GUEST EDITORIAL

New Drugs on the Horizon for VTE

The development of new antithrombotic agents for venous thromboembolism is changing the way we treat venous thrombosis and pulmonary embolism.

The incidence of deep venous thrombosis and pulmonary embolism has remained nearly constant since 1980, with yearly treatment costs in the billions of dollars. Frequent comorbid conditions include cancer, obesity, surgery within 3 months, immobility within 30 days, and hypertension. Acquired causes include old age, malignancy, surgery and trauma, immobilization, hormone replacement and oral contraceptives, pregnancy and the puerperium, and antiphospholipid antibodies. Genetic causes include deficiencies of natural coagulation inhibitors, Factor V Leiden, prothrombin 20210A, blood group non-O, hyperhomocysteinemia, high levels of clotting factors, and gene-gene/gene-environment interactions.

BY THOMAS WAKEFIELD, M.D.

Treatment for venous thromboembolism (VTE) traditionally involves anticoagulation with standard unfractionated heparin followed by coumadin. Recently, heparin has been replaced by low-molecular-weight heparin (LMWH) as the preferred anticoagulant. Analysis suggests an improvement in recurrent thrombosis with LMWH, compared with standard heparin even in patients with proximal above-knee thrombi (those at greatest risk for embolization), as well as improvements in thrombotic complications, major hemorrhage, and mortality rates. Areas of ongoing interest include the use of LMWH for long-term therapy in certain cancer patients, demonstration of no differences in efficacy between once-a-day and twice-a-day LMWH dosing, and the fact that ambulation and the use of good strong surgical compression significantly decrease the incidence and severity of the post-thrombotic syndrome, without causing pulmonary embolism.

Two new classes of agents for venous thrombosis treatment have created excitement: direct thrombin inhibitors and specific factor Xa inhibitors. Ximelagatran, a direct thrombin inhibitor that is most like warfarin, is administered orally, with onset of action at 2 hours vs. 72-96 hours for warfarin. Ximelagatran has no food or drug interactions and has a wide therapeutic window. Thus, no coagulation monitoring has been found necessary. Unfortunately, there is no widely available antidote for its effects. Ximelagatran has been tested successfully for both the prophylaxis of orthopedic surgery and the extended prophylaxis after therapy for deep venous thrombosis (DVT) and pulmonary embolism (PE). However, ximelagatran causes an elevation in liver function tests in up to 6% of patients. Although ximelagatran has been approved in Germany for DVT prophylaxis in elective hip and knee replacement, it has not been recommended for approval by an FDA panel.

Fondaparinux and a relative, idraparinux, are most like LMWH. They target factor Xa without inhibiting thrombin. These drugs are given subcutaneously and demonstrate a half-life of 17 hours (fondaparinux) and 80-130 hours (indrapariux), vs. 4 hours for LMWH. They exhibit no endothelial or protein binding, and unfortunately, have no readily available antidote. Neither drug produces thrombocytopenia. Fondaparinux has been tested for the prophylaxis of major orthopedic surgery. In a metaanalysis of over 7,000 patients, there was greater than 50% risk reduction when fondaparinux was begun 6 hours after surgery, compared with LMWH begun 12-24 hours after surgery. Although major bleeding increased, critical bleeding did not.

Fondaparinux has also been effective in the prophylaxis in general medical patients, compared with placebo, and in abdominal surgery patients. The drug has also been effective for extended prophylaxis after hip fracture. Evaluation of the drug as a treatment for DVT and PE found that it was equal to LMWH for DVT and equal to standard heparin for PE. Fondaparinux has been approved as a once-daily, subcutaneous injection for the treatment of DVT and PE in acutely symptomatic patients. The dose given is based on body weight: 5 mg per body weight <50 kg; 7.5 mg per body weight 50-100 kg; and 10 mg per body weight >100 kg. Treatment for at least 5 days with concurrent administration of oral anticoagulation is recommended, until the INR is 2-3. Fondaparinux has also been approved for thrombosis prophylaxis in total hip, total knee, and hip fracture patients and in the extended prophylaxis of hip fracture patients.

Other antithrombotic agents being evaluated include oral heparins; other direct thrombin inhibitors like lepirudin, bivalirudin, and argatroban; defibrinating agents such as ancrod; anti-inflammatory agents such as P-selectin inhibitors; Factor VIIa inhibitors; tissue factor pathway inhibitor; and activated protein C. Lepirudin and argatroban have been approved for patients with heparin-associated thrombocytopenia. Use of P-selectin inhibitors or an inhibitor to P-selectin receptor is an area of ongoing research in our laboratory. Such an anti-inflammatory approach promises use of an antithrombotic agent that does not have direct anticoagulant activities, thus decreasing bleeding potential, and does not target a specific portion of the coagulation pathway. We anticipate that this approach will represent a significant improvement in patient safety. ■

DR. WAKEFIELD *is the S. Martin Lindenauer Professor of Vascular Surgery, University of Michigan Medical Center, Ann Arbor.*

PRO & CON

Will health savings accounts leave people vulnerable to bankruptcy?

YES

When we studied more than 900 people who had filed for personal bankruptcy, more than half cited medical causes (Health Aff. [Millwood] Feb. 2, 2005; [Web exclusive]). This was true even though three-quarters of the debtors had health insurance at the onset of their illness. Of those, most had private coverage, although a third of those with private coverage lost it during the course of their illness. Those who were on public programs such as Medicare and Medicaid were much less likely to experience gaps in health coverage.

A lapse in health insurance coverage in the 2 years before filing was a strong predictor of a medical cause of bankruptcy. Nearly 40% of the debtors who had a "major medical bankruptcy" had had a lapse in coverage, compared with 27% of debtors who did not have a medical cause.

Of those who didn't have coverage, 56% said premiums were unaffordable, 7% couldn't get coverage because of a preexisting condition, and most others cited employment issues, such as job loss or ineligibility for employer-sponsored coverage, as their reason for being uninsured.

A health savings account, which involves patients paying for their care up to a certain dollar amount, after which a catastrophic coverage policy kicks in, probably would not have helped most of these people. That's because debtors' out-of-pocket medical costs were often below levels that are commonly labeled "catastrophic." In the year before their bankruptcy, out-of-pocket health care costs—not counting insurance premiums—averaged $3,686.

Of course, any coverage that's employer based—as many of these health insurance policies were—often fails to protect families, because illness may lead to job loss and the consequent loss of coverage.

Only broad reforms can address these problems. As it is in Canada and most of western Europe, health insurance should be divorced from employment to avoid coverage disruptions at time of illness. The low rate of medical bankruptcy in Canada suggests that better medical and social insurance could greatly ameliorate this problem in the United States. ■

Steffie Woolhandler, M.D., is associate professor of medicine at Harvard Medical School in Boston.

NO

Undoubtedly some families do indeed have a problem when they get sick or injured and they lose their jobs and their health insurance as well. But the study discussed at left provides absolutely no information about those families. Their real plight is lost in an effort to exaggerate and overstate the case. All credibility is lost in the hyperbole.

Solutions to these problems are not difficult to find, however. Putting everyone on Medicare clearly is not the solution, since the study's conclusion shows that Medicare is no protection against bankruptcy.

But enabling people to own their own insurance plan would help. That would allow people to keep their coverage even when they become too ill to work and lose their job.

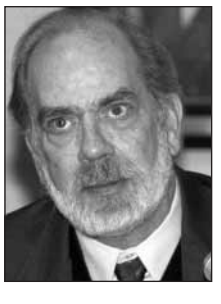
The best remedy might be widespread adoption of Health Savings Accounts (HSAs).

People who are able to save money in an HSA while they are healthy have a nest egg to fall back on when they become ill and incur extraordinary medical expenses, or when they lose their job and have to pay their own health insurance premiums.

Critics argue that HSAs will "fragment the insurance pool" by taking out all the healthy people. But there is no "insurance pool" in the United States. There are tens of thousands of insurance pools, none of which subsidizes the others. Each individual pool pays only the costs of its own enrollees. HSAs do not change that.

President Bush's proposal to create refundable tax credits to help lower-income people afford health insurance coverage would provide further assistance. Those people who can no longer work and enjoy the benefit of an employer subsidy would be able to get help from the federal government instead.

So we can be grateful that Dr. Woolhandler and her colleagues have published this study. Though it is grossly exaggerated, it does call attention to a need for which consumer-driven health care is the much better solution. ■



Greg Scandlen is a consultant who specializes in consumer-driven health care plans, in Hagerstown, Md.