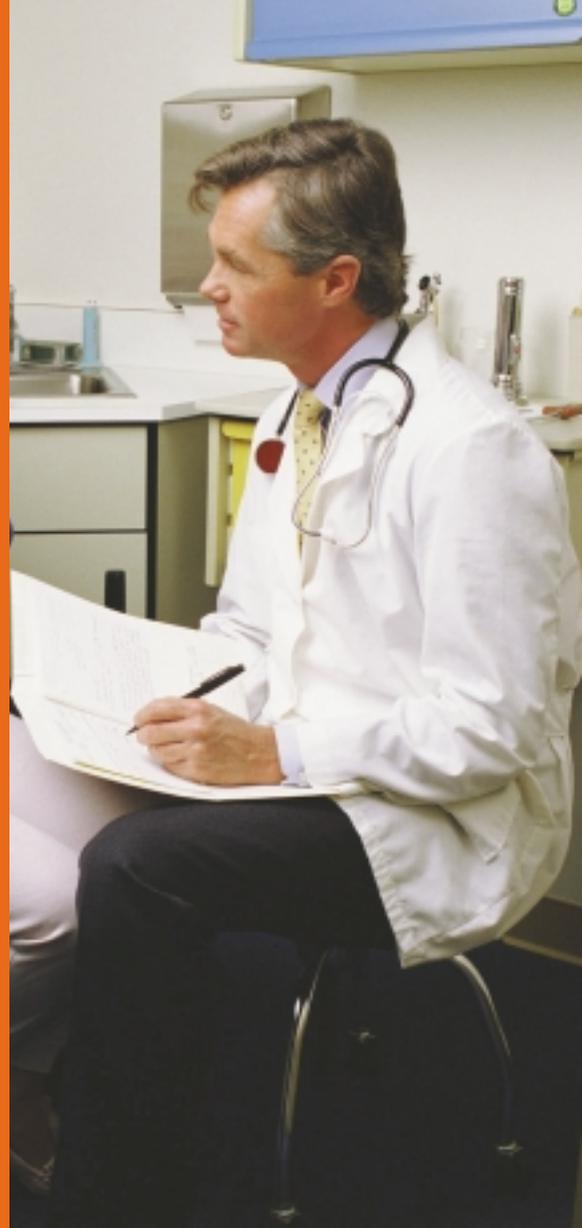
1. "A Patient's Guide to Using Coumadin," a booklet distributed by the DuPont Pharmaceuticals Company.
2. Booth SL, Sadowski JA, Weihrauch JL, Ferland G.: Vitamin K1 (phylloquinone) content of foods: a provisional table. *J Food Comp Anal.* 1993; 6:109-120.
3. Ferland G, MacDonald DL, Sadowski JA.: Development of a diet low in vitamin K1 (phylloquinone). *J Am Diet Assoc.* 1992; 92:593-597.

Improving Safety

with Warfarin Therapy



Robert T. Weibert, Pharm.D.
Clinical Professor,
University of California
San Francisco School of Pharmacy,
San Diego Program, and Anticoagulation Clinic Director, University of
California San Diego Medical Center



Warfarin's complex pharmacology and pharmacokinetics both contribute to its narrow margin of safety. Pharmacists' unique knowledge of pharmacology, pharmacokinetics, drug interactions and drug products makes them particularly well-prepared to assist patients in maintaining safe anticoagulant therapy.

Safety with Warfarin Prescriptions

An accurate and continuing supply of warfarin is essential to the success of long-term anticoagulation. Safety issues with warfarin should cause pharmacists to briefly interview all patients with new and refill prescriptions. Seven key warfarin safety questions are outlined in Table 1.

Prothrombin Time Monitoring

The most important question for all patients is when they last had their prothrombin time measured. Monitoring of the INR and appropriate warfarin dose adjustment are the cornerstones of safe and effective anticoagulation. Patients found to have previously dropped out of monitoring should be given a maximum of a two-week supply of warfarin and assisted in scheduling a prothrombin time measurement before a long-term warfarin supply is issued. Some patients may already have refill authorizations for up to one year; if they have stopped having their prothrombin time measured, they should not be provided with a long-term supply of warfarin. Ensuring follow-up testing is critical for safe warfarin therapy. The INR response depends on the four factors shown in Table 2.

Patient Compliance

Long-term compliance with warfarin therapy and INR monitoring are key factors for successful therapy. Computerized prescription records can flag patients who fail to obtain prescriptions. Compliance with warfarin is frequently better than with many other long-term preventive therapies. However, noncompliance is problematic in many patients and can result in therapeutic failure with recurrent venous or arterial thrombosis or embolism. Young male patients are at a high risk for noncompliance and should be followed closely with limited warfarin supplies. Other patients may continue warfarin without INR monitoring and risk both thrombosis and bleeding complications. Reliable patients can be given multiple refills, which is convenient for the patient, prescriber and pharmacist. Again, pharmacists should always ask about follow-up INR testing when dispensing refills.

Avoiding Mistakes with Warfarin Prescriptions

Three critical factors that strongly influence the response to warfarin treatment are (1) the dose prescribed, (2) the dose dispensed and (3) the dose taken. An error in these factors can cause therapeutic failure (thrombosis) or toxicity (bleeding).

Prescribing Errors

Warfarin is available in nine color-coded strengths under the Coumadin® brand name (DuPont) and in similar color-coded tablets from Barr Laboratories. It is also available in six similar color-coded strengths from Apotecocon. The DuPont warfarin tablets are round, the Barr warfarin tablets are oval and the Apotecocon warfarin tablets are square. Patients should be taught to identify the strength, color and shape of their warfarin tablets. Prescribers should carefully write the warfarin strength and use fractions to denote the 2-1/2 mg and 7-1/2 mg sizes to avoid possible confusion.

Extra caution is necessary when a patient presents a prescription with a change in tablet strength. The change should be verified with the prescriber unless the patient is already aware of the change and can explain how the new strength is to be taken. All prescriptions should be double-checked to avoid inadvertent changes in tablet strength.

Warfarin dose adjustments usually will not exceed 25 to 30% of the prior dose. Larger dose changes should trigger a question to the patient and are acceptable only if the INR is to be retested within 3 to 5 days.

Dispensing Errors

While dispensing errors are rare, they can have catastrophic effects when made with warfarin prescriptions. If patients know to question any change in the color of their warfarin tablets, they can protect against errors. The pharmacist should always inspect warfarin tablets when they are given to the patient as a final safety check.

Patient Dosing Errors

Patients can take incorrect warfarin doses because of inadequate or confusing directions or despite careful and clear instructions. The initial week of warfarin treatment following hospitalization is a high-risk time for patient dosing errors. Not only is warfarin a

new therapy, but many patients are ill and eager to go home. These factors can all contribute to confusion over the instructions given.

Errors made by anticoagulated patients may include the following:

Taking extra doses to “treat” symptoms

Patients with leg swelling following a deep vein thrombosis (DVT) may take double or extra doses for their symptoms, thinking that “more is better.” The overdose results in excessive anticoagulation and can cause severe bleeding. A specific warning should be given to new patients who have sustained a symptomatic episode of venous thromboembolism: they should NOT “self-treat” their symptoms by taking extra doses.

Brand/generic name confusion

Patients often receive a limited supply of warfarin upon discharge from the hospital and then soon thereafter are provided a prescription

Table 1.

Seven Key Warfarin Safety Questions

1. When was your last INR determination? (or, When was your prothrombin “protime” measured last?) What was your last INR value?
2. What is the strength and color of your warfarin tablets? Has the warfarin dose changed from the directions on your prescription?
3. Are you eating poorly or have you made an intentional change in your diet?
4. Have you started or stopped any other medications?
5. Have you been acutely sick recently or noticed a change in any chronic illness?
6. Have you developed any bleeding or changes in the color of your stools or urine?
7. Are you planning to have any surgery, dental surgery or other invasive procedures; or have you had any injury or a “hard” fall?

Table 2.

Four Determinants of the INR Response

1. Dose
2. Diet
3. Drugs
4. Disease

for Coumadin®. They take both, thinking that the prescriptions are for different drugs, and the double dose results in excessive anticoagulation. With the newly available generic warfarins, the risk of this error is significant. To highlight and help prevent this risk, manufacturers have added a warning about the risks of mistaken double-dose therapy to warfarin package inserts.

Confusion after directions to change the dose

The dose of warfarin is changed approximately 30% of the time after an INR determination. Most often, patients are instructed to increase or decrease the warfarin dose by one-half (1/2), or one, tablet on several days of the week. Other patients may have been prescribed two or more strengths of warfarin and instructed to alternate or combine tablets during the week. Another common mistake is for a patient to be instructed to withhold a tablet or take an extra tablet for a one-time correction; however, the patient may continue to follow the one-time dosing instruction on a weekly basis. Conversely, some patients who are instructed to change their dosage on a weekly basis change the dose only one time, reverting back to their previous dosing schedule. Patients should be asked to repeat their new dose directions to assure that they understand them and to avoid mistakes. Ideally, any new dosing schedule should be written or printed for patients and should clearly identify both a) the number of tablets and b) the milligram dosage on a weekly dosing calendar (Figure 1). Previous warfarin dose instruction sheets are possible sources of confusion and should be discarded when new directions are given. Patients should be encouraged to record their warfarin doses on drug calendars, which are available with Coumadin® instruction booklets. Weekly pillboxes are also available from DuPont Pharma and are very useful for patients who vary their warfarin dose on different days of the week.

Mistakes after changing tablet strength

Patients are sometimes prescribed a different strength of warfarin for convenience of dosing. Often a higher strength tablet is prescribed so that the patient will not have to take multiple tablets. Pharmacists should carefully review the new dosing regimen to avoid critical mistakes. Two examples of these types of mistakes are 1) taking both new and old tablets, causing an overdose or 2) following old directions, also resulting in an overdose. Ask yourself, “What is the worst mistake the patient can make with this change?” Then, have the patient explain how the new tablets are to be taken, and what they will do with the old tablets.

Look-alike tablets

Patients may confuse their warfarin with other medications which look similar to warfarin. This confusion can cause serious warfarin dosing errors. For example, patients have confused green 2-1/2 mg warfarin with green 20 mg isosorbide and mistakenly taken warfarin three times daily, causing excessive anticoagulation.

Avoiding foods with Vitamin K

Repeated warnings about vitamin K-containing foods have caused many patients to eliminate all vitamin K-containing foods. After one week of little or no vitamin K intake, patients become vitamin K deficient and excessively anticoagulated. Patients should be encouraged to eat a normal diet and not to eliminate vitamin K foods. If they eat large quantities of foods with an unusually high vitamin K content, they should discuss their diets with the clinicians managing their warfarin therapy.

While these patient dosing mistakes seem simple, they can cause major bleeding. Systematic efforts by pharmacists and prescribers, such as those described here, can improve safety by reducing the incidence of these unnecessary errors.

Figure 1

Warfarin Dose Instruction							
Medical Center Coumadin Clinic	Tablet Strength-			Tablet Color-		Patient	
Date							
Day	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
# of tablets							
milligrams (mg)							

Drug Interactions

Warfarin is reported to have more than 250 drug interactions. Drug interaction screening is an important reason to encourage patients to select a specific, personal pharmacy and pharmacist for all of their medications and consultation regarding their drug therapy. Patients should also be encouraged to bring all of their medicines to their anticoagulation monitoring appointments. Warfarin interactions can occur with prescription drugs, nonprescription drugs, herbal medicines, vitamins, nutritional supplements, alcohol and vitamin K-containing foods. Drug interactions should be anticipated and then managed by adjustment and monitoring of warfarin therapy or by avoidance of the interacting drug. The major classes of interacting drugs are listed in Table 4.

Antibiotics/Antimicrobials

Nearly all patients will eventually be treated for infections. Extra precautions and warfarin dose reductions are needed for patients on trimethoprim/sulfamethoxazole or metronidazole. Erythromycin can cause excessive anticoagulation, especially in patients being treated for pneumonia or severe bronchitis. Antibiotic “drug interactions” are often multifactorial and include the combined effects of the drug, decreased vitamin K intake, fever and infection. Dicloxacillin reduces warfarin anticoagulation. Rifampin is a very powerful hepatic enzyme inducer and may cause a five- to six-fold increase in warfarin dose requirements.

Analgesics

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of gastrointestinal bleeding and should be avoided by patients taking warfarin. Gastroprotective therapy with misoprostol or omeprazole should be required if NSAIDs must be used. Combined low-dose (81 to 160 mg) aspirin can be given with warfarin without a large increased risk of major bleeding. Acetaminophen is generally safe, but can increase the INR in susceptible patients. Limiting acetaminophen to two grams daily for short periods will usually avoid an interaction with warfarin. Patients are at an increased risk of an acetaminophen-warfarin interaction if they regularly drink alcohol or are eating poorly.

Anticonvulsants

Carbamazepine and phenobarbital induce hepatic enzymes and increase warfarin dose requirements. Phenytoin increases the anticoagulant effect of warfarin.

Antiarrhythmics

Amiodarone causes a substantial increase in warfarin anticoagulation, and significant dose reductions will be needed over a several-week period.

Alcohol

Acute alcohol ingestion is a high-risk drug interaction and places patients at risk of intracranial bleeding. Uncontrolled alcohol abuse is a contraindication to warfarin therapy.

Emergency Identification

All patients should carry wallet cards that indicate that they take warfarin. Many patients will also choose to wear “Medic Alert” bracelets that state they take warfarin. In the event of an acute injury, it is critical that emergency personnel know that warfarin anticoagulation may aggravate bleeding and that emergency reversal of anticoagulation may be needed.

Table 3

Potential Causes of Dosing Errors and/or Noncompliance

- Starting warfarin after hospitalization
- Symptoms suggesting thromboembolism
- Non-English speaking patient, if language barrier
- Switching tablet strengths
- Switching between brand name and generic warfarin
- Change in warfarin dose directions
- Multiple tablet strengths
- Addition or deletion of concurrent drug therapy
- Look-alike tablets
- Financial difficulty in obtaining warfarin

Table 4.

Warfarin Drug Interactions: Major Drug Classes

- Antibiotics/Antimicrobials/Antifungals
- Analgesics
- Anticonvulsants
- Antiarrhythmics
- Alcohol

Vigilance

For optimal effectiveness and safety, all health professionals should demonstrate special vigilance when providing care to patients on warfarin therapy. One way that pharmacists can assist is to review the seven key safety questions with all patients taking warfarin (Table 1).

Recommended Reading

1. Ansell JE, Ortel L, Wittkowsky AK. Managing Oral Anticoagulation Therapy. Aspen Publishers, 1997.



Management of Specialized Situations



Steven R. Kayser, Pharm.D.
Clinical Professor of Pharmacy
Department of Clinical Pharmacy
School of Pharmacy
University of California San Francisco

Director, Anticoagulation Clinic
Hospitals and Clinics
The Medical Center at
University of California San Francisco

Introduction

A successful and safe course of oral anticoagulant therapy is the result of appropriate patient selection, monitoring and a relationship where a highly motivated patient and caregiver work together to outline a treatment plan that accounts for routine as well as unanticipated clinical situations. Many variables influence the response to oral anticoagulant therapy, including age, other medications, dietary changes, febrile illnesses, metabolic changes such as hypo- or hyperthyroidism and compliance. It is critically important to maintain the International Normalized Ratio (INR) within the desired range in order to minimize the risk of hemorrhage and to prevent recurrence of the underlying thrombotic condition.

Bleeding

One of the most serious adverse effects of anticoagulants is bleeding. It is often assumed that patients on anticoagulants are entitled to bleed; that is, if bleeding occurs, it is because the patient is on anticoagulant medication. While it is true that the incidence of bleeding in patients on anticoagulant therapy is greater than in patients who are not, bleeding does not occur unless there is some sort of trauma or injury. In many cases, the extent of the injury may be very minor; nonetheless, bleeding should not spontaneously occur. Whenever bleeding does occur, the INR should be checked, since there is a correlation between the extent of anticoagulation and the likelihood for bleeding. Other tests, such as platelet count, should also be evaluated, since alterations in platelet count or function can result in easier bleeding.

Evaluation of bleeding is important and should be characterized and documented in the patient's record. Oftentimes a careful history will place the significance of the episode into perspective. For example, patients complaining of epistaxis (nosebleeds) may also have an upper respiratory infection or work in dry, dusty conditions. These conditions may independently lead to epistaxis and are not necessarily the result of excessive anticoagulation. If a nosebleed lasts for more than 15 minutes, however, patients should be instructed to call for advice or go to an Emergency Department for evaluation. Direct, pinching pressure should be applied, and, if possible, packing should be avoided. Although packing may stop the bleeding, when removed, it will often displace the clot, and the bleeding will resume. Patients who develop chronic epistaxis should be referred to their physicians for evaluation.

Hematuria (urinary tract bleeding) may represent the presence of a urinary tract infection and not necessarily excessive anticoagulation. Both males and females should be referred for evaluation if hematuria occurs because it may represent the presence of another underlying condition. Bright red blood per rectum (BRBPR) is often the result of hemorrhoids and should be documented as such; otherwise the patient should be evaluated to assure the absence of an underlying lesion. If there is discoloration of the stool, particularly if it turns black or tarry, it should be tested for the presence of occult blood. Certain medications, such as iron and bismuth, may turn the stool dark and should be ruled out as the cause of the bleeding.

Bruising (ecchymosis) may occur secondary to trauma even in patients not on anticoagulants or in those with therapeutic INRs. If a patient receives a traumatic injury to an area of soft tissue, he or she should be advised to apply ice immediately and intermittently for at least the first 24 to 48 hours. Heat should be avoided until the bruise has stopped increasing in size. If the bruise occurs over a joint and there is a loss of range of motion or interference with normal joint function, the patient should be evaluated immediately in order to avoid hemarthrosis (blood in the joint). Patients should be told that it usually takes 7 to 10 days for bruises to resolve and that as the bruise heals, its color will change from dark purple to red, green and yellow. Patients who report gum bleeding should be referred for dental evaluation, since gum bleeding is usually indicative of gum disease or periodontal problems. Improper brushing or too aggressive flossing may also result in gum bleeding, so patients should be instructed in the proper techniques for these activities.

In all cases when bleeding is observed, patients should be instructed to seek advice and not to automatically withhold or

PATIENT CARE TIPS

1. Consistency of diet, rather than content, is the most important dietary factor in stabilizing anticoagulant therapy with warfarin.
2. Routine surveillance is the most important factor in minimizing the risk of bleeding from warfarin.
3. Patients taking warfarin should keep accurate and complete records of all medications they consume, including OTC and prescription medications.
4. Patients should wear Medic-Alert identification to alert all health care and emergency personnel that they are taking anticoagulant medications.
5. Patients should be instructed to inform their health care providers if they have any concurrent illnesses that last for more than a few days.

discontinue their medication. It is important to document what the INR is at the time of the bleeding in order to determine the most appropriate course of action. Bleeding that occurs when the INR is *within* the therapeutic range should be evaluated carefully for the presence of an underlying lesion or abnormality, although the most common cause is usually trauma.

Management of Bleeding

When a patient presents with bleeding and it is determined that the INR is *outside* of the therapeutic range, it is important that appropriate measures be taken. Overly aggressive action may reverse the INR but lead to a relatively refractory state of anticoagulation, which places the patient at risk for formation of a new clot.

First, it must be determined if the patient is hemodynamically stable. The blood pressure and pulse should be checked and orthostatic measurements obtained. If blood loss is considered to be excessive, the patient should have an appropriate laboratory evaluation performed, including a complete blood count and investigation of the source, as well as the cause, of the bleeding. If the patient is hemodynamically stable, treatment may consist of simply withholding one or more doses of the anticoagulant. The rate of decline of the INR is dependent on how prolonged it is. In general it will take at least several days for the INR to decrease from moderately elevated levels (INR 5-10) to within the therapeutic range. A technique we have successfully used in our practice is to administer small doses of oral vitamin K₁ (2.5 mg phytonadione) and withhold a dose of warfarin. This technique has proven successful in decreasing the INR from 5-10 to the therapeutic range within 24 to 48 hours without creating resistance to further therapy. The use of small parenteral (administered subcutaneously or intravenously) doses of phytonadione (1.0 mg) may also be useful; however, it is more expensive and carries the risk of adverse effects if administered intravenously. If more prompt reversal is required, larger doses of phytonadione (5-10 mg) or the use of fresh frozen plasma (FFP) may be necessary.

Management of Anticoagulation During Surgery

The risk of bleeding may be increased in patients undergoing certain surgical procedures. To avoid this complication, appropriate planning is essential. Many routine procedures can be performed without interruption of therapy and while the INR is within a therapeutic range. For example, certain dental procedures may be performed with the INR in the range of 2 to 3. Routine dental hygiene and simple extractions may also be performed within this range. If a procedure is an elective one, it may be delayed until the patient has completed the course of therapy, avoiding the need for interruption of therapy at all. Certain procedures carry little risk, but associated interventions may carry more significant risks. For example, sigmoidoscopy carries a small risk of bleeding; however, if a biopsy is performed, the biopsy site may bleed. Therefore it is necessary that good communication be established between the individuals managing the anticoagulation therapy and those performing the procedure. Many patients undergoing surgical procedures may have underlying cardiovascular conditions; therefore it is important to assure that appropriate antibiotic prophylaxis is instituted in these situations.

Drug Interactions

One of the most common causes of variation in the response to anticoagulants are drug interactions. Both over-the-counter and prescription medications may cause fluctuations in the INR. Drug interactions may occur via a number of different mechanisms; however, in general they can be classified as pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions occur secondary to medications that may not alter the INR, but interfere with normal blood clotting. The most common example is aspirin. Aspirin is commonly recommended in doses that are very small (e.g., 325 mg per day or less) for the prevention of acute coronary events and for the treatment of stroke. At these doses, aspirin does not interfere with oral anticoagulants' influence on the INR, but it does decrease platelet aggregation, and, as a result, may lead to easy bruising or bleeding from other sites. Aspirin may cause irritation of the gastric mucosa and lead to bleeding from the gastrointestinal tract. Aspirin use should generally be avoided in patients taking warfarin (Coumadin®), although it is appropriate for some patients. Acetaminophen (Tylenol®) has historically been felt to be the safest alternative for anticoagulant patients requiring an analgesic or antipyretic. However, a recent report suggests that consuming more than 7 regular-strength tablets per week may result in an increase in the anticoagulant effect of warfarin. Patients ingesting acetaminophen should be monitored carefully and, more importantly, should be advised to report any condition that requires chronic acetaminophen consumption.

Pharmacokinetic interactions with warfarin are those that result from drugs that interfere with the absorption, distribution, metabolism or excretion of warfarin. These interactions are more likely to result in a change in the INR and subsequently lead to either bleeding or thrombosis. The most common classes of drugs that interfere with warfarin via this mechanism are the histamine-2 antagonists (e.g., cimetidine), some anti-infectives (e.g., the sulfonamides, including trimethoprim/sulfamethoxazole

[TMP/SMX]), the macrolides, (e.g., erythromycin or metronidazole), nonsteroidal anti-inflammatory drugs (NSAIDs) and barbiturates. Many other medications have been reported to interfere with warfarin. Therefore, the best advice is to view suspiciously the addition or withdrawal of *any* drug from the regimen of a patient taking warfarin.

Certain questions should be answered prior to adding any medications that are likely to interact with warfarin to the regimen of a patient taking warfarin. First, it should be established that there is a clear-cut indication for the new drug. If there is a need for the medication, the time course of the interaction should be characterized. If the interaction is delayed, it may be missed if the INR is checked too soon. Conversely, if the interaction occurs early, waiting too long may miss the change. In most cases, the preferable approach is to avoid drugs that are known to interact with warfarin. However, in many cases, with proper monitoring and in some cases, adjustment of the warfarin dose, the interacting drug can still be used.

Additional Factors That Influence Anticoagulant Response

Factors other than interacting medications may alter the response to anticoagulant therapy. Changes in vitamin K intake or metabolism can influence the patient's response to warfarin. In order to minimize such changes in response, dietary vitamin K intake should be stabilized. It is not necessary to avoid vitamin K-containing foods, and in many cases patients can even maintain vegetarian diets without a need to alter the dose of warfarin. Patients who develop acute gastroenteritis or loss of appetite can develop relative vitamin K deficiencies very quickly. When this happens in association with warfarin therapy, it may result in significant elevations in the INR very quickly. If there is an associated fever, the potentiation of the INR may be exaggerated. Patients who cancel scheduled clinic appointments because of acute illness that includes diarrhea or loss of appetite for more than a day or two, or febrile illness that has been present for more than a day or two, should be evaluated very carefully for bleeding and seen promptly. Patients should be instructed to look very carefully at the ingredients of any supplemental vitamins or health foods for the presence of vitamin K, or to ask for information on similar products known not to contain vitamin K. Patients should also be interviewed for any new illnesses or conditions that may alter the response to warfarin, such as alterations in thyroid status. Patients who are chemically euthyroid and are taking thyroid medications should not demonstrate an altered response.

Conclusion

Safe anticoagulation therapy is dependent upon the development of a "partnership" between the patient and health care provider. Because of their knowledge of drug interactions and the influence of multiple variables on the response to warfarin, pharmacists are in a unique position to partner with patients.

References for this article are available upon written request to: California State Board of Pharmacy, Attn.: Health Notes Anticoagulation References, 400 R Street, Suite 4070, Sacramento, CA 95814.

Risk Management of Warfarin Anticoagulation



Robert T. Weibert, Pharm.D.
Clinical Professor,
University of California
San Francisco School of Pharmacy,
San Diego Program, and Anticoagulation
Clinic Director, University of California
San Diego Medical Center

The risks associated with warfarin therapy include adverse health outcomes for the patients, financial costs for the payors and patients and malpractice issues for health professionals.

Thromboembolic Complications

A therapeutic failure of warfarin treatment leading to venous or arterial thromboembolism can occur from insufficient anticoagulation. Causes of insufficient anticoagulation are noncompliance, an inadequate dose and/or failure to properly monitor and adjust warfarin therapy. Patients with recent venous thromboembolism have a critical risk for rethrombosis during the first 30 days, and inadequate anticoagulation must be avoided. Active malignancy also increases the risk of recurrent thrombosis. Patients should be able to recognize the signs and symptoms of thromboembolic complications (Table 1) and know when and where to get emergency help.

Table 1.
Warning Signs and Symptoms of Venous Thromboembolism

- Increased swelling of a leg or arm.
- Recent development of or increasing pain in a leg or arm.

Patients receiving warfarin therapy for the prevention of systemic embolism from atrial fibrillation, prosthetic heart valves, valvular heart disease, cardiomyopathy or other conditions should be able to identify the warning signs and symptoms of acute stroke. Recent studies indicate that many patients are unaware of stroke signs and symptoms which are listed in Table 2.

Table 2.
Warning Signs and Symptoms of Stroke

- Sudden weakness or numbness of the face, arm or leg on one side of the body.
- Sudden dimness or loss of vision, especially in only one eye.
- Sudden difficulty in speaking or understanding speech.
- Sudden, severe headache with no known cause. Particularly if the headache is the “worst headache ever” or if the patient does not regularly experience headaches.
- Unexplained dizziness, unsteadiness or sudden falls.

Bleeding Complications: Excessive Anticoagulation

The most frequent complication of warfarin therapy is bleeding. The risk of bleeding is dramatically increased by excessive anticoagulation when the INR is greater than 5.0, and an INR greater than 6.0 is a medical urgency. Bleeding complications can also develop with “therapeutic anticoagulation” in high-risk patients or during high-risk situations. The gastrointestinal tract is the most frequent site of major bleeding from anticoagulant therapy, accounting for up to 50% of all episodes. Intracranial bleeding is the most dangerous type of anticoagulant-related bleeding, with up to a 50% mortality rate. Patients need to be able to recognize the signs and symptoms of bleeding complications and know when and where to get emergency help (Table 3).

Table 3.
Warning Signs and Symptoms of Bleeding

- Epistaxis: prolonged or extensive nosebleed
- Gastrointestinal bleeding: dark or black stools (melena), abdominal pain or vomiting “coffee grounds” (hematemesis)
- Gingival bleeding: prolonged oozing from gums
- Hematoma: soft tissue swelling and bruising
- Hematuria: dark brown (tea-colored) or bloody urine
- Hemoptysis: coughing blood (often from posterior epistaxis)
- Hemorrhoidal bleeding: bright red rectal bleeding (hematochezia)
- Intra-articular bleeding: acute joint pain and swelling
- Intracranial bleeding: symptoms of an acute stroke
- Menorrhagia: prolonged, excessive vaginal bleeding
- Hemorrhagic ovarian cyst: sudden severe abdominal pain, usually at midcycle
- Subconjunctival bleeding: bloody red eye without pain or loss of vision
- Retroperitoneal bleeding: severe flank pain from internal bleeding

Excessive anticoagulation without active bleeding is a high risk situation that can be readily corrected with adjusted low-dose oral vitamin K, or, alternatively, if the INR is greater than 5 but less than 9, by withholding warfarin (Table 4). Patients at a higher risk of bleeding should be given vitamin K, while patients who have increased thrombotic risks may be managed by withholding warfarin and daily monitoring of the INR.

Table 4.
Correction of Excessive Anticoagulation Without Bleeding

INR 5.0-5.9	0.5 mg vitamin K p.o.
INR 6.0-9.9	2.5 mg vitamin K p.o.
INR > 10	5.0 mg vitamin K p.o.

- Active bleeding requires higher doses of vitamin K to reverse anticoagulation.
- Serious bleeding requires parenteral vitamin K.
- Major bleeding requires IV vitamin K and fresh frozen plasma or prothrombin complex concentrate.

Bleeding Complications: High-Risk Patients

Any concurrent conditions that increase bleeding will place patients at a higher risk for bleeding complications (Table 5). Individual patient evaluation is needed to determine if the increased risk makes the patient a poor candidate or contraindicates warfarin therapy. For some patients, safety may be improved by protective cotherapy. All patients at higher bleeding risk need more frequent INR and CBC monitoring.

Table 5.
Conditions that Increase the Risk of Bleeding Complications

- History of gastrointestinal bleeding
- History of stroke
- Severe anemia (hematocrit < 30%)
- Comorbid diseases: renal insufficiency, hepatic dysfunction, recent acute myocardial infarction
- Alcohol abuse
- Concurrent NSAID or corticosteroid use
- Malnutrition
- Active malignancy
- Age > 80 years

Bleeding Complications: High-Risk Situations

Any disruption of normal vascular integrity from surgery or trauma establishes a bleeding site, and anticoagulation will increase the extent of bleeding. Excessive anticoagulation with an INR greater than 5.0 also increases bleeding risk. Any changes in dose, diet, drugs or disease can alter anticoagulation control causing insufficient or excessive anticoagulation. Common high-risk situations are listed in Table 6.



Table 6.
High-Risk Situations for Bleeding Complications

- Excessive anticoagulation (INR greater than 5.0)
- First 30 days of warfarin treatment
- Acute illness: congestive heart failure, gout, pneumonia
- Changes in concurrent drug therapy
- Dietary changes
- Dental surgery
- Invasive medical procedures: biopsy, polypectomy
- Surgery
- Trauma

Successful Anticoagulation

Successful anticoagulant therapy is the absence of thromboembolic or hemorrhagic complications. Therapeutic failures and bleeding complications are dramatic and have led to the perception that warfarin is a “very dangerous drug.” The rate of complications can be greatly reduced when health professionals and patients have a better understanding of how to monitor and adjust warfarin therapy and how to anticipate potential problems.

Recommended Reading

1. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998; 105: 91-99.
2. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest* 1998; 114: 511S-523S.

Part Three:

The Importance of a Collaborative Approach: The Anticoagulation Team



Richard H. White, M.D.
Professor of Medicine
Chief, Division of General Medicine
Medical Director, Anticoagulation Service
UC Davis School of Medicine

Pharmacists play an important role in managing anticoagulation therapy, both among hospitalized patients and outpatients. Trained in the basic pathophysiology of blood clotting and the essentials of clinical clotting disorders, pharmacists bring their expertise in clinical pharmacology and knowledge of drug interactions to the arena of patient management. Most physicians do not have the pharmacology training necessary to optimally manage dangerous anticoagulants like warfarin. Many learn strictly by practice, but this can be dangerous if only a few patients are treated each year.

At UC Davis Health System, we have created an anticoagulation service staffed by a number of highly-skilled clinical pharmacists. These pharmacists evaluate and manage essentially all hospitalized patients treated with warfarin, as well as most patients treated with full dose heparin or low molecular weight heparin. The pharmacists give the attending physicians and house-staff important information about potential drug interactions, in addition to daily dosing recommendations. The pharmacists have taken a central role in identifying and educating patients who are candidates for home treatment of venous thrombosis. Many anticoagulation clinics are staffed only by pharmacists, and there is no indication that practice this has led to anything except excellent care. In our anticoagulation clinic, we utilize a nurse practitioner and several pharmacists. We feel this combination provides truly optimal care for a population of patients that carries a high level of comorbidity.



Roles of Other He



William Dager, Pharm.D., FCSHP
Pharmacist Specialist,
Pharmacokinetics/Anticoagulation,
UC Davis Medical Center, Sacramento
Associate Clinical Professor of Pharmacy,
UCSF School of Pharmacy
Assistant Clinical Professor of Medicine,
UC Davis School of Medicine



Kathleen Mahackian, Pharm.D., FCSHP
Clinical Pharmacist, UC Davis Medical Center,
Sacramento, and Assistant Clinical Professor,
UCSF School of Pharmacy

Health Care Professionals

During the course of anticoagulation therapy, a variety of health care professionals is involved with a patient's care. As has been addressed in other sections of this publication, the **pharmacist's role** is multifactorial and can include, but is not limited to, the choice, monitoring, dosing and provision of drug, patient education, drug interaction screening and research. However, it is important to also recognize the impact of **other** health care professionals.

Physicians have long been involved in caring for the anticoagulated patient. The role of the physician can vary from that of a primary care physician to that of an anticoagulation clinic medical director. For the primary care physician, caring for the anticoagulated patient requires constant vigilance and frequent laboratory follow-up. The burden this causes has created opportunities for other health care providers. Clinics staffed by nurses, pharmacists or nurse practitioners have demonstrated that they can have a positive impact on patient care.^{1,2} These clinics are usually under the direction of a physician, and the health care professionals providing the care operate under approved protocols.

The **nurse's** role has expanded to include more than the traditional tasks of drug administration and the drawing of blood for laboratory tests. Nurses are often also responsible for providing patient education, assessing patients for adverse effects or adjusting doses under protocol. Nurses function in a variety of settings, including inpatient areas, outpatient clinics, physician offices, extended care facilities and home health care settings. The nurse's role in each of these settings will vary, depending on each organization's policies.

Lab personnel are involved in the process of determining laboratory results. Tasks include obtaining and transporting a patient's blood sample and setup, calibration and quality assurance of the testing apparatus. Lab personnel are also involved with the reporting and documentation of test results. Notifying the health care provider of critical values is an essential part of their job. Timely notification can lead to prompt action and can result in a decreased incidence of complications. The **medical**

technologist's knowledge of assay interference, biases encountered in particular assays, and the identification of unexpected lab results can be invaluable. The expertise of lab personnel can also be very helpful when evaluating point-of-care devices.

The interactions of warfarin and food provide **dieticians** a role on the anticoagulation team. The impact of diet on warfarin response is well-documented. It is the dietitian's role to work with the patient to ensure a healthy, well-balanced diet that minimizes complications.

Other support personnel are frequently forgotten because they work behind the scenes, but their efforts are also invaluable. The availability of up-to-date dosing and laboratory data for clinic visits is necessary for good clinical decisions. The individuals who work in **medical records** contribute to patient care by assuring that all lab results are placed in patients' charts as soon as possible. Medical records personnel are also responsible for assuring that the patient's chart is delivered to the appropriate clinic on the day of the patient's appointment. **Individuals who schedule appointments and follow-up** if the patient does not show are essential in keeping track of the sometimes-wayward patient. **Discharge planners, home health liaisons, and administrators** are other individuals who serve as critical links in the provision of quality patient care.

The ability of individuals from different professions to perform as a team will ultimately determine the success or failure of an anticoagulation team. An anticoagulation team will also find it difficult to achieve optimal outcomes if good patient care is not continued at home. Therefore, it is important not to underestimate the role of **family and friends**, which is extensive. These caregivers serve as a valuable resource in assuring that quality patient care occurs.

References for this article are available upon written request to: California State Board of Pharmacy, Attn.: Health Notes Anticoagulation References, 400 R Street, Suite 4070, Sacramento, CA 95814.

Part Four:

Establishing Anticoagulation Services



PHARMACIST ANTICOAGULATION MANAGEMENT SERVICES: Improving Outcomes & Controlling Costs



Robert T. Weibert, Pharm.D.
Clinical Professor, University of California San Francisco School of Pharmacy, San Diego Program, and Anticoagulation Clinic Director, University of California San Diego Medical Center



David S. Adler, Pharm.D.
Professor of Clinical Pharmacy, University of California San Francisco, School of Pharmacy; University of California San Diego Medical Center; and VA Medical Center Anticoagulation Clinics

Pharmacist-managed anticoagulation clinics began in the 1970s and are currently the most widespread and successful collaborative drug therapy management programs. Warfarin has a narrow therapeutic index, and tight control of the intensity of anticoagulation is needed to avoid thrombosis from inadequate anticoagulation or bleeding from excessive anticoagulation. Standard dosing is not feasible because of a greater than tenfold variability in dose-response among patients and a substantial inpatient variation over time. Warfarin is a vitamin K antagonist, and the intensity of warfarin anticoagulation changes as a result of dietary modifications. The intensity of warfarin anticoagulation is also altered by drug interactions and disease interactions. In addition, controlled interruption of anticoagulation is needed for surgery, dental surgery and invasive medical procedures. Thus, regular monitoring of the intensity of anticoagulation and proper warfarin dose adjustment are needed to assure safe and effective therapy.



care costs. Accumulating evidence indicates that warfarin management is improved when provided through a dedicated anticoagulation management service (AMS) rather than through routine medical care. Routine medical care (RMC) is typically physician office-based, with telephone follow-up after central laboratory testing. A review of coordinated anticoagulation management services (AMS) showed a 4.6% incidence of major bleeding and a 4.8% incidence of thrombosis.² Direct comparisons of RMC versus AMS in single institutions reported through 1996 are shown in Table 1.² A more recent single institution comparison between a pharmacist-managed anticoagulation clinic and physician RMC found a reduction in major to fatal bleeding (1.6% vs. 3.9%) and thromboembolism (3.3% vs. 11.8%).³ Associated reductions in hospitalizations and emergency department visits resulted in an annual cost savings of \$162,058 per 100 patients.³

Outcomes and Cost-Avoidance from Anticoagulation AMS

Since 1977, the University of California San Diego Anticoagulation Clinic (UCSD AMS) has continuously provided anticoagulation management services. Clinical endpoints of anticoagulation control (INR) and clinical outcomes of bleeding and thrombosis are monitored in order to improve patient management and outcomes. In 1996, there were 424 patients followed in the UCSD AMS for management of oral anticoagulant therapy. Monitoring included evaluation of 3,862 INR determinations, with 68% of the INR values between 2.0 and 4.0. Ninety-two percent of all patients were free of significant bleeding or thrombotic complications.⁴ The outcomes for the Rochester, Minnesota, RMC and the 1996 UCSD AMS were during an equivalent number of patient-years of anticoagulation treatment (Table 2), providing an RMC group for comparison.⁵

Reduction in Bleeding Complications

Major bleeding complications with routine medical care (RMC) occurred at 7.4% and 8.1% per patient-year in studies from Harvard⁵ and Rochester, Minnesota, respectively.⁶ From 1990 through 1996 an average of 2.1% of patients managed by the UCSD AMS developed a major bleeding complication. During 1996, major bleeding occurred at an incidence of 2.7% per patient-year in the UCSD AMS.⁴ Compared to the major bleeding rate of 8.1% in RMC in Rochester, the 1996 UCSD AMS major bleeding rate of 2.7% prevented one major bleeding episode per year for every 18.5 patients.

Warfarin, the primary oral anticoagulant agent prescribed in the United States, has proven effective in preventing primary and recurrent venous and arterial thromboembolism in a variety of clinical disease states. These disease states include venous thromboembolism (venous thrombosis and pulmonary embolism), atrial fibrillation, dilated cardiomyopathy, prosthetic heart valves, valvular heart disease, arterial bypass grafts, arterial embolism, stroke, myocardial infarction and primary pulmonary hypertension.¹

The efficacy and safety of warfarin correlates with the prothrombin time measurement expressed as the international normalized ratio (INR). INR values less than 2.0 are often ineffective and are associated with an increased risk of thromboembolic events. INR values greater than 5.0 are associated with an increasing risk of bleeding; INR values above 6.0 represent a medical urgency due to the risk of gastrointestinal or intracranial hemorrhage, as well as bleeding at other sites. As a result, the therapeutic anticoagulation guideline recommended by the American College of Chest Physicians (ACCP) is a target INR of 2.5 (range 2.0 - 3.0), except for specified mechanical prosthetic heart valves, where the target INR is 3.0 (range 2.5 - 3.5).¹ The intensity of anticoagulation appears to be the most important determinant of both bleeding and thromboembolic risk, and maintaining the INR within a therapeutic range is critical.

Anticoagulation Management Services

Optimal management of anticoagulated patients reduces therapeutic failures and bleeding complications, thereby improving patient outcome and reducing hospitalizations and overall health

Table 1:

Comparison of RMC Versus AMS Within Single Institutions					
	N	Pt-Years	Major Bleeding per 100 Pt-Yrs	Thrombosis per 100 Pt-Yrs	Cost Savings ^a per 100 Pt-Yrs
RMC	480	941+	10.9	16.2	-
AMS	562	993+	2.8	2.4	\$ 226,350

a. The projected cost savings based on published costs of \$7,500 per bleeding episode and \$12,000 per thrombotic episode.²

Reduction in Thrombotic Complications

Thrombotic complications developed in 8.1% in the Rochester study.⁶ In 1996, the UCSD AMS had a rate of thromboembolism of 4.9%. Compared to the thrombosis rate of 8.1% in RMC in Rochester, the UCSD AMS incidence of thromboembolism of 4.9% prevented one episode of thromboembolism per year for every 31 patients.

Cost-Avoidance

Compared to the outcomes of patients managed by RMC at Rochester the UCSD AMS (for an equivalent number of patient years of treatment) had 12 fewer major bleeding episodes and seven fewer thrombotic episodes. The complication rates and cost savings per 100 patient-years are shown in Table 2.

The UCSD AMS cost savings estimate was \$789 per patient-year; however, this may underestimate current costs. The actual average cost available for six cases of major bleeding in 1995-96 was \$17,183. At this cost, the savings from avoidance of bleeding alone is \$92,788, and the cost savings from thrombosis remains \$38,400. The total cost savings is then \$131,188 per 100 patient-years (\$1319 per patient-year). Other estimates of the cost savings from preventing major bleeding and thromboembolism with an anticoagulation management service range from \$800 to \$1621 per patient-year.^{2,3}

Summary

Anticoagulation management services (AMS) improve patient outcome by providing:

- Increased patient compliance.
- Improved warfarin dose regulation, better control of anticoagulation with a higher percentage of INR values within a therapeutic range and a reduced percentage of subtherapeutic or excessive INR values.
- Rapid correction of subtherapeutic or excessive anticoagulation.
- Systematic tracking of patients who fail to keep monitoring appointments.
- Computerized data management for evaluation of anticoagulation control and quality improvement.
- Systematic and continuous patient education.
- Early identification of clinical conditions that increase the risk of thrombosis or bleeding.
- Increased patient satisfaction.



Annually, more than two million patients are treated with warfarin, and, with the aging of the US population and expanded evidence of benefit in treating patients with atrial fibrillation, congestive heart failure and myocardial infarction, the number of patients treated with warfarin is expected to increase. Anticoagulation management services are mandatory for all patients in The Netherlands and have been adopted by many university, managed care and VA health systems. Pharmacist anticoagulation management services are collaborative drug therapy management programs which aid primary care physicians by assuming the responsibility for the essential micro-management of warfarin anticoagulation therapy. Available evidence demonstrates that pharmacist-managed anticoagulation services improve patient outcomes, reducing hospitalizations and emergency care for both bleeding and thrombotic complications and leading to a decrease overall health care costs.

References for this article are available upon written request to: California State Board of Pharmacy, Attn.: Health Notes Anticoagulation References, 400 R Street, Suite 4070, Sacramento, CA 95814.

Table 2:

Clinical Outcomes and Cost Avoidance

	N	Pt-Years	Major Bleeding ^b per 100 Pt-Yrs	Thrombosis per 100 Pt-Yrs	Cost Avoidance ^c per 100 Pt-Yrs
RMC ^a	261	221	8.1	8.1	-
UCSD 1996	424	223	2.7	4.9	\$ 78,900

a. The RMC rate of complications reported by Gitter et al.⁵

b. Major bleeding defined by criteria of Landefeld.⁶

c. The projected cost-savings based on published costs of \$7,500 per bleeding episode and \$12,000 per thrombotic episode.² The annual cost savings for the 223 patient-years of treatment in 1996 was \$174,756.



Creating a Comprehensive Anticoagulant Care System



Kathleen Mahackian, Pharm.D., FCSHP
Clinical Pharmacist,
UC Davis Medical Center, Sacramento, and
Assistant Clinical Professor,
UCSF School of Pharmacy



Jennifer Branch, Pharm.D.
Clinical Pharmacist,
UC Davis Medical Center, Sacramento, and
Assistant Clinical Professor,
UCSF School of Pharmacy

The pharmacists working within the UC Davis Health System provide comprehensive anticoagulation services, including the management of anticoagulation therapy for patients in acute care, home health care and outpatient settings.

Acute Care Anticoagulation Services

In 1995, warfarin was responsible for 16% of the drug-related admissions to UC Davis Medical Center hospital. Many of these adverse drug reactions were the result of patients not fully understanding how to take their warfarin, or failing to realize the importance of their follow-up laboratory or clinic visits. In response to these problems, the Pharmacy and Therapeutics Committee within our health system approved the establishment of a “Pharmacy/Internal Medicine Anticoagulation Service.” This new clinical service was eventually linked with the already established Outpatient Anticoagulation Clinic. This team’s members include inpatient pharmacists, a nurse practitioner and an attending physician. Successful implementation of this program has lowered costs by decreasing the length of hospital stay.

The acute care setting offers pharmacists a variety of opportunities to become an integral part of the anticoagulation team. Chart review, interpretation of laboratory results, recommendations for warfarin or heparin dosage adjustments and physician and patient education are all responsibilities well-suited for management by inpatient pharmacists. By applying the principles of pharmaceutical care to the care of these patients, pharmacists can improve drug efficacy, achieve dosing consistency, anticipate and/or prevent significant drug interactions or adverse drug reactions and thereby improve the quality of care.

At UC Davis Health System, a pharmacist evaluates each patient prior to dispensing the patient’s first dose of warfarin. The patient’s chart is reviewed to 1) determine the indication for anticoagulation, 2) establish a target INR, 3) identify significant social and/or medical history, 4) review prior warfarin dosing history, 5) identify possible interacting medications and 6) determine whether there is a prior history of bleeding complications. Because patients on warfarin commonly require frequent or multiple dosage adjustments, chart review alone cannot be relied upon as the sole source of information. When the pharmacist obtains a drug history from the patient or



caregiver, it is also important to assess the reliability of the information, i.e., is the patient or family member a good historian?

When initiating therapy, a patient may sometimes exhibit sensitivity to warfarin, with a resulting rapid and dramatic increase in his/her INR. A patient who responds with a “therapeutic INR” after only one to two doses of warfarin should not be viewed as “stable” and subsequently be discharged. The pharmacist should use this opportunity to educate physicians and nurses that large INR increases early in therapy can lead to supratherapeutic INRs and can place the patient at risk for bleeding. If discharged, these patients need close (often daily) monitoring and follow-up of their INRs. This provides pharmacists an opportunity to interact with the medical and nursing staff frequently.

The acute care pharmacist working on the Anticoagulation Service at our health-system evaluates as many as 38 patients daily. “Following” a patient includes close monitoring of each patient’s progress and making changes, or providing recommendations for changes, as needed. Examples include providing dosing recommendations, screening orders for drug interactions and monitoring for adverse drug events. All of these pharmacodynamic and pharmacokinetic observations are discussed with the physicians.

Our initial efforts to incorporate a pharmacist into the anticoagulation process involved the provision of education to inpatients who had been started on warfarin therapy.

If patient education was not feasible during the initial contact, the pharmacist attempted to provide educational materials to the warfarin patient within 72 hours of initiating therapy. While there are many causes of adverse drug reactions, we have found that improving patient education has been extremely important in decreasing the number of admissions due to adverse events associated with warfarin therapy.

Our Pharmacy Anticoagulation Team has identified the transition of a patient from inpatient to outpatient status as a critical process. It is not uncommon for patients to be discharged on warfarin before they are stabilized on a particular dose; therefore, it is crucial that these patients be followed closely after they are discharged. At least some of the rehospitalizations of warfarin patients are the result of inadequate follow-up after discharge. To assist with this transition process, the pharmacist assigned to our inpatient anticoagulation service reviews the discharge plans for all warfarin patients to insure that the appropriate referrals are made (e.g., to the Anticoagulation Clinic or to their primary care physicians). The pharmacist also reviews the patient’s discharge prescriptions at this time to assure appropriate warfarin dosing and to prevent drug interactions.

The pharmacist consults with all venous thrombosis or pulmonary embolism patients to determine whether they are candidates for home treatment with low molecular weight heparin, using criteria

developed by our Pharmacy Anticoagulation Team. Patients who are identified as good candidates for home treatment receive thorough education regarding self-administration of low molecular weight heparin, as well as warfarin drug administration. Pharmacists are also often called upon to identify and resolve problems associated with funding these patients' therapies.

Our Pharmacy Anticoagulation Team is also available for consultation on the dosing of both intravenous and subcutaneous heparin; however, these consults account for a small percentage of our patients. We also evaluate patients undergoing orthopedic procedures who are placed on subcutaneous heparin. Because these patients are frequently discharged while still on heparin, they require special education about the risks, benefits, side effects and injection technique associated with this therapy.

As part of daily activities, the inpatient pharmacist reviews a computer printout of patients' INRs that exceed 1.2. If any patient has an INR of greater than 6, the pharmacist will review the patient's history, assess the cause, and recommend a management plan. The case is discussed with an attending physician, and the final recommendations are included in a consult note written by the pharmacist. The primary goal of this activity is to educate the resident physicians and prevent inappropriate reversal of high INRs with large doses of vitamin K.

As with any process, it is important to continually monitor the quality of the service being offered. Since the anticoagulation team follows all patients receiving warfarin or low molecular weight heparin, bleeding complications are reported via our Medication-Related Event Program and each case is reviewed. Difficult cases, complications and recent publications are discussed at monthly Journal Club/Case Conference meetings. These meetings are open to members of the Anticoagulation Team, as well as to other interested pharmacists and physicians. Data concerning patient complications (INRs greater than 6 and bleeding episodes) are forwarded to the continuous quality improvement (CQI) pharmacist for tracking purposes. If a problem in the system is identified, corrective action is implemented. Often this process has identified opportunities for staff education (pharmacist, nursing and/or physician). The complications, as well as the corrective actions, are tabulated and documented in a quarterly report. Significant findings are presented to the Pharmacy and Therapeutics Committee. An annual report is also submitted to the Quality of Care Committee.

The inpatient pharmacists at our health-system perform a variety of tasks meant to improve the outcome of patients receiving warfarin or low molecular weight heparin (Figure 1). Adding pharmacist input regarding dosing warfarin has been widely accepted by other health care providers. A successful anticoagulation team relies on physicians, nurses, nurse practitioners and pharmacists working together to improve the quality of patient care. Our quality improvement program has documented that INRs greater than 6 and warfarin-related admissions have decreased since the Anticoagulation Service was started. Warfarin-related admission rates have decreased by as much as 50%. Data collection to show the impact of the Service on patient outcomes is ongoing. It is evident that an inpatient pharmacist can be a valuable asset to an anticoagulation team.

Figure 1. Inpatient Pharmacist Activities

- Evaluate new warfarin patients before dispensing first dose
- Recommend warfarin doses on each patient daily
- Review computer-generated list for INRs >6
- Evaluate and write consult note on all patients with INRs >6
- Evaluate and report all adverse drug reactions
- Educate all warfarin patients within 72 hours of initiating therapy
- Facilitate referrals to Anticoagulation Clinic
- Assess all discharge doses of warfarin
- Evaluate all requests for low molecular weight heparin
- Educate all low molecular weight heparin (LMWH) patients on the risks, benefits, side effects and injection technique associated with this therapy.
- Facilitate home health and Anticoagulation Clinic referrals for LMWH patients
- Adjust heparin dosing on selected patients

Home Health Anticoagulation Services

Home health agencies provide health care services at home for patients of all ages. Services can range from a single visit to ongoing treatment over several months. Our Anticoagulation Clinic operations include the management of homebound patients and frequently utilize the services of home health agencies. These agencies act as an extension of the clinic and are expected to provide the same quality of care to homebound patients as is provided to clinic patients.

Where cooperative arrangements such as this exist, it is important for the respective parties (in this instance, the home health agency and the Anticoagulation Clinic) to have clearly defined responsibilities and expectations. Our Anticoagulation Clinic provides each home health agency with written instructions that delineates what is expected from the nurse when reporting INRs (see Figure 2). Limited guidelines which describe our standards of practice are also provided to the home health agency (Figure 3). Anticoagulation Clinic staff, working with laboratory personnel, provide the home health agency staff with training and competency assessment on the use of point-of-care testing devices.

Our health-system requires that the visiting nurse evaluate the homebound patient in much the same way as is done if the patient is seen in the Anticoagulation Clinic. This means that the visiting nurse's routine should include a medication history, assessment of compliance with the medication regimen, identification of any refills needed, assessment of the patient for hemorrhagic or thrombotic complications, patient education and any needed laboratory tests. The fact that these patients can be followed at home can shorten hospital stay, prevent admissions to long-term facilities and improve the patient's quality of life.



Figure 2.
Home Health Nurse Report

- RN name
- Agency name and phone number
- Date and time of blood draw
- Method of testing: specify “Coagucheck” or lab test results: PT and INR
- Dosage regimen and compliance history (Report how patient is actually taking drug, not what has been ordered.)
- Any other information pertinent to anticoagulation therapy (e.g., nausea, vomiting, diarrhea, new medications, signs/symptoms of bleed or clot)

Figure 3.
Home Health Nursing Guidelines for Anticoagulation Clinic Patients

- RN to retrieve lab results before the end of day
- For labs drawn late, results may be called in the next morning
- Clinic to interface with RN only (RN will interface with lab and patient)
- INRs > 4, RN may hold warfarin until orders received
- INRs > 5, hold warfarin and page anticoagulation clinic personnel
- RN to refer patient to ER for active bleeding, symptoms of clot (notify clinic if patient is referred or admitted)
- RN to notify clinic if patient requires refill of warfarin

Outpatient Anticoagulation Clinic

The primary goal of an anticoagulation clinic is to reduce the costs associated with the care of patients on anticoagulant therapy by minimizing the incidence of thromboembolic events and hemorrhagic complications. This goal is accomplished by providing a comprehensive set of services that includes monitoring and close follow-up on all patients, education of patients and other health care professionals and specific clinical advice. The benefits of anticoagulation clinics are well documented throughout the literature. Some examples are provided in Table 1.

Table 1.
Articles Describing the Benefits of Anticoagulation Clinics

1. Conte, et al
Warfarin therapy managed by a pharmacist in the clinic resulted in a level of anticoagulation control and morbidity that was acceptable to the physicians associated with the clinic and to the clinic’s patients’ primary care physicians.¹
2. Cortelazzo, et al
An anticoagulation clinic offers a real advantage to patients with mechanical heart valve prostheses in terms of prevention of thromboembolic events and hemorrhagic complications.²
3. Ellis, et al
An inpatient pharmacy-managed warfarin monitoring service improved the warfarin dose determination, patient stability and increased the number of patients referred to the anticoagulation clinic.³
4. Garabedian-Ruffalo, et al
Patients received better treatment in a warfarin anticoagulation clinic staffed by a specially trained pharmacist than they did before they were referred to the clinic.⁴
5. Lee, et al
Warfarin patients monitored in a pharmacist-managed anticoagulation clinic had fewer warfarin related readmissions during the first 90 days after they were discharged from the hospital than did similar patients not seen in the clinic.⁵
6. Wilt, et al
A pharmacist-managed anticoagulation monitoring service in a family practice setting is cost-effective and results in improved outcomes.⁶

Many health care providers participate in the day-to-day activities of an outpatient anticoagulation clinic. In 1997, the Anticoagulation Forum* conducted a survey of, among other things, the type of health care providers participating in care and where anticoagulation management programs are located.⁷ The results of the survey showed that pharmacists participated in the management of anticoagulation care in a higher percentage of programs than any other health care provider, with the exception of physicians (Figure 4), and that most anticoagulation management programs were located in either hospital outpatient clinics or veterans hospitals (Figure 5).

Figure 4.
Types of Health Care Providers Participating in Anticoagulation Care⁷
(# of programs with type of provider / total # of programs)

Physicians	160 (99%)
Nurses	74 (46%)
Nurse Practitioners	25 (16%)
Pharmacists (Pharm.D.)	94 (58%)
Pharmacists (R.Ph.)	32 (20%)
Physician Assistants	5 (3%)
Health Assistants	22 (14%)
Other	43 (25%)

Reprinted with permission from the Anticoagulation Forum.

** The Anticoagulation Forum is a network of health care professionals committed to the therapy of thromboembolic disorders predominately through the venue of anticoagulation management services. The Anticoagulation Forum was founded in 1991 and currently has a membership of approximately 1300 individuals representing approximately 500 different anticoagulation management service (clinics). For more information, visit the website: www.aforum.org.*

Figure 5.
Location of Anticoagulation Management Programs⁷

Hospital Outpatient Clinics	37%
Veteran's Hospital	24%
Private Offices (group practice)	16%
Managed Care Organizations	9%
Other	5%

Reprinted with permission from the Anticoagulation Forum.

The physician, as the medical director of the anticoagulation clinic, is responsible for providing medical consultations and reviewing cases with the anticoagulation clinic staff. Pharmacists, nurse practitioners, nurses and physician assistants frequently function in similar roles in the anticoagulation clinic setting. In most cases these health care providers are operating under a medically approved protocol and work together in the clinic as a multidisciplinary unit. Their activities include, but are not limited to, patient education, obtaining drug histories, assessing patients for signs or symptoms of thrombotic or hemorrhagic complications, obtaining laboratory results (either by using a point-of-care testing device or by ordering the appropriate blood test), adjusting warfarin doses and authorizing refills of warfarin.

At UC Davis Health System, Richard H. White, M.D., established the Anticoagulation Clinic in 1984 and continues to function as its Medical Director today. The Anticoagulation Clinic is staffed with a full-time pharmacist and a nurse practitioner. The Department of Internal Medicine provides ancillary personnel to assist with the activities of the clinic. Health assistants and others schedule patients and track those who do not show up for their appointments.

In the Anticoagulation Forum survey, the mean number of patients managed per program was 366. Our Anticoagulation Clinic follows 550 to 600 patients. During a six-month period in 1998, the Anticoagulation Clinic evaluated and made recommendations on 3,300 INR values. Because the staff of the clinic are working under specific protocols, only anticoagulation issues are addressed. Patients with problems such as elevated blood pressure, high blood glucose or other acute health problems are

triaged and referred to a physician for evaluation in the acute care clinic.

Patients must be referred to the Anticoagulation Clinic by the physician who starts the patients on warfarin or other therapy. The patient can be seen in the clinic within 24 hours of referral, which is sometimes essential for the discharged patient who is not yet on a stable dose of warfarin. When the patient first arrives at the clinic, he/she is checked in at the front desk and vital signs are taken by the nursing staff. The patient is then called by the pharmacist or nurse practitioner to the exam room, where a complete history is taken. Medication lists are updated, and bleeding or thrombotic symptoms are assessed. An INR result is obtained via a point-of-care device (approved for use by pharmacists). Doses are adjusted, if necessary; a follow-up appointment is scheduled; and warfarin is refilled per protocol.

Our Anticoagulation Clinic operations also include the management of home-bound patients and patients using "outside" laboratory facilities. The home-bound patients are followed by a home health agency as described earlier in this article. Some patients use "outside" laboratory facilities. This form of management may be referred to as telemanagement. These patients agree to notify the clinic by voice mail whenever they have had an INR drawn (see Figure 6). The clinic's voice mail message requests that the patient leave 1) the name of the lab used and 2) his/her current warfarin dose. The pharmacist or nurse practitioner in the clinic obtains the laboratory results and, when necessary, makes appropriate adjustments in the dose. The health care provider calls the patient to verify compliance and to determine if any symptoms of bleeding or thrombosis are present. Instructions are then given to the patient regarding any changes in dose and when the next INR should be measured. Patients often feel that this method is more convenient than a visit to the clinic. They can visit a laboratory that is closer to where they, live and they can have the blood drawn at a time that is convenient for them, since they don't have to work around a scheduled appointment. Patients can also avoid the copay that is incurred for clinic visits. There can be problems with this system for patients who are unreliable, noncompliant, poor historians or unavailable by phone during normal working hours.

Table 2.

Studies Demonstrating Anticoagulation Clinic Cost-Effectiveness

Study	Anticoagulation Clinic Management	Other Anticoagulation Management	Savings
Gray, et al (1985) ⁸	0.48 hospital days per patient year	3.22 hospital days per patient year	\$860 per patient year
Wilt, et al (1995) ⁶	0 hospital days or ER visits per patient year	21 hospital days or ER visits per patient year	\$4,072 per patient year
Lee, et al (1996) ⁵	3 hospital admissions per patient year	15 hospital admissions per patient year	Not determined

A clinic staff member is available 24 hours a day, seven days a week, 365 days a year at our health-system. This allows clinic personnel to manage patients closely, which in turn can prevent emergency room visits. The clinic also follows deep vein thrombosis (DVT) patients discharged on low molecular weight heparin, allowing a decreased length of hospital stay in this population of patients. By saving hospital days and/or emergency room visits, the clinic is able to demonstrate its cost-effectiveness. Examples of such savings are summarized in Table 2.

Obtaining reimbursement for pharmacist services provided in the clinic presents many challenges. Medicare and Medicaid do not permit pharmacists to bill directly for warfarin monitoring services. Some pharmacists have been successful in getting reimbursed by private insurance companies, particularly those that offer comprehensive benefits that include preventive services. Pharmacists can contact individual private payers to establish contracts for providing monitoring services. Each third-party payer has to be contacted for the specific forms, certifications or procedures needed for reimbursement, because pharmaceutical care services have not yet been clearly defined by or gained general acceptance from these payers, and billing processes have not been standardized.⁹

Another key player on the “anticoagulation team” is the pharmacist who dispenses the warfarin to the patient. This pharmacist is sometimes in the best position to screen for drug interactions (and intervene before the first dose is administered), reinforce patient education and screen for compliance. Clinic personnel rely on this type of support when taking care of anticoagulation patients.

The ambulatory care setting provides pharmacists with wonderful opportunities to become integral members of the anticoagulation care team. Many clinics are staffed by pharmacists and or nurses working alone; however, at UC Davis Health System we believe that the optimum quality of care is provided by a multidisciplinary team, with each member bringing his/her own special area of expertise.

Figure 6. **Sample Patient Instruction Sheet for Patients Using Outside Labs**

1. When you go to the lab for your INR (anticoagulation blood test), it will be your responsibility to call the Anticoagulation Clinic that same day to inform us that you have gone to the lab.
2. Please do not go to the lab on Friday, Saturday or Sunday, if at all possible.
3. After you have gone to the lab, you may call the clinic from home. Please leave a message with your name, phone number, the date you went to the lab, the lab that you used, and the dose of warfarin that you have been taking.
4. Someone from the clinic will return your call within a maximum of 24 hours. You will receive a call from us each time you have gone to the lab to inform you of your results, provide you with new dosing instructions, and let you know when you need to go to the lab again. **If you do not receive a call, do not assume that your lab results were o.k.**
5. The anticoagulation voice mail line is open 24 hours a day, seven days a week. Do not wait until office hours to call to report that you have gone to the lab.
6. Please do not assume that the lab will be responsible for getting your lab results to us. It is your responsibility to call us, regardless of what you and the lab personnel have agreed upon.
7. If you have any questions regarding these instructions, please call us. We are here to help you!

Suggested Readings:

- Lee Y, Schommer JC. Effect of a pharmacist-managed anticoagulation clinic on warfarin-related hospital re-admissions. *Am J Health-Syst Pharm* 1996; 53:1580-3
- Ansell JE, Hughes R. Evolving models of warfarin management: anticoagulation clinics, patient self-monitoring, and patient self-management. *American Heart Journal* 1996; 132:1095-1100.
- ASHP Commission on Therapeutics. ASHP Therapeutic Position Statement on Antithrombotic therapy in chronic atrial fibrillation. *Am J Health-Syst Pharm.* 1998; 55:376-81.
- Vanscoy GJ, Coax WC. Oral anticoagulation: improving the risk-benefit ratio. *Journal of Family Practice* 1995; 41:261-69.
- Klepser ME, Herbert J. Evaluation of a systematic warfarin-dosing protocol. *P&T* 1994; 866-76.
- Lousberg TR, Witt DM, Beall DG, Carter BL, Malone DC. Evaluation of excessive anticoagulation in a group model health maintenance organization. *Arch Intern Med* 1998; 158:528-34.
- Cannegieter SC, Rosendaal FR, Wintzen AR, Van Der Meer FJM, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *New England J of Med* 1995; 333:11-17.
- Ellis R, Stephens M, Sharp G. Evaluation of pharmacy-managed warfarin-monitoring service to coordinate inpatient and outpatient therapy. *Am J Hosp Pharm* 1992; 49:387-94.
- Fihn S, McDonnell M, Martin D, Henikoff J, Vermes D, Kent D, White R. Risk factors for complications of chronic anticoagulation. *Annals of Internal Medicine* 1993; 118:511-520.
- Kent D, Vermes D, McDonnell M, Henikoff J, Fihn S. A model for planning optimal follow-up for outpatients on warfarin anticoagulation. *Med Decision Making* 1992; 12:132-141.
- References for this article are available upon written request to: California State Board of Pharmacy, Attn.: Health Notes Anticoagulation References, 400 R Street, Suite 4070, Sacramento, CA 95814.*

Specialized Services

IN A LONG TERM CARE SETTING



Laura Wong, Pharm.D.,
Director of Pharmacy Operations,
Propac Pharmacy Services, Inc., Santa Rosa, CA

*N*ursing home residents receive more medications than do noninstitutionalized older persons. With increasing pressure on hospitals to shorten acute-care stays and the increasing aging population, pharmacotherapy for the long term care patient has become an area of major importance. The use of medications in the nursing home represents a complex blending of issues from diverse realms of medical practice. The general patient is elderly, and atypical presentation of disease is common. The elderly patient usually presents with smaller lean muscle mass, reduced renal and hepatic clearance and is more sensitive to medications. All these intrinsic factors must be taken into consideration when assessing the nursing home patient for appropriate response to medication therapy.

PATIENT CARE TIPS

Warfarin monitoring in the elderly

- Elderly patients are more sensitive to medications, have less lean muscle mass and have reduced renal and hepatic clearance of drugs.
- Loading dose of warfarin is not recommended. Start slow and go slow.
- Monitor INR no less than every 3 days during dose changes, then weekly until the target INR is achieved, and every 4 weeks thereafter.
- For subtherapeutic INR, increase dose by 10-20% of weekly dose. Changes should be made as a percent of the weekly dose.
- For supratherapeutic INR, the dose is reduced by 10-20%. When the INR is excessively elevated, one or more doses may be held before resuming therapy at a lower dose.

Patients are provided with 24-hour clinical observation. The nursing home environment may include little physician input, particularly in relation to the severity and complexity of the patients cared for in the facilities. The actual care and decision-making process is initiated by the nurse (or a nursing aide). The nurse identifies the problem, assesses the patient and initiates a phone call to the physician. The physician at this point will either write or phone in a prescription.

This unique care setting provides a lot of opportunity for pharmacist involvement. Since 1974, the Health Care Financing Administration has required that a consultant pharmacist periodically review the drug regimen of all residents of skilled nursing facilities. The nursing home is the only component of the health care system where pharmacist involvement in monitoring drug use is required. The pharmacist's role in this setting can have major impact on the quality of patient care. The pharmacist educates the nurses on medication use, recommends appropriate drug therapy to the physician or nurse and identifies any potential problems related to medication usage.

Physicians may be hesitant to prescribe anticoagulation therapy to elderly patients for several reasons. Nursing home patients can have age-related increased sensitivity to warfarin. The elderly frequently have other diseases that can increase risks with anticoagulation therapy and often take several medications that interact with anticoagulation medications. Falls are common in the elderly and are a concern with this type of drug therapy.

Our pharmacy provides medications, supplies and clinical services to skilled nursing facilities. Pharmacists provide the monthly drug regimen reviews required of all nursing facilities. An anticoagulation clinic, OPTIMA (Optimising Patient Therapy In Medication Administration) was developed and has existed since in April 1997. The goals of OPTIMA are to provide accurate monitoring, maintain therapeutic INR range, and prevent bleeding complications.

Patients may be enrolled into OPTIMA in several ways. One option would be when the nurse identifies patients on warfarin therapy and contacts the anticoagulation pharmacist at Propac. During the monthly drug regimen review, the consultant pharmacist may also identify warfarin patients and enroll patients in the program. Some physicians will write an order to enroll the patient at the time that anticoagulation therapy is initiated.

The pharmacist faxes to the physician for signature a preprinted OPTIMA protocol that allows the pharmacist to monitor and adjust warfarin therapy. Once the patient is enrolled, the anticoagulation pharmacist gathers demographic information (i.e., age, diagnosis on admission, concurrent disease state, allergy information, etc.), indication for warfarin therapy, anticipated length of therapy and target INR. This information is then entered into the Coumacare Patient Management System (CPMS). The system serves as a means to record information on patients in an efficient and timely manner.

The pharmacist orders warfarin, monitors PT/INR and adjusts warfarin dosage as necessary to maintain or achieve target INR per OPTIMA protocol or as ordered by the physician. Laboratory results are faxed to the pharmacy. The INR results and warfarin dose are phoned to the nurse caring for the patient, and the pharmacist verifies the patient's medical condition and medication administration records with the nurse. The nurse then writes the new orders as verbal telephone orders. As a final step, the pharmacist faxes a hard copy of the verbal order to the nurse to be placed in the chart to serve as the chart order.

A licensed vocational nurse (LVN) performs monthly physical assessment on OPTIMA warfarin patients to ensure that medication is administered appropriately, that no adverse medication events are occurring, and that documentation is properly completed. The LVN reports all visits to the anticoagulation pharmacist.

All lab results are documented in CPMS. Warfarin dosing history is maintained in CPMS, and a graph of INR results is printed for the patient's primary physician. A letter is generated monthly to the patient's physician that summarizes the lab results and warfarin dosing history. This letter allows the physician to review the medication therapy provided by the anticoagulation pharmacist. The physician can fax or phone any changes to the registered nurse or to the pharmacy.

The OPTIMA anticoagulation program provides a prospective clinical service in the long term care setting. Pharmacist involvement in this setting is a required service that impacts directly on patient care. The patient's anticoagulation therapy is monitored closely to achieve therapeutic goals and avoid adverse events. All medication-related issues are reviewed to ensure appropriate and beneficial outcomes for each patient. This program is one of many in which pharmacist involvement improves the quality of patient care.

References for this article are available upon written request to: California State Board of Pharmacy, Attn.: Health Notes Anticoagulation References, 400 R Street, Suite 4070, Sacramento, CA 95814.



ANTICOAGULANT THERAPY

A Continuing Education Program for the Pharmacists of California
Universal Program # 113-126-99-026-H01 • 3 Contact Hours (0.3 CEU)



C O S P O N S O R E D B Y T H E :
California Pharmacists Association and the
California Society of Health-System Pharmacists



**Please enter your test answers
to each test question below:**

1. ____
2. ____
3. ____
4. ____
5. ____
6. ____
7. ____
8. ____
9. ____
10. ____
11. ____
12. ____
13. ____
14. ____
15. ____
16. ____
17. ____
18. ____
19. ____
20. ____
21. ____
22. ____
23. ____
24. ____
25. ____

DIRECTIONS FOR OBTAINING CE:

Read the article and take the test below to receive three (3) hours of continuing education credit. Return the entire test page and include a self-addressed, stamped envelope. Please note that the passing grade is 70%. If necessary, one test will be readministered.

This continuing education monograph is jointly sponsored by CSHP and CPhA
and you may return your answer sheet to EITHER:

California Pharmacists Association	California Society of Health-System Pharmacists
CE Exam	CE Exam
1112 I Street, Suite 300	725 30th Street, Suite 208
Sacramento, CA 95814	Sacramento, CA 95816

PLEASE NOTE: IT IS NOT NECESSARY TO SEND THE EXAM TO BOTH CSHP AND CPhA. SELECT ONE.

REMEMBER TO ENCLOSE A SELF-ADDRESSED, STAMPED ENVELOPE WITH YOUR TEST

How do you rate this course? (Excellent) 7 6 5 4 3 2 1 (Poor)	How well did this article meet its stated objectives? (Excellent) 5 4 3 2 1 (Poor)
--	---

How long did it take you to complete the reading and the test? _____ minutes.	Additional comments are appreciated.
--	--------------------------------------

Name: _____ CA license #: _____
ACPE#113-126-99-026-H01

If returning test to CPhA:

- I am a CPhA member. Enclosed is a check for \$10 payable to CPhA.
- I am not a CPhA member. Enclosed is a check for \$25 payable to CPhA.

If returning test to CSHP:

- I am a CSHP member. Enclosed is a check for \$10 payable to CSHP.
- I am not a CSHP member. Enclosed is a check for \$25 payable to CSHP.

CONTINUING EDUCATION CERTIFICATE OF COMPLETION

Date: _____ Course Name: Pharmacist Involvement in
Anticoagulation Therapy: How Patients Benefit. ACPE Universal Program No. 113-126-99-026-H01
This is to certify that the above-mentioned continuing education course was completed by:

Please type or print neatly:

Name: _____
Address: _____
City, State, Zip: _____



The California Pharmacists Association Educational Foundation and the California Society of Health-System Pharmacists are approved by the American Council on Pharmaceutical Education as providers of continuing pharmaceutical education. This course provides three hours of credit, Universal Program #113-126-99-026-H01. Pharmacists completing this course prior to February 1, 2002 may receive credit.

FOR OFFICE USE ONLY

You successfully passed with a score of: _____ percent.

CE Administrator: _____ Date issued: _____

Not valid unless signed by the CE administrator

TEST QUESTIONS

- Strokes, myocardial infarction, acute deep venous thrombosis and pulmonary embolism are all examples of:**
 - Atherosclerosis
 - Thrombotic diseases
 - Myeloproliferative diseases
 - Congestive heart failure
 - All of the above
- Pulmonary embolism is easily identified and always presents with abrupt onset of shortness of breath, tachypnea and tachycardia, with no sign of pneumonia, asthma or myocardial infarction.**
 - True
 - False
- What is the loading dose for the initiation of continuous IV heparin?**
 - 10,000 units for everyone
 - Depends on the baseline aPTT
 - 50 - 80 U/kg intravenous
 - No loading dose is needed
- It is safe to send patients home on low molecular weight heparin (LMWH) if they are taking non-steroidal drugs for arthritis.**
 - True
 - False
- Low molecular weight heparin (LMWH) is associated with a fewer number of bleeds, because it has less of an effect on inhibiting Factor IIa (thrombin).**
 - True
 - False
- All of the following statements regarding bleeding are true, except:**
 - Bleeding usually represents underlying trauma or manipulation.
 - Bleeding always requires discontinuation of warfarin.
 - If bleeding should persist for more than 15 minutes, patients should call for advice or come to an Emergency Department.
 - One of the most common sites for bleeding is into the skin (ecchymosis).
 - Bleeding should always be reported to caregivers.
- Drug interactions with warfarin have been reported to occur with which of the following medications?**
 - Anti-infectives such as sulfonamides and macrolides
 - NSAIDs, nonsteroidal anti-inflammatory agents.
 - Barbiturates
 - Histamine-2 antagonists
 - All of the above
- Which of the following conditions may lead to alterations in anticoagulant response to warfarin as measured by the INR?**
 - Febrile illnesses
 - Alterations in dietary content of Vitamin K
 - Aspirin in daily doses of 81-325 mg
 - a and b
 - a and c
- Responsibilities of the inpatient pharmacist who is following an anticoagulant patient include:**
 - Chart review
 - Lab interpretation
 - Dosage adjustment recommendations
 - Patient education
 - All of the above
- Prior to discharging a patient on warfarin from the hospital, the inpatient pharmacist should:**
 - Insure the patient has outpatient follow up
 - Refer the patient to a home health agency
 - Review the warfarin discharge prescriptions for appropriate dose
 - a and c only
 - All of the above
- The best information regarding a patient's warfarin dose is the patient's chart.**
 - True
 - False
- Anticoagulation clinic care providers frequently include:**
 - Physicians
 - Nurses or nurse practitioners
 - Pharmacists
 - Physician assistants
 - All of the above
- Which of the following traits would make a patient a poor candidate for INR monitoring using outside laboratory facilities?**
 - Unreliability
 - Poor historian
 - Non-compliant
 - All of the above
 - a and c only
- The benefits of providing extensive patient counseling for the anticoagulation patient include:**
 - Improved patient compliance
 - Improved therapeutic control
 - Decreased hospital admissions
 - All of the above
- Which of the following is an incorrect counseling point for patients on warfarin?**
 - Knowledge of dose, tablet color, proper storage; double check of doses, instructions for missed doses
 - Warnings to women of child-bearing potential
 - Restrict vitamin K intake
 - Minimize alcohol intake
 - Consult with the pharmacist prior to taking ANY new medications
- The best time to measure the INR is within the first 8 hours of the first dose of the anticoagulant.**
 - True
 - False
- Which of the following is used to monitor heparin anticoagulation?**
 - Prothrombin time (PT)
 - Activated partial thromboplastin time (aPTT)
 - International Normalized Ratio (INR)
- Which of the following are common causes of errors made by patients on anticoagulant therapy?**
 - Taking extra doses to "treat" symptoms
 - Confusion over brand and generic names
 - Confusion after a change in the dose or change in tablet strength
 - Avoiding foods with vitamin K
 - All of the above
- Many patients prefer going to an anticoagulation clinic rather than to a clinical laboratory to have their warfarin levels monitored for which of the following reasons?**
 - The results are quicker, allowing the medication dose to be adjusted immediately.
 - A finger stick is less painful than a laboratory blood draw.
 - They like the "teamwork" approach to management of their medications, in which they can voice their concerns.
 - All of the above.
- The actual combined cost savings from avoidance of bleeding and thrombosis at the UCSD Anticoagulation Management Service in 1995-96 was:**
 - \$789 per patient-year
 - \$17,183 per patient-year
 - \$226,350 per patient-year
 - \$1,319 per patient-year
- Long term anticoagulation therapy with heparin instead of warfarin is always indicated in what type of patients?**
 - Diabetic
 - Pregnant
 - Hypertensive
 - Asthmatic
 - All of the above
- The biggest advantage of the low molecular weight heparins in the treatment of deep vein thrombosis is that they**
 - Are less expensive than warfarin.
 - Are more efficacious than heparin infusions administered in the hospital.
 - Have a longer, non-dose dependent pharmacologic half-life that allows once or twice daily dosing at home without the need for laboratory monitoring.
 - Are primarily eliminated via the kidneys.
- Elderly patients requiring anticoagulant therapy often present special challenges as a result of an age-related increased sensitivity to warfarin, concomitant diseases that can increase risks with anticoagulation therapy and multiple medications which might interact with anticoagulant therapy.**
 - True
 - False
- Most patients on warfarin will have a target International Normalized Ratio (INR) of:**
 - 1.0
 - 1.5 to 2.5
 - 2.0 to 3.0
 - 2.5 to 3.5
 - 3.0 to 4.0
- Pharmacists can have a valuable influence on the health care of patients who are on anticoagulant therapy by:**
 - Educating patients about their diagnosis and the benefits of anticoagulation therapy.
 - Assessing and monitoring patients receiving oral anticoagulation therapy
 - Improving medication compliance to the prescribed drug regimen.
 - Helping patients establish and adhere to a therapeutic regimen that will result in a decrease in the number of complications, hospitalizations and emergency room visits and as a result, increase patient satisfaction and improve quality of life.
 - All of the above

Making a Difference

DuPont Pharmaceuticals Company

Demonstrating the value of communication, DuPont Pharmaceuticals Company provided an unrestricted educational grant to help support the Board of Pharmacy's Anticoagulation issue of Health Notes.

The Anticoagulation Issue Panel

For encouraging the professional growth of pharmacists by assisting in the peer review and editing of this issue of Health Notes, we thank the following:

Sue Chong, Pharm.D.

Clinical Outcomes Manager

Lori Ho-Ikeda, Pharm.D.

Ambulatory Care Pharmacist

Denis Ishisaka, Pharm.D.

Clinical Education Consultant

Fred L. Meister, Pharm.D.

Clinical Pharmacologist

Martha Pauli, M.Ed., Pharm.D.

Assistant Editor

Carl Peterson, Pharm.D., BCPS

Outcomes Manager, Clinical Affairs

Robert Weibert, Pharm.D.

Clinical Professor

The California Pharmacists Association and the California Society of Health-System Pharmacists

We thank Teresa Miller, Pharm.D., Executive Vice President of CSHP, and Elizabeth Johnson, Senior Vice President, CPbA, and their organizations for advocating that pharmacists provide quality patient care, for editorial review and for developing the continuing education section of this issue of Health Notes.



Bulk Rate
U.S. Postage
PAID
Permit No. 685
Sacramento, CA

State Board of Pharmacy
Department of Consumer Affairs
400 R Street, Suite 4070
Sacramento, CA 95814

(916) 445-5014

