Front cover image: Stained glass window at the Marc Chagall Museum, Nice, France which illustrates the 'Creation of the World'. © Philip Baird
Welcome

The annual International Symposium on Thromboembolism presents clinicians with a prime opportunity to update themselves on the latest developments in thromboembolism.

Organised by the Thrombosis Research Institute in London, and now in its fifteenth year, the meeting is once again bringing together globally recognised leaders and experts from the rapidly developing field of thromboembolism, for what promises to be a most informative and rewarding conference.

This year, the two day programme, to be held in Cannes, France, includes a stimulating range of in-depth plenary sessions as well as interactive workshops. In addition to participating in the lively discussions and ‘Meet the Expert’ sessions, delegates will have the opportunity to meet and network with colleagues.

Highlights of the programme include the varied plenary sessions as well as the ‘Meet the Expert’ sessions examining how to predict those at risk of recurrent VTE as well as ‘Interactive Workshops’ considering amongst other subjects, ‘Antithrombotic therapy: emerging issues’ and ‘cancer-associated thrombosis’.

I hope that the imaginative scientific and social programmes will provide you with a memorable experience over the next few days in Cannes.

With best wishes

Professor Ajay K Kakkar
Chairman
**Day One**  
**Friday 10 October 2008**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.45 – 11.00</td>
<td>Welcome</td>
<td>Welcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A.K. Kakkar, UK</td>
</tr>
<tr>
<td>11.00 – 13.00</td>
<td>Plenary Session I</td>
<td>Update on venous thromboembolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chairs: V.V. Kakkar, UK; M.M. Samama, France</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidemiology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R. White, USA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention and treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. Haas, Germany</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The patient safety perspective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A.K. Kakkar, UK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Generic LMWHs – where are we?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>J. Walenga, USA</td>
</tr>
<tr>
<td>13.00 – 14.15</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>14.15 – 15.45</td>
<td>Plenary Session II</td>
<td>Update on arterial thromboembolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chairs: S. Haas, Germany; A.G.G. Turpie, Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute coronary syndromes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F. Verheugt, The Netherlands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticoagulation for atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>J. Ansell, USA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antiplatelet therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A.G.G. Turpie, Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D. Bergqvist, Sweden</td>
</tr>
<tr>
<td>15.45 – 16.15</td>
<td>Tea</td>
<td></td>
</tr>
</tbody>
</table>
## Day Two  
**Saturday 11 October 2008**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.00 – 10.00</td>
<td>Meet the Expert Sessions</td>
<td></td>
</tr>
<tr>
<td>I.</td>
<td>Predicting those at risk of recurrent VTE</td>
<td>Léger</td>
</tr>
<tr>
<td>II.</td>
<td>VTE prophylaxis for medical patients in the community – is there a role?</td>
<td>Picasso</td>
</tr>
<tr>
<td>III.</td>
<td>The new ACCP guidelines 2008</td>
<td>Chagall</td>
</tr>
<tr>
<td>IV.</td>
<td>Diagnosis of DVT and PE</td>
<td>Matisse</td>
</tr>
<tr>
<td>10.00 – 10.15</td>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td>10.15 – 12.45</td>
<td>Interactive Workshops: emerging issues</td>
<td>Ebéne</td>
</tr>
<tr>
<td>1.</td>
<td>Antithrombotic therapy: emerging issues</td>
<td></td>
</tr>
<tr>
<td>Chairs:</td>
<td>V.V. Kakkar, UK; A. Takada, Japan</td>
<td></td>
</tr>
<tr>
<td>I.</td>
<td>Obesity surgery</td>
<td>J. Arcelus, Spain</td>
</tr>
<tr>
<td>II.</td>
<td>Thromboembolism in medical patients after hospital discharge – how long?</td>
<td>G. Merli, USA</td>
</tr>
<tr>
<td>III.</td>
<td>Cardiometabolic syndrome</td>
<td>J. Harenberg, Germany</td>
</tr>
<tr>
<td>2.</td>
<td>Clinical trials in VTE: where are we going?</td>
<td>Léger</td>
</tr>
<tr>
<td>Chairs:</td>
<td>A.K. Kakkar, UK; H. Büller, The Netherlands</td>
<td></td>
</tr>
<tr>
<td>I.</td>
<td>Should asymptomatic distal DVT count as an endpoint?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>D. Bergqvist, Sweden</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>C. M. Samama, France</td>
<td></td>
</tr>
<tr>
<td>II.</td>
<td>The relevance of arterial thromboembolism in VTE prophylaxis studies</td>
<td></td>
</tr>
<tr>
<td>B. Eriksson, Sweden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Cancer-associated thrombosis</td>
<td>Picasso</td>
</tr>
<tr>
<td>Chairs:</td>
<td>J. McVey, UK; A. Falanga, Italy</td>
<td></td>
</tr>
<tr>
<td>I.</td>
<td>Blood coagulation and cancer - coagulation protease signaling</td>
<td>W. Ruf, USA</td>
</tr>
<tr>
<td>II.</td>
<td>Predicting those at risk of VTE in cancer</td>
<td>C. Francis, USA</td>
</tr>
<tr>
<td>III.</td>
<td>Unusual cases of cancer-associated thrombosis</td>
<td>H. Liebman, USA</td>
</tr>
</tbody>
</table>
4. Atrial fibrillation
   Chairs: S. Schulman, Canada; A.G.G. Turpie, Canada
   I. What is wrong with vitamin K antagonists?
      K. Bauer, USA
   II. What is the burden of disease?
      G. Lip, UK
   III. What is the role of antithrombotic and fibrinolytic therapy in the management of stroke?
      G. Agnelli, Italy

5. Women’s health and thrombosis
   Chair: S. Haas, Germany
   I. Pregnancy
      R. Bauersachs, Germany
   II. Menopause
      B. Brenner, Israel

12.45 – 14.00 Lunch

14.00 – 15.30 Plenary Session III
   Cancer-associated thrombosis
   Chairs: H. Büller, Netherlands; G. Agnelli, Italy
   Prevention
      P. Prandoni, Italy
   Treatment
      C. Francis, USA
   A biological target for cancer therapy?
      A.K. Kakkar, UK

15.30 – 16.15 Plenary Session IV
   Debate
   Chairman: A.K. Kakkar, UK
   Factor Xa is a superior target to factor IIa for antithrombotic therapy
   For
      H. Büller, Netherlands
   Against
      S. Schulman, Canada

16.15 – 16.30 Closing Remarks
   A.K. Kakkar, UK
Ajay K Kakkar

Barts and the London School of Medicine and Dentistry
Queen Mary College, University of London, UK

Ajay Kakkar is Professor and Head of the Centre for Surgical Science and Dean for External Relations at Barts and the London School of Medicine and Dentistry, Queen Mary, University of London; he is also a Consultant Surgeon at St Bartholomews Hospital London and Director of the Thrombosis Research Institute, London, UK. He received his medical education at King’s College Hospital Medical School, University of London, and was awarded an MBBS in 1988, and a PhD in 1998. He was made a fellow of the Royal College of Surgeons of England in 1992.

His awards include Hunterian Professor, Royal College of Surgeons of England 1996, the David Patey Prize, Surgical Research Society of Great Britain and Ireland 1996, the Knoll William Harvey Prize, International Society on Thrombosis and Haemostasis 1997 and the James IV Association of Surgeons Fellow 2006.

Professor Kakkar’s research interests are in the prevention and treatment of venous thromboembolic disease and cancer-associated thrombosis.
Vijay V Kakkar

President, Thrombosis Research Institute, London, United Kingdom

Vijay Kakkar is Emeritus Professor at the University of London, UK, and Founder-Director of the Thrombosis Research Institute, London, United Kingdom.

He graduated from Vikram University, Ujjain, India, in 1960 and qualified as Fellow of the Royal College of Surgeons of Edinburgh and England in 1964.

Professor Kakkar has held a number of appointments at King's College, University of London. He has been the recipient of a number of distinctions and awards, including a Hunterian Professorship from the Royal College of Surgeons, Visiting Professor of Harvard University, Honourable Fellowship of the Association of Surgeons of India, a lifetime achievement award from the Union of Angiology and most recently an Honourary Doctor of Science from the Loyola University of Chicago. He is a member of a number of professional societies and was a founding member of the British Society of Haemostasis and Thrombosis. His publications include over 650 original articles, six books and contributions to over 50 texts.

In 1989, Professor Kakkar first established the Thrombosis Research Institute as a national resource to provide a multi-disciplinary environment dedicated to the study of thrombosis and related disorders.
Sylvia Haas

Technical University Munich, Germany

Sylvia Haas is Professor of Medicine and had been Director of the Haemostasis and Thrombosis Research Group at the Institute for Experimental Oncology and Therapy Research, Technical University of Munich, Germany for almost 30 years. Professor Haas received her medical degree from the University of Freiburg and began her training in paediatric haematology and oncology at the Dr von Haunersche Kinderspital, University of Munich. She continued her training in internal medicine at the Technical University in Munich and received full professorship after having established the Haemostasis and Thrombosis Research group at the Institute for Experimental Surgery, now the Institute for Experimental Oncology and Therapy Research.

Her scientific focus is on the development of new antithrombotic therapies, laboratory monitoring of anticoagulants, biomarkers and tumour-associated thrombosis. Professor Haas is involved in several clinical trials, in particular trials in prevention and treatment of arterial and venous thromboembolism. She also is in charge of various integrated teaching programmes.

Professor Haas is a member of several professional societies, including the International Society on Thrombosis and Haemostasis, the International Society of Angiology, the European Society for Surgical Research, and the German Societies of Surgery, Angiology, and Thrombosis and Haemostasis Research. She is a fellow of the Southern African Society of Thrombosis and Haemostasis and is also a member of the editorial board for peer-reviewed journals, including Current Hematology Reports, International Angiology and Clinical and Applied Thrombosis/Hemostasis.
Mark Levine

McMaster University, Hamilton, Ontario, Canada

Mark Levine is Chair and Professor in the Department of Oncology at McMaster University, Hamilton, Ontario, Canada. He holds the Buffett Taylor Chair in Breast Cancer Research at McMaster University. He is a past recipient of the O. Harold Warwick Prize (1999) from the National Cancer Institute of Canada. Dr Levine received his medical degree from McGill University, Montreal, Quebec, Canada, and completed his residency in internal medicine at McMaster University. He completed his training in haematology and oncology at Duke University Medical Centre, Durham, North Carolina, USA. In addition, Dr Levine received a master’s degree in clinical epidemiology and biostatistics from McMaster University.

In 1982, Dr Levine became a member of both the Faculty of Health Sciences at McMaster University, and a medical oncologist at the Hamilton Regional Cancer Centre (now known as the Juravinski Cancer Centre - Hamilton Health Sciences). He was CEO of the Cancer Centre between 1992 and 1999. Over the past 25 years he has been an active researcher in clinical trials and health services research. His focus is in the areas of breast cancer and venous thromboembolism. A number of the trials he has conducted have impacted healthcare in both Canada and internationally. He helped establish the Ontario Clinical Oncology Group (OCOG) in 1982. Dr Levine has over 220 publications in peer-reviewed journals and has brought much research funding to McMaster. He is Director of the Clinical Trials Methodology Group (CTMG) of the Henderson Research Centre. He was Chairman of Health Canada’s Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Dr Levine is currently an Associate Editor for the Journal of Clinical Oncology.
Giancarlo Agnelli

Department of Internal Medicine, Division of Internal and Cardiovascular Medicine – Stroke Unit, University of Perugia, Perugia, Italy

Giancarlo Agnelli is Professor of Internal Medicine at the University of Perugia, and Director of the Division of Internal and Cardiovascular Medicine – Stroke Unit at the University of Perugia, Italy.

He received his degree in medicine and surgery from the University of Perugia in 1975, where he was subsequently appointed Assistant Professor at the Institute of Internal Medicine. He followed this with positions as Research Fellow at the Department of Medicine and Clinical Fellow of Internal Medicine at McMaster University, Hamilton, Ontario, Canada. In 1986 he was appointed Research Fellow at the Division of Thrombosis and Haemostasis, Department of Haematology, at the University of Amsterdam, The Netherlands. In 1988, he was appointed Associate Member of the Hamilton Civic Hospital Research Centre, McMaster University, and in 1992 Associate Professor of Internal Medicine at the Institute of Internal and Vascular Medicine, University of Perugia.

Dr Agnelli is a member of the Conference on Antithrombotic Therapy of the American College of Chest Physicians, and the Italian Society on Thrombosis and Haemostasis.

Dr Agnelli has authored more than 300 publications in peer-reviewed international journals, and is a member of the editorial boards for Thrombosis Research, Haemostasis, Journal of Cardiovascular Medicine, Acta Cardiologica, and Trends in Medicine. He also is a reviewer for the New England Journal of Medicine, the Lancet, Circulation, Blood, Cardiovascular Research, Journal of Thrombosis and Haemostasis, and the Journal of the American College of Cardiology.
Jack E Ansell, MD, is the Chairman of the Department of Medicine at Lenox Hill Hospital. Dr Ansell received his medical degree from the University of Virginia School of Medicine and completed his medical residency at Tufts New England Medical Center in Boston, Massachusetts. Dr Ansell then completed a fellowship in Haematology at Boston University and in Haematology/Hemostasis at Boston’s Veterans Administration Hospital.

Dr Ansell is an internationally recognised expert in the field of hemostasis and thrombosis. He has well over 200 publications including original research, reviews, editorials chapters, and books. He serves as an associate editor for the Journal of Thrombosis and Thrombolysis and Current Clinical Pharmacology and as an editorial consultant for such journals as the New England Journal of Medicine, Blood, Journal of Thrombosis and Haemostasis, and Circulation.

Dr Ansell’s main areas of research focus on the clinical problems of thrombosis, thrombotic disorders, and antithrombotic therapy. He has had a continued involvement in the application of new modes of delivering and monitoring anticoagulants, particularly in the management of oral anticoagulant therapy and has been increasingly involved in the clinical study of new oral anticoagulants.

Dr Ansell is the founder and immediate past Chair of the Anticoagulation Forum, a network of anticoagulation clinics throughout North America, Co-Founder and Past President of the International Self-Management Association for Oral Anticoagulation and he is currently Chair of the Medical and Scientific Advisory Board of the National Alliance for Thrombosis and Thrombophilia, a patient advocacy group. He is a member of a number of professional organizations including the American College of Physicians (Fellow), the American Society of Hematology, the International Society of Thrombosis and Hemostasis, the American Heart Association (Fellow),
and the American Medical Association. Dr Ansell serves as the Chair of two consensus committees of the American College of Chest Physicians involved in establishing national guidelines on antithrombotic therapy. These include the topics of: Managing Oral Anticoagulation and The Perioperative Management of Antithrombotic Therapy.
Juan I Arcelus

Department of Surgery, University of Granada Medical School, Hospital Universitario Virgen de las Nieves, Granada, Spain

Juan Arcelus graduated in medicine from the University of Granada Medical School, Granada, Spain, in 1982 and obtained a PhD, specializing in thrombosis, from the same university in 1998. Having completed his residency in general and gastrointestinal surgery at the University Hospital of Granada, Dr Arcelus served a research fellowship in the Department of Surgery at Northwestern University, Chicago, Illinois, USA, from 1989 to 1992. He was Associate Director of the Thrombosis and Hemostasis Group at Evanston Hospital, Evanston, Illinois, from 1990 to 1992, and participated actively in a number of studies conducted at Loyola University Medical Center in Maywood, Illinois.

Dr Arcelus became Professor of Surgery at the University of Granada Medical School in 2002 and practices as an attending staff member in the Department of Surgery of the Hospital Universitario Virgen de las Nieves, also in Granada. He acts as visiting professor to several hospitals and universities in Spain and abroad and has delivered over 150 lectures in several countries. His main research interests include the diagnosis, prevention, treatment, and follow-up of Venous Thromboembolism (VTE) in general and in orthopaedic-surgery patients, both in the hospital and as outpatients.

Dr Arcelus has been a Core Group member of the INvestigators Against ThromboEmbolism (INATE) educational programme since 2001 and has an active role in the INATE website (www.inate.org). For the past seven years, he has been actively involved in the Spanish Computerised Registry of Patients with Venous Thromboembolism (RIETE). He is also patron of the Spanish Foundation for the Study of Thromboembolism (FUENTE) and an active member of the International Surgical Thrombosis Forum (ISTF) as well as of the European Task Force for Sharing Expertise in Thrombosis (ETFET). He is the current coordinator of the Working
Group on Thrombosis of the Spanish Surgical Association. A member of numerous societies and of the Royal Academy of Medicine in Granada, Dr Arcelus has presented over 200 abstracts at international meetings, published many papers in international peer-reviewed journals, and has written several book chapters on subjects related to VTE.
Kenneth A Bauer

Beth Israel Deaconess Medical Center, Boston, USA

Kenneth Bauer is Professor of Medicine, Harvard Medical School. His hospital positions include Chief, Haematology Section, VA Boston Healthcare System, and Director, Thrombosis Clinical Research at the Beth Israel Deaconess Medical Center. Dr Bauer received his medical degree from Stanford University School of Medicine in Stanford, California. He completed his residency in medicine at the University of Chicago Hospitals and Clinics in Illinois. He was a Fellow in Medical Oncology and a Clinical/Research Fellow in the Division of Thrombosis and Hemostasis at Dana Farber Cancer Institute and was also a Clinical/Research Fellow in the Haematology-Oncology Division at Beth Israel Hospital, Boston, Massachusetts.

Dr Bauer’s research interests include development and clinical evaluation of sensitive new assays for the detection of hypercoagulable states, definition and elucidation of the mechanisms leading to the development of a prethrombotic state, and clinical evaluation of new antithrombotic drugs. Dr Bauer previously served as Chairman of the Council of the International Society on Thrombosis and Haemostasis (ISTH) and was Chairman of the Subcommittee on Predictive Haemostatic Variables in Vascular Diseases of the ISTH. He is Vice-President and Scientific Program Chair (Clinical) for the XXII ISTH Congress to be held in Boston in July 2009. Dr Bauer has published over 200 original reports, reviews, and book chapters.
Rupert Bauersachs
Johann-Wolfgang-Goethe-Universität, Frankfurt, Germany

Rupert Bauersachs is Professor of Internal Medicine and Director of the Max-Ratschow Klinik for Vascular Medicine at the Klinikum Darmstadt. He received his medical degree from the University of Munich. He was a Postdoctoral Fellow at the Department of Pharmacology, University of Munich, and, subsequently, a Research Fellow of the American Heart Association in the Department of Physiology at the University of Southern California. He completed his residency in Internal Medicine at the München-Bogenhausen Hospital and the Universities of Mainz and Frankfurt. Professor Bauersachs has been certified for Internal Medicine, Angiology, Haemostaseology, Diabetology, Phlebology, and Aviation Medicine, and he is a Fellow and National Delegate of the International Union of Angiology. In 1999, he became faculty member of the University of Frankfurt and head of the department of Angiology. He was one of the founding members of the first German University Vascular Center. In 2003, he was appointed Director of the Max-Ratschow Klinik for Vascular Medicine. Professor Bauersachs is a council member for the German Societies of Angiology and Microcirculation, and is active in various other societies for Vascular Medicine and Thrombosis and Hemostasis.

His interests are venous thromboembolism, thrombophilia, heparin-induced thrombocytopenia, antithrombotic agents and microcirculation. Professor Bauersachs has published more than 50 original papers, and his scientific work has been awarded several prizes.
David Bergqvist
Uppsala University Hospital, Uppsala, Sweden

David Bergqvist studied medicine in Uppsala, Sweden and his PhD thesis examined hemostatic plug formation and stability in the rabbit mesenteric microcirculation. Professor Bergqvist completed his surgical training at the county hospital in Skövde, Sweden and became Associate Professor of surgery at the University of Lund, Sweden in 1979. He has been Professor of Vascular Surgery and Head of Vascular Surgery at the University Hospital, Uppsala, Sweden since 1993.

Professor Bergqvist has authored around more than 700 original articles, several reviews and book chapters and three text books. His main areas in research deal with prophylaxis of post-operative venous thromboembolism, epidemiological and pathogenetic aspects on aortic aneurismal disease and formation of pseudointimal lesions with arterial reconstructive surgery and balloon trauma. He is an honorary member of the Royal Australiasian College of Surgeons Division of Vascular Surgery, Hellenic Angiological Society, American Venous Forum, the Vascular Surgical Society of Great Britain and Ireland, European Society for Vascular Surgery and the Swedish Society for Vascular Surgery.
Benjamin Brenner, MD is Professor of Medicine (Haematology) and Caster Chair in Leukemia Research at the Bruce Rapport Faculty of Medicine, Technion Israel Institute of Technology in Haifa, Israel. He qualified as a medical doctor from the Israel Institute of Technology in 1981. Following residency in internal medicine and haematology at the Rambam Medical Center from 1981 to 1986, and a postdoctoral research fellowship in fibrinolysis at the University of Rochester, New York, USA, from 1987 to 1988, he returned to Haifa as a senior hematologist and was appointed as Director of the Thrombosis and Hemostasis Unit and Deputy Director of the Haematology Institute at Rambam Medical Center in 1994.

Dr Brenner’s research interests over the years have included: fibrinolysis and thrombolysis, inherited bleeding disorders and studies of new antithrombotics and hemostatic agents. His studies in the field of inherited and acquired thrombophilia concentrated on procoagulant in leukemia and solid tumors and on the effect of combined thrombophilic defects on the expression of thrombosis. His main area of interest focuses on issues related to thrombosis in women, in particular the association of thrombophilia with pregnancy loss and late gestational vascular complications. He has recently published on prevention of pregnancy loss in women with thrombophilia by low-molecular-weight heparin (LMWH) and has recently conducted the LIVE-ENOX trial, a multi-center study using two dose regimens of enoxaparin in this indication.
Harry R Büller, MD, is Professor of Internal Medicine, specializing in Vascular Medicine and is Chairman of the Department of Vascular Medicine at the Academic Medical Center in Amsterdam, The Netherlands.

Dr Büller earned his MD and PhD at the University of Amsterdam. After graduating, he completed his research fellowship in hemostasis and thrombosis in the Departments of Medicine and Clinical Epidemiology and Biostatistics at McMaster University in Hamilton, Ontario, Canada.

Dr Büller has authored and co-authored more than 490 scientific articles concerning topics in his field. He has been Co-Chairman for the Amsterdam Institute for Cardiovascular Research and is Chairman of the Vascular Medicine Working Group. He is a reviewer for The New England Journal of Medicine, Archives of Internal Medicine, and European Journal of Clinical Investigation, among others. He is a member of the Internal Interuniversity Institute for Thrombosis and Hemostasis and the International Society on Thrombosis and Haemostasis and Thrombosis and also a member of the editorial board of Annals of Internal Medicine.

Dr Büller was Chairman of the 2004 CHEST conference on antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Dr Büller is the recipient of the Established Investigator Award presented by the Dutch Heart Foundation and received the Dutch Society for Vascular Medicine 2005 Award. Dr Büller was awarded with the prestigious professorship of the Royal Netherlands Academy of Arts and Sciences (KNAW) in 2008.
Bengt I Eriksson  
Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Bengt Eriksson is a Professor of Orthopaedics at the Institute of Surgical Sciences, Gothenburg University, Sweden, a Senior Consultant at the Department of Orthopaedic Surgery at Sahlgrenska University Hospital, Gothenburg and a member of the Scientific Board of the International Surgical Thrombosis Forum. Since obtaining his medical degree and doctorate from Gothenburg University, Dr Eriksson has become a leading researcher of thrombopathogenesis and the prevention of thromboembolic complications after orthopaedic surgery and he is also active in clinical research on soft tissue injuries, posttraumatic chondral lesions and osteoarthritis, with focus on the role of proteases in the repair and degradation processes related to tissue injury and joint surfaces.

Dr Eriksson is guiding the clinical development of many new, synthetic, orally administered anticoagulants. He is the principal investigator of several multinational studies on oral Factor Xa, IXa and IIa inhibitors, and serves as an advisor to many projects in this field, at both the preclinical and clinical stages. Dr Eriksson is currently participating in a project on prevention and treatment of venous thromboembolism, run by the Swedish Health Authorities and the Swedish Council on Technology Assessment in Health Care. He regularly presents results from his research group at international congresses, and has published more than a hundred articles on orthopaedics, and regularly reviews for medical journals.
Anna Falanga

University of Milan, Bicocca, Italy

Anna Falanga is Director of the Haemostasis and Thrombosis Centre, Department of Haematology, Ospedali Riuniti in Bergamo, Italy and Professor of Haematology at University of Milan, Bicocca.

Having received her medical degree and board certification in internal medicine at the University of Naples, Dr Falanga obtained her board certification in haematology at the University of Verona, Italy. Subsequently, she spent three years working as a postdoctoral fellow in the Mario Negri Institute in Milan, Italy, and a further two years at the University of Colorado School of Medicine, Denver, USA.

Dr Falanga’s research interests include the study of the interactions of malignant cells with the haemostatic system, the role of antithrombotic agents in human cancer and experimental models, and the management of venous thromboembolism in cancer patients.

Dr Falanga became an elected member of the Scientific and Standardization Committee’s Class 2008, in 2002, and Chairperson of the Sub-committee on Haemostasis and Malignancy from 2002 to 2006. She is also a member of the committee on Haemostasis of the American Society of Hematology (2006-2008).

Dr Falanga contributed to the preparation of the guidelines for prophylaxis and treatment of venous thromboembolism in patients with cancer, both from the Italian Society of Medical Oncology (AIOM), in 2006, and, as a co-chairman, from the American Society of Clinical Oncology, in 2007. She has an active role in many professional societies, including the International Society of Thrombosis and Haemostasis, the Italian Societies of Haematology and of Haemostasis and Thrombosis, the American Society of Hematology, the American Society for Cancer Research. She is the Vice President of the Italian section of the Medical Women International Association.
Charles W Francis

University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

Charles Francis is Professor of Medicine and of Pathology and Laboratory Medicine at the University of Rochester. He obtained his MD degree at the University of Pittsburgh and was then an Intern and Resident in Medicine at the University of North Carolina. He joined the University of Rochester as a Fellow in Haematology in 1976, and he has remained at that institution where he is Director of the Hemostasis and Thrombosis program.

Dr Francis has been the recipient of a Clinical Investigator Award from the National Heart, Lung and Blood Institute (NHLBI) and of an Established Investigator Award from the American Heart Association. He has served on numerous National Institutes of Health (NIH) review and advisory committees. He is a past Chairman of the Scientific and Standardization Committee of the ISTH and Program Chair of the XVIIth International Congress on Hemostasis and Thrombosis. He serves as the Editor-in-Chief of Thrombosis Research.

Dr Francis has both clinical and laboratory research interests. His laboratory research has focused on the structure of fibrinogen and fibrin and mechanisms of fibrinolysis. Dr Francis’s current work relates to the role of fibrinogen and fibrin in modulating the effects of FGF-2 on endothelial cells. His clinical research has been in the areas of venous thrombosis and new anticoagulants.
Job Harenberg

Clinical Pharmacology, Mannheim, Faculty of Medicine, Ruprecht-Karls University, Heidelberg, Germany

Job Harenberg is Professor of Internal Medicine, specializing in haemostaseology and Chairman of the outpatient care unit vascular geriatrics in cooperation with the 4th Department of Medicine of the university hospital.

Dr Harenberg earned his MD in 1974 at the University of Heidelberg and was appointed as Professor of Medicine in 1992 at the Faculty of Medicine, Mannheim. After graduating, he completed his research fellowship in clinical pharmacology and in haemostasis and thrombosis at the Departments of Clinical Pharmacology and Medicine at the University of Heidelberg. He collaborated with the Department of Blood Coagulation at Columbia University and Blood Coagulation Research at Massachusetts University in Boston between 1980 and 1982.

Dr Harenberg has maintained a stream of coagulation laboratory research programs on methods to determine anticoagulants and on modification of heparins to determine the structure function relationship. In collaboration with Dr Benito Casu at the G. Ronzoni Institute for Chemical and Biochemical Research, Milan he has organised the Glycosaminoglycans Symposia at Villa Vigoni in Italy since 1991. The 16th Symposium took place in September 2008. Several volumes of Seminars in Thrombosis and Hemostasis summarise original publications of individual symposia.

Dr Harenberg’s clinical research interests are in the fields of venous thromboembolism and of all indications for new antithrombotic agents from clinical Phase I to III. He currently is conducting research on the oral direct factor Xa and IIa inhibitors and published data on additional investigations from patients participating in the clinical trials. He has authored and co-authored more than 200 scientific articles concerning topics in his field. He is member of the editorial boards of Seminars in
Thrombosis and Hemostasis and some German journals and is a reviewer for the Lancet, European Journal of Clinical Investigation, the British Journal of Haematology, and several others. At present, he is chairman of the working group on Generic Low-Molecular-Weight Heparins of the Scientific Subcomittee on Anticoagulation of the International Society of Thrombosis and Haemostasis.
Menno Huisman

Section of Vascular Medicine, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

Menno Huisman is Associate Professor in the Department of Medicine at the Leiden University Medical Center, Leiden, The Netherlands. Dr Huisman received his medical degree from the University of Amsterdam. He performed clinical research under the supervision of Professor Jan Wouter ten Cate and Professor Harry Büller. He obtained his PhD degree by successfully defending his thesis with the subject of ‘Objective diagnosis of deep-vein thrombosis’ at the University of Amsterdam. He completed his residency in internal medicine at the Academic Medical Center in Amsterdam. Afterwards, he completed a two year fellowships in haematology at the Academic Medical Center, Amsterdam, and in vascular medicine at the Leiden University Medical Center, Leiden.

Dr Huisman is Chair of the Section of Vascular Medicine within the Department of Medicine at Leiden University Medical Center. He is Chair of the National Education Board of Vascular Medicine in The Netherlands.

His main research interests are within clinical research in the areas of diagnosis and treatment of venous and arterial thromboembolism.
Howard A Liebman

University of Southern California, Los Angeles, California, USA

Howard A Liebman is Professor of Medicine and Pathology at the University of Southern California’s (USC) Keck School of Medicine, Los Angeles, CA, USA. He serves as Medical Director of the Special Haemostasis Laboratory at USC’s Norris Comprehensive Cancer Center and is Interim Chief of the Section of Haematology.

Dr Liebman received his medical degree from USC in 1973. His postgraduate training included a residency in internal medicine and fellowships in medical oncology and haematology at Los Angeles County - University of Southern California Medical Center (1973–1980). Dr Liebman then completed a research fellowship at Tufts University - New England Medical Center, Boston, MA, USA (1981–1984). He held faculty positions at Tufts University and Boston University, before returning to USC.

Dr Liebman’s research interests include clinical management and characterization of haemostatic and thrombotic disorders, management of autoimmune blood disorders and clinical therapy of HIV and AIDS. He has authored or co-authored 80 peer-reviewed publications and 21 reviews and chapters.
Gregory H Lip

University Department of Medicine, City Hospital, Birmingham, UK

Gregory H Lip is Professor of Cardiovascular Medicine, at the University of Birmingham, UK. In addition, he is Consultant Cardiologist and Director of the Haemostasis Thrombosis and Vascular Biology Unit in the University Department of Medicine at City Hospital, Birmingham.

His present appointment allows full clinical responsibilities in cardiovascular medicine (including invasive and non-invasive cardiology); as well as teaching and cardiovascular research.

His research interests are in atrial fibrillation, hypertension, heart failure, thrombosis and antithrombotic therapy, and ethnic differences in vascular disease. In addition, he has a major interest in the psychophysiology and understanding of the disease process in cardiovascular disease (including atrial fibrillation), as well as physician and patient perceptions of antithrombotic management strategies. Finally, he leads a large laboratory-based research group into thrombosis and vascular biology in cardiovascular disease and stroke.

Professor Lip is Editor-in-Chief of the Journal of Human Hypertension, Deputy Editor-in-Chief for Thrombosis and Haemostasis and is a Nucleus Committee Member of the European Society of Cardiology Working Group on ‘Hypertension and the Heart’. He is currently on the Editorial Boards of ATVB, Thrombosis & Haemostasis, Thrombosis Research, Blood Coagulation and Fibrinolysis; Hypertension, American Journal of Hypertension, Circulation, Journal of the American College of Cardiology, European Heart Journal, American Journal of Cardiology, Heart, etc. He has acted as referee for numerous journals, as well as major national and international grant giving bodies.

Professor Lip was Clinical Adviser to the guideline development group which wrote the evidence-based UK
National Institute for Health and Clinical Excellence (NICE) guidelines on the management of atrial fibrillation. He is also a co-author of the American College of Chest Physicians Consensus Guidelines on Antithrombotic Therapy for Atrial Fibrillation, which are established international guidelines on thrombosis and thromboprophylaxis. He has also been involved in local epidemiological surveys of thromboprophylaxis for atrial fibrillation, and formulation of regional/national/international antithrombotic therapy guidelines for atrial fibrillation. He is grant co-applicant for the BAFTA [Birmingham Atrial Fibrillation Treatment in the Aged] clinical trial, comparing aspirin and warfarin in elderly (aged >75) patients with atrial fibrillation in the primary care setting.

Professor Lip has served on many clinical trial steering committees – being involved in study design, organisation and conduct - as well as trial Data Safety Monitoring Boards. He is currently the lead for the cardiovascular research programme for Sandwell and West Birmingham NHS Hospitals NHS Trust.

Professor Lip has published and lectured extensively on the clinical epidemiology of atrial fibrillation and hypertension, as well as on the pathophysiology of thrombosis in cardiovascular disease.
John McVey, PhD, is the Weston Professor of Molecular Medicine at the Thrombosis Research Institute. He has over 20 years of experience in blood coagulation factors. He has held two postdoctoral positions at Middlesex Hospital and Medical Research Council (MRC) National Institute for Medical Research (NIMR) before joining the MRC Haemostasis and Thrombosis Group at its conception. In 2006, he was appointed leader of the MRC Haemostasis and Thrombosis Group.

Dr McVey has authored or co-authored over 80 peer-reviewed papers and many book chapters. He is a communicating editor for Human Mutation and Thrombosis & Haemostasis as well as a member of the Advisory Board of the Journal of Thrombosis and Haemostasis.
Geno J Merli, MD, FACP, is currently Senior Vice President for Clinical Affairs and Chief Medical Officer at the Thomas Jefferson University Hospital; he is also Professor of Medicine, Director Jefferson Center for Vascular Diseases, in the Department of Medicine at the Jefferson Medical College of Thomas Jefferson University. Dr Merli maintains an active practice in vascular diseases and participates in clinical research as a principal investigator and is co-investigator in thrombosis prevention and treatment trials.

Dr Merli graduated from the University of Scranton in 1971 and from Jefferson Medical College in 1975. He completed a residency in rehabilitation medicine and internal medicine at Thomas Jefferson University Hospital from 1975-1980. He was formerly, Ludwig A Kind, Professor of Medicine, Vice Chair for Clinical Affairs and Director Division of Internal Medicine, Senior Associate Dean for Continuing Medical Education.

Dr Merli is a Fellow of the American College of Physicians and a member of the American Venous Forum, the Society of General Internal Medicine, the Society of Vascular Medicine and Biology, and the International Society on Thrombosis and Haemostasis.
Paolo Prandoni MD, PhD is Professor at the Department of Medical and Surgical Sciences, Thromboembolism Unit at the University of Padova. He trained at the University of Padova from 1971 to 1979 before moving to Holland where he studied for his PhD at the University of Amsterdam in 1992. Professor Prandoni’s research and professional experiences cover epidemiology, diagnosis and management of thromboembolism. Of particular interest are studies addressing the association of cancer with venous thromboembolism.

Professor Prandoni has published more than 300 papers in peer-review journals. Key achievements include: the demonstration of the value of real-time compression ultrasonography for the diagnosis of deep vein thrombosis (DVT); the confirmation of the risk for subsequent overt cancer in patients with idiopathic VTE; the demonstration that low-molecular-weight heparins (LMWHs) are as effective and safe as unfractionated heparin (UFH) in the treatment of DVT; the demonstration that LMWHs allow the home treatment of DVT; the description of the natural history of DVT, outlining the particularly high risk of recurrent thromboembolism in cancer patients; the demonstration that both factor V Leiden and G20210A prothrombin variant are independent risk factors for recurrent VTE; the demonstration that residual vein thrombosis is a predictive marker of recurrent thromboembolism; the demonstration that cancer patients with venous thrombosis have a high risk of recurrent thromboembolism while on anticoagulation; the demonstration of an association between atherosclerosis and venous thrombosis; and the demonstration that chronic pulmonary thromboembolic hypertension following an episode of pulmonary embolism is more frequent than commonly thought.
Morten S Rasmussen
Bispebjerg Hospital, Copenhagen, Denmark

Morten S Rasmussen is a Staff Specialist and Consultant Surgeon at the Department of Surgical Gastroenterology, Bispebjerg Hospital, Copenhagen, Denmark. Dr Rasmussen graduated as Medical Doctor in 1986 from the University of Copenhagen, and became a specialist in surgery and surgical gastroenterology in 2001 and 2002.

Dr Rasmussen is associated with the Center for Clinical Thrombosis Research, Bispebjerg Hospital at the University of Copenhagen, Denmark. Dr Rasmussen is Chairman of the preparation of Danish national guidelines of: Thromboprophylaxis for general surgery; anti-platelet treatment and invasive procedures and cancer-associated thrombosis.

Dr Rasmussen’s areas of scientific interest include postoperative thromboembolism, prolonged thromboprophylaxis, cancer-associated thrombosis and risk factors for development of postoperative venous thromboembolism.

Dr Rasmussen is also a member of advisory board at Pfizer AS.
Wolfram Ruf, MD, PhD, is Professor in the Department of Immunology and Microbial Science at The Scripps Research Institute in La Jolla, CA and Margaret Thatcher Professor of Biological Chemistry at the Thrombosis Research Institute in London. He received his MD,PhD degree from the University of Giessen, Germany. In 1988 he joined Scripps as a postdoctoral fellow and continued his career as a faculty member. Dr Ruf’s research program is focused on the tissue factor (TF) initiated coagulation pathway in thrombosis, inflammation, angiogenesis and tumor biology. In addition to an interest in the structural biology, regulatory mechanisms, and cell biology of the TF initiation complex, his current research is focused on signaling roles of coagulation proteases, co-receptors and protease activated receptors (PARs) in genetic mouse models and novel therapeutic approaches that target these pathways.
Charles Marc Samama
Hôtel-Dieu University Hospital, Paris, France

Charles Marc Samama is Professor and Chairman in the Department of Anaesthesiology and Intensive Care of the Hôtel-Dieu University Hospital in Paris, France. He is board certified to practice anaesthesiology and intensive care medicine.

He holds a master’s degree in Haemostasis and Thrombosis and his PhD dissertation was based on an experimental model of thrombosis in the pig. He heads a laboratory in the INSERM 765 research unit and for many years has developed an experimental model of arterial thrombosis and bleeding in the rabbit.

Professor Samama is the Past-President of the Scientific Committee of the French Society of Anaesthesiology and Intensive Care (SFAR). He works as an active member of sub-committee 6, Transfusion and Haemostasis of the European Society of Anaesthesiologists (ESA) and is also a member of the International Society on Thrombosis and Haemostasis (ISTH).

Professor Samama serves as a consultant for a number of professional journals in anaesthesiology, haemostasis and drug safety, and has published more than 100 peer-reviewed articles and anaesthesiology reviews. He has directed the French Guidelines on Perioperative Venous Thromboembolism (VTE) Prophylaxis and has co-authored the VTE prophylaxis section of American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition).
Meyer-Michel Samama

Hôtel-Dieu University Hospital, Paris, France

Meyer-Michel Samama, MD, is Professor Emeritus of Haematology at Hôtel-Dieu University Hospital, Faculty of Medicine, where he was formerly chairman of the Department of Haematology and Scientific Adviser and Delegate Director at Biomnis Laboratory. He qualified as a pharmacist-pathologist then as a medical doctor and then as Professor of Haematology from the Paris VI University School of Medicine. His study on venous thromboembolism prophylaxis in medical patients (MEDENOX study) was selected to be presented at the Presidential Symposium of the International Society on Thrombosis and Haemostasis in 1999 and is a very frequently quoted work published in New England Journal of Medicine. Dr Samama was elected corresponding member of the National Academy of Pharmacy in 2001. He presented three lectures at the National Academy of Medicine.

Dr Samama’s research interests center on haemostasis and pathogenesis of venous thrombosis. Current fields of focus include the diagnosis and treatment of hereditary thrombophilia and the pharmacology of antithrombotic drugs including low-molecular-weight heparins, fondaparinux and new antithrombotic agents. He has published more than 400 original articles and has co-edited a number of books on clinical thrombosis and hypercoagulable states.

He received a Distinguished Career Award for his contributions to haemostasis from the International Society on Thrombosis and Haemostasis. He also received an award from the International Society of Fibrinolysis and Thrombolysis and from the Venous Thrombosis Forum for his contribution to the field. He is a member of the Editorial Board of the Journal of Thrombosis and Haemostasis. He is a member of the American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy. He sits on the review board of several journals and is a member of several professional societies.
Sam Schulman
McMaster University, Hamilton, Canada; Karolinska Institute, Stockholm, Sweden

Sam Schulman MD, PhD is Director of the Thrombosis Service at HHS-General Hospital in Hamilton and also Director of the Clinical Thrombomebolism Program of McMaster University. Dr Schulman graduated from Karolinska Institute, Stockholm, Sweden in 1977 and became a specialist in Internal Medicine in 1984, with subspecialties in Haematology and in Coagulation in 1985. That year he also received his Dr Med Sc with the thesis: “Studies on the Medical Treatment of Deep Vein Thrombosis”. He has worked within the field of coagulation disorders continuously since 1984 and is the Director of the Hemophilia Treatment Center in Stockholm. He did one year of his residency in Internal Medicine at McMaster University in Hamilton, Canada and worked for 4½ years at the National Hemophilia Center at Tel Hashomer, Israel.

Dr Schulman’s major research activities have been clinical studies in venous thromboembolism, including several randomised trials and in hemophilia and its complications. He is currently involved in trials with new antithrombotic agents, such as oral thrombin inhibitors. He was a member of the Executive Committee of the World Federation of Hemophilia (2000-2004) and is Chairman of the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of International Society on Thrombosis and Haemostasis (ISTH). Dr Schulman is Associate Professor in Internal Medicine at Karolinska Institute and since September 2004 also Professor of Medicine at McMaster University.
Akikazu Takada

Hamamatsu University School of Medicine, Hamamatsu, Japan

Professor Akikazu Takada is President of the Japanese Society of Scientific Research of Sugar. Professor Takada graduated from Keio University School of Medicine (1966). He was Assistant Professor of the Department of Pathology of New York State University School of Medicine at Buffalo (1972-75); Professor of Physiology, Hamamatsu University of School of Medicine (1975-2001); Professor Emeritus of Hamamatsu University School of Medicine; Chairman (2000-2004) and Honorary Chairman of Asia-Pacific Society of Thrombosis and Hemostasis (2005-) and President of the 16th Congress of International Society of Fibrinolysis held at Hamamatsu, Japan, 2000.
Alexander GG Turpie

McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada

Alexander GG Turpie is Professor of Medicine at McMaster University, and an internist on the staff of Hamilton Health Sciences, Hamilton, Ontario, Canada. He received his medical education from the University of Glasgow, Scotland. After completing residencies at the Royal Infirmary and Stobhill General Hospital, Glasgow, where he was also a clinical research fellow, he served as a clinic lecturer for the University of East Africa Medical School in Nairobi, Kenya. After returning to the University of Glasgow for additional training in haemostasis and thrombosis, he was appointed MRC Fellow at McMaster University, Hamilton, Canada, where he was appointed to the full-time faculty in the Department of Medicine.

Professor Turpie’s research interests include new antithrombotic drugs for the management of venous and arterial thrombosis, and anticoagulant therapy in patients with prosthetic heart valves. He has served on numerous professional and university-related committees, and is a frequent lecturer at professional meetings worldwide.

Professor Turpie has authored more than 700 published articles, abstracts, book chapters, and books, and he has been a reviewer for many journals, including Annals of Internal Medicine, Circulation, the Lancet and the New England Journal of Medicine, as well as serving on the editorial boards of Vascular Medicine Review and HeartDrug.
Freek W A Verheugt

University Hospital, The Netherlands

Freek W A Verheugt, MD, is Professor of Cardiology at the University of Nijmegen, University Hospital in The Netherlands. He is a member of the Scientific Council Interuniversity Cardiology Institute Netherlands (Royal Netherlands Academy of Sciences) and was the President of the Netherlands Society of Cardiology from 1999 to 2001.

He has co-authored over 320 peer reviewed papers and is a Fellow of the American College of Cardiology, Fellow of the European Society of Cardiology and Fellow of the Council on Clinical Cardiology of the American Heart Association.
Richard H White

University of California, Davis, Sacramento, USA

Richard White is Professor of Medicine, Chief of the Division of General Medicine and Medical Director of the Inpatient and Outpatient Anticoagulation Services at the University of California, Davis School of Medicine, which is in Sacramento, California. He received his medical training at Washington University School of Medicine in St. Louis and completed his internal medicine residency and fellowship training at the University of California, San Francisco.

His chief research interests are related to the epidemiology of venous thromboembolism, improving anticoagulation therapy as well as participating in clinical trials. His recent work has concentrated on the epidemiology of venous thromboembolism in cancer patients. He was a member of the National Quality Forum Steering Committee, and is an active member of the American Society of Hematology (ASH), International Society on Thrombosis and Haemostasis (ISTH), the Anticoagulation Forum, and the Society of General and Internal Medicine (SGIM) Anticoagulation and Thromboembolism Interest Group.
Abstracts
**Epidemiology of Venous Thromboembolism**

*Richard H White, USA*

The epidemiology of venous thromboembolism (VTE) in the general population has been defined by longitudinal study of geographically defined cohorts and by analysis of administrative data. Consistent findings include: a nearly equal incidence of VTE in men and women; an exponential increase in the incidence of VTE with age (up to 80 years); a lower incidence of recurrent VTE if the index event was “provoked” by trauma, surgery or acute medical illness; a higher incidence of recurrent deep-venous thrombosis (DVT) after an index DVT, and a higher incidence of recurrent pulmonary embolism (PE) after an index PE; and a lower incidence of recurrent VTE in women with unprovoked VTE compared to men. The directly standardised incidence of VTE is higher in African-Americans than Caucasians, and the incidence is significantly less common in Asian-Pacific Islanders. Recent trends observed in California include a 14% increase in the total population from 1996 through 2005 (with a 20% increase in persons 55 years or older) but a 60% increase in number of first-time VTE events, with a 70% increase in first-time PE and 50% increase in first-time DVT. In this 10-year period, the number of patients admitted with PE has gone up 40% and the number of patients diagnosed with PE in the hospital has more than doubled. The rise in the incidence of first-time VTE is likely due to three factors: aging of the population, a reduction in the threshold to test for VTE, and greater use of ultrasound imaging of the calf and highly sensitive Computerised Tomography (CT) scanning of the chest. If efforts to promote near universal use of thromboprophylaxis among hospitalised patients are realised, and if in-hospital diagnosis of VTE is used as a measure of hospital quality, there may be modest blunting in the impressive rise in the incidence of VTE in the near future.
VTE Prevention and Treatment

Sylvia Haas, Germany

Anticoagulant drugs are of paramount importance for prevention and treatment of venous thromboembolism (VTE). However, different dose regimens are used for these indications. Usually, low doses of heparins or fondaparinux are given for primary prevention without unfolding full anticoagulation whereas initial treatment of VTE requires higher doses significantly affecting various coagulation tests. For example, the concept of VTE prophylaxis with unfractionated heparin (UFH) is based on doses which normally do not affect aPTT while the dosage required for treatment targets at a 1.5 – to 2.0-fold aPTT prolongation.

VTE prophylaxis with low-dose UFH was established more than three decades ago and has been successfully used in patients who have had elective general surgery and are at moderate-risk of VTE, but it is less effective than other forms of thromboprophylaxis in high-risk patients undergoing major orthopaedic surgery. Low-molecular-weight heparins (LMWHs) possess several pharmacological advantages over UFH, which make them more convenient for both inpatient and outpatient use. When compared to UFH, LMWHs also provide a larger relative risk reduction of VTE after major orthopaedic surgery. Further risk reductions have been achieved by the synthetically synthesized pentasaccharide fondaparinux.

Several trials have provided evidence that the risk of VTE may persist beyond discharge from hospital. Extended out-of-hospital prophylaxis with LMWHs has been shown to be very effective in patients after elective hip arthroplasty and also patients undergoing surgery for cancer may benefit from prolonged LMWH prophylaxis with LMWH. For patients with hip fracture surgery, post-discharge prophylaxis with fondaparinux has been recommended.

For patients with objectively confirmed VTE, initial anticoagulant therapy with subcutaneous LMWH, monitored intravenous or subcutaneous UFH, unmonitored weight-based subcutaneous UFH, or subcutaneous fondaparinux is recommended. Anticoagulation with vitamin K antagonists should be initiated together with LMWH, UFH, or fondaparinux on the first treatment day, and discontinuation of these anticoagulants when the international normalized ratio (INR) is > or = 2.0 for at least 24 h. The recommended duration of secondary prevention with vitamin K antagonists depends on the presence or absence of additional risk factors.

New oral anticoagulants not requiring individual dosing will have the potential to improve prevention and treatment of VTE and to implement recommendations from guidelines into clinical practice.
Update on venous thromboembolism

References


The patient safety perspective

A.K. Kakkar, UK

Venous thromboembolism remains a common and potentially fatal complication for hospitalised patient populations. Indeed, pulmonary embolism remains the commonest avoidable cause of hospital death. Recent attention on this clinical problem has demonstrated its importance in terms of patient safety. As a result, there is an increasing emphasis on risk assessment for patients at the time of hospital admission, in order to identify those who may benefit from routine thromboprophylaxis. Patients identified at moderate high risk for the development of venous thromboembolism may be offered pharmacological or mechanical thromboprophylaxis to reduce their risk for the development of hospital acquired venous thromboembolism.

A systematic approach to the prevention of venous thromboembolism, based upon its patient safety consequences, is now being considered by a number of healthcare systems including the United Kingdom, France, Germany, the United States and Australia. Although the approach varies from country to country the objective of identifying those at highest risk ensuring they receive appropriate thromboprophylaxis is a common theme.

Such an emphasis on the prevention of venous thromboembolism provides the best chance of ensuring that appropriate patients who are at risk of venous thromboembolism receive the appropriate method of thromboprophylaxis either mechanical or pharmacological.
Update on venous thromboembolism

Generic low-molecular-weight heparins – where are we?
Jawed Fareed and Jeanine M. Walenga, USA

The recent recalls globally on heparin were primarily due to the reported adverse reactions and deaths, which were eventually linked to the presence of hypersulfated chondroitin sulfate. However, additional impurities and contaminants were also found in the contaminated heparins.

To investigate the chemical and biological profiles of the main contaminant in recalled unfractionated heparins (UFH) and low-molecular-weight heparins (LMWH), four recalled UFH preparations (3 finished products and 1 powder) were investigated. To obtain the contaminant, each material was treated by exhaustive depolymerization with nitrous acid and heparinase 1 to remove heparin followed by ethanolic precipitation and anion exchange chromatography. The amount of non-digested material ranged 10-30%, most of which was characterized to be hypersulfated chondroitin sulfate (HSCS) by proton and 13C NMR spectroscopy.

The molecular weight profile exhibited a wider dispersity index in comparison to contaminant-free UFH with oligosaccharides ranging from 5-30 kDa (average 16.8 kDa). In addition, a well-characterized porcine cartilage HSCS preparation with average molecular weight of 17.2 kDa was used as a reference material. While varying degrees of dermatan sulfate (high molecular weight) and minor impurities were detected, the HSCS appeared to be the major contaminant in these preparations. To investigate the biological profile of the isolated contaminant, it was subjected to chondroitinase A, B, and C and high potency heparinase 1 (2.5 U/ml) depolymerization. The material was resistant to the action of these enzymes. The contaminant was further profiled in routinely used anticoagulant and anti-protease assays. In the USP assay it exhibited a potency of 26.8 U/mg. It also produced a concentration dependent anticoagulant effect in the whole blood celite activated clotting time (ACT) and saline ACT tests but was weaker than heparin. In the PT assay (extrinsic coagulation system) the contaminant only exhibited very weak activity and did not affect the INR up to a 50 µg/ml concentration.

However, in the global anticoagulant assays such as the aPTT (intrinsic coagulation system) and Heptest, in comparison to UFH, the contaminant produced varying degrees of concentration dependent anticoagulant activity (10-40 U/mg). In the amidolytic anti-thrombin assay it produced a concentration dependent inhibition of thrombin in citrated plasma (~ 25 U/mg). This contaminant did not exhibit any inhibition of FXa in the same systems. In antithrombin (AT) depleted plasma, while the anticoagulant and amidolytic activities of UFH were considerably reduced, the contaminant exhibited measurable concentration dependent effects indicating a non-AT
Update on venous thromboembolism

dependence. In HCII depleted plasma the contaminant lost sizeable anticoagulant and anti-thrombin effects. The dermatan cofactor activity of pre- and post-heparinase digested contaminant was not different, whereas UFH showed a considerable decrease. The contaminant was readily neutralizable by protamine sulfate, polybrene, and PF4 in a similar fashion as UFH. The contaminant mediated contact factor activation as measured by the generation of kallikrein and bradykinin was concentration dependent in plasma and whole blood. UFH also showed this activity in both systems.

Significant differences in contact activation by UFH and the contaminant were noted between citrated and hirudinized whole blood. The contaminant also produced HIF mediated antibody activation of platelets; however, it had a faster onset of action and longer lasting time course of platelet aggregation than UFH. In the 14C-Serotonin Release Assay (SRA) the contaminant produced a strong release of serotonin which sustained at high concentrations and did not follow the parabolic response usually observed with UFH. Studies of the contaminant mixed with UFH in proportions of 3, 6, 12, 25, 50% (amount of contaminant) in plasma and whole blood revealed a non-additive assay dependent synergistic effect of the contaminant on the anticoagulant and anti-thrombin activities. At a 25% level, the contaminant produced a marked increase of the anticoagulant activity of the mixture mimicking the pharmacopoeial potency of ~ 150 U/mg; however, this increase was dependent on different contaminant preparations (different batches). Similar augmentation of the effects of UFH were noted in the thrombin and FXa generation tests as measured by amidolytic methods and measurements of such thrombin generation markers as FPA, TAT, and F1.2. Preliminary studies show that the contaminant may also exhibit direct anti-protease effects by complexing with FVIIa and the prothrombinase complex.

To study the in vivo effect of the contaminant, the effect of contaminated UFH and a potency equivalent contaminant-free preparation were studied in animal models of bleeding and thrombosis. In comparison to the contaminant-free UFH at an identical dosage of 200-800 U/kg, the contaminated UFH produced a marked increase in bleeding. Similarly, the antithrombotic effect in terms of ED50 was markedly stronger with the contaminated preparation. Blood pressure measurements provided variable effects in which both the contaminated and contaminant-free preparations exhibited a hypotensive response in some rats. In contrast to the contaminant-free UFH, the contaminated preparation produced a stronger release of TFPI. Similar studies carried out on two hemi-synthetic HSCS preparations mixed with non-contaminated UFH provided comparable results. Since the contaminated batches of UFH also contain variable amounts of dermatan sulfate, additional studies are in progress at this time on the pharmacologic profile of the
contaminated UFH, isolated contaminant, hemi-synthetic HSCS, hyper-sulfated dermatan sulfate, and their precursors.

Furthermore, additional investigations on the contaminant isolated from commercially available/branded and generic LMWHs are in progress at this time with particular reference to the molecular profile of the contaminant, its subcutaneous PK/PD profile, and immunogenic potential. While the hypersulfated chondroitin sulfate may represent the intentional contaminant, dermatan sulfate and modified carryover products are also present in heparins and may partly be responsible for the adverse reactions and altered pharmacologic profile of heparins.
Update in Acute Coronary Syndromes

Freek WA Verheugt, The Netherlands

Acute coronary syndromes consist of signs and symptoms of myocardial ischemia with ST-segment elevation or no ST-segment elevation on the presenting ECG. The syndromes have different prognoses and different treatment modalities. The cornerstones of the treatment are both anti-ischemic and antithrombotic strategies. Myocardial ischemia can be optimally treated with the use of beta blockers and nitroglycerin, whereas antithrombotic therapy usually consists of anticoagulant and antiplatelet treatment. Furthermore, secondary prevention after the acute event is mandatory.

In ST-segment elevation acute coronary syndrome usually ending in ST-segment elevation myocardial infarction, mechanical rather than pharmacological reperfusion therapy is now common practice. Reperfusion therapy is only useful in the early hours of STEMI when myocardial salvage is still likely. Late opening of occluded coronary arteries is probably not appropriate.¹

Whereas anti-ischemic and antithrombotic therapy in non-ST-segment elevation acute coronary syndromes is essential, an invasive approach in these syndromes is still under discussion. Some large randomised clinical trials did show a positive benefit in the first months to years with regard to myocardial infarction and mortality, but long-term mortality is not improved by a routine invasive strategy in non-ST-segment elevation acute coronary syndrome.² Possibly early intervention in a non-occluded coronary artery with a rupture plaque may harm patients, but also can prevent reinfarction. Definite new randomised trials will probably not be started.

References


Controversies in the management of atrial fibrillation

Jack Ansell, USA

Atrial fibrillation (AF) affects roughly 1% - 2% of individuals in industrialised societies, the majority of such individuals being the elderly (~ 10% of all individuals over the age of 80 years). Its prevalence is increasing rapidly with the increasing numbers of elderly. As a result, physicians often have to address difficult management decisions posed by their patients with AF. Among the most vexing is whether to start a vitamin K antagonist (VKA) as stroke-preventive therapy. In spite of over sixty-five years of experience with the VKAs, and close to 2 decades of experience with AF being a principal indication for oral anticoagulation, there are still many controversies and problems associated with the treatment of AF with a VKA.

This presentation will review a number of common controversies/problems that doctors struggle with in the treatment of AF including: 1) Rate vs rhythm control; 2) Attitudes and preferences of doctors and patients towards treatment; 3) Under treatment of AF on a world-wide basis; 4) VKA vs ASA therapy; 5) Outcome vs intensity of treatment and time in therapeutic range, and other risk factors; 6) Intracranial hemorrhage in the elderly; 7) Treatment of bleeding, especially intracranial hemorrhage; and 8) Bridging anticoagulation in patients with AF. By examining these issues, it is hoped that the practicing physician will have a better understanding and ability to cope with problems related to anticoagulation in atrial fibrillation.
Antiplatelet Therapy

Alexander G G Turpie, Canada

Aspirin remains the mainstay of antiplatelet therapy for the prevention and treatment of coronary, cerebral, and peripheral artery disease. Several properties have contributed to its success including once-daily oral administration; the ability to permanently inactivate platelet cyclooxygenase-1; lack of requirement for laboratory monitoring or dose-titration; and the ability to exert its effect through a moiety with a short half-life which limits extra-platelet effects. Despite its proven efficacy aspirin is a relatively weak antiplatelet drug, as shown by persistent platelet activation and aggregation in patients taking aspirin.

Furthermore aspirin resistance has been associated with an increased risk of atherothrombotic vascular events. Recognition of the central role of platelets in atherothrombotic vascular disease and the need more effective inhibition of platelet function has led to the development of new antiplatelet agents. These agents exert their antithrombotic effect by targeting a variety of platelet receptors or enzymes. Antagonists of the P2Y12, thromboxane/prostaglandin H2 and PAR-1 platelet receptors have undergone clinical testing for prevention and treatment of arterial vascular disease. P2Y12 receptors are G protein-coupled receptors bound to the platelet surface. Binding of adenosine diphosphate (ADP) released from platelet dense granules to P2Y12 receptors reduces adenylate cyclase activity and eventually leads to activation of glycoprotein (GP) IIb/IIIa. Inhibition of the P2Y12 receptor inhibits ADP-induced platelet aggregation. Thienopyridine drugs selectively inhibit ADP-induced platelet aggregation mediated by the P2Y12 receptor. The first generation thienopyridine, ticlopidine and the second generation thienopyridine, clopidogrel have been extensively studied in atherosclerotic vascular disease. Unlike ticlopidine, clopidogrel does not cause life threatening neutropenia and it has a more rapid onset of action and is widely used across the spectrum of arterial thromboembolic diseases. However, clopidogrel has a number of limitations including a delayed onset of action, high inter-patient variability of platelet inhibition, and the potential for interaction with other drugs that are metabolized via the cytochrome P450 3A4 pathway (e.g. lipophilic statins).

A third-generation thienopyridine, prasugrel, is currently under development. Prasugrel is a prodrug that requires hepatic metabolism by cytochrome P450 to generate an active metabolite R-138727, which competes with ADP to bind with the P2Y12 receptor which inactivates the receptor for the lifetime of the platelet. Prasugrel is given once-daily with a loading dose and is more rapidly converted to its active metabolite than clopidogrel. In the TRITON-TIMI 38 trial, prasugrel was more effective than clopidogrel with respect to cardiovascular
Update on arterial thromboembolism

death, myocardial infarction (MI) or ischemic stroke in patients with acute coronary syndrome (ACS) who undergo percutaneous coronary intervention (PCI) but with and increased bleeding.

AZD-6140 is an oral reversible P2Y12 antagonist which binds directly to inhibit the P2Y12 receptor. AZD-6140 has one known active metabolite that is found in about one-third the concentration of the parent compound and it has approximately the same potency as the parent compound. AZD-6140 has a half-life of 12 hours and is administered twice daily. The antithrombotic effect of this agent is reversed 48 hours after drug withdrawal. AZD-6140 is currently being evaluated in coronary artery disease, peripheral vascular disease or cerebrovascular disease. A relatively high frequency of dose-dependent dyspnea and bradycardia was noted in patients who received AZD-6140.

Thromboxane receptors (TP) are G protein-coupled receptors found on vascular smooth muscle cells and platelets. When bound to an agonist, these receptors activate phospholipase C resulting in mobilization of second messenger molecules, including intracellular calcium to induce platelet aggregation. S-18886, the active isomer of S-18204, is a specific TP receptor antagonist. It is given once-daily and its inhibition of platelet aggregation persists for up to 36 hours after an oral dose of 10 to 30 mg. Reversibility of inhibition of platelet aggregation is dose-dependent and occurs within 24 to 48 hours of drug withdrawal. S-18886 has shown promising results in Phase II trials.

The crucial role played by membrane-bound receptors in platelet adhesion, activation and aggregation make platelet receptors attractive targets for new oral antiplatelet agents. Two of these new agents, prasugrel and AZD-6140 (P2Y12 antagonists) may be alternatives to clopidogrel in the prevention and treatment of ACS, and are in the more advanced stages of clinical testing. Both agents appear to exhibit a more rapid onset of action, less inter-patient variability, and a higher level of inhibition of platelet aggregation than clopidogrel. S-18886, TP receptor antagonist, has been shown not only to inhibit platelet aggregation, but also induce flow-mediated vasodilatation and improve endothelial function in early clinical trials. These properties suggest this agent may have benefits for patients with coronary artery disease in addition to its effect on platelets.
Update on peripheral arterial disease (thromboembolism)

David Bergqvist, Sweden

In this abstract peripheral arterial disease means involvement of arteries outside the brain and the heart. From a pathological point of view the dominating diseases are arteriosclerosis and aneurysms. Thrombosis usually is a consequence of the arteriosclerotic process narrowing, destructing and ulcerating the arterial wall. The thrombotic process may lead to occlusion with acute or chronic symptoms or it may embolize with usually acute symptoms. Thrombosis of otherwise healthy vessels is rare but may occur as a part of a thrombophilic syndrome. Embolism usually comes from the heart (fibrillation or myocardial infarction) or from intraaneurysmatic thrombi. Aneurysmal development is probably a common arterial response to several pathological stimuli, a lot of discussion today being focused on genetic defects and infections (i.e. chlamydia) with arteriosclerosis as a secondary phenomenon. To cover peripheral arterial disease in a short time is obviously impossible but to illustrate some important and temporal trends, examples will be given as follows:

1. Swedvasc (The Swedish Vascular Registry): the development over time in treatment of lower extremity ischaemia (acute and chronic), renovascular disease, popliteal and abdominal aortic aneurysms.

2. Inter-society consensus for the management of peripheral arterial disease (TASC II): recommendations dealing with acute and chronic critical limb ischaemia.

3. The situation regarding screening for abdominal aortic aneurysm with a recommendation taken by the Swedish Board for Health Technology Assessment.
Meet the expert sessions

**Predicting those at risk of recurrent VTE**

*Paolo Prandoni, Italy*

The risk of recurrent venous thromboembolism (VTE) approaches 40% of all patients after 10 years of follow-up. This risk is higher in patients with permanent risk factors of thrombosis such as active cancer, prolonged immobilization from medical diseases, and antiphospholipid antibody syndrome; in patients with idiopathic presentation; and in carriers of several thrombophilic abnormalities, including carriers of AT, protein C or S, increased factor VIII, hyperhomocysteinemia, homozygous carriers of factor V Leiden or prothrombin G20210A variant, and carriers of multiple abnormalities.

Patients with permanent risk factors of thrombosis should receive indefinite anticoagulation, consisting of subtherapeutic doses of low-molecular-weight heparin in cancer patients, and oral anticoagulants in all other conditions. Patients with idiopathic VTE, including carriers of thrombophilia, should receive at least 3 months of anticoagulation. The decision as whether to discontinue anticoagulation after this period and go on with conventional or less intense warfarin treatment, should be individually tailored and balanced against the haemorrhagic risk.
VTE prophylaxis for medical patients in the community. Is there a role?

Meyer Michel Samama, France

The annual incidence of venous thromboembolism (VTE) is 1 to 1.6 / 1000 individuals. VTE is a multi-factorial and often silent disease. Incidence rates increase exponentially with age for both men and women. Hospitalization and nursing home residents together account for 55% of the incidence while 45% of the incidence occurs in non hospitalized patients. A history of hospitalization and/or cancer are the most frequently encountered risk factors in these patients.

The Sirius epidemiological study (2002) is a rare study dealing with ambulatory patients. It makes it possible to identify a series of risk factors in patients with DVT; in the Tadeus project (2002) 6% of patients on admission to a general internal medicine unit, without a symptomatic VTE, had a positive doppler ultrasound.

Prophylaxis with low-molecular-weight heparins (LMWHs) or fondaparinux is efficacious and is a 1A recommendation of the 8th American College of Chest Physicians (ACCP) clinical practice guidelines (2008). However, prophylaxis in medical patients in contrast to surgical patients is underused and the most at risk patients are left unprotected (IMPROVE and ENDORSE registries).

The estimation of a potentially preventable factor of VTE is an important objective in order to reduce morbidity and mortality associated with VTE. Prevention of VTE should not be restricted to patients with cancer and/or hospitalized patients. It should be considered in non hospitalized patients at increased risk of VTE according to an assessment of well identified risk factors. Several risk assessment models (RAM) and computer alert programs are available.

Implementing RAMs and recognition of the clinical importance of thrombosis will increase physicians’ awareness of the risk of VTE and encourage more widespread antithrombotic prophylaxis in medical patients and especially in some particular types of malignancies. A reduction of the number of preventable deaths and complications due to VTE can be expected.

References


The new ACCP guidelines 2008 for prevention of venous thromboembolism

David Bergqvist, Sweden

The regular publication of the American College of Chest Physicians (ACCP) guidelines is an important event, resulting from a lot of hard work by a number of specialists. From initially being a North American endeavour, now experts from many European countries also take an active part. The previous guidelines were published in 2004 (Suppl to Chest), the 8th version in June 2005. There are somewhat fewer references but ten more printed pages in the new version. One important practical point is that there are now three instead of four risk groups concerning prophylaxis in high, medium and low which is easier to use clinically. The new recommendations start with hospital prophylaxis. Policy, which is important and has to do with how guidelines are implemented and has been added to. Still there is recommendation against the use of aspirin, and the recommendations on use in patients with renal impairment have been upgraded. There are some variations in grading, usually in favour of stronger evidence. Some new risk groups are considered such as bariatric surgery, forensic surgery, coronary bypass surgery. Fondaparinux has been added as an alternative in many situations.
Diagnosis of deep-vein thrombosis and pulmonary embolism

Menno Huisman, The Netherlands

Clinically suspected deep-vein thrombosis (DVT) and pulmonary embolism (PE) are frequently encountered in daily practice. Since both disorders may lead to considerable morbidity and mortality, both of untreated disease as well as anticoagulant treatment, objective diagnosis is mandatory.

In DVT diagnosis, venous compression ultrasonography is the test of choice for first presentation. For patients presenting with suspected recurrent DVT the diagnostic process is often problematic due to high false positive ultrasound results. Currently there is no good reference test in clinical practice.

For the diagnosis of PE, over the past years spiral computed tomographic pulmonary angiography (CTPA) has become the first line imaging test and this modality has largely replaced ventilation-perfusion lung scanning. Multi-row detector CT scanning has shown increasing sensitivity but specificity may be compromised as technology is progressing towards imaging of smaller arteries. The diagnosis of recurrent PE is problematic since there is no good reference test.

Despite the accuracy of imaging tests, the post-test chance of DVT and PE is dependent on pre-test probability. Standardised clinical evaluation models have been developed and these simple bed-side tools enable us to accurately categorise a patient's probability of having DVT or PE, prior to diagnostic imaging tests. D-dimer blood testing allows for an exclusion of the diagnosis of DVT or PE if clinical probability is sufficiently low and when the D-dimer test is negative. There are now a number of validated quantitative D-dimer assays that have high enough sensitivities, which enable use in combination with clinical probability.

A combination of clinical assessment and D-dimer and imaging enables safe DVT and PE rule-out algorithms without imaging, an ability to suspect false positive imaging results, and more accurate assessment of true positive imaging. These diagnostic strategies, which are feasible in almost all patients, result in efficient, safe and convenient care for patients with suspected venous thromboembolic disease.
Patients with a body mass index (BMI) above 30 Kg/m\(^2\) are defined as obese and have an increased risk to develop postoperative venous thromboembolism (VTE). Actually, half of all fatal postoperative pulmonary embolism (PE) detected in one study from Mayo Clinic occurred in obese patients.\(^1\) Therefore, all obese patients undergoing major surgery should receive prophylaxis.

Patients undergoing surgery for weight reduction usually have a BMI>35-40 Kg/m\(^2\) and are exposed to prolonged surgical procedures with restricted postoperative mobility. In addition, bariatric surgery is associated with significant postoperative hypercoagulability and fibrinolytic shutdown.\(^2\)

Most studies on bariatric surgery have reported incidences of symptomatic VTE between 0.2% and 2% in patients who received prophylaxis with heparin, stockings, or IPC. The incidence of fatal PE is between 0.2% and 0.3%, and the global mortality rate between 0.1% and 2%.$^3,^4$ According to the International Bariatric Surgery Registry (www.asbs.org), which has over 38,000 obese patients operated worldwide, the leading cause of postoperative death is pulmonary embolism. The following independent risk factors to develop VTE after bariatric surgery have been identified: severe chronic venous insufficiency of the legs, BMI>60, abdominal obesity, sleep apnea syndrome, history of previous VTE, smoking, anastomotic leak, and age >50 years.$^5,^6$

The latest American College of Chest Physicians (ACCP) Guidelines recommend routine thromboprophylaxis for patients undergoing inpatient bariatric surgery with low molecular weight heparins (LMWH) or heparin, at higher doses than usual for nonobese patients, or fondaparinux, alone or in combination with intermittent pneumatic compression (IPC).\(^7\) Heparin has been used at doses of 5,000 and 7,500 U every 8 hours or by intravenous infusion of 400 U per hour. Another option is to adjust heparin dose to achieve plasma anti-Xa activity between 0.11 and 0.25 U/ml. LMWH evaluated in bariatric surgery include enoxaparin (40-80 mg/24h), nadroparin (5,700-9,500 U/24h) and dalteparin (5,000U/24h).\(^3,^4\) Mechanical methods, such as stockings or IPCs, are not recommended as the sole method of prophylaxis in very high-risk patients. In fact, they are adjuncts to pharmacological prophylaxis and are the only option in patients at very high bleeding risk in whom anticoagulants are contraindicated. In a prospective cohort study conducted by Scholten and colleagues, two dosing regimens of LMWH were evaluated in sequence: enoxaparin 30 mg twice daily in 90 patients, and 40 mg twice daily in the next 389 patients. All patients also received stockings and IPC.$^8$ The incidence of symptomatic DVT was significantly lower in patients receiving 40 mg twice daily (0.6%) than in those taking 30 mg twice daily (5.4%) (P<0.001). There were not significant differences in the incidence of bleeding complications.
Regarding the duration of prophylaxis after bariatric surgery, some studies have reported a late presentation of VTE that could warrant prolonged prophylaxis. In one study of 106 patients who received heparin during hospital admission, all symptomatic VTE cases occurred after hospital discharge and once prophylaxis had been discontinued. Similar results have been reported in the PROBE study, since of the 7 VTE cases recorded, all were detected after the cessation of prophylaxis. More prospective studies are needed to investigate the optimal dosing and duration of prophylaxis in bariatric surgery.

References
Antithrombotic therapy: emerging issues

Thromboembolism in medical patients after hospital discharge – how long?

Geno J Merli, USA

Acutely ill medical patients are a clinically heterogeneous group at significant risk of venous thromboembolic (VTE) complications. Although thromboembolic disease has not been studied as extensively as the surgical population, the morbidity and mortality is significant in hospitalised medically ill patients. Without prophylaxis the incidence of deep vein thrombosis and pulmonary embolism in general medical patients is comparable to that reported in moderate risk surgical patients ranging from 10% to 30%. In addition autopsy series of hospitalised patients revealed 75% of pulmonary embolic deaths are in the medical population. The Eighth Consensus Conference on Antithrombotic Therapy of the American College of Physicians recommends either low molecular weight heparin or unfractionated heparin for acutely ill medical patients hospitalised with congestive failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease as prophylaxis to prevent VTE in patient with the above risk factors.

Prolonged VTE prophylaxis has been shown to be effective, safe, and cost effective in particularly high risk surgical settings such as orthopedic joint replacement and cancer surgery. This raises the question of the risk of VTE in medically-ill population following hospital discharge. It must be kept in mind that many of the medically-ill patients are not fully mobile and have permanent risk factor which remains in the out patient setting. The EXCLAIM trial demonstrated a reduction in VTE with extended prophylaxis for 30 days with low molecular weight heparin. The purpose of this workshop is to review cases of hospitalised medically-ill patients and discuss their management in the outpatient setting.

References


Antithrombotic therapy: emerging issues

Cardiometabolic syndrome

Job Harenberg, Germany

Antithrombotic therapy in cardiovascular diseases is established for the prevention of venous and arterial thromboembolism (TE) using short-term therapy with activated partial thrombin time (APTT) adjusted heparin, subcutaneous body-weight adjusted low-molecular-weight heparin (LMWH) or fondaparinux. Low doses are given to patients for the prevention of venous TE, and high doses for acute venous and/or prevention and treatment of acute arterial TE. If chronic anticoagulation is required patients are treated with vitamin K antagonists (VKA) adjusted to an INR (international normalized ratio) of 2 to 3. Synthetic inhibitors with immediate inhibition of specific clotting factors are developed due to limitations of therapy with VKA.

The most advanced compounds in clinical development are synthetic oral direct factor Xa and IIa inhibitors. The direct oral thrombin inhibitor ximelagatran was withdrawn from the development due to elevation of liver enzymes and occurrence of unstable angina after termination of therapy. The development of the indirect acting factor Xa inhibitor idraparinux was stopped due to an increased incidence of major bleeding complications based on a 60-day or longer half live after 6 or 12 months of therapy. The oral direct factor IIa inhibitor dabigatran and Xa inhibitor rivaroxaban received approval from the authorities for prevention of venous thromboembolism (VTE) following total hip or knee replacement operations.

The long-term indications for the prevention of embolism in patients with atrial fibrillation are currently being investigated using rivaroxaban, apixaban dabigatran, and idrabiotaparinux. The prevention of myocardial infarction and other severe events is currently investigated in patients with unstable angina using rivaroxaban, apixaban, the intravenously administered otamixaban, dabigatran, and some other compounds. Dabigatran is planning a roll-over study for patients who received the factor IIa inhibitor in the Randomized Study of Long-term Anticoagulant Study (RELY Study) to avoid switching to VKA therapy after termination of the project. The frequency of the control of the liver enzymes has been reduced in the RELY Study due to a lack of a difference in the changes of the liver enzymes between the treatment groups (two doses of dabigatran and warfarin).

New anticoagulants will encounter emerging issues such as compliance of patients; treatment of bleedings; time to steady state after long-term administration; drug interactions; effects of long-term therapy with platelet inhibitors on bleeding, and standardisation of methods to determine the anticoagulant effect of the new anticoagulants.
Should asymptomatic distal DVT count as an endpoint. Yes.

David Bergqvist, Sweden

Although various scoring systems have increased the sensitivity of clinical diagnosis of deep-vein thrombosis (DVT) we learnt from early venographic studies of symptomatic patients that many – in some series up to almost 50% – did not have DVT. On the other hand, using objective diagnostic methods (primarily fibrinogen uptake test and venography) in systematic surveillance of postoperative patients we learnt that many DVT occurring postoperatively were in fact asymptomatic. Therefore it became mandatory to use some objective diagnostic methods in studies on prophylaxis against postoperative DVT. In so doing it became obvious that some operations (i.e. major orthopaedic surgery, abdominal/pelvic cancer surgery) were complicated with very high frequencies of DVT, however, with a significantly prevention using various prophylactic methods. By and by the question was raised on the clinical significance of these asymptomatic DVT, and the most radical opponents advocated the use of total mortality as an endpoint and used the term surrogate for the phlebographically detected asymptomatic DVT. This terminology could, however, be challenged as a thrombus seen at venography – whether symptomatic or not - reflects the disease process which pathologically is a thrombosis. Asymptomatic distal DVT should count as an endpoint in prophylactic studies because:

1. there is a continuum in the pathologic process of distal DVT to proximal DVT, of asymptomatic DVT to symptomatic DVT;

2. asymptomatic DVT indicates a patient with risk for pulmonary embolism;

3. there is a correlation between prevention of distal DVT and fatal pulmonary embolism;

4. the sample size of prophylactic trials can be kept smaller, which has economic implications.

The ideal situation of studying prophylaxis would be to evaluate the prophylactic effect in RCT with some objective thrombodiagnostic method and then analyse the external validity in a large population sample using a very simple clinical protocol.
Clinical trials in VTE: where are we going

Should asymptomatic distal DVT count as an endpoint. No.
Charles Marc Samama, France

The clinical trials assessing the benefit/risk ratio of either old or new antithrombotic agents (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux, anti-Xa (rivaroxaban, apixaban) and anti-IIa agents (dabigatran) etc…) have always been using asymptomatic DVTs assessed by bilateral ascending venography as a surrogate end point. The high rate of events observed with this indirect method has meant that the numbers of patients included into Phase II and Phase III studies have been relatively small. However, although there may be a relationship between venographic and symptomatic thrombosis, it ranges from a factor of 5 for total hip replacement to a factor of 21 for total knee arthroplasty. In addition, the relevance of distal thromboses diagnosed by venography is debatable.

A multicenter international study, the CACTUS study (Contention Alone Versus Anticoagulation for Symptomatic Calf Vein Thrombosis Diagnosed by Ultrasonography), will probably provide useful data in a near future: patients with distal DVTs are randomised into two groups, a treatment group or a placebo group. If, as expected, no difference is observed between the two groups, the interest in distal DVTs will vanish because they will no more represent a valid surrogate endpoint. The new 2008 guidance from European regulators (EMEA) on outcomes in trials of prophylaxis for venous thromboembolism therefore suggests the use of a combination of three criteria, namely, symptomatic or asymptomatic proximal DVT assessed by ultrasound (or venography), pulmonary embolism, and VTE-related death. If these criteria are used in the development of future molecules, the results will probably better reflect the real-life situation, even if it is necessary to significantly increase the number of patients entered into trials.

References
The relevance of arterial thromboembolism in VTE prophylaxis studies

Bengt I Eriksson, Sweden

**Background:** Anticoagulants could be associated with a rebound like effect potentially increasing the risk of thrombosis and cardiovascular events following discontinuation of prophylactic treatment. This controversy has been reiterated in connection with study results on oral thrombin inhibitors and oral factor Xa inhibitors. The lessons from the adverse events reporting on cardiac events observed in the ximelagatran studies have resulted in the greater emphasis from medical authorities on longer follow-up of patients enrolled in orthopaedic surgery studies. Such a detailed follow-up was not undertaken in studies on previous agents, such as low-molecular-weight heparin, and much closer scrutiny of cardiac events has been performed in current studies of new agents. Recently published Phase 3 studies on prevention of venous thromboembolism (VTE) after major orthopaedic surgery have assessed the potential risk of cardiovascular events, mainly acute coronary syndrome (ACS) during and after prophylactic treatment.

**Methods:** ACS data will be extracted from recent phase 3 trials in major orthopaedic surgery in VTE prevention. The data review includes unstable angina, myocardial infarction and cardiac death.

**Results:** Results of ACS events in recent Phase 3 studies on VTE prevention after major orthopaedic surgery, reflecting a possible rebound like effect, will be presented.
Coagulation protease signalling

Wolfram Ruf, USA

The hemostatic system plays important roles in supporting metastasis, tumor growth and angiogenesis. A key feature of aggressive tumor cells is the expression of tissue factor (TF) that triggers coagulation when tumor cells enter the circulation during metastatic spread. Thrombin generation and platelet activation are crucial pathogenic events that support tumor cell homing and survival at distant metastatic sites. TF is also expressed early in tumor progression and promotes primary tumor development.

Recent data provide new insights into mechanisms by which TF supports tumor growth.

1. Ectopic synthesis of factor VIIa by tumor cells under hypoxia shows that a functional TF-VIIa complex can form without prior exposure to the blood. Consequently, tumor cell TF-VIIa is positioned to regulate the angiogenic switch and/or promote an invasive phenotype during tumor progression.

2. Genetic mouse models of spontaneous, oncogene-driven tumor development have uncovered that deficiency of protease activated receptor (PAR) 2, but not of PAR1 impairs tumor development. Therefore, the primary signaling receptor for the TF-VIIa complex, i.e. PAR2, makes a significant contribution to primary breast cancer development, whereas the thrombin receptor PAR1 is not required.

3. An antibody that is a specific inhibitor of tumor cell TF-VIIa signaling blocks tumor growth and is at least as potent as other antibodies that also inhibit TF-dependent coagulation. Thus, it is sufficient and probably also necessary to inhibit TF-VIIa signaling to achieve anti-tumor effects with TF-directed strategies in cancer therapy. In addition, anti-TF therapy at optimal doses can be envisioned without impairing normal haemostasis.

Clinical translation of these novel concepts from basic research will require new diagnostic approaches in order to identify patients that benefit from strategies directed towards the signaling aspects of the TF-initiated coagulation pathway.
Predicting those at risk of venous thromboembolism in cancer

Charles W Francis, USA

Patients with cancer are at elevated risk of venous thromboembolism (VTE) and represent up to 20% of all who present with deep-vein thrombosis (DVT) or pulmonary embolism (PE). Cancer patients are, however, very heterogeneous, and the risk varies greatly among patients with different types of cancer and also over time in an individual patient through the course of diagnosis and treatment. Cancer patients who are hospitalised and those treated as outpatients should be considered separately. A considerable body of information indicates that hospitalised cancer patients undergoing surgery are at particularly high risk and benefit from prophylaxis. Evidence also indicates that cancer patients hospitalised on the medical service are at high risk, and consensus guidelines recommend routine prophylaxis. Less information is available regarding outpatients who represent a particularly important group as cancer treatment has largely shifted to the outpatient setting. Despite the elevated risk, only a few studies have investigated the value of prophylaxis in cancer outpatients, and these have had mixed results. One approach is to risk-stratify cancer outpatients to identify those at highest risk who would benefit from thromboprophylaxis. A rate of symptomatic VTE at approximately 5% to 7% would be similar or greater than that reported in hospitalised or postoperative patients for whom prophylaxis has been shown to be highly effective. We, therefore, have worked to develop a risk stratification model for VTE in cancer outpatients receiving chemotherapy. Using baseline clinical and laboratory variables, we developed a simple model for predicting risk from a derivation cohort of 2701 outpatients from a prospective observational study, and this was validated in an independent cohort of 1365 patients. Five predictive variables were identified in a stage-adjusted multivariate model. Rates of VTE were less than 1% in those in a low risk group, approximately 2% in those at intermediate risk and 7% in high risk groups over a median follow up of 2.5 months. The use of such a model may be helpful in selecting cancer outpatients for studies of thromboprophylaxis.
Approach to the management of unusual cases of cancer-related thrombosis

Howard A Liebman, USA

While the majority of thrombotic events reported in cancer patients present as lower extremity deep venous thrombosis or pulmonary embolus, atypical thrombotic events occur and present a challenge for the clinician in diagnosis and management. Autopsy studies and reported symptomatic venous thromboembolism (VTE) are discordant, suggesting that VTE remains either an under-diagnosed and under-treated phenomenon.1-4 A recent case controlled study of patients with incidental pulmonary emboli detected on computed tomography (CT) scans used for routine cancer staging have find that these events are associated with significant patient morbidity.5, 6 The overall prognosis of the individual cancer patient with incidental pulmonary emboli is unknown, but one case controlled study suggest a worse prognosis.4 Since the majority of patients with unsuspected VTE have advanced malignancy and are receiving ongoing therapy5, 6, the risk of progressive thrombotic events is significant. Under these clinical circumstances antithrombotic therapy with LMW heparin appears justified.7

An increasing number of arterial events are now being reported in clinical trials of anti-angiogenic therapies.8 A meta-analysis of five completed cancer trials using chemotherapy plus bevacizumab, the incidence of arterial thromboembolic events was 3.8%, twice that seen in patients receiving chemotherapy alone.

The mortality associated with these events was 0.8%, again twice that seen with chemotherapy alone (0.4%).8 In patients with advanced malignancy, arterial events and strokes may be associated with the development of non-bacterial, thrombotic endocarditis (NBTE). The development of NBTE is frequently linked to the development of chronic disseminated intravascular coagulation in cancer patients.9, 10 In this presentation, three cases of cancer patients who presented with atypical thrombotic events to the University of Southern California Norris Comprehensive Cancer Center will be presented and the approach to diagnosis and management will be discussed.

References


What is wrong with vitamin K antagonists?

Kenneth A Bauer, USA

Vitamin K antagonists (VKAs) are the only option for oral anticoagulation and have been in use for more than 50 years. The anticoagulant effect of VKAs occurs via interference with γ-carboxylation of coagulation factors II, VII, IX, and X, resulting in reduced biological activity. VKAs are highly effective in the prevention and treatment of venous thromboembolism, and are the only agents indicated for long-term use in the prevention of stroke in patients with atrial fibrillation. However, the dose-response relationship of warfarin is unreliable because it is affected by several genetic and environmental factors. There is a greater than 10-fold inter-individual variability in the dose required to achieve effective anticoagulation and, therefore, frequent coagulation monitoring is required. Genetic polymorphisms account for a significant degree of the variability in dose-response. The pharmacokinetics of warfarin are also altered by diet, drugs, alcohol, and various disease states, necessitating frequent monitoring and dose adjustments to ensure that patients remain within the target international normalised ratio (INR) of 2-3. Other factors that need to be considered when determining the appropriate warfarin dosage are patient age and body weight. Bleeding is the major complication of VKAs – intensity of anticoagulation is the main risk factor for bleeding, but other risks include age greater than 75 years, highly variable INRs, a history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, trauma, malignancy, renal insufficiency, and concomitant medication such as acetylsalicylic acid. Given the multitude of variables influencing the safe and effective management of warfarin therapy, it is not wholly unexpected that even with regular coagulation monitoring, data from studies suggest that patients are within the target therapeutic range only about 60% of the time. The inherent limitations of warfarin, in terms of safety and convenience of treatment, comprise a significant barrier to treatment and oral anticoagulation remains significantly underutilised, particularly among elderly patients.
Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia, and confers a substantial mortality and morbidity from stroke and thromboembolism, as well as heart failure and impaired quality of life. With the increasingly elderly population, the prevalence of AF is increasing, resulting in a major public health problem. Data from the Framingham and Rotterdam studies suggest that we have a 1 in 4 lifetime risk of developing AF.

What is less clear is the required ‘burden’ of the arrhythmia (that is, AF episodes and duration) necessary for precipitating stroke and thromboembolism. Indeed, the number of AF episodes per day – as well as AF burden – can vary greatly. Also, paroxysms of AF are frequently asymptomatic. The only published data on AF burden related to thromboembolism comes from the Italian AT500 Registry Investigators, where the adjusted risk of thromboembolism in a cohort of (relatively elderly) patients suffering from bradycardia and implanted with a pacemaker with antitachycardia pacing therapies, was 3.1 fold increased (p = 0.044), but only in patients with device-detected AF episodes of >24hours during follow-up. Given the nature of this study cohort (elderly, pacemaker, multiple comorbidities, etc), we do need further studies in ‘general’ populations of paroxysmal AF to provide more information into the epidemiology and pathophysiology of AF burden and thromboembolism.

What can we do to prevent the burden of stroke and thromboembolism in AF? The most recent meta-analysis by Hart et al (2007) concluded that when compared with control, adjusted-dose warfarin and antiplatelet agents reduced stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%), respectively. Adjusted-dose warfarin was also more efficacious than antiplatelet therapy (relative risk reduction, 39% [CI, 22% to 52%]) (12 trials, 12 963 participants). The risk of stroke in AF is not homogeneous, and risk factors can be clearly identified that confer a high risk of thromboembolism. These risk factors have been used to formulate risk stratification schema and thromboprophylaxis guidelines.

Key References


Atrial fibrillation


Women’s health and thrombosis

Pregnancy

Rupert Bauersachs, Germany

Venous thromboembolism (VTE) during pregnancy often unexpectedly confronts obstetricians, internists or vascular specialists with a wide variety of complex clinical problems, demanding immediate, difficult and far-reaching medical decisions. The management is challenging, not only because two vulnerable patients have to be treated simultaneously over an extended and critical period, but also because the choice of drugs is limited by potential side effects both to the mother and the unborn baby. Randomised Clinical Trials (RCTs) are very difficult to conduct in pregnant women, and thus good quality, prospective data are scarce, and no antithrombotic drug is licensed for the use in pregnancy. VKAs are highly effective, however, they cross the placenta and have a potential to cause miscarriage, teratogenicity and bleeding in the fetus. Heparins do not cross the placenta, and low molecular weight heparins (LMWH) are now the standard antithrombotic during pregnancy. Pregnant women commonly give a higher priority to the health of the child than to their own health, and thus prefer LMWH, when VKA would be an option, for example with mechanical heart valves. Thus, risk-benefit-assessment is paramount. At least three risk groups for VTE during pregnancy have been identified, ranging from low-risk (e.g. asymptomatic thrombophilia), to high-risk (e.g. prior VTE associated with thrombophilia or hormones), to a very high-risk group with prior VTE and high-risk thrombophilia, such as antithrombin-deficiency or persistent antiphospholipid antibodies (APLA). Accordingly, the antithrombotic management will escalate from watchful waiting with post-partum prophylaxis in the low-risk group, to antenatal prophylactic or intermediate dose LMWH, while for therapeutic LMWH doses are used in acute VTE or mechanical valve patients.

Pregnancy complications, including recurrent miscarriages or pre-eclampsia are correlated with APLA, and active thromboprophylaxis is recommended. Trials imply that pregnancy complications may also be associated with other thrombophilias, suggesting thromboprophylaxis for those women, even though large RCTs have not yet been completed to support this commonly used approach.

Today, reliable recommendations for the antithrombotic management are available for the complex conundrum of pregnancy, VTE and thrombophilia. The efficacy and safety of LMWH in the prevention and treatment of VTE has been demonstrated in thousands of pregnancies, while we are awaiting results for the potential protective of effects of LMWH on pregnancy complications.
**Menopause and thrombosis**

*Benjamin Brenner, Israel*

Randomised controlled trials have shown that the risk of stroke and venous thromboembolism (VTE) is increased with hormone replacement therapy (HRT). In a recent meta-analysis\(^1\) HRT was associated with increases in stroke (OR, 1.32, 95% CI, 1.14-1.53) and VTE (OR 2.05, 95% CI 1.44-2.92). Furthermore, HRT was associated with an increased stroke severity, but not with coronary heart disease (CHD) events. Combined HRT increases the risk of VTE compared with estrogen monotherapy while transdermal HRT are not associated with increased thrombotic risk.\(^2\) Thus it has been suggested that certain sub-groups of patients should be specifically treated with an oral regimen eg those with lipid and lipoprotein abnormalities and impaired glucose tolerance whereas those with a personal or relevant family history of venous thrombosis should be treated with a transdermal regimen.\(^3\) The Women’s Health Initiative (WHI) examined the use of combined HRT (continuous estrogens plus progestins) and the use of estrogens alone in menopausal women. The first study was terminated prematurely at 5.2 years because the number of CHD, strokes, venous thromboembolic disease, and breast cancer were increased in women receiving HRT. The WHI study was criticised for its conclusions as far as cardiovascular disease is concerned because of issues regarding design of the trial.\(^4\) It was suggested that a closer look at the results of the WHI trial reveals that the use of HRT for 5 years should not be considered deleterious for the appearance of breast cancer, cardiovascular diseases, strokes, and pulmonary embolism.

The mechanisms for increased thrombotic risk in HRT users include impaired function of the protein C pathway demonstrated by APC-resistance\(^5\)-\(^6\) and abnormal Protein C Global assays. This was found with the oral preparations of HRT but not with transdermal preparations. HRT may affect coagulation and inflammation.\(^7\) However, genetic polymorphisms in the estrogen receptor 1 (ESR1), CRP and fibrinogen genes were not associated with these effects of HRT.\(^8\) Estrogens may prevent the development of atherosclerosis through favourable effects on an intact endothelium, but once the vascular endothelium is damaged, the prothrombotic and possibly proinflammatory effects of estrogens are likely to predominate and prove harmful.

**References:**


Prevention of venous thromboembolism in patients with cancer

Paolo Prandoni, Italy

The majority of venous thromboembolic (VTE) complications in cancer patients develop spontaneously, and thus are by definition not preventable. Indeed, there is not evidence in support of systematic preventive strategies in cancer patients, nor is there is subgroups of cancers. Among the main triggering risk factors of VTE in cancer patients are prolonged immobilization (especially during hospital stay), surgical procedures, the insertion of central venous lines, chemotherapy, adjuvant therapy, and surgical procedures.

Several investigations have been conducted in recent years showing the advantage of pharmacological prophylaxis in high-risk medical patients, including patients with cancer, and several meta-analyses of the most adequate studies have been performed in order to check the clinical relevance of the administered thromboprophylaxis. They consistently showed that the implementation of adequate pharmacological prophylaxis reduce the risk of clinically symptomatic VTE and that of fatal pulmonary embolism during the period of hospitalization. Among the recommended preventive strategies, prophylactic high-dose low-molecular-weight heparin (LMWH) is the most commonly adopted. The institution of computer-alert programs and electronic tools has the potential to increase physicians’ use of prophylaxis.

In the absence of thromboprophylaxis the incidence of upper limb deep vein thrombosis (DVT) in cancer patients following the insertion of indwelling central venous catheters is high. The incidence is highest when systematic phlebography is used as diagnostic test, and decreases with the use of non-invasive tests, particularly when performed in the only clinically symptomatic patients. Unfortunately, however, the results of recent randomised studies failed to show an advantage of either LMWH or low-dose warfarin over placebo for prevention of catheter-related upper limb DVT.

Patients with cancer are at a particularly high risk of developing both venous and arterial thrombosis when they receive chemotherapy, as convincingly demonstrated by a few investigations conducted in women with breast cancer at various stages. The association of tamoxifen with chemotherapy increases the thrombotic risk over tamoxifen alone. Tamoxifen alone is also associated with risk of complications. According to results of recent studies, this risk is halved by the use of third-generation oral aromatase inhibitors, such as anastrozol. Due to the paucity of clinical information, and the consequent lack of international accepted recommendations, the decision as to give thromboprophylaxis to patients undergoing chemotherapy, with or
without adjuvant hormonal therapy, remains a decision to be adopted on an individual basis. Based on the recommendation delivered by the American Society of Clinical Oncology, an exception should be done for cancer patients receiving thalidomide or lenalidomide in combination with chemotherapy or dexamethasone, who should receive longstanding adequate thromboprophylaxis.

In the absence of thromboprophylaxis, cancer patients have a risk of postoperative DVT that is approximately twice as high as that observed in patients free from malignancy. Of interest, 40% of events occur more than three weeks after surgery. The most appropriate prevention of postoperative VTE in cancer patients requires the proper choice of the drug and the proper duration of prophylaxis. Among the strategies that are recommended, the most commonly adopted is the LMWH in doses that are currently recommended for patients that are candidates to major orthopaedic surgery. Based on the results of recent studies, the advantage conferred by LMWH is further improved by prolonging prophylaxis for at least three weeks after the patient’s discharge.
A biological target for cancer therapy?

A.K. Kakkar, UK

Thrombosis is a common complication in patients with malignant disease. The use of antithrombotic therapy for the prevention and treatment of thromboembolic disease have the potential to impact in a clinical important way on outcomes for patients with malignant disease.

Results of meta-analysis of deep vein thrombosis treatment studies conducted in the 1990s suggest that cancer patients receiving low-molecular weight-heparins for initial treatment of their thrombosis had a prolonged survival. Although of great interest, these findings need to be interrupted with caution as the analysis was retrospective, and conducted without certainty of the appropriate balance of cancer prognostic variables between patient groups.

More recently a number of prospective clinical trials have evaluated the potential benefits of chronic exposure to low-molecular-weight heparin in terms of prolonging survival in patients with malignant disease. These studies, recently subjected to meta-analysis, suggest an important potential benefit to low-molecular-weight heparin exposure for cancer patients.

Mechanistic explanations for the clinical benefit in terms of reduced mortality include a potential reduction in the frequency of fatal pulmonary embolism, interference with activated coagulation proteases which, in the experimental situation, have been demonstrated to influence tumour biology, and potential direct cellular effects of heparin including an antiangiogenic and a proapoptotic mechanism.

A series of ongoing studies are further assessing the potential benefits of antithrombotic therapy to prolong survival in patients with malignant disease.
Debate

Factor Xa is a superior target to factor IIa for antithrombotic therapy. For.

Harry R. Büller, The Netherlands

The coagulation system had for a long time been viewed as a gradually widening cascade and therefore, if the aim is to control excessive coagulation, it is probably wise to have inhibitors that act upstream. Historically, built on our test-tube knowledge of the coagulation system the thrombin-inhibition-dogma emerged. This theory states that compounds, which lack the ability to inhibit thrombin, will be poor antithrombotics. It is for this reason that when pure Xa inhibitors were developed, they were initially shelved because the dogma dictated that they would not be effective, since trace amounts of thrombin would be able to fully activate the system.

This ignores the capacity of the in vivo inhibitory systems to deal with trace amounts of thrombin. Purely from an enzyme-kinetic point of view, inhibition of factor Xa would be preferred, since one Xa molecule is able to generate approx 1000 molecules of thrombin per minute. Fortunately, next to these kinetic arguments there is now a wealth of clinical data supporting the concept that pure Xa inhibitors are at least as effective as (and often superior to) existing anti-thrombotic agents such as low-molecular-weight heparins and unfractionated heparin. The latter compounds, as is well known, are able to inhibit thrombin.

Albeit on theoretical grounds, Xa inhibition is likely to have a better therapeutic margin than IIa inhibitors. Since trace amounts of thrombin are necessary for normal haemostasis, the major challenge with pure thrombin inhibitors is to balance over and under dosing. Thus, antithrombotic agents based on factor Xa inhibition are likely to be superior to factor IIa inhibitors, although after the proper dose finding studies with each of these compounds, the real answer should come from head to head comparisons. These have not been performed and hence we have to rely on between study comparisons. Careful analyses of these studies, which now have entered Phase III evaluations confirm the efficacy and safety of Xa inhibition and indirect comparisons with IIa inhibitors, support the promise of pure factor Xa inhibitors.
Factor Xa is not a superior target to factor IIa for antithrombotic therapy. Against.

Sam Schulman, Canada

It is often claimed that Xa is the optimal target for anticoagulant agents, due to its strategic location where the intrinsic and extrinsic pathways merge. However, in the coagulation pathway thrombin is immediately downstream from Xa, and irrespective of where the inhibition is presented the end result is a diminished fibrin formation. If that occurs where hemostatic effect is needed for trauma to blood vessels, bleeding will ensue. The pentasaccharides are pure factor Xa inhibitors, albeit indirect. Fondaparinux demonstrated good effect in major orthopaedic surgery (MOS) but gave more bleeding than low-molecular-weight heparin (LMWH). Rivaroxaban, a direct Xa inhibitor, was more effective in MOS since also symptomatic thrombosis was reduced. The thrombin inhibitor dabigatran was as effective as LMWH except in the comparison with enoxaparin 30 mg bid, where it failed. There was no significant difference in bleeding between rivaroxaban or dabigatran and the comparator in any of the trials. However, definitions of major bleeding and sample sizing deserve scrutiny.

We know little about the effects of anticoagulants on platelets, vascular cell receptors, mediators of inflammation and cell proliferation. Thrombin inhibitors seem to generate some inhibition of platelet function, additive to the effect of aspirin. This may be an advantage in the treatment of arterial disease. Another setting that needs to be explored is the combination with thrombolytic agents in myocardial infarction. A vast experience from currently approved anticoagulants demonstrates that whereas one agent is safer than another in a specific setting, the reverse may be true when given for another diagnosis. The idraparinux Phase III trials also demonstrated this ambiguity. The optimal anticoagulant will probably depend more on pharmacokinetic and pharmacodynamic characteristics, effects outside of the plasma coagulation, the particular disease and the concomitant drug therapy than on the target being Xa or IIa.
Organised under the auspices of the Thrombosis Research Institute, London, United Kingdom and supported by an unrestricted educational grant from Pfizer, Bristol-Myers Squibb and Eisai.