Oral Anticoagulants

DAVID L MCGLASSON

ABBREVIATIONS: AMS = anticoagulation management service; DVT = deep vein thrombosis; GLA = gamma-carboxyl glutamic acid; GLU = glutamic acid; INR = international normalized ratio; IRP = international reference plasma; ISI = international sensitivity index; OAT = oral anticoagulant therapy; POC = point-of-care device; PT = prothrombin time; VTE = venous thromboembolism; WHO = World Health Organization.

INDEX TERMS: coagulation, ISI, OAT.

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David L McGlasson MS CLS(NCA) is a Research Clinical Laboratory Scientist at the 59th Clinical Research Suadron, Lockland AFB TX.

Address for correspondence: David L McGlasson MS CLS(NCA), Department of the Air Force, 59 MDW/MSRL, 2200 Berquist Dr, Ste 1, Lackland AFB TX 78236-5300. (210) 292-6555, (210) 292-6053 (fax). david.mcglasson@lackland.af.mil

George A Fritsma MS MT(ASCP) is the Focus: Anticoagulation guest editor.

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HISTORY OF ORAL ANTICOAGULATION

The discovery of oral medications to control thrombotic disorders in humans probably started with a report in 1922 by U.S. veterinarian Frank W Schofield. Dr Schofield reported a bleeding diathesis in cattle that simulated hemorrhagic septicemia and "black leg syndrome". He hypothesized that this disorder was due to feeding spoiled sweet clover to the cattle.[1]

In 1935, while studying the sterol metabolism of chicks in Copenhagen, 1943 Nobel Prize winner Henrik Dam discovered a bleeding tendency in the chicks fed a diet deficient in lipids. These results suggested the chicks lacked a substance necessary for normal coagulation; "Koagulations-Vitamin" or vitamin K. He studied this vitamin further with respect to its occurrence and biological function in animals and plants as well as its application in human medicine.[2]

In 1933 a Wisconsin farmer arrived at Karl Paul Link's laboratory at the University of Wisconsin-Madison with a pail of blood that would not coagulate. He also brought a small heap of spoiled sweet clover and a dead heifer in the back of his truck. Isolation and purification of the hemorrhagic compound led to the discovery of dicumarol (3,3-methylene-bis-{4-hyroxycoumarin}).[3] Clinical studies were immediately started on this compound, establishing the basis for rodenticides and the first oral anticoagulant. The compound greatly diminished prothrombin activity and delayed the clotting mechanism in blood. The first prophylactic and therapeutic effects and the drug's mechanism in influencing deep vein thrombosis were described in 1942.[4-6] Link, in 1948, went to the director of the Wisconsin Alumni Research Foundation with the suggestions that the foundation patent the newly synthesized 3-(1-phenyl-3-oxobutyl) 4-hydroxycoumarin as a rodenticide, and that it had applications for human use. Link stated, "From the beginning I had an intuitive feeling that this might be a good thing. A pretty bad thing for rats, but a good thing for humans."[7] The compound now known as Warfarin® is the most commonly used coumarin derivative worldwide. The term Warfarin is an acronym for the Wisconsin Alumni Research Foundation in recognition of its synthesis at the University of Wisconsin in 1948. The available compounds in different countries are either coumarin derivatives or indanedione derivatives.[8]

The vitamin-K dependent coagulation factors (FII, FVII, FIX, and FX) are produced in the liver as nonfunctional precursors. These precursors are activated in the presence of vitamin K by gamma-carboxylation of their glutamic acid (GLU) residues, forming gamma-carboxy glutamic acid (GLA). Carboxy-

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lation allows these coagulation factors to bind calcium, which is essential for their adhesion to platelet phospholipid membranes. The coumarins produce their anticoagulant effect on the vitamin-K dependent proteins by inhibiting the vitamin K conversion cycle and thus producing partially carboxylated proteins with reduced procoagulant activity.[9] Vitamin K antagonists also inhibit carboxylation of the regulatory anticoagulant proteins C and S as well as protein Z and osteocalcin. The reduction of the inhibitors of the coagulation mechanism could therefore cause a procoagulant effect.[9]

MONITORING ORAL ANTICOAGULANT THERAPY

Patients on oral anticoagulant therapy (OAT) require constant monitoring using the prothrombin time (PT). The PT responds to levels of three of the four vitamin K-dependent procoagulant factors, FII, FVII, and FX.

Physicians monitor patients on OAT by ordering monthly repeat measurements of the PT assay. They are then able to maintain each subject in a designated therapeutic range. There are many variables in the performance of the PT that may affect the test results. These include specimen collection and processing, instrumentation used to perform the assay, and the sensitivity of the thromboplastin reagent used to perform the PT assay. Each thromboplastin's sensitivity is indicated by its international sensitivity index (ISI). A wide variability in thromboplastin sensitivity has created problems for physicians when trying to monitor patients in different institutions with different reagent/instrument combinations. A subject monitored with a low sensitivity reagent (high ISI) may give a short PT of 14 seconds, while the same patient measured using a high sensitivity reagent (low ISI) may give a time of 18 seconds. These results may drastically affect the interpretation of the PT assay and the warfarin dosage in individual subjects.[10]

The World Health Organization (WHO) in 1977 introduced a standardized thromboplastin that was touted as an international reference preparation (IRP). The hope was that each laboratory could develop a therapeutic range for PT testing that was to be compared to the IRP-derived range. Further, in 1983 the WHO developed PT standardization based on the international normalized ratio (INR) that used the elements of the PT assay.

The INR is defined as the PT results that a laboratory would obtain if the test were performed using the standardized WHO reference thromboplastin reagent with an assigned ISI value of 1.0. Each assigned thromboplastin ISI could then relate the individual reagent sensitivity to an IRP that has been calibrated with a WHO reference plasma. The INR is calculated using the formula:

$$INR = (\text{patient PT}/\text{mean normal PT})^{ISI},$$

where the ISI denotes the ISI of the reagent thromboplastin used to perform the PT measurement at the testing laboratory.

While the use of the INR has been routinely accepted, it is not perfect. A few of the potential problems with the INR are as follows: the results may not be reliable at the onset of warfarin therapy and for screening for a coagulopathy in patients with liver disease. Problems with the precision of the INR determination and reagent ISI may occur. Effect of instrumentation on ISI values depends on whether the instrument employs mechanical or photo-optic clot detection. Reliability of the ISI result provided by the manufacturer certainly can not be fully generalized since there are over 300 ways to perform a PT in the United States according to College of American Pathology (CAP) surveys. Incorrect calculations of the INR resulting from the use of inappropriate control plasma or laboratories using the wrong method to calculate the INR have occurred. Problems have developed with different citrate concentrations being used to determine the PT. This has improved in recent years. Some reagents with high ISI values have been a problem when monitoring subjects with a lupus anticoagulant (LA). There are several references that discuss potential problems with the INR.[9-12]

Therapeutic application of oral anticoagulant therapy

OAT usage regimens have been established in a number of disease states through clinical trials. Disease states include venous thromboembolism (VTE), deep-vein thrombosis (DVT), subjects with tissue or mechanical prosthetic heart valves, atrial fibrillation, acute myocardial infarction (AMI), and subjects at risk of MI, stroke, recurrent infarction, and subjects with antiphospholipid antibody syndrome.

In most subjects the anticoagulant effect is first detected two to seven days after the starting of OAT. When a rapid response is desired, heparin (fractionated or unfractionated) is given concurrently. Large loading doses of Warfarin are contraindicated as they cause rapid drops in both FVII and protein C, producing thrombophilia. A five mg dose of warfarin usually achieves a therapeutic INR of 2.0 within five days. Heparin is then discontinued. However, it may take longer in some subjects to achieve a stable INR.[13] To date there does not appear to be a standard dosing regimen. Several factors need to be considered such as age, weight, disease state, diet, and medications. Initial

doses of less than five mg could be necessary in the elderly, in patients with impaired nutrition or liver disease, and in patients at risk for bleeding.[13] The dosage required to maintain a therapeutic INR range on subjects greater than 60 years of age decreases with increasing age. This may be because the clearance of warfarin seems to decrease. There may also be drug interactions that influence the warfarin effectiveness in controlling the INR.[14-18] In children there is an even greater necessity to decrease doses to 0.32 and 0.09 mg/kg/day in those less than one year of age and 11 to 18 years of age respectively.[19]

Table 1. Drugs that interact with vitamin K antagonists

Drugs that potentiate vitamin K antagonists

Acetaminophen	Ketoconazole
Amiodarone	Ketoprophen
Androgens	Lovastatin
Aspirin	Methylsalicylate (topical)
β-blockers	Metronidazole
Chloramphenicol	Micanazole
Cimetidine	Oxyphenbutazole
Quinilones:	Phenytoin Piroxican
Ciprofloxacin	Quinidine
Norfloxacin	Simvastatin
Pravastatin	Sulfamethoxazole
Antipyrine	trimethoprim
Corticosteroids	Glutethimide
Disulfiran	Sulfonamides
Erythromycin	Tamoxifen
Fluconazole	Tetracyclines
Fluoxetine	Thyroid hormone
Glucagon	Tolmentin
Indomethacin	Tricyclic antidepressants
Influenza vaccine	Vitamin E

Drugs that decrease anticoagulant response

Antipyrine	Glutethimide
Antithyroid drugs	Griseofulvin
Ascorbic acid	Mercaptopurine
Barbiturates	Methaqualone
Carbamazepine	Nafcillin
Contraceptives, oral	Rifampin
Dichloralphenazone	Simethicone
Dicloxacillin	Sucralfate
Furosemide	Chinese herbal supplement-danshen

Diet and medications play a significant role in the maintenance of a subject on OAT. Patients are encouraged to avoid major changes in diet. In particular they are urged to avoid avocados, kale, and parsley. They should eat up to one daily serving only of broccoli, brussels sprouts, spinach, turnip greens, or other greens. This can also include lentils such as soybeans or garbanzo beans, and meats such as liver. Alcohol intake should be limited to the occasional drink. They should avoid supplements such as vitamin A, C, and E, herbal remedies, and traditional medicines because they influence the anticoagulation.[8] Many medications can either increase or decrease the INR thus making it difficult to regulate the patient in the therapeutic range. For a list of some of these medications see Table 1.

The PT/INR is performed daily until the therapeutic range has been achieved and maintained for at least two consecutive days, then it is monitored two or three times weekly for one to two weeks, then less often depending on the stability of the INR results. If the INR is stable the time between testing can be as long as every four weeks. There is a lot of evidence to suggest that the more frequently a patient is tested the more the dosage will remain in the therapeutic range. Adjustment to the dosing of warfarin may be needed due to changes in the subject's condition so the cycle of frequent monitoring of the INR may again be necessary.[13]

The target range for therapeutic management of the INR is 2.0 to 3.0 in most disease states. Subjects with tissue or mechanical heart valves or recurrent thromboembolic disorders, such as antiphospholipid syndrome should be kept in the 2.5 to 3.5 INR range. The presence of the LA can interfere with the PT assay and give results that may not truly reflect the patients' Warfarin dosing requirements.[11, 20] In this instance, subjects with lupus anticoagulants (LA) may need to be monitored with another assay such as a chromogenic FX assay.

Prophylactic monitoring of oral anticoagulant therapy

Long-term anticoagulation is not without risks. Many disease states require individuals to be anticoagulated for long periods of time, perhaps for the rest of their lives. While there is consensus in prosthetic heart valves, stroke, uncontrolled atrial fibrillation, and antiphospholipid syndrome, dosages in other long-term thrombophilic conditions is still under study.

The primary determinants of the risk of hemorrhage are the duration and intensity of anticoagulation therapy. Recent studies have focused on the duration of OAT that provides the most favorable risk-benefit ratio.[21] It is currently recom-

mended that when VTE develops in a subject with reversible or time-limited risk factors, the patient should be treated with an oral anticoagulant for at least three months; patients with a first episode of idiopathic venous thromboembolic should be treated for six months; and subjects with recurrent idiopathic venous thromboembolism or a long-term risk factor, e.g., cancer, antithrombin deficiency, or antiphospholipid antibody syndrome should be treated for 12 months or longer.[22] However the optimal intensity of OAT has received less attention until now.[21]

Recent studies of long-term, low-intensity VTE prophylaxis have yielded inconsistent results. One study compared conventional anticoagulation (INR: 2.0 to 3.0) and low-density warfarin dosing (INR: 1.5 to 1.9) for extended treatment of unprovoked VTE in a randomized double blind trial study. The study enrolled 739 patients for 2.3 years. Their conclusion was that low-intensity warfarin was less effective than conventional-intensity warfarin for extended treatment of unprovoked VTE and was not associated with less bleeding.[23] A subsequent study compared placebo to low-intensity INR (1.5 to 2.0) in subjects with recurrent VTE, major hemorrhage and death for up to 4.3 years. The investigators concluded that long-term, low-intensity warfarin therapy is a highly effective method of preventing recurrent VTE. Thus low-dosage OAT remains an open question.

Clinical complications of oral anticoagulant therapy

When comparing absolute numbers, vitamin K antagonists cause more fatalities than any other drug.[8] The principal complication, affected by patient condition, is hemorrhage. The gastrointestinal tract, in particular peptic ulcers, is the most common site for major hemorrhages.[25,26] Intracranial bleeding yielded a death rate of 77% in a study of subjects admitted to a neurosurgery service.[27] The risk of an intracranial hematoma after a minor head injury is thought to be ten times higher when a patient is receiving OAT.[8] For a list of predictors for hemorrhagic complications see Table 2.

Nonhemorrhagic complications are not as prominent. They include conditions such as skin necrosis. This condition predominantly affects women and may be related to the distribution of subcutaneous fat. Areas such as the breast, thigh, and buttocks are the most susceptible. The onset is three to ten days after starting the OAT. Necrosis may be caused by an imbalance between severely depressed levels of protein C and S. A pre-existing protein C deficiency or large loading doses of warfarin increase the risk. Vitamin K may be used to reverse necrosis.[8]

Blue toe syndrome may develop three to eight weeks after the start of OAT. This rare condition includes burning pain and dark blue discoloration of the toes and sides of both feet, and occasionally the hands. Most of the patients have underlying problems such as diabetes, heart, and peripheral vascular disease. Discontinuation of the OAT is necessary.

Table 2. Predictors for hemorrhagic complications[8]

Aortic valve prosthesis
Cerebrovascular disease
Elevated thrombomodulin in plasma
Factor IX propeptide mutation
History of alcohol abuse
Hyperanticoagulation
Increasing duration of treatment
Initial phase of anticoagulation
Old age
Peripheral vascular disease
Polymorphisms in cytochrome 450CYP2C9 gene
Poor anticoagulant control

Table 3. American College of Chest Physicians OAT recommendations-1998

INR <5.0 but above therapeutic range: Lower dose or omit next dose.

INR >5.0 but <9.0: If no added risk factors omit next two doses. If at risk omit next dose and give vitamin K orally (1-2.5 mg).

INR >9.0 with no bleeding: Give vitamin K orally (3-5mg).

INR >20.0 with severe bleeding (major overdose): Give vitamin K (10.0mg) IV with slow infusion and FFP or prothrombin complex concentrates.

Life-threatening bleeding: Hold off on warfarin therapy. Administer prothrombin complex concentrate supplemented with vitamin K (10 mg) by slow IV infusion. Repeat as necessary.

Vitamin K antagonists cause teratogenic embryologic abnormalities such as facial hypoplasia, stippled epiphyses, hypoplasia of the digits, optic atrophy, and mental impairment. Fetal central nervous system hemorrhage can occur in any trimester. Subjects should be counseled about the risks of OAT during any phase of pregnancy.[8]

Management of oral anticoagulation: recommendations

The American College of Chest Physicians in 1998 made a series of OAT management recommendations. Table 3 lists the management procedures for critically increased INRs. Table 4 lists the management of OAT during invasive procedures. These are excellent guidelines for the laboratory to understand when assisting the physicians in the management of the patient on OAT.

Table 4. Management of oral anticoagulation during invasive procedures[13]

Patient with low risk of thromboembolism with atrial fibrillation: Stop warfarin four days before surgery. Restart after procedure with low-dose heparin and restart warfarin therapy.

Patient with intermediate risk of thromboembolism: Stop warfarin therapy four days before surgery and allow INR to fall. Give low dose of LMWH to cover patient two days before surgery and then commence with LMWH and warfarin after surgery.

High risk subjects with a history of VTE or mechanical heart prosthesis: Stop therapy four days prior to surgery, allow the INR to return to a normal level, begin therapy with full dose of LMWH and continue infusion. Discontinue five hours before surgery. Restart LMWH and warfarin after surgery.

Subjects with low risk of hemorrhage: Low dose of warfarin with INR 1.3-1.5. Lower dose four to five days prior to surgery. Restart after surgery with LMWH and warfarin.

Dental surgeries: Usually are not at risk except for individuals with pre-existing coagulation problems such as single-factor deficiencies. High-risk subjects should discontinue warfarin for four days prior.

There may be better therapeutic range maintenance in subjects managed by an anticoagulation management service (AMS), typical of Europe, compared to individuals under the care of their personal physician, common in the USA.[13] The AMS system dramatically lowers the risks of major hemorrhage and recurrent thromboembolism. One report provided data on three defined population groups. The first group was treated by an initial AMS system. A primary care physician for OAT maintenance monitored a second cohort. Each of the AMS groups reported an impressive reduction in the incidence of major hemorrhage and thromboembolism, and the one group that evaluated death due to bleeding or thromboembolism found a reduction that approached a statistical difference.[29]

AMS programs have also been found to be cost effective because patients have fewer hospitalizations, emergency room visits, and in-patient days. One study cited a pharmacy-managed AMS with a reduction of $4,072 per patient-year.[30]

Most PT/INR testing is performed on plasma in hospital and clinic laboratories. This system requires patient travel, phlebotomy, and specimen transport. Point-of-care (POC) devices significantly improve time in-range.

Most POC devices require a capillary whole blood specimen. Test cartridges are coated with a thromboplastin reagent and clotting time results are converted to the equivalent of a plasma PT/INR result. Correlations to plasma results have been consistently favorable, especially when a local calibration method of the ISI against an IRP was compared to both the blood and plasma methods.[31]

POC allows properly trained patients to self-test and assist in self-management of their OAT. Self-testing promotes greater testing frequency much in the same manner that an insulin-dependent diabetic assists in monitoring their condition. Self-testing could also lead to better patient compliance because of the convenience of the testing. Several studies have confirmed the accuracy of patient-self testing in monitoring their condition. Almost all of the patients actually preferred the home-monitoring method of testing. One study in monitoring 325 patients split them into two distinct groups. Group one had 163 subjects, with their doses managed by a single investigator based on INR results from patient-self testing at home. In comparison, private physicians using venous sampling treated a second group, with 162 subjects. Over a six-month period the investigators recorded a rate of major hemorrhage of 12% in the second group versus 5.7% in the group that self-tested.[32]

There are a growing number of studies that indicate the superiority of studies that tout patient self-management and self-testing over the care of a primary care provider. However, this is after special subject training to implement the care and with a knowledgeable provider center.[13]

CONCLUSIONS

A recent article titled *Warfarin for Venous Thromboembolism, Walking the Dosing Tightrope*, states that it is possible that new, direct thrombin inhibitors will prove to have better safety and efficacy profiles than warfarin.[21] However, all anticoagulants carry the risk of bleeding complications. The fundamental problem is that antithrombotic agents in current use or in development are unable to distinguish between a pathologic thrombus, which is potentially dangerous, and hemostatic thrombus, which forms physiogically to restore and maintain vascular integrity and is therefore protective. The author goes on to state: "Until a magic bullet of antithrombotic therapy is found that specifically targets pathologic thrombi, we will continue to walk the tightrope of anticoagulant dosing."[21]

It is the responsibility of the clinical laboratory scientist to work closely with the physicians to give them best possible result to monitor subjects on OAT safely.

REFERENCES

1. Schofield FW. A brief account of a disease in cattle simulating hemorrhagic septicaemia due to feeding sweet clover. Can Vet Rec 1922;3:74.
2. Henrik Dam. Bibliography. Nobel Lectures, Physiology or Medicine 1942-1962, Elsevier Publishing Company, Amsterdam.
3. Overman RS, Stahmann MA, Sullivan WR, and others. Studies on the haemorrhagic sweet clover disease: IV. The isolation and crystallization of the haemorrhagic agent. J Biol Chem 1941;141:941.
4. Allen EV, Barker NW, Waugh JM. A preparation from spoiled sweet clover (3,3'-methylene-bis-(4-hydroxycoumarin)) which prolongs coagulation and prothrombin time of the blood: a clinical study. JAMA 1942;120:1009.
5. Butsch WC, Stewart JD. Clinical experience with dicoumarin, (3,3'-methylene-bis-(4-hydroxycoumarin). JAMA 1942;120;1256.
6. Lehmann J. Hyperprothrombinaemia produced by methylene-bis-(hydroxycoumarin): its use in thrombosis. Lancet 1 1942; 318.
7. Wisconsin Alumni Research Foundation Web Site. From WARF: Fifty Years, edited by WR Jordan III. Copyright 2003 Wisconsin Alumni Research Foundation.
8. Williams Hematology 6th ed. Schulman S. Oral anticoagulation, 2001;Chapter 132: p 1777.
9. Hirsh J, Dalen JE, Anderson DR, and others. Chest 2001;119:8S-21S.
10. McGlasson DL. A review of variables affecting PTs/INRs. Clin Lab Sci 1999;12:353-8.
11. McGlasson DL. Laboratory variables that may affect test results in prothrombin times (PT)/International Normalized Ratios (INR). Lab Med 2003;34:124-8.
12. WHO Technical Report Series. Guidelines for thromboplastins and plasma used to control oral anticoagulant therapy. In: WHO Expert Committee on Biological standardization. WHO, Annex 3 1999; 889;64-93.
13. Ansell J, Hirsh J, Dalen J, and others. Managing anticoagulant therapy. Chest 2001;119:22S-38S.
14. Gurwitz JH, Avorn J, Ross-Degnan D, and others. Aging and the anticoagulant response to warfarin therapy. Ann Intern Med 1992;116:901-4.
15. Redwood M, Taylor C, Bain BJ. The association of age with dosage requirement for warfarin. Age Ageing 1991;20:217-20.
16. James AH, Britt RP, Raskino CL and others. Factors affecting the maintenance dose of warfarin. J Clin Pathol 1992;45:704-6.
17. Mungall D, White R. Aging and warfarin therapy. Ann Intern Med 1992;117:878-9.
18. Bowles SK. Stereoselective disposition of warfarin in young and elderly subjects. Clin Pharmacol Ther 1994;55:172.
19. Andrew M, Marzinotto V, Brooker LA and others: Oral anticoagulation therapy in pediatric patients: A prospective study. Thromb Haemost 1994;71:265.
20. Bijsteerveld NR, Middeldorp S, Berends F, and others. Monitoring therapy with vitamin K antagonists in patients with lupus anticoagulant: effect on different tests for INR determinations. J Thrombosis Thrombolysis. 2000;9:263-9.
21. Schafer AI. Warfarin for venous thromboembolism-walking the dosing tightrope. N Eng J Med 2003;348:15.
22. Hyers TM, Agnelli G, Hull RD, and others. Antithrombotic therapy for venous thromboembolic disease. Chest 2001;119: (Suppl): 176S-93S.
23. Kearon C, Ginsberg JS, Kovacs M, Anderson DR and others. Low-intensity (INR 1.5-1.9) versus conventional-intensity (INR 2.0-3.0) anticoagulation for extended treatment of unprovoked VTE: a randomized double-blind study. Blood 2002;100(Suppl):150a abstract.
24. Ridker PM, Goldhaber SZ, Danielson MIA, and others. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003;348:15.
25. White RH, McKittrick T, Takakuwa J, and others. Management and prognosis of life-threatening bleeding during warfarin therapy: National Consortium of Anticoagulation Clinics. Arch Intern Med 1996;156:1197.
26. Choudari CP, Rajgopal C, Palmer KR. Acute gastrointestinal haemorrhage in anticoagulated patients: diagnoses and response to endoscopic treatment. Gut 1994;35:464.
27. Mathiesen T, Benediktsdottir K, Johnsson H, and others. Intracranial traumatic and non-traumatic haemorrhagic complications of warfarin treatment. Acta Neurol Scand 1995;91:208.
28. Feder W, Auerbach R. "Purple toes": an uncommon sequela of oral coumarin drug therapy. Ann Intern Med 1961;55:911.
29. Chiquette E, Amago MG, Bussey HI. Comparison of an anticoagulation clinic and usual medical care: anticoagulation control, patient outcomes and health care costs. Arch Intern Med 1998;158:1641-7.
30. Wilt VM, Gums JG, Ahmed OI, and others: Pharmacy operated anticoagulation service: improved outcomes in patients on warfarin. Pharmacotherapy 1995;15:732-79.
31. Tripodi A, Chantarangkul V, Clerici M, and others. Determination of the international sensitivity index of a new near-patient testing device to monitor oral anticoagulant therapy. Thromb Haemost 1997;78:855-8.
32. Beyth RJ, Landefeld CS. Prevention of major bleeding in older patients treated with warfarin: results of a randomized trial [abstract]. J Gen Intern Med 1997;12:66.