Bleeding Complications With Warfarin Use

A Prevalent Adverse Effect Resulting in Regulatory Action

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Background: Warfarin sodium is widely used and causes bleeding; a review might suggest the need for regulatory action by the US Food and Drug Administration (FDA).

Methods: We accessed warfarin prescriptions from the National Prescription Audit *Plus* database of IMS Health (Plymouth Meeting, Pennsylvania), adverse event reports submitted to the FDA, deaths due to therapeutic use of anticoagulants from vital statistics data, and warfarin bleeding complications from national hospital emergency department data.

Results: The number of dispensed outpatient prescriptions for warfarin increased 45%, from 21 million in 1998 to nearly 31 million in 2004. The FDA's Adverse Event Reporting System indicated that warfarin is among the top 10 drugs with the largest number of serious adverse event reports submitted during the 1990 and 2000 decades. From US death certificates, anticoagulants ranked first in 2003 and 2004 in the number of total mentions of deaths for drugs causing "adverse effects in therapeutic use." Data from hospital emergency departments for 1999 through 2003 indicated that warfarin was associated with about 29 000 visits for bleeding complications per year, and it was among the drugs with the most visits. These data are consistent with literature reports of major bleeding frequencies for warfarin as high as 10% to 16%.

Conclusions: Use of warfarin has increased, and bleeding from warfarin use is a prevalent reaction and an important cause of mortality. Consequently, a "black box" warning about warfarin's bleeding risk was added to the US product labeling in 2006. Physicians and nurses should tell patients to immediately report signs and symptoms of bleeding. A Medication Guide, which is required to be provided with each prescription, reinforces this message.

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THE ANTICOAGULANT WARfarin sodium (Coumadin; Bristol-Myers Squibb, Princeton, New Jersey) is approved for the prevention and/or treatment of venous thrombosis, pulmonary embolism, and thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement and to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events after myocardial infarction. It is used to treat patients in hospitals and in long-term care and outpatient settings and has well-recognized bleeding complications as an adverse effect of treatment. In 1997, warfarin and insulins were identified as the drugs most commonly implicated in adverse events in an emergency department at a single institution[1] and in nationally representative emergency department data in 2002[2] and 2004 through 2005[3] in the United States. In a sample of 9 National Electronic Injury Surveillance System (NEISS) hospital emergency departments from July 17, 2002, through September 30, 2002,[2] warfarin and insulin products together accounted for 16% of all adverse drug events and, in patients 50 years and older, they accounted for 69% of unintentional overdoses and 33% of all adverse drug events. Similarly, from January 2004 through December 2005, in a nationally representative sample of all hospitals in the United States and its territories, warfarin or insulins were implicated in 1 of 7 estimated adverse drug events in emergency departments (14.1%; 95% confidence interval [CI], 9.6%-18.6%) and in more than 25% (95% CI, 17.3%-35.2%) of estimated adverse drug event hospitalizations.[3]

In the 2001 report of the Sixth American College of Chest Physicians, Levine et al[4] reviewed data on the incidence of bleeding with warfarin use (and other anticoagulants) and found that rates of bleeding classified as major (defined as intracra-

nial, retroperitoneal, leading directly to death, or resulting in hospitalization or transfusion) were variable, although most (with the exception of a few that were higher) were in the 0% to 10% range. A review article published in December 2002[5] reported that the incidence of major bleeding in patients prescribed warfarin ranged from 0% to 16%, and the incidence of fatal bleeding was 0% to 2.9%.

Variations in the frequency of bleeding in studies depend on many factors including, for example, definitions of bleeding and major bleeding, patient mixes with various indications and risks of bleeding, targeted international normalized ratios (INRs) and treatment protocols, treatment settings, and lengths of follow-up. However, the frequency of major bleeding with warfarin use, which is estimated to be as high as 10% to 16%,[4,5] contrasts with much lower frequencies (< 1/1000) for known serious adverse events of most drugs.

Despite this information, we noted that the product information for warfarin did not contain a boxed ("black box") warning to communicate information about its serious bleeding outcomes. Consequently, we compiled and analyzed data, presented herein, concerning the use of warfarin and its prevalence of bleeding complications in the United States to support a requirement by the Food and Drug Administration (FDA) for a boxed warning in the professional product information and for a patient Medication Guide.

METHODS

We accessed several databases to obtain information on the use of warfarin and its prevalence of serious bleeding complications, and we selected those that provided a representative and/or national perspective on use and bleeding prevalence with warfarin.

The number of outpatient prescriptions dispensed for Coumadin and generic warfarin for the years 1998 through 2004 were obtained from the National Prescription Audit *Plus* database of IMS Health (Plymouth Meeting, Pennsylvania).[6] This database provides the projected national number of outpatient prescriptions dispensed by retail pharmacies in the United States. The following channels are included as retail pharmacies: chain, independent, food store, long-term care, and mail order.

We accessed the FDA's Adverse Event Reporting System (AERS) that includes voluntarily submitted reports of adverse events suspected of being caused by prescription drugs[7,8] to obtain a ranking of drugs having serious outcomes (death, hospitalization, life threatening, disability, congenital anomaly, and intervention required). We also used AERS to obtain the top-ranking adverse events reported for warfarin and to obtain numbers of reports of US patients with fatal and serious bleeding outcomes for the suspect drug warfarin from 1993 through mid-July 2006. The following high-level terms (and sublevels) were used to identify reports of bleeding events: *coagulopathies and bleeding diatheses (excluding thrombocytopenic)*, *central nervous system haemorrhage and cerebral vascular accidents*, *intra-abdominal haemorrhage*, *vascular hemorrhagic disorders*, and *hematuria*. Reports were not individually reviewed to remove duplicate reports.

The annual number of US deaths in which anticoagulants were attributed by certifiers as the underlying cause of death or as total mentions (the sum of mentions of anticoagulants as the immediate, contributing, or underlying cause or as a significant condition leading to death) on death certificates[9,10] were obtained from the Division of Vital Statistics of the National Center for Health Statistics (NCHS) and from an NCHS Web site. The data were obtained for 1998 through 2004, the latest year for which they were currently available. Deaths attributed to the use of warfarin and other anticoagulants are coded as "Anticoagulants causing adverse effects in therapeutic use" (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code E934.2 for year 1998[11] and *International Statistical Classification of Diseases, 10th Revision* [*ICD-10*] code Y44.2 beginning in 1999).[12] The information is not specific for warfarin because the names of individual anticoagulants are not available from these data. Crude population rates of death associated with the therapeutic use of anticoagulants were calculated using the total mentions of death among the US resident population.[13,14]

Public use data from the National Hospital Ambulatory Care Survey (NHAMCS), a national probability sample survey of visits to emergency departments of nonfederal, short-stay, and general hospitals in the United States, were obtained from the NCHS Web site[15] for the years 1999 through 2003 to determine the number of visits to emergency departments associated with warfarin and the number of warfarin visits associated with a diagnosis of bleeding. Warfarin visits were defined as patient visits in which warfarin (prescribed, supplied, administered, or currently used) was mentioned. The codes for bleeding were selected from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*),[16] and the codes for warfarin were based on NCHS drug codes. Results were projected to the national level and divided by 5 to obtain the annual mean ± SE number of visits. Because the survey has a multistage sampling design, the standard errors of the estimates were computed using SUDAAN (Research Triangle Institute, Research Triangle Park, North Carolina), which takes the sampling design into account.

Table 1. Number of Outpatient Prescriptions Dispensed for Coumadin[a] and Generic Warfarin Sodium in the United States, 1998-2004[b]

Year	Prescriptions	Coumadin, %
1998	21 095 000	85
1999	22 458 000	74
2000	24 442 000	67
2001	26 100 000	62
2002	27 781 000	52
2003	28 842 000	38
2004	30 632 000	29

[a] Bristol-Myers Squibb (Princeton, New Jersey) brand of warfarin sodium.
[b] Source: National Prescription Audit *Plus*.[6]

RESULTS

USE DATA

Table 1 presents the number of outpatient prescriptions dispensed for Coumadin and generic warfarin for the 7-year period 1998 through 2004.[6] The number increased 1.45-fold (45%) from 21.1 million to 30.6 million. The proportion of prescriptions for the trade name Coumadin steadily declined from 85% in 1998 to only 29% in 2004, while those for generic warfarin had a large simultaneous proportional increase.

Table 2. Top 30 Ranking Adverse Events Reported for Warfarin Sodium in AERS (United States), From January 1993 to Mid-July 2006

Adverse Event[a]	No. of Reports[b]
Prothrombin level decreased	3922
INR increased	3901
Drug interaction NOS	2179
Gastrointestinal tract hemorrhage	1914
Hemorrhage NOS	1435
Hematuria	956
Prothrombin level increased	926
Prothrombin time prolonged	772
Anemia NOS	725
Epistaxis	698
Melena	648
INR decreased	635
Drug ineffective	612
Asthenia	606
Rectal hemorrhage	547
Coagulopathy	511
Dizziness	494
Dyspnea	483
Hematocrit level decreased	479
Hemoglobin level decreased	474
Ecchymosis	460
Medication error	413
Hematemesis	410
Hematoma	408
Hemorrhagic stroke	394
Fall	360
INR abnormal	359
Hemoptysis	351
Cerebrovascular accident	331
Diarrhea	327

Abbreviations: AERS, Adverse Event Reporting System; INR, international normalized ratio; NOS, not otherwise specified.
[a] Adverse events are not mutually exclusive; more than 1 may be reported per patient.
[b] Based on case counts (duplicate reports removed by computer identification).

Table 3. Number of Cases of Bleeding[a] Reported in AERS for the Suspect Drug Warfarin Sodium (United States), From January 1993 Through Mid-July 2006

Year	Total Bleeding Cases, No.	Fatal Bleeding Cases, No. (%)	Bleeding Cases With Serious Outcome, No. (%)[b]
1993	630	68 (11)	492 (78)
1994	470	54 (12)	440 (94)
1995	733	54 (7)	560 (76)
1996	662	48 (7)	504 (76)
1997	662	57 (9)	433 (65)
1998	708	63 (9)	644 (91)
1999	769	94 (12)	714 (93)
2000	728	77 (11)	683 (94)
2001	804	109 (14)	766 (95)
2002	714	94 (13)	662 (93)
2003	840	82 (10)	702 (84)
2004	772	61 (8)	676 (88)
2005	898	100 (11)	775 (86)
2006	376	38 (10)	364 (97)
Total	**9766**	**999** (10)	**8415** (86)

Abbreviation: AERS, Adverse Event Reporting System.
[a] Cases were identified in AERS using the following search terms: *coagulopathies and bleeding diatheses (excluding thrombocytopenic)*, *central nervous system haemorrhage and cerebral vascular accidents*, *intraabdominal haemorrhage, vascular hemorrhagic disorders*, and *hematuria*.
[b] Serious outcome includes death, hospitalization, life threatening, disability, congenital malformation, and required intervention.

AERS DATA ON BLEEDING WITH WARFARIN USE

A review in AERS of all primary suspect drugs with serious outcomes by decade indicated that warfarin sodium ranked second only to fluoxetine hydrochloride (Prozac; Eli Lilly and Co, Indianapolis, Indiana) during the 1990s. Based on a ranking of the number of reports with serious outcomes for all drugs (by ingredient and as of July 2006), the top primary suspect drugs in the United States during the 1990s were fluoxetine, with 5326 case report counts, followed very closely by warfarin sodium, with 5324 counts. For the decade of the 2000s (as of August 2006), warfarin sodium, with a case report count of 4581, ranked number 9 in the United States among primary suspect drugs having serious outcomes.

Table 2 provides a list of the 30 top-ranking adverse events reported for warfarin in the United States for the period June 2003 through mid-July 2006. Most of these are indicative of, or associated with, bleeding events. The adverse events in this table are more important for their relative positions than their absolute counts, since underreporting is common, especially for older drugs with well-known reactions such as bleeding with warfarin use.

Table 3 presents the US annual number of bleeding cases, fatal bleeding cases, and bleeding cases with a serious outcome entered in AERS for the period 1993 through mid-July 2006. During this period, a total of 9766 US bleeding cases were entered for warfarin including 8415 (86%) of cases with a serious outcome and 999 (10%) with a fatal outcome. These data contrast with those for all drugs for the same period, in which 30% of the 1.8 million case reports entered in AERS had a serious outcome and 7%, a fatal outcome.

ANTICOAGULANTS ATTRIBUTED AS CAUSES OF DEATH ON US DEATH CERTIFICATES

Table 4 presents the number of deaths listed on US death certificates from 1998 through 2004, in which an anticoagulant was listed as the underlying cause of death.[9,10] It also presents the total mentions (the sum of mentions of anticoagulants as the immediate, contributing, or underlying cause of death or as a significant condition leading to death) of anticoagulants on death certificates. The total mentions ranged from a low of 1169 in 1999 to 1539 in 2002, and crude rates based on the resident US population ranged from 0.43 per 100 000 in 1999 to 0.53 per 100 000 in 2001 and 2002. Total exposure to anticoagulants in all settings was not available, but based on the data of dispensed outpatient prescriptions for warfarin, anticoagulant use appears to have increased substantially during this period. Among the various drug cat-

egories having *ICD* codes for "drugs, medicaments, and biological substances causing adverse effects in therapeutic use," the category of anticoagulants ranked number 1 in total mentions in 2003 and 2004.

NHAMCS DATA ON WARFARIN AND BLEEDING

The NHAMCS sample for years 1999 through 2003 included 698 warfarin visits to US emergency departments, including 43 with a diagnosis code indicative of bleeding.[15] After projection, these sample visits represented 484 407 ± 45 634 annual visits made to US emergency departments for patients receiving therapy with warfarin during this period. Of these visits, 28 682 ± 6492 were associated with bleeding. For visits associated with bleeding, the most frequently identified type of bleeding was gastrointestinal (46%).

Table 4. Deaths Attributed to Anticoagulants in Therapeutic Use as the Underlying Cause and as Total Mentions on US Death Certificates, 1998 Through 2004[a]

Year	Underlying Cause, No. of Deaths With Anticoagulants as the Underlying Cause	Total Mentions[b]	Crude Rate[c]
1998	12	1222	0.45
1999	17	1169	0.43
2000	39	1312	0.46
2001	39	1521	0.53
2002	27	1539	0.51
2003	44	1482	0.52
2004	46	1521	0.52

[a] Source: National Center for Health Statistics.[9]
[b] Total mentions is the sum of mentions of anticoagulants as the immediate, contributing, or underlying cause of death or as a significant condition leading to death.
[c] Per 100 000 population. Rates based on US resident population, Population Estimates Program.[13,14]

COMMENT

The data presented herein indicate that warfarin is a frequently used drug in the United States, and consistent with studies in the medical literature, adverse event data from AERS, US death certificates, and the NHAMCS database of emergency department visits, indicate that bleeding complications with warfarin use continue to be a highly prevalent cause of considerable morbidity and mortality. The data were reviewed to determine the need for placement of the highest level of drug warning, the boxed warning, in the product's labeling to communicate the bleeding risk information to physicians[17,18] and for required distribution of a Medication Guide to communicate information on safe use to patients.[19] Concerning boxed warnings, the federal regulations[17,18] state, "Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box." In support of Medication Guides, the federal regulations state, in brief, that the FDA may require the distribution of FDA-approved patient information

> for human prescription drug products, including biological products, that the Food and Drug Administration (FDA) determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information.

The regulations apply primarily to products used on an outpatient basis for which patient information could help prevent serious adverse effects (pertinent to warfarin use), affect patients' decisions to use or continue to use the product, or affect patients' adherence to directions for use when adherence is crucial to the product's effectiveness (pertinent to warfarin use). Studies have shown that a patient's lack of knowledge and/or poor compliance with warfarin use can lead to poor anticoagulation control and that increasing patient knowledge as part of the overall treatment plan may reduce the likelihood of major bleeding events.[20,21]

Despite the consistency in results showing that bleeding continues to be a prevalent and serious adverse reaction for warfarin, each data set used in this analysis has limitations. The spontaneously reported adverse event data of the FDA have many limitations that have been discussed in detail elsewhere.[7,8] Reports from AERS provide the suspect drug and an outcome, but their causal relationship is often unknown. However, in the case of warfarin, anticoagulation and its extension, bleeding, are physiological effects of the drug; consequently, warfarin would be expected to have a causal role in reports of bleeding. We did not analyze the reports individually, and therefore, the relatively small proportion of duplicate reports was not identified and removed; also, the potential association of warfarin use and bleeding with concomitant or concurrent drug use was not investigated. Reports from AERS are subject to underreporting,[7,8] which is particularly egregious for older drugs with known reactions such as bleeding with warfarin use. Estimates of reporting adverse drug reactions to voluntary reporting databases have been on the order of 4% to 6%.[22-24] Consequently, it is not possible to obtain incidence rates or incidence trends based on AERS reports and warfarin exposure. Despite these limitations, we believe the AERS data are remarkable for warfarin's high rank of adverse events reports compared with those for all other drugs, the high rank of bleeding events among warfarin's adverse events, and the high proportion of serious outcome reports for bleeding with warfarin use.

The US death certificate information provides the number of deaths attributed to therapeutic use of anticoagulants as a cause of death in all settings (institutionalized and outpatient). However, without access to the certificates, it is not currently possible to identify the individual anticoagulants (eg, warfarin, heparin sodium, enoxaparin sodium, and dalteparin sodium), although warfarin would be expected to be prominent. Also, death certificate data are subject to underreporting of bleeding with warfarin, particularly as a contributing cause of death. We included these data because they are national mortality data that show anticoagulants as the top-ranking code among those for "adverse effects in therapeutic use of drugs" and because the data can be tracked

on an annual basis, although warfarin's contribution to mortality based on these data are not currently known.

The NHAMCS data provide the number of visits to emergency departments in which warfarin was mentioned and bleeding was diagnosed. Because of a small sample size, we were unable to analyze the data for possible risk factors associated with bleeding; however, the NHAMCS data provide the prevalence of bleeding in patients using or supplied warfarin in a representative sample of US emergency departments.

While these data sources have limitations, they are complemented by medical literature studies that consistently show that bleeding with warfarin use remains a prevalent adverse drug event and a considerable cause of morbidity and mortality in the United States. Besides the studies mentioned previously,[1-5] the following are worth noting. In a 1993 review of randomized trials of patients with any of 4 indications (cerebrovascular disease, ischemic heart disease, hip surgery, and atrial fibrillation), bleeding occurred in 14% of 3931 warfarin-treated patients compared with 3% of 3583 patients not treated with an anticoagulant.[25] The relative risk for fatal bleeding with warfarin was 4.8 (95% CI, 2.1-10.8); for major bleeding, it was 6.6 (95% CI, 4.0-10.8); and for major and minor bleeding, it was 4.0 (95% CI, 3.3-4.9). The mean annual frequency of fatal bleeding events was 0.6% (95% CI, 0.4%-0.7%); of major bleeding events, 3.0% (95% CI, 2.6%-3.4%); and of major and minor bleeding events, 9.6% (95% CI, 8.8%-10.3%). Also, in a study of the US government's MedPAR (Medicare Provider Analysis and Review) database of Medicare patients admitted to US hospitals in 1998,[26] anticoagulants ranked fourth among all drug classes in frequency of adverse reactions based on *ICD-9* E (external event) codes. Also, anticoagulants were reported to rank third for death among all drug classes in patients who experienced an adverse drug reaction.

After reviewing the data indicating the increasing use of warfarin and the associated high prevalence and seriousness of bleeding, the FDA requested that Bristol-Myers Squibb and the market authorization holders of the generic brands of warfarin place a "black box" on their products warning of the bleeding complication. This was accomplished in October 2006. The boxed warning reminds physicians prescribing warfarin about the risk factors for bleeding,[4,27-33] including high intensity of anticoagulation (INR > 4.0), age 65 years or older, highly variable INRs, history of gastrointestinal tract bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs, and long duration of warfarin therapy. It suggests that regular monitoring of INR be performed on all treated patients and that those at high risk may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. It also suggests that physicians take particular care to instruct patients about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding. Educational brochures designed for patients prescribed warfarin such as the one designed by the Cleveland Clinic[34] and the Medication Guide,[35] which is required to be handed out with each prescription, should help reinforce this message.

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