CLINICAL RESEARCH STUDY

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Warfarin Dosing Algorithms and the Need for Human Intervention

Scott E. Kasner, MD, MSCE, Le Wang, MS, Benjamin French, PhD, Steven R. Messé, MD, Jonas Ellenberg, PhD, Stephen E. Kimmel, MD, MSCE, COAG Trial Steering Committee

Department of Neurology and the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia.

ABSTRACT

BACKGROUND: Dosing algorithms for warfarin incorporate clinical and genetic factors, but human intervention to overrule algorithm-based dosing may occasionally be required. The frequency and reasons for varying from algorithmic warfarin management have not been well studied.

METHODS: We analyzed a prospective cohort of 1015 participants from the Clarification of Optimal Anticoagulation through Genetics trial who were randomized to either pharmacogenetic- or clinically-guided warfarin dosing algorithms. Clinicians and participants were blinded to dose but not international normalized ratio (INR) during the first 28 days. If an issue arose that raised concern for clinicians but might not be adequately accounted for by the protocol, then clinicians contacted the unblinded medical monitor who could approve exceptions if clinically justified. All granted exceptions were logged and categorized. We analyzed the relationships between dosing exceptions and both baseline characteristics and the outcome of percentage of time in the therapeutic INR range during the first 4 weeks.

RESULTS: Sixteen percent of participants required at least one exception to the protocol-defined warfarin dose (15% in the genotype arm and 17% in the clinical arm). Ninety percent of dose exceptions occurred after the first 5 days of dosing. The only baseline characteristic associated with dose exceptions was congestive heart failure (odds ratio 2.12, 95% confidence interval, 1.49-3.02, $P < .001$). Neither study arm nor genotype was associated with dose exceptions.

CONCLUSION: Despite rigorous algorithms, human intervention is frequently employed in the early management of warfarin dosing. Congestive heart failure at baseline appears to predict early exceptions to standardized protocol management.

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KEYWORDS: Anticoagulants; Congestive heart failure; Pharmacogenomics; Warfarin

Warfarin is one of the most commonly prescribed medications but is difficult to manage because of substantial variability in dose requirements within and across individuals. Despite the advent of newer oral anticoagulants for atrial fibrillation and deep venous thrombosis, warfarin continues to be widely used for these and many other clinical indications. While some clinicians use an empiric approach to adjust the dose of warfarin, there are computer-assisted algorithms that have been shown to improve time in the therapeutic international normalized ratio (INR) range compared with empiric dosing.[1,2] Widely available algorithms for choosing the initial dose of warfarin incorporate clinical factors including: age, race, body surface area, smoking status, history of diabetes, history of stroke, deep vein thrombosis or pulmonary embolism as the primary indication for warfarin therapy, target INR, and major interacting medications (ie, amiodarone or fluvastatin).[3,4] When available, the addition of pharmacogenetic data, including genotypes for cytochrome P-450 family 2

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Requests for reprints should be addressed to Scott E. Kasner, MD, Department of Neurology, University of Pennsylvania Medical Center, 3W Gates Bldg., 3400 Spruce Street, Philadelphia, PA 19104.

E-mail address: kasner@mail.med.upenn.edu

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subfamily C polypeptide 9 enzyme (*CYP2C9*) and vitamin K epoxide reductase complex 1 (*VKORC1*), appeared to further improve warfarin dose prediction in some models,[4] but not in a randomized clinical trial.[5]

The key components of dosing algorithms cannot account for every circumstance affecting each individual, and human intervention to overrule algorithm-based dosing may occasionally be required.[2] The frequency and reasons for varying from algorithm-based warfarin management have not been well studied.

The Clarification of Optimal Anticoagulation through Genetics (COAG) trial[5] was a randomized clinical trial that aimed to determine if initiation of warfarin therapy using algorithms based on genotype and clinical information (ie, pharmacogenetic-guided dosing) improved the time in the INR range compared with algorithms based on clinical information alone (ie, clinically-guided dosing). The trial found no significant difference between study arms, but provided a rare opportunity to study the applicability of warfarin dosing algorithms. During the first 28 days after enrollment in COAG, the actual dose of warfarin was blinded to both clinicians and patients, but was directed by a series of standardized computerized algorithms. Clinicians were aware of INRs. If an issue arose that raised concern for clinicians but might not be adequately accounted for by the algorithm, then clinicians contacted an unblinded COAG medical monitor who could approve exceptions to the protocol algorithm if clinically justified.

In order for these algorithms to be relied upon in clinical practice, providers should know before their use if there are specific patients or circumstances in which they might fail and how often, and if the addition of genetic data limits the need for these exceptions. We hypothesized that the baseline characteristics that would predict which patients require exceptions to algorithm-based dosing would be other medical comorbidities or indications for warfarin therapy not included in current algorithms, and location of the patient (inpatient vs outpatient) on the day of enrollment. If confirmed, these findings could lead to refinements of existing algorithms that would improve warfarin dosing in the future. Moreover, those predicted to require frequent overruling of the standard algorithms might be better served with an alternative anticoagulant.

CLINICAL SIGNIFICANCE

- We found that a substantial fraction of patients (16%) treated with warfarin required manual overrides of a standardized dosing algorithm during the first 4 weeks of therapy.
- We further identified an association between congestive heart failure and the need for human oversight and intervention in the management of warfarin dosing.
- As heart failure remains one of the leading disorders for which warfarin is still prescribed in this era of newer anticoagulants, this finding suggests an ongoing and unmet need for improved therapy in this population.

METHODS

This study was a secondary but prespecified analysis of data collected during the COAG trial. The design, rationale, and primary results of the COAG trial were previously reported.[6,7] Briefly, we randomly assigned 1015 patients at 18 clinical centers in the US to initiate warfarin therapy using either a pharmacogenetic-guided or a clinically guided dosing strategy, applied during the first 5 days of therapy. The genetic variants included in the pharmacogenetic algorithms were *CYP2C9* and *VKORC1*. For each dosing strategy, a dose-initiation algorithm was used during the first 3 days of therapy,[3] and a dose-revision algorithm was used on day 4, day 5, or both.[4] Randomization was stratified by self-reported race (African American vs non-African American) and study site. The trial was approved by the institutional review board at each participating site.

All study participants and clinicians were blinded to the intervention and the dose of warfarin by the use of blinded encapsulated warfarin tablets during the first 4 weeks of therapy. During the first 3 days, INRs were not required. If an INR was obtained during that time, algorithmic dose adjustments were made without any information available to clinicians about the magnitude of those adjustments. The first INR mandated by the protocol was on day 4 or 5 and again provided no information to clinicians about the revised dose. The frequency of subsequent INR testing was guided by protocol for the first 28 days. During that period, clinicians were aware of the percent change in warfarin dose but not the actual dose itself. The primary outcome of COAG was the percentage of time in therapeutic INR range (PTTR) during the initial 4 weeks, using a standard linear interpolation method between successive INR values.[8]

For the present analysis, the primary outcome of interest was an exception to the dosing algorithm during the first 4 weeks of therapy due to clinical issues or concerns, as defined by the medical monitor. If the medical monitors granted an exception, then their nonalgorithmic warfarin dose was provided to the study pharmacist but not to the clinical team. The medical monitor maintained a log of every dose exception decision. Every discrepancy between the calculated and dispensed dose was categorized as one of the following: interacting medication or concurrent illness, nutritional status, adherence issue or participant error, bleeding, invasive procedure, too many adjustments due to overly frequent (usually daily) INR, clinician concern due to persistently low INR, clinician concern due to persistently high INR, adjustment after prior zero dose, and conflicting or nonstudy INR. An adjustment after a prior zero dose could not be calculated