

## Anticoagulation

## Delivery of Optimized Anticoagulant Therapy: Consensus Statement from the Anticoagulation Forum

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Millions of patients receive anticoagulant therapy to prevent or treat thromboembolism. High-quality evidence documenting the benefit of antithrombotic therapy for patients with mechanical heart valves, a history of venous thromboembolism, or atrial fibrillation is abundant.<sup>1-3</sup> However, antithrombotic agents are associated with a risk of bleeding. On death certificates, anticoagulants ranked first in 2003 and 2004 in the number of total mentions of “deaths for drugs causing adverse effects in therapeutic use.”<sup>4</sup>

In the US, the Joint Commission has brought significant attention to the safety of antithrombotic agents by challenging hospitals to “reduce the likelihood of patient harm associated with the use of anticoagulation therapy” as 1 of 2 new National Patient Safety Goals for 2008.<sup>5</sup> Warfarin, the only oral anticoagulant available in North America, is notorious for having both a narrow therapeutic index as well as numerous drug and dietary interactions.<sup>6-10</sup> The fear of bleeding complications and the need for frequent blood sampling are among the reasons that oral anticoagulant therapy is underutilized.<sup>11-14</sup>

The safety and effectiveness of both short- and long-term anticoagulation can

**OBJECTIVE:** To provide recommendations, policies, and procedures pertaining to the provision of optimized anticoagulation therapy designed to achieve desired clinical endpoints while minimizing the risk of anticoagulant-related adverse outcomes (principally bleeding and thrombosis).

**STUDY SELECTION AND DATA EXTRACTION:** Due to this document’s scope, the medical literature was searched using a variety of strategies. When possible, recommendations are supported by available evidence; however, because this paper deals with processes and systems of care, high-quality evidence (eg, controlled trials) is unavailable. In these cases, recommendations represent the consensus opinion of all authors who constitute the Board of Directors of The Anticoagulation Forum, an organization dedicated to optimizing anticoagulation care. The Board is composed of physicians, pharmacists, and nurses with demonstrated expertise and significant collective experience in the management of patients receiving anticoagulation therapy.

**DATA SYNTHESIS:** Recommendations for delivering optimized anticoagulation therapy were developed collaboratively by the authors and are summarized in 9 key areas: (I) Qualifications of Personnel, (II) Supervision, (III) Care Management and Coordination, (IV) Documentation, (V) Patient Education, (VI) Patient Selection and Assessment, (VII) Laboratory Monitoring, (VIII) Initiation and Stabilization of Warfarin Therapy, and (IX) Maintenance of Therapy. Recommendations are intended to inform the development of care systems containing elements with demonstrated benefit in improvement of anticoagulation therapy outcomes. Recommendations for delivering optimized anticoagulation therapy are intended to apply to all clinicians involved in the care of outpatients receiving anticoagulation therapy, regardless of the structure and setting in which that care is delivered.

**CONCLUSIONS:** Anticoagulation therapy, although potentially life-saving, has inherent risks. Whether a patient is managed in a solo practice or a specialized anticoagulation management service, a systematic approach to the key elements outlined herein will reduce the likelihood of adverse events. The need for continued research to validate optimal practices for managing anticoagulation therapy is acknowledged.

**KEY WORDS:** anticoagulant, antithrombotic, thromboembolism, vitamin K antagonist, warfarin.

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be optimized by a “systematic,” evidence-based approach to therapy, often in the context of dedicated anticoagulation management services (AMS).<sup>15,16</sup> The benefits of AMS are well documented.<sup>16,17</sup> However, the majority of anticoagulated patients in North America do not receive care from such services. Thus, recommendations for delivering optimized anticoagulation therapy (OAT) should apply to all clinicians involved in the care of outpatients receiving anticoagulation, regardless of the structure and setting in which that care is delivered.

This document is focused on outpatient care and describes policies and procedures designed to achieve desired clinical endpoints while minimizing the risk of anticoagulant-related adverse outcomes (principally, bleeding and thrombosis). Recommendations in this document are, whenever possible, supported by the best available evidence. However, for some issues, published evidence is inconclusive or unavailable. In all instances, recommendations herein represent the consensus opinion of all authors. We constitute the Board of Directors of the Anticoagulation Forum, an organization dedicated to optimizing anticoagulation care for all patients ([www.acforum.org](http://www.acforum.org)).

**Section I: Qualifications of Personnel**

1.1 Optimized anticoagulant therapy should be provided by healthcare professionals licensed in a patient-oriented field (eg, medicine, nursing, pharmacy) possessing core competency related to anticoagulation therapy.

**COMMENT**

Healthcare professionals involved in the management of antithrombotic therapy should be educated in a clinical discipline, trained in patient assessment and care, and licensed in a patient-oriented healthcare field. Technical support personnel (eg, medical assistant, pharmacy technician,

nurse technician) may assist in selected aspects of anticoagulation management, including obtaining laboratory test results, scheduling appointments, and other nonclinical duties, but should not be directly involved in patient assessment and therapy management.

Because anticoagulant therapy is complex and associated with substantial risks, additional training is recommended. This training may be obtained in the work environment, through a formal didactic and/or experiential training program, or through self-study.<sup>15</sup> Such additional training, however, should not replace the aforementioned requirements regarding clinical training and licensing necessary to provide patient care. Examples of formal anticoagulant therapy management training programs are listed in Table 1. Core domains of competency for providers of OAT are outlined in Table 2. The National Certification Board of Anticoagulation Providers has been a pioneer in helping US healthcare professionals document (and be recognized for) their expertise in this area ([www.ncbap.org/](http://www.ncbap.org/)).

**Section II: Supervision**

2.1 In situations where OAT is provided by a dedicated AMS, a collaborative practice agreement with the healthcare practitioner(s) or organization ultimately responsible for patient care should be established. The collaborative practice agreement should assign day-to-day responsibility for anticoagulation management to AMS personnel and should clearly describe responsibilities, accountability, and job descriptions.

**COMMENT**

Optimized anticoagulation therapy is provided by a dedicated AMS in numerous healthcare settings, each with unique characteristics and structural elements and influenced by internal and external regulatory requirements as

**Table 1. Anticoagulation Therapy Training Programs**

Program	Comment
Certified Anticoagulation Provider	provided by the The National Certification Board for Anticoagulation Providers to formally recognize anticoagulation providers meeting educational and patient-care experiential requirements
Research Institute of the American College of Clinical Pharmacy Anticoagulation Training Program	a 4- to 6-wk intensive training program provided through the University of Texas and the Anticoagulation Clinics of North America
American Society of Health-System Pharmacists Foundation Antithrombotic Pharmacotherapy Traineeship	curriculum consists of a self-study program and a 5-day experiential program
University of Southern Indiana College of Nursing and Allied Health Professions Anticoagulant Therapy Management Certificate Program	interactive 6-wk, 40-h Internet certificate program for nurses, pharmacists, and physicians
Lovelace Clinic Foundation Advanced Preceptorship in the Management of Anticoagulation Therapy and Clinical Thrombosis	an in-depth course designed to meet the needs of physicians, nurses, and pharmacists working in or setting up clinics to monitor and coordinate the care of patients on anticoagulation therapy; each conference is limited to 30–40 participants to promote interaction with course faculty and provide networking opportunities

well as state and federal law.<sup>16,18-20</sup> Regardless of the practice setting, the overall AMS supervisory process and administrative matrix should be described with clarity. Furthermore, the roles and responsibilities of each member of the healthcare team involved in providing OAT, including the referring provider, should be clearly defined. Examples of AMS practice guidelines have been published.<sup>21</sup>

### Section III: Care Management and Coordination

3.1 Written policies and procedures for the delivery of optimized anticoagulation therapy should be established and approved by the individual who is ultimately responsible for the delivery of anticoagulant care. Policies and procedures should facilitate communication between all parties with a vested interest in the outcomes of anticoagulant therapy.

#### COMMENT

Policies and procedures serve as a clinical tool and a quality assurance mechanism to reduce variability in the delivery of care.<sup>22</sup> Any individual or dedicated AMS providing OAT should establish policies and procedures that address common and/or controversial issues that may arise (Table 3). Policies and procedures should be reviewed, updated as evidence becomes available, and approved regularly by appropriate committees (eg, a pharmacy and therapeutics or medical executive committee) and should be widely disseminated throughout the organization. These policies and procedures should also include protocols for routine dosing and follow-up determinations and should be available for review within the clinic at all times.

Coordination of anticoagulation therapy requires timely interaction among the anticoagulation providers, referring physicians, surgeons, specialists, dentists, pharmacists, laboratory personnel, skilled nursing facilities, assisted living facilities, and the patients and their caregivers.<sup>23</sup> Communication failures can result in poor patient outcomes.<sup>24</sup> Effective policies and procedures for the delivery of OAT

should reduce fragmentation of care by facilitating communication and transitions between healthcare team members with regard to anticoagulation therapy issues. Communication is essential to ensure optimal therapeutic outcomes and should conform to expectations set forth by applicable regulatory agencies (eg, boards of pharmacy, nursing, and medicine). Examples of AMS policies and procedures have been published.<sup>21</sup>

3.2 An efficient system for scheduling and tracking patients should be utilized.

#### COMMENT

Suboptimal anticoagulant therapy is often attributable to fragmented systems of care.<sup>24</sup> Key components supporting the delivery of OAT can be categorized as: (1) scheduling, (2) testing, (3) decision support, and (4) communication. A tracking system (eg, an electronic database) should be implemented to minimize the possibility that a patient on anticoagulation therapy could be lost to follow-up, even for a brief period.

### Section IV: Documentation

4.1 Accurate and easily accessible documentation systems should be used so that information pertinent to anticoagulation therapy can be retrieved in a timely fashion.

#### COMMENT

Computer software programs specifically designed to manage all aspects of anticoagulation therapy are widely available.<sup>25</sup> It is also possible to adapt existing computer software applications to meet anticoagulation monitoring needs or to use paper forms. The optimal anticoagulation therapy tracking system for a given healthcare environment should be dictated by factors such as the number of patients being monitored and existing information technology resources. For most settings, computerized anticoagu-

**Table 2.** Core Domains for Competency for Providers of Optimized Anticoagulant Therapy

Applied physiology and pathophysiology of thromboembolic disorders working knowledge regarding the normal physiological processes of hemostasis and thrombosis, and the etiology, risk factors, and clinical manifestations of pathologic thrombus formation
Patient assessment and management knowledge, skills, and competencies to manage and monitor patients on anticoagulant therapy including the ability to assess the efficacy and toxicity of the prescribed anticoagulant treatment, determine whether the therapeutic goals have been achieved, and identify patient-related variables that affect therapy
Patient education ability to provide patient education that is tailored to patients' specific needs to promote safety, enhance adherence, and positively affect clinical outcomes; perform an educational assessment; develop an educational plan; and document the educational activities in the patient's medical record
Applied pharmacology of antithrombotic agents in-depth knowledge regarding the pharmacologic properties of all antithrombotic drugs

<b>Table 3. Anticoagulation Management Issues for Which Established Policies and Procedures May Be Useful</b>
Assessing the risks and benefits of anticoagulation therapy
Documenting patient's understanding of anticoagulation therapy
Indications for anticoagulation therapy
Indication-specific target INR values
Determining the planned duration of anticoagulation therapy
Initiating anticoagulation therapy
Managing therapeutic and nontherapeutic INR values
Determining monitoring intervals for INR and other laboratory parameters pertinent to anticoagulation therapy (eg, complete blood cell counts, urinalysis)
Defining and documenting adverse events (eg, major bleeding, thromboembolism, death)
Defining the mechanism by which missed appointments will be flagged
Establishing a system for the timely reporting of laboratory results
Managing nonadherence to blood tests or clinic visits
Managing transitions between care settings (eg, inpatient to outpatient, inpatient to skilled nursing, outpatient to inpatient)
Defining criteria for discharging patients from a dedicated AMS
Reimbursement procurement
Defining and assessing quality measures
Interrupting anticoagulation for invasive procedures
Managing anticoagulation therapy during pregnancy
Coordination of anticoagulation therapy during travel
Defining eligibility criteria and follow-up requirements for patient self-testing
AMS = anticoagulation management service; INR = international normalized ratio.

lation tracking applications offer increased efficiency.<sup>25</sup> Table 4 contains a list of parameters that may be helpful to include in an anticoagulation tracking database, regardless of the type of documentation system used.

The documentation system should facilitate access to information relevant to quality assessment. It is suggested that parameters such as percent time-in-therapeutic-range, rates of major bleeding, thromboembolic events, and total deaths be recorded. To assess staff and other resource needs, trends in the number of patients managed should also be tracked.

### Section V: Patient Education

5.1 The delivery of optimized anticoagulant care should address the educational needs of patients and their caregivers.

#### COMMENT

Patient safety is enhanced when patients are actively involved in, understand, and take responsibility for their care.<sup>26</sup> Adherence to a

<b>Table 4. Elements of an Anticoagulation Patient-Tracking and Record-Keeping System</b>
Demographic
name
date of birth
sex
contact information for patient and caregivers (eg, phone numbers, home address, email address)
Treatment
indication(s) for anticoagulant therapy
target INR intensity
start date
anticipated/recommended duration of therapy
tablet strength(s) of vitamin K antagonist
risk factors for bleeding and clotting influencing anticoagulation therapy (eg, fall risk, alcoholism, inherited or acquired thrombophilia)
name, dose, route, frequency of administration, and start and stop dates for concomitant medications that could interfere with vitamin K antagonist (prescription and over-the-counter) including herbal products and dietary supplements
chronological flowchart documenting INR results and vitamin K antagonist dosages and other information pertinent to the patient's anticoagulation care
Communication
patient
documentation of patient education processes
copies of all letters sent to patients
documentation of other patient communications (eg, telephone calls, emails, postal letters)
other healthcare practitioners
summaries of all communications with other healthcare practitioners pertaining to anticoagulation therapy
Miscellaneous
complications of anticoagulation therapy (eg, bleeding, thromboembolism)
other pertinent laboratory values (eg, hemoglobin, hematocrit, urinalysis, fecal occult blood screening)
missed appointments
use of anticoagulants other than vitamin K antagonist (eg, unfractionated heparin, low-molecular-weight heparin, fondaparinux)
plans for interrupting anticoagulation therapy for invasive procedures
INR = international normalized ratio.

plan of care and the stability of anticoagulant effect, as measured by the international normalized ratio (INR), are improved when this is achieved.<sup>27,28</sup> Knowledge of anticoagulation therapy can be effectively imparted through face-to-face interactions and the use of written materials and other audiovisual resources to review and reinforce the educational process.<sup>29</sup> An approach to the learning process based on established models of education may be more likely to improve a patient's knowledge level compared with ad hoc programs.<sup>30</sup>

A knowledge assessment tool may help the clinician to assess an individual patient's educational needs.<sup>31</sup> Written materials at an appropriate reading level should be provided and, when possible, in the patient's native language. Local health literacy rates (a significant concern in many parts of the US) should be considered when patient educational materials are developed.<sup>32</sup> Important aspects of patient education related to anticoagulation therapy are summarized in Table 5.

### Section VI: Patient Selection and Assessment

6.1 Optimized anticoagulant therapy should be instituted only after careful consideration of the risk and benefit for an individual patient.

**COMMENT**

The ability to deliver OAT is highly dependent on patient selection, vigilant INR monitoring, and evidence-based treatment recommendations.<sup>1,33-36</sup> The initial patient assessment should include a comprehensive medical histo-

ry; family history of bleeding and/or clotting disorders; medications (including dietary supplements and over-the-counter drugs); social, lifestyle, and employment profile; health beliefs and attitudes; level of understanding; health literacy; personal health motivation; and healthcare resources. Risk factors for vitamin K antagonist-associated bleeding have been published.<sup>37,38</sup> Patients and/or their caregivers should be involved in the discussion of the risks and benefits associated with anticoagulation therapy and should agree with the decision as to whether to initiate/continue therapy.

6.2 The appropriateness of a treatment plan for any individual patient should be periodically reviewed throughout the course of therapy.

**COMMENT**

A thorough assessment of the various factors that influence warfarin dosing requirements (eg, diet, disease, other medications, alcohol use, adherence) should be completed at all routine patient visits. Since a patient's risk of thrombosis and bleeding can change over time, the indication, intensity, and length of anticoagulation therapy should be reevaluated periodically.<sup>39</sup> Ongoing reassessment will also allow the treating clinician(s) to apply new therapies, algorithms, or guidelines that may be developed.

### Section VII: Laboratory Monitoring

7.1 Optimized anticoagulation therapy should incorporate regular laboratory monitoring of anticoagulant effect. Vita-

**Table 5. Important Aspects of Anticoagulation Therapy Patient Education**

Indicate the reason for initiating anticoagulation therapy and how it relates to clot formation.
Review the name of anticoagulant drug(s) (generic and trade) and discuss how they work to reduce the risk of clotting complications.
Discuss the potential duration of therapy.
Explain the meaning and significance of the INR.
Explain the need for frequent INR testing and target INR values appropriate for the patient's treatment.
Discuss the narrow therapeutic index of warfarin and emphasize the importance of regular monitoring as a way to minimize the risk of bleeding/thrombosis.
Describe the common signs/symptoms of bleeding and what to do if they occur.
Describe the common signs/symptoms of clotting complications and what to do if they occur.
Outline precautionary measures to minimize the risk of trauma or bleeding.
Discuss the influence of dietary vitamin K use on the effects of vitamin K antagonists.
Discuss potential drug interactions (prescription, over-the-counter, herbal) and what to do when normal medication regimens change.
Discuss the need to avoid or limit alcohol consumption.
Explain the need for birth control measures for women of child-bearing age.
Review the importance of notifying all healthcare providers (eg, physicians, dentists) of the use of anticoagulation therapy.
Review the importance of notifying the anticoagulation provider when dental, surgical, or invasive procedures and hospitalization are scheduled.
Explain when to take anticoagulant medications and what to do if a dose is missed.
Discuss the importance of carrying identification (ID card, medical alert bracelet/necklace).
Document the fact that education of the patient (or caregiver) has occurred.
ID = identification; INR = international normalized ratio.

min K antagonists should be monitored with use of the prothrombin time test and reported as an INR.

#### COMMENT

Unique preanalytic, analytic, and postanalytic sources of error may, as with all laboratory tests, affect prothrombin time results.<sup>40,41</sup> Even when all of these variables are tightly controlled, there remains a clinically significant amount of variability between different test systems, depending on the specific coagulometer and thromboplastin combination utilized.<sup>42-44</sup> The reproducibility of results when repeated testing is performed on the same test system is quite precise, with a coefficient of variation generally below 5%. Replicate testing of the same sample on multiple different test systems results in a much greater degree of variation, and this variation increases significantly with higher intensity of anticoagulation.<sup>45,46</sup> Despite this variation between different test systems, the prothrombin time (and its derivative, the INR) has been shown to correlate with important outcomes in multiple clinical trials.<sup>6-8,47,48</sup>

The INR is a standardization method that attempts to minimize differences between thromboplastin reagents through a calibration process in which all commercial thromboplastins are compared with an International Reference Preparation (IRP) maintained by the World Health Organization (WHO).<sup>49</sup> The INR method is not perfect in correcting for differences among different laboratories utilizing different thromboplastin reagents, but it does reduce the variation among different laboratories and provides clinically useful results.<sup>50,51</sup>

7.2 Prothrombin time testing for optimized anticoagulation therapy should be performed on either plasma samples in a clinical laboratory or on whole blood capillary (fingerstick) samples utilizing point-of-care devices.

#### COMMENT

Both approaches have been validated and both provide results equivalent to results obtained with WHO IRP preparations. Both plasma (venipuncture) and whole blood (fingerstick) methods of prothrombin time testing have been used for decision-making in anticoagulant-related clinical trials.<sup>52-54</sup>

7.3 Prothrombin time testing for optimized anticoagulation therapy should be performed by professional laboratory staff, professional clinical staff, or properly trained patients or caregivers.

#### COMMENT

Laboratory testing has traditionally been performed in a clinical laboratory by trained laboratory professionals. The

development of whole blood prothrombin time testing has more recently allowed for the testing to move outside of the clinical laboratory. Multiple studies have validated that not only nonlaboratory medical professionals, but also properly trained patients, are capable of performing reliable prothrombin time testing. The bulk of the data suggest that, for properly selected patients, self-testing (at home) is cost-effective and leads to outcomes at least as good as those achieved with standard INR testing (at a clinical laboratory or in a clinic).<sup>52,55</sup> Barriers to widespread adoption of patient self-testing in the US include: (1) the lack of a single, evidence-based approach to identifying eligible patients, (2) reluctance on the part of many third-party payers to fund the machines and the test strips, and (3) the absence (in many primary care settings) of a well-developed system with which self-testing patients can be identified, educated, and have their follow-up ensured. Whether it is performed by the patient (at home) or by a healthcare professional (in a medical office), point-of-care testing offers efficiency for the clinician and eliminates any potential for delay between INR measurement and patient notification of results.

### Section VIII: Initiation and Stabilization of Warfarin Therapy

8.1 The initiation of optimized anticoagulation therapy should use a systematic, evidence-based approach.

#### COMMENT

The initiation of OAT should ensure that therapeutic concentrations of anticoagulant medications are achieved in a timely manner and that the risk of supratherapeutic INR values is minimized. Various approaches to achieving this goal are outlined in evidence-based guidelines and the medical literature and should be used in the development of systems for the initiation of OAT.<sup>56-60</sup> Clinicians should consider patient-specific factors such as age, weight, height, concomitant medications, and comorbidities when deciding on the starting doses of anticoagulant medications. Irrespective of the starting dose used, INR values should be monitored at least 2–3 times per week for the first 7–10 days (or until a stable dose is achieved) of vitamin K antagonist therapy.<sup>56</sup>

Although the presence of certain polymorphisms in the genes for CYP2C9 and vitamin K epoxide reductase complex subunit 1 is associated with lower maintenance doses, the role of pharmacogenetic testing in clinical practice remains uncertain. Several clinical trials designed to test the hypothesis that pharmacogenetic testing will improve patient care are ongoing. At this time, however, we do not believe that there is sufficient evidence of benefit to recommend routinely genotyping patients who initiate vitamin K antagonist treatment.<sup>61-63</sup>

Patients being started on vitamin K antagonist treatment often require concomitant unfractionated heparin, low-molecular-weight heparin (LMWH), or synthetic pentasaccharide (fondaparinux) during vitamin K antagonist initiation.<sup>56</sup> Healthcare professionals supervising initiation of vitamin K antagonist treatment should define the answers to questions such as: What laboratory parameters should be checked and how often? When should “overlap” heparin/LMWH/fondaparinux therapy be discontinued?

## Section IX: Maintenance of Therapy

9.1 The delivery of OAT should use a systematic process for longitudinal patient assessment, adjustment of anticoagulant drug doses, and scheduling of follow-up laboratory monitoring.

### COMMENT

Follow-up evaluation during OAT should document changes in medication, health status, diet, and adherence. Patients should also be assessed regularly for signs and symptoms of bleeding or clotting complications. Standardization of follow-up procedures using checklists or flow diagrams may increase the consistency of care.<sup>64</sup> For patients on a stable dose of a vitamin K antagonist, individual circumstances, such as medication changes, concurrent illness, or unexplained INR instability, will dictate the interval between follow-up assessments. However, current guidelines indicate that even patients with repeatedly therapeutic levels of anticoagulation should undergo INR measurement every 4 weeks.<sup>56</sup>

Validated algorithms for adjusting vitamin K antagonist doses should be incorporated into operating procedures. Evidence-based guidelines should be used to establish a systematic approach to responding to extreme INR values (eg, >4.5 and <1.5).<sup>56</sup> Likewise, a systematic approach that incorporates pharmacokinetic and pharmacodynamic principles should be employed to determine the interval between INR tests that maximizes the amount of time that anticoagulant concentrations are maintained within their therapeutic range.

9.2 The delivery of optimized anticoagulation therapy should utilize a systematic approach to the elective interruption and resumption of anticoagulant therapy for elective invasive procedures.

### COMMENT

Patients receiving a vitamin K antagonist may require temporary interruption of anticoagulant therapy to minimize bleeding risk associated with invasive procedures. The risk of excessive or uncontrolled bleeding associated with the procedure should be carefully weighed against the

potential for recurrent thromboembolism associated with the interruption in anticoagulation therapy.<sup>65-67</sup> Although no high-quality evidence to guide perioperative anticoagulation decisions exists, local (or institutional) standards regarding protocols, communication with interventionists, and patient education will reduce inconsistency when patients require invasive procedures. Both the person responsible for managing anticoagulation therapy and the person performing the invasive procedure should be in agreement regarding the anticoagulation therapy plan. Consensus guidelines, although based on evidence of limited quality, addressing this common clinical situation have been published (ref *Chest*, ACC/AHA, *International Angiology*).<sup>34-36,56</sup>

9.3 The delivery of optimized anticoagulation therapy should use a systematic approach in management and documentation of unexpected events (eg, bleeding, clotting, other potential anticoagulation-related adverse effects, or medical problems not related to anticoagulant therapy).

### COMMENT

Patients experiencing unexpected adverse events should be triaged and managed in a setting where the required care can be provided in a timely manner. Preferred interventions for the prompt reduction of the INR in bleeding patients (eg, infusions of fresh-frozen plasma, prothrombin complex concentrates, or recombinant factor VIIa, along with vitamin K) should be developed collaboratively with emergency care providers and based on available evidence.<sup>56</sup> The severity and location of the bleeding and the level of the INR should influence the approach and choice of a reversal agent. Policies should also be in place for managing patients with subtherapeutic INR results and/or thromboembolic events in a timely manner. As with patients who experience (or are at risk for) bleeding events, the plan for those presenting with a low INR or signs/symptoms of a thrombotic event will be dictated by clinical circumstances such as the underlying risk of thrombosis and the length of time during which the INR has been subtherapeutic. Systems should be developed to facilitate continuity of care when patients first seek medical attention in an emergency department. Any treatment rendered should be documented and communicated in a timely fashion to the person managing anticoagulation therapy.

## Summary

Anticoagulation therapy, although potentially life-saving, has inherent risks. Whether a patient is managed in a solo practice or a specialized AMS, a systematic approach to key elements will reduce the likelihood of adverse events. The guidelines in this article are intended to help healthcare providers at the point of delivery to optimize anticoagulation therapy. Even as new anticoagulant medications emerge, the

principles of patient selection, provider education and training, interruption of treatment for invasive procedures, and careful follow-up are likely to remain relevant.

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## References

1. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(suppl):401S-28S.
2. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903-12.
3. Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest* 2001;119(suppl):220S-7S.
4. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Arch Intern Med* 2007;167:1414-9.
5. Joint Commission. [www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/08\\_hap\\_npsgs.htm](http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/08_hap_npsgs.htm) (accessed 2008 May 28).
6. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003;349:1019-26.
7. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994;120:897-902.
8. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1996;335:540-6.
9. Juurlink DN. Drug interactions with warfarin: what clinicians need to know. *CMAJ* 2007;177:369-71.
10. Khan T, Wynne H, Wood P, et al. Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. *Br J Haematol* 2004;124:348-54.
11. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med* 2000;160:41-6.
12. Cohen N, Almozino-Sarafian D, Alon I, et al. Warfarin for stroke prevention still underused in atrial fibrillation: patterns of omission. *Stroke* 2000;31:1217-22.
13. Fang MC, Stafford RS, Ruskin JN, Singer DE. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. *Arch Intern Med* 2004;164:55-60.
14. Partington SL, Abid S, Teo K, Oczkowski W, O'Donnell MJ. Pre-admission warfarin use in patients with acute ischemic stroke and atrial fibrillation: the appropriate use and barriers to oral anticoagulant therapy. *Thromb Res* 2007;120:663-9.
15. Dager WE, Branch JM, King JH, et al. Optimization of inpatient warfarin therapy: impact of daily consultation by a pharmacist-managed anticoagulation service. *Ann Pharmacother* 2000;34:567-72. DOI 10.1345/aph.18192



16. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. *Chest* 2005;127:1515-22.
17. Locke C, Ravnani SL, Patel R, Uchizono JA. Reduction in warfarin adverse events requiring patient hospitalization after implementation of a pharmacist-managed anticoagulation service. *Pharmacotherapy* 2005;25:685-9.
18. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med* 1998;158:1641-7.
19. Ernst ME, Brandt KB. Evaluation of 4 years of clinical pharmacist anticoagulation case management in a rural, private physician office. *J Am Pharm Assoc* 2003;43:630-6.
20. Holden J, Holden K. Comparative effectiveness of general practitioner versus pharmacist dosing of patients requiring anticoagulation in the community. *J Clin Pharm Ther* 2000;25:49-54.
21. Oertel L. Personnel needs and division of labor. In: Ansell JE, Oertel L, Wittkowsky AK, eds. *Managing oral anticoagulation therapy*. New York: Aspen, 2003;4:1-4:30.
22. Tillman DJ, Charland SL, Witt DM. Effectiveness and economic impact associated with a program for outpatient management of acute deep vein thrombosis in a group model health maintenance organization. *Arch Intern Med* 2000;160:2926-32.
23. McCormick W. Medical-legal implications of anticoagulation therapy. In: Ansell J, Oertel L, Wittkowsky A, eds. *Managing oral anticoagulation therapy*. 2nd ed. St. Louis: Wolters Kluwer Health, Inc., 2005;14:1-14:7.
24. Ryan E. Risk management and anticoagulation therapy. In: Ansell J, Oertel L, Wittkowsky A, eds. *Managing oral anticoagulation therapy*. 2nd ed. St. Louis: Wolters Kluwer Health, Inc, 2005;9A-1, 1-11.
25. Oertel L, Mungall D. Software applications in anticoagulation management. In: Ansell J, Oertel L, Wittkowsky A, eds. *Managing oral anticoagulation therapy*. 2nd ed. St. Louis: Wolters Kluwer Health, Inc, 2005;5A-2, 1-11.
26. Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. *Ann Intern Med* 2000;133:687-95.
27. Saligari E, Belle L, Berry C, et al. [Evaluation of an education program of patients undergoing oral anticoagulation treatment] French. *Ann Cardiologie Angeiol (Paris)* 2003;52:297-301.
28. Barcellona D, Contu P, Marongiu F. Patient education and oral anticoagulant therapy. *Haematologica* 2002;87:1081-6.
29. Stone S, Holden A, Knapic N, Ansell J. Comparison between videotape and personalized patient education for anticoagulant therapy. *J Fam Pract* 1989;29:55-7.
30. Newall F, Monagle P, Johnston L. Patient understanding of warfarin therapy: a review of education strategies. *Hematology (Amsterdam)* 2005;10:437-42.
31. Zeolla MM, Brodeur MR, Dominelli A, Haines ST, Allie ND. Development and validation of an instrument to determine patient knowledge: the oral anticoagulation knowledge test. *Ann Pharmacother* 2006;40:633-8. Epub 21 Mar 2006. DOI 10.1345/aph.1G562
32. Estrada CA, Martin-Hryniewicz M, Peek BT, Collins C, Byrd JC. Literacy and numeracy skills and anticoagulation control. *Am J Med Sci* 2004;328:88-93.
33. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(suppl):483S-512S.
34. Salem DN, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease—native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(suppl):457S-82S.
35. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists; endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;114:e84-231.
36. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (writing committee to revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e257-354.
37. 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;105:91-9.
38. Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. *Chest* 2006;130:1390-6.
39. Kearon C. Long-term management of patients after venous thromboembolism. *Circulation* 2004;110(9 suppl 1):I10-8.
40. Delate T, Witt DM, Jones JR, Bhardwaja B, Senser M. Falsely elevated international normalized ratio values in patients undergoing anticoagulation therapy: a descriptive evaluation. *Chest* 2007;131:816-22.
41. Johnson SG, Witt DM, Eddy TR, Delate T. Warfarin and antiplatelet combination use among commercially insured patients enrolled in an anticoagulation management service. *Chest* 2007;131:1500-7.
42. van Rijn JL, Schmidt NA, Rutten WP. Correction of instrument- and reagent-based differences in determination of the international normalized ratio (INR) for monitoring anticoagulant therapy. *Clin Chem* 1989;35:840-3.
43. Lind SE, Pearce LA, Feinberg WM, Bovill EG. Clinically significant differences in the international normalized ratio measured with reagents of different sensitivities. SPAF Investigators. *Stroke Prevention in Atrial Fibrillation*. *Blood Coagul Fibrinolysis* 1999;10:215-27.
44. Woodhams BJ, Klein N, Harz D, Rose M, Ruiz JA. A study of the variability seen in the international normalized ratio obtained using different sensitivity thromboplastin reagents on different instrument types. *Blood Coagul Fibrinolysis* 1999;10:423-7.
45. Horsti J, Uppa H, Vilpo JA. Poor agreement among prothrombin time international normalized ratio methods: comparison of seven commercial reagents. *Clin Chem* 2005;51:553-60.
46. Olson JD, Brandt JT, Chandler WL, et al. Laboratory reporting of the international normalized ratio: progress and problems. *Arch Pathol Lab Med* 2007;131:1641-7.
47. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;349:631-9.
48. Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism (comment). *N Engl J Med* 2003;348:1425-34.
49. Loeliger EA, van den Besselaar AM, Lewis SM. Reliability and clinical impact of the normalization of the prothrombin times in oral anticoagulant control. *Thromb Haemos* 1985;53:148-54.
50. Hirsh J, Poller L. The international normalized ratio. A guide to understanding and correcting its problems. *Arch Intern Med* 1994;154:282-8.
51. Pi DW, Raboud JM, Filby C, Carter CJ. Effect of thromboplastin and coagulometer interaction on the precision of the international normalized ratio. *J Clin Pathol* 1995;48:13-7.
52. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. *Lancet* 2006;367:404-11.
53. Kaatz SS, White RH, Hill J, Mascha E, Humphries JE, Becker DM. Accuracy of laboratory and portable monitor international normalized ratio determinations. Comparison with a criterion standard. *Arch Intern Med* 1995;155:1861-7.
54. Menendez-Jandula B, Souto JC, Oliver A, et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. *Ann Intern Med* 2005;142:1-10.

55. Regier DA, Sunderji R, Lynd LD, Gin K, Marra CA. Cost-effectiveness of self-managed versus physician-managed oral anticoagulation therapy. *CMAJ* 2006;174:1847-52.
56. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(suppl):204S-33S.
57. Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. *Ann Intern Med* 2003;138:714-9.
58. Crowther MA, Ginsberg J, Kearon C, et al. A randomized trial comparing 5 mg and 10 mg warfarin loading doses. *Arch Intern Med* 1999;159:46-8.
59. O'Connell MB, Kowal PR, Allivato CJ, Repka TL. Evaluation of warfarin initiation regimens in elderly inpatients. *Pharmacotherapy* 2000;20:923-30.
60. Siguret V, Gouin I, Debray M, et al. Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. *Am J Med* 2005;118:137-42.
61. Joffe HV, Xu R, Johnson FB, Longtine J, Kucher N, Goldhaber SZ. Warfarin dosing and cytochrome P450 2C9 polymorphisms. *Thromb Haemos* 2004;91:1123-8.
62. Gage BF, Eby C, Milligan PE, Banet GA, Duncan JR, McLeod HL. Use of pharmacogenetics and clinical factors to predict the maintenance dose of warfarin. *Thromb Haemos* 2004;91:87-94.
63. Anderson JL, Horne BD, Stevens SM, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* 2007;116:2563-70.
64. Oertel L. Managing maintenance therapy. In: Ansell J, Oertel L, Wittkowsky A, eds. *Managing oral anticoagulation therapy*. 2nd ed. St. Louis: Wolters Kluwer Health, Inc., 2005, 4B-3, 1-5.
65. Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. *Arch Intern Med* 2004;164:1319-26.
66. Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: a systematic review. *Arch Intern Med* 2003;163:901-8.
67. Kovacs MJ, Kearon C, Rodger M, et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation* 2004;110:1658-63.

Fournir une Thérapie Anticoagulante Optimale: Prise de Position du Forum d'Anticoagulation.

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#### RÉSUMÉ

**OBJECTIF:** Donner des recommandations, des politiques, et des procédures concernant l'offre d'un service d'anticoagulation optimisé visant l'atteinte de résultats cliniques tout en minimisant le risque de résultats indésirables liés à la thérapie anticoagulante (saignements et thromboses).

**SÉLECTION DES ÉTUDES ET DE L'INFORMATION:** Considérant l'envergure du document, la littérature médicale a été scrutée à l'aide de différentes stratégies. Lorsque possible, les recommandations furent supportées par les évidences disponibles. Cependant, parce que ce manuscrit fait référence aux processus et systèmes de soins, des évidences de haute qualité (telle une étude randomisée) ne sont pas disponibles. Dans ces cas, les recommandations représentent un consensus d'opinions des auteurs participant au Conseil des Directeurs du Forum d'Anticoagulation, une organisation dédiée à optimiser les soins en anticoagulation. Ce conseil est composé de médecins, pharmaciens, et infirmières ayant démontré une expertise et une expérience significative dans le traitement de ces patients.

**RÉSUMÉ:** Les recommandations pour fournir une thérapie anticoagulante optimisée furent développées en collaboration avec les auteurs et se résument en 9 éléments clés: (1) Qualification du personnel, (2) Supervision, (3) Gestion des soins et sa coordination, (4) Documentation, (5) Education du patient, (6) Sélection du patient et évaluation, (7) Monitoring de laboratoire, (8) Initiation et stabilisation de la thérapie, et (9) Maintien de la thérapie. Les recommandations veulent favoriser le développement de systèmes de soins dont les éléments ont démontré des bénéfices dans l'amélioration des résultats des patients anticoagulés. Les recommandations pour dispenser une thérapie optimisée de soins de santé s'appliquent à tous les cliniciens impliqués dans les soins à ces patients, peu importe la structure et l'endroit où les soins sont donnés.

**CONCLUSIONS:** La thérapie anticoagulante, bien que salutaire, comporte des risques. Lorsqu'un patient est suivi par une personne seule ou par un service spécialisé en anticoagulation, une approche systématique comportant les 9 éléments cités permettra de réduire les risques inhérents à cette thérapie. La recherche continue pour dispenser une thérapie anticoagulante optimale est nécessaire et le besoin reconnu.

Traduit par Marc M Perreault