EDITORIALS

Treating Acute Venous Thromboembolism — Shift with Care

Mary Cushman, M.D.

Venous thromboembolism is the third leading cause of vascular death,[1] with a high incidence, especially among older persons. Incidence rates increase from 1 per 10,000 annually among persons less than 40 years of age to nearly 1% annually among persons 80 years of age or older[2]; more than one third of cases occur in persons older than 60 years of age.[3] The mainstay of treatment for more than a generation of physician experience involves bridging anticoagulation therapy from a parenteral heparin-type anticoagulant to a vitamin K antagonist such as warfarin, which requires laboratory monitoring. Given the rapid expansion of knowledge about venous thromboembolism and its treatment, it is important to carefully consider how to translate knowledge regarding new treatments into clinical practice.

Now in the *Journal*, Agnelli et al.[4] report on the next in a line of trials[5-7] testing the use of unmonitored, new oral anticoagulants in the treatment of acute venous thromboembolism. The investigators randomly assigned 5400 patients with acute deep-vein thrombosis or pulmonary embolism in double-blind fashion to receive apixaban, at a dose of 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months, or conventional therapy with subcutaneous enoxaparin bridging to warfarin for 6 months. Apixaban was noninferior to conventional therapy for the primary end point of symptomatic recurrent venous thromboembolism or death related to venous thromboembolism, which occurred in 2.3% of patients who received apixaban and in 2.7% who received warfarin. The risk of major bleeding favored apixaban; major bleeding occurred in 0.6% of patients, as compared with 1.8% of patients who received warfarin. Including this study as well as trials of rivaroxaban[6,7] and dabigatran,[5] the reported experience comparing new oral anticoagulants to conventional treatment now includes more than 15,000 patients. Notably, the current trial had many exclusion criteria, and the study was completed in 28 countries, with no results provided according to geographic region. For these and other reasons, much additional information is needed.

How can practitioners translate the knowledge from this and other, similar trials into practice? Currently, in the United States, rivaroxaban is the only new oral anticoagulant approved by the Food and Drug Administration for the treatment of acute venous thromboembolism; dabigatran is being used off-label.[8] To optimize the use of new anticoagulants in the treatment of patients with acute venous thromboembolism at our center, my colleagues and I created a protocol incorporating six key factors to ensure high-quality care (Table 1).

New anticoagulants are not for every patient, and there is ongoing research to optimize the use of vitamin K antagonists, so it is unlikely that these will disappear from practice. Advances during the past decade include the emergence of prothrombin-time self-testing, anticoagulation clinics, the diminished frequency of monitoring for selected patients,[9] and the potential for basing dosing decisions on genetic information.[10]

As we translate knowledge from the era of vitamin K antagonists to new agents, it is critical that we consider the factors discussed here. More information is needed on reversal strategies, monitoring (e.g., in the presence of interacting drugs, extremes of patient weight, or bleeding or thrombosis complications), approaches to treatment failure, comparisons of adherence to treatment among new drugs and warfarin, and formal cost-

Table 1. Key Components of a Protocol for the Use of New Anticoagulant Agents in Patients with Acute Venous Thromboembolism.

Patient preference: Treatment options are presented along with advantages and disadvantages of each.
Patient selection: Selection criteria for treatment are drawn from key trials. (In the current trial,[4] patients with provoked venous thromboembolism due to a transient risk factor [e.g., surgery] were not included unless they had another irreversible risk factor requiring 6 months of treatment. Only 143 patients with cancer were enrolled, and only 18% of the patients were 75 years of age or older.)
Drug interactions: Potentially interacting drugs, such as inducers or inhibitors of P-glycoprotein and the cytochrome P-450 enzyme 3A4, should be taken into consideration. The interactions differ among the three new anticoagulants (apixaban, rivaroxaban, and dabigatran) available in the United States and may relate to characteristics of the patient such as age, body weight, and presence or absence of kidney disease. Readers should refer to the product monograph for each medication.
Compliance: An individualized written "treatment contract," signed by the patient at the start of treatment, is used to ensure that patients understand the treatment instructions. Patients in the real world may be less compliant than those in clinical trials. The new anticoagulants have short half-lives, as compared with warfarin, and some, like apixaban, require twice-daily dosing. If patients miss doses, anticoagulation is rapidly reversed, and they are at risk for recurrent thrombosis. This might be especially true during the first few weeks of treatment.
Follow-up: Follow-up is no less intense than with conventional treatment that requires frequent contact for laboratory monitoring. A few days after treatment initiation or hospital discharge, patients are called by a nurse to ensure compliance. The first clinic visit is 1 to 2 weeks after the start of treatment or hospital discharge, and pill counts are performed in order to document compliance.
Monitoring: Experience with the protocol is recorded for periodic review and revision. Adverse events are reported to the hospital pharmacy and therapeutics committee.

effectiveness analyses. Comparative-effectiveness studies and postmarketing surveillance are key.

After 60 years of warfarin, it is an exciting time in thrombosis care. Shifting with care to new treatments is essential to safe and effective practice.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Department of Medicine, University of Vermont and Fletcher Allen Health Care — both in Burlington.

This article was published on July 1, 2013, at NEJM.org.

1. The Surgeon General's call to action to prevent deep vein thrombosis and pulmonary embolism. Washington, DC: Department of Health and Human Services, 2008.
2. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med 2004; 117:19-25.
3. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007;5:692-9.
4. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.
5. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.
6. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.
7. The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.
8. Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC. National trends in oral anticoagulant use in the United States, 2007 to 2011. Circ Cardiovasc Qual Outcomes 2012;5:615-21.
9. Schulman S, Parpia S, Stewart C, Rudd-Scott L, Julian JA, Levine M. Warfarin dose assessment every 4 weeks versus every 12 weeks in patients with stable international normalized ratios: a randomized trial. Ann Intern Med 2011;155:653-9.
10. French B, Joo J, Geller NL, et al. Statistical design of personalized medicine interventions: the Clarification of Optimal Anticoagulation through Genetics (COAG) trial. Trials 2010;11:108.

DOI: 10.1056/NEJMe1307413

A New Era in the Treatment of Amyloidosis?

Helen J. Lachmann, M.D.

Amyloidosis is a diverse group of diseases caused by extracellular accumulation of protein in a highly ordered, abnormal, insoluble fibrillar form. These diseases can be hereditary or acquired and localized or systemic. Most are progressive and fatal. Among the almost 30 different proteins that have been found to form amyloid in humans, transthyretin, a carrier molecule of