

Chicago Chosen as Site for 2007 National Conference

The 8th National Conference was a huge success with over 650 people coming together to focus on new issues in anticoagulation care. Attendees were treated to insightful lectures by 16 speakers, 50 original poster presentations, many interesting exhibits and wonderful camaraderie. The Proceedings of the meeting will be published in February in the *Journal of Thrombosis and Thrombolysis*. The Ritz-Carlton in Orlando, Florida was a beautiful resort and the meals and receptions were enjoyed by all. Thank you to all of the attendees who joined us – we are looking forward to seeing you all in 2007!

Speaking of 2007, we have selected the Chicago Marriott Downtown for our next conference, scheduled for May 3-5, 2007. This luxury hotel is situated in the liveliest section of the Magnificent Mile, close to shopping, restaurants and nightlife. The hotel has won numerous awards for excellence in meeting services and outstanding culinary and banquet staff. The hotel has perfect meeting space for our group and we expect it to be another wonderful conference.

We hope that you save the date and plan on joining us in Chicago, May 3-5, 2007!

CACP News Update

The National Certification Board for Anticoagulation Providers (NCBAP) is pleased to announce the establishment of their new website! Please visit www.ncbap.org and you'll find helpful information pertaining to the certification and re-certification process.

The most recent certification examination was offered last May in conjunction with the Anticoagulation Forum's Conference. The NCBAP is pleased to announce the most recent recipients of the CACP credential below.

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Understanding the Variability of Warfarin Dosing: A New Finding

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Initiation of coumarin therapy (e.g. warfarin) is accompanied by a high incidence of adverse events. During the first weeks of therapy the International Normalized Ratio (INR) is often out of range and rates of bleeding are high. To reduce the risk of hemorrhage, experts advocate prescribing the anticipated maintenance dose to patients who are beginning warfarin, (1-3) and pharmacogenetics may help clinicians to estimate that dose.

Warfarin has a narrow therapeutic index and its rate of metabolism depends on the presence of single nucleotide polymorphisms (SNPs) in the cytochrome P450 (CYP) 2C9 system, (4-7). Two common CYP2C9 SNPs are associated with impaired metabolism of S-warfarin, the more active isomer of warfarin. The SNP in exon 3 (CGT→TGT) is denoted as CYP2C9*2 while the SNP in exon 7 (ATT9→tCTT) is called CYP2C9*3. Patients with one or two of these SNPs have reduced warfarin requirements and a 2–3 fold elevated risk of bleeding when beginning warfarin. (4, 7, 8)

CYP2C9 SNPs are one determinant of warfarin dose, but SNPs in the gene for vitamin K epoxide reductase complex 1 (VKORC1) may be more important. In 2004, two groups independently identified the location of this gene on chromosome 16 (9, 10). This 5-kilobase gene has 3 exons and codes for a protein of 163 amino acids. As detailed below, several groups (11-14) recently identified novel SNPs in this gene that correlate with warfarin dose.

Investigators at the University of Washington (Seattle) and Washington University (St. Louis) recently identified informative SNPs in VKORC1. (11) They performed direct resequencing of PCR amplicons encompassing the upstream promoter region, intragenic sequence, and the downstream region of VKORC1. They found ten (all non-coding) common SNPs and defined a set of 4 SNPs that could be used to infer haplotype. A single promoter SNP, designated 6853 [rs17886369], predicted 21%–25% of the variability in the warfarin dose in Caucasian patients taking warfarin. The prevalence of this promoter differed by race and appeared to contribute to the lower warfarin doses in Asian populations. The 6853 SNP correlated with greater expression of vitamin

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Congratulations to our newest CACPs!

Rhonda Ammann, PharmD West Palm Beach, FL
 Jerome Amrhein, RPh Portage, MI
 Evangelina Berrios-Colon, PharmD East Elmhurst, NY
 Jennifer Bowes, PharmD Syracuse, NY
 Sharon Britain, RN Colorado Springs, CO
 Beth Clark, PharmD Woodstock, MD
 Heather Congdon, PharmD Frederick, MD
 Ted Crum, RPh Avon Lake, OH
 Brian Cryder, PharmD Oak Forest, IL
 Tamara Daniel, PharmD Fairacres, NM
 Bridget Franciose, APN South Portland, ME
 Karen Gleason, RPh Ormond Beach, FL
 Maria Goldman, RN Reisterstown, MD
 Patricia Gully, RN Lisle, IL
 Margo Hollenbeck, RPh Bellevue, WA
 John Hutchinson, RPh Taos, NM
 Patricia Kokoski, PharmD Marriottsville, MD
 Ming Chai Kong Singapore
 Linda Nahlik, RPh Hinsdale, IL
 Lucy Pasquale, APN Mountainside, NJ
 Susan Patterson, APN Madison, MS
 Shawn Slenker, PharmD York, PA
 Lisa Tong, PharmD San Francisco, CA
 Elaine Lindsay Twedt, PharmD Chapin, SC
 Elisa Vila, RPh Edmonds, WA
 Angela Volquardsen, PharmD Milwaukee, WI
 Lesley Welch, PharmD Highlands Ranch, CO
 Diane Wirth, APN Lawrenceville, GA

At this exam, 9 clinicians sat for the examination in order to obtain re-certification of their CACP credential. We are pleased to announce that all who sat for re-certification did achieve a passing grade on the examination. The following people recertified their CACP credential:

Marilyn Allen, APN West Carrollton, OH
 Gail Carey, RN Groton, MA
 Edward Leung, PharmD Evansville, IN
 Denise Ritchie, PharmD Atlanta, GA
 Brian Schilling, PharmD Eagle River, AK
 Patricia Schoch, PharmD Denver, CO
 Claudia Swenson, PharmD Olympia, WA
 JoAnne Taheri, PharmD Louisville, KY
 Kim Thorn, PharmD San Anselmo, CA

Our next certification examination will take place in December in Las Vegas. The submission deadline has already passed for this exam date. Examination dates for next year have yet to be determined. Please check the CACP website to learn of examination dates and locations as they become known.

The Certified Anticoagulation Care Provider credential is governed and awarded by the NCBAP and is the only multidisciplinary credentialing opportunity in the United States. This certification process is designed and intended for practitioners whose primary role as an anticoagulation provider includes systematic, organized, and on-going patient education and drug therapy management. ■

Visit our website at: www.acforum.org



Understanding the Variability of Warfarin Dosing: A New Finding

K epoxide reductase activity suggesting these patients require greater warfarin doses to inhibit that greater activity.

Italian investigators sequenced VKORC1 in 147 patients taking warfarin therapy and discovered 4 SNPs. The 1173 C>T [rs9934438] SNPs in intron 1 correlated with the therapeutic warfarin dose, predicting 14% of the variability in the warfarin dose. A new Dutch study found that patients with the 1173 C>T SNP had a higher risk of bleeding when beginning phenprocoumon(15), but this relationship was not significant in new users of acenocoumarol. (The Dutch investigators did not examine patients beginning warfarin.)

Taiwanese investigators sequenced VKORC1 in 11 warfarin-sensitive patients (maintenance warfarin dose < 1.5 mg/day) and 5 warfarin-resistant patients (maintenance warfarin dose > 6 mg/day).

They identified a promoter polymorphism, -1639 G>A [rs9923231] that was in high linkage disequilibrium with the VKORC1 1173 C>T polymorphism and correlated with greater VKORC1 expression in a transfected cell line. All warfarin-resistant patients carried the G allele at -1639 while none of the warfarin-sensitive patients did. In 104 randomly selected Han Chinese patients taking warfarin, only 21 patients carried this allele and their average warfarin dose was 1 mg/day (38%) greater than 83 patients who lacked this polymorphism.

Swedish investigators genotyped 200 warfarin-treated patients for common SNPs in VKORC1. (12) They found a VKORC1 non-coding SNP [rs2359612] in intron 2 that was linked with the above non-coding SNPs and explained 29% of the variability in warfarin dose. They combined this SNP, the CYP2C9*2 and CYP2C9*3 SNPs, and clinical factors (weight, age, interacting drugs, and indication for warfarin treatment), to derive a regression model that accounted for 56% of the variability in the warfarin dose.

In summary, investigators in three continents have confirmed that

Understanding the Variability of Warfarin Dosing:

common SNPs in VKORC1 correlate with the therapeutic warfarin dose. Although estimates vary, it seems likely that either of the promoter SNPs (6853 or -1639) explain about one-fourth of the variability in the therapeutic warfarin dose. By providing an estimate of the therapeutic coumarin dose, pharmacogenetics-based therapy could help improve the time in range in patients beginning coumarin therapy. Because of this potential, at least one pharmaceutical company is developing a rapid genotyping assay for CYP2C9 and VKORC1 and the FDA will be meeting over the coming months to consider revising the package insert for warfarin therapy.

Despite this enthusiasm, several practical questions remain unanswered. First, if patients have a lower-dose genotype, how much should the initial warfarin dose be reduced? Likewise, should INR monitoring also be more frequent in these patients because of their apparent higher risk of hemorrhage? Alternatively, should clinicians just monitor the INR more frequently in everyone beginning a coumarin and skip the genetic testing? We hope to organize a multi-centered trial to answer some of these questions.

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National Alliance for Thrombosis and Thrombophilia (NATT) – An Update

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History

In August 2003 the patient advocacy group NATT (National Alliance for Thrombosis and Thrombophilia) was formed. The CDC had long seen the need for a national consumer advocacy group to (a) lobby in Washington for more funding for thrombosis and hemostasis centers, so that better care could be provided to patients suffering from thrombosis and thrombophilia, and (b) raise the awareness of these disorders in the public and the medical community so that more physicians would find coagulation a worthwhile subspecialty field to go into. Over a period of 2 years the CDC had explored options for such a patient advocacy group through patient focus group meetings and discussions with health care providers and existing patient interest groups. This fostered and eventually led to the formation of the independent and volunteer patient interest group NATT in August 2003. NATT was incorporated in December 2003 and received non-profit 501c3 status in December 2004.

NATT's Goals

NATT is a community-based, volunteer organization. Board members are individuals affected personally or through family members by thrombosis and/or thrombophilia. NATT's goals are to (a) promote greater awareness of thrombosis and thrombophilia in the public and health care provider community, (b) to ensure better diagnosis and treatment of patients with blood clots, and (c) to foster research on these disorders. The long-term objectives are to

- create a grassroots advocacy network
- pursue a national policy agenda
- develop and promote standards of care
- increase the availability of high quality care
- promote educational activities
- develop patient support groups throughout the country
- encourage, enable and initiate clinical and basic research.

NATT's Activities Until Now

- NATT was incorporated in December 2003
- received non-profit 501c3 status in December 2004
- launched a website: www.nattinfo.org
- recruited a Medical and Scientific Advisory Board Members (MASAB)
- met with the CDC and developed a research project to determine the specific needs of patients who have suffered from or are at risk for thrombosis

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National Alliance for Thrombosis and Thrombophilia (NATT) – An Update

- sent a letter to all Congressmen and Senators introducing NATT
- attended a workshop in Washington organized by ASH for NATT in May 2004
- met with NHLBI in February 2005 to discuss thrombosis/thrombophilia research needs
- identified existing educational materials for patients and materials still needed; created materials in fields where gaps had been determined
- organized 4 regional patient education seminars (Denver, Charlotte, Detroit, Chicago) and co-sponsored a seminar in Pittsburgh, PA.
- Presented 2 scientific posters at the AC Forum meeting in Orlando, FL in May 2005
- Published and sent-out its first newsletter, available at www.nattinfo.org/newsletter%20spring%202005.pdf

NATT's 2005/2006 Priorities

- Organize and co-sponsor additional patient education seminars
- create further thrombosis/thrombophilia educational materials
- establish a Q/A section on its website (www.nattinfo.org)
- bring out further newsletters (next in November 2005)
- continue advocacy efforts in Washington
- start defining standards of care for thrombosis/thrombophilia and

identify research priorities

- increase fundraising efforts and secure regular funding for the organization
- reach more patients and their families.

How NATT Can Assist AC Forum Members

Health care providers have access to NATT's compilation of patient education materials on thrombosis and thrombophilia on NATT's website. These are accessible at www.nattinfo.org/learn-resources.htm and consist of downloadable PDF files. They can be used in anticoagulation and thrombosis clinics as handout education materials to patients.

Furthermore, collaborations between Anticoagulation Clinics, Thrombosis/Hemostasis Centers and NATT are possible in organizing patient education seminars. Interested health care providers can turn to the NATT Patient Education Seminar Subcommittee Chairperson Gina Coleman, Utah: gcdenver@comcast.net

How AC Forum Members Can Assist NATT

NATT wants to reach more patients with thrombosis and thrombophilias. It would help NATT grow further if AC Forum health care providers made their patients aware of NATT. A downloadable PDF file for patients with the essential information on NATT is accessible at www.nattinfo.org/natt_broch.pdf and can be printed out to be handed out to patients. ■

Anticoagulation **FORUM**

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