Anticoagulation Management Services: Are we providing a service or disservice?

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Introduction

The risks and benefits of a drug is an important consideration before starting any new therapy. In anticoagulant therapy, it is even more important as life threatening bleeding may occur in patients treated over long term. Because of the narrow therapeutic index, vitamin K antagonist therapy must be monitored carefully. The most common vitamin K antagonist, warfarin, will be discussed in this review. Drug levels below the target range afford less protection against thrombosis, whereas levels above the target range increase the risk of bleeding.

The essential components of anticoagulation depend on a vigilant physician, a co-operative patient and a reliable monitoring service. Any physician who manages anticoagulation realizes the time and effort that must be expended to achieve a therapeutic International Normalized Ratio (INR). Routine INR testing, appropriate dosing adjustment, active communication with patients and ongoing patient education are all part of the "routine".

In the last 10 to 15 years, there has been a shift in management from traditional physician-based settings to anticoagulation management services which is a clinic model staffed by pharmacists, nurses or physician assistants. Warfarin is challenging to use because of (1) the individual variability in dose response, (2) interactions with other drugs, (3) diet influences the variation of the dose, (4) monitoring that can be challenging, and (5) problems with miscommunication or non-adherence to the dosing regimen. The American College of Chest Physicians Consensus Conference on Antithrombotic and Thrombolytic Therapy endorses anticoagulation management services and concluded that failure to use them likely increases the risk of liability.[1]

Anticoagulation Management Services (AMS)

When the anticoagulation therapy is managed by a patient's personal physician along with the other patients in that physician's practice – the terminology is termed "usual/routine medical care." In these settings there may be no special system to track the patients, to educate them, or to ensure that they follow up with care. Dosing decisions are made based on knowledge and experience of the physician. In some practices a nurse is assigned to monitor the INRs, call the patient's with the results, and make dosing adjustments after the physician has reviewed the results.

An anticoagulation management service, often referred to as the Anticoagulation Clinic, employs a focused and coordinated approach to managing the patients. It is specialized and patient focused primarily on oral anticoagulation with warfarin. The individual differences between AMS vary depending on the health care setting. A program is often directed by a single physician who assumes no responsibility for the primary care of the patient under management. The actual management is conducted by registered nurses, nurse practitioners, clinical pharmacists, or physician assistants who function according

to protocols and acquire in depth experience managing these patients that are referred to the AMS. In some settings, these AMS providers will manage a panel of patients with direction provided by different primary or referring physicians for the individual patients, though this is becoming less popular.

The comprehensive management of the patients requires a knowledgeable health care provider, an organized system of follow-up, reliable monitoring and good patient communication.

National Certification Board for Anticoagulation Providers (NCBAP)

Anticoagulation providers are being encouraged to certify with the National Certification Board for Anticoagulation Providers (NCBAP).

The national certification process:

- was developed by a multi-disciplinary board to provide health care professionals a credentialing process.
- evaluates the provider's knowledge and skill to manage anticoagulation therapy.
- requires evidence of experience and a passing score on a comprehensive examination.
- can be one means to improve patient care in anticoagulant therapy by providing a framework to validate achievement of advanced knowledge and skills related to antithrombotic therapy.
- affords opportunity for professional recognition – it is the only multidisciplinary credentialing opportunity.
- is an incentive for career development, personal satisfaction.
- introduces a mechanism to implement a consistent standard of care nationwide.

Table 1: NCBAP History

1996	established multidisciplinary working group, developed domains, test items, etc.
1997-98	began process to develop & validate test items
1998	established the National Certification Board for Anticoagulation Providers
1999	awarded Certification credential for first time

Certification process is as follows:

1. Obtain Candidate Handbook & Domains (all web based)
2. Review eligibility criteria (Note: US license requirement cannot be waived.)

3. Submit application packet and fee (60 days prior to exam date)

   Experiential component is satisfied by documenting details of 36 patient clinical encounters. Entire application packet is reviewed before permission is granted to sit for exam.

4. Achieve passing score (>80%) on examination
5. Credential valid for 5 year period

Anticoagulation Forum (ACF)

Through the model of anticoagulation clinics, the Anticoagulation Forum (ACF) was established as a network of professionals involved in direct patient care in the setting of an AMS. The ACF promotes coordinated management of oral anticoagulation. The Anticoagulation Forum is a network of physicians, nurses and pharmacists involved in the therapeutic modality of oral anticoagulation therapy and the management of thrombotic disorders. Through the process of information exchange, medical education and scientific investigation, the Anticoagulation Forum promotes professional development and strives to enhance the quality of anticoagulation care.

Since its founding the Anticoagulation Forum has grown from a few dozen members to more than 3500 members representing more than 1500 anticoagulation clinics throughout the world. The ACF continues to be an important source of information and education for its expanding membership.

Through the years the ACF has been an advocate for improved patient care. Beginning in the early 1990s, the ACF strongly endorsed the use of an International Normalized Ratio (INR) to report prothrombin time results. It is a strong supporter of point-of-care prothrombin time monitoring and the concept of patient self-testing and patient self-management. The ACF has worked with the U.S. government to develop reimbursement schemes for the elderly who are covered through the U.S. Medicare system. More recently, the ACF has been a supporter of home treatment of venous thromboembolism with low molecular weight heparin since anticoagulation clinics are in an ideal position to be the focal point for overseeing home treatment programs. The ACF has also been active in educating its members about new anticoagulant therapies.

In its efforts to enhance the quality of anticoagulation care, the Anticoagulation Forum has:

1. Established guidelines for the development of anticoagulation clinics;[2]
2. Promoted the appropriate monitoring of anticoagulation through the use of International Normalized Ratio (INR);
3. Encouraged the expanded use of anticoagulation for established indications (atrial fibrillation);

4. Developed guidelines for the certification of anticoagulation providers;
5. Lobbied third-party payers to appropriately reimburse healthcare providers for the management of therapy;
6. Promoted the use of point-of-care monitoring for home monitoring of anticoagulation therapy (patient self-testing/self-management);
7. Collaborated in the development of guidelines for the implementation of patient self-testing/self-management;[3]
8. Advocated for improved reimbursement of patient self-monitoring;
9. Developed a website including an online resource to locate an anticoagulation clinic anywhere in the world;
10. Organized and sponsored biannual national education meetings on antithrombotic therapy and served as a venue for the publication of original research related to anticoagulation care.

Although the Anticoagulation Forum has not directly engaged in research, it serves as a conduit to channel research studies to interested participants. Access to the ACF network and its interface with hundreds of thousands of patients is a resource for answering questions and solving problems related to anticoagulation therapy. The Anticoagulation Forum's educational effort is its biannual education and research conference. Since 1991 the ACF has organized nine major national conferences held throughout the United States with more than 600 health care participants. Besides organizing an international roster of speakers recognized as experts in the field, the conference also provides a venue for ACF members to present the results of important new research. The ACF is funded primarily by unrestricted educational grants. There is no charge for members to join the Forum.

Usual Care versus AMS

There is growing evidence that better care is achieved in patients that are managed by anticoagulation clinics rather than with usual care (UC). In two randomized clinical trials comparing UC to AMS, discordant results were found. Matchar et al.[4] found that AMS in a managed care organization did not show improved care when compared to usual care. The effect was limited by the utilization of the service, adherence to the recommended target range, and additionally there was high turnover of patients. In the other study, Wilson et al.[5] found that AMS in three Canadian tertiary hospitals provided a modest improvement when compared to family physicians.

In other non RCT studies, the results were variable. A clinical pharmacist-run clinic reduced thrombosis rates (3.3% vs. 11.8% per patient-year) and reduced significant bleeding (8.1% vs. 35.0% per patient year).[6] In a study assessing the quality of AMS, a retrospective review of subjects being treated by general internists and family practitioners in Rochester, NY and the Research Triangle area of North Carolina, only 34% of eligible patients with atrial fibrillation received warfarin. The INR values were out of the target range close to 50% of the time, and the response to these out of range INR values was not always timely.[7]

Therapy managed by telephone has also been investigated. In a centralized, telephonic, pharmacist-run AMS, 39% of the subjects were less likely to experience a complication than patients in the UC group. This was mediated through improved therapeutic INR control. These patients spent 63.5% of their time within their target INR compared to 55.2% in the UC group.[8] At a Veterans Administration hospital, the telephone model was compared to the AMS. There was no difference between the two groups with respect to the time within the INR range, the rate of thromboembolic or serious bleeding events. These authors suggest that the telephone model may be a viable modification to the AMS model.[9] In two university affiliated AMS, differences in major bleeding and thromboembolic events between telephone-managed and face-to-face managed patients were not statistically different.[10]

Initiation and Maintenance of Dosing

A number of randomized studies have supported the use of lower initiation doses. Starting with a dose of 5mg warfarin resulted in an INR of >2.0 in about five days with less excessive anticoagulation when compared to 10mg initiation dose in hospitalized patients.[11, 12] For ambulatory patients, a higher initiation dose of 10mg for the first two days resulted in a 1.4 day earlier achievement of a therapeutic INR, without a difference in excessive anticoagulation.[13] If treatment is non-urgent (example: chronic stable atrial fibrillation) warfarin can be started without concurrent heparin administration. However, patients with protein C and/or S deficiency, require initiation of heparin simultaneously to protect against a possible hypercoagulable state caused by a reduction in the vitamin K-dependent coagulation factors.[14]

Therefore judicious selection of the dose is recommended and will depend on the patient's co-morbidities which affect anticoagulation (examples: impaired nutrition, liver disease, congestive heart failure and those that are high risk for bleeding).

Monitoring should begin after the first two or three doses of oral anticoagulation. When the INR is stable, the frequency of testing can be reduced to intervals as long as every four weeks. This will depend on patient compliance, fluctuations in co-morbidities and the addition or discontinuation of medications, dietary changes and the quality of dosing regimens.

Optimal Therapeutic Range of Anticoagulation

This is influenced by the indication for anticoagulation and by patient characteristics. Studies have focused on the optimal lowest effective therapeutic range. For venous thromboembolism and tissue heart valves, in patients with an INR intensity of 2.0 to 3.0 experienced less bleeding without sacrificing efficacy. Therapy with fixed

mini-dose warfarin (1mg or 2mg) is considered much less effective than that with dose adjusted warfarin in moderate to high risk situations (example: orthopedic surgery, deep vein thrombosis or pulmonary embolus). The results of many randomized controlled trials[15-19] have demonstrated the efficacy of warfarin in preventing strokes in patients with atrial fibrillation. The recommended target range of INR 2.0 to 3.0 was more effective than the combination of fixed-dose warfarin (3mg) and aspirin. INR values have not been evaluated in patients with acute myocardial infarction.

Table 2: Therapeutic Range of anticoagulation

	INR 2.0 to 3.0 (goal 2.5)	**INR 2.5 to 3.5 (goal 3.0)**
DVT or Pulmonary embolus	√	
Atrial fibrillation	√	
Tissue Heart valves	√	
Mechanical heart valves		√
Antiphospholid syndrome	Start with this goal	*Only if recurrent thrombosis
Lupus anticoagulant	Start with this goal	*Only if recurrent thrombosis
Protein C deficiency and Protein S deficiency	Start with this goal	*Only if recurrent thrombosis

Management of Nontherapeutic INRs

Fluctuation may occur due to a number of reasons: inaccuracy in INR testing, dietary changes in vitamin K intake, changes in absorption of the drug or vitamin K, effects of concomitant drug use and patient noncompliance.

INRs just outside the therapeutic range can be managed by adjusting the dose increments of 5 to 20% up or down. This usually based on the weekly dose of warfarin.

Table 3: Warfarin dosing schedule

Mon	Tue	Wed	Thu	Fri	Sat	Sun	Total Weekly dose
5	5	5	5	5	5	5	35 mg
5	5	5	5	5	5	**2.5**	32.5 mg
2.5	5	5	**2.5**	5	5	5	30 mg
2.5	5	**2.5**	5	**2.5**	5	5	27.5 mg

A single strength tablet of 5 mg is recommended for most patients. Fractions or multiples of the tablet can be used for different doses and/or alternative doses per week can be given on different days of the week. Dose adjustments should be done with increases or decreases of 5 to 20% and spread out over the week.[20]

Table 4: Managing Anticoagulation Therapy in Patients Requiring Invasive Procedures

Condition	Description
Low risk of thromboembolism*	Stop warfarin therapy approximately 4 d before surgery, allow the INR to return to near normal, briefly use postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH and simultaneously begin warfarin therapy; alternatively, a low dose of UFH or a prophylactic dose of LMWH can also be used preoperatively
Intermediate risk of thromboembolism	Stop warfarin approximately 4 d before surgery, allow the INR to fall, cover the patient beginning 2 d preoperatively with a low dose of UFH (5,000 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
High risk of thromboembolism†	Stop warfarin approximately 4 d before surgery, allow the INR to return to normal; begin therapy with a full dose of UFH or a full dose of LMWH as the INR falls (approximately 2 d preoperatively); UFH can be given as an SC injection as an outpatient, and can then be given as a continuous IV infusion after hospital admission in preparation for surgery and discontinued approximately 5 h before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery; it is also possible to continue with SC UFH or LMWH and to stop therapy 12–24 h before surgery with the expectation that the anticoagulant effect will be very low or have worn off at the time of surgery
Low risk of bleeding	Continue warfarin therapy at a lower dose and operate at an INR of 1.3–1.5, an intensity that has been shown to be safe in randomized trials of gynecologic and orthopedic surgical patients; the dose of warfarin can be lowered 4 or 5 d before surgery; warfarin therapy can then be restarted postoperatively, supplemented with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH if necessary

Chest 2004;126:204S-33S

* Low risk of thromboembolism includes no recent (> 3 mo) venous thromboembolism, atrial fibrillation without a history of stroke or other risk factors, and bileaflet mechanical cardiac valve in aortic position.

† Examples of a high risk of thromboembolism include recent (< 3 mo) history of venous thromboembolism, mechanical cardiac valve in mitral position, and old model of cardiac valve (ball/cage).

Table 5: Managing Elevated INRs or Bleeding in Patients Receiving VKAs

Condition	Description
INR above therapeutic range but < 5.0; no significant bleeding	Lower dose or omit dose, monitor more frequently, and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required
INR ≥5.0 but < 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently and resume at lower dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K1 (≤ 5 mg orally), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 (2 to 4 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K1 (1 to 2 mg orally) can be given
INR ≥9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K1 (5–10 mg orally) with the expectation that the INR will be reduced substantially in 24–48 h. Monitor more frequently and use additional vitamin K1 if necessary. Resume therapy at lower dose when INR therapeutic
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K1 (10 mg by slow IV infusion), supplemented with fresh plasma or prothrombin complex concentrate, depending on the urgency of the situation; recombinant factor VIIa may be considered as alternative to prothrombin complex concentrate; vitamin K1 can be repeated every 12 h
Life-threatening bleeding	Hold warfarin therapy and give prothrombin complex concentrate supplemented with vitamin K1 (10 mg by slow IV infusion); recombinant factor VIIa may be considered as alternative to prothrombin complex concentrate; repeat if necessary, depending on INR

Chest 2004;126:204S-33S

* If continuing warfarin therapy is indicated after high doses of vitamin K1, then heparin or LMWH can be given until the effects of vitamin K1 have been reversed and the patient becomes responsive to warfarin therapy. It should be noted that INR values > 4.5 are less reliable than values in or near the therapeutic range. Thus, these guidelines represent an approximate guide for high INRs.

Patient Self-Management of Anticoagulation

With the introduction of point-of-care (POC) prothrombin time monitors, the potential for patient self-testing and self-management has evolved.

After structured training by professionals, suitable patients are able to determine their anticoagulation intensity accurately and are able to adjust their dosages accordingly.[3, 21-26] POC testing devices give INR results which are comparable with those obtained in the laboratory. The most frequent testing frequency is weekly but lower frequency testing can be justified based on individual conditions.

A recent survey revealed that less than 1% of patients being managed by U.S. anticoagulation clinics use self-testing instruments. Barriers were the cost of self-testing instruments, cost of reagent cartridges, and fear of unintended self-management. 75% of the respondents believed that some reimbursement for the cost of the devices and supplies would increase the likelihood that anticoagulation clinics would recommend POC testing.[27]

Centers for Medicare and Medicaid Services (CMS) has approved coverage for mechanical heart valve patients to perform weekly in-home testing. CMS has issued their draft decision memo recommending a limited expansion of coverage for home monitoring devices. CMS is proposing to add coverage for home monitoring for patients with DVT and atrial fibrillation. Following this draft decision, the AC Forum submitted a second public comment recommending that they expand coverage to other indications as well. CMS' final ruling will be made within the next few months.

Health Literacy in Anticoagulation Management

Warfarin therapy requires frequent monitoring and dose changes to maintain anticoagulation within the therapeutic window. Education on the risks and benefits of the drug, understanding the dosing schedule, and diet and drug interactions all entail adequate provider communication for patients to be able to comprehend the information. Poor patient knowledge and lack of communication from providers are associated with worse outcomes that result in increased thrombotic or hemorrhagic events.[28, 29]

Brochures and patient education materials from industry and health advocacy groups are written at grade levels beyond the comprehension of most patients and therefore low-literacy brochures are needed.[30] Low literacy and numeracy were found to be associated with poor anticoagulation control.[31] A British study showed that there were gaps in the knowledge of patients from different ethic minorities and that the information provided by the providers to these minorities was deficient.[32]

Economic Consequences of Chronic Warfarin Therapy

Although warfarin reduces disability and thromboembolic events, it can result in fatal hemorrhage. Frequent monitoring of the INR is required. Since the advent of POC, patients can determine their INR without traveling to a clinic or a laboratory. Patients with POC will undoubtedly check their INRs more often and are within range more often than those tested in an anticoagulation clinic.

Table 6: Annual Anticoagulation Management Costs Per Patient

Number of Tests per Year					
Management Strategy	**Baseline**	**(Range)**	**Costs to Managed Care Organization**	**Costs to Patients and Their Caregivers**	**Total Management Costs**
Usual care	14	(9–23)	$157*	$239sup§	$396
Anticoagulation clinic testing	23	(11–28)	$233‡	$520"	$753
Patient self-testing	52	(29–73)	$660‡	$200¶	$860

J Gen Intern Med. 2000 January; 15(1): 31–37.

*Baseline estimates assume 2 minutes physician (MD) time for 90% of tests valued at $72/h, 13 minutes of nursing (RN) time per test valued at $23.40/h, equipment and supply cost of $4 per test

†Baseline estimates assume 2 minutes MD time for 10% of tests valued at $72/h, 15 minutes of RN time per test valued a t $23.40/h, $4 reagent cartridge per test and $1,385 per capillary monitor per 200 patients served, allocated over 5 years of use

‡Baseline estimates assume 2 minutes of MD time for 10% of tests valued at $72/h, 8 minutes of RN time per test valued at $23.40/h, $4 reagent cartridge per test, and $1,385 per capillary monitor allocated over 5 y of use

§Baseline estimates assume 17 minutes of patient (PT) and caregiver (CG) time per test valued at $14.10/h with CG accompanying 30% of PTs, 26 mi per test valued at $0.30/mi (CG assumed to travel with PT) and 52 travel minutes per test valued at $14.10/h (no mileage or travel time for 7 tests assumed to coincide with routine office visits)

‖Baseline estimates assume 20 minutes of PT and CG time per test valued at $14.10/h with CG accompanying 30% of PTs, 26 mi per test valued at $0.30/mi (CG assumed to travel with PT) and 52 travel minutes per test valued at $14.10/h (no mileage or travel time for 7 tests assumed to coincide with routine office visits)

¶Baseline estimates assume 15 minutes of PT and CG time per test valued at $14.10/h with CG assisting 9% of PTs with self-testing

Table 7: Adverse Event Costs

	Average Cost per Event	
Event Severity	**Thromboembolic Events**	**Hemorrhagic Events**
Fatal	$5,112	$11,232
Life-threatening	$19,280	$20,980
Serious	$10,684	$3,044

J Gen Intern Med. 2000 January; 15(1): 31–37.

Table 8: Number of Adverse Events per 100 Patients Over 5 Years

		Thromboembolic Events			Hemorrhagic Events		
Management Strategy	**Total**	**Fatal**	**Life-threatening**	**Serious**	**Fatal**	**Life-threatening**	**Serious**
Usual care	30.65	0.05	1.50	11.91	0.17	2.24	14.78
Anticoagulation clinic testing	26.95	0.04	1.27	10.48	0.14	1.85	13.17
Patient self-testing	22.10	0.03	0.82	6.92	0.12	1.62	12.60

J Gen Intern Med. 2000 January; 15(1): 31–37.

A cost-effective analysis based on 1997 dollars reveals that moving from UC to AMS would result in a total of 1.7 thromboembolic events and 2.0 hemorrhagic events avoided

per 100 patients over five years. Another 4.0 thromboembolic events and 0.8 hemorrhagic events would be avoided by moving to patient self-testing.[33] There are health and economic benefits of anticoagulation management services and patient self-testing.

Patients may accept inconveniences of therapy in the knowledge that it is beneficial to their health. Fear of stroke has been identified as a major factor influencing patients' decision to take warfarin.[34] Patients placed more value on the avoidance of stroke and less value on the avoidance of bleeding than did physicians who treat patients with atrial fibrillation.[35]

Conclusion

As health care providers we can reduce the economic burden of disease. We can ensure that patients who can benefit from anticoagulant therapy are actually receiving appropriate therapy and by efforts we can improve antithrombotic therapy to achieve a level of efficacy seen in RCTs. One of the principal means of controlling costs is to avoid out-of-range INR values.

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Websites

1. *National Certification Board for Anticoagulation Providers*:
   www.ncbap.org
   Multi-disciplinary group of anticoagulation providers that has established a national certification process in the US for anticoagulation providers, leading to the CACP (Certified Anticoagulation Provider) credential. Founded in 1998.

2. *Anticoagulation forum*:
   www.acforum.org
   Anticoagulation clinic provider group, predominantly pharmacists, nurses and some physicians. Founded in 1991.