ASTH NEWSLETTER
The Australasian Society of Thrombosis and Haemostasis

Editor: Emma Jones-Perrin
Email: emma_perrin@health.qld.gov.au OR ae_perrin@optusnet.com.au Telephone: (07) 3350 8531 Fax (07) 3350 8879 Vol 10, No 2 September 2004

Dear Fellow Clotter

Welcome to the September edition of the newsletter. Thank you to all the members who made contributions to the newsletter. In this edition we have details of the Barry Firkin oration to be held on the education day of the HAA in Melbourne. Please find enclosed the preliminary program and registration form for the ASTH Workshop. The Annual General Meeting is scheduled during the HAA in Melbourne for Monday October 18th at 1-2 pm; check the conference program for details.

Included in this edition are conference reports from ASH 2003, the ISTH SCC held in Venice in June and the International Congress on Thrombosis held in Slovenia. Also included are updates from the Clinical Trials Group and the New and Emerging Technologies Group.

Hope to see many of you in Melbourne. The next edition is planned for Nov/Dec, any contributions are most welcome.

Emma Perrin

BARRY FIRKIN ORATION

Barry Firkin was born in Newcastle, New South Wales in 1930. He studied Medicine at the University of Sydney and graduated with honours in 1954. Throughout his undergraduate years he developed a strong interest in both medical research and the history of Medicine which he maintained throughout his life. In 1958, Barry went to St Louis, Mo, USA where he joined Carl Moore and his team at Washington University. The experience at Washington University influenced Barry throughout his academic life. His interest in the scientific foundation of Haematology was born and set his life course. He became a strong advocate of the notion that clinical research started with the identification of the problem at the bedside, followed by carefully designed experiments in the laboratory to solve the questions and finally returning back to the patient with the answers. This to him was completing the loop and the dream of any clinical investigator. He returned to Sydney in 1961, to head the Clinical Research Department at the Royal Prince Alfred Hospital. It is there that he made his first major scientific breakthrough describing different enzyme patterns in patients with orotic aciduria. His clinical research interest is very well exemplified by his performance of the first successful bone marrow transplant in the world on a patient with aplastic anaemia who had a twin sister. The twins are still alive to date and both enjoy good health.

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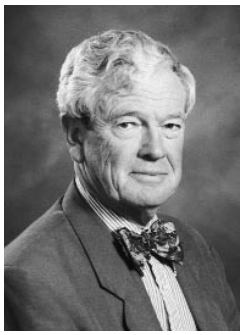
ASTH COUNCIL 2003-2005

Professor Hatem Salem	President	hatem.salem@med.monash.edu.au
Professor Alex Gallus	Vice-President	alexander.gallus@flinders.edu.au
Dr Paul Harper	Secretary & Webmaster, Discussion Group	paulh@adhb.govt.nz
Dr Tim Brighton	Treasurer & Chair, Clinical Trials Group Subcommittee	BrightonT@sesahs.nsw.gov.au
Dr Mark Smith	Chair, Scientific Programme Committee	mark.smith@cdhb.govt.nz
Ms Emma Jones-Perrin	Newsletter Editor	ae_perrin@optusnet.com.au
Dr Murray Adams	Chair, New & Emerging Technologies Group	m.adams@curtin.edu.au
Dr Chris Ward	Sydney 2005 Programme Committee	cward@med.usyd.edu.au
Dr Ross Baker	Executive Director	ross.baker@health.wa.gov.au

Barry Firkin Oration *Continued*



Barry Firkin

Inspired by the organization of the young clinical investigators in the USA, Barry set-up a similar model in Australia. This organization, The Australian Society for Medical Research has grown to become the strongest political force in Medical Research in Australia.

In 1969, Barry Firkin accepted the position of Foundation Professor of Medicine at the Alfred Hospital in Melbourne, Victoria. Soon after moving to his new position, he made his most significant contribution to haematology when he discovered that Ristocetin caused platelet clumping in a von Willebrand factor dependent manner. This was critical to our understanding of the biology and biochemistry of von Willebrand factor. This observation facilitated the development of an assay for von Willebrand factor (the Ristocetin cofactor assay) that we continue to use today. Over the ensuing 20 years, Barry continued to build Haematology in Australia, and at the same time maintained strong links with the International haematology scene. He played key roles in the activities of the International Society of Haemostasis and Thrombosis as well as the International Society of Haematology. He was Councilor to the International Society of Haematology and a Senior Member of the Scientific Advisory Council of the International Society of Haemostasis and Thrombosis.

Barry Firkin was an inspiration to many Australian Haematologists and Physicians. He is regarded as a leader and the father of Modern Australian haematology. His immense contributions will be recognized by an annual oration delivered by an eminent haematologist. The first oration will take place on the educational day at the Melbourne meeting. The society has selected Professor Michael Berndt to deliver the inaugural oration. Michael is a distinguished scientist who has made major contributions to the field and has advanced our knowledge on the role of platelet in haemostasis and thrombosis. The oration promises to be one of the highlights of this year's meeting.

Hatem Salem

CLINICAL TRIALS GROUP REPORT

The ASTH Clinical Trials Group (CTG) will next meet during the HSANZ/ANZSBT/ASTH Annual Scientific meeting in Melbourne October 2004. The main topics for discussion are the ASPIRE Study and a new proposal for a randomised study of treatment for Adult Acute Primary Immune Thrombocytopenia.

The ASPIRE study is now almost ready to move from the initial pilot phase to the main study. This study examines the efficacy and safety of low-dose aspirin as prophylaxis against recurrent venous thrombosis after initial warfarin therapy in patients with unprovoked DVT or pulmonary embolism. Additional funding has been forthcoming from NSW Dept of Health in addition to funding from the ASTH CTG, Bayer International, and the NH MRC project grant. The first ASPIRE Study newsletter is about to be distributed to active sites. There are currently 8 sites actively recruiting patients with a further 9 sites almost ready to go. As of 31st July 2004 there are 49 patients on study (Auckland NZ – 5, Box Hill Melbourne – 4, Mater Newcastle – 2, Prince of Wales Sydney – 2, Princess Alexandria Brisbane – 2, Queen Elizabeth Adelaide – 2, Royal Perth – 14, St George Sydney – 19). The inaugural Trial Management Committee meeting on 23rd August will bring together Italian, Australian and New Zealand investigators. The WARFASA study in Italy, a study of almost identical design to ASPIRE, commenced recruitment in May 2004 and will involve 50 Italian centres. At the Melbourne CTG meeting on 26th May a number of sub-study proposals were discussed. The current proposal incorporates probable and various novel determinants of recurrent vein thrombosis including residual thrombus burden assessed by ultrasonography, D-dimer, and other laboratory analytes. With 3000 patients and about 400-500 recurrent events a number of important questions can be answered with the ASPIRE dataset. I encourage potential and current investigators to become really involved in the ASPIRE project.

Tim Brighton recently circulated a feasibility survey regarding an AITP study proposal across the HSANZ, ANZSBT and ASTH membership. This study is a simple randomised study of standard oral prednisone versus oral high-dose dexamethasone for initial haemostatic control of acute adult AITP. Results of the survey and the draft protocol will be circulated for comment prior to the Melbourne meeting.

CTG Investigators are also busy with industry-sponsored proposals. These studies bring resources to the group for collaborative research and international recognition of the ASTH. Current active studies amongst members of the CTG include extended prophylaxis in medical patients with clexane (EXCLAIM, Aventis Pharma), the Van Gogh DVT and PE treatment studies with idraparinux (Sanofi-Synthelabo & Organon), the Van Gogh Extension study, and the ODIXa-DVT study (Bayer). A number of new study proposals will probably emerge in the next few months.

A CTG update will occur in Melbourne on Monday 18th at 7.15am-8.15am so please check your program. See you in Melbourne.

Comments and suggestions are always welcome.

Tim Brighton
Chairman CTG

NEW AND EMERGING TECHNOLOGIES GROUP REPORT

It has been a busy few months since the last report, with a substantial amount of effort dedicated to organizing the major event of 2004, the ASTH Melbourne Workshop. This will be held the day before the 6th Joint Scientific Meeting of the HSANZ, ANZBT and ASTH on Saturday 16th October at the Alfred Hospital. Please refer to the program of topics and speakers, registration form and tax invoice, which are included with this edition of the ASTH newsletter.

I would like to thank the following individuals for their input, advice and help in organising the Workshop; Emma Perrin, Ray Dauer, Sarah Just, Michael Wheeler, Emmanuel Favaloro and Tom Exner, and also the presenters who have enthusiastically agreed to contribute to the success of the day.

For further information or queries about the ASTH Melbourne Workshop please contact Murray Adams [(08) 9266 4316, M.A*dams@curtin.edu.au*] or Emma Perrin [(07) 3212 5531, Emma_Perrin@health.qld.gov.au].

The 2004 AIMS National Workshops were recently held at Curtin University and local diagnostic laboratories in Perth (30th June – 2nd July 2004). These were a tremendous success with approximately 180 delegates from around Australia attending the various sessions across all streams of Medical Laboratory Science.

The Coagulation sessions especially were very popular and well attended. In the first of these ("Case studies in coagulation – a potpourri of clinical and laboratory cases,") Melissa Camenzuli (dysfibrinogenaemia), Wanda Randall (haemophilia B and neonatal haemochromotosis), Stan Howarth (thrombophilia in pregnancy) and Leesa Ivey (acquired factor inhibitors) presented an interesting series of unusual case studies. The second ("D-Dimers: thrombosis answered?") was a half-day session, which initially provided an excellent overview (Grace Gilmore) and discussion on negative predictive value and the use of D-Dimers as clinical indicators (Nick Michaelopolous). This was followed by presentations and discussions on commercially available methods and rounded off with quality control issues (Jim Thom) and discussion (Nick Michaelopolous). The third ("Point of care testing and instrumentation – the new revolution?") was chaired by Richard Olsen (Helena Laboratories). This was an excellent session, which generated provocative discussion on many aspects of point of care testing and whether medical scientists in Australia have missed the opportunity to appropriately co-ordinate this important aspect of diagnostic medicine.

In the meantime, membership of the New and Emerging Technologies Group has grown to 38, updated details of which have been recently distributed by email. Please continue to circulate the e-newsletters and distribution lists and/or forward me the details of others who would be interested in hearing about what is happening in diagnostic labs around Australia and New Zealand.

As always, I appreciate any feedback or suggestions.

Murray Adams
Chair
New and Emerging Technologies Group

UPCOMING MEETINGS

MEETING	WHERE/DATES	CONTACT
British Society of Thrombosis & Haemostasis/ UKHCDO Joint Scientific Meeting	Edinburgh 4-6 October 2004	Sarah.lapsley@b-s-h.org.uk UKHCDO – UK Haemophilia Centre Doctors' Organisation
ASTH Workshop	Melbourne 16 October 2004	M.Adams@curtin.edu.au
6th HSANZ/ANZBT/ASTH ASM	Melbourne 17-20 October 2004	www.waldronsmith.com.au/HAA2004
XXVI International Congress of the World Federation of Hemophilia	Bangkok 17-21 October 2004	www.wfh.org
XIth International Congress on Antiphospholipid Antibodies,	Sydney 14-18 November 2004	http://www.xith-icaa2004.unsw.edu.au/sydney/index.html
The American Society of Haematology 46th Annual Meeting	San Diego 4-7 December 2004	www.hematology.org
RCPA Pathology Update	Sydney 11-13 March 2005	Suzanne Marks Phone: 61 2 8356 5806 www.rcpa.edu.au/pathologyupdate
45th British Society of Haematology ASM	Manchester 11-13 April 2005	www.b-s-h.org.uk
XVIIIth International Symposium on Technological Innovations in Laboratory Haematology	San Francisco 11-14 May 2005	www.islh.org
AIMS National Scientific Meeting	Sydney 6-8 July 2005	www.aims.org.au
XXth Congress of the International Society of Thrombosis & Haemostasis (ISTH 2005)	Sydney 6-12 August 2005	www.isth2005.com

ASH 2003

Staying sane at ASH or surviving visits to very large art museums demands the same game plan: define the desired outcomes and be very selective. Trying to see it all just doesn't work. My picks from ASH 2003 were the First Plenary symposium and anything clinically thrombotic or antithrombotic (authors quoted below can be traced in the abstract issue of 'Blood' or the ASH meeting CD).

One Plenary highlight was the visually stunning presentation complete with video-clips of vessel wall, circulating micro-particle and tissue factor interactions, marred only by the absence of the medical student responsible – snow bound in Boston by winter's first hurricane. Why ASH is always in the first weeks of December defies my understanding.

Another was the multinational ECLAP study, a randomised placebo-controlled 3 year evaluation of low-dose aspirin (100 mg/d) in polycythemia vera (about 1/3 of the 1630 potentially eligible subjects were randomised). The now published study (NEJM) shows a 40% risk reduction in the composite trial outcome measure of cardiovascular death, nonfatal MI or nonfatal stroke, though with the expected trend towards more gastro-intestinal bleeding. This result differs from that of a much smaller and earlier polycythemia trial where the dominant effect of aspirin was to increase bleeding risk. A later oral presentation (Caruso) added perspective. The causes contributing to the total observed mortality of 35 per 1000 patient years were cardiac (8.9), stroke (3.0) cancer (11.7) and haematological transformation (5.3).

ASH is attracting (or accepting) more thrombosis presentations than before, though it remain swamped by myeloma, lymphoma, and other impedimenta.

ASH 2003 completed the recent cycle of large trials with novel antithrombotic drugs. Results of the ximelagatran VTE treatment trial and the fondaparinux DVT and PE treatment trials (previously shown at ISTH) were presented again. Ximelagatran (the orally absorbed prodrug for melagatran, a direct thrombin inhibitor) proved to be 'non-inferior' to the now standard therapy of low molecular weight heparin (LMWH) then warfarin for DVT with or without symptomatic PE. Fondaparinux (an antithrombin dependent synthetic pentasaccharide with highly selective anti-Xa activity that is given by daily subcutaneous injection) proved to be 'non-inferior' to standard therapy after DVT or PE. Safety of these novel antithrombotics was similar to that of standard therapy, although a ximelagatran effect on liver enzyme levels during long-term administration remains under evaluation. 'Non-inferiority' needs explanation; it means the novel drug was no less effective than standard therapy. In large DVT prevention trials, fondaparinux was effective in a placebo-controlled study of medical patients and 'non-inferior' to the LMWH dalteparin after abdominal surgery, while ximelagatran was more effective but caused more bleeding than warfarin after knee replacement. Present interest is focused on how soon the new anti-thrombotics can replace warfarin throughout the 3-6 month treatment period for VTE.

There are several new and promising oral antithrombotic drugs other than ximelagatran that might also substitute for warfarin. A dose-ranging trial of DVT prevention in knee replacement suggests that Razaxaban, a new direct acting factor Xa inhibitor, is very likely to be orally effective. Other oral antithrombin and anti-Xa drugs are in Phase I or Phase II evaluation.

The optimal management of people with antiphospholipid phospholipid antibody syndrome (APLA) and thrombosis has been uncertain. Those who attended ASH 2002 may remember a Canadian comparison in APLA with thrombosis (now published in NEJM) where the previously recommended high-dose warfarin regimen with target INR of 3-4 was no more effective than a standard dose-effect of INR 2-3. At ASH 2003, these observations were confirmed by a prospective and randomised Italian multicentre trial presented by Finazzi: thrombosis rates during 36 months of follow-up were 8.9% when the target INR was 3-4 (n=54) and 5.3% when target INR was 2-3 (n=55). The respective bleeding rates were 26.8% and 12.5%.

There was a particularly impressive presentation (Cushman) of final results from the Women's Health Initiative trial of estrogen plus progesterone for post-menopausal hormone replacement therapy. The now published results indicate that hormone replacement in women aged 50-79 doubles thrombosis risk (DVT or PE) from 1.7 to 3.5 per 1000 patient years. Risk appears to be further increased in women with factor V Leiden but not the prothrombin G20210A mutation. When asked about statistical significance of some of the hypothesis – generating subgroup analyses, she pointed out that any statistical testing for significance was not appropriate as these were not pre-specified comparisons (loud cheers from this audience who is hypersensitive to over-interpreted data-dredging).

Still on the thrombosis front, there was a useful report (limited by small numbers) of low vein thrombosis rates after laparoscopic surgery regardless of preoperative 'risk assessment' or prophylaxis (Tincani). And analysis of US health plan claims (Hauch) suggests that in 'real-life' there is a much higher rate of recurrence during 6 months of warfarin therapy for VTE than experience from recent clinical trials suggests. Reported recurrence rates during 3 months of initial therapy in clinical trials are 3.5-6%. In 'real-life' they appear to be 9% and mostly associated with cancer, heart disease and a relatively low treatment-associated INR.

Speaking of warfarin, one large area of uncertainty is how best to manage 'bridging' (i.e., anticoagulant therapy when people on warfarin because of valve replacement or recent

ASH 2003 *Continued*

thrombosis need surgery or some other invasive procedure likely to transiently increase their bleeding risk). The preliminary report of a North American registry found high thrombotic and/or bleeding rates (6-15%, depending on 'bridging' anticoagulant – unfractionated or low molecular weight heparin) and confirmed the need for continued study of this very controversial area (Spyropoulos). Self-management of oral vitamin K antagonists improves quality of life (Gradisseur) and may improve anticoagulant control in selected patients (O'Shea).

Predicting the long-term risk of recurrence once patients stop warfarin therapy after VTE is one of the more desirable but elusive aims of clinicians in this area. Secondary prevention by warfarin is highly effective but the significant bleeding risk argues against indefinite therapy for all.

An individual patient meta-analysis of data from 2474 patients enrolled in 5 randomised anticoagulant trials after VTE and followed for 15-48 months (Pinede) confirmed that people with temporary risk factors have a lower recurrence rate (4% per annum) than those with ongoing predisposition (8.4% p.a.), that recurrence rates are higher after proximal DVT (7.5% p.a.) than distal DVT (4% p.a.), after DVT with symptomatic PE (9.3% p.a.) than without (6.5% p.a.), and that people with symptomatic PE at presentation tend to have PE as their recurrence. These observations confirm the wisdom of continuing for at least 6 months of therapy after proximal DVT, especially if there is also symptomatic PE.

There is increasing evidence that the extent of residual thrombosis found with ultrasonography after 3 months of warfarin therapy may predict a high risk of subsequent recurrence off anticoagulant therapy. A randomised trial (DACUS) from Italy (presented by Siragusa) adds to that evidence. 2% of subjects had a recurrence during 12 months of follow-up after 3 months of initial therapy if residual thrombosis occupied <60% of the affected vein lumen and 15.6% had a recurrence if residual thrombus occupied >60% of the vein lumen. Continued anticoagulation for 1 year in people with >60% residual thrombosis reduced the subsequent recurrence rate to 7.3% during the first year. Russel Hull presented data from a meta-analysis where clot burden when measured by repeat venography (Marder score) done after exposure to low molecular weight heparin following DVT correlated with recurrence observed during 3-12 months of followup. Others find a negative D-Dimer test when warfarin is stopped after 3 months is a good negative predictor for subsequent thrombosis recurrence. This is clearly a promising but evolving area subject to methodological uncertainty (how and when do we best measure 'residual thrombosis'?).

Registries have become very popular. Usually funded by industry but administered by independent data analysts interested in clinical outcomes, they are a good way to examine how well clinical practice guidelines are applied in real life. A Canadian register of medical inpatients (A Panju) found only 23% of eligible medical inpatients received VTE prevention, and this was 'appropriate' in 21%. A multinational joint replacement registry (Friedman) found that prophylaxis complied with ACCP guidelines in 38% of American and 54% of non-US patients having knee or hip joint replacement; and almost 2/3 of American orthopaedic surgeons using warfarin aimed for a non-validated target INR of 1.5 – 1.9. Clearly, there is a long way to go before we have consistently translated clinical science to clinical practice.

Send 12 haematologists to ASH and you will hear 12 different stories and these are mine (remember the one about the 12 blind-folded savants each describing the same elephant).

Alex Gallus

ANTICOAGULATION ON THE ADRIATIC –ISTH-SSC (VENICE) AND ICT 2004 (LJUBLJANA)

In June this year, the Riva degli Schiavoni, Venice's finest promenade, was flooded with tourists, eddying around the garish souvenir stalls on their footsore way to St Marks' square. Among the sweaty crowd was a surprising number of Australia's coagulation experts, waiting patiently for a ferry boat. Their vaporetto soon filled with colleagues from around the world and set off across the lagoon to the small island of San Giorgio Maggiore. Here, the soaring Palladian church and quiet cloisters formed a peaceful and timeless setting in which to discuss new developments in coagulation. Clearly, the magical Venetian setting was a major drawcard, but the meeting was also good value – more so than one colleague's 50 euro ($100) breakfast!

The Scientific and Standardization Committee (SSC) meetings of the ISTH are often entertaining as well as educational, with many of the world's experts gathered in one room and engaged in "vigorous" debate. Over two and a half days, a wide range of clinical and laboratory issues were canvassed, with additional symposia focussing on new therapies or difficult clinical problems. In a symposium on VTE prevention, Turpie reviewed the well-publicised trials of fondaparinux and ximelagatran, while looking forward to trials of several oral anti-Xa inhibitors currently underway. Fixed dosing of fondaparinux appeared effective in the obese, but low body weight and impaired remal function were risk factors

Continued page 6

ANTICOAGULATION ON THE ADRIATIC –ISTH-SSC (VENICE) AND ICT 2004 (LJUBLJANA) *Continued*

for accumulation. Bauer reported that fondaparinux had not been associated with clinical HITTS post-orthopaedic surgery, and that some cases of HITTS had been successfully managed with this agent. Kearon discussed the vexed issue of duration and intensity of warfarin therapy. While prolonging therapy beyond 6 months is effective in preventing recurrent events, sadly there seems to be no additional reduction in recurrence risk once warfarin therapy is stopped. In cases of unprovoked VTE, his practice is to continue (conventional-intensity) therapy beyond 6 months if the bleeding risk appears low and the patient consents. Some sobering data came from Eichinger and Kyrle, who noted a significantly higher VTE recurrence rate for men compared to women (30% cf 9% after 5 years) after unprovoked first VTE. Women under 45 in particular, had a low risk of recurrence, which did not seem due to avoiding oestrogen therapy.

Many sessions focussed on new assays, including the measurement of microparticles and the contentious entity of "blood-borne" tissue factor; many of the investigators feel that tissue factor activity is limited to a sedimentable fraction (microparticles) despite the results of "soluble TF" assays. Global assays for coagulation and fibrinolysis were canvassed in the workshop on Women's Health. Platelet physiology featured strongly; a fascinating session on "aspirin resistance" covered the wide range of theories and definitions in the current literature. Pulcinelli and others felt that this could only be defined as a failure to inhibit thromboxane production, and that a standardised (plasma-based) assay was needed to interpret clinical data. Clopidogrel "resistance" is an even murkier concept, but may reflect variable contributions from the two ADP receptors in different patients. A survey of platelet function studies in North America (primarily aggregometry) showed a distressing degree of variability, in both methods and interpretation. The PFA-100 assay was also reviewed by Hayward, who felt that a normal closure time could not exclude a mild platelet disorder. Other factors, such as reduced haematocrit and being blood group O (lower vWF levels?) also prolonged closure times. Finally, several working groups reminded us of their registries of rare conditions, such as AT3 deficiency in pregnancy (J. Conard); through the ISTH, cases from around the world can be gathered, to guide future practice.

Even us well-travelled clinicians would struggle to justify a 3-day visit to Italy; so, most assembled again on the "Casanova" express, en route to Slovenia for the 18th International Congress on Thrombosis. The train failed to live up to its namesake, running out of power short of the Italian border. Ljubljana turned out to be a delightful city, a pocket-sized old town under the Castle mount, surrounded by some truly awful concrete edifices. The conference featured primarily European groups and, like

Lake Bled, Solvenia (Tim Brighton, Alison Street and Chris Ward).

the infamous Eurovision song contest, standards varied wildly. I can't recall being at a meeting before where presenters at oral sessions failed to show up! Standout sessions included a thrombophilia symposium covering the genetic control of thrombosis (Bernadi) and elevated levels of coagulation factors (Bertina). Baglin addressed the paradox of why known thrombophilic factors such as FV Leiden predict a first VTE but have much less effect on recurrence; he hypothesized that the cohort having a first event carry many unknown thrombophilic factors as well. If the unknown risk factors outnumber or equal the known ones and have similar potency, then we can expect the prevalence of, say, FV Leiden to remain stable between the groups with a first and second event. A session on TAFI and a review of fibrinolysis by Kluft were also highlights. Finally, on post-thrombotic syndrome (PTS), the 8-year follow-up on the PREPIC IVC filter study (Queneti) found very high cumulative incidences (70%) which had converged in both patients with and without permanent filters. Reasons for their extremely high rates could include advanced age, many with prior VTE and no systematic use of stockings. A metanalysis of thromboprophylaxis found that interventions did reduce the risk of PTS years after surgery, by preventing asymptomatic VTE. The recently defined PTS score (Villalta) may assist future studies.

Other telltale signs of a European meeting, were the chain-smoking delegates and the wine served with lunch. We were also treated to some Slovenian culture, both in the conference and on the streets outside as the locals celebrated the summer holidays with everything from rock concerts to plainchant. A fitting final excursion for our haematologists was to the mountain resort of Bled. Slovenia's only island sits in Lake Bled topped by a fine church. Local bridegrooms are expected to carry their brides up a steep flight of 100 marble steps – but to drop her would bring bad luck!

Chris Ward