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Genetic Warfarin Dosing:

Tables Versus Algorithms

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Abstract

Objectives—The aim of this study was to compare the accuracy of genetic tables and formal pharmacogenetic algorithms for warfarin dosing.

Background—Pharmacogenetic algorithms based on regression equations can predict warfarin dose, but they require detailed mathematical calculations. A simpler alternative, recently added to the warfarin label by the U.S. Food and Drug Administration, is to use genotype-stratified tables to estimate warfarin dose. This table may potentially increase the use of pharmacogenetic warfarin dosing in clinical practice; however, its accuracy has not been quantified.

Methods—A retrospective cohort study of 1,378 patients from 3 anticoagulation centers was conducted. Inclusion criteria were stable therapeutic warfarin dose and complete genetic and clinical data. Five dose prediction methods were compared: 2 methods using only clinical information (empiric 5 mg/day dosing and a formal clinical algorithm), 2 genetic tables (the new warfarin label table and a table based on mean dose stratified by genotype), and 1 formal pharmacogenetic algorithm, using both clinical and genetic information. For each method, the proportion of patients whose predicted doses were within 20% of their actual therapeutic doses was determined. Dosing methods were compared using McNemar's chi-square test.

Results—Warfarin dose prediction was significantly more accurate (all $p < 0.001$) with the pharmacogenetic algorithm (52%) than with all other methods: empiric dosing (37%; odds ratio [OR]: 2.2), clinical algorithm (39%; OR: 2.2), warfarin label (43%; OR: 1.8), and genotype mean dose table (44%; OR: 1.9).

Conclusions—Although genetic tables predicted warfarin dose better than empiric dosing, formal pharmacogenetic algorithms were the most accurate.

Keywords

coumarins; dose prediction; dosing algorithms; FDA label; genetic tables; pharmacogenetics; warfarin

In August 2007, the U.S. Food and Drug Administration updated the warfarin (Coumadin, Bristol-Myers Squibb, Princeton, New Jersey) product label to add pharmacogenetic information (1). In January 2010, the agency added specific instructions on how to use genotype to predict individualized doses: the new label provides a concise table of dosing recommendations, stratified by genotype (2). In contrast, most research on pharmacogenetic warfarin dosing has focused on developing and validating complex predictive algorithms (3,4), which integrate clinical and genetic factors to predict dose on the basis of regression equations. These algorithms accurately predict warfarin dose (4–8), although they may not be as accurate in African Americans (9).

Formal predictive algorithms require the use of a computer or web-based application (10) to conduct mathematical calculations and are difficult to summarize in written form. Providing an estimated dose in a table, such as the one in the new warfarin label, renders a genotype-specific dose readily accessible and easier to implement in clinical practice. However, no published study has quantified the accuracy of the new table. As a result, clinicians prescribing warfarin might increase their use of pharmacogenetic dosing without a clear understanding of its accuracy.

In this study, we compared the accuracy of warfarin dose prediction in a formal pharmacogenetic algorithm with 2 genetic tables, the aforementioned warfarin label table (reproduced in Table 1) and a similar table constructed from the mean dose by genotype in a separate cohort (Table 2). We also compared these dosing methods with 2 nongenetic methods: a clinical predictive algorithm and standard empiric dosing of 35 mg/week (11).

Methods

Patient population

The cohort comprised 1,378 patients taking warfarin at the University of Pennsylvania, the University of Florida, and Washington University. Most of these patients were originally recruited as part of prior prospective cohort studies (3,12–14), and many were also later included in the International Warfarin Pharmacogenetics Consortium cohort (accessed via PharmGKB accession number PA162355460) (4,15). Participants were required to have achieved a stable therapeutic dose of warfarin, defined as the dose that led to therapeutic international normalized ratio (INR) values on 2 or 3 consecutive visits (4), and to have complete data for dose prediction by all dosing methods. Because of institutional review board restrictions on access to individual, patient-level data for clinical and genetic variables for some of the patients in our cohort, we could not determine the overall frequency of the clinical and genetic variables discussed in the following; however, these frequencies are summarized online for the subset of our patients who were part of the International Warfarin Pharmacogenetics Consortium cohort ($n = 1,025$) (Online Table 1). Of note, predicted and actual warfarin doses were available at the patient level for all patients in our cohort.

Dose prediction methods

EMPIRIC DOSE—Patients were assigned the population average dose of 35 mg/week.

CLINICAL ALGORITHM—Patients were assigned a dose on the basis of a formal regression equation (3). The factors included in this validated algorithm are age, body

surface area (BSA), African American race, amiodarone usage, target INR, smoking status, and warfarin indication.

WARFARIN LABEL—Patients were assigned a dose equal to the midpoint of the daily dose range provided in the table in the newly revised warfarin label (Table 1) (2). The exact methods used by the Food and Drug Administration to derive this table are not publicly available. Doses were multiplied by 7 to provide consistent units of milligrams per week.

GENOTYPE MEAN TABLE—Patients were assigned the mean dose in those with the same genotype, on the basis of the *CYP2C9* *2, *CYP2C9* *3, and *VKORC1* (−1639 G>A) genetic variants. Mean dose was determined in a separate population, consisting of the International Warfarin Pharmacogenetics Consortium cohort minus those patients used in the analysis cohort described previously (final n = 2,858) (Table 2).

PHARMACOGENETIC ALGORITHM—Patients were assigned a dose according to a previously validated formal regression equation (3). This is similar to the algorithm available at www.warfarindosing.org; however, the online version has been expanded since the original validation studies to also accommodate newer single-nucleotide polymorphisms that have minor effects on dose. Factors included in this algorithm are *CYP2C9* and *VKORC1* genotype, age, BSA, African American race, amiodarone use, target INR, smoking status, and warfarin indication.

Data analysis

The accuracy of each dosing method was based on whether the predicted dose fell within a clinically meaningful range of within 20% of the stable therapeutic dose, as used in other studies (4). Because this is a matched dataset, the proportion of patients whose predicted doses fell within this range was compared between each method using McNemar's chi-square test. The resultant odds ratio (OR) in this test reflects the odds of patients' being dosed within range by one method versus the other. Comparisons of all possible pairwise combinations of the 5 dosing methods were made, with no correction for multiple comparisons.

Additionally, to quantify the extent to which each dosing method was either overestimating or underestimating warfarin dose, we examined the proportion of patients whose predicted doses were above or below the stable therapeutic dose by at least 20%. Finally, we examined the proportion of patients predicted at therapeutic dose $\pm$ 20% on the basis of whether the patient required a low ($\leq$ 21 mg/week), intermediate ($>$ 21 and $\leq$ 49 mg/week), or high ($>$ 49 mg/week) therapeutic dose of warfarin.

To explore how clinical judgment may affect the accuracy of the warfarin label, we conducted a secondary analysis in which patients older than age 60 years (the cut point in the warfarin label at which patients "appear to exhibit greater than expected [prothrombin time]/INR response to ... warfarin" [2]) were assigned the lower estimate of the dose range, and patients age 60 years or younger were given the upper estimate of the dose range. All principal analyses were then repeated. Additionally, we conducted a similar secondary analysis incorporating more of the clinical variables used in the algorithms in the subset of patients for which we had access to all of these variables at the individual level. Patients were given the upper estimate of the dose range in the warfarin label if they were age $\leq$ 60 years, had BSAs $>$ 2.25 m² ($>$ 1 SD above the mean), were African American, or had target INRs $>$ 2.0 to 3.0. Patients were given the lower estimate of the dose range in the warfarin label if they were age $>$ 60 years, had BSAs $<$ 1.75 m², or used amiodarone. If patients had

factors that both raised and lowered their predicted warfarin doses, they were assigned the midpoint of the dose range in the warfarin label.

To examine the effect of race on dosing method accuracy, a secondary analysis was conducted in which the cohort was stratified by race and all principal analyses were repeated.

Analyses were performed using SPSS Statistics 17.0 (SPSS, Inc., Chicago, Illinois) and SAS 9.1 (SAS Institute Inc., Cary, North Carolina).

Results

The percents of patients whose predicted doses were within 20% of their stable therapeutic doses for the empiric dose (37%), clinical algorithm (39%), warfarin label (43%), genotype mean table (44%), and pharmacogenetic algorithm (52%) dosing methods are shown in Figure 1. The observed mean therapeutic doses by genotype compared with the doses predicted by the warfarin label and genotype mean table are shown in Online Tables 2 and 3, respectively.

As shown in Figure 2, the pharmacogenetic algorithm was significantly more accurate compared with each of the other dosing methods: empiric dose (OR: 2.18; 95% confidence interval [CI]: 1.82 to 2.61), clinical algorithm (OR: 2.17; 95% CI: 1.79 to 2.64), warfarin label (OR: 1.79; 95% CI: 1.48 to 2.17), and genotype mean table (OR: 1.85; 95% CI: 1.50 to 2.29). The 2 genetic tables were more accurate than either the empiric dose or clinical algorithm. The difference between the warfarin label and genotype mean tables was not statistically significant.

The extent of overestimation and underestimation of warfarin dose by each dosing method is shown in Figure 3, and both were lowest with the pharmacogenetic algorithm. Additionally, all methods performed best in patients requiring intermediate warfarin doses. The pharmacogenetic algorithm performed better than all other methods in predicting dose in those requiring higher (>49 mg/week) and lower (≤ 21 mg/week) doses (Online Fig. 1).

The age-adjusted warfarin label was minimally better than the warfarin label based on the table midpoint (OR: 1.16; 95% CI: 0.95 to 1.42), but the pharmacogenetic algorithm was still significantly better than the former method (OR: 1.59; 95% CI: 1.31 to 1.93). The warfarin label adjusted for several clinical factors was minimally better than the warfarin label based on the table midpoint (OR: 1.12; 95% CI: 0.86 to 1.47) as well as the age-adjusted warfarin label (OR: 1.21; 95% CI: 0.75 to 1.96), but it was significantly worse than the pharmacogenetic algorithm (OR: 1.62; 95% CI: 1.29 to 2.05).

The percents of patients predicted at therapeutic dose $\pm 20\%$ for the empiric dose, clinical algorithm, warfarin label, genotype mean table, and pharmacogenetic algorithm dosing methods were 36%, 42%, 41%, 38%, and 42%, respectively, in African Americans and 37%, 38%, 43%, 45%, and 54% in non-African Americans.

Discussion

Recent research on warfarin dose prediction has focused on the use of formal pharmacogenetic algorithms based on complex regression equations. However, in January 2010, the Food and Drug Administration updated the warfarin label to include pharmacogenetic dosing information in the form of a more straightforward table of estimated warfarin dose, stratified by genotype. This change may potentially increase the use of pharmacogenetic dose prediction by clinicians prescribing warfarin; thus, it is critical

to determine the accuracy of this method. In this analysis, we compared the accuracy of these various dosing methods on the basis of whether the predicted dose fell within a clinically meaningful range of within 20% of the stable therapeutic dose, as done previously (4).

In our study, dosing based on genetic tables was somewhat more accurate than that based on nongenetic methods. Using the warfarin label or the genotype mean tables, accurate dosing could be predicted 43% or 44% of the time, respectively, compared with 39% using a clinical algorithm and 37% using an empiric 5 mg/day dose. However, the pharmacogenetic algorithm was superior to all other methods, including these tables. Using a pharmacogenetic algorithm, accurate dose prediction was achieved 52% of the time. Furthermore, the pharmacogenetic algorithm had lower rates of both dose overestimation and underestimation than all other dosing methods (Fig. 3) as well as better dosing prediction in those requiring high and low warfarin doses (Online Fig. 1).

Both genetic tables were found to be an improvement over empiric dosing and a clinical algorithm, affirming the importance of genetics in determining warfarin dose. Because both genetic tables performed similarly, it seems likely that their suboptimal performance relative to the pharmacogenetic algorithm is based on inherent limitations of using tables, rather than the result of inaccurate estimates. Formal algorithms would be expected to more precisely quantify the effects of multiple genetic factors on dose, compared with the average effects that are used in dosing tables. Moreover, age, BSA, target INR, drug interactions, and other clinical factors have all previously been shown to affect warfarin dose (11). Thus, it is unsurprising that the combination of clinical factors with genotype in the context of a formal pharmacogenetic algorithm seemed to be the most beneficial for improving the accuracy of dose prediction.

The warfarin label does in fact state that clinical factors should be accounted for; however, it does not give guidelines on how both clinical and genetic factors should be combined to determine an appropriate dose. As a result, there was no way to formally test the impact of clinical factors on the use of the genetic table in the warfarin label. Analyses that approximated how clinicians may account for clinical factors led to minimal improvement in the accuracy of the warfarin label; however, the formal pharmacogenetic algorithm remained superior.

One possible reason that adjusting for clinical factors did not result in more improvement in dosing accuracy is that the magnitude of the effect on warfarin dose varies from factor to factor and that level of complexity is difficult to account for in a simple table. Additionally, another limitation of the warfarin label is that it gives a wide relative dosing range for those most sensitive to the drug. Thus, any simplified table most likely will not be able to capture the full complexity of personalized warfarin dosing, because it will not be able to easily and accurately quantify the effects of both genetic and clinical factors.

Nonetheless, even with the pharmacogenetic algorithm, 48% of patients were ultimately not dosed accurately. There are several reasons why such a substantial proportion of patients may not be dosed correctly. First, clinical factors other than those included in our study (and, to our knowledge, not included in well-validated dosing algorithms) can affect warfarin dose (16–22). Second, genes other than *CYP2C9* and *VKORC1* may affect warfarin dose, such as *CYP4F2*, *GGCX*, *EPHX1*, and *ApoE* (14,23–25), although their effects on warfarin dose require confirmation (26–28). These and other genes could be incorporated into future pharmacogenetic algorithms or tables to improve their accuracy; however, studies are needed to assess their clinical utility.

Finally, as expected on the basis of previous results (9,29,30), both the pharmacogenetic algorithm and the genetic tables were less accurate in African Americans. In fact, the clinical algorithm seemed to perform just as well as these methods in African Americans, although our analysis cohort did not have sufficient power to formally compare dosing methods within this group. To show their greatest benefit, pharmacogenetic algorithms will likely have to incorporate genetic information from studies done in African Americans. In short, it is clear that despite the extensive amount of research that has been done on warfarin dosing variability, a substantial percent of that variability remains to be explained (9,29–34).

Perhaps most important, although we know that pharmacogenetic algorithms lead to more accurate warfarin dose prediction, it remains unknown whether using a formal pharmacogenetic algorithm will actually improve laboratory or clinical outcomes. Although some observational research suggests that this may be the case (35), the answer to these questions awaits the results of large randomized clinical trials that are currently under way (36–38).

The average cost of warfarin-related genetic testing is currently almost \$400 per patient (39). This cost could fall in the near future, making genotyping more feasible for routine clinical practice. However, given the substantial number of patients started on warfarin each year, the added cost of genotyping over the current standard of care will still be significant. Thus, it is critical to use the information gained from genetic testing in the most effective way possible.

Our results suggest that the genetic table provided in the updated warfarin label is an improvement over empiric dosing and thus may be appropriate under certain circumstances. However, tables are less accurate than a formal pharmacogenetic algorithm for warfarin dose prediction. As a result, it seems advisable for clinicians to use a formal pharmacogenetic algorithm instead of a genetic dosing table when feasible. Should dosing algorithms prove effective at improving clinical outcomes in ongoing randomized trials, methods to improve access to these algorithms could include publication in the warfarin label, web-based access, and incorporation into handheld devices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

BSA	body surface area
CI	confidence interval

CYP2C9	cytochrome P450 2C9
INR	international normalized ratio
OR	odds ratio
VKORC1	vitamin K epoxide reductase complex subunit 1

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APPENDIX

For supplementary tables and figures and their legends, please see the online version of this article.

Figure 1. Dosing Method Accuracy

The proportion dosed within 20% of the stable therapeutic dose was calculated for each dosing method. Having a predicted dose within 20% of the therapeutic dose was considered a clinically meaningful degree of accuracy. **Error bars** indicate ± 1 SE.

Figure 2. Two-Way Comparisons of Dosing Methods

The proportion dosed within 20% of stable therapeutic dose was compared using McNemar's chi-square test. The resultant odds ratio reflects the odds of a patient's being properly dosed by the first method versus the second. **Error bars** represent exact 95% confidence intervals.

Figure 3. Dosing Method Accuracy

The proportions dosed below 80%, within 20%, and above 120% of the stable therapeutic dose were calculated for each dosing method.

Table 1
FDA Label: Range of Expected Therapeutic Warfarin Doses (mg/day) Based on *CYP2C9* and *VKORC1* Genotypes

<i>VKORC1</i> -1639	<i>CYP2C9</i> *1*1	<i>CYP2C9</i> *1*2	<i>CYP2C9</i> *1*3	<i>CYP2C9</i> *2*2	<i>CYP2C9</i> *2*3	<i>CYP2C9</i> *3*3
GG	5–7	5–7	3–4	3–4	3–4	0.5–2
GA	5–7	3–4	3–4	3–4	0.5–2	0.5–2
AA	3–4	3–4	0.5–2	0.5–2	0.5–2	0.5–2

Reproduced from updated warfarin (Coumadin, Bristol-Myers Squibb, Princeton, New Jersey) product label (2).
CYP2C9 = cytochrome P450 2C9; FDA = U.S. Food and Drug Administration; *VKORC1* = vitamin K epoxide reductase complex subunit 1.

IWPC Cohort: Mean Therapeutic Warfarin Dose (mg/day) by *CYP2C9* and *VKORC1* Genotype in 2,858 Patients

Table 2

<i>VKORC1</i> -1639	<i>CYP2C9</i> *1*1	<i>CYP2C9</i> *1*2	<i>CYP2C9</i> *1*3	<i>CYP2C9</i> *2*2	<i>CYP2C9</i> *2*3	<i>CYP2C9</i> *3*3
GG	6	5	4	4	4	3
GA	5	4	3	3	2	1
AA	3	3	2	2	1	2

IWPC = International Warfarin Pharmacogenetics Consortium; other abbreviations as in Table 1.