



ISTH 2009 DAILY

XXII CONGRESS INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS



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Long-acting Factor VIIa had Longer Duration of Action in Hemophilic A Mice

Although recombinant Factor VIIa and long-acting recombinant Factor VIIa had the same maximum efficacy, the long-acting derivative had a prolonged duration of action in hemophilic A mice.

Heidi L. Holmberg, from the hemostasis pharmacology section of Novo Nordisk, presented the study results Wednesday morning.

Holmberg and colleagues compared the dose-response relationship between recombinant Factor VIIa and long-acting recombinant Factor VIIa in hemophilia A mice after IV administration.

Long-acting recombinant Factor VIIa, a glycopegylated derivative of recombinant Factor VIIa, was designed to have a longer circulating half life.

The effect of the two molecules was

measured by thromboelastography. Both molecules normalized the response and had the same maximal efficacy; however, higher doses of the derivate were needed.

“Encouraged by these data we then

moved on to a study to show that [long-acting recombinant Factor VIIa] had a long duration of action,” Holmberg said.

Initially, the researchers measured

(Holmberg, continued on page 12)



Boston Pops to Entertain Delegates

The Boston Pops Orchestra will entertain delegates tonight at the All Congress Party to be held at the Bank of America Pavilion. Please see registration for tickets. To learn more about the Boston Pops Orchestra visit www.bso.org.

Analogue of Factor VIIa had Improved Efficacy, Duration in Hemophilic Mice

Bay7, a novel Factor VIIa analogue, demonstrated improved efficacy and duration compared to traditional Factor VIIa, according to results presented Wednesday by **Haiyan Jiang, PhD**, of Bayer Healthcare LLC.

This analogue shows increased af-

finity to platelets due to mutations in the Gla domain and improved pharmacokinetics attributed to additional N-linked glycans.

In a study of hemophilia A mice, the novel analogue more effectively

treated acute bleeding in tail-clipped hemophilia A mice and showed an increased half life.

To compare the two therapies, the researchers assessed acute bleeding induced by tail clip in hemophilic mice. The mice received an IV injection of escalating dosing of each drug.

Compared to traditional Factor VIIa,

(Jiang, continued on page 12)

THURSDAY AT A GLANCE

Ongoing
Oral Communications, State-of-the-Art Lectures, Abstract Symposia, Nurses' Sessions

9:45 a.m. – 10:30 a.m.
Plenary Lecture: von Willebrand Assembly and Secretion (J. Evan Sadler)

12:30 p.m. – 2:15 p.m.
Posters Attended

5:15 p.m. – 6:00 p.m.
Plenary Lecture: Stem Cells, Pluripotency, and Nuclear Reprogramming (Rudolf Jaenisch)

6:30 p.m. – 10:00 p.m.
All Congress Party (Pre-registration Required)

Thank You to Our Volunteer Editors

ISTH 2009 would like to thank the following people for volunteering their time this week to serve as scientific editors for the 2009 ISTH Daily.

Beth Bouchard
Robert Flaumenhaft
Peter Gross
Howard Leibman
Nigel Mackman
Freida Pammias
Cameron Trenor
Jeffrey Zwicker

TIPS OF THE DAY

Today is the last day to buy tickets for tonight's All Congress Party – inquire at the Registration Desk. There is a strict ID policy in Boston regarding the sale of alcohol. You may be asked for ID at the beverage stations at the Congress Party to ensure that you are older than 21 years of age. Don't forget to bring identification.

Airport shuttles from the Convention Center cost \$2 today between 2:30 p.m. and 6:30 p.m. Inquire at the Registration Desk for details.

Stay connected at the Cyber Café & Message Center in the Exhibition Area.

Remember to recycle your Congress bag by returning it to the Registration Desk, if you don't want to keep it. Thank you!

Remember to recycle your badge holder by returning it to the Registration Desk, if you don't want to keep it. Thank you!

Factor IX Mutation a Novel Risk Factor for Thrombophilia

Researchers in Italy and the United States have concluded that FIX-R338L appears to be a novel risk factor for thrombophilia.

Paolo Simioni, MD, PhD, chair of internal medicine at the University of Padua Medical School in Padua, Italy, presented the results of a study exploring X-linked thrombophilia during a plenary session Tuesday afternoon. He said the Factor IX variant could play a role in treatment of patients with hemophilia B.

"This FIX variant offers an attrac-

tive alternative for future development of novel therapies for hemophilia B," he said.

Dr. Simioni and colleagues evaluated members of an Italian family after the proband, a 23-year-old man, developed spontaneous DVT. They did not find an inherited risk factor for thrombophilia, but, instead, the man's Factor IX



Paolo Simioni, MD, PhD

activity was 776% of normal.

Following an extensive thrombophilia workup, the researchers found normal levels of Protein C, Protein S and antithrombin III, and an absence of Factor V Leiden or prothrombin variant 20210A. Dr. Simioni said that there was no sign of lupus anticoagulant.

The patient and family members who shared a mutation at FIX-R338L, dubbed FIX Padua after the Italian city where it was discovered, presented with normal FIX antigen lev-

els and as much as a ninefold increase in FIX functional activity compared with wild-type FIX. Dr. Simioni said the mutant FIX circulates at normal antigenic levels but exhibits eightfold increased clotting activity

"Recombinant FIX-R338L, characterized in the laboratory of **Valder Ar-ruda, MD, PhD**, from the Children's Hospital of Philadelphia, University of Pennsylvania, exhibited eightfold higher specific activity compared with the wild-type protein," he added.

The results are consistent with a gain-of-function FIX mutation as a novel risk factor for thrombophilia and has potential for protein replacement or gene-based strategies for the treatment of hemophilia B, Dr. Simioni said.

Hemophilia: Management and Future Directions of Treatment

Starting prophylactic replacement therapy earlier in a hemophilic child's life provides better prevention of joint damage, according to **Kathelijm Fischer, MD, PhD**.

Dr. Fischer, from the Van Creveld-kliniek, University Medical Center Utrecht in the Netherlands, said that when prophylaxis is started at age 1 or 2 years directly after the first joint bleed, patients benefit. "The earlier treatment improves outcome," she said.

The most efficacious regime is weekly treatment that begins before age 3, Dr. Fischer said at an education session. The value of high vs. low doses is still under debate.

Also unclear is the value of different outcome assessments. For the short term, Dr. Fischer said, the annual number of joint bleeds is the "most important parameter." For the long-term outcomes, both radiological and clinical scores are used.

Radiological scores were devel-

oped in 1981 and use plain X-rays in two directions to evaluate the ankles, knees and elbows. "It is all about bony changes," Dr. Fischer said. Clinical scores were developed in 1993. Based on a physical examination, clinical scores consider pain, swelling, range of motion and flexion, but "they are not very precise," she said.

Advances in Therapy

Great advances in Factor VIII and IX replacement therapy have not occurred in 20 years, according to **Professor Edward G.D. Tuddenham**, from the Cancer Institute at University College London.

For more than 20 years, there have been three recombinant Factor VIII products, he said. "There has been incremental progress in their formulations but little change." However, with patents ending on the formulations, there is now a "flurry of research into development of innovations for Factor VIII and IX.

"My impression is that within two or three years, we may have all of our patients on experimental treatments," Dr. Tuddenham said. The commercial field is fast moving, with perhaps 20 to 50 approaches that are under investigation for treatment therapies.

One of these approaches is the "me-too similars," although none are yet in phase-3 trials. Another effort is to develop ways to prolong the half-life of treatment so that patients would need fewer infusions. Strategies to develop more acceptable forms of administration, such as subcutaneous treatment, and improvements to the stability of products are also being investigated.

"It is an exciting time to be in the field of hemophilia treatment," Dr. Tuddenham said.

Gene Therapy

Arun Srivastava, PhD, chief of the division of cellular and molecular therapy at the University of Florida

College of Medicine, outlined the possibilities for gene therapy to potentially cure hemophilia. This research has included use of recombinant adeno-associated virus to deliver genes to a predetermined site.

The AAV is a human virus that is nonpathogenic and is "very efficient in Factor IX delivery and expression," Dr. Srivastava said. Research with dogs showed long-term efficacy, with no bleeding out to eight years.

Finding the appropriate dose for humans has been challenging; one dose did nothing in humans and another was therapeutic, but by six to eight weeks the Factor IX level "crashed and disappeared."

"We now know that use of self-complementary vectors gets higher gene expression. But it takes two to six months before we begin to see expression," he said. Recent research is focusing on use of tyrosine-mutant AAV2 vectors, which show better promise than single-strand vectors, he said.

Kindlin3 Mutation Tied to Disease

A previously unrecognized human deficiency disease has been identified in a pair of siblings born five years apart.

Tatiana V. Byzova, PhD, from Learner Research Institute, The Cleveland Clinic in Ohio, described Integrin Activation Deficiency Disease during a plenary session on Tuesday.

Dr. Byzova said that both children developed life-threatening bleeding, frequent infections and osteopetrosis within the first months after birth. Both had "profoundly deficient function" of integrins in their platelets, leukocytes and bone marrow mesenchymal cells. The children's platelet lymphocytes and neutrophils did


not adhere, spread or aggregate in response to stimulation with ADP, thrombin, PMA or collagen. "These manifestations were due to the lack of integrin activation," Dr. Byzova said.

The patients' mesenchymal stem cells exhibited substantially higher than normal calcium accumulation and production of bone and cartilage in bone formation assays. Dr. Byzova said that the patients' platelets and leukocytes expressed normal levels of integrins but could not transform integrins from a low affinity to a high affinity state for ligand recognition. The genetic basis for the disease was traced to a single point mutation in the cytoskeletal protein, Kindlin3.

Directions to Bank of America Pavilion



The All Congress Party will be held tonight from 6:30 p.m. - 10 p.m. at the Bank of America Pavilion, which is just a short walk from the Boston Convention and Exhibition Center. Buses will depart from 6:30 p.m. - 7 p.m. on Level 0 to transport delegates to the party. Pre-registration is required. Please inquire at registration to purchase tickets.



Thrombosis—with no apparent link to clinical presentation—should increase your suspicion of PNH.

Add PNH to your hypercoagulation panels for patients with unexplained thrombosis.

- PNH patients are 62 times more likely than the general population to experience venous thromboembolism¹
- This incidence of thromboembolism in PNH is markedly elevated, even when compared to other hypercoagulable states such as AT deficiency, PS deficiency, PC deficiency, PT mutation, and Factor V Leiden¹
- Venous or arterial thromboses account for approximately 40% to 67% of PNH-related deaths²
- First thrombotic event (TE) increases risk for death 5- to 10-fold²
- Incidence of first ever ischemic stroke (FEIS) is elevated in PNH patients; age of FEIS in the PNH population (median age 46) is markedly lower than the general population (median age 72)^{3,4}

→ Visit us at booth #711 to learn about the progressive and destructive nature of PNH, as well as the increased risk of thrombosis, end organ damage, and mortality.

References: 1. De Stefano V, Rossi E, Paolaroni K, Leone G. Screening for inherited thrombophilia: indications and therapeutic implications. *Haematologica*. 2002;87:1095-1108. 2. Hillmen P, Muus P, Duhrsen U, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2007;110:4123-4128. 3. Data on file, Alexion Pharmaceuticals Inc. 4. Gostynski M, Engelter S, Papa S, Ajdacic-Gross V, Gutzwiller F, Lyrer P. Incidence of first-ever ischemic stroke in the Canton Basle-City, Switzerland. *J Neurol*. 2006;253:86-91.

ISTH Council Sets Site for 2017 Congress

At its meeting on Monday night, the ISTH Council voted on the site of the XXVI Congress in 2017, to be held in Berlin, Germany, with **Johannes Oldenburg, MD**, as Congress President.

The ISTH convenes an international Congress biennially, while the Scientific and Standardization Committee (SSC) and its scientific subcommittees meet annually. In Congress years, Society and SSC meetings are held in conjunction.

ISTH Executive Director **Gilbert C. White II** noted that these events are large and complex undertakings, requiring years of planning. "We are

enormously grateful to our volunteer Congress presidents and the presidents of our SSC meetings for their willingness to take on this important responsibility. Our meetings would simply not be possible without their generous commitment of time and service."

Contact information for all meetings may be obtained through ISTH Headquarters, 610 Jones Ferry Road, Suite 205, Carrboro, NC 27510, USA; fax: 919-929-3935; e-mail: headquarters@isth.org. Those interested in sponsorship should contact Margo Price, Director of Corporate Relations; 919-929-2381; e-mail: margo_price@med.unc.edu.

Future ISTH Meetings

56th Annual SSC Meeting

Nevine Kassim, President
Cairo, Egypt
May 22 to 25, 2010
<http://www.ssc2010.org>

XXIII ISTH Congress with 57th Annual SSC Meeting

Yasuo Ikeda, President
Kyoto, Japan
July 23 to 29, 2011
<http://www.isth2011.com>

58th Annual SSC Meeting

Cheng-Hock Toh, President
Liverpool, United Kingdom
June 27 to 30, 2012

XXIV ISTH Congress with 59th Annual SSC Meeting

Frits R. Rosendaal, President
Amsterdam, The Netherlands
June 29 to July 4, 2013

XXV ISTH Congress with 61st Annual SSC Meeting

Sam Schulman, President
Toronto, Canada
2015

XXVI ISTH Congress with 63rd Annual SSC Meeting

Johannes Oldenburg, President
Berlin, Germany
2017

Intermediate Phase of Platelet Production Identified

By developing a method of isolating released proplatelets in culture, researchers have identified a new intermediate stage in platelet production: the preplatelet.

"We have just recently developed this new method of isolating released proplatelets in culture, which we have

used to show, both quantitatively and qualitatively, platelet release," **Jonathan N. Thon, PhD**, from the translational medicine division at Brigham and Women's Hospital in Boston, said during the Presidential Plenary session.

"This has enabled us to demonstrate that proplatelets will mature into mul-

tiples individual platelets in vitro as well as in vivo in a microtubule-dependent fashion, a characteristic we are now beginning to describe mechanistically."

Thon and colleagues developed a centrifugation and gradient sedimentation procedure to purify released proplatelets. They assessed the mech-

anisms by which proplatelets mature into individual platelets and quantified platelet production using both immunofluorescent microscopy and flow cytometry.

By doing so, the researchers defined and quantified various stages in platelet maturation and related the temporal changes to cytoskeletal rearrangements. Both barbell-shaped proplatelets and preplatelets are released from megakaryocytes in culture; preplatelets contain mature granules and appear to have the capacity to reversibly convert into proplatelets, according to Thon.

Fluorescence time-lapse microscopy of preplatelets isolated from EB3-GFP and beta 1-tubulin-GFP-expressing cells demonstrated that twisting microtubule-based forces elongate preplatelets, causing them to assume barbell-shapes; two smaller mature platelets are released from the barbell ends in a fission process, he explained.

Individual alpha-granules eventually concentrate at the loops of each end after moving bidirectionally within the barbells and translocating between platelet-sized swellings.

When cultured for six hours, isolated proplatelets converted the bulk of their mass into mature platelet-sized particles containing microtubule coils. Similarly, after two hours of transfusion of fluorescently-tagged proplatelets into recipient wild mice, mature platelets were found.

"In terms of where this work is headed, we hope to use these techniques and others to establish a mechanism of platelet release, determining signaling pathways involved in this process. We can appreciate that this process most likely occurs in the blood stream and determine the contribution of shared forces to platelet production," he said.

ISTH Membership? Why not?

Cathy Cole,
ISTH Executive Secretary

Overheard between two registrants passing through the Washington convention center at the XVII ISTH Congress in 1999:

"Did you notice that ISTH members have red ribbons on their badges that say 'MEMBER?'"

"Yup, I saw that. They're just trying to push us to become members." (Shrug.)

That memory always makes me smile – for a couple of reasons. First, I hope that those two attendees found the 1999 Congress to be valuable to their scientific work and their careers, and that they continue to attend ISTH and Scientific and Standardization Committee (SSC) meetings, whether they ever become members.

Second, ISTH members are valued and appreciated, and they

deserve a red ribbon, at the very least!

Third, everyone who has attended an ISTH Congress, submitted an abstract, participated in an SSC meeting or submitted a paper to the *Journal of Thrombosis and Haemostasis: JTH* knows that ISTH is a truly inclusive organization, serving the international medical and research communities, in addition to its members.

Who Are ISTH Members?

ISTH members are the organizers, participants and attendees of these Congresses. They are the editors, authors and reviewers of *JTH*. They are the chairs, members and attendees of the SSC's scientific subcommittees and working groups. They are the officers and members of Council. They are your mentors and your colleagues, your students, trainees and peers.

They come from every part of the world and they help each other further their research, patient care, teaching and leadership in the scientific community. They care for those who are afflicted by the diseases of thrombosis, the disorders of abnormal coagulation, and they look for underlying causes of these problems.

If you are a member, you enjoy some immediate benefits, like a complimentary subscription to *JTH*, priority registration for meetings and a generous membership discount and participation in the ISTH Forum. Members elect the leadership of the Society and become part of the international network of experts in this area.

And Another Thing...

ISTH is one of the truly international medical organizations in the world today. What a great Society!

I can't think of any reasons not to be a part of this outstanding organization. Can you? Go to www.isth.org for an application.

The "CSL Behring - Prof. Heimburger Award" to support scientific research in the field of coagulation will be awarded again in 2010. The global grant is sponsored by CSL Behring.

CSL Behring - Prof. Heimburger Award 2010

The global grant is named in honour of Prof. Norbert Heimburger, a pioneer of modern coagulation. One of his major contributions in this area was the development of virus-inactivated products based on pasteurisation. Due to his research efforts, CSL Behring launched the first effectively virus-inactivated FVIII concentrate in 1981.

Eligibility:

CSL Behring will set up 5 start-up grants for the cycle 2010. The grants are targeted at young investigators, who hold an MD degree. Applicants with less than 5 years faculty experience in haemostaseology will be preferred. The grants will be available for pre-clinical and/or clinical research in the area of coagulation.

Grant: € 20,000

Upcoming cycle in 2010
- apply now!

Application forms are available from the following address:

CSL Behring GmbH
Att. Dieter Pluennecke
Commercial Development Coagulation
Emil-von-Behring-Strasse 76
35041 Marburg
Germany
T: +49 6421 394191
E-mail: Heimburger.Award@cslbehring.com
or log onto
www.cslbehring.com/ProfHeimburgerAward
online application available

In addition to the application forms, the applicant's current CV and research proposal (one-pager) should be attached. Please submit application to the address above.

Closing date for applications: 9th of October 2009



PLENARY LECTURE

TODAY at 9:45 am — 10:30 am: Grand Ballroom

von Willebrand Factor Assembly and Secretion (J. Evan Sadler)



Dr. J. Evan Sadler will deliver the Brinkhous Memorial Lecture today, speaking on von Willebrand factor assembly and secretion. His state-of-the-art lecture will describe elegant work delineating the structural features underlying the assembly and secretion of multimeric von Willebrand factor. Throughout his career, Dr. Sadler's research has focused on the molecular mechanisms of hemorrhagic and thrombotic disease, particularly von Willebrand disease and thrombotic thrombocytopenic purpura. He has also played many important leadership roles in the field of hemostasis and thrombosis. His distinguished contributions have been recognized by numerous awards and honors, including the Damashek

prize from the American Society of Hematology and the Investigator Recognition Award from the ISTH.

Dr. Sadler is chief of hematology at Washington University School of Medicine, St. Louis. He received his MD and PhD degrees from Duke University, North Carolina. During his hematology fellowship with Earl Davie at the University of Washington, Seattle. Dr. Sadler cloned the gene for von Willebrand factor. The derived complete amino acid sequence of this clinically important protein set the stage for subsequent work establishing the structural basis for the functions of von Willebrand factor and the molecular basis for the different forms of von Willebrand disease.

Kenneth M. Brinkhous (1908-2000) was one of the 16 original members of a committee organized in 1954 as the International Committee for the Standardization of the Nomenclature of the Blood Clotting Factors. The nomenclature of the blood clotting factors that were being discovered was complex and the committee was formed to bring order to the process. In 1969, this committee expanded into the ISTH with 173 members. Dr. Brinkhous was elected as one of the founding board members of the ISTH, and he served as the Secretary General for the first 12 years of the Society's existence. He received the Society's highest honor, the Robert Grant Medal, in 1985 for his outstanding accomplishments and service. His research, for which he received many awards nationally and internationally, focused on blood coagulation mechanisms. Among his many discoveries were the isolation of factor VIII, the development of the first plasma concentrates of factor VIII, the separation of factor VIII and von Willebrand factor, the establishment of hemophilia A, hemophilia B, and von Willebrand animal models and some of the initial attempts at gene transfer in hemophilia. The lecture in Dr. Brinkhous' name was established in 2007 and the initial lecturer was given by Ian Peake.

TODAY at 5:15 pm — 6:00 pm: Grand Ballroom

Stem Cells, Pluripotency and Nuclear Reprogramming (Rudolf Jaenisch)



The ISTH community will hear one of today's Plenary Lectures given by **Dr. Rudolf Jaenisch**. He will speak on his cutting-edge research, and his lecture will offer the ISTH community a look into the fertile world of induced pluripotent stem (iPS) cells. Dr. Jaenisch will share his views on altering somatic cells into a pluripotent embryonic stem cell-like state by using nuclear reprogramming.

Dr. Jaenisch's work is not only biologically intriguing, but also has the potential to impact medical research and medicine by identifying and generating a source of patient-specific cells.

Dr. Jaenisch is an esteemed member of the Whitehead Institute for Biomedical Research and a professor of biology at Massachusetts Institute of Technology. He is the author of more than 400 peer-reviewed articles.

Désiré Collen established a lectureship in 2000 through a contribution to the Society from the Collen Foundation. Collen, who is the founding director of the Molecular Cardiovascular Medicine Group in Leuven, Belgium, and chief executive officer and chairman of the board of ThromboGenics Ltd., a biopharmaceutical drug development company of Ireland, established the lectureship to further the scientific mission of the Society. Eighteen years ago, he also provided a generous donation to start what is now the Reach the World program that supports the travel of young individuals from all over the world to our meetings. Author of more than 620 papers, Collen has research interests in the molecular biology and pathophysiology of hemostasis and thrombosis, the development of novel thrombolytic and antithrombotic agents, the pathogenesis and treatment of atherosclerosis, and gene targeting and gene transfer studies of the cardiovascular system. His team initially developed therapeutic tissue plasminogen activator (t-PA), a drug that revolutionized the treatment approach in patients with thrombotic disorders. Previous lectures endowed by the Collen Foundation were delivered by Judah Folkman, Charles Esmon, Ryozi Nagai and Bruce Furie.



**56th Annual Meeting
Scientific And Standardization Committee
of the ISTH
22 May - 25 May 2010
Cairo - Egypt**

www.ssc2010.org

Message from the President of ISTH 2011



Dear Colleagues and Friends,

It is my great pleasure to announce that the XXIII Congress of the International Society on Thrombosis and Haemostasis and 57th Scientific and Standardization Committee (SSC) Meeting will be held in Kyoto in 2011. Japan's most historic and unique city will welcome you as it hosts this important event.

Kyoto, which was the capital of Japan for more than 11 centuries, combines antique charms and modern conveniences. Bejeweled by more than 2,000 temples and shrines, gardens and promenades, Kyoto is a charming city. In fact, the city is so cherished that many visitors return to this place often. Most of the historical architecture was constructed by nobles and samurais to demonstrate their power and their spiritual beliefs. It was their self-expression. Thus, not only are the buildings splendid and gorgeous, but they are also serene and soulful. This is what makes Kyoto unforgettable.

Regarding the scientific programs, the members of the Japanese Society on Thrombosis and Haemostasis, along with our international colleagues in ISTH, are making every effort to make it attractive. Above all, however, we are looking forward to your scientific contribution to the constructive discussion. In addition to the scientific and educational programs, Kyoto will charm you with its rich culture.

Once in a lifetime, why not visit Kyoto?
Yokoso (Welcome)!

Professor Yasuo Ikeda, MD

President

*XXIII Congress of the International Society on Thrombosis and Haemostasis
57th SSC Meeting*

Guideline Development: Quality of Evidence is Key

Translating research into practice through clinical guidelines is a process that takes time and is heavily dependent on the quality of evidence.

"We are interested in assessing quality of evidence with reasons which may affect it, separately from the bounds of benefits and harms ... called the strength of recommenda-

offered insight into the process and reviewed how recommendations are made according to the widely accepted Grades of Recommendation Assessment, Development and Evaluation Standardization system.

According to Dr. Jaeschke, the most important and unexpected challenge of developing clinical practice guidelines is identifying the questions, both

be able to interpret clinical data appropriately." Clinicians should be the frontline decision makers in the process, he said.

Incorporating Guidelines into Practice

Gordon Lowe, MD, professor of vascular medicine at the University of Glasgow, Scotland, said methods are needed for predicting which people are at highest risk for arterial and venous thromboembolism as well as recommendations for management. Evidence-based consensus on clinical risk predictors, lifestyle advice, medication to reduce the risk, and baseline risk predictors are available.

Data are still needed, however, about whether emerging risk factors improve risk stratification and which of those risk factors predict benefit and harm from antithrombotics.

"In many cases our current guidelines have an excellent evidence base; in others, the guidelines have been not quite as strong. They were based on the evidence at the time, but they continuously need revision because in many areas of our practice and in our guideline recommendations, we need a more reliable evidence base," he said.

Dr. Lowe cited two examples of

guidelines that need more evidence: use of aspirin for primary prevention of coronary heart disease and stroke, and use of compression stockings for stroke prevention.

More stakeholders should be included in the guideline development process, including primary care physicians, nurses, pharmacists and allied professionals in medicine and public health.

"While specialist society guidelines are where it all started, for major conditions including cardiovascular disease, these guidelines will be replaced in time in each country by national guideline organizations that include all the stakeholders," he said.

“While specialist society guidelines are where it all started, for major conditions including cardiovascular disease, these guidelines will be replaced in time in each country by national guideline organizations that include all the stakeholders.”

— Gordon Lowe, MD

tions ... that are heavily influenced by our values and preferences," said **Roman Jaeschke, MD**, clinical professor in the department of medicine at McMaster University.

The session on Saturday was a follow-up to a meeting held by the ISTH Scientific and Standardization Committee in London earlier this year that explored the development of practice guidelines.

As a contributor to clinical practice guideline development, Dr. Jaeschke

descriptive and actionable, that will lead to collection of quality evidence and result in recommendations.

Quality evidence, which indicates the level of confidence that estimate effects are true, is the key to developing both strong and weak recommendations.

"In order to make practice guidelines, you cannot be an expert in methodology. You have to have people with 10 to 20 years of experience in the field; methodologists will never



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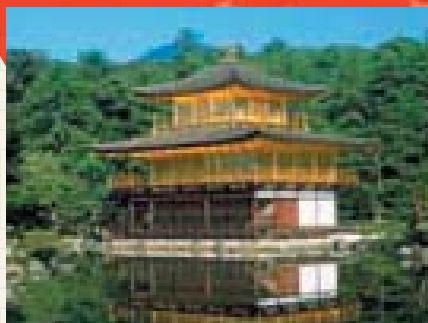
KYOTO JAPAN

XXIIIrd Congress of the International Society on Thrombosis and Haemostasis

57th Annual SSC Meeting

Venue : ICC Kyoto (Kyoto International Conference Center)

Dates : **July 23-29, 2011**



See You in Kyoto 2011



www.isth2011.com

Warfarin Efficacious for Stroke Prevention in Atrial Fibrillation

Warfarin has been shown to reduce stroke risk without a significant increase in major bleeding events in patients with atrial fibrillation.

According to **Elaine M. Hylek, MD, MPH**, associate professor in medicine at Boston University Medical Center, 9 million people in the United States will have atrial fibrillation by 2020, an epidemic of the new millennium. Morbidity and mortality associated with atrial fibrillation is vast worldwide, accounting for 15% of all strokes.

These statistics point to the value of therapeutic prevention of stroke in atrial fibrillation. According to Dr. Hylek, the efficacy of warfarin has been demonstrated in clinical trials with small patient populations and no comparative drugs. Although there were questions about the proper INR therapeutic range of warfarin, the overall reduction in the stroke risk was 68% across all of the trials.

Predicting, Preventing Stroke

In her presentation on Sunday, Dr. Hylek recommended use of the CHADS₂ Score to predict which patients are at risk for stroke, which ones are eligible for warfarin therapy and

to determine the appropriate dosage. The scoring system categorizes risk based on several patient characteristics: history of congestive heart failure, history of hypertension, age, history of diabetes, previous stroke symptoms or transient ischemic attack.

In 2006, the American College of Cardiology, the American Heart Association and the European Society of Cardiology updated their practice guidelines, and recommended aspirin for patients with no risk factors, aspirin or warfarin for those with a CHADS₂ score of one, and warfarin for those with a CHADS₂ score >1.

“Despite the dramatic efficacy of an almost 70% risk reduction, around the world in country after country when you look at registries, about half of high-risk patients with atrial fibrillation receive warfarin therapy,” Dr. Hylek said.

In addition, data have demonstrated that warfarin use does not dramatically increase as CHADS₂ scores increase. This could be due to fear

of anticoagulation in the elderly, the perceived bleeding risk, lack of proximity to INR monitoring sites, patient preference and the inherent difficulties of warfarin, she said.

Dr. Hylek noted randomized trials with highly selected, closely monitored patient populations as caveats to published data on hemorrhage risk, despite a demonstrated 2% to 3% incidence of major bleeding events associated with warfarin. Data have also shown elderly patients to be at highest risk for bleeding.

Given these risks, optimizing treatment benefit in elderly patients with atrial fibrillation is important. Data from three pooled trials of aspirin vs. placebo demonstrated a 21% relative risk reduction in stroke. According to Dr. Hylek, aspirin is not efficacious and is not harmless.

Data from the ACTIVE trials demonstrated that warfarin was superior to clopidogrel plus aspirin. Adding clopidogrel to aspirin reduced major vascular events and stroke risk but increased major hemorrhage in patients unsuitable for vitamin K antagonists.

The rate of ischemic stroke significantly surpasses the rate of intracranial hemorrhage associated with oral anticoagulation therapy, she said.



Elaine M. Hylek, MD, MPH

ISTH 2009 BY THE NUMBERS

Total Registered Delegates . . .	7,733
Countries represented	99
Invited speakers	128
Oral Abstract Presentations	
<i>Late Breaking</i>	5
<i>Oral Communications</i>	650
<i>Abstract Symposia Talks</i>	48
<i>Presidential Abstracts</i>	6
TOTAL	709
Posters	2,477
Developing World	
Scientist Awards	80
Young Investigator Awards	180

“It would be remiss not to mention and emphasize the importance of blood pressure control,” she also said. “If you are prescribing anticoagulants to older patients, it is critical that the blood pressure be vigilantly and closely monitored because it will reduce not only hemorrhagic stroke but also ischemic stroke, which has been shown in several studies.”

New Risk Loci for Cardiovascular Disease Identified

Using genome-wide association studies, researchers from the Wellcome Trust Case Control Consortium in the United Kingdom have identified 12 loci that confer risk for cardiovascular disease and myocardial infarction.

Willem H. Ouwehand, MD, PhD, FRCPath, from the University of Cambridge, NHS Blood & Transplant, Cambridge, and the Wellcome Trust Sanger Institute, presented information on the discovery of genes associated with myocardial infarction on Tuesday.

“We have made a long journey, and over a three-year period we have nailed down a substantial number of new risk loci that confer a small risk for disease in patients with cardiovascular disease,” Dr. Ouwehand said.

The Wellcome Trust Case Control Consortium was established in 2005 and includes 50 research groups in the United Kingdom. Using genotyping, the group identified 24 novel association signals for seven common diseases,

including coronary artery disease.

“You might say, why should we look for genes that are conferring small risks for CVD? The answer is pretty clear: Cardiovascular disease remains the No. 1 killer in Western society and is expected in 10 years to be the leading cause of death at the global scale,” he said.

Genetic Link to Cardiovascular Risk

Dr. Ouwehand and colleagues identified an association signal for coronary artery disease on chromosome 9. A subsequent combined analysis of two genome-wide association studies demonstrated that chromosome 9 was the site of a massive association signal and identified seven loci associated with CAD.

Next, Dr. Ouwehand and his colleagues replicated their results in a case-control study that demonstrated that of the seven genes from the combined analysis, at least four associations were confirmed.

The group then turned their focus to platelet function. They determined that COMMD7, an inhibitor of NF-κB and not previously known to be operational in platelets, influenced platelet function and may be

botic phenotype and silencing of COMMD7 and LRRFIP1 resulted in reduced thrombus formation.

Dr. Ouwehand and colleagues then looked at platelet volume and count.

“Platelet count and platelet volume are negatively correlated in the population at large,” he said. “And, more importantly, platelet volume is an



“...platelet volume is an independent risk factor for poor outcome after CAD events.”

— Willem H. Ouwehand, MD, PhD, FRCPath

a risk factor gene for CVD. Association with CVD of two other genes, LRRFIP1 and GTF2A2, identified by platelet function studies did not reach statistical significance, according to Dr. Ouwehand.

Using zebra fish, the group determined the function of the three genes on thrombus formation. Silencing of GTF2A2 resulted in a prothrom-

independent risk factor for poor outcome after CAD events.”

By genotyping data for 5,000 individuals, the group identified 12 loci that regulated platelet volume and three loci that regulated platelet count. At chromosome 12, the researchers identified a single nucleotide polymorphism that consistently conferred risk for CVD (OR=1.15).



ISTH 2009 DAILY PICTURES



HIT: Diagnosis, Treatment, and Immunology

Heparin-induced thrombocytopenia is caused by FcγRIIa mediated platelet activation, according to **Andreas Greinacher, MD**, who gave the Pia Glas-Greenwalt Memorial Lecture on Wednesday morning.

"HIT is a misdirected host defense," said Dr. Greinacher, head of the department of transfusion medicine and immunohematology at the University of Greifswald, Germany. "Our immune system thinks our platelets are bacteria and have to be destroyed."

Condition is Overdiagnosed

In his overview of HIT, Dr. Greinacher cautioned that the condition is "notoriously overdiagnosed" and said that it is a clinico-pathological syndrome. Both clinical symptoms and antibodies must be present for correct diagnosis.

The onset of HIT is typically within two weeks of heparin administration. The relative decrease in platelet count falls generally at day five; if the count decreases by more than 50%, "it is HIT unless proven otherwise,"

Dr. Greinacher said.

Platelet count monitoring should not begin until day five and should continue through day 10. If the platelet count falls in the first four days it is usually not HIT, he said.

Complications associated with HIT are venous thrombosis, including DVT and embolism, the most



“HIT is a misdirected host defense. Our immune system thinks our platelets are bacteria and have to be destroyed.”

— **Andreas Greinacher, MD**

frequent complications; followed by arterial thrombosis, including lower limb arterial thrombosis, stroke and acute myocardial infarction; skin lesions at the heparin injection site; acute systemic reactions following heparin infusion; and disseminated intravascular coagulation, the least frequent complication.

For diagnosis, use of antigen tests, which detect IgG, IgM and IgA; and a function test to detect IgG, the current "gold standard" method is optimum.

Even without thrombosis, treatment should begin at the time of "high clinical suspicion, with a lab test being used to confirm the diagnosis

retrospectively," Dr. Greinacher said.

It is most dangerous to simply suspend heparin. Patients need an alternative anticoagulant. Those most strongly recommended are danaparoid, lepirudin, and argatroban.

The risk of HIT depends on the patient group, with reduced HIT risk in patients treated with low molecular

weight heparin rather than unfractionated heparin after a major surgical procedure.

What is the Antigen in HIT?

According to Dr. Greinacher, recent research has indicated that HIT seems to be a "very well-defined immune response."

Platelet Factor 4 is the involved protein, the "key player," he said. The positively charged PF4 aligns with the negatively charged heparin. Antibodies enhance phagocytosis of bacteria.

"Our immune system thinks that our platelets are all bacteria and have to be destroyed," he said.

Why venous thrombosis is so frequent in HIT is not yet known. However, researchers can now "use this very well-defined immune response that we know happens within five to 10 days of heparin use to dissect the immunology of this immune response in humans."

ERRATUM:

On page 6 of Wednesday's paper, pictures of **Drs. Andreas Greinacher and Shaun P. Jackson** were reversed in the Plenary Lecture previews.

Factor XI Activation Essential for Hemostasis In Vivo

Factor XI at low tissue factor levels is essential in generating an adequate ambient level of thrombin to allow embryonic development, according to data from a



Henri M. H. Spronk, PhD

study presented Tuesday at the Presidential Plenary Session.

"Activation of Factor XI by Factor IIa exists in vivo and is essential for he-

mostasis at low tissue factor levels," said **Henri M. H. Spronk, PhD**, department of internal medicine, laboratory for clinical thrombosis and hemostasis, Cardiovascular Research Institute Maastricht, Maastricht University, said during his presentation.

Dr. Spronk and colleagues examined the feedback activation of Factor XI in plasma and genetically altered mice. Using fluorescence-based assays, the researchers determined that particle-bound throm-

bin caused thrombin generation in plasma, both in the absence of tissue factor and in the presence of active site inhibited Factor VIIa, Dr. Spronk explained.

Thrombin did not activate Factor XII and thrombin generation was almost eliminated by an anti-Factor XIa antibody and in Factor XI-deficient plasma. However, surface-bound thrombin induced complex formation of Factor XI with its C1 inhibitor, even in Factor XII-deficient plasma, in a time- and dose-dependent manner.

The researchers then used tissue factor deficient mice with reduced thrombin formation to determine whether thrombin-driven Factor XI

activation was important for hemostasis in vivo. Mice with low tissue factor were crossed with mice that were Factor XII, Factor XI or Factor IX deficient.

Intrauterine death of embryos due to hemorrhage occurred in mice with double deficiency in tissue factor and either Factor IX or Factor XI. Conversely, the bleeding phenotype among tissue factor and Factor XII-deficient mice was unchanged from low tissue factor animals, Dr. Spronk said.

"Looking at these data revealed that the lethality of low-level tissue and deficiency of Factor XI were due to peritoneal bleeding during the development of these animals," he said.

Holmberg

(continued from page 1)

the prolonged action of long-acting recombinant Factor VIIa by thromboelastography. The researchers injected mice with 20 mg/kg of recombinant Factor VIIa or long-acting recombinant Factor VIIa. At 0.8, one, six, and 24 hours they took citrate stabilized blood samples and then determined the thromboelastography profile.

The effect of long-acting recombinant Factor VIIa on the thromboelastography response persisted for 24 hours compared with recombinant Factor VIIa, which was only detected for eight hours.

Next, they measured length of action by blood loss in a tail bleeding model. Again the mice were injected with 20 mg/kg of recombinant Factor VIIa or long-acting recombinant Factor VIIa. Blood loss was determined after 30 minutes, 0.8, six, 24 and 48 hours.

"Both recombinant Factor VIIa and a long-acting derivative significantly decreased the blood loss compared to the vehicle treated animals," Holmberg said. "After six hours we have a significant decrease in blood loss for the long-acting treatment compared to recombinant Factor VIIa. "This shows that not only do we have a long half life, we also have a long duration of action," she said.

Jiang

(continued from page 1)

Bay7 required an approximate five-fold lower dose to achieve acute efficacy. "Bay7 significantly prolonged prophylactic efficacy relative to recombinant Factor VIIa in hemophilic mice," Dr. Jiang said.



Haiyan Jiang, PhD

"At one hour

post-dosing, it was necessary to raise the dose to 1 mg/kg of recombinant Factor VIIa in order to achieve survival greater than 50%, whereas Bay7 achieved survival of about 80%.

"At six hours post-dosing, Bay7 had sustained efficacy, allowing more than 50% of animals to survive," Dr. Jiang said. "The same prophylactic efficacy was achieved as with a fivefold lower dose of Bay7 relative to recombinant Factor VIIa. At the same dose, Bay7 achieved a sixfold longer efficacy than recombinant Factor VIIa."