Welcome to Warsaw, welcome to Poland!

Dear colleagues and guests!

On behalf of Polish Foundation Against Thrombosis it’s my great pleasure welcome all participants and members of faculty to Warsaw on Third Warsaw Symposium on Thromboembolism, supported by unrestricted grant of Pfizer, Boehringer-Ingelheim, Bayer Schering Pharma.

Polish Foundation Against Thrombosis supported by Pfizer, Boehringer-Ingelheim, Bayer Schering Pharma was in a position to organize Third Warsaw Symposium on Thromboembolism. Rapidly developed proceedings in thromboembolism is excellent reason for successive – third meeting, addressed to primary prophylaxis, management and treatment of deep venous thromboembolism.

Deep venous thrombosis and pulmonary embolism remain major health problems with potential very serious outcomes. Acute pulmonary embolism may be fatal and is still unrecognized and untreated in many patients. Although venous thromboembolism is potentially preventable, effective prophylaxis is still difficult to achieve.

I hope, Third Warsaw Symposium on Thromboembolism will be important scientific opportunity for polish clinicians to update themselves on the latest developments in management, treatment and prophylaxis of venous thromboembolism, resulting in improvement of everyday clinical practice.

Prepared by members of faculty, who are the leading worldwide recognized experts on venous thromboembolism, interesting one-day scientific programme includes plenary sessions as well as workshops, which provides delegates with the latest scientific achievements regarded venous thromboembolism.

I trust you take home not only good impressions regarded scientific programme, plenary sessions and interesting discussions but also good vibrations connected with exciting days spent in Warsaw.

Witold Z. Tomkowski
President of Polish Foundation Against Thrombosis
Professor of Medicine, MD, PhD, FCCP
Friday, 18 June 2010

11.00-11.15 Welcome – W. Tomkowski (Poland)

11.15-11.55 Overview of Xa and Thrombin Inhibitors – R. M. Knabb (USA)

11.55-12.35 Antithrombotic prophylaxis in orthopaedic surgery in 2010
– M. R. Lassen (Denmark)

12.35-13.05 Controversial issues in orthopaedic surgery – thromboprophylaxis in patients with isolated leg injuries. YES or NO? – D. Chmielewski (Poland/Spain)

13.05-13.45 Antithrombotic prophylaxis in general surgery in 2010 – D. Bergqvist (Sweden)

13.45-15.00 Lunch

15.00-15.40 Physical methods in management of VTE – H. Partsch (Austria)

15.40-16.10 Treatment of VTE in 2010 – S. Haas (Germany)

16.10-16.30 Coffee break

16.30-17.10 VTE recurrence… why accept this? – A. Lensing (The Netherlands)

17.10-17.50 Cancer and VTE complications – management and treatment in 2010
– M. Prins (The Netherlands)

17.50-18.00 Closing remarks – W. Tomkowski (Poland)

20.00 Dinner

Saturday, 19 June 2010

9.00-9.30 Epidemiology of VTE; influence of patients awareness of VTE symptoms and burden on rate of DVT – W. Tomkowski (Poland)

9.30-10.00 Management and treatment of patients with inserted Vena Cava Filters
– B. Hajduk (Poland)

10.00-10.30 Hormonal therapy and VTE – K. Zawilska (Poland)

10.30-11.00 Management and treatment of antiphospholipid (APL) syndrome
– J. Musiał (Poland)

11.00-11.30 Discussion

11.30-12.00 Coffee break

12.00-13.30 WORKSHOPS

I Management and treatment of VTE – P. Kuca, W. Tomkowski
Diagnostyka i leczenie zakażenia żylnego a żył głębokich

II Orthopedic surgery – prophylaxis and VTE events management
– D. Chmielewski
Powikłania zakażenia żylnego w chirurgii ortopedycznej

III General surgery (including oncology) – prophylaxis and VTE events management – T. Urbanek, A. Jawień
Powikłania zakażenia żylnego w chirurgii ogólnej i onkologicznej

13.30-15.00 Lunch

All sessions translated simultaneously into Polish/English.
Witold Z. Tomkowski (Poland)

M.D., Ph.D., Professor of Medicine
President of Polish Foundation Against Thrombosis,
Chairman of Scientific Council and Head of Cardio-
Pulmonary Intensive Care Division at the National
Tuberculosis and Lung Diseases Research Institute,
Warsaw, Poland,
Chairman of Anti-thrombotic Treatment Centre, Warsaw,
Poland

Witold Z. Tomkowski is Professor of Medicine,
specializing in cardiology, internal and vascular
medicine. He is the Chairman of Scientific Council
and Head of Cardio-Pulmonary Intensive Care Division
at the National Tuberculosis and Lung Diseases Research Institute.

In 1980 Professor Tomkowski earned his M.D. at the Medical University
in Warsaw. After graduating, he completed his research fellowship in cardiology,
internal and vascular medicine.

Professor Tomkowski has authored and co-authored more than 200 scientific
articles, mainly in polish and international scientific literature, concerning
pericardial diseases and venous thromboembolism.

He was a reviewer for the CHEST, CMAJ, AJC, BJC.

Professor Tomkowski has also maintained a vascular stream of clinical
investigations, being involved as a member of steering committees in ARTEMIS
trial dedicated to thromboprophylaxis in medical patients and AMADEUS clinical
trial, which evaluated the long-acting anticoagulant idraparinux for prevention
of stroke in patients with atrial fibrillation and is serving as a member of Study
Management and Coordinating Committee in EINSTEIN II + III and BOTTICELLI
trials, which evaluated rivaroxaban and apixaban in patients with venous
thromboembolism.

Professor Tomkowski is also, a pioneer in intrapericardial administration
of different chemotherapeutic agents for management and treatment
of malignant pericardial effusion and co-author of European Cardiology

Abstract is later – according to the program in English.
Robert M. Knabb received his undergraduate degree from the Pennsylvania State University and a Ph.D. in Physiology from the University of Virginia. His doctoral research investigated the role of adenosine in the regulation of coronary blood flow under the direction of Dr. Robert M. Berne. He received postdoctoral training in the Cardiology Division, Department of Internal Medicine at Washington University in St. Louis. His basic and applied research during the early era of thrombolysis and myocardial reperfusion led him to pursue a career in pharmaceutical research. He began his career in drug discovery with the E.I. du Pont de Nemours and Company in 1985 and worked in the areas of myocardial reperfusion injury, thrombolysis, and coagulation factor inhibitors. He led a multidisciplinary team that advanced one of the first orally active Factor Xa inhibitors into clinical trials, and followed this with a series of compounds that led to the discovery of apixaban. He transitioned to clinical research with Bristol-Myers Squibb and is part of a large team that is currently developing apixaban for a number of indications. He has authored over 60 scientific articles and is a co-inventor on a number of patents. His research interests focus on the application of novel oral antithrombotic agents to meet unmet medical needs in a variety of thrombotic disorders.

Over the past several years we have begun to see results of late stage clinical trials of two new classes of oral anticoagulants: inhibitors of Factor Xa (FXa), and inhibitors of thrombin, or Factor IIa. Because of the high morbidity and mortality of thrombotic diseases, few areas in medicine have received as much attention as the discovery and development of new antithrombotic agents. While the past two decades have seen new antiplatelet agents that work by a variety of mechanisms, in the area of anticoagulation, we have been mainly working with agents that have been in use for many years, if not decades. Heparins and vitamin K antagonists have been the centerpiece of anticoagulant therapy for several decades, and clearly have been among some of the most important life-saving medicines ever developed. Both agents interact with multiple components of the coagulation system, and both agents have significant liabilities that impact their use. A major goal of efforts to discover and develop specific inhibitors of FXa and thrombin has been to overcome those liabilities, and approach the characteristics of the ideal anticoagulant.

Unlike the indirect inhibitors of FXa, such as fondaparinux, small molecule inhibitors of FXa or thrombin interact directly with the active site of their target enzyme. Most have been selected for their oral bioavailability, and are accordingly suitable for both acute settings such as prevention of venous thromboembolism (VTE), but also for chronic indications including VTE treatment, and stroke prevention in patients with atrial fibrillation.

Experience with thrombin and FXa inhibitors from nature, as well as with parenteral inhibitors such as the argatroban or DX-9065a established proof of principle for these mechanisms. This led to the development of the thrombin inhibitor ximelagatran, or Exanta, which many people believed would be the beginning of a new age of anticoagulation. Although Exanta was shown to be efficacious in a number of indications, hepatotoxicity prevented its widespread approval, and led to its removal from the market. An understanding of the potential benefits of direct inhibition of thrombin was gained from Exanta, and has led to the continued pursuit of thrombin inhibitors such as dabigatran and AZD0837. An even larger number of inhibitors of FXa have entered clinical development.
Currently, the three novel oral anticoagulants that are the most advanced in clinical studies are the thrombin inhibitor dabigatran, and the FXa inhibitors rivaroxaban and apixaban.

Dabigatran is a direct inhibitor of thrombin developed by Boehringer-Ingelheim. Like ximelagatran, it is administered as a prodrug, dabigatran etexilate, which is activated after absorption from the gastrointestinal tract. It is a highly potent and selective thrombin inhibitor, that has completed three phase 3 trials in orthopedic surgery, and is approved for VTE prevention after total knee replacement (TKR) or total hip replacement (THR) in Europe and several other countries. Results of a large study in atrial fibrillation, and one study in VTE treatment have also been published.

Rivaroxaban is a direct inhibitor of FXa that is being developed by Bayer and Johnson & Johnson. It is highly potent and selective, and has been shown to be effective in VTE prevention after TKR and THR, for which it is also approved in Europe and other countries. Phase 3 studies of rivaroxaban for VTE treatment, stroke prevention in atrial fibrillation, and secondary prevention of acute coronary syndromes are ongoing.

Apixaban is a direct inhibitor of FXa that was discovered at DuPont, and is being developed by Bristol-Myers Squibb and Pfizer. It is not yet been approved in any country. Phase 3 studies have been completed in TKR and THR, and are ongoing in VTE treatment, atrial fibrillation, and acute coronary syndromes.

Although theoretical differences between the inhibition of FXa and thrombin may suggest potential benefits of one mechanism over the other, the proof of any such benefit will await the completion of the large number of ongoing clinical studies of the three drugs discussed above, as well as from several other drugs in late stage development. We will also await these results to learn to what extent the direct inhibitors of FXa and thrombin will approach the characteristics of an ideal anticoagulant, and replace agents like heparin and warfarin in the fight against thrombotic diseases.
Michael Rud Lassen (Denmark)
Dept of Orthopaedics, Spine Clinic, Clinical Trial Unit, Hørsholm Hospital, Hørsholm, Denmark
Date of birth: 15th August 1953
Private address: Skovgæren 6, DK-2960 Rungsted Kyst
Work address: Hørsholm Hospital, Spine Clinic, Clinical Trial Unit, Usserød Kongevej 102, DK-2970 Hørsholm
Telephone: +4548292778
E-mail: mirula@noh.regionh.dk
Education: 1982: M.D., University of Copenhagen, Denmark
Scientific positions:
1982: Registrar, Depts. of Orthopedics, Aalborg Hospital
1985-1994: Depts. of Orthopedics, Aalborg Hospital
1994-1995: Spine Section, University Hospital of Aarhus
1995-2002: Dept. of Orthopedics, Hillerød Central Hospital
2002 – Consultant Surgeon, Chair of Clinic for Spine Surgery and Chairman of Clinical Trial Unit Hørsholm Hospital
Aarhus
Pharmaeconomics, clinical studies in non-fusion techniques in degenerative disc disease
Awards: Best oral Award, Dansk Ortopædisk selskabs annual meeting Copenhagen 1995
Main publications:
Michael Rud Lassen

Antithrombotic prophylaxis in orthopedic surgery in 2010

The need for standard thromboprophylaxis is well accepted for major orthopaedic surgery, especially for hip fracture surgery, total hip or knee replacement. The first routine regimen used for thromboprophylaxis was standard unfractionated heparin as 5000 units sc BID or TID during the hospital stay. In the 1970’ies it was discovered that small fragments of unfractioned heparin had a stronger antithrombotic potential, leading to the development of Low-Molecular-Weight-Heparin. Turpie et al. (1986) published the first clinical trial with LWMH. Several different LMWH’s have been introduced, all with different molecular weights and specific anti factor IIa and Xa ratios. In 1980’ies researchers identified a specific sequence of sugar molecules in heparin to be responsible for the factor Xa inhibition through antithrombin. By a very complex chemical process a synthetic pentasaccharide was developed and tested. This pentasaccharide, fondaparinux, had a high affinity to antithrombin, however, many researchers were sceptical that a pure factor Xa inhibitor would be successful. The clinical trials however, clearly demonstrated that a single target approach was significant better than standard regimens of LMWH in orthopaedic setting. Fondaparinux was approved in 2000 in many contries.

The single target idea led to screening for small molecules with direct inhibition of thrombin (factor Ila) and factor Xa. The first drug was melagatran that was given as an oral prodrug Ximelagatran. After a huge research program the drug, Exanta, was approved in Europe, but not in the US. The reason for not approving Exanta in the US was suspicition of rebound thromboembolism and myocardial infarction, together with a suspicion of hepatic impairment. This was finally the reason for the redraval of the drug in 2006. These problems with hepatic enzyme increase has lead to a rigorous screening of all new antithrombotic drugs. Two new anticoagulants, the direct thrombin inhibitor dabigatran etexilate and the direct factor Xa (FXa) inhibitor rivaroxaban, are now approved in Europe for the prevention of venous thromboembolism (VTE) in patients undergoing elective total hip or knee replacement (THR/TKR). Key differences from conventional anticoagulants are that these newly approved agents are administered orally and – unlike the vitamin K antagonists – possess more predictable pharmacokinetic and pharmacodynamic profiles and can be used without the need for routine monitoring and dose adjustment.

The direct FXa inhibitor apixaban is also in the late stages of clinical development.
Several large-scale phase III trials have compared the efficacy and safety of the new oral anticoagulants and the low molecular weight heparin, enoxaparin, in patients undergoing THR or TKR. In the six phase 3 trials employing the standard European enoxaparin dose (40 mg qd) as comparator, dabigatran, rivaroxaban and apixaban provided levels of protection against the primary composite end point of VTE and all-cause mortality that were statistically non-inferior or superior to those achieved with enoxaparin.\textsuperscript{2-4,7-9} Composite rates of major and clinically relevant non-major bleeding were either similar to those with enoxaparin, or significantly lower. Importantly, interpretation of these results requires close scrutiny of the trial designs, including practical aspects such as dosing, timing of first dose and duration of prophylaxis and definition of end-points.

Although the full impact of the new oral agents remains to be determined, it is hoped that their introduction will increase the use of thromboprophylaxis, thereby helping more patients avoid the potentially devastating consequences of VTE. It will be important to understand how the differences in timing, dosage, pharmacokinetic and pharmacodynamic parameters between the novel anticoagulants influence their use and outcomes in clinical practice.
Dariusz Chmielewski (Poland)

Doctor of Medical Sciences
Specialist in orthopedic surgery and traumatology of bones and joints
Head of Orthopedic Surgery and Traumatology Team at HOSPITEN Hospital – Lanzarote, Spain
For many years an assistant professor at the Chair and Clinic of Orthopedics and Traumatology of Bones and Joints, Medical University of Warsaw, consultant in the area of orthopedics at the Institute of Tuberculosis and Lung Diseases, Head of Clinic for Osteoporosis and Bone Tissue Metabolic Diseases at the Chair and Clinic of Orthopedics and Traumatology at Medical University of Warsaw, Head of Unit for Bones and Joints Metabolic Diseases at “Instytut Matki i Dziecka” (Institute of Mother and Child) in Warsaw, lecturer at the Polish Foundation of Osteoporosis, Polish Medical Society of Radiology and Polish Society of Orthopedics and Traumatology.

Author of 7 monographic chapters, medical books, over 40 articles published in foreign and national medical journals.

Co-author of the “Principles of venous thrombosis prevention in orthopedics and traumatology of bones and joints” – national guidelines developed by the group of experts appointed by the National Consultant for Orthopedics and Traumatology of Bones and Joints.


Controversial issues in orthopaedic surgery – thromboprophylaxis in patients with isolated lower leg injuries. YES or NO?

Current international and national guidelines define most of the clinical situations regarding the use of antithrombotic prophylaxis. However some of those are still controversial, like knee arthroscopy or lower-leg immobilization. To solve this problem or to precise the actual consensus (if exists) the delegates of Cochrane Peripheral Vascular Disease Group (part of Cochrane Database of Systematic Review) searched four worldwide registers of medical publication and contacted pharmaceutical companies to investigate the current literature on thromboembolic practice and to assess the need for concrete guidelines. Six randomized controlled trials with a total of 1490 patients were included in the analysis. Incidence of venous thromboembolism was ranging from 4.3% to 40% in patients who had a leg injuries splinted with casts or braces for at least one week and who received no prophylaxis. This number was significantly lower (event rates ranging from 0% to 37%, odds ratio 0.49) in patients who received daily prophylaxis with low molecular weight heparins (LMWH) (in two studies – nadroparin, in one – tinzaparin, nadroparin, reviparin). The authors decided to present an implication for practice advising administration of LMWH during the entire period of immobilization of the lower extremity. This advise accounts for both lower and above-knee casts or braces.

Similar, but not such categorical conclusion was presented in a similar research of actual bibliography on intervention for preventing venous thromboembolism in adults undergoing knee arthroscopy prepared by the same Group of Cochrane Collaboration in 2008. It was concluded that the surgeon need to evaluate a personal ratio of risks and benefits of thromboembolic prophylaxis in every patient undergoing arthroscopic surgery, taking into account the previous history of injuries, splinting and immobilization. It is essential that future studies categorize patients according to theirs risk factors, and also stratify arthroscopic procedures.
David Bergqvist (Sweden)

Department of Surgery, Academic Hospital, Uppsala, Sweden

Date of birth: 2nd of August 1941
Family: Married. Two daughters
Present appointment: Professor of Vascular Surgery, University of Uppsala, Head of Department of Vascular Surgery, Academic Hospital.
Previous appointments: Department of General Surgery, Uppsala, Skövde and Malmö.
Appointments as examiner: Associate Professor, University of Lund. Professor of Vascular Surgery, University of Uppsala.
Supervisor: 38 Ph.D. theses

Membership of societies:
- Swedish Society of Medicine
- Swedish Surgical Society
- Scandinavian Association for Vascular Surgery
- Swedish Society for Transplantation Surgery
- European Society for Vascular Surgery (hon.)
- International Union of Angiology
- Swedish Society for Vascular Surgery (hon.)
- American Venous Forum (hon.)
- International Society of Technology Assessment in Health Care
- Norwegian Society for Vascular Surgery (corr.)
- South African Vascular Society (corr.)
- Society for Vascular Surgery (corr.)
- Vascular Surgical Society of Great Britain and Ireland (hon.)

Lectures abroad:
- Several

Publications:
David Bergqvist

Antithrombotic prophylaxis in general surgery in 2010

Thromboprophylaxis in connection with surgery has been discussed for around 100 years but more generally evaluated and accepted since around 1970. To begin with vitamin K antagonists and unfractionated heparin dominated but around 1985 various low molecular weight heparins (LMWH) were approved. The main aim of prophylaxis to surgical patients is to prevent fatal pulmonary embolism (FPE). Without prophylaxis this occurs in around 1% in general surgical patients. It is important that patients undergoing surgery are classified into risk groups in need of prophylaxis to avoid prophylaxis to everybody. One common way has been suggested by the American College of Chest Physicians (ACCP): low risk minor surgery to mobile patients, moderate risk most general surgical patients and high risk abdominal and pelvic cancer surgery. Of the prophylactic methods approved today one of the LMWHs by far dominate the market. Although every LMWH is a unique pharmacological substance there are no indications that they differ in clinical effect. There are now a large number of studies as well as metaanalyses showing a statistically significant reduction in the frequency of FPE. The influence on postthrombotic syndrome is less clear and not sufficiently studied. The factor Xa inhibiting pentasaccharide fondaparinux has also been shown thromboprophylactically effective in general surgery. One special risk group within general surgery includes patients undergoing surgery for abdominal/pelvic malignancy, where several factors contribute to an increased risk for venous thromboembolism as well as a prolonged risk period. There are now some studies as well as a metaanalysis showing that this group of patients benefit from prolonging the prophylaxis to around one month with a significant reduction of deep vein thrombosis compared with prophylaxis for one week. Prophylaxis with LMWH is effective with a very minor bleeding risk. In patients with an increased risk of bleeding mechanical prophylactic methods may be used. The new specific IIa and Xa inhibitors are effective in orthopaedic surgery but has yet to be evaluated in general surgical patients. A principal problem when evaluating new thromboprophylactic methods is that to start with only high risk orthopaedic surgery is studied, not high risk general surgery, which has an influence on indications and recommendations.

To conclude, today there are pharmacological substances to use in general surgery – both effective and safe.
Hugo Partsch (Austria)

Professor of Dermatology
Born in Vienna

Education and Academic career:
School of Medicine, University of Vienna, Freiburg i.Br. and Kiel/Germany
Graduation (M.D.), University of Vienna, Austria
Senior Registrar Dermatologic Department, Wilhelminen-Hospital
Head of the Vascular Service, Hanusch-Hospital, Vienna
Professor of Dermatology, University of Vienna
Head of the Dermatological Dept., Wilhelminen-Hospital, Vienna.
Retired, working in private practice

Scientific work and clinical main-interests:
More than 360 papers in scientific medical journals and contributions
in books. Main-subjects: peripheral vascular diseases, instrumental
methodology (nuclear medical methods, non-invasive investigations, indirect
lymphography), neuropathic foot, lymphoedema, deep vein thrombosis,
leg-ulcers, compression therapy.

Awards and Scientific societies:
Awards from the Swiss and from the German Societies of Phlebology, from
the World Union of Wound Healing Societies Congress 2008, and from
different Austrian Organizations. Honorary member of the British Venous
Forum, the American Venous Forum, of the Swiss, French and German
Society of Phlebology and of the American College of Phlebology, the Swiss,
German and the Czech Society of Angiology, the American Society for
Dermatological Surgery, the Austrian Wound Association (AWA), and the
Associazione Italiana Ulcere Cutanee (AIUC). Corresponding member of the
Slovak Society of Angiology. Fellow Emeritus of the Australasian College
of Phlebology. Honorary Affiliate Member of the American Society for
Dermatologic Emeritus Co-editor of VASA, Journal for Vascular Diseases,
Past-Chairman and Founder of the Austrian Working Group for Phlebology
President of the Austrian Society of Angiology 1995/96.

Physical methods in the management of VTE

Background
The anti-stasis principle of physical methods is well established for prevention
but not so much for the management of venous thromboembolism (VTE).
When a patient, develops a deep vein thrombosis and anticoagulation therapy
is initiated, many health professionals ask, “When should this patient have
physical therapy and/or ambulate?” Fear of causing a pulmonary embolism with
increased activity drives this question. Often, an order for bed rest is prescribed
based more on tradition than on evidence-based medicine.1

Material and Methods
53 patients with acute proximal DVT were enrolled into a randomised controlled
trial comparing bed rest and no compression (n = 17), Unna boot bandages
+ walking (n = 18) and thigh-length compression stockings (23-32 mm Hg)
+ walking (n = 18). All patients received therapeutic doses of low molecular
weight heparin (dalteparin 200 IU/kg body weight). Pain and swelling was
followed by 9 days. Safety was checked by repeat lung-scans and Duplex2.
A follow up was performed two years later. Telephone interviews could be done
in 11 patients, 37 patients were reinvestigated by independent observers
(11 from the bed rest-group, and 26 from mobile patients; from the mobile
patients 13 were treated primarily by bandages and 13 by stockings).3

Results
In the acute stage compression and walking led to a significantly more intense
and faster improvement of swelling and pain compared to bed rest and thrombus
progression was reduced. Bandages did better than the stockings concerning pain
reduction but there was no significant difference concerning reduction of oedema.

9/11 patients after bed rest, but only 16/26 in the mobile
groups showed a larger calf circumference on the diseased leg (n.s.). Compression
stockings up to the time of the follow up were worn by 8/11 from the bed rest
patients and by 13/26 from the mobile patients. Judged by the Villalta-Prandoni
scale, which combines 5 subjective symptoms with 6 objective signs,
a significantly better outcome could be found in the mobile group (mean score 5.1)
than in the bed rest group (mean score 8.2) (p < 0.01). (“Mild PTS” = score 5-14, “severe PTS” score > 15). 18/26 mobile patients, but only 2/11 bed rest patients had a score < 5.0 (“no PTS”).

Conclusion

Immediate mobilisation with compression reduces pain and swelling in the acute stage of DVT and also the incidence and the severity of PTS after two years. High levels of physical activity at one month were shown to be associated with reduced severity of postthrombotic symptoms during the subsequent 3 months.


HugoPartsch@meduniwien.ac.at
Sylvia Haas (Germany)

Technical University of 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. Professor Haas received her medical degree from the University of Freiburg and began her training in paediatric haematology and oncology at the University Hospital in 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 anti-thrombotic 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.

Sylvia Haas

VTE Treatment in 2010

Deep vein thrombosis (DVT) and pulmonary embolism (PE) share a common pathophysiology and may be summarised under the term of venous thromboembolism (VTE). Therefore, it is unsurprising that their treatment involves broadly similar strategies and methods. Anticoagulation is the mainstay of VTE treatment and effective anticoagulant therapy is a prerequisite to meet all objectives in the acute, intermediate and long-term phase of the disease.

The concept of VTE treatment with anticoagulants has been described as early as in 1960 by Barritt and Jordan who were the first to show that intravenous heparin given in combination with an oral vitamin K antagonist reduced death and recurrence of VTE compared with no anticoagulant therapy. Since then, several clinical landmark trials have significantly influenced the anticoagulant therapy of VTE although the concept of overlapping therapy with heparin or a heparin derivative has remained unchanged up to now.

The introduction of LMWHs in 1980s has revolutionised the early treatment of VTE by simplifying dosing and administration. In the meantime, the pentasaccharide fondaparinux has become available for initial treatment of VTE providing similar efficacy and safety when compared to LMWH. Fondaparinux can be given in fixed dose regimens to a broad variety of patient populations however, its use still requires parenteral administration. Therefore, the development of new oral anticoagulants with short on- and offset of action is an unmet clinical need and first clinical results have become available from clinical trials with various direct Factor Xa- and IIa-inhibitors.

Rivaroxaban is a small molecule, oral, direct FXa inhibitor which selectively and reversibly inhibits both free (Ki = 0.4 nM) and clot-associated FXa activity, as well as prothrombinase activity. Rivaroxaban has high oral bioavailability and a rapid onset of action, reaching maximum plasma concentrations 2.5-4 hours after administration. It has a half-life of up to 9 hours in healthy young subjects, and up to 12 hours in elderly subjects.

Apixaban is a small-molecule, oral, direct FXa inhibitor which selectively and reversibly inhibits both free FXa (Ki = 0.08 nM) and prothrombinase activity. Apixaban has high oral bioavailability, and has a half-life of approximately 12 hours in humans. It has multiple pathways of elimination, including renal and intestinal excretion.

Dabigatran etexilate is a prodrug of dabigatran, a specific and reversible thrombin inhibitor. After oral administration, dabigatran etexilate is rapidly and completely
Apixaban is also in phase III development. The VTE treatment program consists of two trials. The AMPLIFY trial is a 6-month trial investigating apixaban compared to enoxaparin plus warfarin in approximately 4,800 patients with acute DVT or PE. The AMPLIFY-EXT trial is a 12-month trial investigating apixaban compared to placebo for extended treatment to prevent recurrent VTE in approximately 2,400 patients who have completed 6 to 12 months of treatment for DVT or PE. (AMPLIFY study information available: www.clinicaltrials.gov; NCT00643201; AMPLIFY-EXT study information available: www.clinicaltrials.gov; NCT00633893).

The phase III programme of dabigatran etexilate consists of four trials. (RE-COVER study information available: www.clinicaltrials.gov; NCT00291330; RE-COVER II study information available: www.clinicaltrials.gov; NCT00680186; REMEDY study information available: www.clinicaltrials.gov; NCT00329238; RESONATE study information available: www.clinicaltrials.gov; NCT00558259). The RECOVER study was conducted in 2539 patients with acute symptomatic VTE who were randomized to 6 months of treatment with either dabigatran etexilate 150 mg twice daily or warfarin once daily, given in doses adjusted to an international normalized ratio (INR) of 2 to 3. All patients received initial treatment for 6 days with a parenteral anticoagulant (either intravenous heparin or a subcutaneous low-molecular-weight heparin derivative), to allow the dose of warfarin to be adjusted to achieve an INR of 2 to 3. The final analysis was conducted on 1274 patients who received dabigatran and 1265 who received warfarin. The primary end point was recurrent VTE or fatal PE, which was confirmed in 2.4% of patients receiving dabigatran and 2.1% of patients receiving warfarin. The hazard ratio was 1.1 (95% confidence interval [CI], 0.65-1.84), and this shows non-inferiority. Major bleeding was seen in 1.6% of patients receiving dabigatran and in 1.9% of patients receiving warfarin, which is not significantly different (Schulman S et al. N Engl J Med. 2009;361:2342-52).

Summarising first evidence from clinical trials it can be concluded that oral factor Xa inhibitors may have the potential to replace heparins for initial VTE treatment and that oral factor Xa- and IIa-inhibitors may be able to replace warfarin for long-term treatment of VTE.

Apixaban is also in phase III development. The VTE treatment program consists of two trials. The AMPLIFY trial is a 6-month trial investigating apixaban compared to enoxaparin plus warfarin in approximately 4,800 patients with acute DVT or PE. The AMPLIFY-EXT trial is a 12-month trial investigating apixaban compared to placebo for extended treatment to prevent recurrent VTE in approximately 2,400 patients who have completed 6 to 12 months of treatment for DVT or PE. (AMPLIFY study information available: www.clinicaltrials.gov; NCT00643201; AMPLIFY-EXT study information available: www.clinicaltrials.gov; NCT00633893).

Apixaban is also in phase III development. The VTE treatment program consists of two trials. The AMPLIFY trial is a 6-month trial investigating apixaban compared to enoxaparin plus warfarin in approximately 4,800 patients with acute DVT or PE. The AMPLIFY-EXT trial is a 12-month trial investigating apixaban compared to placebo for extended treatment to prevent recurrent VTE in approximately 2,400 patients who have completed 6 to 12 months of treatment for DVT or PE. (AMPLIFY study information available: www.clinicaltrials.gov; NCT00643201; AMPLIFY-EXT study information available: www.clinicaltrials.gov; NCT00633893).
Anthonie W. A. Lensing (The Netherlands)

Center for Vascular Medicine, Academic Medical Center, Amsterdam; BayerHealthCare

1988 M.D.
1996 Vascular neurologist
1986-1988 Post-doc, university of Padua, Italy
1990-1992 Post-doc, university of Hamilton, Canada
1986-2008 Department of Vascular Medicine, Academic Medical center, Amsterdam, the Netherlands
1999-2004 consultant for Organon, the Netherlands and Sanofi-Synthelabo for conducting clinical studies with fondaparinux and idraparinux
2004-2008 consultant for Bayer Healthcare and Johnson & Johnson for conducting clinical studies with oral Xa inhibitors

Publications > 130 international peer-reviewed articles

Anthonie W. A. Lensing

VTE recurrence... why accept this?

Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic venous thromboembolism (VTE).
The Einstein-Extension study

Background

Patients with idiopathic PE or DVT and those with persistent risk factors remain at risk for recurrent VTE. Several studies in patients with VTE addressed the risks and benefits of different durations of VKA therapy. All studies showed a statistically significant protection against recurrent VTE during prolonged VKA therapy. This reduction was counterbalanced by a statistically significant increase of major bleeding during prolonged VKA therapy. As a result, patients with PE or DVT are usually treated for a limited period of time in which the efficacy benefit clearly outweighs the risk of bleeding.

Recent trials evaluating continued low-intensity VKA did not demonstrate an improved benefit-risk and studies evaluating continued VKA in high-risk patients selected by D-dimer or ultrasound detected residual thrombosis showed limited value. Therefore there remains equipoise about the optimal duration of VKA therapy in various categories of PE or DVT patients. Besides the increase of major bleeds, continuation of VKA also implies the need for long-term regular laboratory control and subsequent dose adjustments.

New oral anticoagulants hold the promise of simple fixed-dose regimens without the need for monitoring and could make continuation of therapy more attractive. The Einstein-Extension study was therefore designed to assess the relative efficacy and safety of rivaroxaban, a direct oral factor Xa inhibitor, versus placebo in patients who had completed 6 to 12 months of anticoagulant treatment for their acute episode of VTE. Patients in whom there was a clear indication for continued anticoagulant treatment were not eligible.

Study Design

This randomized, double-blind, placebo-controlled, superiority study evaluated therapy with rivaroxaban 20 mg once-daily for an additional 6 or 12 months. The primary efficacy outcome was symptomatic recurrent VTE (i.e., the composite of recurrent DVT, non-fatal PE, and fatal PE). The principal safety outcome was major bleeding. Also the occurrence of clinically relevant non-
major bleeding (e.g. nose bleeds, large skin hematomas, and macroscopic hematuria) was recorded. The study was event-driven requiring a minimum of 30 confirmed recurrent events. All outcomes were adjudicated by an independent blinded committee.

Results
A total of 1197 patients were randomized between February 2007 and May 2009 by 280 study sites in 28 countries. The intention-to-treat population consisted of 602 rivaroxaban and 594 placebo patients. Baseline characteristics and risk factors for VTE were comparable between the two groups. The mean duration of study treatment was 190 days in both groups. During the treatment period, symptomatic recurrent VTE events occurred in 42 (7.1%) of the placebo treated patients and in 8 (1.3%) of the rivaroxaban recipients (hazard ratio, 0.18; 95% CI, 0.09-0.39; p < 0.0001). After the stop of study medication, 6 symptomatic recurrent VTE events occurred in each group during the one month observational period. Major bleeding did not occur in placebo patients and was observed in 4 (0.7%) rivaroxaban recipients (p = 0.106). None of these bleeding events were fatal or in a critical site. Clinically relevant non-major bleeding was noted in 7 (1.2%) and 32 (5.4%) of the placebo and rivaroxaban recipients, respectively. Two (0.3%) patients in the placebo group died versus 1 (0.2%) in the rivaroxaban group. No patients were observed to have an alanine aminotransferase (ALT) rise above 3 times the upper limit of normal (xULN) combined with a total bilirubin above 2 xULN.

Conclusion
A fixed dose of 20 mg of rivaroxaban once-daily is associated with an 82% relative risk reduction in the recurrence of VTE in patients who had completed a 6 to 12 month course of anticoagulant therapy for their index event. Based on the estimated cumulative incidence rates, approximately, 15 patients need to be treated to prevent one recurrent VTE event. This clinically relevant reduction in recurrence was associated with a low incidence of major bleeding (0.7%). This oral once-daily regimen provides the clinician with a simple option for patients in whom continued anticoagulant treatment is indicated.
Martin H. Prins (The Netherlands)

Professor M. H. (Martin) Prins completed his training as M.D. in 1983. After a period as Physician-Officer in the Royal Dutch Navy he started training in internal medicine in 1989. He spent 2 years in Hamilton, Canada at McMaster University, where he studied clinical epidemiology and performed research in thrombosis. In 1992 he completed his internal medicine education and in 1993 he defended his thesis entitled “Clinical and methodologic studies in thrombosis”. He then worked in Amsterdam Medical Center as head of the trial unit until 2001 when he went to Maastricht University as Professor of Clinical Epidemiology and Chairman of the department of Clinical Epidemiology and Medical Technology Assessment. He has coached 30 Ph.D. students, has co-authored more than 300 scientific publications and has a Hirsh-index of 62.

Martin H. Prins

Cancer and VTE complications – management and treatment in 2010

Based on available data, derived from clinical trials performed throughout the years, certain recommendations on the application of heparins in oncological patients can be made. The underlying data will be discussed.

Screening for cancer among patients with venous thromboembolisms

- While there is a substantial risk of harboring an undetected cancer in patients who present with spontaneous VTE, there is little evidence that, provided clinical acumen is high, doing routine tests like abdominal ultrasound or CT-scanning is effective in detecting these malignancies, let alone in improving prognosis.

Primary prophylaxis

- Hospitalized medical oncological patients are at high risk of developing VTE, prophylaxis with LMWH once daily or UFH 3 times a day is recommended during hospitalization.
- The incidence of VTE can be effectively lowered on prophylactic LMWH treatment in ambulant medical oncological patients undergoing combination therapy with chemotherapeutic agents and for instance thalidomide.
- Prophylactic low-dose warfarin is not recommended in ambulant medical oncological patients because the risk of bleeding on warfarin equals the risk of VTE without installed therapy.
- Initial prophylaxis in cancer patients undergoing surgical procedures is well established for abdominal, gynecological and colorectal surgery. There is no significant difference in efficacy and bleeding between UFH and LMWH.
- Initial prophylaxis with LMWH in cancer patients undergoing brain surgery is both safe and effective.
- Prolonged post-hospital therapy with LMWH after major cancer surgery reduces the incidence of VTE without increasing the risk of major bleeding.

Secondary prophylaxis

- The use of LMWH or UFH in treatment of VTE in cancer patients with solid tumors is preferred over vitamin K antagonists and significantly reduces the risk of recurrent thrombosis, without implications for bleeding or mortality rate.
Survival
- There is no convincing evidence for a beneficial effect for warfarin or UFH on survival in cancer patients.
- The median survival improves significantly in patients in patients with small cell lung cancer receiving LMWH in addition to chemotherapy compared to chemotherapy alone.
- LMWH for the sole purpose of prolonged survival is not documented to be effective in cancer patients without thrombosis.
Witold Z. Tomkowski

Epidemiology of VTE: influence of patients awareness of VTE symptoms and burden on rate of DVT

Background
Influence of public awareness of thrombotic burden and DVT symptoms on diagnosed rate of DVT has never been investigated.¹

Aim
Comparison of DVT rates, among patients treated by primary care physicians, under regular and increased awareness of DVT symptoms and burden.

Methods
In two populations, comprised patients at age 20 years, events rate of symptomatic DVT was investigated. Study was conducted between December 2007 and December 2008. Population A (104262 people) comprised inhabitants of large city district. To all apartments and houses of A population, leaflets regarding DVT symptoms and burden were distributed four times a year. Advertisements in local newspapers and posters were also addressed to this population. Population B (1574736 people) was a referenced population, and comprised GPs’ patients.

In all symptomatic cases, regardless of pre-test Wells’ score’s results, standardized compression ultrasound (CUS) of whole legs was performed². Results of CUS were analyzed by independent committee. Only results of CUS performed at presentation were investigated. Due to logistic reasons and patients’ compliance, CUS repeated after 5-7 days in high pre-test probability group, were not analyzed.

Results
Total number of DVT events, confirmed by CUS was 48 in A and 226 in B. One-year rate of all symptomatic DVT (proximal and distal) events was \(46/100000\, (95\%\, CI = 33.0-59.1)\) in A and \(14.4/100000\, (95\%\, CI = 12.5-16.2)\) in B. Difference between rates was highly statistically significant \((p < 0.0001)\).

Conclusions
Public awareness of DVT symptoms and burden significantly increases rate of symptomatic, confirmed by CUS venous thrombosis.

Discussion
The results obtained confirmed the thesis that conducting actions for the raising of awareness of clinical symptoms and risks related to DVT is reflected in the increased incidence of DVT events confirmed by the objective test. However population A was “younger” than B (expected annual incidence rate of DVT in population A should be lower than expected in older B population), the study revealed that incidence of both all DVT events and distal DVT events were higher in younger population A, while the average result of pre-test probability of DVT did not. This indicates that patients visiting doctors had similar clinical profile and risk factors, reflected also in Wells’ score. Also no differences between the populations in the incidence of proximal DVT events were found. This most probably results from the fact that in patients with the involvement of proximal portion of deep vein system, symptoms are more apparent and worrying, which encourages the patient to seek medical advice from his/her primary care physician. Ailments related to the distal portion usually did not worry the patient; thus, only an increased awareness of DVT-related threats may encourage her/him to visit doctor’s surgery. That is of enormous effect on further patients’ outcome, resulting in earlier treatment commencement, inhibition of proximal veins involvement and, probably, reduction in the incidence of post-thrombotic syndrome and mortality; however, the latter effect was not analysed by our trial.

The results obtained reflected only a fraction of annual DVT incidence³. Probably a significant fraction of patients of both populations suffering from acute sudden symptoms sought medical assistance in Emergency Rooms, where DVT was confirmed and appropriate management implemented. That was of particular importance during weekends. Probably another group that did not visit primary care physicians comprised patients post surgical procedures, who usually present themselves to their surgeons in the event of new complaints, such as symptomatic DVT. Subsequent group comprises members of both populations hospitalised for various other reasons in medical or surgical departments, where DVT was diagnosed. Thus, we are able to assess only a fraction of the annual
incidence of symptomatic DVT concerning patients presenting themselves to primary care physician, but we managed to prove that thanks to an increase in public awareness of DVT symptoms the fraction may be increased. That was however associated with an increase of costs of CUS tests (number of CUS tests/100,000 individuals/year was significantly higher in population A). In population A percentage of CUS-confirmed DVT versus the number of ultrasound test performed was lower than in general population.

We consciously decided not to apply within AVTERS trial a protocol involving D-dimer determination, as availability of the examination and variety of marketed tests of various sensitivity and specificity would introduce logistic and methodological chaos in the assessment of results obtained. Thus, we decided to perform CUS test in any case of suspected symptomatic DVT (even these of low probability) to avoid potential logistic and interpretation problems related to D-dimer determination by various methods. However, in any case of suspected symptomatic DVT, e.g. a diagnostic scheme published this year involving D-dimer determination may be used, considerably reducing the necessity for CUS tests, and thus the costs designated for DVT diagnosis4,5.

References:
Bogdan Hajduk

Management and treatment of patients with inserted Vena Cava Filters

Background
The long-term outcome of patients with inferior vena cava (IVC) filters who remain anticoagulated has not been studied in a controlled comparison. The aim of this study was to compare the rate of pulmonary embolism (PE) and deep vein thrombosis (DVT) in two groups of patients prospectively followed, one with and one without IVC filters, who received anticoagulant therapy indefinitely due to high thrombosis risk. The incidence and management of filter thrombosis was also studied.

Methods
121 patients in group A had indications to undergo permanent IVC filter placement. Another 120 consecutive patients with an indication for anticoagulation for an indefinite period were enrolled in group B. At least annual examinations and ultrasound surveillance were conducted, with ultrasound examination of the IVC filter in group A patients. In both groups oral anticoagulants (OA) were given during the entire follow-up (INR target = 2.5).

Results
Symptomatic DVT occurred in 24 of 121 patients in group A (20%; 95% CI 14-28%) and in 27 of 120 patients in group B (23%; 95% CI 16-31%). Symptomatic PE was diagnosed in 6 (including 1 fatal PE) of 121 patients in group A (5%; 95% CI 2-10%) and in 9 (including 2 fatal PE) of 120 in group B (8%; 95% CI 4-14%). Differences in the rate of symptomatic DVT and PE were not statistically significant (p = 0.6 and 0.4, respectively).

Conclusions
Patients who have received IVC filters after PE or DVT have a similar prognosis to those receiving anticoagulation alone so long as anticoagulation is continued, the patients with filters receive periodic ultrasound surveillance of the filter, and their prognosis is not otherwise limited by venous thromboembolism (VTE)-unrelated disease. During anticoagulant therapy, no statistically significant differences were observed in the rate of PE and DVT in VTE patients – with and without inserted IVC filters being permanently anticoagulated.
Krystyna Zawilska (Poland)

Department of Haematology and Internal Medicine, J.Strus Hospital, Poznan, Poland

Krystyna Zawilska received her medical education at the Karol Marcinkowski University of Medical Sciences of Poznan, Poland. She was board certified in internal medicine, haematology and vascular medicine. In 1977 she became Associate Professor, and in 1989 full Professor, at the Karol Marcinkowski University of Medical Sciences of Poznan, Poland, where she was responsible until 2009 for the Blood Coagulation and Thrombosis Laboratory in the Department of Haematology. Since 1997 she has been Head of the Department of Haematology and Internal Medicine, J. Struś Hospital in Poznan, Poland.

Professor Zawilska is a founder member of the Haemostasis Group of the Polish Society of Haematology and Blood Transfusion. Her research interests are in the prevention and treatment of venous thromboembolism, as well as in the diagnosis and treatment of thrombophilia. She has been author or lead author on many papers in scientific journals and on chapters in a number of medical books.

Hormonal therapy and venous thromboembolism

Oral contraceptives (OCs)

After the first report of venous thromboembolism (VTE) during oral contraceptive use in 1961, several case-control and cohort studies were published, reporting an increased risk of VTE associated with OC use, mainly those containing a 50-150 μg estrogen dose and a progestine, typically norethindrone (first-generation OCs). Because estrogen was suspected of increasing the risk of venous thromboembolism, contraceptives that contain less than 50 μg estrogen and a new progestin - levonorgestrel, were introduced (second-generation OCs). Initial efforts to reduce the risk of VTE by reducing estrogen content dose proved successful – a marked decline of approximately 80% in reports of nonfatal VTE per 100 000 users has been noted. In the Oxford planning study, lower incidence of rates were noted among users of low-dose contraceptives (39 per 100,000 person-years) compared with users of high-dose contraceptives (62 per 100,000 person-years). Compared with non-OC users, women who take second-generation OCs have a risk of VTE that is increased about fourfold.

The progestins desogestrel, gestodene, and norgestimate, in combination with no more than 35 μg of ethinyl estradiol, constitute third-generation OCs. They increase the risk of VTE approximately twofold over second-generation products.

The risk of VTE with oral preparations for the newer progestins (eg. drospirenone – Yasmin or cyproterone acetate – Diane 35, Estelle 35) has been less well studied but should not be presumed to be less than that seen with third-generation products. They produce acquired APC resistance similar to that fund in women taking third-generation products.

The VTE risk associated with use of vaginal ring (ethinyl estradiol or etonogestrel) is unknown.

The VTE-associated risk of progesterone-only containing contraceptives has been studied in eight case-controlled studies, and none of them has shown a statistically significant increased risk of VTE.

This risk of VTE is particularly high among carriers of hereditary thrombophilia. A pooled analysis of eight case-controlled studies found an odds ratio of 10.25 (95% CI, 5.69 to 18.45) for OC use in FV Leiden and 7.14 (95% CI, 3.39 to 15.04) in women with prothrombin G20210A mutation. In a prospective cohort study of 236 asymptomatic female carriers of FV Leiden, almost all of...
whom were heterozygotes, the risk of VTE was 1.8% per year of OC use. Thrombophilic women are more likely to develop thrombosis early in their OC use, with a 19-fold increase reported in the first 6 months, and 11-fold increase noted during the first year. In individuals with prothrombin G20210A and FV Leiden mutations the use of OCs is strongly and independently associated with an increased risk of cerebral vein thrombosis. A synergistic effect of OC use, obesity and of air travel of at least 8 hours on the risk of VTE has been reported in thrombophilic women.

On the basis of postmarketing adverse event reporting for the U.S. FDA transdermal hormonal contraception cannot be assumed to carry a lower risk of VTE than is seen with oral preparations.

Combined hormonal contraception is believed to be contraindicated in women with a personal history of VTE, because is associated with an unacceptable risk of recurrent events. Information on the use of progestin-only contraceptives in this setting is limited.

Hormonal replacement therapy (HRT)

The estrogens commonly prescribed for hormone replacement are chemically different than those in oral contraceptives and are considered to have substantially lower biologic potency. The use of HRT, however, leads to a considerably larger number of excess cases of thrombosis, as a result of an overall age-related increase in the incidence of thrombosis. Observational studies as well as clinical data from HERS trial and Women's Health Initiative (WHI) trial have reported a two – to threefold increase in relative risk for venous thromboembolic events with the use HRT. The risk appeared to be highest during the first 2 years of use and tended to decline with time. In WHI trial venous thrombosis occurred in a total of 167 women who were taking estrogen plus progestin (3.5 per 100 person-years) versus 76 women who were taking placebo (1.7 per 1000 person-years). The HR for DVT was 2.07 (95% CI, 1.49 to 2.87), and for PE, it was 2.13 (95% CI,1.39 to 3.25). In women with a hysterectomy who received estrogen alone, the risk was attenuated, with an HR of 1.33 (95% CI, 0.99 to 1.79). Analysis revealed that the risk associated with HRT increased with age and was also increased in overweight and obese women.

Factor V Leiden positivity increased the HRT-associated risk of VTE by 6.69-fold over that reported in women on placebo without the mutation (95% CI, 3.09 to 14.49). A 2.6-fold increase was seen among heterozygotes and a 7.5-fold increase was noted among homozygotes, leading to an estimated absolute risk of VTE of 0.8% per year among woman carrying a FV Leiden mutation and taking HRT. Different from users of OCs, other measured genetic variants of thrombophilia were not found to modify the association of HRT with VTE. It is possible that the lower estrogen dose in HRT versus that in OCs explains this difference.

Some data suggest that the mode of supplying estrogen may be crucial to the risk of VTE. In the case-controlled Estrogen and Thromboembolism Risk (ESTHER) study the estimated risk of VTE in users of oral HTR was 3.5 (95% CI, 1.8 to 6.8); in users of transdermal HTR, it was 0.9 (95% CI, 0.5 to 1.6) compared to nonusers. It is possible that transdermal estrogen therapy has little effect on haemostasis. Several confounding variables may exist in ESTHER study, therefore data from further large studies are necessary to determine the safety of transdermal estrogen therapy.

HRT is generally believed to be contraindicated in women with history of VTE because of the high risk of recurrent events.

In women who need to take HRT but who are at high risk of VTE anticoagulation with warfarin or low molecular weight heparin may be considered, but no clinical trials have been performed to date to confirm safety of this approach.

Phytoestrogens have been also used to relieve postmenopausal symptoms – the few prospective studies have not found any potential adverse effects of soy products on the coagulation system.
Jacek Musiał (Poland)

Personal Data: Born on 31 July 1948
Married, 2 sons born in 1973 and 1976
Nationality: Polish

Personal address: Burów 112, 32-083 Balice

Current position: Full Professor, Head of 2nd Chair of Internal Diseases, Jagiellonian University, Collegium Medicum, 31-066 Cracow, 8 Skawińska Str.
tel. (12) 430-5314, fax (12) 430-5068
e-mail: mamusia@cyf-kr.edu.pl

Professional Experience: 1972 M.D. Diploma (with distinction), Nicolaus Copernicus Medical University, Cracow
1972-1973 postgraduate internship
1973-1978 junior assistant, Clinic of Allergy and Immunology, Nicolaus Copernicus Medical University, Cracow
1975 I degree of specialization in internal diseases
1978-1987 senior assistant and assistant professor, as above
1981 II degree of specialization in internal diseases
1987-1996 Senior Academic, Clinic of Allergy and Immunology, Jagiellonian University, Collegium Medicum, Cracow
1996-2003 associate professor, as above
2006 specialization in Clinical Immunology
2006 specialization in Allergology
since 2001 Head of Centre for Immunological and Environmental Diseases, as above
since 2004 Full Professor, as above

Scientific degrees and titles: 1978 Doctor of Medical Sciences
1987 Doctor of Medical Sciences, Ph.D.
1996 Professor of Medical Sciences

Scientific internship: 1987 postdoctoral fellowship (11 months), Specialized Center for Thrombosis Research, Temple University, Philadelphia, US
1982-1983 postdoctoral fellowship (14 months), Department of Surgery, University of Pennsylvania, Philadelphia, US
1988-1989 visiting scientist (14 months)

Postgraduate scientific supervision: thesis supervisor of 12 completed doctoral degrees

Elective functions at scientific associations:
President of the Main Board of Polish Internists Society (since 2008)
Secretary General of the European Thrombosis Research Organization (since 2003)

Languages: Polish, English (speaking and writing), Italian (speaking), Russian (in the past good knowledge, currently - poor)

Current number of publications: 175
Current Impact Factor: 190,63
Paweł Kuca (Poland)

Dr Paweł Kuca graduated in medicine from Second Medical Faculty in Warsaw Medical University in 1995. He completed his fellowship and specialized in internal medicine in 2004. He obtained a Ph.D. from the National TB and Lung Diseases Research Institute in 2001.

Dr Kuca works in the Cardio-Pulmonary Intensive Care Division and in the Laboratory of Molecular Diagnostics and Immunology at the National TB and Lung Diseases Research Institute. He is the member of the Scientific Council of the Institute and the Polish Foundation Against Thrombosis.

His research interest cover diseases of pulmonary circulation: acute pulmonary embolism and pulmonary hypertension, pericardial diseases, acute decompensation of chronic respiratory insufficiency, non invasive ventilation in acute and chronic settings and alpha-1 antitrypsin deficiency.

Dr Kuca participated as investigator and coordinator in numerous clinical trials in the field of thromboprophylaxis and antithrombic treatment.

Dr Kuca is a member of Polish Respiratory Society, European Respiratory Society and American Thoracic Society.
Tomasz Urbanek (Poland)

Department of General and Vascular Surgery
Medical University of Silesia, Katowice, Poland

e-mail: urbanek.tom@interia.pl

Tomasz Urbanek is associated professor, vascular surgeon and angiologist at the Department of General and Vascular Surgery Medical University of Silesia, Katowice, Poland. His research interests include: VTE prophylaxis and treatment, pathogenesis and treatment of chronic venous disorders as well as prevention and treatment of postthrombotic syndrome.

Dr Urbanek graduated in medicine from Medical University of Silesia in Poland in 1992 and obtained a Ph.D. from the same university in 1998. He completed his fellowship in general surgery, vascular surgery as well as in angiology, visiting also many European and some North American vascular and surgical medical centers.

Dr Urbanek is an investigator in several clinical trials on the prevention and treatment of VTE. He is also reviewer for several journals of vascular medicine as well as the author and co-author of more than 80 papers published in pre-reviewed journals and more than 150 congress presentations. In 2001 dr Urbanek awarded International Union of Phlebology Research Fellowship.

Dr Urbanek is member of several European and Polish professional societies as well as a member of the Executive Committee of Polish Angiological Society, Polish Phlebological Society and Polish Society for Vascular Surgery.
Prof. Arkadiusz Jawień (Poland)

Professor Arkadiusz Jawień graduated from Poznan University of Medical Sciences in 1977. His professional career started in the city of Bydgoszcz, where he became a specialist in general surgery (1984), as well as vascular surgery and angiology (2002 and 2003 respectively). In 1983 he became a Doctor of Medical Sciences (Medical University of Gdansk), and in 1988 he obtained his M.D., Ph.D. at Medical University of Bydgoszcz. In 1993 he became an associate professor of Medical University of Bydgoszcz and in 1998 the President of the Republic of Poland awarded him a title of full professor.

At first he worked for the Chair and Clinic of General and Vascular Surgery at Medical University of Bydgoszcz. In 1991 he became a Head of General Surgery Unit at the Provincial Hospital, which in 1993 was transformed into a Chair and Clinic of General Surgery. Professor Jawień was appointed a head of Chair and Clinic and he has been performing this function to this day.

During last 30 years of his career he participated in numerous professional training programs abroad. He used to frequently visit the Clinic of Cardiovascular Surgery of the Catholic University in Leuven, Belgium. He also underwent an eight-month internship at the Clinic of Vascular Surgery in Paris (Salpetriere-Pitie Hospital). In 1988-1991 he stayed at the Department of Surgery in Seattle (University of Washington).

He was a chairman and a president of many scientific associations, such as European Venous Forum, Polish Angiological Society or Polish Phlebological Society. He was also re-elected for the second term of chairmanship of the Polish Wound Management Association.

For more than 10 years he has been an editor-in-chief of Acta Angiologica, and since 4 years he has been an editor and founder of “Surgical and Angiological Nursing” magazine. He is a member of editorial committees of numerous medical journals, e.g. International Angiology, Acta Phlebologica, Phlebology. For 3 years he was also a member of editorial committee of European Journal for Vascular and Endovascular Surgery.

Author of over 300 scientific papers published in Polish and foreign magazines.

His hobby is travelling and genealogical tree of his family.