Genotype-Guided Dosing of Warfarin

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Vitamin K antagonists (VKAs)2 have been used to treat thromboembolic disease for over 60 years, and they continue to be the most commonly prescribed anticoagulants worldwide. However, VKAs such as warfarin have a narrow therapeutic index, and the mean daily dose of warfarin varies widely from patient to patient. Underdosing can leave patients undertreated for their thromboembolic diseases; overdosing can result in bleeding. As such, patients are forced to undergo frequent blood testing, and dose adjustments are made on the basis of the resulting international normalized ratio (INR) values. To achieve a therapeutic INR, which is defined as a value between 2.0 and 3.0 for conditions such as atrial fibrillation and venous thromboembolism, the daily dosing of warfarin can range over 20-fold, from <1 to over 20 mg (1).

The variability in warfarin dosing depends on several factors, including demographics, the environment, and genetics. Specifically, variants in the genes that encode an enzyme responsible for the metabolism of warfarin [cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9)]3 and the molecular target of warfarin [vitamin K epoxide reductase complex, subunit 1 (VKORC1)] influence warfarin dosing. The Food and Drug Administration has noted these findings, and the warfarin label recommends that if a patient’s genotype is known, then this information should be considered when initiating therapy. Nonetheless, debate continues about the utility of routine genetic testing in this setting, a topic that has been addressed by several studies, including the EUropean Pharmacogenetics of AntiCoagulant Therapy (EU-PACT) and Clarification of Optimal Anticoagulation through Genetics (COAG) trials (2, 3).

The EU-PACT trial enrolled 455 patients initiating warfarin treatment, of whom approximately 72% had atrial fibrillation and 28% venous thromboembolism. In this open-label study, patients were randomized to either warfarin dosing based on an algorithm that included genetic information or a warfarin loading dose consistent with the local standard of care. Genotype information was available at the time that the therapies were started. The study concluded that the primary endpoint of the time in therapeutic INR range between 2.0 and 3.0 during the first 12 weeks of warfarin therapy was significantly higher among the genotype-guided group than the standard-of-care group (67.4% vs 60.3%, P < 0.001), and the genotype-guided group also had fewer supratherapeutic values and a shorter time to achieve a therapeutic INR.

A second contemporaneous trial conducted in the US, COAG, included 1015 patients requiring warfarin therapy; 22% of the patients had atrial fibrillation, 58% venous thromboembolism or pulmonary embolus, and 20% a combination or another indication. In total, 67% of the population had inpatient initiation of warfarin treatment. Patients were randomly assigned in a double-blind fashion to receive warfarin dosing using either a clinical algorithm or one that incorporated both clinical and genetic factors. Genotype data were available for 45% of the participants before the first dose of warfarin and 94% before the second dose. The primary endpoint of the trial was time in therapeutic INR range between 2.0 and 3.0 during the first 4 weeks of warfarin therapy. The study concluded that the addition of genetics to a warfarin-dosing algorithm based on clinical factors did not improve coagulation control in the first 4 weeks (45.2% vs 45.4%, P = 0.91).

Why did EU-PACT and COAG generate different conclusions? First, the warfarin dosing strategies varied in the 2 trials. COAG assessed whether an algorithm that included genetics in addition to clinical variables could outperform an algorithm with clinical variables alone. Ultimately, the impact of genotype on dosing in this situation was small. For example, the mean (SD) difference between the dose calculated for patients without genotype data on day 1 vs the dose they would have received if the genotype data were available was −0.1 (0.4) mg per day. It follows that there would be minimal impact of genotyping on coagulation control. In contrast, EU-PACT compared a genetic-guided dosing algorithm to a standard, fixed loading-dose regimen. In this case, patients in the genotype-guided group achieved a stable warfarin dose more quickly.
than the comparator group and coagulation control was improved. Thus, understanding the comparator dosing strategies in the 2 trials helps explain the findings.

Several factors related to the patient populations may have also influenced the divergent results. Whereas the majority of patients in EU-PACT initiated warfarin for atrial fibrillation, more patients in COAG were being treated for venous thromboembolism. While the medical condition itself should not impact the warfarin dose and coagulation control in a given patient, the clinical context might. For example, in COAG, approximately two-thirds of the patients started warfarin while in the hospital and over half were being administered heparin at the time; these factors could influence the type of care administered and the coagulation parameters. Regarding other population differences, the proportions of self-reported black patients were 1% in EU-PACT and 27% in COAG. Both trials tested CYP2C9 *2 and *3 and VKORC1 3673G→A. It has been proposed that if additional alleles (such as CYP2C9 *5, *6, *8, and *11) are not tested, the accuracy of genotype-guided algorithms in the black population is diminished. It should also be noted that the primary endpoint was ascertained through 4 weeks in the COAG trial vs 12 weeks for EU-PACT, although the differences in the times in therapeutic range between the 2 dosing strategies in EU-PACT became apparent between days 5 and 10 and were statistically significant through 4 weeks. Finally, EU-PACT was conducted in Sweden and the UK, with patients in COAG being enrolled from centers in the US. As such, regional differences in the population and practices could have affected the findings.

Despite the apparent differences in the studies, some similar themes were identified in the 2 trials. Both trials implemented frequent INR testing for assessment of the primary endpoints, as well as for patient care. For example, in EU-PACT, INR values were measured on days 1, 4, 6, 8, 15, 22, 57, and 85, with additional testing as deemed necessary. In COAG, there was a median of 6 INR values tested in the first 4 weeks of warfarin therapy in both arms of the study. If INR values are checked frequently enough and the warfarin dose is appropriately titrated, then any intervention to predict a particular dose is less pressing. However, many patients who start treatment with warfarin cannot undergo INR monitoring and dose titration with this degree of regularity. In these cases, having patient-specific information, such as access to clinical and genetic data, to guide dosing decisions becomes increasingly important.

Both trials also highlight the strengths and weaknesses of using a surrogate endpoint, as the primary endpoint in both trials was time in therapeutic INR range between 2.0 and 3.0. These trials did an impressive job of obtaining the INR data needed to calculate this endpoint, and they also captured detailed dosing information. The findings of the studies were then reported on the basis of summary statistics across the populations. If a small number of patients have INR values that are out of range, then these data points may not shift the aggregate results of the study. Nonetheless, even a few patients with supratherapeutic INR values could increase the bleeding risk. As clinical studies have demonstrated, the risk of serious bleeding such as an intracranial hemorrhage is relatively low, but can be devastating when it occurs.

Ultimately, monitoring the percentage of time in an INR range serves as a proxy for understanding a patient’s bleeding and thromboembolic risk. Although both EU-PACT and COAG were designed to test differences in INR values, even within these studies, the rates of serious bleeding in patients managed with genotype-guided dosing tended to be less than the rates in the comparator arms. Studies focused on clinical endpoints, while challenging owing to the sample sizes needed, would further clarify the role of warfarin pharmacogenetics. Moving forward, patients and physicians will also have access to alternatives to warfarin that circumvent the challenges of routine monitoring and frequent dose adjustments. Now, after 60 years, direct factor Xa and IIa inhibitors are available, and these target-specific drugs will impact decisions about how best to treat patients who require anticoagulant therapies (4).

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