To the editor:

Relative contribution of *VKORC1*, *CYP2C9*, and INR response to warfarin stable dose

Li et al reported recently in *Blood* that much of the information provided by *CYP2C9* and *VKORC1* genotypes during warfarin initiation therapy in outpatients is captured by early international normalized ratio (INR) responses.[1] This confirms and extends previous observations in hospitalized, heavily medicated patients, that dose-adjusted INR (INR/dose) at day 4 is the most important predictor of warfarin dose at day 14.[2] However, the predictive power of the best regression models in both studies, expressed by the correlation coefficient (r^2) values of 0.40[1] and 0.51,[2] between predicted and observed doses, is not superior to that of several pharmacogenetic dosing algorithms without an INR covariate, including the algorithm that we developed for Brazilian patients.[3-10] We now report that adding INR/dose as a variable in multistep regression modeling of the stable warfarin dose in the Brazilian cohort leads to a novel algorithm with greater predictive power. Details of the original study design and linear multiple regression modeling of the stable warfarin dose have been published.[3]

For the present model development, we used the first available INR/dose measurement from 260 patients chosen randomly from the 390 patients in our cohort; the remaining 130 patients were used for model validation. The most informative regression model retained the same covariates previously identified as associated with stable warfarin weekly dose in this cohort (age, weight, treatment indication, comedication with amiodarone or simvastatin, *VKORC1* and *CYP2C9* genotypes) but included also an INR/dose term (Table 1). The r^2 for the correlation between observed and model-predicted warfarin weekly dose in the development and the validation sets, was 0.60 and 0.59, respectively (Table 2), compared with 0.51 for our previous algorithm, which did not include an INR term.[3] The mean absolute difference between model-predicted and observed doses, 6.5 and 6.2 mg/week in the development and validations sets, respectively (Table 2), did not differ from 6.9 mg/week for our previous algorithm.[3]

Table 1. Multiple linear regression model for prediction of weekly warfarin dose

Variable	Partial regression coefficient	*P*	Partial R^2 statistic, %
Age, y	−0.0054	1.10^{-1}	0.3
INR/dose (first available)	−2.9909	3.10^{-8}	4.9
Weight, kg	0.0157	3.10^{-5}	2.7
Therapeutic indication			3.8
Heart valve prosthesis	0.5726	1.10^{-6}	
Thromboembolic disease	0.4333	3.10^{-2}	
Simvastatin	−0.4442	10^{-2}	1.0
Amiodarone	−0.7748	10^{-9}	5.9
***CYP2C9* *2/*3/*5/*11**			5.7
One variant allele	−0.5115	2.10^{-6}	
Two variant alleles	−1.1043	10^{-5}	
***VKORC1* 3673G>A**			20.1
3673GA	−0.8352	5.10^{-7}	
3673AA	−1.6841	$<10^{-12}$	

The partial R^2 statistics measures the degree of association between 2 random variables, with the effect of a set of controlling random variables removed.

Table 2. Model performance

Sample set	Correlation coefficient, r^{2*}	Mean absolute difference, mg/wk
Development set (n = 260)	0.60	6.5
Validation set (n = 130)	0.59	6.2

Based on the following regression equation: Square root of warfarin weekly dose (mg/week) = 5.5691 − 0.0054 × (age in years) −2.9909 × (INR/ dose, mg/week) + 0.0157 × (weight in kg) + 0.5726 × 1 (if patient has heart valve prosthesis) or 0 (if no heart valve prosthesis) + 0.4333 × 1 (if patient has thromboembolic disease) or 0 (if no thromboembolic disease) −0.4442 × 1 (if prescribed simvastatin) or 0 (if no prescribed simvastatin) − 0.7748 × 1 (if prescribed amiodarone) or 0 (if not prescribed amiodarone) − 0.5115 × 1 (if patient has one *CYP2C9* variant allele) or 0 (if not) − 1.1043 × 1 (if patient has 2 *CYP2C9* variant alleles) or 0 (if not) − 0.8352 × 1 (if *VKORC1* 3673GA genotype) or 0 (if not) − 1.6841 × 1 (if *VKORC1* 3673AA genotype) or 0 (if not).

*Correlation coefficient (r^2) between weekly warfarin dose predicted by the dosing algorithm (predicted dose) and the dose actually taken by the patient (observed dose).

VKORC1 genotype remained the most important predictor of warfarin weekly dose in the novel algorithm (Table 1). This contrasts with the predominant contribution of INR-associated terms, and the relatively small contribution of *VKORC1* and *CYP2C9* genotypes in Li et al[1] and Michaud et al[2] Differences in population cohorts, clinical settings (eg, expertise in INR-guided warfarin dose titration),[1] assessed outcomes and time of INR/dose measurements might account for this discrepancy. A distinct feature of our algorithm is that the individual INR/dose term does not represent a fixed time point after starting warfarin therapy, but rather the first measurement taken after admission of the patients in the anticoagulant unit. This feature is potentially useful for patients under continuous warfarin treatment, who had not reached stable dosing despite repeated dose adjustments.

In summary, we confirmed that inclusion of an INR-related term increased (from 0.51 to 0.60) the predictive power of warfarin-dosing pharmacogenetic algorithms for Brazilian outpatients under chronic warfarin therapy. However, INR measurements did not entirely capture the information provided by *CYP2C9* and, especially *VKORC1* genotypes, the latter remaining the most informative predictor of stable warfarin dose requirements in our cohort.

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To the editor:

Referral of patients with thrombocytopenia from primary care clinicians to hematologists

Immune thrombocytopenic purpura (ITP) is an uncommon disorder, with an annual incidence of 2.7 adults/10^5 per year.[1] To estimate the prevalence of ITP with a focus on patients who may require treatment, we planned to survey all hematologists in the state of Oklahoma. To determine the validity of contacting only hematologists, we assessed primary care clinicians' self-reported practices regarding referral of patients with isolated thrombocytopenia to a hematologist. Approval was obtained from the University of Oklahoma Health Sciences Center Institutional Review Board for these studies. Informed consent was obtained in accordance with the Declaration of Helsinki.

Surveys were sent to 127 primary care clinicians who participate actively in the Oklahoma Practice-Based Research Network (OKPRN), representing approximately 4% of the total primary care clinicians in Oklahoma. The survey presented 5 case vignettes, each describing a healthy 35-year-old woman who had taken no medications, had no symptoms other than the described bleeding, and who had normal blood counts except for thrombocytopenia, criteria suggesting the diagnosis of ITP.[2] The scenarios ranged from mild, asymptomatic thrombocytopenia to severe thrombocytopenia with significant bleeding symptoms. Eighty-four (66%) practitioners completed the survey. Of these, 67 (80%) were MDs, 8 (9%) were DOs, 5 (6%) were nurse practitioners, and 4 (5%) were physician's assistants. Among the respondents, 43 (51%) had been in practice for 6 to 20 years, 10 (12%) for less than 6 years, and 31 (37%) for more than 20 years.

The referral pattern demonstrated by this survey (Figure 1) is similar to recommendations of the ASH ITP Practice Guideline, which recommends that patients presenting with platelet counts greater than 30 000/μL may not require treatment.[2] Potential barriers to referrals were revealed. Sixteen (19%) stated that there was a not a hematologist within 50 miles of their practice, and 33 (39%) stated that there was not a hematologist they routinely called for advice and to whom they referred patients. One clinician added a comment that illustrated an additional potential barrier: "I have had difficulty identifying a 'hematologist.' Most 'heme/onc' specialists view themselves solely as 'oncologists' and are unhelpful for anything short of 'cancer.'" This potential barrier to referral of patients with benign hematologic disorders deserves further study.

Referral patterns among physicians have been extensively studied because they affect both the quality and cost of health care.[3] However, there are no previous data on referral of patients with isolated thrombocytopenia from primary care clinicians to hematologists, perhaps reflecting the low incidence of ITP.[1] A 17-month study of the referral decisions of 141 family physicians documented no patients with isolated thrombocytopenia among 184 conditions seen during 34 519 office visits.[4]

Previous studies have validated the use of patient vignettes to measure the quality of clinical practice.[5] Although some aspects of the practice of the clinicians who participated in the OKPRN survey may not be representative of all US primary care clinicians, the overall referral practices of family physicians in practice-based research networks are similar to a national sample of primary care physicians.[4]

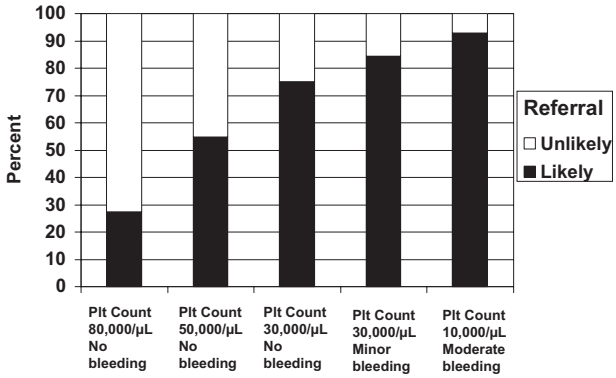

Figure 1. Clinicians' self-reported likelihood of referral to a hematologist of patients presenting with various severities of thrombocytopenia and bleeding symptoms. The bars represent responses of 84 primary care clinicians who responded to questions describing a 35-year-old woman with thrombocytopenia and either no bleeding or bruising symptoms, mild bleeding symptoms (minor bruising and prolonged menstrual periods; mild petechiae on her ankles and legs), or moderate bleeding (blood blisters in her mouth and gum bleeding). For each patient scenario, the clinicians were asked, "How likely are you to send her to a hematologist?" and given 4 possible answers from which to choose: very likely, likely, unlikely, and very unlikely. For this figure, very likely and likely were combined; unlikely and very unlikely were also combined.