Warfarin Pharmacogenetics
A Rising Tide for Its Clinical Value

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Warfarin has been in clinical use for nearly 60 years, and in 2010 there were >25 million prescriptions for warfarin in the United States. Although warfarin is highly efficacious, it has a narrow therapeutic window to achieve desired anticoagulation without excess risk of bleeding. Anticoagulation status is monitored with the International Normalized Ratio (INR), where the most common target INR is 2 to 3. Not only does warfarin exhibit a narrow therapeutic index, but there can be 10- to 20-fold differences in the warfarin dose required to achieve target INR. Thus, the early period after warfarin therapy initiation requires frequent INR monitoring to determine the proper dose for the patient, it is often associated with multiple dose adjustments, and many patients experience prolonged periods of over- or underanti-coagulation while the appropriate dose is identified. These challenges lead to warfarin being a leading cause of emergency department visits and hospitalizations for an adverse drug reaction and to significant underuse of the drug in patients for whom it is strongly indicated, in particular, those with atrial fibrillation.1

The difficulties associated with warfarin use led to great enthusiasm for the new oral anticoagulants. Dabigatran and rivaroxaban were approved in the past 18 months, yet they have made only a small dent in the market share for oral anticoagulants, with warfarin remaining the predominant anticoagulant used clinically. For example, in the first year of use in the United States, ~1.1 million dabigatran prescriptions were dispensed, in contrast to the 25 million prescriptions per year for warfarin.2 Reasons for the lack of uptake may include recent concerns about excess bleeding risk with dabigatran,3 lack of reversibility of the anticoagulation, twice daily dosing, challenges with dosing in renally impaired patients, bothersome adverse effects (in particular, gastrointestinal adverse effects with dabigatran), and cost, among others. Overall, these new agents have not been widely embraced in the manner anticipated, suggesting that warfarin will remain the mainstay of oral anticoagulant therapy for the foreseeable future. Thus, there remains a need to identify ways to more safely and effectively use warfarin.

That genetic polymorphisms might influence the variability in warfarin dose requirements was first recognized in 1999, and since then a vast body of literature has documented the effects on warfarin dose of genetic variation in cytochrome P450 2C9 (CYP2C9), the major drug metabolizing enzyme of S-warfarin, and vitamin K epoxide reductase (VKORC1), the protein target of warfarin.4 Numerous studies have shown that polymorphisms in these genes explain up to 35% of the variability in warfarin dose requirements, and, through consideration of additional clinical factors (eg, body size, age, interacting drugs), >50% of interpatient dose variability can be explained.3–6

That a better approach to identification of the therapeutic dose for a given patient is needed is highlighted by data from numerous studies suggesting that bleeding risk during the first 1 to 3 months of therapy is up to 10-fold higher than subsequent monthly risk.1 Use of genetic and clinical information to guide initial dose selection holds promise as such an approach. Indeed, numerous warfarin pharmacogenetic algorithms have been developed that incorporate both genetic and clinical factors, and the best validated among these come from the International Warfarin Pharmacogenetics Consortium3 and Gage et al.4 And, in 2010, the US Food and Drug Administration revised the warfarin product label to include dose recommendations based on CYP2C9 and VKORC1 genotype.7 The study by the International Warfarin Pharmacogenetics Consortium in >5000 patients from 4 continents clearly documented that its pharmacogenetic algorithm was superior to a clinical algorithm, or the usual 5 mg daily starting dose in estimating the stable warfarin dose.5 A later analysis by Finkelman et al6 confirmed this and documented that algorithm-based dosing was also superior to the US Food and Drug Administration dosing table. Based on these and numerous other studies, the Clinical Pharmacogenetics Implementation Consortium recently recommended use of the International Warfarin Pharmacogenetics Consortium or Gage algorithms as the preferred approach for genetic-guided initial warfarin dose selection.3

Although there is little debate that genetic information allows for more precise initial dose selection, questions have remained about whether this leads to any real therapeutic advantage, such as fewer out-of-range INRs, greater time within the therapeutic range, or reduced incidence of adverse events, in particular, thromboembolic events and bleeds. Several small studies have attempted to address these issues, but none have been adequately powered, and thus there has continued to be a lack of clarity regarding the potential clinical benefits of pharmacogenetic-guided warfarin dosing.
It is in this context that the article by Anderson et al represents an important advance. CoumaGen-II was a well-powered 2-part study of genotype-guided warfarin dosing. Part 1 was a randomized controlled trial testing a 1-step, modified version of the International Warfarin Pharmacogenetics Consortium warfarin pharmacogenetic algorithm versus a 3-step algorithm. In the 1-step algorithm, genetic information was incorporated no later than the second dose, but 84% had the genetic information incorporated for determination of the first dose. The 3-step algorithm incorporated VKORC1 but not CYP2C9 genotype for the first dose, with CYP2C9 genotype incorporated starting with dose 2 (step 2), with further incorporation of genetic information through a dose-revision algorithm based on the day 4/5 INR (step 3). Both patients and clinicians managing the warfarin therapy were blinded to the dosing algorithm used, and events were evaluated by a blinded events adjudication committee.

The comparison of the 2 dosing algorithm approaches found that the 3-step algorithm approach was noninferior, but not superior to the 1-step algorithm, suggesting there is little reason to use the more complex 3-step approach. Based on similarity of the data from the 2 dosing algorithms, these data were combined to compare with the parallel standard care cohort.

The findings from the pharmacogenetic versus standard care analysis were most impressive and suggest there is clinical benefit associated with the use of genetic information to guide warfarin dosing. Nearly all the end points tested showed significant benefits with the pharmacogenetic-guided dosing, including out-of-range INRs, percentage of time in the therapeutic range (PTTR), and serious adverse events. Specifically, the pharmacogenetic cohort had a 10.3% absolute (and 25% relative) reduction in the out-of-range INRs at 1 month, with similar differences at 3 months. This finding was primarily attributable to significantly fewer INR values <1.5, which coincided with a significant 66% lower rate of deep vein thrombosis. The reduced number of out-of-range INRs led to a greater PTTR in the pharmacogenetic cohort, with 69% and 71% PTTR at 1 and 3 months versus 58% and 59% PTTR, respectively, in the parallel control group. Thus, the absolute improvements in PTTR were 10.5% and 12.6% at 1 and 3 months, respectively. This compares favorably with the estimated 5% to 10% absolute improvements in PTTR associated with management of patients in a specialty anticoagulation clinic and exceeds the 5.5% absolute improvement in PTTR for which the National Institutes of Health Clarification of Optimal Anticoagulation through Genetics (COAG) trial is powered. Importantly, these benefits in the pharmacogenetic cohort accrued in a setting where warfarin-treated patients were typically managed by standard protocol by an anticoagulation service/clinic.

Additionally, although not powered to show differences in serious adverse events, such differences were noted. Incident serious adverse events at 90 days were 4.5% in the pharmacogenetic cohort and 9.4% in the parallel controls, for a 54% lower rate in the pharmacogenetic cohort. This was primarily attributable to significantly lower rates of death and deep vein thrombosis and borderline significant lower rates of moderate/severe hemorrhage. Globally, these are impressive differences in clinically important end points that point to the value of pharmacogenetic-guided dosing of warfarin.

The benefits from the pharmacogenetic dosing (in comparison with an assumed 5 mg daily initial dose) are presumed to derive from the more accurate initial dose prediction. Whether analyzed as the mean change or mean absolute change in warfarin dose from initial to stable dose, changes were significantly lower in the pharmacogenetics cohort for those with no or >1 CYP2C9 or VKORC1 variant alleles (where 3 is the number possible). For example, those with standard dosing with no variant in either gene required average 10.5 mg/wk increases, and those with >1 variant required 11 mg/wk decreases, assuming a 35 mg/wk (5 mg/d) initial dose. In contrast, the mean dose changes in the pharmacogenetics cohort in the 0 and >1 variant groups were 0.31 and 0.25 mg/wk, respectively. Those with 1 variant allele have their dose similarly predicted by a standard 5-mg dose or by pharmacogenetic guidance.

Some will argue that the parallel control group is not an appropriate comparator, because there might have been differences in the management of these patients, or specifically that the pharmacogenetic cohort was more aggressively managed because the clinicians knew those patients were in the pharmacogenetic study. Although it is not possible to rule this out, the fact that the average number of INRs measured was essentially identical between the 2 groups would not support differential management of the patients. Additionally, the standard care group spent 59% of time in therapeutic range, which is consistent with 2 recent analyses, suggesting that the average PTTR in the United States ranges from 55% to 58%. This suggests that the parallel standard care arm patients were treated similarly to the standard of care in the United States. There were also demographic differences in the 2 groups that might have contributed to differences in clinical outcomes, the most significant being the indication for warfarin therapy, where the pharmacogenetic cohort had a higher percentage of patients undergoing orthopedic surgery. However, stratified analyses of orthopedic and nonorthopedic patients found significant and nearly identical benefits of pharmacogenetic dosing in both groups for out-of-range INRs and PTTR.

There are at least 4 large, randomized controlled trials ongoing to test the benefits of pharmacogenetic guidance of warfarin dosing, 2 in the United States, 1 in Europe, and 1 in Asia. These trials will provide important additional insights into the efficacy of pharmacogenetic dosing in a tightly controlled clinical trial setting. These trials will test hypotheses regarding warfarin pharmacogenetic dosing in a more robust manner than this comparative effectiveness study, and will answer some questions that were not addressed by the current study. However, the current study by Anderson et al...
provides us with excellent insight into the effectiveness of utilizing pharmacogenetics in a real-world setting. In fact, if this study approximates the potential benefit of pharmacogenetic dosing in patients managed in an anticoagulation clinic, one can imagine the benefits might be even greater for the vast majority of warfarin-treated patients who do not have access (geographically or otherwise) to an anticoagulation clinic, and therefore have their INR monitored less frequently, with poorer anticoagulation control.

One limitation of the current study is that the participants were nearly all individuals of European ancestry, the group for whom the warfarin pharmacogenetic dosing algorithms are most predictive.\(^5,6\) It is therefore possible the benefits in blacks or Asians would be less than observed in the present study. The ongoing clinical trials have broader ethnic representation and therefore will provide insights for those ethnic groups.

This study represents a landmark in the very large warfarin pharmacogenetics literature. For the first time, we have a vision of the potential clinical benefits associated with use of genetic information to guide warfarin dosing. It suggests that clinicians should more seriously consider adoption of warfarin pharmacogenetics into clinical practice and validates the recommendations from the Clinical Pharmacogenetics Implementation Consortium on warfarin pharmacogenetics.\(^3\) And, as we move toward a time when more and more patients will have their genetic information available, the current study data suggest that clinicians will be hard pressed to justify ignoring genetic information in selection of an initial warfarin dose, if the necessary genetic information is available. Anderson et al should be congratulated for this excellent contribution to the field.

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**Disclosures**

Dr Johnson is a leader of the International Warfarin Pharmacogenetics Consortium and is a member of the Executive Committee and site principle investigator for the National Institutes of Health Clarification of Optimal Anticoagulation through Genetics (COAG) trial.

**References**


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