

ANTICOAGULATION FORUM

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President's Column

David Garcia, MD

Thank you to all who participated in our online membership survey – we received over 700 responses! We are in the process of analyzing the information and thinking of ways to implement your comments and suggestions. The AC Forum Board of Directors is meeting at the beginning of March for a strategic planning session and will use the information from this survey to guide our decisions. Thank you again for your time and important feedback.

If you did not receive an email to participate in our survey, it means that we do not have your email address in our database. Please email egoldstein@acforum.org with your contact information so that we can update our files.

As a follow-up to the letter sent by the AC Forum to the Centers for Medicare and Medicaid Services printed in our last newsletter, we would like to report that CMS has issued their draft decision memo recommending a limited expansion of coverage for home monitoring devices. CMS is proposing to add coverage for home monitoring for patients with DVT and atrial fibrillation. Following this draft decision, the AC Forum submitted a 2nd public comment recommending that they expand to other indications as well. We will hear CMS' final ruling within the next few months.

As you will see, this edition of the newsletter contains an informative piece from Dr. Alex Spyropoulos. I am very grateful that Alex, a true expert in the area of emerging anticoagulants, agreed to send us this very up-to-date discussion of such an important topic. I hope that many of you will find it to be both informative and useful.

It's not too early to start planning for the AC Forum's 10th National Conference. Please save the dates May 7-9, 2009 and plan on joining us in San Diego. I look forward to seeing you there! ■



Anticoagulation
FORUM

Emerging Anticoagulants in the Management of Venous Thromboembolism

*Alex C Spyropoulos, MD, FACP, FCCP
Medical Director – Clinical Thrombosis Center
Lovelace Medical Center, Albuquerque, NM*

The management of venous thromboembolism (VTE) with anticoagulant therapy has undergone major developments in the past 10 years. For acute treatment, indirect inhibitors such as low-molecular-weight heparin (LMWH) and the pentasaccharide fondaparinux constitute improvements over traditional therapies such as unfractionated heparin. These agents have more predictable pharmacokinetic profiles with subcutaneous administration and lack of need for monitoring - enabling outpatient-based treatment strategies. For long-term treatment and secondary thromboprophylaxis, the only approved oral agents remain the Vitamin K antagonists (VKA) such as warfarin, with inherent limitations of multiple food and drug interactions, a narrow therapeutic index, slow onset and offset, and frequent need for monitoring, usually in specialized anticoagulation clinics. A new oral agent that did not require routine monitoring - the direct thrombin inhibitor ximelagatran – showed promising results in late phase clinical trials for prevention and treatment of VTE and was briefly approved outside of the US for short-term thromboprophylaxis in orthopaedic patients. It was taken off the world market in

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THE ANTICOAGULATION FORUM HAS MOVED!

Our new contact information is:

Anticoagulation Forum
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Phone: 617.454.1004
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egoldstein@acforum.org

NATT Update

*Alan P. Brownstein, MPH, NATT Executive Director
abrownstein@nattinfo.org*

In the fall 2007 Anticoagulation Forum Newsletter, NATT's President Randy Fenninger reported that NATT received grants from the Centers for Disease Control and Prevention (CDC) for our Stop the Clot™ Learning Project. The health professional education component of Stop the Clot™ is now taking shape with the formation of a Curriculum Development Team (CDT) that includes Anticoagulation Forum members. The CDT will guide NATT (with CDC) in the development of a curriculum that incorporates accurate clinical content and learning design methods. The curriculum will also be shaped by the results of a needs assessment that includes a sample of Anticoagulation Forum members. Once completed, NATT will use the curriculum in regional "train-the-trainer" workshops which will include health professionals from Thrombophilia centers and Anticoagulation Forum's member clinics.

Mary Ellen McCann, RN, MA is the program manager in the Stop the Clot™ Learning project. Recruited last month as Director of Health Learning and Marketing, Mary Ellen is providing the leadership and professional support to the Curriculum Development Team, which is having its first meeting March 13-14 in New York. If you have any thoughts about what should be included or emphasized in the curriculum, contact Mary Ellen at mmccann@nattinfo.org.

Mary Ellen comes to NATT with a wealth of nursing, management, professional and patient education and marketing experience and skills well suited to this position. For 10 years she was the Cardio-pulmonary Clinical Nurse Specialist with the Visiting Nurse Service of New York (VNS), providing clinical direction to 2,200 nurses. In this capacity she developed health professional and patient education tools that were provided through publications and the use of e-learning options.

CDC Selects Thrombosis in Top Three Priorities

Also, Dr. Roshni Kulkarni, Director of CDC's Division of Blood Disorders, reported that the CDC's National Center for Birth Defects and Developmental Disabilities has designated thrombosis as one of the three top priorities for the Center. This, along with NATT's CDC grant, will help bring thrombosis and thrombophilia issues to the forefront.

Minnesota Chapter Takes Shape

Another recent NATT initiative is the selection of Minneapolis-St. Paul as the base for a pilot Minnesota regional chapter and the Stop

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Save the Date!

The 10th National Conference on Anticoagulant Therapy will be held May 7-9, 2009 in San Diego, California. Our conference will feature world renowned expert speakers, small group discussions, original research poster session, exhibitors, opportunities to network with colleagues, and much more. Please save the date and plan to join us in sunny California next year.

Case Vignette

Management of warfarin dose in a patient with fatty liver disease

Lynn Oertel, RN, CACP

Ann Wittkowsky, PharmD, CACP, FASHP, FCCP

The Call

The laboratory calls with a critical INR value of 7.4. This is an acute elevation in the INR for a patient who has been on a stable weekly warfarin dose of 13 mg/week and with INRs consistently in therapeutic range, target 2.5.

The Case

This is a 67 year- old female on chronic warfarin therapy for atrial fibrillation. She has a history of cancer (colon and breast), controlled hypertension, and a long history of abnormal liver function tests. Current medications are: Arimidex, atenolol, cardizem, MVI, nexium, cyanocobalamin IM every month. She reports a recent mild weight gain. Recent liver function tests:

	ALT (7-30 U/L)	AST (9-32 U/L)	ALKP (30-100 U/L)	TBili (0-1 mg/dl)	DBili (0-0.4 mg/dl)	Alb (3.3-5 G/DL)
10/17/2007	45	124	198	0.9	0.4	4.1
12/31/2007	26	94	255	1.8	0.8	3.6

A recent MRI reveals hepatomegaly with fatty infiltration without focal hepatic lesions.

The Problem

There are many challenges associated with maintaining a patient's INR values in therapeutic range. It is notable that this patient's INR and weekly dose were stable prior to this acute episode. When an acute change from the stable course is observed, it warrants a closer investigation to assess potential

causes for the acute deviation from baseline. Query the patient about common causes such as:

- Confirmation of correct dose and correct pill size
- Additions/deletions/changes to prescription drugs, OTC medications or herbal products
- Change in diet
- Change in alcohol (or street drug) consumption pattern
- Episode of recent illness; especially with diarrhea, vomiting, fever, etc.
- Recent travel
- Recent hospitalization or visit to a health care provider

Creating a standard list of assessment questions can be helpful. In this case, an in-depth patient assessment did not reveal a clear explanation to her acute INR elevation as she only reported some weight gain. Seeing her recent out-of-range LFTs may lead one to assume the "cause" for this acute elevation in INR was a change in liver function.

The Resolution

Managing a patient with chronic liver disease is challenging. Hepatic disease is often associated with varying INR responses. However, patients may present with a chronic liver condition (for example, fatty liver disease) and have normal liver synthetic function.

As this case illustrates, often there is no easy explanation to unstable INRs and it's a challenge to manage such patients. In such cases, increasing the frequency of INR testing along with a conservative approach to adjust the weekly dose is a safe way to proceed. Of note, this patient now requires over a 50% less weekly warfarin dose to maintain a therapeutic INR. ■

References

1. Wittkowsky AK. Warfarin and other coumarin derivatives: pharmacokinetics, pharmacodynamics, and drug interactions. [Review] [52 refs] *Seminars in Vascular Medicine*. 3(3):221-30, 2003 Aug.
2. <http://www.mayoclinic.com/health/nonalcoholic-fatty-liver-disease/DS00577/DSECTION=1>

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Emerging Anticoagulants

February 2006 due to continuing safety concerns surrounding hepatotoxicity.

Emerging anticoagulants represent an improved understanding of the molecular mechanisms of coagulation and thrombosis within the coagulation cascade. These drugs can broadly be classified [Figure] as interfering with the initiation of coagulation (tissue factor-Factor FVIIa complex inhibitors), slowing the propagation of coagulation (indirect and direct inhibitors of FXa and FIXa), or inhibiting thrombin activity (direct thrombin inhibitors). Many of these are synthetically derived, orally-active drugs that are tailor-made to target specific procoagulant complexes and do not require

routine monitoring. This brief review will focus on emerging anticoagulants that have completed or are near completion of late phase clinical trials. They include the parenteral indirect FXa inhibitor idraparinux, the oral FXa inhibitors rivaroxaban and apixaban, and the oral direct thrombin inhibitor dabigatran.

I. Indirect FXa inhibitors

A. Idraparinux

Idraparinux is a second-generation pentasaccharide developed by Sanofi-Aventis with sulfated side chains resulting in a high

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The National Certification Board for Anticoagulation Providers has a new address. All future applications and correspondence with the NCBAP should be sent to:

**4974 N. Fresno St., Suite 202
Fresno, CA 93726
Phone: 559-761-1522
Email: info@ncbap.org**

We are also pleased to announce that Marie Walker has taken on a new role as Administrative Director. Marie has been instrumental in moving the NCBAP forward, particularly in the areas of the website and online exam. We are extremely fortunate that she is able to expand her role with our organization.

Several exams have been scheduled for 2008. Upcoming exam dates include Feb. 19, 2008 in Albuquerque, NM; Oct. 10, 2008 in Franklin, TN in conjunction with the SECAPS meeting; and Dec., 2008 in Orlando, FL in conjunction with the ASHP Mid-Year Meeting. An exam in Evansville, IN also is being planned and a summer date is pending. As details are finalized, they will be posted on the NCBAP website www.ncbap.org.

The NCBAP would like to congratulate those CACPs who have recently renewed their certifications. If you were certified on or before December 31, 2002 and have not renewed your certification, you are now past due and should contact Marie Walker at info@ncbap.org to make arrangements for recertification. If you were certified between January 1, 2003 and December 31, 2003, you should make arrangements to recertify prior to December 31, 2008. Please see the NCBAP website for more details www.ncbap.org.

Finally, the NCBAP is pleased to acknowledge and congratulate our newest Certified Anticoagulation Care Providers. The following individuals successfully earned the CACP credential in November and December 2007. ■

Barbara Sager, RN	Keri Justice, PharmD
Brian Musiak, PharmD	Kevin Cook, RPh
Carol Savluk, RPh	Lauryl Kristufek, PharmD
Corina Grancorvitz, PharmD	Nathan Sauers, PharmD
Cynthia Cihak, RN	Palmie Riposa, RN
Cynthia Hawkesworth, RN	Pamela Burgwinkle, APN
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Jennifer Maune, PharmD	Steven Totterdale, PharmD
Jennifer Williams, PharmD	Thomas Grubaugh, RPh
Jenny Legge, PharmD	Todd Marcy, PharmD
Kaitlyn Solola, PharmD	Valery Lau Chu, PharmD

binding affinity to antithrombin and an approximate 120 hr elimination half-life allowing for once-weekly administration. The recently completed Van Gogh studies revealed that the agent met the prespecified non-inferiority criteria in reducing the risk of VTE in patients with deep vein thrombosis (DVT) but not in pulmonary embolism (PE). The extended treatment study (Van Gogh Extension) revealed that idraparinux was more effective than placebo in the prevention of symptomatic VTE during a 6-month extension period, but it was associated with more major bleed events in patients initially treated with the drug prior to randomization. Although a newer biotinylated form of idraparinux with the ability to neutralize the drug by a specific protein (avidin) is currently being studied in phase III studies, the overall net clinical benefit of idraparinux remains uncertain.

II. Oral direct FXa inhibitors

A. Rivaroxaban

Rivaroxaban is a small molecule selective oral FXa inhibitor developed by Bayer with rapid absorption and a terminal half-life of approximately 4 – 9 hrs at steady-state. Preclinical studies reveal that it is well-tolerated without drug-drug interactions or major CYP induction (with the exception of strong CYP3A4 inhibitors). As a result of dose finding studies (albeit a flat dose-response curve), the 10mg/day dose was selected for evaluation in phase III studies. The phase III RECORD program compared rivaroxaban to enoxaparin in over 10,000 patients worldwide undergoing orthopaedic surgery. Data from patients undergoing total hip and knee replacement confirmed that rivaroxaban was superior to enoxaparin given at 40mg/day for the prevention of VTE, without an increase in major bleeding. There were no clinically important or consistent liver enzyme elevations. Bayer has recently applied to the FDA and EMEA for approval of the drug for thromboprophylaxis in orthopaedic patients.

For acute VTE treatment, results of the phase II studies (EINSTEIN-DVT and ODIXa DVT) revealed that there was no significant dose-response relationship for the primary efficacy endpoint (or major bleeding) when comparing either a once-daily or twice-daily regimen of rivaroxaban across a range of doses to conventional therapy with a heparin and dose-adjusted VKA. In addition, there were no significant effects on liver enzymes during the 12 week treatment period. A large phase III program with rivaroxaban - EINSTEIN VTE – is underway for initial and extended treatment of VTE.

B. Apixaban

Apixaban is an orally-active, small molecule, highly potent direct FXa inhibitor with an effective half-life of 9 hrs for once-daily

dosing and 14 hrs for twice daily dosing that has been developed by Bristol-Myers Squibb. It has no CYP interaction and modest effects on traditional markers of anticoagulation, the International Normalized Ratio and activated partial thromboplastin time. Results from phase II studies in elective total knee replacement reveal that primary efficacy rates were lower across 6 doses of apixaban versus the comparators enoxaparin given at 30mg twice-daily or open-label warfarin. Bleeding rates were also dose-dependent. Preliminary results from the phase II treatment study – the BOTTICELLI study – revealed that the primary efficacy endpoint and safety outcome were similar for all doses of apixaban and standard therapy with LMWH/warfarin group. There was no signal for significant hepatotoxicity. There are currently three multinational VTE prevention phase III studies of apixaban being conducted in patients undergoing orthopaedic surgery and in patients with advanced metastatic cancer. A phase III VTE treatment study is also planned. It is expected that, depending upon the results of these phase III programs, US regulatory approval will be filed in the second half of 2009.

C. Other direct FXa inhibitors

YM150 and LY517717 are both selective, small molecule oral FXa inhibitors without significant food interactions that are given once daily. Results from phase II studies in patients undergoing orthopaedic surgery using enoxaparin as the comparator revealed a dose-response relationship with higher doses of the drugs. Major bleed rates were low in all treatment arms. Other studies in advanced phases of clinical development are planned.

III. Oral direct thrombin inhibitors

A. Dabigatran

Dabigatran etexilate is a small molecule, orally active direct thrombin inhibitor prodrug developed by Boehringer Ingelheim. It has limited oral bioavailability, a peak plasma concentration at 2 hrs post-dose, and a half-life of ~ 14-17 hrs. It is mainly metabolized via renal excretion. After dose-finding studies, 2 doses (150mg and 220mg) of dabigatran were selected for evaluation in the large phase III RE-VOLUTION thromboprophylaxis clinical trial program that would enroll over 27,000 patients worldwide. Phase III studies in patients undergoing orthopaedic procedures revealed that dabigatran was non-inferior to the comparator enoxaparin if it was given 40mg/day, with comparable major bleed rates. However, preliminary results from the RE-MOBILIZE study in patients undergoing total knee replacement using the comparator enoxaparin given 30mg twice-daily revealed that the selected doses of dabigatran did not meet non-inferiority criteria for efficacy. Pooled analysis revealed similar major bleed rates for the 2 doses of dabigatran and enoxaparin, 40-60mg/day. There was no significant incidence of liver enzyme elevations across groups. On January 24, 2008 EMEA approved the use of dabigatran for thromboprophylaxis in patients undergoing orthopaedic surgery.

A large phase III VTE treatment and extension study comparing dabigatran to standard therapy with heparin plus adjusted-dose VKA is underway. Preliminary results are forthcoming.

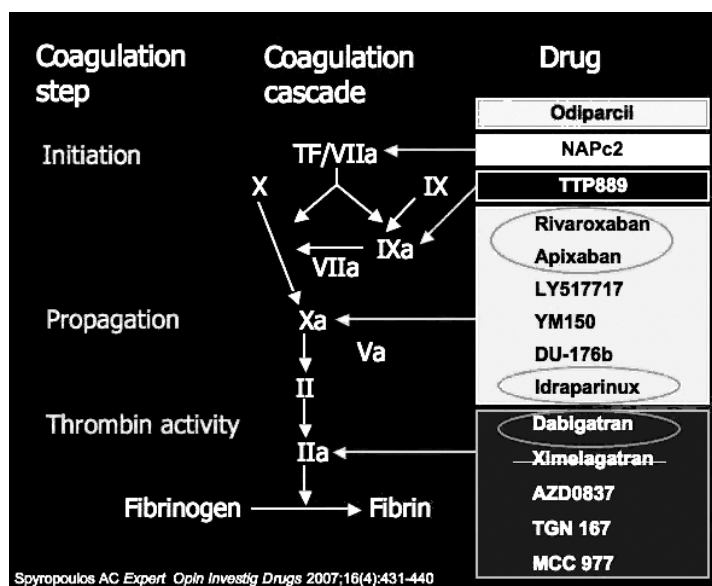
Conclusions

The use of emerging anticoagulants will change the paradigm of the antithrombotic management of VTE in the next 5 years. If successful, these emerging target-selective oral antithrombotic agents will eliminate the traditional distinction of acute vs. long-term treatment of VTE as they may be used throughout the spectrum of disease, without the need for overlap therapy. In addition, oral agents with a rapid onset, predictable pharmacokinetic/pharmacodynamic characteristics used in a simple, fixed-dose, once- or twice-daily regimen without significant food or drug interactions and with the ability to have compliance assessed, will have major advantages over the existing oral anticoagulants. Furthermore, oral agents with an excellent long-term safety profile, a half-life that provides both safety and ease-of-use (especially during temporary interruption for elective procedures or surgeries), and tolerability with antiplatelet agents will have further advantages.

Whether small-molecule oral agents are as efficacious in high risk patients with VTE (such as those with large clot burden, major PE, and cancer-associated VTE), or whether they exert pleiotropic effects (such as seen with heparin-based agents) remains to be seen. Lastly, whether there are clinical advantages of blocking initial thrombin formation via the prothrombinase complex or blocking thrombin directly, and whether there is a clinically meaningful effect of blocking clot-bound (in addition to free) thrombin, also remains undetermined.

A brave new world of antithrombotic management of VTE has begun. ■

Figure. Mechanisms of action of emerging anticoagulants.



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Anticoagulation Updates

from the Literature



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ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007;116:e148-e304.

Comment: The ACC/AHA 2007 Guidelines for the management of patients with unstable angina and non-ST-elevation myocardial infarction represents an extensively referenced and comprehensive overview of anticoagulant and platelet-directed therapies. An updated version of

guidelines published in 2002, the current document highlights the results of numerous large-scale clinical trials, translating their findings to a desired objective of optimal patient care and evidence-based management strategies. ■

(1) Ray JG, Kearon C, Yi Q, Sheridan P, Lonn E, for the Heart Outcomes Prevention Evaluation. Homocysteine-Lowering Therapy and Risk for Venous Thromboembolism: A Randomized Trial. *Ann Intern Med.* 2007;146:761-67.

(2) den Heijer M, Willems HPJ, Blom HJ, Gerrits WBJ, Cattaneo M, Eichinger S et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: a randomized, placebo-controlled, double-blind trial. *Blood.* 2007; 109:139-44.

Summary: Homocysteine remains a conundrum for clinicians interested in the diagnosis and management of both arterial and venous thrombosis. Reasonably strong evidence supports a relationship between increased levels of homocysteine and arterial thrombosis, and weaker evidence supports this relationship for venous thrombosis. However, unlike other “modifiable” risk factors reductions in the levels of homocysteine do not appear to reduce the risk of arterial or venous events. Thus, Ray and colleagues (1) failed to demonstrate that clinically important reduction in the level of homocysteine reduced the risk of first venous thrombosis. This observation confirms a prior study (2) which demonstrated that effective homocysteine lowering therapies fail to reduce the risk of recurrent venous thromboembolism. Similar observations have been made on the “arterial side”; carefully performed studies within which homocysteine was reduced have not demonstrated clinically important reductions in clinical events. Surprisingly, some such studies have actually suggested that patients receiving homocysteine lowering therapy had an increased risk of atherosclerotic vascular events. The final results of the HOPE-2 study are of singular importance in this area given the size and methodological rigor of the study.

At 145 clinical centers in 13 countries, 5522 persons 55 years of age or older with known cardiovascular disease or diabetes mellitus were allocated to receive a daily supplement of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12 or matching placebo for 5 years. (1) This “sub-study” of the HOPE-2 trial found that the geometric mean homocysteine level decreased by 2.2 mol/L in the vitamin therapy group and increased by 0.80 mol/L in the placebo group. The rate of new venous thromboembolism was the same in the vitamin therapy group and the placebo group (0.35 per 100 person-years; hazard ratio, 1.01 [95% CI, 0.66 to 1.53]). A similar lack of effect was seen for deep vein thrombosis, pulmonary embolism and unprovoked venous thromboembolism.

Comment: What do these observations mean for scientists interested in homocysteine? Perhaps most importantly they suggest that elevated levels of homocysteine may be more of an epiphenomenon and not a cause of venous and arterial thrombosis. Inquiry should focus on underlying mechanisms which both increase the risk of thrombosis and the levels of homocysteine. ■

State of the Art 2007. *J Thrombosis Haemostasis* 2007; 5: i-331.

Summary: The XXIst Congress of the International Society of Thrombosis and Haemostasis was held in Geneva July 6-12 2007. One component of the biannual Congress is the State of the Art lecture series, which is also published in a supplement to JTH. These lectures are presented by internationally recognized experts and combine basic and clinical science aspects of various topics in thrombosis and hemostasis. This year, 43 separate

topics were addressed, many of which will be of interest to clinical practitioners.

Comment: The AC Forum Board of Directors invites the membership to review the topics covered in the ISTH State of the Art 2007 lecture series, as published in the July supplement to JTH. ■

Glynn RJ, Ridker PM, Goldhaber SZ, Buring JE. Effect of Low-Dose Aspirin on the Occurrence of Venous Thromboembolism: A Randomized Trial. *Ann Intern Med.* 2007;147:525-533.

Summary: Whether aspirin may be able to reduce the risk of venous thromboembolism (VTE) in healthy adults is not known. In this analysis of data from the Women's Health Study, the authors report VTE rates in 39,876 health professionals randomly assigned to low-dose aspirin or placebo for 10 years. VTE rates were not different and were low in both groups: 1.18 per thousand person-years among women assigned to aspirin; 1.25 per thousand person-years among women assigned to placebo (relative hazard, 0.95 [95% CI, 0.79 to 1.13]). Although rates of VTE were higher among women with inherited thrombophilia (e.g. those who were heterozygous for factor V Leiden mutation), aspirin did not reduce rates of VTE compared to placebo, even in this higher risk subgroup.

Comment: This study reinforces the hypothesis that aspirin, a very effective agent for the prevention of platelet-rich arterial thrombi, has a much weaker (if any) effect on thrombotic events on the venous side of the circulation. Many patients who consider discontinuing warfarin therapy 6-12 months after a first VTE event ask whether taking aspirin will offer protection against VTE recurrence. In order to definitively answer this question (i.e. does aspirin have a role in the secondary prevention of VTE), we must await the results of ongoing controlled trials. In the meantime, although aspirin may be indicated to reduce the risk of stroke or MI, we should be cautious about our hopes for its ability to prevent DVT/PE. ■

Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. *Arch Intern Med* 2007; 167:1471-5.

Summary: This population-based study identified 1897 patients who had been diagnosed with VTE, 73.7% of whom were outpatients at the time of diagnosis. Among these patients, 23.1% had undergone surgery in the preceding 3 months, 36.8% had been hospitalized in the preceding 3 months, and 67% experienced VTE within 1 month of hospitalization. Among patients with recent hospitalization who subsequently developed VTE, only 42.8% had received VTE prophylaxis during the hospitalization,

half of which were less than 4 days in length. One third of cases of outpatient VTE occurred in patients with malignancy.

Comment: There is growing evidence that extended prophylaxis following hospital admission is warranted. Identification of patients at highest risk should be the target of future investigations. In the mean time, improved use of VTE prophylaxis during hospital admissions is necessary. ■

Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: A prevalent adverse effect resulting in regulatory action. *Arch Intern Med* 2007; 167:1414-9.

Summary: Using data from the National Prescription Audit Plus database, adverse events reported to the FDA, current vital statistics data, and national hospital emergency data, these investigators describe in detail the current state of warfarin use and complications in the US. In 2004, over 30.6 million prescriptions for warfarin were dispensed, an increase of 45% from 1998. From 1993 through mid-July 2006, nearly 10,000 cases of warfarin-related major bleeding were reported to the FDA, 10% of which were fatal and 86% of which resulted in a serious outcome. Comparatively, serious adverse events for all other drugs were reported in 30% of cases,

and fatal events in 7% of cases. In 2004, anticoagulants were listed as the immediate, contributing or underlying cause of death for 0.52 per 100,000 deaths.

Comment: Warfarin use continues to increase, as does warfarin-related bleeding complications, including fatalities. These data provide convincing epidemiologic evidence of the dangers of oral anticoagulation, and can be used as a starting point to make the case for the role of anticoagulation management services as a method to improve patient safety. ■

Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet.* 2007;370:493-503.

Summary: 973 patients aged 75 years or older (mean age 81.5 y) with atrial fibrillation were recruited from primary care and randomly assigned to warfarin or aspirin (75 mg per day). Patients for whom warfarin was the clear choice were not eligible. Mean length of follow-up was 2.7 years. The primary endpoint was fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism. There were 24 primary events (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in people assigned to warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin (yearly risk 1.8% vs 3.8%, relative risk 0.48, 95% CI 0.28-0.80). Yearly risk of extracra-

nial haemorrhage was 1.4% (warfarin) versus 1.6% (aspirin) (relative risk 0.87, 0.43-1.73; absolute risk reduction 0.2%, -0.7 to 1.2).

Comment: Among older patients with atrial fibrillation for whom there is uncertainty as to whether warfarin or aspirin is the preferred therapy, warfarin was found to be superior to aspirin for the prevention of stroke (1.8% versus 3.8% per year) and no more hazardous than aspirin in terms of major hemorrhage (1.9% versus 2.0% per year). This study demonstrates that even among lower risk patients, warfarin is more effective than aspirin. ■

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NATT Update

the Clot™ learning project. With the Stop the Clot forums in 4-6 cities across the country in the year ahead, Minnesota was chosen as the nucleus to develop the Stop the Clot™ Forums, the Stop the Clot™ Support Groups and a regional infrastructure to ensure that these educational and community-based awareness initiatives are sustained over time. The Twin-Cities area was selected based on the combination of volunteer/patient leadership and wonderful medical facilities in the area as well as the opportunity to collaborate with the Hemophilia and Thrombosis Center at the University of Minnesota Medical Center, Fairview. We just hired Ms. Cynthia Arnold as the Minnesota Chapter Director and Mr. Greg Zandlo will serve as the first Chapter President, with Dr. Mark Reding as the Chair of the Chapter's Medical Advisory Board. Ms. Arnold has been an award-winning public relations and fundraising executive for small to medium-sized nonprofits for more than 20 years.

NATT has a lot of exciting educational initiatives regarding thrombosis and thrombophilia, and we will continue to work with the Anticoagulation Forum and other partners to further educate the public and health care professionals about this daunting public health issue. ■

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