Periprocedural Anticoagulation Management in Orthopedic Patients: Overview and Description of a Program Utilizing Pharmacogenetics

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Abstract

Objective: To review current recommendations for periprocedural anticoagulation management strategies in orthopedic patients and to describe a program utilizing pharmacogenetics in warfarin management of orthopedic surgical patients.

Methods: Review of the literature and descriptive report.

Results: A large body of evidence supports the use of anticoagulation in surgical patients, and strategies for optimizing its use have been developed. Genetic markers, including single nucleotide polymorphisms (SNPs) found in cytochrome P450-2C9 (CYP2C9) and vitamin K 2,3-epoxide reductase complex 1 (VKORC1), have been identified that aid in the management of warfarin, a drug with a narrow therapeutic index complicated by the wide variability in dose–response. Several algorithms incorporating genetics have been published that demonstrate the potential for these models to predict warfarin doses. In our orthopedic patients (n > 1000), we have found a high correlation between actual therapeutic dose and pharmacogenetic-predicted dose (56%) as well as pharmacogenetic-refined dose (79%) and have demonstrated decreased adverse effects of supratherapeutic international normalized ratios and major bleeding.

Conclusion: The optimal method for periprocedural management of orthopedic surgical patients will depend on an institution’s policies and procedures as well as patient and clinician preferences. If warfarin is chosen for anticoagulation and an institution has the ability to genotype patients, the option to use patient-specific genetic information in addition to a variety of important patient-specific clinical information is available and has shown promising results for improved patient outcomes. A randomized trial is needed to determine the exact role of pharmacogenetics in patient management.

Venous thromboembolism (VTE), a frequent complication in patients undergoing orthopedic surgery, is costly, often debilitating, and can be life-threatening. In 2004, a study evaluating the pharmacoeconomic burden of VTEs demonstrated that 2.2% of patients developed a VTE over the 90-day period following total hip replacement, major knee surgery, or hip fracture repair. Patients who developed VTE in the hospital incurred charges $17,552 higher than those who did not develop VTE in the hospital, and those who developed VTE after discharge incurred charges $5765 higher than those who did not [1]. Several management strategies exist for preventing VTE in patients undergoing orthopedic surgeries, with a range of evidence supporting various methods.

Pharmacogenetic-based anticoagulation is a relatively new strategy that has emerged over the last few years that utilizes patient-specific therapy based largely on genetic factors in addition to known clinical factors. In this paper, we summarize the evidence for current practices in periprocedural anticoagulation for orthopedic patients, review the literature regarding pharmacogenetic-based clinical outcomes, and describe one approach using pharmacogenetics for VTE prophylaxis in patients undergoing total joint arthroplasties.

Prevention of VTE in Orthopedic Surgery Patients—Current Practices

Many risk factors are associated with the development of VTE including major surgery, prolonged immobility, obesity, increasing age, and a history of thromboembolism [2]. There is also evidence that factor V Leiden and prothrombin gene G20210A mutations make VTE more likely in some patients [3]. Other coagulopathies such as activated protein C resistance and protein C and S deficiencies also contribute to the likelihood of VTE occurrence [4,5]. Factors considered protective...
against VTE include ambulation before postoperative day 2, use of pneumatic compression devices in patients with BMI greater than 25 kg/m², and warfarin use after discharge [2].

Currently, American College of Chest Physicians (ACCP) guidelines for the prevention of VTE [6] recommend thromboprophylaxis for orthopedic surgeries given the favorable risk-to-benefit ratio and the associated reduction in hospital costs. ACCP recommends that patients undergoing total hip arthroplasty, total knee arthroplasty, or hip fracture surgery receive thromboprophylaxis for at least 10 days using a low-molecular-weight heparin (LMWH), fondaparinux, or adjusted-dose vitamin K antagonist (ie, warfarin) with an international normalized ratio (INR) target range of 2 to 3. As a patient’s stay is usually less than 10 days, this recommendation implies that postdischarge prophylaxis should be provided [6]. ACCP recommends an extended duration of prophylaxis for up to 28 to 35 days after surgery for total hip arthroplasty and hip fracture surgery patients who are at high risk for VTE [6]. The decision of when to initiate therapy (ie, preoperatively vs. postoperatively) should be based on an analysis of the risks and benefits of giving the pharmacologic agent. For LMWH, only small differences have been observed between starting pre- or postoperatively, and therefore both options are acceptable [6].

Of the 3 available LMWHs, enoxaparin has the most literature available on safety and efficacy, as it has been the most studied [7–9]. Dalteparin is indicated only for total hip arthroplasty, but enoxaparin is indicated for both total hip arthroplasty and total knee arthroplasty [7,8]. The dose of enoxaparin used for VTE prophylaxis is 30 mg subcutaneously every 12 hours for total hip arthroplasty and total knee arthroplasty; for those patients undergoing total hip arthroplasty, a dose of 40 mg subcutaneously with the first dose given 12 hours prior to surgery can be used [7].

Enoxaparin has been shown to reduce the incidence of VTE compared with warfarin when used as prophylaxis [4]. Colwell et al found that total hip arthroplasty patients managed with enoxaparin (30 mg every 12 hours) had a lower rate of VTE than those managed with adjusted-dose warfarin (0.7% vs. 1.1%; P = 0.008) [10]. Leclerc et al showed a statistically significant difference in deep vein thrombosis (DVT) occurrence among total knee arthroplasty patients who received enoxaparin 30 mg every 12 hours compared with those who received warfarin (DVT rate, 36.9% vs. 51.7%; P = 0.003); the absolute risk difference was 14.8% (95% confidence interval [CI], 5.3%–24.1%) [11]. Fitzgerald et al found that VTE developed in significantly fewer patients treated with enoxaparin as compared with those treated with warfarin (25.4% vs. 45.5%; P < 0.001) [12]. However, there was a statistically significant increase in bleeding (any clinically important hemorrhage) associated with enoxaparin (33.5% with enoxaparin vs. 23.3% with warfarin; P = 0.04); no difference in the rate of major hemorrhage between groups was seen [12]. Leclerc et al showed no significant difference in clinically overt bleeding between groups (warfarin, 26.6% [95% CI, 22.2%–31.7%]; enoxaparin, 30.1% [95% CI, 25.4%–35.2%; P > 0.2]) as well as no difference in the rate of major hemorrhagic complications (warfarin, 1.8% [95% CI, 0.8%–3.8%]; enoxaparin, 2.1% [95% CI, 1.0%–4.2%]; P > 0.2) [11].

In patients needing interruption in long-term anticoagulation, warfarin is typically stopped in time to allow the INR to fall to a value of 1.5 [13,14]. In patients with no known genetic variations, this time generally correlates to approximately 5 days for patients whose INR goal is 2 to 3, 6 days for patients whose INR goal is 3 to 4.5, and longer in patients who are slow warfarin metabolizers (exact length of time for each genetic variation is not known) [15]. LMWHs have been shown to reduce the risk of developing VTE when used as bridging therapy and offer an alternative to intravenous unfractionated heparin (UFH) for perioperative anticoagulation [15–19]. One such protocol described in the literature discontinues warfarin 5 to 6 days before surgery, initiates enoxaparin 1 mg/kg subcutaneously every 12 hours beginning 36 hours after the last warfarin dose and with the last dose of enoxaparin given 24 hours prior to procedure; postoperatively, enoxaparin 1 mg/kg is given subcutaneously every 12 hours (with the consideration of giving 30 mg subcutaneously every 12 hours on postoperative day 1 if patient is at high risk of bleeding), and warfarin is started (5 mg or the patient’s preoperative dose); finally, enoxaparin is discontinued when the INR is between 2 and 3 for 2 consecutive days [15,16]. The authors assessed patients for major and minor bleeding for 30 days after surgery and found major bleeding in 2.9% (95% CI, 0.8%–10.0%) and minor bleeding in 1.4% (95% CI, 0.3%–7.8%). The authors concluded that administration of LMWH according to a standardized bridging protocol has an acceptably low rate of bleeding complications and offers an alternative to inpatient UFH [15,16].

The newest agent used for VTE prophylaxis is fondaparinux. In clinical trials, fondaparinux has been shown to be more effective than enoxaparin in preventing VTE in major orthopedic surgery [20–24]. A phase 2 multicenter, double-blind, dose-ranging trial (PENTATHLON) evaluated fondaparinux 30 mg every 12 hours and fondaparinux 0.75, 1.5, 3, 6, and 8 mg once daily [21,22]. All doses of fondaparinux reduced the risk of VTE compared with enoxaparin, but 3 mg was the only dose with which there was a significant reduction (1.7% vs. 9.4%; P = 0.011). The risk of major bleeding increased with increasing doses of fondaparinux (0.75 mg [0% risk], 1.5 mg [0.5% risk], 3 mg [4.5% risk]), so the dose of 2.5 mg daily was eventually chosen [21,22]. Eriksson et al evaluated fondaparinux 2.5 mg daily plus placebo versus enoxaparin 40 mg daily plus placebo in hip fracture surgery patients [20]. Fondaparinux was associated with a 56.4% reduction in risk of VTE when compared with
Genetic Testing for Warfarin Dosing

Two genes have been extensively studied for their effects on warfarin dosing: cytochrome P450 2C9 (CYP2C9) and vitamin K 2,3-epoxide reductase complex 1 (VKORC1). CYP2C9 is responsible for the majority of warfarin metabolism, and VKORC1 is responsible for determining a patient’s sensitivity to warfarin. Variations in these genes can be homozygous (presence of mutation at both chromosomes) or heterozygous (presence of mutation at 1 chromosome). Knowledge of these 2 genes is likely to assist clinicians in understanding the time course of warfarin response (ie, patients who are slower metabolizers will take longer to reach steady state) as well as the strength of warfarin needed to successfully anticoagulate a patient (eg, 1 mg daily in sensitive patients vs. 10 mg daily in insensitive patients). Frequencies of genetic variations in both of these genes and the impact of these variations on stable warfarin dosing have been studied in a variety of populations.

Eight retrospective studies have been conducted to develop mathematical models (formulas based on patient variables) that will calculate an estimated dose for a priori warfarin dosing based on CYP2C9 and/or VKORC1 genotypes and other clinical variables [26–33]. The genotypic and ethnic make-up of the patient populations studied are summarized in Table 1. The models generated ranged from relatively simple models using only age and CYP2C9 genotype [32] to models using multiple clinical variables and genotypes for factor VII and factor X variants [33]. The most commonly utilized clinical variables were age, sex, and height and weight or body surface area (Table 2). Presence of either CYP2C9*2 or *3 (2 known variants of this gene causing slower metabolism) significantly reduced warfarin clearance compared with wild-type, the term used for the nonmutated gene known as CYP2C9*1 [28,32]. Presence of CYP2C9 variants accounted for between 5.7% [32] and 18.3% [26] of the variability in warfarin dosages. Mean warfarin dosages were significantly lower for patients with CYP2C9*2 or *3 compared with wild-type, with patients homozygous for the variants requiring lower doses than heterozygotes (Table 3) [26–29,31–34]. However, 1 study found no difference in mean warfarin doses between wild-type and CYP2C9*2(32), and another showed no difference between wild-type and CYP2C9*5(29). Patients with CYP2C9*2, or *3 are also more likely to be overanticoagulated during induction [34]. Hetero- and homozygosity for VKORC1 variants have also been associated with lower dosage requirements compared with wild-type [27,28,30,31,33]. Presence of a VKORC1 variant allele accounted for 15% [28] to 28.8% [33] of the variability in warfarin dosages. Combining clinical variables and genotypes for both CYP2C9 and VKORC1 yielded models that accounted for 20.4% [32] to 79% [31] of the variability in warfarin dosages. Addition of factor VII and factor X genotypes [33] resulted in a model that explained 51.4% of the variability in warfarin dosages and does not appear to improve the predictive ability than other models that do not include factor VII/X genotypes.

In addition to several small (<50 participants) prospective studies examining the accuracy of pharmacogenetic-guided warfarin management, there have been 3 prospective studies that validated pharmacogenetic dosing models [27,35,36]. Tham and colleagues tested their model against a validation cohort of 108 patients [27]. They found that a majority of predicted doses (51.9%) were within 1 to 0.5 mg/day of the actual doses. However, their model tended to overdose patients with VKORC1 variants, with the model predicting as much as a 2-fold higher dose than the actual dose. Caraco and colleagues compared the use of a clinical algorithm to a genetic algorithm in 191 inpatients. Patients dosed using the genetic-based algorithm reached therapeutic INR and stable warfarin dose faster than patients dosed using the clinical algorithm (P<0.001). Additionally, patients remained in their therapeutic range longer (80% vs. 63%) and experienced less adverse effects (minor bleeding events, 3.2% vs. 13%) if they were dosed using the genetic algorithm (both results were statistically significant) [36]. You and colleagues estimated that the marginal increase in cost using a pharmacogenetic dosing approach would be offset by a decrease in bleeding rates [37]. However, while these small retrospective and prospective studies provide validation of a pharmacogenetic approach to warfarin dosing, a randomized clinical trial comparing pharmacogenetic dosing with the current standard of care is still needed.

A Program Utilizing Pharmacogenetics in Warfarin Management of Orthopedic Surgical Patients

Barnes Jewish Hospital at Washington University (BJH), in St. Louis, MO, is the largest hospital in Missouri. This 1228-bed hospital employs 9373 and is staffed by 3000 physicians (30% of which are residents, interns, or fellows). In 2006,
there were more than 50,000 inpatient admissions, 16,000 inpatient surgeries, and 75,000 emergency department visits.

In 2004, the Anticoagulation Service (ACS) at BJH began offering service to the division of orthopedic reconstructive surgery. Our intention was to create a clinical and research service that would manage the anticoagulation for patients scheduled for elective orthopedic surgery with the intent to provide continuity of preoperative care, perioperative management, and postoperative follow-up using knowledge of each patient’s clinical and genetic factors. The ACS comprises a medical director, 3 pharmacists, a clinical research assistant, 2 statisticians, and various residents, interns, and medical and pharmacy students. In addition, the ACS works closely with a hematologist and several genetics lab supervisors as well as a senior research scientist who manages several projects in the laboratory. The ACS primarily serves patients undergoing total hip or total knee arthroplasty. As of 2006, the ACS began expanding their service to management of nonorthopedic patients requiring anticoagulation, such as those with atrial fibrillation, mechanical valves, stroke, or VTE.

Program Description

Our service is notified of all patients scheduled for elective orthopedic surgery, including total hip arthroplasty, high-risk patients undergoing total knee replacements, Birmingham hip resurfacing, reimplantation, and open wound drainage of infected hips as well as other procedures. Usually, the service is notified weeks in advance, but often, the ACS is notified immediately of new patients needing anticoagulation. Patients older than 18 years are invited to participate in our clinical research evaluating the efficacy of pharmacogenetic-based anticoagulation. Patients interested in participating give a mouthwash sample and a blood sample (taken during preoperative testing) for DNA testing. Informed consent is obtained. Patients not interested in participating in the study are managed and followed by the ACS without knowledge of their genotype.

The clinical research assistant prepares charts for each patient with upcoming surgeries. The patients are contacted and asked a series of questions that are used to predict their first 2 warfarin doses. These questions include age, race, gender, ethnicity, height, weight, previous use of warfarin, smoking status, and previous history of VTE, stroke, myocardial infarction, major bleed, or current liver disease. Additionally, a complete medication history is collected from each patient, with particular attention to known warfarin interactors (eg, amiodarone, cotrimoxazole, azoles, statins). Genotyping is performed by members of our team in

<table>
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<th>Study</th>
<th>Ethnicity</th>
<th>CYP2C9, %</th>
<th>VKORC1, %</th>
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CYP2C9 = cytochrome P450 2C9; V = variant; VKORC1 = vitamin K 2,3-epoxide reductase complex 1; WT = wild-type.
†Includes both hetero- and homozygous patients with the *2 variant.
‡Includes both hetero- and homozygous patients with the *3 variant.
§Includes both *1/*2 and *2/*2.
¶Includes both *1/*3 and *3/*3.
the hematology lab. Pyrosequencing and polymerase chain reaction are used to identify the genotypes of study patients using the sample of mouthwash and blood. Single nucleotide polymorphisms (SNPs) analyzed include CYP2C9*2, CYP2C9*3, and VKORC1 3673 G > A. Genotyping can often be completed in 4 to 6 hours when the need for the information is urgent; however, this is rarely needed for elective surgery.

Clinical and genetic information is entered into Excel databases by the clinical research assistant. As a verification method, clinical pharmacists or pharmacy students then enter the same information into the ACS Web site, WarfarinDosing.org, a NIH-funded site created in 2006 by the medical director of the ACS. This Web site uses our validated algorithms for orthopedic patients for initial and refinement dosing. The Web site (as well as the databases) calculates a predicted warfarin dose for the patient after incorporating various clinical (and genetic, if available) variables collected during the patient interview (as described earlier). Clinicians then round this number to the nearest whole number if greater than 4.0 or the nearest half if less than 4.0 and a prescription for 1 dose is called into a pharmacy of the patient’s choice. Patients are called the week prior to surgery and notified that a prescription for warfarin has been called into their local pharmacy and are asked to pick up the prescription and take it the day before their surgery at noon. This results in earlier therapeutic INRs without affecting surgical bleeding.

In the hospital, patients take warfarin at 5 PM with daily INR tests drawn around midnight. Target INR is 1.8 to 2.5 (per the hospital’s orthopedic practice) for most patients and 2 to 3 for high-risk patients. Clinical pharmacists round on these patients daily and evaluate daily INR response, medication interactions, estimated blood loss, and the patient’s clinical picture (ie, changes in patient’s kinetics or health status). Using this information and refinement dose suggestions from the Web site, adjustments in the warfarin dose are made after the second, third, and fourth warfarin doses. The clinical pharmacists’ warfarin recommendations are given to the orthopedic nurse practitioner who writes the daily warfarin orders. Patients are educated regarding warfarin safety and the management they will receive by the ACS on discharge. Patients are given a discharge prescription of their most recent estimated warfarin maintenance dose. Most patients are discharged home or transferred to an outside rehabilitation facility on the second or third day following surgery. Home health care or rehabilitation care orders are provided for nurses to obtain INRs on Mondays and Thursdays. Patients are anticoagulated for 32 days (6 weeks in high-risk patients) and biweekly INRs are obtained until the patient’s discontinuation date (more frequent testing is occasionally warranted). Pharmacists along with their students make clinical decisions at each INR and manage subtherapeutic and supratherapeutic INRs as needed.

### Measurement

We are continuously collecting and analyzing data to determine which variants affect dosing regimens and by how much. In earlier studies, the service evaluated cytochrome P450 genotype and its effect on mean warfarin doses [29]. From these studies, we developed and validated our pharmacogenetic dose initiation algorithm. This first collaborative prospective, open-label study used CYP2C9 genotype in addition to body surface area, amiodarone use, target INR, statin use, gender, age, and race to dose orthopedic patients immediately after surgery (all patients received 5–10 mg preoperatively). Results showed no significant difference in the proportion of patients who reached stable therapeutic INRs based on their genotype, but did show a significant difference in the percentage of patients with an adverse

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**Table 2. Clinical Variables Used in Pharmacogenetic Dosing Models**

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<tr>
<th>Study</th>
<th>Age</th>
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<th>Sex</th>
<th>Height</th>
<th>Weight</th>
<th>Ethnicity</th>
<th>Target INR</th>
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CYP2C9 = cytochrome P450 2C9; INR = international normalized ratio.

*Also included use of CYP2C9 inhibitors and dietary vitamin K intake.

†Also included history of liver disease, estimated blood loss during surgery, INR after 3 warfarin doses, and 1st and 2nd warfarin doses.
outcome (defined as INR > 4 or major bleed), indicating patients with CYP2C9 variants were at higher risk of an adverse event [35]. We proceeded to conduct several retrospective studies to understand how to combine CYP2C9 and VKORC1 SNPs plus clinical factors to estimate patients’ warfarin doses. These studies led to our second prospective, open-label study using CYP2C9 and VKORC1 genotype to preoperatively predict warfarin dose for orthopedic patients. These patients were also followed postoperatively, with dose adjustments made daily using a nomogram (R² value of 53% for predicted dose vs. therapeutic dose). We performed a multivariate analysis on 92 patients to determine which factors affect warfarin dose on day 3 following surgery. The results showed that INR on day 3, CYP2C9, estimated blood loss during surgery, and smoking were among the most likely to affect warfarin dose. Other factors less significant included first and second warfarin dose and VKORC1. This analysis comparing predicted dose and therapeutic dose produced an R² of 79% [31]. Using this information, we developed and validated our pharmacogenetic dose refinement algorithm in orthopedic surgical patients.

Given that several institutions are not currently genotyping patients, we also developed and validated clinical dosing algorithms [36,38]. In this study of approximately 370 orthopedic surgical patients, INR, estimated blood loss, warfarin doses, and statin use significantly predicted the therapeutic warfarin dose after 3 days of therapy (R² of 53% in the derivation cohort and 42% in the validation cohort). To answer the question of which algorithm is best, we are comparing a cohort of patients that received pharmacogenetic dosing with patients that received pharmacogenetic dosing and will have results available soon. We hope to soon begin a large randomized controlled trial to determine whether pharmacogenetic-based warfarin management is superior to warfarin management without knowledge of genotype. Data derived from our ongoing studies and continuous data analysis are used to update the pharmacogenetic and clinical dosing algorithms on WarfarinDosing.org (specific formulas have been published elsewhere [31,35,38].

**Innovation**

Although the field of pharmacogenetics is being incorporated into areas such as oncology, its utility in cardiovascular diseases, such as VTE prevention and treatment, is only recently beginning to be better understood. There are many advantages to pharmacogenetic testing. First, genotype adds another variable when looking at the patient scenario and making a decision on how to adjust warfarin dose. Knowledge of the patient’s genotype may better guide that decision, for example, lowering the dose if the patient is a slow metabolizer in order to prevent markedly elevated INR values [39]. Based on current research findings, the U.S. Food and Drug Administration has changed the label for

<table>
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<td>28.6 ± 10.4</td>
<td>20.9 ± 10.1</td>
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CYP2C9 = cytochrome P450 2C9; V = variant; VKORC1 = vitamin K 2,3-epoxide reductase complex 1; WT = wild-type.

†Average dose for *2/*3 and *3/*3 combined.
‡Reported in mg/week.
§Includes both hetero- and homozygous patients with the *2 variant.
¶Includes both hetero- and homozygous patients with the *3 variant.
††Includes both *1/*2 and *2/*2.
**Includes both *1/*3 and *3/*3.
warfarin to encourage practitioners to take into account a patient’s genetics when dosing the drug.

Limitations
In addition to the potential benefits of genetic testing for warfarin dosing, there are potential limitations. One potential limitation is cost. Genotyping platforms vary in cost but can be expensive. In addition, DNA samples can cost more than $200 each, depending on quantity and additional collection or reporting fees. However, insurance companies may cover these tests with appropriate documentation from the provider. Additionally, these costs may decrease over time in light of the warfarin labeling change. A limitation for applicability is how quickly an institution is able to genotype patients. In this population, patients are scheduled for elective surgery; therefore, the turnaround time for genotyping can take several days to weeks if necessary. Some have argued that there are insufficient data to support the widespread use of pharmacogenetic-guided warfarin dosing and that careful INR monitoring and consideration of clinical variables may be just as effective [40]. Finally, some are concerned that the genetic information could be used improperly, potentially increasing the risk of bleeding or thrombosis, for example, in the wrong patient population, in the absence of INR monitoring, or by ignoring other patient characteristics.

Summary
Several options exist for preventing VTE in patients before, during, and immediately after orthopedic surgery. The literature supports using LMWH, fondaparinux, or warfarin for patient undergoing hip or knee arthroplasty. Given warfarin’s complexity of use and the need for optimal management in the orthopedic patient due to their short duration as an inpatient, alternative management strategies other than existing published nomograms are needed. Achieving a therapeutic INR goal and minimizing adverse outcomes is possible when incorporating patient genotype into the clinical picture. Although preliminary data suggest that pharmacogenetic management of warfarin may be superior to clinical management alone, continued studies are needed to determine the optimal method for the management of warfarin.

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References


