

Long-Term, Secondary Treatment of Deep Venous Thrombosis

Jack Ansell, M.D.

The thinking about the appropriate duration of the long-term secondary treatment of deep venous thrombosis (DVT) has undergone significant change in the last few years based upon a better understanding of the risk factors for recurrent DVT and the incidence of recurrence in different patient groups. Patients with idiopathic DVT or those with underlying ongoing risk factors such as cancer or thrombophilia have a risk of recurrence after 6 months of therapy of approximately 8 – 10% per year⁽¹⁻⁵⁾.

Three recently completed randomized trials assessed the benefit of continuing anticoagulant treatment after 6 months of treatment for up to 2 ½ years with different interventions and balanced that benefit against the risk of bleeding⁽⁶⁻⁸⁾. Each study was a double blind, randomized trial of an oral anticoagulant compared to a placebo or to different intensities of oral anticoagulation. Where warfarin was studied, sham INRs were employed to maintain blinding. In two studies (PREVENT⁽⁶⁾, THRIVE⁽⁸⁾) patients had been treated for approximately 6 months prior to randomization, while in the third (ELATE)⁽⁷⁾, a shorter pre-randomization was allowed (3-4 months). In two studies (PREVENT, ELATE) all patients had idiopathic DVT or ongoing risk factors while in the third (THRIVE) patients could have been enrolled whose initial DVT was associated with a reversible risk factor. The PREVENT trial compared warfarin low intensity oral anticoagulation (INR 1.5 – 2.0) with placebo, while the ELATE trial compared warfarin full intensity oral anticoagulation (INR 2.0 – 3.0) with low intensity therapy. The THRIVE trial compared ximelagatran, a new oral anticoagulant, with placebo.

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Anticoagulation Forum National Conference May 5-7, 2005, Orlando, Florida

The 8th National Conference on Anticoagulant Therapy is only 6 months away! Conference details are being finalized and the conference registration brochure will be mailed out in the next few weeks. The Anticoagulation Forum's conference provides unique opportunities to meet with colleagues from around the world with wide-ranging anticoagulation research interests and expertise in diagnosis and treatment. The program will include a pre-conference session, meet the expert lectures, poster presentations and special lectures focusing on recent advances and important issues in the field of anticoagulation. We anticipate close to 1000 attendees as well as exhibitors displaying related products and services.

Please visit our website at www.acforum.org for up-to-date conference information. Registration will be available on-line through our website beginning November 15, 2004.

The 2005 conference is being held at the Orlando World Center Marriott Resort in Orlando, Florida, which was recently highlighted as one of the seven best JW Marriott properties in the world. The hotel is located only 1.5 miles from Walt Disney World Resort and close to many other Orlando attractions including SeaWorld and Universal Studios. So consider planning a family vacation and please join us May 5-7, 2005 in Orlando for the Anticoagulation Forum's 8th National Conference. We look forward to seeing you there! ■

For more information on the
Anticoagulation Forum, please visit our
website at: www.acforum.org



**Anticoagulation
FORUM**

Medication Safety for Seniors

*Alison Rein, Assistant Director, Food & Health Policy,
National Consumers League*

SOS Rx, a coalition focused on improving senior outpatient medication safety, is developing a campaign to improve the safety of patients taking warfarin. Convened by the National Consumers League in July 2003, **SOS Rx** is now comprised of more than 60 organizations, including patient and safety organizations, pharmacist and provider groups, employers, and government - all committed to working toward the goal of safer use of outpatient medication, with an initial focus on warfarin.

There are two central goals of the warfarin campaign:

- 1) to heighten awareness among warfarin patients (and their health care providers) about the interaction risks posed by other medications (prescription and over-the-counter), dietary supplements, herbals, and some foods, and
- 2) to get patients and providers to take some action that will reduce potentially risky behaviors.

We expect to provide patients with a framework for discussing the risk of interactions and the importance of monitoring - either on their own (where applicable) or with the assistance of a physician, pharmacist, or other health care professional. The campaign also will encourage patients to avoid initiation of any new treatment without first consulting a health care professional. In addition to targeting patients on warfarin, the campaign will reach out to health care professionals who prescribe and manage patients on warfarin. Because patients turn to professionals for advice, we want these parties to have tools they can use to assist

with delivering the campaign messages. For health care professionals, the campaign will reaffirm the importance of interaction messages to patients, provide them with techniques to enhance patient awareness and compliance with the message, and perhaps encourage broader use of external resources such as anticoagulation clinics.

Recognizing the significant benefits derived from participation in anticoagulation clinics, the campaign likely will incorporate messages suggesting the use of anticoagulation clinics where and whenever possible. For this reason, Coalition members are very interested in reaching out to members of the anticoagulation clinic community to learn about management techniques and messages that are effective in helping patients maintain INR values in their desired range.

As part of the Coalition's research agenda, we will be conducting focus groups and in-depth interviews with various stakeholders (including anticoagulation clinic staff) to learn more. Through this process, the campaign will gain a better understanding of the messages and management techniques, as well as the communication opportunities, which help patients take warfarin more safely. The Coalition expects these research efforts to inform development of an effective message strategy that will:

- 1) identify the specific actions patients should take to improve safe use and adherence,
- 2) signal when patients are open to receiving and acting on campaign messages, and
- 3) provide the evidence to support behavior change.

Given the critical role you play in managing warfarin patients, **SOS Rx** welcomes the participation of anticoagulation clinic staff and health care professionals in the development of this public education campaign. If you are interested in assisting with the campaign, please contact Alison Rein at alisonr@nclnet.org. To learn more about the **SOS Rx** coalition, visit the **SOS Rx** website at www.sosrx.org. ■

Certified Anticoagulation Care Provider (CACP) - Credentialing Update

There continues to be strong interest in the certified anticoagulation care provider (CACP) credentialing process despite the potential introduction of an oral direct thrombin inhibitor and its impact on anticoagulation therapy management clinics. Perhaps the biggest barrier to individuals seeking certification is time - both time spent assembling the necessary application materials as well as time traveling to and taking the certification exam. The board is exploring mechanisms to streamline the application process as well as administering the certification exam electronically at decentralized locations. The impact of any proposed changes on the cost of the certification process will be carefully evaluated.

The CACP exam will be administered on December 5, 2004 immediately prior to the American Society of Health-System

Pharmacists (ASHP) Mid-Year Clinical Meeting in Orlando, Florida. The next exam will be offered in May 2005 during the AC Forum Meeting in Orlando, Florida. The deadline for submitting applications will be March 1, 2005. Other exam locations and dates are currently being explored including Seattle, Cleveland, and Las Vegas. The 2005 candidate guide and applications will be available on-line and through the AC Forum in January 2005.

Several of the initial pioneers who successfully completed the certification process in the Spring of 1999 have been certified for 5 years now and their credentials are due to expire in December 2004. The board has agreed in principle that the re-certification process will be by examination only. However, implementation of the recertification process has been delayed until January 2005 in order to provide sufficient time for the board to explore electronic methods for administering the certification exam. Therefore, anyone with the CACP credential due to expire this year has been automatically granted a 1 year extension, to December 2005.

Individuals who have already completed the certification process are encouraged to submit new items (questions) to be used on

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The accompanying table summarizes the important outcomes of recurrent venous thromboembolism and major bleeding. In each trial, the mean age of patients was in the 50s; there were slightly more males than females; and many of the patients had had more than one previous episode of DVT. In two trials, there was a high frequency of underlying thrombophilia in subjects. In a third, there was an approximate 5% presence of cancer.

Comparative outcomes of VTE or major bleeding of three trials

| Parameter | PREVENT | ELATE | THRIVE |
|-----------------------------|---------|-------|--------|
| Number of Patients | 508 | 738 | 1223 |
| Mean follow-up (yrs) | 2.1 | 2.3 | 1.5 |
| VTE Recurrence ¹ | | | |
| Placebo | 7.2 | | 8.4 |
| Low dose warfarin | 2.6 | 1.9 | |
| Full dose warfarin | | 0.7 | |
| Ximelagatran | | | 1.9 |
| Major Bleed ¹ | | | |
| Placebo | 0.4 | | 0.9 |
| Low dose warfarin | 0.7 | 1.1 | |
| Full dose warfarin | | 0.9 | |
| Ximelagatran | | | 0.7 |

¹ Number per 100 patient yrs

upcoming certification exams. Exam items must be submitted on a standard form available from Elizabeth Goldstein at (617)638-7265 or Elizabeth.Goldstein@bmc.org.

The National Certification Board of Anticoagulation Providers is pleased to announce several new members. The 2005-2006 Board Members are:

- | | |
|-------------------------------------|----------------------------|
| Stuart T. Haines, Pharm.D. (Chair) | Baltimore, Maryland |
| Lynn B. Oertel, RN, MSN (Secretary) | Boston, Massachusetts |
| Faye Anderson, RN | Salt Lake City, Utah |
| James Groce, III, Pharm.D. | Greensboro, North Carolina |
| Geno Merli, MD | Philadelphia, Pennsylvania |
| Cheryl Nadeau, RN | New York, New York |
| Joyce Thomas, Pharm.D. | Evansville, Indiana |
| Gordon Vanscoy, Pharm.D., MBA | Pittsburgh, Pennsylvania |

Individuals who wish to be a CACP application peer reviewer, considered for Board membership, or serve on the CACP examination writing committee should contact Stuart T. Haines at 410-706-1865 or shaines@rx.umaryland.edu. ■

In treating patients with venous thromboembolism (VTE), a physician must balance the benefits of continued treatment with the real risks of bleeding. These three trials are the first to make this assessment in the long-term treatment of DVT after a standard course of therapy employing three novel approaches to long-term therapy. The PREVENT trial showed that low intensity warfarin therapy was more effective than placebo and just as safe, while monitoring of therapy was less frequent making it more tolerable. The ELATE trial showed that full intensity warfarin therapy was more effective than low intensity therapy, a not surprising result, yet at the same time, was just as safe as low intensity therapy suggesting that this is the more ideal therapy. This latter finding, however, must be considered in the context of the usual management of warfarin therapy outside of a randomized trial where it is well established that routine therapy may be associated with as much as a 10% incidence of major bleeding per patient year of therapy⁽⁹⁾. Thus, the ELATE approach may not be as safe in the real world. Finally, the THRIVE trial tested ximelagatran, a new oral anticoagulant direct thrombin inhibitor, against placebo, and showed a significant benefit without the risk. Ximelagatran is interesting in that it does not require anticoagulation monitoring and is not influenced significantly by diet or other medications. Ximelagatran is associated with an approximate 6% - 9% increase in alanine aminotransferase (> 3 x the upper limit of normal) that returns to normal whether the drug is continued or withdrawn. Ximelagatran is currently under FDA review.

What then is the recommended long-term treatment for physicians to follow? For patients who have had an idiopathic DVT or have an underlying cancer or ongoing risk factor, treatment should be extended beyond 6 months. Whether full or low dose warfarin is employed should be balanced by an individual-specific risk assessment of recurrent venous thromboembolism (possibly with the help of D-dimer assay or residual vein thrombosis on ultrasound), major bleeding, and quality of warfarin dose management and patient compliance. Therapy should be extended for at least one to two years, and probably longer, but until very long-term studies are completed, it is difficult to say just how long. Whether new agents such as ximelagatran will prove to be better will require head-to-head studies, but compared to placebo, ximelagatran appears to be a good alternative, and certainly simpler to manage.

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Job Postings on www.acforum.org

The Anticoagulation Forum is happy to announce the addition of a Job Postings section on our website at www.acforum.org. Beginning December 1, 2004, AC Forum members will be able to advertise and browse through job openings across the country in the anticoagulation field. Listings will generally be posted within one week of receipt and will remain online for three months. There is no charge for members to post a job or to search through the listings.

If you are interested in posting a job, please send an email to Liz Goldstein at Elizabeth.goldstein@bmc.org with "Job Posting" in the Subject line. Please include the following information:

- Job title
- Organization name (optional)
- Geographic location
- Detailed description of the position
- Acceptable methods of response and contact information (email, fax, mail, phone)

Members may immediately begin submitting job postings, however the listings will not be online until December 1, 2004. We hope you find this resource a useful addition to our website. ■