CLINICAL RESEARCH   **Clinical Trial**

Warfarin Genotyping Reduces Hospitalization Rates

Results From the MM-WES (Medco-Mayo Warfarin Effectiveness Study)

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Objectives   This study was designed to determine whether genotype testing for patients initiating warfarin treatment will reduce the incidence of hospitalizations, including those due to bleeding or thromboembolism.

Background   Genotypic variations in *CYP2C9* and *VKORC1* have been shown to predict warfarin dosing, but no large-scale studies have prospectively evaluated the clinical effectiveness of genotyping in naturalistic settings across the U.S.

Methods   This national, prospective, comparative effectiveness study compared the 6-month incidence of hospitalization in patients receiving warfarin genotyping (n = 896) versus a matched historical control group (n = 2,688). To evaluate for temporal changes in the outcomes of warfarin treatment, a secondary analysis compared outcomes for 2 external control groups drawn from the same 2 time periods.

Results   Compared with the historical control group, the genotyped cohort had 31% fewer hospitalizations overall (adjusted hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.58 to 0.82, p < 0.001) and 28% fewer hospitalizations for bleeding or thromboembolism (HR: 0.72, 95% CI: 0.53 to 0.97, p = 0.029) during the 6-month follow-up period. Findings from a per-protocol analysis were even stronger: 33% lower risk of all-cause hospitalization (HR: 0.67, 95% CI: 0.55 to 0.81, p < 0.001) and 43% lower risk of hospitalization for bleeding or thromboembolism (HR: 0.57, 95% CI: 0.39 to 0.83, p = 0.003) in patients who were genotyped. During the same period, there was no difference in outcomes between the 2 external control groups.

Conclusions   Warfarin genotyping reduced the risk of hospitalization in outpatients initiating warfarin. (The Clinical and Economic Impact of Pharmacogenomic Testing of Warfarin Therapy in Typical Community Practice Settings [MHSMayoWarf1]; NCT00830570)   (J Am Coll Cardiol 2010;55:2804–12) © 2010 by the American College of Cardiology Foundation

Warfarin is an anticoagulant that has been the standard of care for more than 50 years to prevent and treat thromboemboli. Approximately 2 million Americans initiate warfarin therapy annually (1), and currently there are no oral alternatives available in the U.S. Because of the overriding need for effective anticoagulation, warfarin remains a commonly used drug in spite of the significant morbidity and mortality associated with its use. It is the second leading drug-related reason for emergency department visits (2) and the most often cited reason for drug-related mortality (3). Methods to improve the safety and effectiveness of warfarin therapy are urgently needed.

Reaching a stable, therapeutically effective dose of warfarin is difficult because it is dependent on multiple factors, including age, weight, diet, concurrent medications, and genetic variability in drug response (4,5). Most drug-related

adverse events are due to problems in establishing the effective dose; it can take many weeks to evaluate, adjust, and stabilize the dose for an individual patient. During the dose adjustment phase, patients are at serious risk for hemorrhage or thrombosis (1,5). Event rates for bleeding or thromboembolism range as high as 16.5% and 25% during the first 6 months of warfarin treatment in usual care settings (6,7).

Over the past decade, variations in 2 genes have been shown to predict individual response to warfarin dosing (8–11). One gene determines the activity of the hepatic

isoenzyme cytochrome P450 2C9 (*CYP2C9*), which plays a significant role in metabolizing S-war-farin into its inactive form (12). The other gene, *VKORC1* (VKOR complex subunit 1), determines the activity of vitamin K epoxide reductase (VKOR), an enzyme that produces the active form of vitamin K necessary for blood clotting (13). The *CYP2C9* and *VKORC1* polymorphisms account for more than one-third of the variance associated with stable therapeutic dosing (8,9,14,15). Simultaneous evaluation of a patient's deoxyribo-nucleic acid for allelic variations in these 2 genes is known as *warfarin sensitivity genotyping*.

Laboratory tests for *CYP2C9* and *VKORC1* polymorphisms are commercially available, but their use in warfarin treatment has been very limited. Without data substantiating the clinical utility of warfarin genotyping, many clinicians have been reluctant to adopt warfarin sensitivity testing in standard practice (12,16,17). A few small studies have evaluated the impact of warfarin genotyping on clinical events (such as bleeding or thrombosis), and they have shown mixed results (17–21). No published studies to date have been powered adequately to evaluate the impact of genotyping on clinical outcomes, although a few studies are underway to address this.

Our study is the first national, prospective, comparative effectiveness study of the impact of warfarin sensitivity genotyping in patients who initiate warfarin therapy in typical practice settings. The study was designed to evaluate the impact of genotype testing on hospitalization rates in the first 6 months of warfarin treatment, comparing genotyping with usual care.

Methods

Study design. We enrolled patients in naturalistic settings with minimal protocol-based constraints on patients or physicians that might limit its external validity. To achieve this objective, we employed a quasi-experimental design, which is a well-established means of evaluating an intervention in an environment with significant natural variability in clinical practices (22–24). This design strategy enabled us to enroll a broader and more representative range of providers and patients than is typical in randomized, controlled clinical trials.

For the primary intervention, we invited patients initiating outpatient warfarin treatment to undergo free genotype testing with their physician's approval. These patients were drawn from the member populations of prescription benefit plans that agreed to participate in the study. Medical claims for these patients were tracked for the occurrence of hospitalizations during the 6 months following the start of warfarin treatment (the date of the index prescription). Hospitalization rates for these patients were compared with rates for a historical control group of similar patients who were new to warfarin treatment, but began treatment during the preceding year. The principal comparison was the difference in event-free time during the first 6 months after treatment onset, comparing outcomes for the intervention group with the historical controls.

To quantify potential temporal trends over the same 2 time periods, we constructed 2 external control groups using similar criteria: a cohort that began warfarin therapy during the same time period as the intervention group (external concurrent controls), and a cohort that began treatment during the prior year (external historical controls). Hospitalization rates for the 2 external control groups were compared to determine whether changes in the intervention group could be attributed to temporal changes in general clinical practice.

Study sample. Patients in all of the study groups were members of prescription benefit plans managed by Medco for a representative range of benefit plan sponsors (employers, health plans, and government organizations) with plan membership spanning the U.S. The plans included health maintenance organizations, preferred provider organizations, and traditional fee-for-service plans.

Entry criteria for the intervention group were kept to a minimum. Beginning in July 2007, any adult from participating plans who was 40 to 75 years of age and initiated outpatient warfarin therapy was eligible for study entry. Patients were excluded if they had a prescription for warfarin in the previous 180 days, had a hospitalization longer than 7 days before starting warfarin, were prescribed short-term use of warfarin, had a prior history of genetic testing for warfarin, had a known hypersensitivity to warfarin, or had no known telephone number to initiate contact for study participation. Patients had to be continuously eligible for prescription benefits during the 6 months before to the index prescription to ensure accurate evaluation of their prior medication use, medical conditions, and lack of prior warfarin use. The same inclusion and exclusion criteria were applied to patients in all of the control groups. Participants in the intervention group had to supply informed consent for the study, as did their treating physician.

A total of 29 benefit plan sponsors agreed to have their members identified for participation in the intervention group. For these original plan sponsors, 1,635 patients were initially enrolled and genotyped as part of the intervention group. By the time the study closed, the requisite medical claims data for longitudinal outcomes evaluation were available for 23 plans, leaving a total of 896 evaluable genotyped patients in the intervention group; all of these patients were included in the study analysis. Patients in the historical control group were drawn from the same 23 plans, and they were matched in age and sex on a 3:1 basis with patients in the intervention group. The external control groups were derived from 56 plans unrelated to these 23 plans and were similarly matched for age and sex on a 3:1 basis with the intervention group.

Abbreviations and Acronyms

CI = confidence interval

HR = hazard ratio

INR = international normalized ratio

PP = per-protocol

Intervention. Utilizing real-time pharmacy claims data, we identified candidates for the intervention on the day their warfarin treatment was initiated on an outpatient basis. Study candidates and their physicians were contacted to secure their consent to participate in the study; all were advised that their participation was voluntary. Terms of participation were defined in the study protocol, which had been reviewed and approved by the Mayo Clinic Institutional Review Board and an independent, external Institutional Review Board contracted by Medco, and recorded on Clinicaltrials.gov (NCT00830570).

The intervention comprised 2 primary steps: 1) gathering the patient's deoxyribonucleic acid for *CYP2C9* and *VKORC1* genotyping; and 2) delivering the results in a report with interpretation to the physician. To approximate conditions of typical clinical practice, and consistent with the product label during the study period, there were no mandated interventions following delivery of the laboratory report. Physicians provided usual care supplemented by testing for genetic variations that could affect the patient's sensitivity to warfarin. They had the option to adjust warfarin dosing based on the patient's genotype test results, but their treatment practices were unconstrained by study protocol.

Genotype testing. During the first half of study recruitment, a Medco-affiliated nurse visited the patient's home to collect a blood sample for genetic testing. After the Mayo Clinic confirmed the reproducibility of test results between blood and buccal swab samples, we mailed buccal swabs to increase convenience and reduce study costs. After procuring patients' informed consent, the test samples were sent to the Mayo Clinic for genotype testing.

The *CYP2C9* and *VKORC1* tests were performed by the Mayo Clinic on a Luminex platform using reagents acquired from Luminex Molecular Diagnostics (Austin, Texas). These tests were approved for use in clinical practice as in-house developed tests as authorized by the Clinical Laboratory Improvement Act, 42 CFR 493.

During clinical validation of the test, *CYP2C9* *2 and *3 variants and *VKORC1* A/A, G/A, and G/G variants were detectable in >98% of cases evaluated (11). Although other variants of *CYP2C9* and *VKORC1* may be present, these alleles (all of which are identified by the Luminex Molecular Diagnostics assay) are the most important for determining dose (9), and they are the only ones considered by the U.S. Food and Drug Administration to be valid biomarkers for warfarin dosing (25).

The report to the physician included genotype and predicted phenotype. The phenotype represents the patient's likely sensitivity to warfarin based on genotype (Table 1). The physician report also included patient-specific clinical considerations and some general information about potential drug-drug interactions with warfarin (sample report shown in Online Tables 1 and 2).

Outcome measures. The primary study end point for all groups was the incident hospitalization rate (measured as event-free time) during the 6 months following the start of outpatient warfarin treatment. The event-free time is the number of days between warfarin initiation and the first hospitalization due to any cause or the first hospitalization due to bleeding or thromboembolism. Events due to bleeding or thromboembolism were identified from medical claims using International Classification of Diseases-Ninth Revision codes that have been shown to have a high degree of validity as measures for cardiovascular adverse events (26–28). Baseline characteristics for patients in all groups were derived from benefit eligibility and drug utilization databases maintained by Medco, and from medical utilization data supplied by participating plans.

Statistical analysis. Using chi-square tests for categorical variables and *t* tests for continuous variables, baseline characteristics were compared between the intervention and historical control groups and between the 2 external control groups. Unadjusted comparisons of the primary outcome

Table 1	Phenotype Characteristics of Intervention Group Patients			
	Genotype Combination			
Warfarin Sensitivity	**VKORC1**	**CYP2C9**	**Prevalence**	**Clinical Considerations***
Very high	A/A	*1/*3, *2/*2, *2/*3, *3/*3	23 (2.6%)	Dose decrease and frequent INR monitoring
	G/A	*3/*3		
High	A/A	*1/*2	36 (4.0%)	Dose decrease and frequent INR monitoring
	G/A	*2/*3		
	G/G	*3/*3		
Moderate	A/A	*1/*1	238 (26.6%)	Dose decrease and frequent INR monitoring
	G/A	*1/*2, *1/*3, *2/*2		
	G/G	*2/*3		
Mild	G/G	*1/*2, *1/*3, *2/*2	109 (12.2%)	Frequent INR monitoring
Normal	G/A	*1/*1	262 (29.2%)	Likely to experience normal response to warfarin
Less than normal	G/G	*1/*1	228 (25.4%)	Dose increase may be required to maintain optimal INR
Total			896 (100%)	

Values are n (%). Genotype is defined by the combination of measured allelic variations in *CYP2C9* and *VKORC1*. Phenotype is the expected warfarin sensitivity based on genotype. *Complete wording as it appeared in laboratory report is provided in online supplement (Online Table 2).

INR = international normalized ratio.

Table 2	Baseline Characteristics of Study Population		
Characteristic	Historical Control (n = 2,688)	Intervention Group (n = 896)	p Value
Mean age, yrs (SD)	65.2 (8.0)	65.2 (8.3)	0.921
Men	60.5%	60.5%	1.000
Medications			
Amiodarone*	4.0%	3.2%	0.313
Statins*	14.5%	17.0%	0.071
Sulfamethoxazole*	4.4%	5.2%	0.268
Fluconazole*	2.4%	2.6%	0.803
NSAIDs	19.6%	19.9%	0.865
Clopidogrel	10.8%	10.2%	0.574
Corticosteroids	12.4%	13.6%	0.354
Conditions			
Atrial fibrillation	40.4%	41.1%	0.709
Pulmonary embolism	11.0%	11.8%	0.501
Deep vein thrombosis	24.6%	25.8%	0.489
GI bleed	3.6%	4.0%	0.539
Hypertension	47.0%	54.2%	<0.001
Diabetes	15.3%	11.6%	0.007
Prior hospitalizations			
Any cause	54.4%	52.8%	0.405
Bleeding or thromboembolism	23.6%	24.8%	0.469

Age is determined as of index warfarin prescription date. Medication use is identified by any prescription for a drug or drug class during the prior 6 months; days' supply may be concurrent with warfarin use. Medical conditions are identified during the prior 6 months using prescription claims (diabetes) or medical diagnosis per International Classification of Diseases-Ninth Revision codes in medical claims (all other conditions). Prior hospitalizations are identified during the prior 6 months based on medical claims. *Inhibitors of *CYP2C9* metabolism: fluconazole (strong inhibitor), amiodarone and sulfamethoxazole (moderate inhibitors), and statins (variable).

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

measures (incident hospitalization rates) were conducted using Kaplan-Meier methods and log-rank tests.

To address potential selection bias, we used propensity scores to control for factors that may be associated with patients' likelihood of participating in genotype testing. Using a logistic regression model, we developed a propensity score to measure the likelihood of being tested. The model included age, prescription medications known to interact with warfarin metabolism (amiodarone, statins, sulfamethoxazole, fluconazole), other commonly used medications (nonsteroidal anti-inflammatory drugs, clopidogrel, corticosteroids), and history of hospitalization for bleeding or thromboembolism in the 6 months before initiating warfarin. The propensity analysis found very little difference between patients in the intervention and historical control groups based on these parameters.

Adjusted comparisons were based on multivariate Cox proportional hazards models, controlling for primary indications for warfarin treatment (atrial fibrillation, pulmonary embolism, deep vein thrombosis), selected comorbid conditions (gastrointestinal bleed, hypertension, diabetes), and propensity score quintiles. We analyzed the data using an intention-to-treat analysis whereby all hospitalizations following the start of warfarin therapy were included, even if hospitalizations occurred before genotyping (in the intervention group).

We also performed a per-protocol (PP) analysis in which only the events occurring after genotyping were counted for patients in the intervention group. In the PP analysis, event rates for the control groups were adjusted by randomly assigning nonmeasured intervals following each patient's first warfarin prescription. The distribution of these nonmeasured intervals matched the intervals between the first prescription and genotype testing in the intervention group, so that early events in the control groups were discounted to an equal degree.

Results

Patients in both study groups averaged 65 years of age, and 61% were male (Table 2). The 2 groups were balanced in prevalence of primary indications for warfarin therapy (atrial fibrillation, pulmonary embolism, deep vein thrombosis). Among comorbid conditions, the prevalence of hypertension was higher in the intervention group than in the historical control group, but the prevalence of treated diabetes was lower. The 2 groups were balanced with respect to concomitant medications (including *CYP2C9* inhibitors) that could be potential confounding variables. The groups were also well matched in hospitalization rates for any cause or for bleeding or thromboembolism during the prior 6 months. The geographic distribution of these groups was also balanced. Participants in each group were drawn from 49 of the 50 U.S. states.

The genotype distribution for the intervention group is shown in Table 3, and the corresponding phenotype distribution is summarized in Table 1. For these patients, 29.2%

Table 3   **Genotype Distribution of Intervention Group Patients**

VKORC1	CYP2C9						
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	Total
G/G	228 (25.4%)	69 (7.7%)	36 (4.0%)	4 (0.4%)	5 (0.6%)	2 (0.2%)	344 (38.4%)
A/G	262 (29.2%)	82 (9.2%)	49 (5.5%)	8 (0.9%)	8 (0.9%)	1 (0.1%)	410 (45.8%)
A/A	94 (10.5%)	26 (2.9%)	18 (2.0%)	1 (0.1%)	2 (0.2%)	1 (0.1%)	142 (15.8%)
Total	584 (65.2%)	177 (19.8%)	103 (11.5%)	13 (1.5%)	15 (1.7%)	4 (0.4%)	896 (100.0%)

Values are n (%). Data are provided for each measured allele combination.
CYP2C9 = cytochrome P450 2C9; VKORC1 = vitamin K epoxide reductase complex subunit 1.

had normal warfarin sensitivity, 25.4% had lower-than-normal sensitivity (suggesting a higher dose might be required), 12.2% had mild sensitivity (suggesting that more frequent monitoring might be prudent), and 33.2% had moderate to very high sensitivity (suggesting a lower dose might be required, along with frequent monitoring). The possible dose adjustments summarized in Table 1 were included in the reports to the patients' physicians. In total, the genotype results for 58.6% of patients in the intervention group (those with less-than-normal, moderate, high, or very high sensitivity) would be considered indicative of a potentially higher or lower dose than average.

The impact of genotyping on hospitalizations is summarized in Table 4. On an unadjusted basis in the intention-to-treat analysis, patients in the intervention group showed a 28% lower rate of hospitalization for any cause, compared with patients in the historical control group (18.5% vs. 25.5%, p < 0.001). The intervention group showed a similar 27% reduction in hospitalization risk for bleeding or thromboembolism, compared with the historical controls (6.0% vs. 8.1%, p = 0.039). In the PP analysis, the unadjusted differences between the 2 groups were even larger; patients in the intervention group showed a 31% lower rate of all-cause hospitalizations (14.0% vs. 20.5%, p < 0.001) and a 40% lower rate of hospitalizations for bleeding or thromboembolism (3.7% vs. 6.2%, p = 0.005). By contrast, none of the differences between the external control groups was statistically significant.

Adjusted hospitalization rates based on the intention-to-treat analysis showed a similar pattern (Fig. 1). Compared to the historical controls, patients in the genotyped group had 31% fewer hospitalizations overall (adjusted hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.58 to

0.82, p < 0.001) and 28% fewer hospitalizations for bleeding or thromboembolism (HR: 0.72, 95% CI: 0.53 to 0.97, p = 0.029) over the 6-month follow-up period. No significant differences in adjusted hospitalization rates were observed between the external control groups.

Adjusted hospitalization rates based on the PP analysis (Fig. 2) reveal stronger differences between the intervention group and the historical control group. Compared with historical controls, patients who were genotyped had 33% fewer hospitalizations overall (HR: 0.67, 95% CI: 0.55 to 0.81, p < 0.001) and 43% fewer hospitalizations for bleeding or thromboembolism (HR: 0.57, 95% CI: 0.39 to 0.83, p = 0.003). No significant differences in hospitalization rates between the external control groups were observed.

Discussion

In this comparative effectiveness study, which encompassed thousands of outpatients in practice settings across the country, we found significant reductions in adverse events for patients who were genotyped early in the course of warfarin treatment. Compared with historical controls, genotyped patients had 31% fewer all-cause hospitalizations and 28% fewer hospitalizations for bleeding or thromboembolism. Our findings suggest that the addition of genotyping to usual care reduces the risk of hospitalization by approximately 30% among patients initiating warfarin. This reduction is consistent with a meta-analysis conducted by Eckman et al. (17), which found a trend toward a 32% reduction in major bleeding across 3 randomized trials.

Published studies of genotype testing for warfarin have been conducted in controlled clinical settings (18–21). Although the controlled nature of these studies generates the *internal validity* needed to account for confounding factors, these studies do not allow us to extrapolate that the findings apply to a wider array of "real-world" warfarin users in representative patient care settings. Our study provides insight into the *external validity* of genotype testing in warfarin therapy by evaluating the clinical outcomes of testing for a wide range of patients treated by a wide variety of practitioners across the U.S.

Given the nature of our study design, our findings have applicability to a wide range of outpatients. We intentionally imposed few inclusion or exclusion criteria on participants in the study. As a result, participants represented a

Table 4   **Unadjusted Incident Hospitalization Rates**

Analysis	Historical Control (n = 2,688)	Intervention Group (n = 896)	p Value
Intention to treat			
Any cause	25.52	18.45	<0.001
Bleed or thromboembolism	8.13	5.97	0.039
Per-protocol			
Any cause	20.45	14.04	<0.001
Bleed or thromboembolism	6.22	3.71	0.005

Values are Kaplan-Meier hospitalization rates per 100 patients. The p value is obtained using log-rank test.
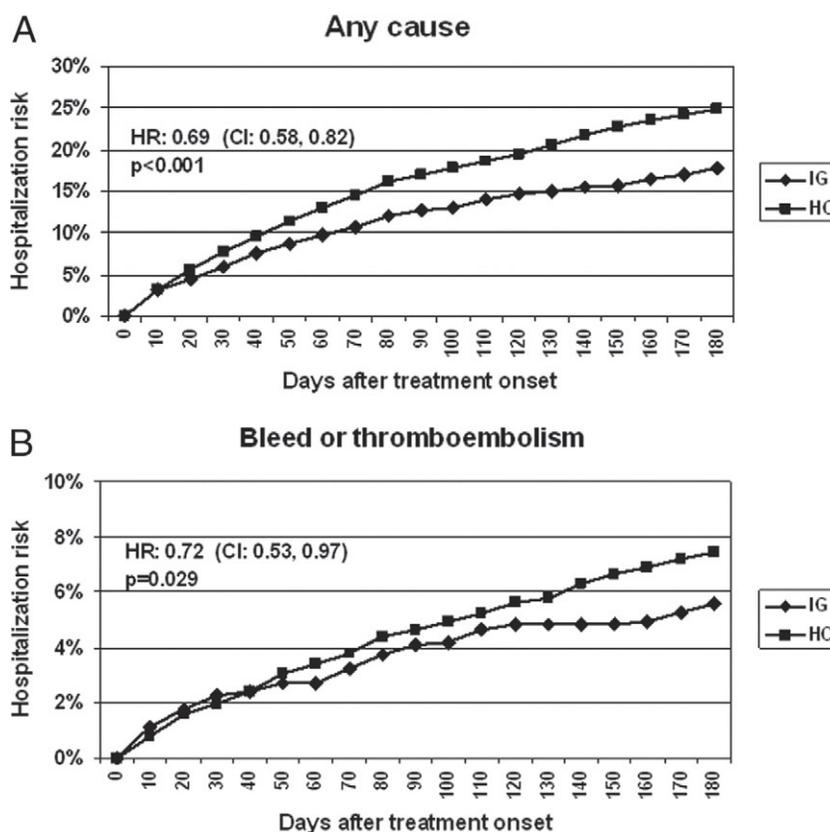
Figure 1   Adjusted Hospitalization Rates: Intention to Treat Analysis

The figure shows the hospitalization rate for patients in each study group during the 6-month period following initiation of warfarin treatment. **(A)** Events due to any cause; **(B)** events due to bleeding or thromboembolism. CI = confidence interval; HC = historical control; HR = hazard ratio; IG = intervention group.

broad range of geographic regions, comorbid conditions, concomitant medications, treatment indications, and health benefit plans. However, our results may not generalize to other populations, such as inpatients who often have more focused care.

Physicians in this study were diverse in geographic distribution, practice settings, and practitioner types. In the intervention group, 29.4% of physicians were cardiovascular specialists, 49.1% were in primary care, and the remainder in a mix of other specialties. The distribution for the historical controls was very similar (29.6% cardiovascular, 49.1% primary care), making it unlikely that differences in practitioner types or practice settings account for the observed differences in outcomes. It is also worth noting that 75.0% of the contacted physicians agreed to order the genotype tests for their patients—a very high response rate, which reduces the risk of self-selection bias.

Although our study design did not include direct monitoring of treatment changes by physicians following receipt of the genotype data, pharmacy claims suggest that they responded to the information with dosage changes that reflect the reports (Table 5). For patients with moderate to very high sensitivity to warfarin, new prescriptions showed a decrease in dose during the 21 days following receipt of the laboratory results; the size of the decrease was proportional to the level of sensitivity. Similarly, patients with less-than-normal sensitivity showed an increase in dose during the 21 days following receipt of the laboratory results.

Several weeks often elapsed between therapy initiation and delivery of the genotype results to the physician; the interval ranged from 11 to 60 days, with a median of 32 days. The interval reflected several factors, including time to receive the order from the treating provider, obtain consent from the patient, collect biological samples, and return samples to the laboratory. We found a progressive reduction in risk the closer genotyping was to warfarin initiation. Unadjusted hospitalization rates for bleeding or thromboembolism were 5.32%, 5.47%, 6.34%, and 6.76%, based on quartiles of time to genotype (quartile means: 22, 29, 37, and 48 days, respectively). This suggests that genotyping information is helpful whenever it is received during the first 2 months of treatment, but outcomes improve the earlier the test results can be provided.

Because we did not randomize patients to intervention and control groups, unmeasured differences in baseline characteristics (e.g., body mass index, cigarette smoking,
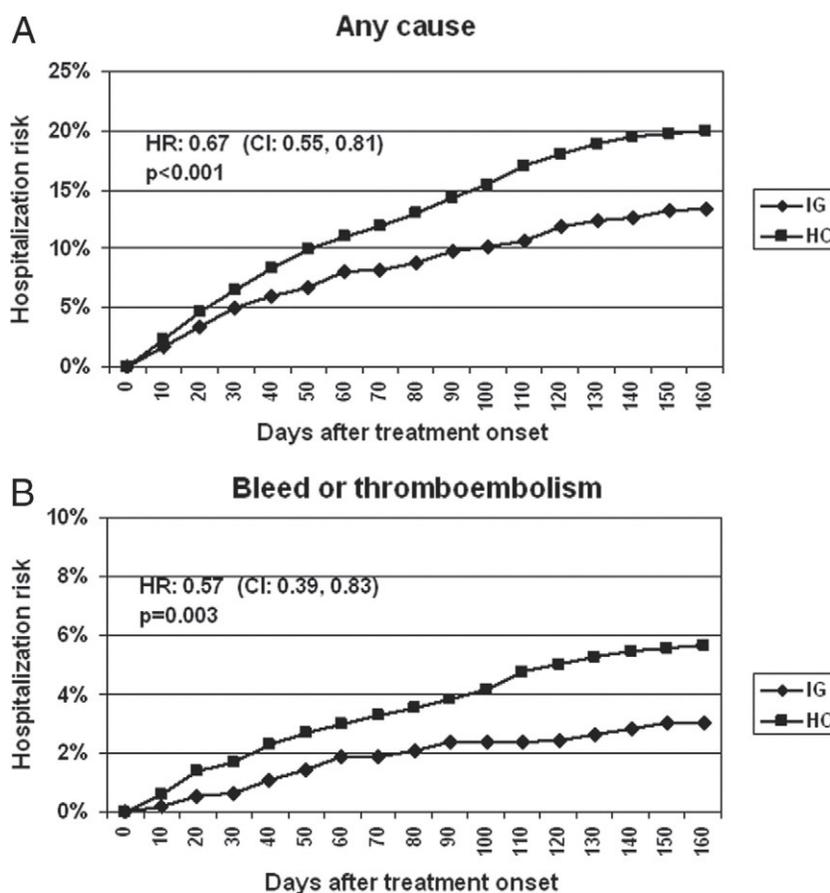
Figure 2   **Adjusted Hospitalization Rates: Per-Protocol Analysis**

The figure shows the hospitalization rate for patients in each study group during the 6-month period following initiation of warfarin treatment, including only the events that occurred after genotyping (intervention group) or the events for measured intervals (historical controls). **(A)** Events due to any cause; **(B)** events due to bleeding or thromboembolism. Abbreviations as in Figure 1.

dietary patterns, or over-the-counter drug usage) could confound the results. To minimize this risk, we drew the intervention and historical control groups from the same set of employers and health plans, thus enrolling patients with similar jobs, socioeconomic status, insurance coverage, and geography. Additionally, we noted few differences between

Table 5	**Warfarin Dosage Changes Following Genotyping**		
Warfarin Sensitivity	**Patients n (%)**	**Weekly Dose Change (mg)***	**p Value**
Very high	10 (2.4%)	−17.33 (4.54)	<0.001
High	17 (4.0%)	−10.14 (3.18)	0.040
Moderate	106 (25.0%)	−3.65 (1.56)	0.003
Mild	49 (11.6%)	+3.21 (3.41)	0.206
Normal	119 (28.1%)	+1.10 (1.40)	0.496
Less than normal	123 (29.0%)	+6.65 (1.98)	<0.0001
Total	424		

For patients who had a new prescription filled within 21 days of genotype testing (n = 424), the table shows the difference between the average weekly dose for the new prescription and the average weekly dose for the index warfarin prescription. The p value is based on paired *t* test. *Values are mean (SE).

our intervention and control groups in prevalence of comorbid conditions, treatment indications, or prior hospitalizations, and all of these variables were controlled for in the Cox proportional hazards models. Although the study design did not include randomization, it effectively adjusted for major confounding factors through multiple regressions, propensity scores, and balancing of patient characteristics (Table 2).

It is possible that physicians in the intervention group were aware of being enrolled in a study and were thus more vigilant in their care, as is frequently the case in controlled clinical trials that have intensive oversight and protocol-driven care. In our study design, we kept the physician intervention to a minimum, thereby minimizing any Hawthorne effect. Beyond requesting a test order and reporting the laboratory results with interpretation, there was no further communication with physicians, and no protocol-based constraints on patient care.

Our study includes an intention-to-treat design in which we attributed adverse events to the intervention group, even

if they occurred before patients completed their genotype tests. This is the most conservative approach to measuring outcomes, because it overestimates adverse outcomes in the genotype group and thus biases against the hypothesis that genotyping improves outcomes. Even in the intention-to-treat analysis, we noted a 30% decrease in hospitalizations.

Warfarin genotyping does not replace or obviate the need for routine monitoring of international normalized ratio (INR). Although we did not mandate a specific protocol for INR measurement in the laboratory report to physicians, the reports noted that frequent INR measurements might be indicated, especially with certain genotypes. Our study did not directly assess the impact of genotyping on the frequency or optimal protocol for INR measurement.

Further research is warranted to replicate and extend our findings. Important questions include whether age, indication, comorbidity, practice setting, and co-medications affect the relative value of genotyping in patients initiating warfarin treatment. It would also be informative to determine which adverse events were reduced and in whom. A preliminary subanalysis suggests that the reductions in hospitalization were due primarily to reductions in thromboemboli. Future clinical effectiveness studies should compare new anticoagulants to genetically guided warfarin treatment regimens.

Our study found that warfarin genotyping lowered the overall risk of hospitalization, including the risk of hospitalization for bleeding or thromboembolism. These lower rates of adverse events may offset some or all of the cost of warfarin genotyping. Although an economic analysis is outside the scope of this report, our data should help to determine the net financial cost of paying for genotype testing as a component of warfarin therapy.

Conclusions

Warfarin genotyping reduces the risk of hospitalization for bleeding or thromboembolism in patients who initiate warfarin treatment in outpatient practice settings. These effects appear to be large, statistically significant, and clinically meaningful. Clinicians should seriously consider genotyping their outpatients who are beginning warfarin treatment.

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Key Words: warfarin ■ genotyping ■ pharmacogenomics ■ comparative effectiveness.

▶ **APPENDIX**

For supplemental tables of a sample report, please see the online version of this article.