InetCE

Volume 9 **2005** **Number 1**

Karen J. MacKinnon, R.Ph.
Editor

Linda S. Swanson
Copy Editor

Internet Continuing Education (***InetCE***) provides free, continuing education to pharmacists and other health care providers for 24 hours a day over the Internet at www.InetCE.com. Since 1997, these home study programs have assisted in keeping practitioners apprised of treatment-related topics, general pharmacy, and law in the changing health care environment.

InetCE grew out of a need for relevant, continuing education in health care, and to make it accessible to pharmacy practitioners in various practice settings. This format provides convenient instruction, on-line testing, evaluation, and certification. Continuing education examinations are graded automatically and, if successfully passed, the user can print the statement of credit.

Accreditation

ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Program Number 221-999-05-002-H01 has been assigned to this home study program (initial release date February 14, 2005). This program is acceptable for 2.0 contact hours (0.20 CEUs) in states that recognize ACPE providers. The program is provided at no cost to participants. Statements of credit will be issued on-line upon successful completion (> 70% score) of the posttest.

Faculty Disclosure

It is the policy of ProCE, Inc. to ensure balance, independence, objectivity and scientific rigor in all of its continuing education programs. Faculty must disclose to program participants any significant relationships with companies that manufacture or market products discussed during their presentation. Dr. Singla reports receiving grant and/or research support from American Pharmaceutical Association, Astra-Zenica, Roche Diagnostics, Upsher-Smith Labs, Procter & Gamble, Aventis, and Pfizer. Dr. Singla also reports serving as a consultant and/or speaker for Biovail Pharmaceuticals, Pfizer Pharmaceuticals, Arizona Pharmacy Foundation, and Upsher-Smith Labs.

Please note: The opinions expressed in this program should not be construed as those of the CE provider. The information and views are those of the faculty through clinical practice and professional literature. Portions of this program may include the use of drugs for unlabeled indications. Use of drugs outside of labeling should be considered experimental, and participants are advised to consult prescribing information and professional literature.

ProCE, Inc.
848 W. Bartlett Rd., Ste. 9E
Bartlett, IL 60103
www.ProCE.com

Anticoagulation Therapy Update

InetCE 221-999-05-002-H01

Dana Singla, Pharm.D.
Assistant Professor
Department of Pharmacy Practice
Midwestern University College of Pharmacy-Glendale
Glendale, Arizona

PLEASE NOTE: The content of this article was current at the time it was written. The exam for this article is not valid for CE credit after February 14, 2008.

LEARNING OBJECTIVES

1. Differentiate among the available anticoagulant agents in regard to mechanism of action, dosing, side effects, and monitoring.
2. Compare the recommendations of the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy with the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy as they apply to the patient requiring long-term anticoagulation therapy.
3. Identify the potential advantages of anticoagulants in development.
4. Describe how to initiate and monitor anticoagulation therapy in the acute and non-acute patient.

ABSTRACT: Thrombotic disorders include both acute and chronic syndromes and represent a significant source of morbidity and mortality worldwide. The pharmacologic management of these disorders began over 50 years ago when heparin and warfarin became commercially available. Since that time, there have been significant advances in the management of thrombotic disorders. In the late 1980s, the low-molecular-weight heparins (LMWHs) became available followed by the injectable direct thrombin inhibitors and recently the injectable pentasaccharides. Oral direct thrombin inhibitors are currently undergoing clinical trials and are expected to be available within the next decade.

Besides advances in pharmacologic therapy, Guidelines have also been developed regarding the use of antithrombotic agents. These Guidelines are updated and published by the American College of Chest Physicians (ACCP). The first ACCP Guidelines on antithrombotic therapy were published almost 20 years ago. Since that time, there have been multiple revisions to these Guidelines, with the most recent update published in September 2004.

This article will review the pharmacology of the available anticoagulant agents and the updated recommendations of the Seventh ACCP Conference Guidelines as they apply to the long-term management of anticoagulation therapy. Two anticoagulation therapy management cases will be presented. Upcoming anticoagulant agents and potential new indications will be reviewed where applicable.

ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. An on-screen statement of credit verifying participation in 0.20 CEUs (2.0 contact hours) will be displayed for printing to participants who successfully complete the examination. This article has been

assigned ACPE ID number 221-999-05-002-H01. For more information, visit http://www.InetCE.com

ANTICOAGULATION THERAPY UPDATE

Introduction

Thrombotic disorders include both acute and chronic syndromes and represent a significant source of morbidity and mortality worldwide. The pharmacologic management of these disorders began over 50 years ago when heparin became commercially available in the 1930s and warfarin in the 1950s. Since that time, there have been significant advances in the management of thrombotic disorders.[1] In the late 1980s, the LMWHs became available followed by injectable direct thrombin inhibitors, injectable pentasaccharides, and, recently, an oral direct thrombin inhibitor completed phase III clinical trials.

Besides advances in pharmacologic therapy, evidence-based guidelines have been developed regarding treatment, monitoring, and outcomes of antithrombotic agents. These guidelines are updated and published by the ACCP. The first ACCP guidelines on antithrombotic therapy were published in 1986.[2] Since that time, 6 revisions to the guidelines have been published with the most recent release in September 2004.[3] Over the past 20 years, the number of available agents discussed in these guidelines has tripled, the evaluation of agents has become more rigorous, and the grading system for the recommendations has been refined.

This article will briefly review the pharmacology of the available anticoagulant agents and the updated recommendations of Seventh ACCP Conference Guidelines as they apply to the initiation and long-term management of anticoagulation therapy. Two anticoagulation therapy management cases will be presented where the pharmacologic principles of the available anticoagulants and the updated guidelines will be applied. Upcoming anticoagulant agents and potential new indications will be reviewed where applicable.

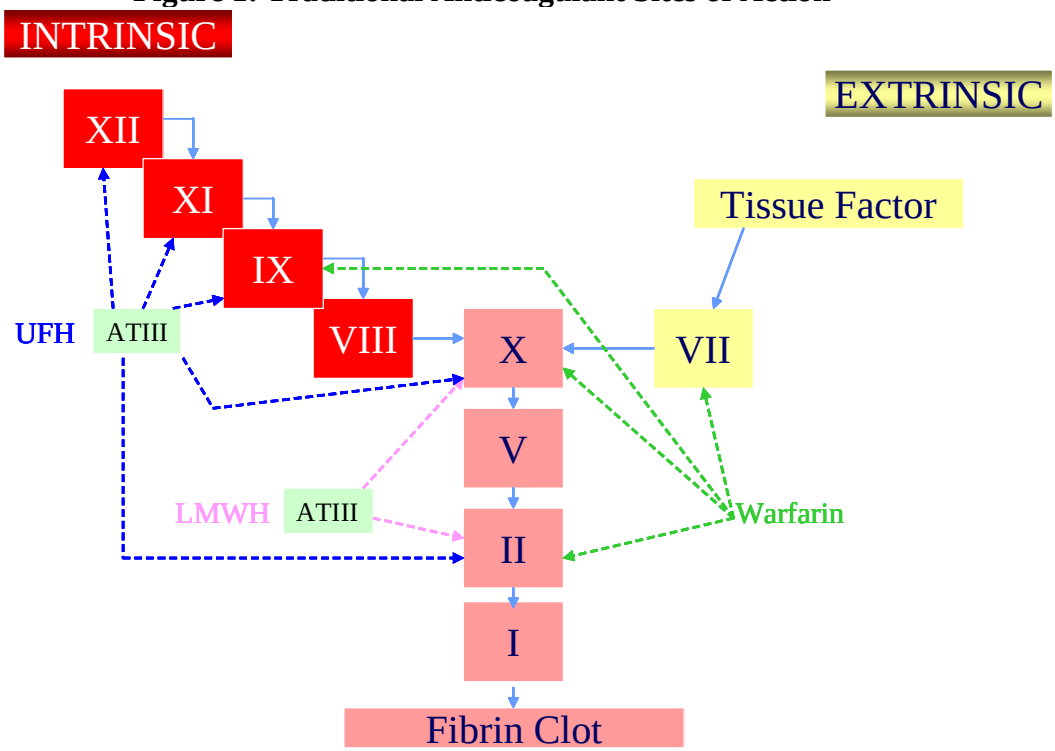
Anticoagulant Pharmacology

Heparin

Unfractionated Heparin (UFH)

Heparin is a glycosaminoglycan isolated from porcine and bovine lung or gut mucosa. It is composed of polysaccharide chains that contain an essential pentasaccharide sequence that binds to antithrombin III (ATIII). This results in a conformational change in ATIII that enhances its inactivation of thrombin (IIa) and factor Xa. Other clotting factors inhibited by heparin include IXa, XIa, and XIIa (Figure 1). The molecular weight of heparin ranges from 3000-30000 Daltons. Only about one-third of these molecules exert a pharmacologic effect. Heparin is cleared rapidly from the plasma with an average half-life of approximately one hour.

Figure 1: Traditional Anticoagulant Sites of Action



The test most widely used to monitor the therapeutic effect of heparin is the activated partial thromboplastin time (aPTT). For many years, the optimal therapeutic effect for the treatment of thromboembolism was defined as prolongation of the aPTT to greater than 1.5 to 2.5 times the control value.[4] However, owing to limitations such as extreme variability with the aPTT among laboratories, a newer approach to heparin monitoring includes targeting antifactor Xa activity for treatment of venous thromboembolism (VTE).[5,6] The College of American Pathologists and the American College of Chest Physicians recommend against the use of a fixed aPTT therapeutic range in favor of a therapeutic aPTT range calibrated specifically for each reagent lot and coagulometer.[7] This is accomplished by determining the aPTT values that correlate with therapeutic heparin levels for treatment of venous thromboembolism (VTE), equivalent to 0.3 to 0.7 IU/mL by factor Xa inhibition. The therapeutic range for coronary indications is unknown but is likely to have an upper limit of 0.6 IU/mL.[7]

Several weight-based dosing nomograms have been developed to assist in attaining and maintaining heparin in the therapeutic range.[8-10] Initial dosing of heparin for treatment of venous thromboembolism is 80 U/kg bolus followed by an 18 U/kg/h infusion.[10] Doses of heparin for treatment of patients with acute coronary syndromes are typically lower.[6] For prevention of thromboembolism, heparin can be administered in doses of 5000 U subcutaneously every 8-12 hours.[7]

Besides an increased risk of bleeding, heparin can cause an antibody-mediated adverse reaction known as heparin

induced thrombocytopenia (HIT). HIT is defined as an unexplained platelet count falling to below 50% of baseline, even if the platelet count nadir remains > 150 x 10^9/L, accompanied by HIT antibody formation.[11,12] Platelet counts should be checked every 2-3 days to monitor for this complication.[12] Osteoporosis has been reported in patients receiving heparin for greater than one month.[6] The bone demineralization caused by heparin can progress to vertebral and long bone fractures, and may not be reversible. Contraindications and precautions include any active or recent major bleeding, surgery, trauma, stroke, uncontrolled hypertension, and previous hypersensitivity reactions. Protamine sulfate may be used in the treatment of heparin overdosage.[6] One milligram of protamine sulfate neutralizes approximately 100 units of heparin. Because of the short half-life of heparin, the protamine dose required must be decreased depending on the timing of the heparin administration. For example, if protamine is given 30 minutes after heparin, half the usual dose may be sufficient.

Low-Molecular-Weight Heparin

Low-molecular-weight heparins (LMWHs) are enzymatically cleaved heparin with an average molecular weight of 4000-6000 Daltons. The activity of LMWH against factor Xa is greater than its activity against factor IIa. This is in contrast to heparin, which inhibits factors Xa and IIa equally (Figure 1). Three agents are currently available in the United States: dalteparin, enoxaparin, and tinzaparin. There are several major advantages of LMWH over UFH, including greater bioavailability and a longer half-life. This allows for fixed weight-based dosing with no therapeutic monitoring. These agents are also associated with less HIT and bone loss.[13,14] Their indications and dosing are reviewed in Table 1.[15] The correct dosing of these agents in the extremely obese and in those with renal impairment (with the exception of enoxaparin[15]) remains unclear and the Seventh ACCP Guidelines recommend monitoring therapeutic anti-Xa activity in these patients.[6] It should be noted that UFH is preferred to provide full therapeutic anticoagulation in patients with renal insufficiency.[6]

Table 1. Low Molecular Weight Heparins (United States)[15]

Agent	Indication	Dose (SQ)	Renal Dose
Dalteparin	*****DVT prophylaxis: Hip surgery	5000 IU QD	
	DVT prophylaxis: Abdominal surgery	2500 IU or 5000 U QD	
	******ACS	120 IU/kg q 12 h (max of 10000 IU per dose)	
Enoxaparin	DVT prophylaxis: Hip surgery	30 mg q 12 h or 40 mg QD	30 mg QD
	DVT prophylaxis: Knee surgery	30 mg q 12 h	30 mg QD
	DVT prophylaxis: Abdominal surgery	40 mg QD	30 mg QD
	DVT prophylaxis: Medical patients during acute illness	40 mg QD	30 mg QD
	Treatment of DVT with or without *******PE	1 mg/kg q 12 h or 1.5 mg/kg QD (inpatient only)	1 mg/kg QD
	ACS	1 mg/kg q 12 h	1 mg/kg QD
Tinzaparin	Treatment of DVT with or without PE	175 anti-Xa IU/kg QD	

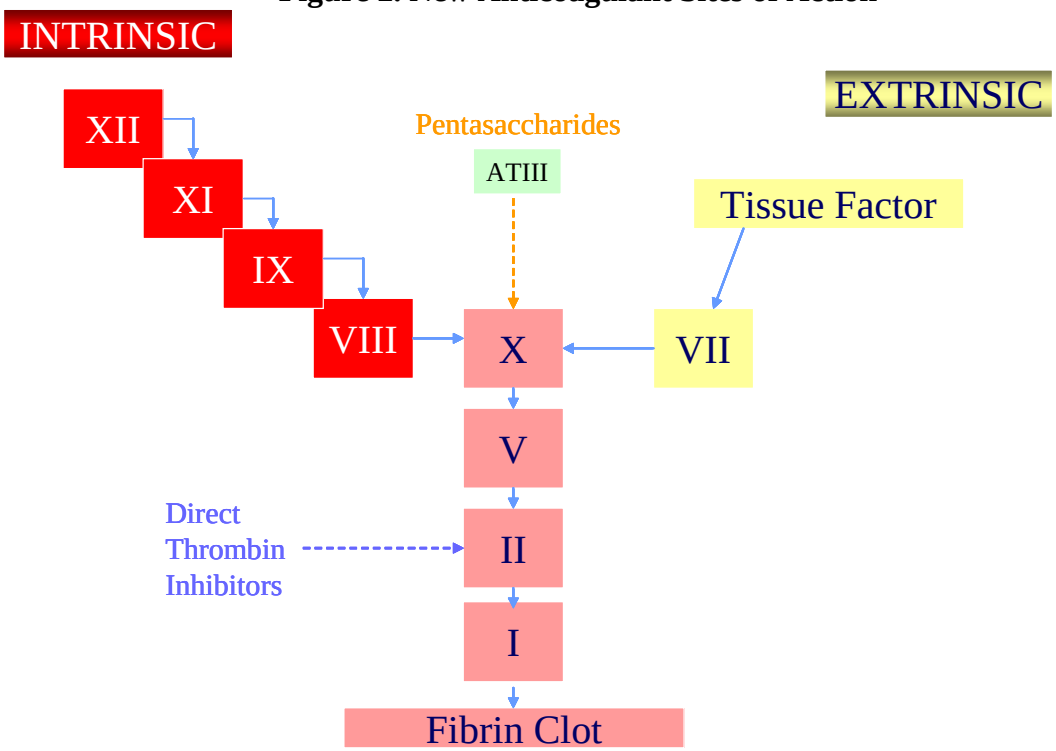
*****Deep vein thrombosis (DVT), ** Acute Coronary Syndromes (ACS), ***Pulmonary embolism (PE)

Properties associated with one LMWH cannot be extrapolated to a different LMWH. Contraindications and precautions include any active or recent major bleeding, surgery, trauma or stroke, uncontrolled hypertension, and previous hypersensitivity reactions. Protamine sulfate may be used in the treatment of enoxaparin overdosage.[16] The dose of protamine sulfate varies based on the time of enoxaparin administration: within 8 hours, a 1 mg:1 mg ratio of protamine sulfate to enoxaparin may be administered and between 8 and 12 hours, a 0.5 mg:1 mg ratio may be administered. After 12 hours, protamine administration may not be required.

Pentasaccharides

The pentasaccharides are synthetic derivatives of heparin with a biochemical structure similar to the essential pentasaccharide sequence necessary for heparin to bind to ATIII. Pentasaccharides allow for inhibition of factor Xa but not thrombin because these molecules lack the units necessary to produce thrombin inhibition by ATIII (Figure 2).

Figure 2. New Anticoagulant Sites of Action



Fondaparinux 2.5 mg administered subcutaneously (SC) once daily is indicated for DVT prophylaxis in hip and knee replacement surgery and hip fracture surgery. It has recently been studied and approved for the treatment of acute DVT and pulmonary embolism (PE).[17] In the MATISSE DVT trial 2205 patients with DVT were randomized to receive either weight-adjusted fondaparinux or treatment dose enoxaparin for 5 days followed by a minimum 3-month course of treatment with an oral vitamin K antagonist. At 3 months, the rates of recurrent symptomatic venous thromboembolism with fondaparinux or enoxaparin were 3.9% and 4.1%, respectively, whereas major bleeding rates were 1.1% and 1.2%, respectively. None of these differences was statistically significant. The recommended dose for these indications is as follows: 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight >100 kg) by SC injection once daily for at least 5 days and until a therapeutic oral anticoagulant effect is established (INR 2.0 to 3.0).[18] Theoretically, fondaparinux should be associated with a much lower incidence of HIT.[12] Its long half-life and greater specificity allows for fixed, once daily dosing. The Food and Drug Administration (FDA) recently approved safety changes to the product labeling reflecting contraindications in patients weighing less than 50 kg and in patients with severe renal impairment (creatinine clearance < 30 ml/ min) and cautious use in patients with moderate renal impairment (creatinine clearance, 30-50 ml/ min).[19]

Another pentasaccharide, idraparinux, an extended-release derivative of fondaparinux, which allows for once weekly administration, is currently

undergoing phase III clinical trials.[20,21] The AMADEUS Trial, a randomized, open-label trial is comparing idraparinux SC once weekly with vitamin K antagonists for prevention of thromboembolic events in patients with atrial fibrillation (AF).[20] The VAN GOGH Trials, randomized, double-blind, placebo-controlled trials are comparing idraparnix subcutaneously with vitamin K antagonists or placebo in patients with DVT or PE.[21] Whether idraparinux might be a useful alternative to long-term warfarin therapy remains to be determined pending availability of results from these large phase III trials.

Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) either bind directly to thrombin in a reversible (argatroban, bivalirudin—formerly know as hirulog, desirudin) or irreversible (lepirudin) manner (Figure 2). Agents that bind irreversibly are associated with a higher incidence of bleeding.[22] Hirudin, the prototype DTI, is a 65 amino-acid cysteine-rich polypeptide produced by the salivary gland of the medicinal leech, which is now produced as a recombinant molecule (lepirudin). Treatment indications for the DTIs include treatment of HIT (argatroban, lepirudin), patients with angina undergoing percutaneous transluminal coronary angioplasty (bivalirudin), and prophylaxis of DVT in hip replacement surgery (desirudin). These agents are dosed as an IV bolus followed by a continuous infusion and are based on patients' weight and renal function. Dosing references such as *Drug Facts and Comparisons*[15] or The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines[3] should be consulted for specific dosing guidelines. Optimal therapeutic effect is determined when a continuous IV infusion is administered in doses sufficient to prolong the aPTT to greater than 1.5 times the control value. Contraindications and precautions include any active or recent major bleeding, cerebral aneurysm, and previous hypersensitivity reactions. More frequent adverse reactions include bleeding, pain, hypotension, nausea, and headache.

DTIs are currently available in the injectable form; however, an oral preparation, ximelagatran, has recently been studied in VTE prophylaxis[23-25] and treatment,[26] acute coronary syndromes,[27] and stroke prevention in patients with atrial fibrillation.[28] Advantages of ximelagatran include fixed, oral BID dosing, rapid onset of action, no therapeutic monitoring, and no known drug or dietary interactions.[29] Potential limitations include no dosing recommendations for renal impairment, no antidote for overanticoagulation, and inability to monitor for therapeutic effectiveness. In September 2004, the FDA advisory committee recommended against approval of this agent for short- and long-term use citing safety concerns owing to elevation of serum transaminases and possible increased risk of myocardial infarction post knee replacement surgery.[30] In October 2004, the manufacturer (AstraZeneca) announced that the FDA did not grant approval for this drug.

Vitamin K Antagonists

Vitamin K antagonists (VKAs) interfere with clotting factor synthesis by inhibiting the regeneration of vitamin K_1 epoxide in a dose-dependent fashion. Therapeutic doses decrease vitamin K–dependent clotting factors (II, VII, IX,

X, proteins C and S) by 30%-50% (Figure 1). Warfarin is the oral VKA available in the United States. Its duration of action is 3-5 days and it does not reach its antithrombotic effect until thrombin is inhibited (approximately 4-5 days). It is highly protein bound and metabolized in the liver and kidney, making it subject to many drug- and disease-state interactions. Warfarin is also prone to dietary interactions with foods containing high amounts of vitamin K. Monitoring of the international normalized ratio (INR) is routinely required to ensure therapeutic effectiveness. Dosing varies based on the patients' individual response and the INR. The INR target range for the majority of patients is 2.0-3.0, with a higher range of 2.5-3.5 for most patients with mechanical heart valves.[31] The most commonly reported adverse event associated with warfarin therapy is bleeding, and its therapeutic effects can be reversed with the administration of vitamin K. Guidelines for the administration of vitamin K will be reviewed in the following section of the manuscript.

Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

Grading of Recommendations[32]

The grading of recommendations as defined in the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines is as follows:

- Grade 1: Experts very certain benefits do/do not outweigh risks, burdens, and costs
- Grade 2: Experts less certain benefits do/do not outweigh risks, burdens, and costs
- Grade A: Consistent results from randomized controlled trials (RCTs)
- Grade B: Inconsistent results from RTCs
- Grade C/C+: Observational studies (+ indicated very strong effects or secure generalizations from RTCs)

A new feature of the Guidelines is terminology expressing the strength of the recommendation. The Guidelines use the language "we recommend" for strong recommendations (Grades 1A, 1B, 1C/C+) and "we suggest" for weaker recommendations (Grades 2A, 2B, 2C/C+).

The Pharmacology and Management of the Vitamin K Antagonists[33]

This section provides recommendations on selecting an initial dose, therapeutic monitoring, management of non-therapeutic INRs, and management during invasive procedures. When compared with the Sixth ACCP Conference[34], the Seventh ACCP Conference allows for greater flexibility when selecting an initial dose and has assigned a grading to the recommendation for those who may require a lower starting dose. The grading system was also applied to the frequency of suggested INR monitoring.

Seventh ACCP Guidelines Recommendations on Initiation and Maintenance Dosing and Frequency of Monitoring

- We suggest the initiation of oral anticoagulation therapy with doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with

subsequent dosing based on the INR response (Grade 2B).

- In the elderly, for patients who are debilitated, malnourished, have congestive heart failure, or have liver disease we suggest the use of a starting dose of ≤5 mg (Grade 2C).
- We suggest starting INR monitoring after the initial 2 or 3 doses of oral anticoagulation therapy (Grade 2C).
- For patients who are receiving a stable dose of oral anticoagulants, we suggest monitoring at an interval of no longer than every 4 weeks (Grade 2C).

For management of dosing when the INR is nontherapeutic, the Seventh ACCP Conference suggests that for patients with a sub-therapeutic INR, the weekly dose of warfarin be increased by 10% to 20%, and that more frequent monitoring take place until the INR is stable. For the patient with a supratherapeutic INR, preference continues for oral administration of vitamin K_1 for the significantly elevated INR without major bleeding. Higher doses of oral vitamin K_1 are recommended for patients with INRs ≥9.0 with no significant bleeding, and a new statement regarding the preferred use of oral vitamin K_1 has been added and given a grade 1A recommendation.

Seventh ACCP Guidelines Recommendations on the Management of the Non-Therapeutic INR

- For patients with INRs above the therapeutic range but < 5.0 who have no significant bleeding, lower the dose or omit the dose, monitor more frequently, and resume therapy at a lower dose when the INR is in the therapeutic range. If only minimally above the therapeutic range, no dose reduction may be required (all Grade 2C).
- For patients with INRs ≥5.0 but < 9.0 and no significant bleeding, omit the next one or two doses, monitor more frequently, and resume therapy at a lower dose when the INR is in the therapeutic range. Alternatively, omit a dose and administer oral vitamin K_1 (1-2.5 mg), particularly if the patient is at an increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, oral vitamin K_1 (≤5 mg) can be given with the expectation that a reduction of the INR will occur in 24 hours. If the INR is still high, additional oral vitamin K_1 (1 to 2 mg) can be given (all Grade 2C).
- For patients with INRs ≥9.0 who have no significant bleeding, hold warfarin therapy and administer a higher dose of oral vitamin K_1 (5 to 10 mg) with the expectation that the INR will be reduced substantially in 24 to 48 hours. Monitor the patient more frequently and use additional vitamin K_1, if necessary. Resume therapy at a lower dose when INR is in the therapeutic range (all Grade 2C).
- In patients with serious bleeding and elevated INRs, we recommend holding warfarin therapy and administering vitamin K_1 (10 mg) by slow IV infusion, supplemented with fresh plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation. Vitamin K_1 administration can be repeated every 12 hours (all Grade 1C).
- In patients with life-threatening bleeding and elevated INRs, we

recommend holding warfarin therapy and administering prothrombin complex concentrate or recombinant factor VIIa supplemented with vitamin K_1 (10 mg) by slow IV infusion. Repeat the procedure if necessary, depending on INR (Grade 1C).

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

For anticoagulation management when an invasive procedure is required, the principal concern remains the risk of thromboembolism when anticoagulation therapy is interrupted. The Seventh ACCP consensus Guidelines use the same classification of low, intermediate, and high risk of thromboembolism that was used in the Sixth ACCP Guidelines.[34] Low risk of thromboembolism includes no recent (> 3 months) VTE, atrial fibrillation without a history of stroke or other risk factors, and bileaflet mechanical cardiac valve in aortic position. The addition of bileaflet mechanical cardiac valve in aortic position to the low risk category is new to the Seventh ACCP Conference. Examples of high risk of thromboembolism include recent (< 3 mo) history of VTE, mechanical cardiac valve in mitral position, and any old model cardiac valve (ball/cage). Intermediate risk of thromboembolism is not defined in the Guidelines.

Seventh ACCP Guidelines Recommendations for Management of Oral Anticoagulation During Invasive Procedures

- For patients with a low risk of thromboembolism: stop warfarin therapy approximately 4 days before surgery, allow the INR to return to near-normal values, briefly use postoperative prophylaxis (if the intervention increases the risk of thrombosis) with a low dose of UFH (5000 U SC), or use a prophylactic dose of LMWH and simultaneously begin warfarin therapy. Alternatively, a low dose of UFH or a prophylactic dose of LMWH also can be administered preoperatively (all Grade 2C).
- For patients with an intermediate risk of thromboembolism: stop warfarin approximately 4 days before surgery, allow the INR to fall, cover the patient beginning 2 days preoperatively with a low dose of UFH (5000 U SC) or a prophylactic dose of LMWH, and then commence therapy with low-dose UFH (or LMWH) and warfarin postoperatively; some individuals would recommend a higher dose of UFH or a full dose LMWH in this setting (Grade 2C).
- For patients with a high risk of thromboembolism: stop warfarin therapy approximately 4 days before surgery to allow the INR to return to normal at the time of surgery and begin therapy with a full dose of UFH or a full dose of LMWH as the INR falls (approximately 2 days preoperatively). UFH can be administered as a SC injection on an outpatient basis and as a continuous IV infusion after hospital admission in preparation for surgery and should be discontinued approximately 5 hours before surgery with the expectation that the anticoagulant effect will have worn off by the time of surgery. An alternative is to continue to use SC UFH or LMWH

preoperatively and to stop therapy 12 to 24 hours before surgery with the expectation that the anticoagulant effect will be very low or have worn off by the time of surgery. Then, commence administering a full dose of UFH (or LMWH) and warfarin postoperatively (Grade 2C).

- For patients with low risk of bleeding, continue warfarin therapy at a lower dose and operate at an INR of 1.3 to 1.5. The dose of warfarin can be lowered 4 or 5 days before surgery. Warfarin therapy then can be restarted postoperatively, supplemented with a low dose of UFH (5000 U SC) or a prophylactic dose of LMWH, if necessary (Grade 2C).
- In patients who are undergoing dental procedures with a need to control local bleeding, we suggest the use of tranexamic acid mouthwash (Grade 2B) or epsilon amino caproic acid mouthwash without interrupting anticoagulant therapy (Grade 2B).

In addition to the recommendations of the Sixth ACCP Conference[34], the Seventh ACCP Conference added the following suggested recommendations to the 3 risk categories:

- Low risk: the option of using prophylactic dose LMWH was added with a consideration to use either LMWH or UFH preoperatively.
- Intermediate risk: the option of using full dose UFH or LWMH was added.
- High risk: the use of full-dose UFH and LMWH in addition to warfarin postoperatively was added.

With each of these options, the length of time off warfarin and the duration of heparin or LMWH use preoperatively can be shortened by administering vitamin K_1 24 to 48 hours before surgery. The Seventh ACCP Conference also makes the statement that LMWH therapy appears to be at least as effective, if not more effective, and less costly than UFH therapy. It appears that outpatient bridge therapy with LMWH may be the preferred management strategy. The Seventh ACCP Conference no longer supports interruption of anticoagulation therapy for dental procedures.

<u>Antithrombotic Therapy for Venous Thromboembolic Disease</u>[35]

More definitive recommendations for the treatment of acute VTE have been made regarding when to initiate warfarin in conjunction with the heparin product and when the heparin product can be discontinued compared with the Sixth ACCP Conference recommendations.[36] For example, recommendations against the routine monitoring of anti-factor Xa levels for patients on LMWH, the suggested use of IV heparin over LMWH for patients with severe renal failure, the recommendation for LMWH to be used during the first 3 to 6 months in cancer patients, and recommendations for treatment of upper extremity DVT.

Seventh ACCP Guidelines Recommendations for the Initial Treatment of Acute DVT and PE

- In acute DVT or acute non-massive PE, we recommend initial treatment with LMWH or UFH for at least 5 days (1C).
- We recommend initiation of VKA together with LMWH or UFH on the

first treatment day and discontinuation of heparin when the INR is stable and > 2.0 (1A)

- In patients with acute DVT or acute non-massive PE treated with LMWH, we recommend against routine monitoring with anti-factor Xa level measurements (1A).
- In patients with severe renal failure, we suggest IV UFH over LMWH (2C).
- For patients with DVT or PE and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (1A). For these patients, we recommend anticoagulant therapy indefinitely or until the cancer is resolved (1C). *Remark:* The regimens of LMWH that have been established to be effective for long-term treatment in randomized trials are dalteparin, 200 IU/kg qd for 1 month, followed by 150 IU/kg qd thereafter, and tinzaparin at 175 IU/kg SC qd.
- For patients with acute upper extremity DVT, we recommend initial treatment with UFH (1C+) or LMWH (1C+).

The duration of anticoagulation therapy post VTE has also been updated. Table 2 compares the Sixth ACCP Conference recommendations with the Seventh ACCP Conference recommendations regarding duration of anticoagulant therapy post VTE.

Table 2. Recommended Duration of Anticoagulation Post VTE[35,37]

	Sixth ACCP Conference	Seventh ACCP Conference
Reversible or time-limited risk factors	3 months (1A)	3 months (1A)
First episode, idiopathic	At least 6 months (1A)	At least 6 to 12 months (1A); we suggest that patients with first episode, idiopathic VTE be considered for indefinite therapy (2A).
Recurrent idiopathic or continuing risk factor	12 months or longer (1C)	First episode VTE with thrombophilia, at least 6 to 12 months (1A); patients with first episode VTE and APLA or who have 2 or more thrombophilias, 12 months (1C+); we suggest indefinite therapy in these patients (2C).
2 or more episodes of VTE	12 months to lifetime (1C)	Indefinite (2A)

Antithrombotic Therapy in Atrial Fibrillation[37]

Paroxysmal AF and atrial flutter are included in the recommendations for selection of an antithrombotic agent compared with the Sixth ACCP Conference, which did not include specific, graded recommendations for

these.[38] The Seventh ACCP consensus Guidelines use the same stroke risk stratification of low, intermediate, and high risk that was used in the Sixth ACCP guidelines; however, the features that classify a patient's risk have changed. High risk includes the presence of any of the following: prior ischemic stroke, transient ischemic attack (TIA), or systemic embolism; older than 75 years; moderate or severely impaired left ventricular systolic function and/or congestive heart failure; history of hypertension; or diabetes mellitus. Intermediate-risk patients include aged 65 through 75 years and none of the above risk factors. Low risk includes patients with AF who are 65 years and younger with no risk factors or clinical evidence of cardiovascular disease. Diabetes and coronary artery disease (CAD) with preserved left ventricular function were previously considered intermediate risk factors. For the selection of an antithrombotic agent, the Seventh ACCP Conference continues to recommend warfarin for high-risk patients and either warfarin or acetylsalicylic acid (ASA) 325 mg/day for intermediate-risk patients. However, the efficacy of warfarin is emphasized in preventing ischemic stroke, and ASA 325 mg/day is recommended for low-risk patients. The grading of the recommendation for patients has increased from 2C to 1A.

Seventh ACCP Guidelines Recommendations on Anticoagulation Therapy in Atrial Fibrillation

- In patients with persistent or paroxysmal (intermittent) (PAF) at high risk of stroke (i.e., having any of the following features: prior ischemic stroke, TIA, or systemic embolism, older than 75 years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus), we recommend anticoagulation with an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0), Grade 1A.
- In patients with persistent AF or PAF, aged 65 to 75 years, in the absence of other risk factors, we recommend antithrombotic therapy (Grade 1A). Either an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0), or aspirin, 325/day, are acceptable alternatives in this group of patients who are at intermediate risk of stroke.
- In patients with persistent AF or PAF 65 years and younger and with no other risk factors, we recommend aspirin, 325 mg/day (Grade 1B).
- *Underlying values and preferences*: Anticoagulation with an oral VKA, such as warfarin, has far greater efficacy than aspirin in preventing stroke, and particularly in preventing severe ischemic stroke, in AF. We recommend the option of aspirin therapy for lower-risk groups in estimating the absolute expected benefit of anticoagulant therapy may not be worth the increased hemorrhagic risk and burden of anticoagulation. Individual lower-risk patients may rationally choose anticoagulation over aspirin therapy to gain greater protection against ischemic stroke if they value protection against stroke much more highly than reducing risk of hemorrhage and burden of managing anticoagulation.

- For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (Grade 2C).

Heparin-Induced Thrombocytopenia: Recognition, Treatment, and Prevention[39]

The Seventh ACCP Consensus Conference includes a chapter dedicated to heparin-induced thrombocytopenia (HIT). Major recommendations regarding platelet count monitoring are listed below, as they would apply to patients who may receive UFH or LMWH for treatment of acute venous thromboembolism or as peri-operative bridge therapy. Major treatment recommendations are also provided. A complete review of HIT is beyond the scope of this article.

Seventh ACCP Guidelines Recommendations on Monitoring for Heparin-Induced Thrombocytopenia

- For patients receiving heparin in which the risk of HIT is considered to be > 0.1%: we recommend platelet count monitoring over no platelet count monitoring (Grade 1C).
- For patients receiving therapeutic-dose UFH: we suggest at least every-other-day platelet count monitoring until day 14, or until UFH is stopped, whichever occurs first (Grade 2C).
- For patients receiving post-operative antithrombotic prophylaxis with UFH (HIT risk > 1%), we suggest at least every-other-day platelet count monitoring between post-operative days 4 to 14, or until UFH is stopped, whichever occurs first (Grade 2C).
- For medical/ obstetric patients receiving prophylactic-dose UFH, post-operative patients receiving prophylactic-dose LMWH, post-operative patients receiving intravascular catheter UFH "flushes," or medical/obstetric patients receiving LMWH after first receiving UFH (HIT risk, 0.1% to 1%): we suggest platelet count monitoring every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical (Grade 2C).
- For medical/obstetric patients receiving only LMWH, or medical patients receiving only intravascular catheter UFH flushes (HIT risk < 0.1%), we suggest clinicians do not use routine platelet count monitoring (Grade 2C).
- For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis: we recommend use of an alternative, non-heparin anticoagulant, such as lepirudin (Grade 1C+), argatroban (Grade 1C), bivalirudin (Grade 2C), or danaparoid (Grade 1B), over further UFH or LMWH therapy, and over no further anticoagulation (with or without vena caval filter).
- For patients with strongly suspected or confirmed HIT: we recommend against the use of vitamin K antagonist (coumarin) therapy until after the platelet count has substantially recovered (e.g., to at least 100 x 10^9/L, and preferably, 150 x 10^9/L); that the VKA be administered only during overlapping alternative anticoagulation (minimum 5-day overlap), and begun with low

maintenance doses (maximum, 5 mg, warfarin; 6 mg, phenprocoumon); that the alternative anticoagulant not be stopped until the platelet count has reached a stable plateau, and with at least the last 2 days the INR within the target therapeutic range (all Grade 1C).

- For patients receiving VKAs at the time of diagnosis of HIT: we recommend use of vitamin K (Grade 2C).
- For patients with strongly suspected HIT, whether or not complicated by thrombosis: we recommend against use of LMWH (Grade 1C+).

Antithrombotic Therapy in Valvular Heart Disease—Native and Prosthestic[40]

Table 3 summarizes the Seventh ACCP Conference recommendations for intensity of anticoagulation for mechanical and bioprosthetic heart valves. Several changes are noted from the Sixth ACCP Conference[41]: patients with bioprosthetic valves in the aortic position may now be treated with either dose-adjusted warfarin to a target INR of 2.5 or with low-dose ASA for the first 3 months; for long-term treatment of bioprosthetic valves, the ASA dose has been revised to 75-100 mg/day, and for bileaflet mechanical aortic valves with AF, low dose ASA is now suggested, in addition to dose-adjusted warfarin to a target INR of 3.0. For all patients with mechanical prosthetic heart valves, vitamin K antagonists are recommended (Grade 1C+). For all patients with heart valve replacements, administration of UFH or LMWH until the INR is stable and at a therapeutic level for 2 consecutive days is suggested (Grade 2C).

Table 3. Anticoagulation Recommendations for Heart Valves[40]

Target INR of 2.5 (range 2.0 to 3.0) or aspirin	**Target INR of 2.5 (range 2.0 to 3.0)**	**Target INR of 3.0 (range 2.5 to 3.5)**	**Target INR of 3.0 (range 2.5 to 3.5), combined with 75 to 100 mg/d aspirin**
Bioprosthetic valves in the aortic position, for the first 3 months after valve insertion (warfarin, Grade 2C). (ASA 80-100 mg, Grade 1C).	St. Jude Medical bileaflet valve in the aortic position (Grade 1A).	Tilting disk valves and bileaflet mechanical valves in the mitral position (Grade 1C+)	Any mechanical valve and additional risk factors such as AF, myocardial infarction, left atrial enlargement, endocardial damage, and low ejection fraction (Grade 1C+)

Bioprosthetic valves that are in sinus rhythm and do not have AF, we recommend long-term therapy with aspirin, 75 to 100 mg/d (Grade 1C+).	CarboMedics bileaflet valve or Medtronic Hall tilting disk mechanical valves in the aortic position, normal left atrium size, and sinus rhythm (Grade 1C+).		Caged ball or caged disk valves (Grade 2A)
	Bioprosthetic valves with a history of systemic embolism, we recommend vitamin K antagonists for 3 to 12 months (Grade 1C)		Mechanical prosthetic heart valves that suffer systemic embolism despite a therapeutic INR (Grade 1C+)
	Bioprosthetic valves in the mitral position, for the first 3 months after valve insertion (Grade 1C+).		
	Bioprosthetic valves with AF (Grade 1C+)		

Anticoagulation Therapy Management Cases

In this section, 2 anticoagulation therapy management cases are presented. The first case involves a patient with an acute DVT and the second case involves a patient who requires anticoagulation for new onset AF. Anticoagulant pharmacology and the updated recommendations of the Seventh ACCP Conference will be applied to each case.

Case 1: Acute DVT

A.F. is a 40-year-old female who presents to her physician today complaining of calf pain and swelling. A venous doppler ultrasound was performed with results consistent for a right lower extremity (RLE) DVT.

Past medical history (PMH): Prior DVT at age 35; treated with warfarin x 1 year**;** intrauterine device (IUD) placed at age 35

(Family history (FH): Father died at age 47 from myocardial infarction (MI), Mother alive at age 71 with congestive heart disease (CHD), sister alive and well. No FH of VTE reported.

Social history (SH): Patient lives with her husband and 16-year-old son; works in a department store as a cashier. No history of alcohol, tobacco, or drug use

Meds: Multivitamin tablet daily

Allergies (All): Codeine (urticaria)

Review of systems (ROS): Negative for fever, chills, cough, shortness of breath (SOB), chest pain, or diaphoresis. Positive for acute pain and feeling of tightness in right lower leg, swelling of the right calf to twice the normal size.
Vital signs (VS): BP 130/80 mmHg, P 70, respiratory rate (RR) 16, T 98.6, Ht 5'4," Wt. 130 lbs.
Labs (nonfasting):

Na 139 mEq/L	K 3.8 mEq/L
CL 103 mEq/L	CO_2 26 mEq/L
BUN 10 mg/dL	Scr 0.7 mg/dL
Gluc 119 mg/dL	Plt 177 x 10^3/mm^3
Hgb 13.4 g/dL	Hct 39.5%
WBC 5.4 x 10^3/mm^3	INR 1.0

Hypercoagulability profile: positive for Factor V Leiden Mutation

What is/are the most appropriate anticoagulants and duration of anticoagulant therapy for A.F.?
For the acute phase of her therapy, she can receive either full dose UFH (80 U/kg bolus followed by an 18 U/kg/h infusion), LMWH (e.g., enoxaparin 1 mg/kg Q12h), or fondaparinux 7.5 mg QD (body weight 50-100 kg). The Seventh ACCP Guidelines do not make a preferential recommendation for LMWH or UFH in the treatment of acute DVT; however, they do state that the major advantages of LMWH appear to be convenience of administration and cost savings associated with home therapy or early hospital discharge.[35] As A.F. does not have any contraindications to anticoagulation therapy, her warfarin should be initiated on the first treatment day at a dose of between 5 and 10 mg for the first 1 or 2 days, with subsequent dosing based on the INR response. The UFH or LMWH may be discontinued after at least 5 days of therapy and when the INR is stable and > 2.0. A.F. has had 2 or more episodes of VTE along with the continuing risk factor of a coagulation disorder; therefore, indefinite therapy with dose-adjusted warfarin to a target INR of 2.5 is indicated. For prevention of post-thrombotic syndrome, AF should wear graduated compression stockings with a pressure of 30-40 mmHg at the ankle for at least 2 years (Grade 1A).[35]

A.F. comes in for her INR check and informs you she is having a colon polypectomy one week from today. It is 2 months since her acute DVT. The surgeon has instructed her to hold her warfarin prior to surgery in order to obtain an INR of 1.5 or less on the day of surgery. Her INR is 2.5 on a warfarin dose of 35 mg/wk.
AF is in the high-risk category for VTE, and since her acute DVT was less than 3 months ago, she will need to be bridged with either full-dose UFH or LMWH (preferred) preprocedure and postprocedure. She should be instructed to hold her warfarin starting 4 days prior to her surgery. Two days prior to surgery, she should begin full dose LMWH and to discontinue 12 to 24 hours before surgery. After surgery, she should resume full-dose LMWH and warfarin.

Case 2: New-Onset AF
M.B. is a 70-year-old female who was found to be in AF while undergoing a peri-operative evaluation before planned cataract surgery last week.
PMH: Hypothyroidism**,** Hyperlipidemia**,** Hypertension
FH: Father died at age 70 of a brain tumor; Mother CHD, AF, hypothyroidism, GI bleed, and died of an embolic stroke at age 82.
SH: M.B. is a retired teacher and lives at home with her husband; she has 2

daughters. She drinks up to 2 glasses of wine daily. She does not smoke and she participates in aerobics or walking for 60 minutes 3-4 times a week.

Meds: Levothyroxine 0.125 mg/day, HCTZ 25 mg/day, Metoprolol 50 mg/BID x 1 week

All: NKDA

ROS: No HA, blurred vision, chest pain, dizziness, or fainting spells: complains of occasional palpitations.

VS: BP 124/82 mmHg, P 100 bpm irregularly irregular, RR 20, T 97.6, Ht 5'5", Wt 150 lbs.

ECG: AF with a ventricular rate 120

Fasting Labs

Na 140 mEq/L	K 4.2 mEq/L
CL 99 mEq/L	CO_2 26 mEq/L
BUN 10 mg/dL	Scr 1.0 mg/dL
Gluc 96 mg/dL	Plt 293 x $10^3/mm^3$
Hgb 14.6 g/dL	Hct 42%
TSH 1.8 µU/ml	INR 1.0
TC 291 mg/dL	LDL 185 mg/dL
HDL 75 mg/dL	TG 150 mg/dL

What is the most appropriate antithrombotic therapy for M.B.?

M.B. has one intermediate stroke risk factor (age) and one high stroke risk factor (history of hypertension). Owing to the presence of at least one high risk factor, she should receive anticoagulation with dose-adjusted warfarin to a target INR or 2.5. M.B. has no contraindications to warfarin therapy, but because of her age, she should begin warfarin with $\leq$ 5mg/day for the first 2-3 days, with subsequent dosing based on the INR response. INR monitoring should begin after the initial 2 or 3 doses of oral anticoagulation therapy. Once stabilized, she should have her INR monitored every 4 weeks.

M.B. has been on a dose of 17.5 mg/wk (one 2.5 mg tablet daily) for the past week, her INR today is 1.8, decreased from 2.6 at the last visit.

The Seventh ACCP Conference does not make any specific recommendations for the management of the sub-therapeutic INR; however, they do suggest the weekly dose of warfarin be increased by 10% to 20% and that more frequent monitoring take place until the INR is stable. A dose adjustment of between 1.75 and 3.5 mg/wk may be prudent provided that the patient has been compliant with her regimen, her diet and alcohol intake have remained steady, and her medication regimen and her health status are unchanged. Using the patient's tablet strength of 2.5 mg, her weekly dose may be increased by 2.5 mg to 20 mg/wk. The change should be spread out over the course of the week (3.75 mg on Monday and Thursday with 2.5 mg on other days) and her INR should be rechecked in approximately one week.

M.B. has been maintained on 20 mg/wk of warfarin for the past 4 months. She comes in for her visit today and informs you that her cardiologist started her on amiodarone 2 weeks ago. She states that she started with 800 mg/day and is now on 400 mg/day. Her metoprolol was decreased to 50 mg QD to account for the drug interaction between metoprolol and amiodarone; however, no other medications have changed. Her INR today is 7.8, and she denies bleeding complaints.

The Seventh ACCP Conference gives us 2 options for patients with INRs $\geq$5.0 but < 9.0 who have no significant bleeding. Warfarin can be held for one or 2 days and resumed at a lower dose when the INR returns to normal.

Another option is to hold warfarin and administer oral vitamin K_1 in a dose of 1-2.5 mg. Oral vitamin K_1 is available as a 5-mg tablet. The cause of this patient's INR is attributable to a well-documented and significant drug interaction with amiodarone, which usually results in decreased warfarin requirements of 30%-50%.[42] Because of the significance of the drug interaction and the long half-life of amiodarone, it may be prudent to discontinue warfarin and administer oral vitamin K_1 in a dose of 2.5 mg to this patient. The INR should be rechecked within 24 to 48 hours and when it returns to normal, warfarin should be resumed at a dose of 8.75 mg-12.5 mg/wk.

Conclusion

Many changes have occurred in the management of thromboembolic disorders over the past several decades. Several new and more specific anticoagulant agents have been developed that do not require therapeutic drug monitoring owing to a predictable dose response. Guidelines for the management of patients requiring anticoagulation have been developed and are continually updated. The future of anticoagulant therapy will continue to bring new and more specific antithrombotic agents and antithrombotic combination therapy will become more prevalent in the treatment and prevention of thrombosis. Bleeding is the main complication of all antithrombotic agents. Pharmacists can play a vital role in providing management services to patients needing current and future antithrombotic therapy to ensure safety and efficacy.

References

1. Shapiro SS. Treating thrombosis in the 21st Century. *N Engl J Med.* 2003;349:1762-64.
2. ACCP-NHLBI National Conference on Antithrombotic Therapy. American College of Chest Physicians and the National Heart, Lung and Blood Institute. *Chest.* 1986;89:1S-106S.
3. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. *Chest.* 2004;126:163S-696S.
4. Hirsh J, Anand SS, Halperin JL, et al. Guide to Anticoagulant Therapy: Heparin. A Statement for Healthcare Professionals From the American Heart Association. *Circulation.* 2001;103:2994-3018.
5. Rosborough T, Shepherd M. Achieving target antifactor Xa activity with a heparin protocol based on sex, age, height, and weight. *Pharmacotherapy.* 2004;24(6):713-19.
6. Hirsh J, Raschke R.. Heparin and Low-Molecular-Weight Heparin: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy**.** *Chest.* 2004;126:188S-203S.
7. Geerts WH, Pineo GF, Heit JA, et al. Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:338S-400S.
8. Hull RD, Raskob GE, Rosenbloom D, et al. Optimal therapeutic level of heparin therapy in patients with venous

thrombosis. *Arch Int Med.* 1992;152:1589-95.
9. Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a standard care nomogram; a randomized controlled trial. *Ann Int Med.* 1993;119:874-81.
10. Cruickshank MK, Levine MN, Hirsh J, et al. A standard heparin nomogram for the management of heparin therapy. *Arch Int Med.* 1991;151:333-7.
11. Spinler S and Dager W. Overview of heparin-induced thrombocytopenia. *AJHP*. 2003;60:5S-11S.
12. Warkentin T, Greinacher A. Heparin-Induced Thrombocytopenia: Recognition, Treatment, and Prevention: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy**.** *Chest.* 2004;126:311S-337S.
13. Warkentin TE, Levine MN, Hirsh J, et al. Heparin induced thrombocytopenia in patients treated with low molecular weight heparin or unfractionated heparin. *N Engl J Med.* 1995;332:1330-35.
14. Bhandari M, Hirsh J, Weitz JI, et al. The effects of standard and low molecular weight heparin on bone nodule formulation in vitro. *Thromb Haemost.* 1998;80:413-17.
15. *Drug Facts and Comparisons* 2004 ed. Available at: http://www.efactsweb.com. Accessed December 2004.
16. Lovenox package insert. Aventis, 2004.
17. Buller H, Davidson B, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis. *Ann Int Med.* 2004;140:867-73.
18. Arixtra package insert. GlaxoSmithKline, 2004.
19. www.fda.gov/medwatch/SAFETY/2004/may04.htm. Accessed August 25, 2004.
20. A safety and efficacy trial evaluating the use of SanOrg34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation. http://clinicaltrials.gov/show/NCT00070655. Accessed 12/14/04.
21. SR34006 Compared to Placebo in Patients who have Completed 6 Months of Treatment for Symptomatic Pulmonary Embolism or Deep Vein Thrombosis. http://clinicaltrials.gov. Accessed 12/14/04.
22. Weitz J, Hirsch J, Samama M. New Anticoagulant Drugs: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:265S-286S.
23. Eriksson H, Wahlander K, Lundstrom T, et al. The oral direct thrombin inhibitor ximelagatran, and its subcutaneous form melagatran, compared with enoxaparin for prophylaxis of venous thromboembolism in total hip and total knee replacement: the EXPRESS Study-Preliminary Results. *Int J Clin Pract.* 2003;57:57-59.
24. Francis CW, Berkowitz SD, Comp PC, et al. Randomized,

double-blind, comparisons of ximelagatran, an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism after total knee replacement [abstract]. Presented at the American College of Hematology 44th Annual Meeting; December 2002; Philadelphia, Pa.

25. Eriksson H, Wahlander K, Lundstrom T, et al. Extended secondary prophylaxis with the oral direct thrombin inhibitor ximelagatran for 18 months after 6 months of anticoagulation in patients with venous thromboembolism: a randomized, placebo-controlled trial. *J Thromb Haemost.* 2003;suppl 1:abstract 0C005.
26. Halperin JL. A long-term randomized trial comparing ximelagatran with warfarin for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [abstract]. Presented at the 52nd Annual Scientific Session of the American College of Cardiology; March-April 2003; Chicago, IL.
27. Huisman MV. Efficacy and safety of the direct thrombin inhibitor ximelagatran compared with current standard therapy for acute, symptomatic deep vein thrombosis, with or without pulmonary embolism: A randomized, double-blind, multinational study. *J Thromb Haemost.* 2003;suppl 1: abstract 0C003.
28. Wallentin L, Wilcox RG, Weaver WD, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomized controlled trial. *Lancet.* 2003;362:789-797.
29. Eriksson UG, Bredberg U, Gislen K, et al. Pharmacokinetics and pharmacodynamics of ximelegatran, a novel oral direct thrombin inhibitor, in young healthy male subjects. *Eur J Clin Pharmacol.* 2003;59:35-43.
30. Dow Jones Newswires September 10, 2004.
31. Hirsh J, Fuster V, Ansell J, et al. AHA/ACC guide to warfarin therapy. *Circulation*. 2003;107:1692-711.
32. Guyatt G, Schunemann H, Cook D, et al. Applying the grades of recommendation for antithrombotic and thrombolytic therapy: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy**.** *Chest.* 2004;126(3):179S-187S.
33. Ansell J, Hirsch J, Poller L, et al. The Pharmacology and Management of the Vitamin K Antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy**.** *Chest.* 2004;126(3):204S-233S.
34. Ansell J, Hirsh J, Dalen J, et al. Managing Oral Anticoagulant Therapy. *Chest.* 2001;19: 22S-38S.
35. Buller H, Giancardo A, Russell D, et al. Antithrombotic therapy for venous thromboembolic disease: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy**.** *Chest.* 2004;126(3):401S-428S.
36. Morris TA, Samama M, Tapson V, et al. Antithrombotic Therapy for Venous Thromboembolic Disease. *Chest.* 2001;119: 176S-193S.

37. G. Singer D, Albers G, Dalen J, et al. Antithrombotic therapy in atrial fibrillation: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy**.** *Chest.* 2004;126(3):429S-456S.
38. Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic Therapy in Atrial Fibrillation. *Chest.* 2001;119: 194S-206S.
39. Warkentin T, Greinacher A. Heparin-Induced Thrombocytopenia: Recognition, Treatment, and Prevention: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy**.** *Chest.* 2004;126(3):311S-337S.
40. Salem D, Stein P, Al-Ahamad A, et al. Antithrombotic Therapy in Valvular Heart Disease—Native and Prosthetic: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy**.** *Chest.* 2004;126(3):457S-482S.
41. Stein PD, Alpert JS, Bussey HI, et al. Antithrombotic Therapy in Patients With Mechanical and Biological Prosthetic Heart Valves. *Chest.* 2001;119: 220S-227S.
42. Rotmensch HH, Belhassen B. Amiodarone in the management of cardiac arrhythmias: current concepts. *Med Clin North Am.* 1988;72:321-58.