ANTICOAGULATION THERAPY

Genotype-guided anticoagulation therapy —the jury is still out

Three studies published in the *New England Journal of Medicine*, two of which were presented at the 2013 AHA Scientific Sessions, have produced conflicting results on the role of genotype-guided anticoagulation therapy. “Although they vary in organization and structure,” comments Bruce Furie, in an accompanying Editorial, “these trials all examine the initiation of therapy with vitamin K antagonists (VKAs)”.

The response of an individual patient to VKAs can be affected by a number of factors, including age, body weight, and ethnicity. In addition, polymorphisms in two genes are known to affect the pharmacokinetics of these drugs: *CYP2C9*, which encodes an enzyme involved in the metabolism of S-warfarin, and *VKORC1*, which encodes an enzyme involved in the vitamin K cycle. As yet, no definitive evidence-based data exist to support the use of genetic testing for these polymorphisms in patients receiving VKA therapy. The aim of the three randomized, controlled trials discussed here was to establish whether a genotype-guided VKA dosing strategy (including data for *CYP2C9**2, *CYP2C9**3, and *VKORC1*) improved the time in the therapeutic range (international normalized ratio [INR] 2–3).

In the US-based, double-blind Clarification of Optimal Anticoagulation through Genetics (COAG) trial, 955 patients with an indication for warfarin therapy were enrolled and completed the intervention period. The median age was 59 years and 57 years in the genotype and

clinical groups, respectively, and 27% of all patients were black. Patients were randomly assigned to genotype-guided or clinically guided dosing of warfarin. Genetic information was complete for 45% of patients in the genotyping group for the first warfarin dose, and 99% of these patients for the third dose.

After 4 weeks of therapy (only the first 5 days of which were guided by the randomly-assigned strategies), the mean percentage of time in the therapeutic range was not significantly different between the two groups (genotype-guided 45.2% vs clinically guided 45.5%). Neither were any differences between the strategies observed in time spent above the target INR, time to first INR, bleeding, thromboembolism, or other adverse events. “There’s a lot of debate about when to bring genetics into clinical practice,” commented lead investigator Stephen Kimmel in a news conference at the AHA meeting. “For a drug as complex as warfarin, the COAG trial demonstrates the utility of performing such trials.”

By contrast to the COAG study, the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) group showed that dosing of warfarin guided by genotype and clinical data was superior to fixed dosing (control) among 455 patients from Sweden and the UK. The population of this single-blinded, randomized study differed from that of the COAG trial in that patients were older (mean age 67.3 years) and 98.5% were white. Participants in this study had atrial fibrillation (AF) or venous thromboembolism (VTE) as the indication for warfarin therapy. As in the COAG trial, the study intervention was conducted for 5 days at the start of treatment. A ‘loading-dose’ algorithm was used on days 1–3, which allowed for dose individualization in the first 5 days. After 12 weeks of follow-up, the mean percentage of time spent in the target INR (2–3) was 67.4% in the genotype-guided dose group and 60.3% in the control group (7% difference, 95% CI

3.3–10.6%, $P < 0.001$). In addition, time to first INR was shorter, and patients were less likely to have an INR > 4 , in the genotyped group than the control group. No significant difference in the number of bleeding events between the groups occurred. “Our study very much fits in with the concept of personalized medicine, which aims to get the right drug, at the right dose, to the right patient,” said Munir Pirmohamed who presented the study at the AHA meeting.

The EU-PACT consortium also conducted a similar study of two other VKAs—acenocoumarol and phenprocoumon—among 548 patients from Greece and the Netherlands who had AF or VTE. Participants were randomly assigned to dosing guided by genotype and clinical factors or by clinical factors alone. No significant differences were seen for the primary end point of time spent in the target INR (2–3), or in any of the secondary end points. In the combined analysis of both drugs, the time in INR 2–3 was longer for genotype-guided than clinically guided therapy during the first 4 weeks (52.8% vs 47.5%, $P = 0.02$). The investigators commented that “the *CYP2C9* enzyme has much less influence on the pharmacokinetics of phenprocoumon than ... warfarin.”

In his Editorial, Dr Furie suggests that, rather than focusing on genotype, “perhaps we should concentrate on improvements in the infrastructure for INR testing, ... in patient adherence to therapy, ... and in increased diligence by medical and paramedical personnel”.

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Original articles Kimmel, S. E. *et al.* A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N. Engl. J. Med.* doi:10.1056/NEJMoa1310669 | Pirmohamed, M. *et al.* A randomized trial of genotype-guided dosing of warfarin. *N. Engl. J. Med.* doi:10.1056/NEJMoa1311386 | Verhoef, T. I. *et al.* A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *N. Engl. J. Med.* doi:10.1056/NEJMoa1311388

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