

Development and implementation of a pharmacist-managed inpatient warfarin protocol

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Because of the complexities of warfarin administration and its bleeding complications, a pharmacist-managed protocol for warfarin administration was developed at Baylor University Medical Center. The protocol incorporated current clinical guidelines and evidence-based medicine. Clinical outcomes under the protocol were compared with those of usual care, physician management, in a pilot study. Twenty-nine patients were enrolled in the protocol group and 22 in the control group between August 2004 and November 2004. Results showed that patients in both groups achieved therapeutic ranges of warfarin within 6 days. However, the pharmacist-managed patients exhibited a trend toward fewer adverse drug reactions (7% vs 14%) and fewer supratherapeutic international normalized ratios (17% vs 27%) than the control group, although the difference was not statistically significant. Based on these results and the results of similar larger studies showing the effectiveness of pharmacist-managed warfarin administration, Baylor University Medical Center made the protocol available for use in the hospital in May 2005.

Warfarin administration presents several challenges. The first challenge is optimal dosing, with the goal of administering the lowest effective dose needed to maintain the target international normalized ratio (INR), which is 2 to 3 for most indications (1). Patients must be carefully monitored after each dose; the INR begins to increase within 24 to 36 hours of dosing, but antithrombotic effects are not present until approximately the fifth day of therapy. The pharmacodynamic response to warfarin is not only delayed but also difficult to predict: patient sensitivity to the drug, varying drug elimination rates, and varying half-life rates of vitamin K-dependent clotting factors are some of the factors involved in the pharmacodynamics. Drug interactions and certain dietary issues also play an important role in patients' response to warfarin.

A second challenge is the seriousness of warfarin's complications. According to one metaanalysis, warfarin administration is associated with a 0.6% annual risk of bleeding-related death, a 3% annual risk of a major bleeding event, and a 9.6% annual risk of a major or minor bleeding event, with the risk being highest at the start of therapy (2). Although numerous risk factors for bleeding have been identified—including comorbidities, older age, and concurrent medications—the risk can be reduced by less intense therapy. Less intense therapy can be defined as a goal INR of <3 compared with a goal INR of >3 (3).

Because of the complexity of warfarin dosing, it was not surprising that warfarin was the most commonly reported medication associated with adverse drug reactions and medication variances

at Baylor University Medical Center. A retrospective chart review conducted at Baylor in 2000 showed four main variances related to warfarin therapy: 1) inappropriate administration of warfarin loading dose, 2) use of vitamin K when not recommended by American College of Chest Physicians guidelines, 3) inconsistent overlapping of heparin with warfarin, and 4) inconsistent provision of patient education (4).

Evidence-based guidelines for warfarin administration already exist (5). Improving health care quality, increasing patient safety, and reducing errors are about bridging the gap between such evidence and actual practice. Standardization is one method used to bridge this gap. By creating and testing a protocol, an institution can apply the guidelines in a systematic response that works in its setting.

A standard protocol was the method chosen for improving warfarin administration at Baylor. In addition, physician leaders suggested that pharmacists manage the protocol. Pharmacists are in a position to take center stage to help correct flaws within the medication system (6). It has been documented that pharmacist interventions reduce the number of adverse drug events, both in the inpatient and outpatient settings (7).

A study of a pharmacist-managed protocol was initiated in 2001 but was discontinued due to difficulty enrolling patients. The protocol was then updated in 2004, with the goal of providing physicians with a safe and effective warfarin dosing service. Before making the protocol available for use in all eligible inpatients, a pilot study was conducted comparing results from the protocol with results from usual, physician-directed warfarin therapy.

METHODS

In spring 2004, the warfarin protocol developed in 2001 was reviewed and updated, and institutional review board approval for the pilot study was obtained. Education about the protocol was offered to both clinical pharmacists and order verification pharmacists. Several groups of physicians were invited to participate in the pilot study, including pulmonologists, vascular surgeons, and two internal medicine hospitalist groups. These physicians were most likely to have patients using warfarin. Nurses and unit

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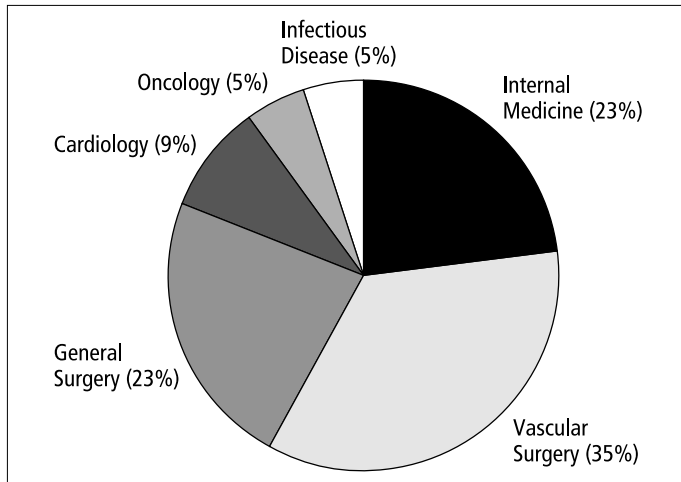


Figure 1. Referral source for subjects in the control group, with physician-managed warfarin.

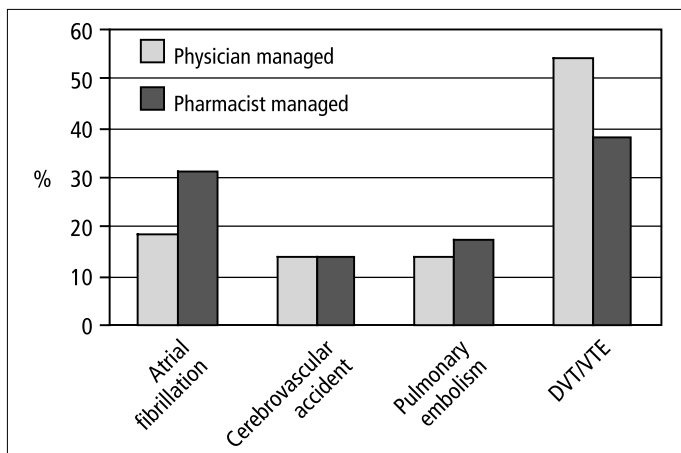


Figure 2. Indication for warfarin therapy. DVT/VTE indicates deep vein thrombosis/venous thromboembolism.

secretaries on all units were educated by their pharmacy liaison and were instructed on how to enter a warfarin protocol in the computer so it was received by the pharmacy. Nurses on all units were also educated on the procedure to follow if a patient on the protocol showed signs of bleeding or had an INR >5.

All patients in the identified service lines with an indication for warfarin were eligible to participate in the study unless one of the following exclusion criteria was met: a prosthetic heart valve; target INR >3.0; active bleeding; hematocrit <25%; elevated baseline INR (>1.3) without being on warfarin therapy prior to admission; epidural catheter; ventriculostomy; or lumbar puncture within 24 hours. Both patients newly started on warfarin and patients restarted on the drug after it had been withdrawn for procedures or other medical reasons were eligible for the study.

Patient characteristics

Between August 2004 and November 2004, 22 patients were enrolled in the physician-managed group, and 29 patients were enrolled in the pharmacist-managed protocol group. Most of the physician-managed patients came from the internal medicine, vascular surgery, and general surgery service lines (Figure 1). Enrollees received warfarin therapy primarily for deep vein thrombosis/venous thromboembolism or atrial fibrillation (Figure 2).

Table 1. Dosing adjustments indicated by the pharmacist-directed warfarin protocol

| Day of warfarin therapy | International normalized ratio | Dose (mg)* |
|-------------------------|--------------------------------|------------|
| 2 | <1.5 | 5 |
| | 1.5–1.9 | 2.5 |
| | 2.0–2.5 | 1–2.5 |
| | >2.5 | No dose |
| 3 | <1.5 | 5–10 |
| | 1.5–1.9 | 2.5–5 |
| | 2.0–2.5 | 0–2.5 |
| | 2.6–3.0 | 0–2 |
| | >3.0 | No dose |
| 4 | <1.5 | 10 |
| | 1.5–1.9 | 5–7.5 |
| | 2.0–3.0 | 0–5 |
| | >3.0 | No dose |
| 5 | <1.5 | 10 |
| | 1.5–1.9 | 7.5–10 |
| | 2.0–3.0 | 0–5 |
| | >3.0 | No dose |
| 6 | <1.5 | 7.5–12.5 |
| | 1.5–1.9 | 5–10 |
| | 2.0–3.0 | 0–5 |
| | >3.0 | No dose |

*If a medication is initiated that is known to interact with warfarin, the pharmacist will reduce doses or increase doses of warfarin according to clinical judgment.

Pharmacist-managed warfarin protocol

Once the physician wrote the order for “warfarin protocol per pharmacy,” the pharmacist obtained data on the patient’s age, weight, and allergies. Baseline laboratory values for INR and hematocrit were ordered, unless such tests had already been ordered within the previous 24 hours. An initial warfarin dose of 5 mg was then given at 6:00 PM on day 1 of the protocol. The pharmacist wrote an initial progress note in the medical chart, documenting indication for warfarin, goal INR, current INR, interacting medications, feeding status, plan of care, and other relevant information.

The pharmacist obtained INR results on day 2 of therapy and every day until a therapeutic value of 2 to 3 was present for 2 consecutive days or until the patient was discharged. Laboratory tests were ordered at the discretion of the clinical pharmacist. Based on the results, the pharmacist adjusted the warfarin dose (Table 1). Dosage changes continued on day 7 of warfarin therapy until discharge by adjusting the dose 10% to 20% if the patient was still not within the target therapeutic range. Pharmacists placed daily progress notes in the chart regarding the patient’s course of treatment, INR, interacting medications, signs and symptoms of bleeding, and other relevant information.

Heparin or low-molecular-weight heparin was discontinued by the pharmacist per protocol after the INR was >2 for 2 consecutive days; it could also be discontinued at the physician’s discretion. The patients received at least 5 total days of heparin or low-molecular-weight heparin therapy, and heparin was used for at least 3 days of bridge therapy.

The nurse was to notify the pharmacist and physician of any INR results >5 and of any incidents of skin necrosis, cerebrovascular accident, bleeding from any site, emboli, or hematocrit drops of 5% over 24 hours. Once the INR was >5, the patient was taken off the protocol-based dosing and treated based on the pharmacist's clinical judgment.

A pharmacist also provided warfarin education to all patients before discharge, using a patient handout. Such education was documented in the chart. In addition, if the patient was started on an interacting medication before discharge, the pharmacist informed the physician so follow-up procedures could be initiated if needed.

It was recognized that the pharmacist might need to deviate from the protocol to individualize warfarin therapy. For example, if the patient was admitted while on a maintenance dose of warfarin, the pharmacist would check the INR. If the result was therapeutic, that dose would be continued. Similarly, if warfarin was discontinued and needed to be restarted, the pharmacist would restart the patient on the previous dose that had been therapeutic. If a medication known to interact with warfarin was initiated, the pharmacist would reduce or increase doses of warfarin according to clinical judgment.

Data collection and analysis

Study data for all subjects were collected on a data collection sheet. This sheet included demographic information, baseline laboratory values, the indication for warfarin and goal INR, concomitant diseases, and a list of other medications. It noted each dose of warfarin and each INR result by day of therapy. The form also recorded whether the first dose of warfarin was 5 mg, whether the patient was eating, whether vitamin K was given, whether the hematocrit percentage dropped, whether a transfusion was required, whether fresh frozen plasma was given, and whether the patient was discharged prior to reaching therapeutic INRs. Finally, it documented manifestations of clinical bleeding and other adverse events.

Analysis of data began in November 2004, when enrollment of patients in the pilot study was closed.

RESULTS

Results showed that outcomes in the protocol group were at least as good as those in the physician-managed group (Table 2). In particular, the protocol ensured that all patients received the appropriate first dose and was equal to, if not somewhat better than, usual care in decreasing the number of supratherapeutic INRs and adverse drug events.

Despite adherence to the guidelines, two patients in the protocol group experienced minor bleeding. One patient experienced mild hematuria; the other, mild hemoptysis. In the physician-managed group, one patient experienced mild hematuria, while two patients had a hematocrit drop of >5%, which the attending

Table 2. Clinical outcomes of the physician-managed and pharmacist-managed patients in the pilot study

| Indicator of appropriate warfarin management | Usual care: Physician-managed group (n = 22) | Intervention: Pharmacist-managed group (n = 29) |
|--|--|---|
| Average time to therapeutic INR (range) | 5.6 days (4–11 days) | 6 days (4–11 days) |
| Patients who had supratherapeutic INR (% INR range) | 6 (27%, 3.4–6.2) | 5 (17%, 3.3–7.4) |
| Patients receiving an interacting medication (%) | 8 (36%) | 14 (48%) |
| Patients in the supratherapeutic range who also received an interacting medication (%) | 4 (67%) | 4 (80%) |
| Patients experiencing bleeds/adverse drug events (%) | 3 (14%) | 2 (7%) |
| Patients who received the correct first dose of 5 mg (%) | 15 (68%) | 29 (100%) |
| Patients who were discharged before reaching a therapeutic INR (%) | 7 (32%) | 8 (28%) |

INR indicates international normalized ratio.

physicians attributed to warfarin. All adverse reactions experienced by patients in both groups were considered minor by the attending physicians.

Drug interactions played an important role in the number of patients with supratherapeutic INRs. A majority of patients in both groups with INRs over the target range of 2 to 3 were also on medications that can interact with warfarin and increase the INR. The most common interacting medication in both groups was levofloxacin. In the pharmacist-managed protocol group, 2 of the 5 patients with supratherapeutic INRs were on levofloxacin concomitantly. In the physician-managed group, 3 of the 6 patients with supratherapeutic INRs were also on levofloxacin. Phenytoin, fluconazole, gemfibrozil, and amiodarone, all known to potentially interact with warfarin and increase INR, were also regularly prescribed concomitantly with warfarin during the pilot study.

One patient was removed from the protocol and managed based on the pharmacist's and physician's clinical judgment after her INR reached 7.4. She was started on the protocol upon admission, and her INR was maintained between 2 and 3 for several days. She required a transfer to the intensive care unit, where she received fluconazole. Within 2 days, her INR was 7.4 and the physician ordered 10 mg of vitamin K, which she received. Her INR was later stabilized and she had no further warfarin issues for the remainder of her hospitalization.

DISCUSSION

This small pilot study showed that the pharmacist-managed inpatient warfarin protocol is an effective way of ensuring adherence to the latest evidence-based guidelines for warfarin administration. Most physician service lines were pleased to have the option of pharmacists managing their patients' warfarin, and feedback regarding the results has been very positive.

In the pilot study, more than half of the subjects in the physician-managed group were treated by physicians who are more likely to have patients using warfarin because of their patient populations. Those physicians may be more experienced in managing anticoagulant therapy than other physician groups. If

the “usual care” arm of the study had been more representative of all the patients in Baylor’s 1029-bed hospital, the difference between the usual-care group and the protocol group may have been greater.

The study showed that management of drug interactions could be further improved. Most patients in both study groups who had supratherapeutic INRs were on a medication that can interact with warfarin and increase INR. Such a situation is very common in all health care environments: one study involving 134,833 patients showed that 81.6% of patients receiving long-term warfarin were taking at least one other prescription drug that could interact with warfarin (8). Pharmacists can assist by recommending a warfarin dose adjustment or selecting an alternative therapy when appropriate.

As with other pilot studies, the sample size in this study was small, and that is always an important limitation. Nevertheless, Baylor University Medical Center has successfully implemented many evidence-based protocols using small pilot studies. In addition, several other studies have shown that pharmacist-managed warfarin protocols have been successful (9–14). For example, Witt et al’s 2005 study of 6645 inpatients and outpatients showed that patients in the intervention group—with a centralized, pharmacist-managed anticoagulation monitoring service—were 39% less likely to experience a complication from anticoagulation therapy than the control group (9). Further, patients in the intervention group spent more days within the target INR range than the control group (63.5% vs 55.2%, $P < 0.001$) (9). A retrospective study of 717,396 Medicare patients who were treated in 1995 showed that hospitals without pharmacist management of warfarin therapy had 6.20% higher death rates, 5.86% longer lengths of stay, 2.16% higher Medicare charges, 8.09% higher rates of bleeding complications, and 22.49% higher transfusion rates than hospitals with pharmacist management (11).

Based on the results of the pilot study, Baylor’s other experience with protocols, and the experience of other centers, physician and pharmacy leaders at Baylor agreed to make the protocol available as an option hospitalwide in May 2005 rather than testing the protocol in more patients. With the protocol, evidence-based guidelines will be systematically applied to patients receiving warfarin, and Baylor can make further progress in its goal to deliver “STEEEP”: safe, timely, effective, efficient, equitable, and patient-centered care.

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