Patient Reported Receipt of Medication Instructions for Warfarin is Associated with Reduced Risk of Serious Bleeding Events

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BACKGROUND: Adverse drug events are an important cause of preventable hospitalizations.

OBJECTIVE: To identify whether patient report of receipt of medication instructions and markers of complex care (multiple physicians, recent hospitalization) predict the risk of serious bleeding for older adults on warfarin.

DESIGN: Prospective cohort study of older adults.

PARTICIPANTS: Subjects filled new or refill prescriptions for warfarin at the time of enrollment.

MEASUREMENTS: Hospitalizations were identified through a state-wide registry. Discharge summaries of hospitalizations for possible warfarin related bleeding events were reviewed by trained abstractors and clinical experts. Incidence rate ratios (IRR) were estimated based on person-months of exposure using Poisson regression models.

RESULTS: From March 2002 through May 2003, we enrolled a total of 2346 adults on warfarin. Over a two-

year follow-up period, there were 126 hospitalizations due to warfarin-related bleeding (4.6 hospitalizations per 100 person-years of exposure). Patients who reported receiving medication instructions from either a physician or nurse plus a pharmacist had a 60% reduced rate of subsequently experiencing a serious bleeding event over the next 2 years (adjusted IRR 0.40, 95% CI 0.24–0.68). Having ≥ 4 physicians providing medication prescriptions over the last 3 months and filling prescriptions at >1 pharmacy over the last 3 months were independently associated with increased bleeding rates (adjusted IRRs 2.37, 95% CI 1.22–4.57 and 1.61, 95% CI 0.97–2.67, respectively).

CONCLUSIONS: The rate of warfarin-related hospitalization for bleeding is substantially lower for patients who report receiving medication instructions from a physician or nurse and a pharmacist.

KEY WORDS: anticoagulation; patient communication; medication safety.

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INTRODUCTION

Warfarin is frequently cited as a leading drug involved in preventable serious adverse drug events.¹ Management of warfarin is improved in monitored settings, such as clinical trials and anticoagulation clinics, where close attention is given to levels of anticoagulation and warfarin dose.² We hypothesized that barriers to optimal communication between patients, pharmacists and physicians increases the risk of adverse events due to warfarin.

A prior study has demonstrated that disagreement between patient and provider reports of warfarin dosing regimens is associated with excessive levels of anticoagulation.³ However, no studies have linked the adequacy of medication information communication to patients with subsequent clinical outcomes. Thus, this study sought to identify patient-reported characteristics of information exchange with physicians, nurses, and

pharmacists that subsequently predicted serious bleeding events for older adults on outpatient warfarin therapy.

METHODS

We conducted a prospective cohort study of serious bleeding events among older adults receiving warfarin. The study protocol was approved by the institutional review board at the University of Pennsylvania. All study participants provided written informed consent.

Study Site

The study sample was drawn from beneficiaries of the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE). This state-run program offers comprehensive prescription coverage to Pennsylvanians over the age of 65 who are not eligible for Medicaid and meet income eligibility requirements.

Subject Enrollment

Details regarding the process of subject enrollment have been reported previously.⁴ Briefly, subjects were identified through electronic claims transmitted to the PACE program by participating pharmacies. We used a sampling algorithm intended to recruit 2000 new or continuing users of warfarin over a 13-month sampling period (May 1, 2002 through May 31, 2003). Exclusion criteria for the analyses presented in this paper included absence of any claims for warfarin in the PACE database during the follow-up time period and residence in a skilled nursing facility.

Data Collection

Telephone Interviews. Participants completed an interview at baseline and 12 months. For participants who were unable to complete the interview (typically due to cognitive impairment), a proxy interview was sought with a next of kin or caregiver. The baseline interview was conducted within two to four weeks of the pharmacy visit to fill warfarin. Cognitive function was assessed with the six-item cognitive impairment test (6 CIT, score range 0–28),^{5,6} which at a cutoff of scores ≥ 8 has a sensitivity and specificity for mild to severe dementia of 90% and 100%, respectively.⁶ Additional questions regarding receipt of medication instructions were derived through focused interviews conducted by a geriatric nurse with older adults visiting community centers prior to the initiation of this study.⁴ Specifically, we asked patients to indicate receipt of “any instructions that you may have been given for your warfarin. These instructions might include things you shouldn’t do when taking your medication and things you should do. They could have been written instructions or spoken instructions. You could have received the instructions from the doctor, nurse, or pharmacist. These are not related to the instructions written on your pill bottle. Were you given any instructions of this sort?”

Hospitalization Data. All subjects were followed for 24 months from the month of enrollment. In order to identify hospitalizations

during the follow-up period, data were obtained from the Pennsylvania Healthcare Cost Containment Council (PHC4) for within-state hospitalizations. These data are collected quarterly under a mandatory reporting law. We developed a broad list of ICD-9 CM codes suggestive of possible warfarin-related bleeding events. For any hospitalization with a discharge diagnosis (whether principal or not) matching any code on the list, we requested a copy of the discharge summary from the hospital. The codes were purposely selected to maximize sensitivity for case finding.⁷

Hospital discharge summaries were abstracted to collect information on four criteria relevant to each hospitalization’s likelihood of being due to a warfarin-related bleeding event: a) evidence of clinical signs and symptoms of bleeding, b) evidence of elevated international normalized ratio (INR) upon admission, c) a physician’s attribution in the discharge summary of the hospitalization as due to warfarin toxicity, and d) evidence of administration of vitamin K or fresh frozen plasma. Any hospitalization with clinical signs and symptoms of bleeding with at least one of the other criteria was considered a probable warfarin-related bleeding event. All hospitalizations deemed a probable event were then independently reviewed by two authors. The reviewers independently determined whether a hospitalization was definitely due to warfarin-related bleeding. When the two reviewers disagreed, a third expert independently reviewed the discharge summary and the majority opinion ruled. The rate of initial independent agreement on the presence or absence of a definite warfarin-related bleeding event was 78% (95% CI, 74%–82%).⁷

Our primary measure of serious bleeding event was any hospitalization due to warfarin-related bleeding.⁸ However, we separately collected information on whether the bleeding event included intracranial hemorrhage and/or resulted in death.

Data Analysis

Defining Exposure Time. Time at risk was divided for purposes of analysis into 24 consecutive 30-day periods based on the date of enrollment. In keeping with the PACE program’s convention of allowing prescriptions only for 30-day periods, we assumed that each prescription recorded was a 1-month supply.

Defining Risk Factors. For each month of exposure, we counted the number of non-toxicity-related hospitalizations for that month and the prior month. From the PACE database, we calculated the number of unique prescriptions filled per month as a measure of comorbidity and medication complexity.⁹ We also estimated the total number of different prescribing physicians and unique pharmacies for 3-month rolling windows of exposure to assess the frequency of patient contacts with different physicians. Study subjects who reported receipt of medication instructions at baseline were categorized as receiving instructions throughout the follow-up period. However, for those patients reported not receiving instructions at the baseline interview, their status was updated at the 12-month follow-up interview.

Defining Hospitalization Outcomes. Outcome events were counted if they occurred during a month with a prescription for warfarin or within 30 days of such a prescription month. We disregarded bleeding events that occurred more than

1 month after a drug exposure month, whether at the end of a sequence of exposure months or during a “gap” of known drug prescriptions, because we did not have concurrent evidence of exposure to warfarin during those periods in order to calculate unbiased estimates of bleeding risk.

Statistical Analysis. We calculated the overall rate of observed hospitalizations due to warfarin-related bleeding. We calculated incidence rate ratios (IRRs) using multivariable Poisson regression analysis on person-month level data with the number of warfarin related hospitalizations as the dependent variable, and with robust variance estimates (generalized estimating equations) to allow for differing rates of toxicity across subjects that could not be explained by the observed covariates.¹⁰ Variables were then considered for a complete-case-based multivariable model if they were statistically significant in bivariable analysis ($p < 0.1$) or were pre-specified of clinical interest based on risk factors identified in prior studies. (i.e., use of anticoagulation clinic, cognitive function, advanced age, multiple comorbid conditions).^{11–14}

Because of the patterns of missing data, use of only subject months with complete data reduced the sample size for multivariable regression (93.3% of all subject months had complete data). We tested the potential impact on bias of using complete case analysis by using multiple imputation to generate a full dataset for comparison purposes.¹⁵ The results from multiple imputation did not differ from those of the complete case analysis and are not presented.

All analyses were conducted with SAS Version 9.1 (Cary, NC).

RESULTS

Of 3956 eligible patients filling warfarin prescriptions and contacted by the PACE program, 2370 (60%) consented to participate and completed the baseline telephone interview. Of these, 95.7% ($N=2268$) completed the 12 month follow-up interview and 85.0% ($N=2015$) completed 24 months of follow-up. The major reason for failure to complete the follow-up interviews was death ($N=325$, 13.7% of the cohort).

When compared to data from PACE, 23 members of the enrolled cohort (1.0% of total) did not have any claims for warfarin (i.e., were erroneously identified initially) and were dropped. The most common indications for warfarin prescriptions included atrial fibrillation (39%), deep venous thrombosis (21%), stroke (18%), heart valve replacement (11%), and pulmonary embolism (9%).

Characteristics of the Cohort

The majority of study subjects were female (77%), white non-Hispanic (95%), and >75 years of age (65%). Only 8% of the participants required a proxy to complete the baseline telephone interview. However, an additional 9% of participants had CIT scores in the moderate and severe cognitive impairment range (scores 8–10 and ≥ 11 , respectively) (Table 1).⁶

Only 55% of participants reported that they received any medication instructions from a physician or nurse at the time they received their warfarin prescription and 31% reported receiving instructions from both a physician or nurse and a pharmacist (Table 2).

Table 1. Characteristics of Study Subjects

Characteristic	Number (%)
Sex	
Female	1804 (77%)
Age	
≤70 years	283 (12%)
71–75 years	539 (23%)
76–80 years	663 (28%)
81–85 years	577 (25%)
≥86 years	285 (12%)
Race	
White non-Hispanic	2169 (95%)
White Hispanic	30 (1%)
Non-white	92 (4%)
Marital status	
Married	502 (21%)
Single	385 (17%)
Widowed	1453 (62%)
Highest level of education	
Grade school	352 (15%)
Less than high school	586 (25%)
High school	1165 (50%)
College	231 (10%)
Living arrangement	
House	1583 (68%)
Apartment	526 (22%)
Assisted living	14 (1%)
Retirement community	73 (3%)
Other*	148 (6%)
Lives alone	1228 (52%)
Required proxy interview	187 (8%)
Cognitive impairment (CIT)	
CIT score ≥ 8	352 (17%)
Treated in anticoagulation clinic [†]	133 (6%)
History of warfarin use	
First time use [‡]	615 (26%)
Currently taking NSAIDs and/or ASA [§]	478 (20%)

*Includes mobile home, trailer, and religious community

[†]Anticoagulation clinic defined as any clinic site where the patient obtained regular monitoring of anticoagulation and medication adjustment not directly associated with visit to the primary care provider or other medical specialist

[‡]First time use defined based on absence of any pharmacy claims for warfarin during the 12-month period preceding enrollment

[§]NSAIDs: non-aspirin, non steroidal anti-inflammatory drugs. ASA: aspirin. Patients self reported use based on drug specific (brand and generic) prompts

Warfarin-related Bleeding Events

The median length of exposure on warfarin was 11 months (range 1 to 24 months). We identified a total of 126 hospitalizations that were determined to be warfarin-related bleeding events. While the majority of events were gastrointestinal bleeds (67% of total), 11% ($N=14$) were intracranial bleeding events, 3% ($N=4$) were trauma related and 4% ($N=5$) resulted in patient death. Overall, 56 out of the 126 hospitalizations (44%) had a documented international normalized ratio (INR) elevation (>3.5) at the time of admission.

The overall risk of hospitalization due to warfarin-related bleeding event was 4.6 events per 100 person-years of exposure to warfarin (95% CI 3.8, 5.5). The risk of intracranial bleeding was 0.5 events per 100 person-years and the risk of bleeding resulting in death was 0.2 events per 100 person-years. For new users of warfarin, the risk of any serious bleeding event was 4.5 events per 100 person-years of exposure to warfarin (95% CI 2.9, 6.8); and for chronic users

Table 2. Self-reported Information on Medication Utilization Practices

Question	Responses	N (%) [*]
Who usually prescribes your warfarin?	PCP [†]	1856 (84%)
	Other physician specialist	329 (15%)
	No answer	23 (1%)
What type of clinician provides you with instructions on how to take warfarin?	No instruction	513 (22%)
	Only MD or nurse	548 (24%)
	Only pharmacist	226 (10%)
	Both MD/nurse and pharmacist	729 (31%)
	Other person [‡]	303 (13%)
How are medication instructions given?	No instruction	513 (24%)
	Verbal explanation	278 (13%)
	Written sheet	351 (17%)
	Both verbal and written	976 (46%)
Were you instructed on what to do if you missed doses?	No	1194 (56%)
Were you instructed on what drugs to avoid	No	1421 (66%)

^{*}Difference in total column percentages due to rounding. Risk factors totals will differ because of missing values

[†]PCP: primary care provider including general internist, family practitioner, general practitioner or geriatrician

[‡]Other includes family members or friends

of warfarin the risk was 4.7 events per 100 person-years of exposure (95% CI 3.7, 5.8). In addition, the risk of bleeding was not significantly different during the first month of follow-up in the cohort compared to all other months (unadjusted IRR=0.9, 95% CI 0.4, 1.8).

Risk Factors

In unadjusted analyses, the following factors were associated with a reduced rate of subsequent hospitalization due to warfarin-related bleeding: reporting that medication instructions were received from either a physician or nurse plus a pharmacist (unadjusted IRR=0.48 95% CI 0.28, 0.75), reporting that it was clear what to do if a dose of warfarin was missed (unadjusted IRR=0.65, 95% CI 0.43, 0.98), and reporting that it was clear what other drugs to avoid while on warfarin (unadjusted IRR=0.55, 95% CI 0.34, 0.88).

In analyses adjusting for age, cognitive function, NSAID and/or aspirin use, total number of medications filled, and indication for warfarin, a patient report that he/she received medication instructions for warfarin from either a physician or nurse plus a pharmacist was associated with a reduced risk of subsequent hospitalization due to warfarin-related bleeding compared to reporting that no instructions were received (adjusted IRR 0.40, 95% CI 0.24, 0.68) (Table 3). In absolute terms, subjects reporting no receipt of medication instructions experienced 8.0 bleeding events per 100 person-years of warfarin exposure compared to 3.3 events per 100 person-years of exposure for patients reporting receipt of instructions from either a physician or nurse plus a pharmacist. In addition, filling prescriptions written by ≥ 4 physicians in the last 3 months compared to only 1 physician writing prescriptions (adjusted IRR 2.37, 95% CI 1.22, 4.57) and filling prescriptions at >1 pharmacy in the last 3 months (adjusted IRR 1.61, 95% CI 0.97, 2.67) were independently associated with the risk of serious bleeding. Other patient factors, such as

education level, and visual and auditory functions were neither independent predictors of serious bleeding events nor modifiers of the association between report of receipt of medication instruction and risk of bleeding.

In a separate analysis adjusting for all the same factors, substituting the type of instructions (verbal vs. written) for the source of instruction, we observed that compared to receiving no instructions, patient reports of receiving written instructions alone or written plus verbal instructions were associated with a reduced risk of bleeding events (adjusted IRR 0.38, 95% CI 0.18, 0.80 and adjusted IRR 0.47, 95% CI 0.29, 0.76, respectively). Patient report of receiving verbal instructions alone was not associated with a reduced risk of bleeding events compared to no instructions (adjusted IRR 0.95, 95% CI 0.51, 1.76).

These specific risk factor estimates remained unchanged after excluding all proxy interviews. In addition, there was no evidence for an interaction between the effect of patient report of receipt of medication instructions and whether the patient was a new vs. chronic user of warfarin. Finally, restriction of the outcome to those bleeding events with a documented INR elevation (>3.5) at the time of admission yielded even stronger measures of association. For example, patient report that he/she received medication instructions from either a physician or nurse plus a pharmacist was associated with an 80% reduction in the subsequent risk of hospitalization due to warfarin-related bleeding (adjusted IRR 0.21, 95% CI 0.09, 0.50).

In models that examined the risk of hospitalization due to any cause during the follow-up period, exposure to multiple physicians and multiple pharmacies remained significant risk factors for any type of hospitalization. However, reporting that medication instructions for warfarin were received from either a physician or nurse plus a pharmacist compared to no instructions was not significantly associated with the risk of any hospitalization (adjusted IRR 0.87, 95% CI 0.71, 1.05).

DISCUSSION

Patients who report receiving medication instructions from either a physician or nurse plus a pharmacist after they fill prescriptions for warfarin were at substantially reduced risk of experiencing hospitalization due to warfarin-related bleeding over the next two years. Moreover, this reduced risk was independent of patient age, cognitive function, home living arrangement, and number of co-administered medications. The reduced risk was also specific for hospitalization due to warfarin-related bleeding as reporting receipt of medication instructions was not associated with a reduced risk of hospitalization overall.

The overall rate of serious bleeding events in this study (4.6 events per 100 patient-years) is comparable to prior studies which reported rates of serious or major bleeding ranging from 4 to 7 events per 100 patient-years of warfarin exposure.^{12,16} Prior studies of risk for warfarin-related bleeding events have largely emphasized patient clinical and demographic factors,^{12,13,17} along with co-administration of potential interacting medications.¹⁸ Our study adds to this literature by demonstrating that if patients do not recall receiving instructions on the proper way to use warfarin, they are at increased risk of suffering a serious warfarin-related bleeding event. It is important to recognize that for community-dwelling patients, few systems currently exist to monitor administration and prevent medication errors.¹⁹ In this regard, it is notable that

Table 3. Unadjusted and Adjusted Incidence Rate Ratios for Hospitalizations due to Warfarin-related Bleeding*

Risk factor	Levels	Person-years [†]	Bleeding events N=111 [†]	Unadjusted		Adjusted	
				IR ratio	95% CI	IR ratio	95% CI
Source of medication instructions	No instruction	464	36	Ref		Ref	.
	MD/nurse	469	18	0.67	0.40, 1.14	0.60	0.34, 1.05
	Pharmacist	245	8	0.51	0.26, 1.02	0.44	0.20, 0.93
	MD/nurse + Pharmacist	624	19	0.46	0.28, 0.75	0.40	0.24, 0.68
Age categories	Other [§]	556	30	0.58	0.31, 1.09	0.54	0.27, 1.08
	≤70	304	14	Ref	.	Ref	.
	71–75	577	19	0.83	0.40, 1.70	0.69	0.31, 1.51
	76–80	677	31	0.99	0.50, 1.96	1.09	0.52, 2.26
	81–85	554	37	1.56	0.82, 3.00	1.61	0.78, 3.32
	≥86	244	10	1.16	0.54, 2.50	1.13	0.43, 2.94
Cognitive impairment	CIT 0–2	1330	61	Ref		Ref	.
	CIT 3–7	619	37	1.30	0.83, 2.04	1.19	0.76, 1.86
	CIT 8–10	254	12	1.16	0.65, 2.06	0.95	0.50, 1.82
	CIT ≥ 11	153	1	0.14	0.02, 1.00	0.14	0.02, 1.08
Indication	Other**	2051	77	Ref		Ref	
	Valve	305	34	2.83	1.82, 4.38	3.02	1.91, 4.78
Anticoag clinic	No	2202	98	Ref		Ref	.
	Yes	154	13	1.35	0.68, 2.67	1.63	0.84, 3.14
NSAID/ ASA ^{††}	No	1890	82	Ref		Ref	.
	Yes	466	29	1.87	0.98, 3.60	1.37	0.88, 2.12
MD asks about meds	No	1410	53	Ref		Ref	.
	Yes	946	58	1.72	1.17, 2.55	1.35	0.89, 2.07
Nr. of MDs prescribing ^{‡‡}	1	744	18	Ref		Ref	.
	2–3	1209	57	1.91	1.19, 3.06	1.58	0.92, 2.68
	≥4	403	36	3.76	2.20, 6.43	2.37	1.23, 4.57
Nr. of pharmacies filling ^{§§}	1	2149	92	Ref		Ref	.
	≥2	207	19	2.01	1.26, 3.21	1.61	0.97, 2.67
Nr. of unique meds ^{***}	1–3	363	9	Ref		Ref	.
	4–8	1444	62	1.58	0.81, 3.07	1.51	0.76, 3.00
	≥9	550	40	2.31	1.14, 4.67	2.18	1.03, 4.61
Nr. of hospitalizations ^{†††}	0	2157	93	Ref		Ref	.
	≥1	200	18	2.23	1.41, 3.53	1.48	0.87, 2.53

*Incidence rate ratios (IR ratio) and 95% confidence limits are calculated from Poisson regression, modeling the number of hospitalizations due to warfarin toxicity each month of warfarin exposure, with the total number of warfarin exposure months per patient as a covariate in all models. Unadjusted estimates include only the exposure of interest, adjusted estimates include all exposures in the table. For the multivariable model there were 30,705 person months of exposure with no missing data (93.3% complete)

[†]Person-years of exposure based on total number of person-months in each exposure category divided by 12. Unequal follow-up across categories accounts for differences in exposure time in this table vs. Tables 1 and 2 describing baseline characteristics

[‡]Fifteen of the 126 hospitalizations due to warfarin-related bleeding in the cohort were dropped because of missing data that reduced the overall number of observations in the final adjusted model

[§]Other includes family members or friends

^{**}Other indications for warfarin include atrial fibrillation, deep venous thrombosis, pulmonary embolism and stroke

^{††}NSAIDs: non-aspirin, non-steroidal anti-inflammatory drugs. ASA: aspirin. Based on patient self-report at the baseline or 12-month interview. The interview used specific brand and generic drug name prompts

^{‡‡}Number of unique MD codes on prescriptions filled in last 3 months. Time varying exposures were assessed at monthly intervals throughout the follow-up period

^{§§}Number of unique pharmacy codes on prescriptions filled in last 3 months. Time varying exposures were assessed at monthly intervals throughout the follow-up period.

^{***}Number of unique prescriptions filled within current month, based on unique National Drug Codes. Time varying exposures were assessed at monthly intervals throughout the follow-up period

^{†††}Number of hospitalizations were counted anytime during the current month of exposure to warfarin and prior month of exposure. Hospitalizations occurring in the same month after a hospitalization due to warfarin related bleeding as well as any hospitalizations due to warfarin related bleeding were not counted. Time varying exposures were assessed at monthly intervals throughout the follow-up period

only 6% of patients in this study reported receipt of care in a clinic setting dedicated to monitoring anticoagulation levels.

Importantly, we measured patient report of receipt of medication instruction, not the actual receipt of medication instruction. It is likely that in many cases, medication instructions were actually provided by physicians or nurses and pharmacies, but were not recalled by patients when interviewed. Nevertheless, the fact that patients do not recall receiving these instructions is a key predictor of future adverse events.

It is possible that patients' reports that they received medication instructions from their health care providers might be a

surrogate for other elements, such as trust in providers, that improve clinical outcomes by increasing medication adherence and reducing adverse drug events. Physician offices that are more effective at providing medication instruction may also more closely monitor interacting drugs and more appropriately monitor INR levels. In addition, patients who report receiving medication instructions may be more actively involved in managing their healthcare and thus more likely to prompt physicians and nurses for such instructions. Moreover, such patients may be more likely to act to reduce their risk of bleeding, such as reporting to clinic appointments for INR monitoring, and report-

ing mild symptoms that may identify bleeds at an earlier stage. Thus, this study does not establish that failure to report receipt of medication instructions is causally related to subsequent warfarin-related bleeding events.

A key strength of this study was the prospective design which allowed us to assess patient reported behaviors and knowledge prior to the occurrence of any adverse events, avoiding ascertainment bias. However, one limitation of this study is the potential non-representativeness introduced by non-participants. Our limited comparisons of characteristics indicate that non-participants were older, more likely to be living alone and in the lower income categories.⁴ We also could not measure all factors that might have confounded the observed associations in this study. Previously reported studies predicting bleeding events for patients on warfarin have included specific comorbid conditions (e.g., diabetes mellitus, GI bleeding, alcoholism, hepatic disease), drug interactions (e.g., antiplatelet agents) and laboratory abnormalities (renal insufficiency),^{16, 20} which we could not control for in this study.

Prior work has established that as patients become more active and informed participants in health conversations with providers, outcomes are likely to improve.²¹ Indeed, since the time of this study, new regulation now requires the distribution of a medication guide with all warfarin prescriptions,²² and the Centers for Medical Services now provides a reimbursement mechanism for medication counseling for Medicare recipients,²³ but the effectiveness of these interventions is unknown. Regardless of whether such interventions lead to more consistent and better medication counseling activities, a key finding of this study is that patients who do not recall such instructions are at increased risk for bleeding events. Future studies should examine the effectiveness and cost-effectiveness of office-based or home-based programs to identify and more carefully manage these high risk patients on warfarin.

In summary, patients and their caregivers remain key participants in assuring the safe use of medications in outpatient settings. Developing interventions to screen for and manage high risk patients and situations is a critical next step in assuring safer use of warfarin and possibly other high risk medications.

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