

ANTICOAGULATION UPDATE

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We have many therapeutic options available to achieve immediate anticoagulation of patients with acute thrombotic disorders. Choices include unfractionated heparin, low molecular weight heparin, fondaparinux, and direct thrombin inhibitors. In 1993, our only option was unfractionated heparin. So the field is expanding quickly.

In May 2007, the FDA approved low molecular weight monotherapy without warfarin for treatment of patients with cancer and DVT or pulmonary embolism. This decision was based upon the CLOT Trial (Lee AYY et al. NEJM 2003; 349: 146). In that randomized study, low molecular weight monotherapy with dalteparin halved the rate of recurrence compared with a conventional strategy of bridging patients to warfarin.

In July 2007, new data were presented from the EXCLAIM Trial, indicating that high-risk medical patients benefit from extended enoxaparin prophylaxis against venous thromboembolism at the time of hospital discharge. The symptomatic venous thromboembolism rate was reduced by 74%.

Genetic determinants of warfarin dose-response have recently been identified. Therefore, a comprehensive pharmacogenetics approach to warfarin therapy has the potential to improve the safety and effectiveness of warfarin initiation. Maintenance warfarin dosing can be estimated from demographic, clinical, and pharmacogenetic factors.

Some patients have an extremely low warfarin dose requirement of 1.5 mg or less in the absence of liver dysfunction, drug interaction, or concomitant disease. They usually possess CYP2C9 variant alleles associated with impaired hydroxylation of S-warfarin. If their warfarin pharmacogenetic profile is not known when warfarin is initiated, these individuals have a potentially high risk of bleeding complications. Screening for CYP2C9 variants, with rapid turnaround of the results, may allow clinicians to develop individualized dosing protocols to reduce the risk of excessive anticoagulation.

Some patients have an extremely high warfarin dose requirement that exceeds 10 mg daily. Recently, vitamin K receptor gene haplotypes have been discovered that can help stratify patients into low, intermediate, or high dose warfarin groups. Variants in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) explain about 25% of the variance in warfarin dosage. Genetic profiles from CYP2C9 and VKORC1 can be combined to improve categorization of individual warfarin dose requirements.

The American Enterprise Institute and the Brookings Institute (www.aei-brookings.org) collaborated to study the potential impact of rapid turnaround genetic testing for warfarin. Their report was published in November 2006 and is entitled: "Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin." Their conclusions are illuminating: "We estimate that formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually. We estimate the reduced health care spending from integrating genetic testing into warfarin therapy to be \$1.1 billion annually."

However, genotype-guided dosing of warfarin remains controversial. In the only randomized trial ever done, which included 206 patients, the primary endpoint was time within the therapeutic target range. There was no difference whatsoever between the two dosing strategies.¹

In 2008, the National Heart Lung and Blood Institute will launch a definitive randomized controlled trial to test genotype-guided dosing. The trial will enroll 1,500-2,000 patients. The endpoint will be time within the therapeutic target range.

In 2008, the safety of anticoagulant bridging has been called into question by a provocative cohort study. The thrombosis rate was 0.7% without bridging. But the major hemorrhage rate was 3.7% with bridging. Most thrombotic events occurred in patients whose warfarin was held for more than 5 days.²

2008 will also mark further progress in developing novel oral anticoagulants. They hold promise for rapid anticoagulation using fixed dosing that does not require laboratory coagulation monitoring or dose

adjustment. Their eventual role in the anticoagulation armamentarium remains to be determined. Initial trials with total hip replacement prophylaxis against venous thromboembolism appear promising.³

REFERENCES

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