

## What Happened to Ximelagatran?

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The vitamin K antagonists (VKA) (e.g., warfarin, phenprocoumon, acenocoumarol) are excellent anticoagulants, but to achieve the desired outcomes, exquisite dose management is required. Such management is not the rule in the United States or worldwide. An entire industry (i.e., anticoagulation clinics) has evolved to provide the systematic management needed to achieve the outcomes reported in well designed and well managed prospective trials. Health care providers have been hopeful about the prospect

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## 8<sup>th</sup> National Conference

The Anticoagulation Forum's 8<sup>th</sup> National Conference on Anticoagulant Therapy is just two months away! The conference is being held at the Ritz-Carlton Grande Lakes Resort in Orlando, Florida on May 5-7, 2005. Final planning is underway for a wonderful conference. If you haven't already done so, please register on-line at our website [www.acforum.org](http://www.acforum.org).

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 the diagnosis and treatment of thrombotic disorders. The program will include a pre-conference session, meet the experts lectures, poster presentations of original research, and special lectures focusing on recent advances and important issues in anticoagulation therapy. We are expecting over 800 attendees as well as many exhibitors displaying anticoagulation products and services.

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## The National Alliance for Thrombosis and Thrombophilia

The National Alliance for Thrombosis and Thrombophilia (NATT) is a nationwide, community-based, volunteer health organization established in August 2003. Committed to preventing and treating the array of major health problems caused by clots, our charter members were visionary patients attending a thrombosis and thrombophilia awareness meeting at the Centers for Disease Control and Prevention.

Our personal and family histories of clotting issues are our driving force. We are passionate about the causes, genetic links, complicating factors, and prevention of thrombosis and thrombophilia. Our goal is to promote greater awareness, continued research, and to ensure better diagnosis and treatment of patients with blood clots. We are the only patient-based organization focused on this condition.

Each year, at least 200,000 new cases of venous thromboembolism—or clots in veins—are diagnosed in the United States. At least 60,000 people die each year in the U.S. due to venous thromboembolism. This number is greater than the number of people who die annually of AIDS, breast cancer, and accidents combined.

We have identified the following key problems relating to blood clots and clotting disorders and are committed to addressing them on a national level:

- Insufficient awareness of risk factors for blood clots among health-care providers and the public, leading to missed diagnosis, or delayed diagnosis
- Insufficient screening for risk factors and lack of consistent screening guidelines
- Insufficient use of known preventive measures, including the use of blood thinners for prophylaxis
- Insufficient knowledge about the availability of treatment options, and lack of standard of care
- Insufficient number of thrombosis specialists and specialized treatment centers
- Insufficient availability of care in many geographic areas

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## 8<sup>th</sup> National Conference

If you are interested in submitting an abstract for the poster presentation, the deadline has been extended to March 18. Details regarding the format and submission of abstracts can be found on our website.

We are excited to be offering a heavily discounted group rate of \$189/night at the Ritz-Carlton and JW Marriott Resorts. You can make your hotel reservations on-line at [www.grandelakes.com](http://www.grandelakes.com). To receive the group rate, you must use the group code ACTACTA.

If you and/or your family are planning on visiting Disney World, we have partnered with Grande Lakes Orlando Destination Services to offer discount Disney World tickets. You can purchase the tickets in advance by clicking on a link in the conference section of our website [www.aforum.org](http://www.aforum.org). Grande Lakes Orlando Destination Services will also have a table at the Ritz-Carlton during conference registration so you



can buy your tickets on-site and have your Disney questions answered.

We look forward to seeing everyone in Orlando! If you have any questions regarding the conference, please contact Liz Goldstein in the Anticoagulation Forum office at 617-638-7265 or [Elizabeth.goldstein@bmc.org](mailto:Elizabeth.goldstein@bmc.org). ■

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of new oral anticoagulants with improvements similar to those achieved with the parenteral anticoagulants (e.g., low molecular weight heparin and fondaparinux). New agents, such as factor Xa and IIa inhibitors, offer target specificity compared to the broad affect of the VKAs, oral availability, limited (if any) interaction with other drugs or with diet, predictable pharmacokinetics such that monitoring is not required, and metabolic half-lives that make once or twice daily dosing possible. The landscape looked quite promising for these new agents, with ximelagatran being the most clinically advanced, and many others in development; that is, until the FDA reviewed the submission for ximelagatran and rejected it for the indications sought. What happened to ximelagatran?

The FDA did not approve ximelagatran primarily for safety reasons related to the drug's effect on liver function in 6% - 12% of patients taking ximelagatran for at least 3 to 6 months. However, the FDA made a number of other statements that are troublesome, indicating an inconsistency in their procedures, a lack of understanding of the risks and benefits of current oral anticoagulation therapy, and a flawed interpretation of relevant studies. The following quotes from the FDA report ([www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4069b1.htm](http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4069b1.htm)) illustrate some of these problems.

*In reference to the atrial fibrillation trials (SPORTIF III AND SPORTIF V)...*

*"Since SPORTIF V was double-blind, it could be considered as the pivotal efficacy study and the other study (SPORTIF III) serves as a supportive study that provides additional safety information."*

Since when did the FDA not except open label trials as support for efficacy? Both SPORTIF III AND SPORTIF V were almost identical studies except that the former was open label (conducted primarily in Europe) and the latter was double-blind (in North

America). These studies were the largest studies in AF conducted to date and showed a dramatic consistency in the efficacy of ximelagatran, but differences in the benefit of warfarin (no surprise!). The FDA had trouble understanding why one would not obtain the exact same benefit with warfarin in the two studies.

*Another comment about the AF trials . . .*

*"Based on one double-blind study of Exanta [ximelagatran] versus the active control warfarin, there is very little evidence that Exanta is effective at reducing the risk of the combined incidence of stroke or systemic embolic events."*

*And further . . .*

*"On the primary endpoint, both studies failed to show a difference between Exanta and warfarin."*

Taking these two statements together, one would conclude that ximelagatran is ineffective in reducing the risk of stroke or systemic embolism in AF and that it is no different than warfarin. In fact, the FDA criticized the earlier landmark warfarin/AF trials (early 1990s) and raised questions about whether warfarin is really protective against stroke and systemic embolism in patients with AF.

*"Here, we have a scenario where the magnitude of the effect of warfarin versus placebo is not precisely known for this patient population."*  
*and*

*"There is some uncertainty about the magnitude of the effect of warfarin relative to placebo because of the variability between the six historical trials in terms of their design and the observed results. Consequently, there is a great deal of uncertainty about whether Exanta retains a significant portion of the benefit of warfarin, and even if Exanta is better than placebo"*

If this is the case, perhaps warfarin should not have FDA approval for stroke prevention in AF? For a clear understanding of the efficacy of ximelagatran, one is referred to the following references<sup>(1-3)</sup>.

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The FDA also had several interesting comments and analyses of ximelagatran's efficacy and safety in the orthopedic studies. Ximelagatran has been shown to be significantly better than warfarin in the prevention of venous thromboembolism in patients undergoing elective total knee replacement<sup>(4,5)</sup>, but the FDA commented...

*"However, the benefit was mainly due to a reduction in asymptomatic distal DVT diagnosed by venography which is not clinically meaningful."*

Perhaps the FDA should re-review the outcome measures in the studies submitted for approval of fondaparinux and the low molecular weight heparins before they totally disregard venogram documented asymptomatic DVT.

*Another comment . . .*

*"There are several major problems with using warfarin as an active comparator in these two studies. Warfarin is not approved for this short-term indication. The comparison is unfair, because warfarin will take about 3-5 days to reach therapeutic level, while Exanta reaches therapeutic levels within hours."*

First, warfarin is approved for the "prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism."<sup>(6)</sup> It is used by at least half of the orthopedic surgeons in this country and many others world-wide. It has been studied extensively in major joint replacement and is recommended by expert consensus groups<sup>(7)</sup>. Second, one reason orthopedic surgeons like warfarin is because it takes several days to have an effect (thus, less risk of bleeding at the surgical site), but also offers less protection early on. An advantage of ximelagatran as an oral anticoagulant is its rapid onset of action, and thus, protection. Because of this difference in pharmacokinetics, the ximelagatran patients did experience a slight increase in bleeding, which was criticized by the FDA, but there was no significant difference in major bleeding.

The other major concern raised by the FDA, and correctly so, was a signal indicating the possibility of increased cardiovascular events in patients on ximelagatran. Such events were only considered as an outcome measure, and thus adjudicated, in the AF trials (SPORTIF trials) and in the acute coronary syndrome trial (ESTEEM trial)<sup>(8)</sup>. Adjudicated coronary events were actually fewer in the ximelagatran group in the ESTEEM trial, and was not different from the warfarin group in the SPORTIF trials. However, unadjudicated coronary events were greater in the ximelagatran groups in the venous thromboembolism trials (THRIVE III<sup>(9)</sup> and THRIVE treatment trial<sup>(10)</sup>). This requires further evaluation, perhaps in a well managed post-marketing surveillance study.

Although there are many other aspects of the FDA review that deserve comment, space is limited and I am unable to address them here. My final thoughts about the proceedings are that the FDA may have arrived at the right conclusion, but for many of the wrong reasons. Their analysis lacked expertise; it failed to recognize the efficacy of ximelagatran which is supported by the literature and

uniformly recognized by experts in the field; and it erected almost insurmountable hurdles for new drug development in this field. I am gravely concerned that the FDAs review will stifle or retard such development. The FDA has lately been under duress related to the approval of other drugs with unrecognized adverse events. Although it is charged with protecting the American public from dangerous drugs, the FDA may have done a disservice in the process, by setting back the potential development of new drugs in a field that is ripe for improvement?

## References

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4. Francis CW, Berkowitz SC, Comp PC, et al. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med* 2003;349:1703.
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**There's still time**

**The deadline to submit an abstract  
for the conference has been  
extended to March 23, 2005**

# Certified Anticoagulation Care Provider (CACP) – Credentialing Report

Interest in the Certified Anticoagulation Care Provider (CACP) credentialing process has surged after the FDA's unfavorable review of ximelagatran (oral direct thrombin inhibitor) in September 2004. We encourage everyone who is involved in anticoagulation therapy management, in both inpatient and outpatient settings, to consider becoming board certified. One of the biggest barriers to individuals seeking certification is time and money – both time spent assembling the necessary application materials as well as time and expense traveling to the examination site. The board is exploring mechanisms to streamline the application process as well as administering the certification exam electronically at decentralized locations. The board has solicited formal proposals from computer-based examination vendors but no final agreement has been made. Computer-based exam delivery is potentially very expensive and any cost increases must be passed on to the examinees. Therefore, the board is carefully weighing the potential cost increases relative to any cost savings related to travel before making a final decision. Your input is welcomed.

The CACP exam was administered in December 2004 immediately prior to the American Society of Health-System Pharmacists (ASHP) Mid-Year Clinical Meeting in Orlando, Florida. The following individuals successfully met all of the application requirements and passed the certification exam:

Wendy Black, Pharm.D.  
Nicholas Brabander, Pharm.D.  
Nancy Crist, RN  
Aaron Dush, Pharm.D.  
Bernard Eck, R.Ph.  
Brigitte Gerl, Pharm.D.  
Jacqueline Dawn Guy, Pharm.D.  
Aaliya Khan, Pharm.D.  
Eunah Lai, Pharm.D.  
Victoria Lambert, Pharm.D.  
Carrie Nichols, Pharm.D.  
Jackie Raskind, Pharm.D.  
Susan Redmond, Pharm.D.  
Terry Thornhill, Pharm.D.  
Leeann Webster, R.Ph.

The next exam will be offered on May 5, 2005 immediately prior to the AC Forum Meeting in Orlando, Florida. Candidates for the May exam will be notified prior to April 1, 2005 whether

Register for the  
8th National Conference on  
Anticoagulant Therapy  
on-line at  
[www.acforum.org](http://www.acforum.org)

or not their application has been favorably reviewed and accepted. The exam will also be offered prior to the ASHP Mid-Year Clinical Meeting in Las Vegas on December 4, 2005. To obtain a 2005 candidate guide and application, please contact Elizabeth Goldstein at [Elizabeth.Goldstein@bmc.org](mailto:Elizabeth.Goldstein@bmc.org).

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 expired in December 2004. However, anyone whose CACP credential expired in December 2004 has been automatically granted a 1 year extension. The board has agreed at this time that re-certification is by examination only. Individuals who wish to recertify must complete the CACP application and submit the requisite \$300 fee (per usual) but are **NOT** required to submit 75 patient encounters for review. The board continues to explore computer-based methods for administering the certification exam but until that option is available individuals who wish to re-certify in 2005 must take the exam in either May or December 2005.

The 2005 National Certification Board of Anticoagulation Providers includes:

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*

New board members will be elected in May 2005. Individuals who wish to be considered for board membership or who are willing to serve as a CACP application peer reviewer or on the examination writing committee should contact Stuart T. Haines at 410-706-1865 or [shaines@rx.umaryland.edu](mailto:shaines@rx.umaryland.edu). ■



# NIH Conference on Dietary Supplements, Coagulation, and Antithrombotic Therapies

*Ann K Wittkowsky, PharmD, CACP, FASHP*

Anticoagulation specialists are well aware of the potential dangers associated with concurrent use of warfarin and a number of dietary supplements. The growing rate of supplement use in the US, and the increasing number of case reports describing significant interactions between warfarin and non-drug products has elevated the level of concern about the safety of dietary supplements when used in conjunction with antithrombotic agents.

As defined by Congress in the 1994 Dietary Supplement Health and Education Act, these products include vitamins, minerals, herbals or other botanical products, and amino acids intended to supplement the diet. Unlike drugs, dietary supplements do not have to be proven safe or effective prior to marketing, and do not have to be produced according to the Good Manufacturing Practices that assure the quality of drug products in the US. Many consumers consider these products safe because they are “natural”, but case reports and clinical trials have shown otherwise, particularly in patients who take these products concurrently with antithrombotic agents. Nonetheless, information regarding dietary supplement interactions with antithrombotic agents is limited.

The National Institutes of Health (NIH) recently held a 2-day conference on dietary supplements, coagulation, and antithrombotic

therapies. It was sponsored by the National Heart, Lung and Blood Institute (NHLBI), in collaboration with the Office of Dietary Supplements (ODS), and the National Center for Complementary and Alternative Medicine (NCCAM), as well as a number of other centers and institutes within NIH.

The purpose of the conference was to increase understanding of the potential for dietary supplements to interfere with hemostasis and antithrombotic therapy and to “discuss current knowledge, review regulatory and safety issues, share recent clinical trial findings, and identify opportunities for further research”. (<http://www.nhlbi.nih.gov/meetings/coagulation/index.htm>)

The conference was presented and attended by representatives of the NIH, the FDA, and experts from academia, industry, and numerous professional, regulatory and patient-advocacy organizations. Proceedings of the conference will be published in December 2005 in *Thrombosis Research*. Until then, background material related to the conference is available at: <http://www.nhlbi.nih.gov/meetings/coagulation/index.htm>. The full agenda can be viewed at: <http://www.nhlbi.nih.gov/meetings/coagulation/agenda.htm>

AC Forum members may also want to access additional information about dietary supplements at the ODS website, including: **IBIDS Database:** International Bibliographic Information on Dietary Supplements

[http://ods.od.nih.gov/Health\\_Information/IBIDS](http://ods.od.nih.gov/Health_Information/IBIDS)

**CARDS Database:** Computer Access to Research on Dietary Supplements)

[http://ods.od.nih.gov/Research/CARDS\\_Database.aspx](http://ods.od.nih.gov/Research/CARDS_Database.aspx) ■

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## The National Alliance for Thrombosis and Thrombophilia

To address these issues, we formulated an ambitious agenda for 2004-2005. In 2004, we launched our website at [www.nattinfo.org](http://www.nattinfo.org) to inform patients, the public, and healthcare providers about critical issues regarding thrombosis and thrombophilia; we received our 501c3 tax-exempt non-profit status; we recruited members for the Medical and Scientific Advisory Board; and we conducted three patient education seminars in Denver, Charlotte, and Detroit.

More than 425 thrombosis/thrombophilia patients, family, friends, and healthcare professionals attended these seminars to learn and cope with the daunting effects of blood clots. The personal responses shared from the seminar questionnaires, email responses, and phone conversations provided us with vital information that will enhance the developmental design of future programs. Our desire is to provide the latest information to meet personal needs of patients and to inform the community of issues related to thrombosis and thrombophilia.

In 2005, we plan to implement the following critical projects:

- Expand our educational seminars and other programs to directly and proactively reach more patients, healthcare providers, and the public to increase awareness of thrombosis and thrombophilia
- Conduct a patient needs assessment in conjunction with the Centers for Disease Control and Prevention to determine the gaps in medical care, awareness, and education of those suffering from thrombosis and thrombophilia
- Launch a national patient advocacy campaign to increase the allocation of federal funds to improve research, prevention, and treatment of thrombosis and thrombophilia

Effective preventive measures, diagnostics, and treatments for blood clots exist in the healthcare system today. However, people are still dying because these measures are not widely known, not widely available, and not widely used. We are changing this situation and contributing to saving and improving patients' lives. To learn more, please visit our Website at [www.nattinfo.org](http://www.nattinfo.org), contact Lori Preston at (410) 828-0759 or [lpreston@keelan.com](mailto:lpreston@keelan.com), or visit our table at the May Anticoagulation Forum meeting in Orlando, Florida. ■

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