

Q: Should we use pharmacogenetic testing when prescribing warfarin?

MARY ROUSE, MPH

Center for Personalized Healthcare, Cleveland Clinic

CARI CRISTIANI, PharmD

Department of Pharmacy, Cleveland Clinic

KATHRYN A. TENG, MD*

Director, Center for Personalized Healthcare, Cleveland Clinic; Assistant Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

A: The answer is not clear. There is evidence in favor of pharmacogenetic testing, but not yet enough to strongly recommend it. However, we do believe that physicians should consider it when starting patients on warfarin therapy.

See related commentary, page 477

■ WARFARIN HAS A NARROW THERAPEUTIC WINDOW

Although newer drugs are available, warfarin is still the most commonly used oral anticoagulant for preventing and treating thromboembolism.¹ It is highly effective but has a narrow therapeutic window and wide inter-individual variability in dosage requirements, which poses challenges to achieving adequate anticoagulation.¹⁻³ Inappropriate dosing contributes to a high rate of bleeding events and emergency room visits.⁴

Warfarin is monitored using the prothrombin time. Because the prothrombin time varies depending on the assay used, the standardized value called the international normalized ratio (INR) is more commonly used.

Clinical factors such as age, body size, and drug interactions affect warfarin dosage re-

quirements and are important to consider,⁵ even though they account for only 15% to 20% of the variability in warfarin dose.⁶

Genetic factors also affect warfarin dosage requirements. The combination of genetic and clinical factors accounts for up to 47% of the dose variability.⁷

■ GENES THAT AFFECT WARFARIN

Several genes are known to influence warfarin's pharmacokinetics and pharmacodynamics. Of these, the two most clinically relevant and well studied are CYP2C9 (which codes for cytochrome P450 2C9) and VKORC1 (which codes for vitamin K epoxide reductase).⁷ These genes are polymorphic, with some variants producing less-active enzymes that allow warfarin to be more active. Therefore, patients who carry these variants need lower doses of this drug (see below).

CYP2C9 variants

The CYP2C9 gene has several variants. Of these, CYP2C9*2 and CYP2C9*3 are associated with the lowest enzyme activity.

Patients with either of these variants require significantly lower warfarin doses to reach therapeutic levels than those with the wild-type gene (ie, CYP2C9*1). CYP2C9*2 reduces warfarin clearance by 40%, and the CYP2C9*3 variant reduces it by 75%.⁷ Having a *2 or *3 allele increases the risk of bleeding during warfarin therapy and the time needed to achieve a stable dose.⁸ Other variants associated with lower warfarin dose requirements are *5, *6, and *11.

The prevalence of these variants is significantly higher in people of European ancestry (roughly one-third) than in Asian people and

There is evidence in favor of testing, but not yet enough to strongly recommend it

*Dr. Teng has disclosed consulting for the Natural Molecular Testing Corporation.

doi:10.3949/cjcm.80a.12184

African Americans,⁷ although no one has recommended *not* testing in these low-prevalence populations. Limdi et al⁹ reported that by including the *5, *6, and *11 variants in genetic testing (in addition to *2 and *3), they could identify more African Americans (9.7%) who carried at least one of these abnormal variants than reported previously. Differences among ethnic groups need to be taken into account when interpreting pharmacogenetic studies.

VKORC1 variants

Patients also need lower doses of warfarin if they carry the VKORC1 -1639G>A variant, and they spend more time with an INR above the therapeutic range and have higher overall INR values. However, having this variant does not appear to increase the risk of bleeding.

The -1639G>A variant is the most common variant of VKORC1. Rarer ones have also been described, but most commercially available tests do not detect them.

Racial differences exist in the prevalence rates of the various VKORC1 polymorphisms, with the most sensitive (low-dose) genotype predominating in Asians and the least sensitive (high-dose) genotype predominating in African Americans. Over 50% of people of European ancestry carry the intermediate-sensitivity genotype (typical dose).⁷

CURRENT RECOMMENDATIONS FOR OR AGAINST TESTING

FDA labeling

In 2007, the US Food and Drug Administration (FDA) required that the warfarin package insert carry information about initial dosing based on CYP2C9 and VKORC1 testing. This recommendation was revised in 2010 to include a table to help clinicians select an initial warfarin dose if CYP2C9 and VKORC1 genotype information is available. However, the FDA does not require pharmacogenetic testing, leaving the decision to the discretion of the clinician.⁷

American College of Chest Physicians

The American College of Chest Physicians recommends *against* routine pharmacogenetic testing (grade 1B) because of a lack of evidence that it improves clinical end points or that it is cost-effective.⁵

WHAT EVIDENCE SUPPORTS GENETIC TESTING TO GUIDE WARFARIN THERAPY?

To date, no large randomized, controlled trial has been published that looked at clinical outcomes with warfarin dosing based on pharmacogenetic testing. However, several smaller studies have suggested it is beneficial.

One trial found that when dosing was informed by pharmacogenetic testing, patients had significantly more time in the therapeutic range, a lower percentage of INRs greater than 4 or less than 1.5, and fewer serious adverse events (death, myocardial infarction, stroke, thromboembolism, and clinically significant bleeding events).¹⁰ Patients whose dosage was determined using pharmacogenetic algorithms as opposed to traditional clinical algorithms maintained a therapeutic INR more consistently.¹¹

In addition, compared with historical controls, patients whose physician used pharmacogenetic testing to guide warfarin dosing had a rate of hospitalization 31% lower and a rate of hospitalization specifically for bleeding or thromboembolism 28% lower during 6 months of follow-up.^{12,13}

Several studies have attempted to assess the cost-effectiveness and utility of pharmacogenetic testing in warfarin therapy. As yet, the results have been inconclusive.¹⁴ Larger prospective trials are under way and are estimated to be completed in late 2013.¹⁵ These include:

- COAG (Clarification of Optimal Anticoagulation Through Genetics)
- GIFT (Genetics Informatics Trial of Warfarin to Prevent Venous Thrombosis)
- EU-PACT (European Pharmacogenetics of Anticoagulant Therapy-Warfarin).

We hope these studies will provide greater clarity on the clinical utility and cost-effectiveness of pharmacogenetic testing to guide warfarin dosing.

HOW SHOULD GENETIC INFORMATION BE USED TO GUIDE OR ALTER THERAPY?

Algorithms are available for estimating initial and maintenance warfarin doses based on genetic information (CYP2C9 and VKORC1), race or ethnicity, age, sex, body mass index,

Patients with CYP2C9*2, CYP2C9*3, or VKORC1 -1639G>A need lower doses of warfarin

smoking status, and other medications taken. In addition, models incorporating the INR on day 4 and days 6 to 11 have been developed for dose refinement.¹⁵ The algorithms explain 30% to 60% of the variability of the data, with lower values for African Americans.⁷

A well-developed dosing model that includes traditional clinical factors and patient genetic status is publicly available online at www.warfarindosing.org.⁴

CPIC: A leader in applied pharmacogenetics

In late 2009, PharmGKB joined forces with the Pharmacogenomics Research Network of the National Institutes of Health to form the Clinical Pharmacogenetics Implementation Consortium (CPIC). This organization issues guidelines that are written by expert clinicians and scientists and then are peer-reviewed, published in leading journals, and simultaneously posted to the PharmGKB website along with supplemental information and updates.

CPIC's goal is to review the current evidence and to address barriers to the adoption of pharmacogenetic testing into clinical practice. Its guidelines do not advise when or which pharmacogenetic tests should be ordered. Rather, they provide guidance on interpreting and applying such testing, should the test results be available.⁷

CPIC has guidelines on *CYP2C9* and *VKORC1* genotypes and warfarin dosing.⁸ If a patient's genetic information is available, CPIC strongly recommends the use of pharmacogenetic algorithm-based dosing. If such an algorithm is not accessible, use of a genotype dosing table is recommended.⁸

Monitoring is still needed

Many factors can affect an individual's response to warfarin above and beyond the above-noted clinical and genetic traits. These include diet, concomitant medications (both prescription and over-the-counter and herbal), and disease state. There may also be additional genetic polymorphisms not yet identified in various racial and ethnic groups that may affect dosing requirements. And as with all medications, patient compliance and dosing errors have a large potential to affect individual response. Therefore, clinicians should still be diligent about clinical monitoring.¹⁵

Most useful for initial dose

As with most pharmacogenetic information, the greatest benefit can be achieved when this information is used to guide the initial dose, although there is also some effect noted when this information is known and acted upon into the 2nd week of treatment.⁸

Patients on long-term warfarin treatment with stable doses and those unable to achieve stable dosing because of variable adherence or dietary vitamin K intake are less likely to benefit from genetic testing.

There are no published guidelines on the utility of pharmacogenetic testing if a patient is already on a stable dose of warfarin or has a known historical stable dose. There are also no published guidelines on changing the frequency of monitoring based on known genotype.

In children, the data are sparse at this time regarding the utility of pharmacogenetically informed dosing.

■ HOW DOES ONE ORDER TESTING, AND WHAT IS THE COST?

The FDA has approved four warfarin pharmacogenetic test kits. To be used in clinical decision-making, these tests must be done in a laboratory certified by the Clinical Laboratory Improvement Amendments (CLIA) program.

Testing typically costs a few hundred dollars and may take days for results to be returned if not available on site.¹⁵ At Cleveland Clinic, *CYP2C9* and *VKORC1* testing can be run in-house at a cost of about \$700. Generally, many third-party payers do not reimburse for testing without a prior-approval process.

■ TO TEST OR NOT TO TEST

Pharmacogenetic testing is available and may help optimize warfarin dosing early in treatment, as well as help maintain therapeutic INRs more consistently. There is preliminary evidence that using this information to guide dosing improves clinical outcomes. Several large trials are under way to address additional questions of clinical utility, with results expected in the next year. There are also readily available decision-support tools to guide therapeutic dosing, and when pharmacogenetic

There is preliminary evidence that using this information to guide dosing improves clinical outcomes

test results are available, utilization of a warfarin dosing algorithm is recommended.

The largest barrier remaining appears to be cost (relative to perceived benefit), and until larger trials of clinical utility and cost-effectiveness are completed and analyzed, hurdles exist to obtaining coverage for such testing.

If it is readily available (and can be paid for by insurance companies or out-of-pocket) and test results can be obtained within 24 to 48 hours or before prescribing, pharmacogenetic testing can be a valuable tool to guide and

manage warfarin dosing. Particularly for patients who want to be as proactive as possible, warfarin pharmacogenetic testing offers the ability to participate in this decision-making and to potentially reduce their risk of adverse drug events. And in view of the evidence and FDA recommendations, we propose that the discussion with our patients is not whether we should consider pharmacogenetic testing, but that we have considered pharmacogenetic testing, and why we have decided for or against it. ■

REFERENCES

1. **Jacobs LG.** Warfarin pharmacology, clinical management, and evaluation of hemorrhagic risk for the elderly. *Clin Geriatr Med* 2006; 22:17–32, vii–viii.
2. **Rieder MJ, Reiner AP, Gage BF, et al.** Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 2005; 352:2285–2293.
3. **Higashi MK, Veenstra DL, Kondo LM, et al.** Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA* 2002; 287:1690–1698.
4. **Shehab N, Sperling LS, Kegler SR, Budnitz DS.** National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus aspirin and from warfarin. *Arch Intern Med* 2010; 170:1926–1933.
5. **Holbrook A, Schulman S, Witt DM, et al; American College of Chest Physicians.** Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 suppl):e152S–e184S.
6. **Gage BF, Eby C, Johnson JA, et al.** Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther* 2008; 84:326–331.
7. **Cavallari LH, Shin J, Perera MA.** Role of pharmacogenomics in the management of traditional and novel oral anticoagulants. *Pharmacotherapy* 2011; 31:1192–1207.
8. **Johnson JA, Gong L, Whirl-Carillo M, et al; Clinical Pharmacogenetics Implementation Consortium.** Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther* 2011; 90:625–629.
9. **Limdi NA, McGwin G, Goldstein JA, et al.** Influence of CYP2C9 and VKORC1 1173CT genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. *Clin Pharmacol Ther* 2008; 83:312–321.
10. **Anderson JL, Horne BD, Stevens SM, et al.** A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). *Circulation* 2012; 125:1997–2005.
11. **Yip VL, Pirmohamed M.** Expanding role of pharmacogenomics in the management of cardiovascular disorders. *Am J Cardiovasc Drugs* 2013; 12 Apr; Epub ahead of print.
12. **Epstein RS, Moyer TP, Aubert RE, et al.** Warfarin genotyping reduces hospitalization rates: results from the MM-WES (Medco-Mayo Warfarin Effectiveness Study). *J Am Coll Cardiol* 2010; 55:2804–2812.
13. **Wang L, McLeod HL, Weinshilboum RM.** Genomics and drug response. *N Engl J Med* 2011; 364:1144–1153.
14. **Kitzmiller JP, Groen DK, Phelps MA, Sadec W.** Pharmacogenomic testing: relevance in medical practice: why drugs work in some patients but not in others. *Cleve Clin J Med* 2011; 78:243–257.
15. **Carlquist JF, Anderson JL.** Using pharmacogenetics in real time to guide warfarin initiation: a clinician update. *Circulation* 2011; 124:2554–2559.

ADDRESS: Kathryn Teng, MD, Cleveland Clinic, Center for Personalized Healthcare, 9500 Euclid Avenue, NE5-203, Cleveland, OH 44195; e-mail: tengk@ccf.org

Several large trials are under way, with results expected in the next year