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Special Report: A Look at Warfarin

Statewide stroke project achieves dramatic improvements in warfarin use

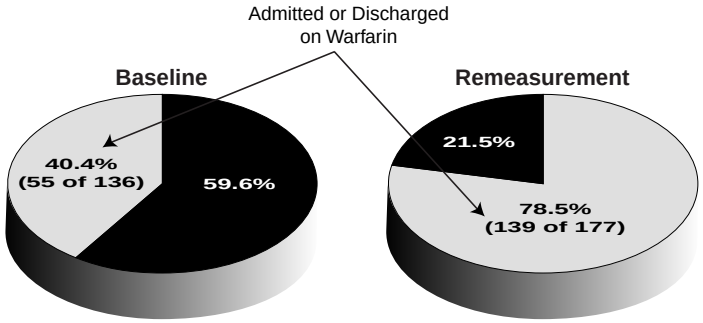
AF prevention collaborative helps patients, saves health care dollars

The atrial fibrillation (AF) team at HealthInsight, a nonprofit community quality improvement organization in Las Vegas, initiated a stroke prevention project that sought to increase the use of warfarin in eligible AF candidates in both inpatient and outpatient settings.

To accomplish the substantial improvements the team was aiming for, it decided to design the project as a statewide collaborative and obtain the cooperation of as many Nevada facilities as possible. The circle graphs accompanying this story **(below)** demonstrate the project's accomplishments: statistically significant improvement in the percentage of eligible AF patients admitted or discharged on warfarin from 40.4% at baseline to 78.5% at remeasurement.

Kevin Kennedy, MHS, senior health care analyst at HealthInsight, says as with all of the quality improvement organization's efforts, the focus of this project was on providers and health care organizations throughout the state of Nevada, where there is a total of 24 hospitals.

Percentage of Patients Receiving Warfarin



Source: Charts here and on p. 83 are courtesy of HealthInsight, Las Vegas, 1999.

By gaining the support of physician leaders, the team was able to get the facilities to sign on.

"[We did it] mainly by acquiring what we called physician 'champions' who promoted the project out in the community and within their own hospital setting," says **Justine Bizette**, RN, MSN, the project's senior coordinator. "We called them 'champions,' because if they supported the project, others in the community would follow.

"HealthInsight's medical director, William Berliner, MD, was actively involved with our project team," says Bizette, "and he made presentations to hospitals and physician groups around the state."

Nine out of 24 hospitals participated, accounting for 80% of the AF discharges.

"Warfarin's effect on stroke prevention is not a controversial topic, and a quality improvement department can take on a similar project and accomplish satisfying results," Bizette says. "Hospitals may want to alter the interventions to meet their own needs, but they can easily run a project like ours." ■

The message is clear: Warfarin saves money

$700 for therapy vs. $100,000 for stroke care

There is clear evidence in the research literature that getting warfarin to atrial fibrillation (AF) patients saves money. There have been several nationwide studies on how much it costs to treat and prevent stroke. According to *Cost Management in Cardiac Care*, a sister publication of *Drug Utilization Review*, it costs about $15,000 to prevent a stroke; the average total cost for a 65-year-old stroke patient in this country is $100,000.

Kevin Kennedy, MHS, senior health care analyst at Las Vegas-based HealthInsight, says, "If you treat 100 AF patients with warfarin, you prevent approximately three strokes." Clinical trials demonstrate that stroke rates in control groups (without warfarin) were 4.5% annually, compared to 1.4% in those taking warfarin.[1] "That's where you get the 3.1% absolute risk reduction," he says.

Stroke costs, risk reduced

A few years ago, researchers in Palo Alto, CA, estimated that acute and annual chronic costs of moderate to severe stroke were $34,200 and $18,000, respectively.[2] HealthInsight estimates it costs $700 annually to treat one patient with warfarin. "In Nevada, if we can prevent 74 strokes, that would save more than $2 million in health care costs." The population of Nevada is 2 million, and the cost savings would be much larger if they are extrapolated to a more populous state.

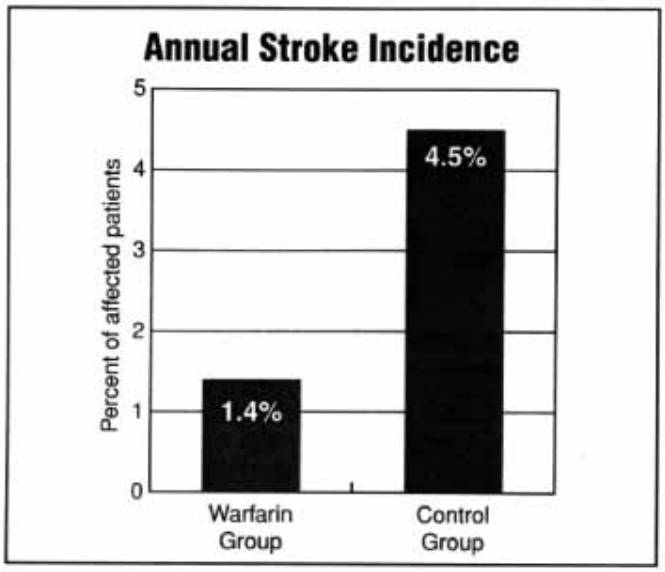
More than 2 million people in this country have AF, especially those over age 65. The risk of stroke in AF patients without coexistent risk factors increases slowly with age, and the annual stroke rate almost doubles between patients under 65 and those over 75 with coexistent risk factors.

The stroke rate of patients with AF is five to six times that of those without AF; 30% of AF patients will have a stroke. Pooled results from five trials show an annual stroke rate of 4.5% in controls vs. 1.4% for warfarin-treated patients — a 68% risk reduction.[3] **(See bar graph on annual stroke incidence, p. 67.)**

As early as 1995, the Agency for Health Care Policy and Research's Patient Outcomes Research Team reported warfarin is effective in preventing stroke in many patients with AF. Yet warfarin is still underutilized in eligible patients, and only 25% receive the therapy. The agency points out that half of the country's strokes could be avoided through more judicious use of warfarin, resulting in an annual savings of $600 million.[4]

COMING IN FUTURE MONTHS

- Will pharmacogenomics revolutionize drug therapy?
- How the generic market lost its value
- Chemotherapy error prevention policies
- Pharmacist review of discharge medications



Warfarin underutilization is avoidable. Education is key because under-use of the drug has been linked to misperceptions about its risks and benefits. Misunderstandings include:

- Providers may overestimate the risks of bleeding and underestimate the importance of optimal dosing to prevent that complication.
- Age is perceived to be a contraindication rather than an indication for warfarin.
- Physicians have concerns regarding patient noncompliance.
- Prothombin time/International Normalized Ratio (PT/INR) testing is considered complex and time-consuming.[5] Warfarin is contraindicated in some AF patients because the blood thinner potentiates bleeding disorders. The drug is contraindicated in any patient with aneurysms, cerebrovascular, or other hemorrhagic tendencies, gastrointestinal bleeding tendencies, or active ulcerations. Factors that increase hemorrhagic risk are:
- Three or more conditions, including seizures, peptic ulcer disease, liver disease, bleeding tendency, alcohol.
- INR >4.
- Highly variable INR.
- Acute warfarin therapy.

Patients who are senile, alcoholic, or psychotic and have a tendency to fall are not candidates, nor are those with pericarditis, bacterial endocarditis, hepatic or renal insufficiency, or an allergy to warfarin. In patients for whom warfarin is contraindicated, aspirin, while about half as effective as warfarin, has been shown to be of benefit in stroke reduction.

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ACCP, AHCPR standards form basis for project

Med-surg technologies make stroke preventable

HealthInsight, a nonprofit community quality improvement group in Las Vegas, has created an atrial fibrillation project based on the standards of the Irving, TX-based American College of Chest Physicians' (ACCP) Fourth Consensus Statement on Antithrombic Therapy and the Agency for Health Care Policy and Research.[1]

"Our main goal was to improve compliance with the standards of practice and guidelines so that the quality of care could be improved," said Kevin Kennedy, MHS, HealthInsight senior health care analyst, and Justine Bizette, RN, MSN, senior project coordinator, in a written statement.

Stroke is now considered to be as preventable as heart attack. Primary prevention — reducing risk by stopping smoking, losing weight, and lowering blood pressure — is the first line of defense. Current ACCP guidelines and the Fifth Consensus (issued last November) reconfirm the efficacy of warfarin for stroke prevention.[2]

"There have been several important studies on stroke prevention in atrial fibrillation since 1995," said **Daniel Singer**, MD, ACCP Fifth Consensus panel member and a cardiologist at Massachusetts General Hospital in Boston. "The guiding principle is that oral anticoagulation markedly decreases

Project gets attention, results

To improve warfarin utilization, HealthInsight in Las Vegas created "Project-in-a-Box," a box of tools for hospitals and physicians. It includes videos and brochures with educational materials for both physicians and patients. The project team mailed the resource to physicians and hospitals throughout Nevada who requested it and made it available at nursing stations and medical libraries.

For details, contact HealthInsight, 500 S. Rancho Drive, Suite C-17, Las Vegas, NV 89106. ■

the risk of ischemic stroke in patients with atrial fibrillation and that aspirin is much less effective [than warfarin]."

The 1998 guidelines include revised recommendations that consider recent clinical trials evaluating the use of warfarin and aspirin. For example, the recommendation that patients with a history of hypertension but no other risk factors be considered for oral anticoagulation has been strengthened. Other changes relate to a reprioritization of risk factors, such as diabetes, which was found to be a less consistent risk factor in the clinical trials reviewed. "Long-term oral anticoagulation is strongly recommended for prevention of stroke in AF patients who have suffered a recent stroke. . . . A target INR of 2.5 is recommended. Oral anticoagulation is also beneficial for prevention of recurrent stroke in patients with several other high risk cardiac sources," the guidelines state.

The challenge is to identify patients with a low enough AF risk to forego anticoagulation safely. "It appears that AF patients younger than 65 with no risk factors for stroke are at low enough risk to be treated with aspirin," Singer said. "For older patients with AF, especially those with risk factors [including hypertension, prior stroke or transient ischemic attack, or left ventricular dysfunction], warfarin is recommended."

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FDA reprimands drug companies for ads

False, misleading claims being targeted

A lawsuit and countersuit between Zeneca Pharmaceuticals and Eli Lilly over advertisements and marketing strategies for Zeneca's tamoxifen and Lilly's raloxifene, two new drugs aimed at postmenopausal women, have shed light on the Food and Drug Administration's growing oversight of direct-to-consumer ads. Print, broadcast, and radio ads by drug companies have increased, based in part on the easing of restrictions included in the recent FDA overhaul legislation passed by Congress.

As part of the paperwork filed in the lawsuit, each drug company included letters from the FDA accusing the other of producing misleading ads about the drugs. A review of files within the FDA's division of drug marketing, advertising, and communications finds a host of FDA cautions, reprimands, and orders to rewrite or pull ads. Because the FDA is a federal agency, its documents are public record. The agency is empowered to conduct enforcement based on the federal Food, Drug and Cosmetic Act.

Ads were pulled voluntarily

The FDA cited Zeneca's tamoxifen ads for a rewrite because the ads did not include the drug's risks of blood clots and uterine cancer. Lilly was targeted because its ads implied that raloxifene can prevent breast cancer. Raloxifene was approved last year specifically as an osteoporosis prevention treatment, though much of the press surrounding the drug centered on additional studies of its success in early trials against breast cancer, an indication Lilly is pursuing for the drug.

Tamoxifen has been on the market for years as a breast cancer treatment, and last year it was granted an expanded indication for use in reducing the risk of breast cancer. Zeneca filed its lawsuit against Lilly in February, asserting that Lilly's salesforce has been telling doctors its drug could prevent breast cancer and should be used instead of Zeneca's tamoxifen. Lilly countersued in March accusing Zeneca of slander.

(Continued on page 93)

DRUG CRITERIA & OUTCOMES™

Computer-generated medication profile review acts as replacement for automatic stop orders

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• **Introduction**

At the University of Utah Hospital, we have instituted a procedure in which pharmacists and physicians use a computer-generated "profile review" form for monitoring pharmacotherapy. **(See insert.)** Our procedure incorporates sophisticated computer logic that determines when a patient's profile is scheduled for review and documents the pharmacist's role in patient medication monitoring.

• **Background**

University Hospital is a 402-bed, tertiary care center located within the University of Utah Health Sciences Center. The center includes a full range of ambulatory care clinics as well as a home health care operation. During the two years the described program has been in place, inpatient therapy services were provided from eight satellite locations. The satellites provided order entry and unit-dose filling functions in an integrated pharmacy practice model composed of five specialty practice teams: perinatal, medicine, surgery, oncology, and neuropsychiatry. Intravenous order entry and compounding were conducted as a central operation independent of other pharmacy services.

University Hospital implemented the inpatient module on a departmentwide computer system (MSMEDS, Release 5.2.1, Mega Source Inc.). Under our current procedure, prescribers' medication orders are faxed to the central pharmacy area for computer processing. All orders consist of a manually written or preprinted order that is separated and the copy dedicated to pharmacy use. Pharmacy order processing is now computer-based for on-line processing, drug interaction and compatibility checking, label and report generation, and automated patient billing. Orders are entered into the computer by both technicians and pharmacists, but technician entries do not bill or print on medication administration records (MARs) until verified by a pharmacist.

The department computer system is used to produce an integrated 24-hour MAR, which is delivered nightly. New medication orders are transcribed by the nursing department directly to existing MARs. The configuration of the new computer system included the capability to set automatic stops based on a variety of criteria (e.g. American Hospital Formulary Service classes). In the traditional use of this approach, the computer would discontinue the order upon reaching the automatic stop date. Appropriate discontinuation must be monitored by a computer-generated report of pending stops and follow-up on individual orders.

The option of implementing the departmental policy regarding automatic stop orders as a restrictive function of the computer system led to a total rethinking of the effectiveness of this approach. Informal interviews with pharmacy and nursing staff revealed that the policy frequently was circumvented and rarely enforced as written.

Under the old procedure for automatic stop orders, and before the implementation of our computer-generated MAR, the nursing department used a manually written seven-day MAR form. This form was used as a guideline for monitoring the requirement for rewrites or automatic stops every seven days. Intensive care units, where the standard was three days, simply would mark out

all blanks after three days when initiating a new form. When the available spaces on the MAR were filled, it was the responsibility of the nursing department to contact the physician and have the orders rewritten before any further doses could be administered.

In teaching hospitals, order rewrites typically are done by resident physicians. The physician on duty often will respond to a need for order rewrites by copying directly from the old MAR onto the order sheet. This is the source of numerous medication errors: both errors of omission and errors of content from incorrect transcription. It has been noted in the literature, as well as at our institution, that automatic stop orders are not only of questionable value, but actually can lead to decreased quality of care because of inappropriate discontinuation of therapy.

Many attempts have been made to improve the policy or discontinue it altogether. Setting this policy into the computer system could lead to termination of orders without the knowledge of the physician, nurse, or pharmacist. The drugs given the strictest automatic stop orders (e.g., narcotics, anticoagulants, and antibiotics) — because of the potential harm or runaway costs that can result from failure to properly monitor and terminate orders — also could cause great harm and/or pain and suffering if inappropriately terminated.

A discussion ensued regarding the possibility of replacing the existing policy with a computer-driven process requiring reevaluation of all existing medication orders based on a periodic review cycle. This required periodic review of the patient's entire drug profile, which would be conducted jointly by pharmacist and physician. It was asserted that this would overcome many of the shortcomings of individual drug automatic stop orders as a function of drug classification (e.g., narcotics) by ensuring a comprehensive review of all the patient's medication orders at one time.

Furthermore, it was felt that by requiring both pharmacist and physician signatures, the computer-generated reorder form could act as a vehicle for clinical pharmacy, highlighting the pharmacist's role in monitoring ongoing therapy.

- **Methods**

The program was implemented through a custom programming project extracting data from files organic to the vendor's base system, supplemented with a custom file to hold the date of the patient's last periodic review. It was necessary to use the vendor's programming language to extract data from the established file system. When an institution purchases a pharmacy computer system, it actually buys a database management system along with language compiler and query facility from a third party.

The pharmacy system vendor's product is a collection of file definitions and application programs that depend on the database management system to function. Any owner of the system can write programs that run in the same language. However, the vendor's program code cannot be altered without violating the support arrangement. Because the vendor's product includes a pop-up window from which to run custom applications, the new application appears seamless to the end user.

Under our program, MAR computer selection can be controlled in several ways. Most practice areas use the standard method in which the computer-selected patients are printed in a batch process early each morning and picked up by the decentralized staff as they begin the day shift. An alternative procedure can be used — forms for all patients on a unit (e.g., rehabilitation) can be printed as a batch. Also, the pharmacist can adjust the patient's last review date so a certain team's patients print on a selected day. This is possible because the program supports display and alteration of the existing record used to track the review cycle. The program will display the last review dates for an individual patient or print a report to the screen sorted by unit. It also will allow form generation for a unit or individual patient with the pharmacist deciding whether to reset the review date.

The proposed new procedure was approved by the pharmacy and therapeutics committee and medical board as a replacement for the existing policy on automatic stop orders. Hospital policy indicates, "The physician and pharmacist shall review the patient's medication profile and evaluate for the following drug-related issues and problems: (1) indications for use, (2) appropriateness of drug therapy, (3) appropriateness of dose, (4) potential or actual drug interactions, (5) potential or actual adverse drug effects, (6) other drug therapy related issues."

Pharmacists receive specially designed physician order forms containing the selected patient's entire medication profile. Then they review the patient's profile and make recommendations and notations as indicated. The pharmacist indicates his or her review of the current therapy by affixing a signature and placing the form in the patient's

medical chart. The physician then indicates by initialing the corresponding column for each medication whether it is to be continued, discontinued, or changed. The physician's signature appears on the form below that of the pharmacist.

A custom form was designed with a similar appearance to the one typically used for physician orders, but with a free format so changes can be made to the computer-programmed output when necessary. As a two-part form, the original becomes a permanent part of the medical record, whereas the copy is sent to pharmacy for updating the profile. The pharmacist need only discontinue or change the existing orders because the hard copy is a duplicate of the order previously entered in the on-line patient profile.

Form generation takes three days for intensive care units and seven days for all others. The computer program scans the patient information files for new patients each day, adding them to the profile review data file and starting the clock at day one of admission. Each daily batch process causes an examination of the patient's present bed location (to determine the interval) and any transfers since admission. Movement in or out of an intensive care unit requires rewriting all orders. Therefore, the computer resets the start date when it detects this transfer. In addition to batch production, individual forms can be printed on demand, with the option of resetting the clock that will time the next required review.

• **Results**

To establish compliance with the procedure, a quality monitoring study was conducted. During a seven-day period, all forms generated were checked in the charts 24 hours later. A total of 134 patient profiles were screened. There were three forms unaccounted for; 24 patients were discharged before auditing; six forms were unnecessary because of transfer to / from ICU; and five patients had charts with them in clinic or surgery at the time of auditing. Subtraction of the total of 38 exceptions left 96 valid cases for audit. Of the valid cases, 90.6% contained the pharmacist's signature, and 86.5% contained the physician's signature. All had at least one signature.

A second quality monitoring study was conducted using the same methods. During this seven-day period, all forms generated were checked in the charts 24 hours later. A total of 143 patient profiles were screened. No forms were unaccounted for; 27 patients were discharged before auditing; four forms were unnecessary because of transfer; and seven patients had charts with them in clinic or surgery at the time of auditing. Subtraction of the total of 38 exceptions left 105 valid cases for audit. Of the valid cases, 98.1% contained the pharmacist's signature, and 87.6% contained the physician's signature.

The results of the studies were printed and distributed to all pharmacists in the department. There was general satisfaction with the compliance rate indicated by the studies. Discussions among clinical team members led to more formal tracking methods to determine which review forms had not been signed by the physicians.

• **Discussion**

We believe this program is helping increase quality of care while reducing costs because:

1) The program has eliminated the need for physicians to physically "rewrite" orders due to automatic stops. This often was done by copying directly from the MAR with consequent error.

2) The profile review form also freed pharmacist time that previously had been spent on interventions due to transcription errors or ambiguous and hard-to-read handwritten orders.

3) It also freed nursing time previously spent contacting physicians to request that orders be rewritten, and then producing a new MAR.

4) The program created a structured approach to monitoring pharmacotherapy, thereby increasing the chance that errors will be caught before serious misadventure.

We also attach significance to the procedure of requiring a pharmacist's signature before the physician's on the review form. This positions the pharmacist as a primary reviewer of current medication therapy on all patients in the hospital and represents another step toward greater involvement by pharmacists in the medication prescribing process. The procedure continues to evolve as needs and problems are identified.

An unresolved problem is caused by our patient ADT system because of a lack of transfer for patients going to the operating room. This makes it necessary for the pharmacist to change the last review date manually to reflect postoperative order rewrites. If one of the advantages of computer-generated profile forms is the avoidance of physician's handwritten orders, then this idea should be applied whenever possible. With an efficient ADT system, the review form could be generated automatically by the computer whenever a patient transfer required new orders.

We have made small changes to the format of the review form, such as printing the stop dates for chemotherapy drugs to clarify to the physician that his signature does not indefinitely continue therapy. Other helpful additions have been identified, such as authorization for leave of absence and prompting for weights in neonates. We also have created a signature block for the nurse, below that of the physician, because this signature was felt to be necessary by some teams.

The new procedure needs further research into its impact on the medication process, although we believe it has improved efficiency compared to the old system. While discussion of enforcement mechanisms has taken place several times, at this writing, the procedure remains nonpunitive to physicians; it is the responsibility of the pharmacist to contact the physician after 24 hours to ensure the profile is reviewed and signed. Although it is debatable whether the nurse's signature should appear on the order form, the de facto policy and procedure needs to be standardized for all clinical areas.

Whereas some practice areas insist that the profile review form is a physician order and, therefore, requires a nurse's signature, other teams felt it is unimportant. Nurses' signatures appeared on 54.2% of the forms audited originally. The second study found 55.2% of forms signed by nurses. The use of review forms could be expanded greatly in the future. Information printed on the forms is extracted from files stored in the pharmacy computer system. Any data stored in these files could be included on the review forms.

As pharmacy computer systems evolve, essential data (e.g., lab work-ups), as well as the analysis of expert systems and artificial intelligence processing, could be included in the medication review process. This is no longer an ivory tower idea because some current pharmacy systems contain rule-processing capabilities that evaluate the contents of data fields (e.g., labs, demographics) as a function of medication order processing.

• **Conclusion**

Computer-generated medication profile review appears to benefit both patients and health care practitioners. More research and development should be done to optimize patient care.

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Special Report: A Look at Warfarin

Quality assurance program monitors warfarin use

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• **Introduction**

Guidelines by the American College of Chest Physicians (ACCP) recommend monitoring warfarin with the International Normalized Ratio (INR). Although the concept of the INR has been endorsed by experts for many years, physicians and laboratories have not universally adopted the INR system. A review of monitoring practices within our institution identified a substantial lack of standardization and the need for pharmacists to assume a more active role in warfarin monitoring. We describe the development of a quality assurance program for warfarin monitoring in a university hospital.

• **Background**

Significant differences in the dose-response to warfarin therapy is adjusted on the basis of the prothrombin time (PT), which is sensitive to changes in the activity of the vitamin K-dependent clotting factors. However, the sensitivity of different thromboplastin reagents to changes in clotting factor activity may vary considerably, depending on the reagent's source and method of preparation. Because of this variability, interpretation of PT results without knowledge of the reagent's sensitivity can result in serious misinterpretation of the actual intensity of anticoagulation. This problem is a particular concern for patients having PTs performed by multiple labs or labs that frequently change thromboplastin reagents.

The INR is a mathematical correction used to standardize PT reporting. The INR adjusts for differences in thromboplastin sensitivity and reflects the PT that would have been obtained with the World Health Organization (WHO) reference thromboplastin reagent. The INR is calculated as follows:

INR = (patient PT / mean normal PT) ISI.

The ISI is the International Sensitivity Index for a particular thromboplastin reagent as compared to the WHO standard, which by definition has an ISI of 1.0. Many professional organizations now endorse the use of the INR and are actively encouraging the education of all health care providers on this system.

Questions about the consistency of warfarin monitoring in our institution were triggered by the transfer from another hospital of a patient with a possible cerebrovascular accident. The patient had a history of valvular heart disease and was taking warfarin. Although the patient's clinical presentation was consistent with a thrombotic stroke, doubts were raised by the report of a "therapeutic" PT from the other hospital.

Further investigation by the clinical pharmacist revealed that, although the PT of 15 seconds was within the hospital's "therapeutic range," the actual INR was 1.5, which is below the recommended range of 2.5 to 3.5 for patients with mechanical valves. Subsequent clinical evaluation and work-up confirmed the diagnosis of cerebrovascular accident. The implications of this case, along with concerns that many physicians in our institution were relying solely on the PT, provided the impetus for the pharmacy department to develop a quality assurance program for warfarin monitoring.

• **Methodology**

Initiated by the department of pharmacy, the program consisted of four components:

1) evaluation and documentation of current warfarin monitoring practices in order to identify problem areas;

2) development of an educational program for pharmacists and physicians;

3) implementation of an ongoing drug utilization evaluation (DUE) to assess the outcomes of our educational program and ensure optimal patient care;

4) continuous evaluation and review of the DUE to ensure outcomes are achieved.

The first step was an evaluation of current monitoring practices to document the need for a quality assurance program and to target problem areas that should be addressed. Monitoring trends were evaluated using both a physician survey and retrospective DUE. The physician survey was developed to determine which lab methods physicians used to monitor warfarin, familiarity with the INR, and compliance with the ACCP recommended target ranges for anticoagulation.

The survey was validated by three physicians and two pharmacists before distribution to 217 physicians. The survey group consisted of first-, second-, third-, and fourth-year residents and fellows in the departments of medicine, family practice, and surgery. Results were analyzed for the total group and for each department.

A retrospective DUE then was developed to verify problems identified by the physician survey and to determine if patients were receiving adequate anticoagulation in accordance with current ACCP recommendations. The retrospective DUE was limited to patients with atrial fibrillation (AF) because this is the most common indication for long-term warfarin therapy in our institution and these patients could be identified easily through medical records.

Indicators for appropriate use included the following:

1) All patients with AF were discharged on warfarin except those younger than 60 with lone AF or those with a contraindication.

2) The discharge INR was therapeutic based on ACCP target ranges.

3) Patients discharged before obtaining a therapeutic INR were scheduled for appropriate outpatient follow-up.

4) Patients unable to take warfarin were discharged on aspirin unless contraindicated.

The retrospective review was performed by the clinical coordinator and a cardiology faculty member. Based on problems identified by the physician survey and retrospective DUE, an educational program was developed for both physicians and clinical pharmacists. The program consisted of a special edition of the *Pharmacy and Therapeutics DUE Newsletter,* as well as continuing education lectures for pharmacists and physicians.

The goals of the educational component were to increase awareness of the potential hazards to the current PT reporting system and to increase understanding and use of the INR system. The presentations included the findings of the physician survey and retrospective DUE, a review of the ACCP guidelines, and a discussion of specific

case studies. After the educational component, a concurrent DUE was implemented.

A pharmacist data collection form was designed to evaluate all patients receiving warfarin therapy. The final form included several modifications based on suggestions from clinical pharmacists involved in the early data collection. The methods of data collection were reviewed with all pharmacists assigned to patient care units. Pharmacists were asked to complete the form for all patients on their units receiving warfarin, regardless of indication. Incomplete forms were tagged for follow-up chart review by the clinical coordinator.

• **Results: Evaluation of current monitoring practices**

Results of the physician survey and retrospective DUE documented significant problems, which will need to be addressed through an ongoing quality assurance program. The response rate for the physician survey was 39%. Departments represented were medicine (75%), family practice (14%), and surgery (11%). This departmental distribution closely corresponded to the actual percentages of warfarin prescriptions written by these departments: 78% written by medicine, 12% by family practice, and 10% by surgery.

Although many physicians order the INR along with the PT, only 31% reported they were "very familiar" with the INR, whereas 52% were "somewhat familiar," and 17% were "unfamiliar." Physicians' lack of familiarity with the INR concept was further substantiated by the fact that of those who considered themselves familiar with the INR, only 38% understood how the INR is derived.

The survey also showed that a majority of physicians were not following the current ACCP recommendations for target INR ranges. For example, the recommended INR range for a patient with AF is 2.0 to 3.0. The survey found that only 35% of physicians used this range. A slightly higher range of 2.5 to 3.5 is recommended for patients with mechanical valves. However, only 20% of the surveyed physicians reported using this range.

Findings of the retrospective DUE also verified the inadequacies of warfarin monitoring in our institution. Medical records from 50 patients with a diagnosis of AF were reviewed.

Laboratory Methods Used to Monitor Warfarin Therapy

	Percent of Physicians (%)			
	Total (n=85)	Medicine (n=64)	Family Practice (n=12)	Surgery (n=9)
PT only	29	23	33	45
PT Ratio only	0	0	0	0
PT/PT Ratio	2	0	17	44
INR Only	29	30	17	0
PT/INR	28	38	0	0
PT Ratio/INR	2	3	0	0
PT/PT Ratio/INR	10	6	33	0

PT = prothrombin time
PT Ratio = patient prothrombin time/mean normal prothrombin time
INR = international normalized ratio

Source: Charts on this page are courtesy of University of Kansas Medical Center, Kansas City.

Discharge INR Data for Patients Receiving Warfarin

Discharge INR		No. of patients (%)	(n=200)
Therapeutic	1	60	(30)
Subtherapeutic	2	125	(2.5)
Supratherapeutic	3	15	(7.5)

1 Based on ACCP guidelines
2 See text for discussion
3 INR = international normalized ratio

Modification in Warfarin Therapy Based on Pharmacist Interventions

Recommendation	Frequency (n=82)
Check INR	26
Adjust dose for drug interaction	18
Decrease dose	21
Increase dose	13
Clarify dosing regimen	2
Discontinue warfarin	2

The DUE found that 44% of patients with AF were discharged on warfarin. A contraindication for warfarin therapy was documented in the chart for 46% of the patients. However, approximately 10% of patients were discharged without

warfarin, and no contraindication or explanation was documented. Aspirin is recommended as an alternative antithrombotic agent for patients with AF who are not candidates for warfarin.

Of the 28 patients who did not receive warfarin, 12 received aspirin, 10 had a contraindication to both drugs, and the remaining six patients were eligible for aspirin but did not receive the drug. Among those patients receiving warfarin, 53% were discharged with a therapeutic INR based on current ACCP guidelines. Approximately 42% of the patients had a subtherapeutic INR that could place them at risk for a thromboembolic event.

Conversely, 5% of patients were discharged with an INR above the recommended range that could increase the risk of hemorrhagic complications. Of particular concern is the fact that the vast majority of the nontherapeutic patients had no documentation of a scheduled follow-up visit within one week.

• Education

Findings of the physician survey and DUE indicated a need for ongoing education and standardization of warfarin monitoring within our institution. A special edition of the pharmacy and therapeutics newsletter summarized the findings of the physician survey and DUE and discussed the need for standardized monitoring.

Educational lectures were presented to both physicians and pharmacists focusing on the fundamentals of the INR system, recommendations for achieving optimal levels of anticoagulation, and the importance of adjusting the warfarin dosage to obtain a therapeutic INR before discharge or, if necessary, through outpatient follow-up. Interaction with the clinical pharmacists during these presentations revealed a general lack of confidence in their ability to recommend specific warfarin dosage changes. In an effort to increase the pharmacists' competence and ability to intervene effectively, additional educational sessions were held to review specific case studies. Reference articles and sample warfarin dosing protocols also were provided.

• Concurrent DUE

Our clinical pharmacists monitored 200 patients receiving oral anticoagulation. The most common indications for warfarin were surgical procedures, thromboembolism, AF, cardiomyopathy, and artificial valves. No significant differences were observed between medical specialties.

Overall, only 30% of the patients had a therapeutic INR at the time of discharge. Although this number seems alarmingly low, it appears to result from many physicians discharging patients when the INR was still subtherapeutic but approaching the therapeutic range. For example, an additional 23% of patients were discharged with an INR between 1.5 and 2.0.

This approach is acceptable provided there is adequate follow-up to ensure the patient actually achieves and maintains a therapeutic INR. A major concern identified by the DUE is the fact that fewer than half of these patients (41%) had documentation in the chart as to whether a follow-up appointment was scheduled. Seventy-nine of the 200 patients (39.5%) were discharged before the INR reached 1.5, and only 19% had a documented scheduled follow-up appointment.

An even greater concern is that 15 patients (7.5%) left the hospital with an INR above the therapeutic range, and only two patients had documentation of a scheduled follow-up. In fairness, it must be noted that some of these patients may have been scheduled for appointments by individual departments, even though the visit was not documented in the chart.

However, this approach causes concern because it prevents pharmacists and others from obtaining appropriate monitoring information and increases the risks of patients being lost to follow-up as physicians on various services change. No significant differences were found in the length of stay for warfarin patients, which averaged seven to nine days regardless of the status of the discharge INR.

During this early phase of the concurrent DUE, clinical pharmacists were responsible for 82 specific recommendations for patients receiving warfarin therapy. These recommendations represent approximately a 90% acceptance rate for pharmacist interventions.

• Discussion

Significant inconsistencies were identified in our institution's warfarin monitoring through the use of a physician survey and retrospective

DUE. Based on both physician and pharmacist responses, a major reason for the lack of appropriate monitoring was inadequate knowledge and understanding of the potential problems associated with the PT reporting system and an unfamiliarity with the INR system.

Although our educational programs appear to have met this need temporarily, the effort must be ongoing because of the continuous turnover in staff that is common to all teaching medical centers.

The ongoing concurrent DUE appears to be the most feasible vehicle for dealing with this problem. The early findings of the concurrent DUE have identified a number of concerns. First, a high percentage of patients (approximately 70%) are discharged from the hospital before obtaining a therapeutic INR.

Although that approach is reasonable, given the high costs of hospitalization, more standardized methods need to be developed to ensure that patients receive appropriate outpatient follow-up. If patients are lost to follow-up, they are clearly at risk for thromboembolic or hemorrhagic complications that may result in rehospitalization and even greater costs.

Second, although the data suggest that pharmacists can have a positive impact on warfarin monitoring, it is clear that many pharmacists lack confidence for making specific recommendations in this therapeutic area.

Conclusion

Overall, the number of pharmacist recommendations was low and, as might be expected, the majority was attributed to the pharmacists with the most experience in anticoagulation. Ongoing education and training will be necessary to help pharmacists acquire the necessary degree of competence to intervene effectively.

The high physician acceptance rate for pharmacist recommendations indicates that with proper training and experience, pharmacists can assume a leadership role in assuring the appropriate use of warfarin.

[For additional information, contact Patricia Howard, PharmD, BCPS, University of Kansas Medical Center, Department of Pharmacy, 3901 Rainbow Blvd., Kansas City, KS 66160. Telephone: (816) 235-5490.] ■

New FDA Approvals

✔ **Injectable low molecular weight heparin Fragmin (dalteparin sodium) by Pharmacia & Upjohn.** Approved for prevention of deep vein thrombosis (DVT) after hip replacement surgery, once-daily treatment approved after two randomized Phase III trials. In one trial of 382 patients, total incidence of DVT lowered by 25.8%; in another by 42%, where post-operative treatment averaged from five to 10 days. Available in 10 single-dose prefilled syringes in 2,500 and 5,000 IU strengths.

✔ **Injectable formulation of Sporonax (itraconazole) by Janssen.** Approved for treating complicated, serious systemic fungal infections, histoplasmosis, blastomycosis, and refractory aspergillosis common to HIV infection. Capsule form of intraconazole approved in 1992. Should not be used with astemizole, cisapride, triazolam, oral midazolam, lovastatin or simvastatin, or in patients with severe kidney impairment.

✔ **Post-herpetic neuralgia (PHN) transdermal pain treatment Lidoderm (lidocaine 5%) by Endo Pharmaceuticals.** Skin patch approved to treat pain caused by shingles complication PHN, approved for application to site of sensory nerve damage. Approval follows placebo-controlled trials, from which some cases of erythema or edema developed.

✔ **Menopause complication tablets Cenestin, a synthetic conjugated estrogen, by Duramed Pharmaceuticals.** Plant-derived synthetic made from soy plants and yams, approval is for moderate to severe vasomotor symptoms such as night sweats, hot flashes. Follows 12-week trial of 120 patients. Contraindicated in pregnant patients and those with breast cancer, estrogen-dependent neoplasia, genital bleeding, thrombophlebitis, or thromboembolic disorders. Common side effects from trials: headache, insomnia, asthenia, paresthesia, depression. Available in 0.625 mg and 0.9 mg.

✔ **Bronchospasm inhalant Xopenex (levalbuterol HC1) by Sepracor Inc.** Approved for use with a nebulizer for prevention/treatment of bronchospasm, approval follows four-week Phase III trial of 362 patients resulting in comparable lung-function response to 2.5 mg doses of racemic albuterol. Available in 0.63 mg and 1.25 mg. ■

(Continued from page 84)

An FDA spokesperson says both companies voluntarily have pulled the ads following criticism by the agency. "It's the obvious overstatement of a drug's benefits and the understatement or lack of statement of its risks, the direct attack ads on competitors that fuel those fires, and some cases of promoting unapproved uses that we're seeing more of and we're going after," says the FDA spokesperson.

The FDA has the authority to screen ads before they are published or aired and can pull an ad or order "corrective" advertising in particularly egregious cases. In most cases, the FDA says, drug companies will rewrite or withdraw ads voluntarily. FDA oversight also can cover the tactics drug companies — and their advertising agencies — use to distract the public from the information they want to downplay.

For example, among the many actions taken by the FDA over the last year is a letter to Wyeth-Ayerst concerning its osteoporosis drug Premarin. The letter criticized the way a TV ad's visual montage distracts viewers from the wording of the drug's risks, which are required to be included, while a more sedate background runs behind the text describing the drug's benefits.

Similarly, the FDA said a TV commercial for Pharmacia & Upjohn's injectable contraceptive Depo-Provera mixed its audio and visual messages about the drug's risks too awkwardly, "virtually assuring that consumers will have trouble fully comprehending any of the information."

Novartis was criticized for "false, misleading, unbalanced and incomplete" information in ads for its cholesterol drug Lescol, which did not speak to the warnings of the drug's effect on the liver. Pharmacia & Upjohn was stung again by the FDA for an ad for Caverject, billed as an alternative to Viagra, because the ad did not state the drug required a direct injection into the penis.

Bristol Myers Squibb was notified to change its ads for Pravachol, used to reduce the risk of heart attack, because the ad featured visuals of female athletes, though the FDA says women were not included in the clinical trials on which that indication was based. A Glaxo Wellcome print ad for its herpes treatment Valtrex was cited as "false or misleading and lacking in fair balance" because it did not include common side effects found in trials.

The FDA also monitors how ads directly tout one drug over a competitor. In one case, the FDA sent letters to three antihistamine makers, Hoechst Marion Roussel (Allegra), Schering-Plough (Claritin), and Pfizer (Zyrtec), telling all three to stop saying their drugs were better than their competitors'. The FDA says that based on information it has from the American Association of Advertising Agencies, pharmaceutical manufacturers spent $1.3 billion on ads in 1998, up from $595 million in 1996. ■

Millennium resources

Many professional organizations offering help

If your computer system uses only the last two digits of each year to represent the current date, a year 2000 (Y2K) test is in order to see if your computer will think January 1, 2000, is Jan. 1, 1900.

"Many systems, especially newer computers and software programs, are Y2K compliant. Some systems may originally have been compliant but, because of customization, may now be noncompliant," says **Joel Weber**, PharmD, FCHSP, director of health system solutions at Bergen Brunswig Drug Co. in Orange, CA. The company has been consulting with its health system clients on Y2K compliance issues.

Y2K Web sites

- ✔ **FDA Year 2000 Impact on Biomedical Equipment:** www.fda.gov/cdrh/yr2000/year2000.html
- ✔ **American Hospital Association Year 2000 Resource Center:** www.aha.org/y2k/default.html
- ✔ **American Medical Association Preparing for the Year 2000 Program:** www.ama-assn.org/not-mo/y2k/index.html
- ✔ **Healthcare Intelligence Network medical journal database:** www.hin.com
- ✔ **National Wholesale Druggists Association Year 2000 Resources & Solutions:** www.nwda.org/year2000/year2000.htm

In one case, a California health care group found more than 110 systems had suspect dating applications during a Y2K inventory program. This year, the General Accounting Office issued an unflattering report of the Health Care Financing Administration's (HCFA) system readiness, an important development for pharmacies filing Medicare and Medicaid claims. HCFA has responded that its system will be trouble-free, and in its own letter to health care agencies, HCFA warned that hospitals should not delay testing their systems.

Another issue being discussed in the industry is that of patients hoarding or stockpiling drugs toward year's end, something the American Red Cross has advised the public to do. That was the topic of the Y2K Supply Chain Conference held earlier this year in New Jersey.

The flow of drugs, from the ordering of raw materials all the way to dispensing, is forecasted by the wholesaler industry, which says stockpiling could be a bigger issue than computer system problems. Currently, the industry operates on about a one-month supply, meaning it will have to watch the coming months carefully to determine whether patients are stockpiling drugs.

The American Society of Health-System Pharmacists says information it has received from organizations like the Pharmaceutical Research and Manufacturers of America and the National Wholesale Druggists Association have left it feeling confident of the readiness of major vendors.

The bottom line of the conference was public relations —- making sure consumers don't worry about getting their prescriptions. "If people believe there will be a disruption, then there will be a disruption," says **Gary Loeb** of drug wholesaler McKesson Corp. "Perception is going to drive the events leading up to the year 2000." ▼

New HEDIS measures

The National Committee for Quality Assurance has added five new outcomes measures to its Health Plan Employer Data (HEDIS) program. They are asthma, blood pressure, chlamydia, diabetes, and menopause. The performance standards are used for accrediting programs and consumer comparison shopping. The additions are part of the HEDIS 2000 program, bringing the total number of quality measures to just over 60.

[For details, contact NCQA at (800) 275-7585.] ▼

Endostatin shows promise in reducing plaque

It also may work against cancerous tumors

A formulation of the natural protein endostatin, developed at Harvard University, created a lot of interest earlier this year as a potentially new kind of treatment against cancerous tumors.

The studies, conducted in mice, measured the protein's ability to block the growth of blood vessels tumors need to survive. Now a similar study is showing early success for the drug's ability to affect the growth of arterial plaque tissue that causes atherosclerosis, which leads to heart attack and angina.

Like tumors, blood cells and smooth muscle cells also rely on their own network of capillaries to grow. The study of 73 mice given a high-cholesterol diet found that mice given the drug had 85% less plaque build-up in heart aortas.

The study was published in the April 6 issue of the American Heart Association journal *Circulation*. ▼

Follow-up

Anesthesiologist group issues herbal warning

The American Society of Anesthesiologists (ASA) says surgery patients should stop taking herbal medicines at least two to three weeks before a procedure as a safety precaution against the risk of an adverse reaction. The organization is not issuing the warning based on hard science or specific studies, but instead has been getting growing anecdotal evidence that "significant" changes in heart rate or blood pressure have occurred in patients later found to be taking an herbal product.

That, coupled with an in-house survey finding that seven of 10 patients taking herbals don't tell their physicians about it, prompted the warning, as well as statistics showing that the public's use of the products has grown by 60% in a year, according to ASA president **John Neeld**, MD.

"All we want to do is make the public aware that these products could pose a serious health

risk if they are taken prior to surgery," he said. The statement echoes those of national pharmacy organizations, which have been urging hospital pharmacists to ask patients if they are taking herbals.

The ASA also is asking its members to urge patients to bring herbal containers for their physicians to see prior to surgery. The organization says the depression treatment St. John's Wort may intensify the effects of narcotic anesthesia agents; the circulatory products ginkgo biloba and feverfew could reduce or interfere with platelet counts needed for post-surgery clotting; and ginseng has been linked to hypertension and tachycardia.

[For details, contact ASA at (847) 825-5586 or ASAhq.org.] ▼

Pharmacists hail OTC labeling inclusion

"Ask your doctor or pharmacist." That simple phrase, now mandated by the Food and Drug Administration as part of its new, final regulations on over-the-counter labeling, is being seen as a hard-fought victory for the pharmacy industry. The FDA has added "pharmacist" to the phrase patients are accustomed to seeing on prescription brochure labeling after a nearly 20-year lobbying campaign by the industry.

"This is truly a landmark event and we applaud the FDA's recognition of the pharmacist as a vital source of information that will reinforce the pharmacist's role as an important member of the health care team as more prescriptions medicines are being switched to OTC status, meaning the need for consultation will only increase," says **Calvin Anthony**, executive vice president of the National Community Pharmacist Association.

Clinical pharmacy groups say the ruling will benefit hospital pharmacists and their patients, who regularly obtain retail OTCs. The American Pharmaceutical Association (APhA) says the new labeling will being appearing in early 2000. "We encourage the industry to implement labeling changes as quickly as possible and we look forward to providing additional assistance," says APhA executive vice president **John Gans**, MD.

Last year, the organization sponsored a consumer survey on OTC pain relievers that found high levels of confusion concerning which drugs to use and how to use them. ▼

Study: Interventions fail to cut Medicaid costs

Pharmacist intervention projects aimed at reducing Medicaid costs failed clinically and financially, according to a review of two pilot programs overseen by the Health Care Financing Administration (HCFA). Pharmacist reimbursement for the clinical interventions was included in the programs, modeled after Medicaid reimbursement piloted in Mississippi.

The programs were set up for pharmacists in treatment groups to review drug utilization when computer system messages signaled potential prescription problems. Interventions included the performance and documentation of cognitive services. Reimbursement rates were $4 for consultations of six minutes or less, and $6 for those lasting longer. Analysis of the programs found the interventions did not "change the utilization of or expenditures on prescription drugs, hospital admissions, professional services, emergency room encounters, or aggregate medical care."

[For details, contact HCFA at (410) 966-3000 and ask about the Abt Associates study.] ▼

Antiformulary bills introduced in three states

Lawmakers in three states have introduced antiformulary bills into state legislatures. A New Hampshire bill (HB 321) would require health plans to cover any prescription medication submitted, regardless of a health plan's formulary. Some pharmacy groups are opposed to the bill, arguing it could drive up costs and that most plans in the state already allow formulary exceptions by physician prescription.

Two Senate bills in Maryland (SB 135 and 109) would allow nonformulary exceptions in cases where a drug is prescribed by a patient's health care provider and if the provider determines a drug is necessary.

A bill in Connecticut (HB 5682) would require health plans to accept drugs regardless of dosage or preauthorization if a health care provider deems them necessary. ▼

Antibiotic resistance reviewed in 4,000 patients

Physicians should consider changing antibiotics when community resistance tracking rates reach between 15% and 20% in patients with urinary tract infections, advise the authors of an antibiotic resistance study published in the *Journal of the American Medical Association* (*JAMA* 1999; 281:736-38).

The study followed 4,000 patients from 1992 to 1996 enrolled in a Washington state HMO and found rising resistance to trimethoprim, ampicillin, cephalothin, and trimethoprin-sulfamethoxazole. The authors found more successful treatment resulted from the use of gentamicin, nitrofurantoin, and ciprofloxacin hydrochloride. ■

IN THE PIPELINE

✔ **Antibiotic Zyvox (linezolid) by Pharmacia & Upjohn.** From oxazolidinone class, aimed at treating active and resistant gram-positive bacteria. Company reports positive Phase II open-label trials on skin and soft tissue infections and community-acquired pneumonia from gram-positives. Oxazlidinone class arrests development of bacteria growth. In trials of 273 patients isolating *Staphylococcus aureus, S. epidermidis, S. pyogenes, Enterococcus,* long-term follow-up success rates reached 93.2%, Pharmacia reports. Patients were given two or three daily doses of 250 mg, 375 mg or 625 mg. The drug is being formulated in IV, oral, and suspension form.

✔ **Type II diabetes treatment INS-1, and investigational compound by INSMED Pharmaceuticals.** As reported to the American Diabetes Association, compound led to positive results in double-blind, placebo-controlled, randomized one-month Phase II study of 110 patients not already receiving drug treatment. Parameters of glycemic control and lipid profiles improved without inducing weight gain, the company reports. Patients with above-normal lipid profiles showed equal or greater improvement, with reduced plasma triglyceride, LDL cholesterol, and glycemics following an oral glucose load. ■

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