# XXV Congress of the ISTH 2015 & 61st Annual SSC Meeting

# CONFERENCE REVIEW

Making Education Easy

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## In this review:



### Abbreviations used in this review

**A/VTE** = arterial/venous thromboembolism
**CDT** = catheter-directed thrombolysis
**CT(PA)** = computed tomography (pulmonary angiogram)
**DVT** = deep vein thrombosis
**LMWH** = low-molecular-weight heparin
**PE** = pulmonary embolism
**PTS** = post-thrombotic syndrome
**SC** = subcutaneous
**TTP** = thrombotic thrombocytopenic purpura
**vWF** = von Willebrand factor

## Welcome to this review of the XXV Congress of the International Society on Thrombosis and Haemostasis (ISTH), including the 61st annual meeting of the Scientific and Standardization Committee (SSC), the largest and most important event for all scientists and clinicians with an interest in thrombosis and haemostasis.

The Congress is attended by delegates from numerous countries where new research data, ideas, opinions and suggestions for future collaboration are exchanged. Selection and commentary of the presentations for this review have been made by Dr Eileen Merriman and Dr Paul Ockelford, who attended the conference in Toronto, Canada in June. More information can be found at the Congress' website, and the abstracts have been published in J Thromb Haemost 2015;13(Suppl 2) and can be freely downloaded.

We hope you enjoy this conference review, and we look forward to receiving your comments and feedback.

Kind regards,


**Dr Paul Ockelford**
paulockelford@researchreview.co.nz

**Dr Eileen Merriman**
eileenmerriman@researchreview.co.nz


## Screening for occult malignancy in patient with unprovoked venous thromboembolism: an open randomized controlled trial using a comprehensive abdomen/pelvis computed tomography (SOME trial)

**Authors**: Carrier M et al, and on behalf of SOME investigators


**Summary**: The SOME trial randomised 862 patients with first unprovoked symptomatic DVT (55%), PE (32%) or both (13%), 48% and 15% prior and current smokers, respectively, to open-label limited occult cancer screening (basic blood work, chest x-ray and breast/cervical/prostate cancer screening) with or without comprehensive abdominal/pelvic CT (involving virtual colonoscopy and gastroscopy, biphasic enhanced CT, parenchymal pancreatogram and uniphasic enhanced CT of distended bladder); the completion rate in the comprehensive abdominal/pelvic CT group was 92%. At the time of reporting, the 1-year malignancy incidence was 4.3%, and 122 participants were ongoing in the trial.


**Comment (EM)**: The prevalence of previously undiagnosed cancer in those with unprovoked VTE events is 10% within 12 months of VTE diagnosis. An extensive diagnostic workup including CT abdomen and pelvis could, by detecting cancers earlier, result in earlier treatment and a reduction in mortality. This large randomised trial confirms that 'less is more'. There was no significant difference in the rate of cancers detected at 1-year follow-up between the limited and extensive screening groups, and no significant difference in mean time to cancer diagnosis or cancer-related mortality. A more pragmatic approach with additional tests only added if there are sufficient concerns, such as change in bowel habit, will reduce anxiety, save money and reduce exposure to unnecessary radiation.

***Late Breaking Abstract Session: Thrombosis and Anticoagulation; LB001***

## Initial results of the RE-VERSE AD trial: idarucizumab reverses the anticoagulant effects of dabigatran in patients in an emergency setting of major bleeding, urgent surgery, or interventions

**Authors**: Pollack C et al.

**Summary**: The RE-VERSE AD is evaluating two 2.5g intravenous bolus doses of idarucizumab for rapid reversal of dabigatran-induced anticoagulation in a target of 250–300 participants who experience life-threatening or uncontrolled bleeding or require emergency surgery or procedures. A prespecified interim analysis undertaken with >50 patients enrolled revealed that idarucizumab had restored and sustained clotting times in the normal range in >90% of the first 26 participants. Updated results were reported at the conference.

**Comment (EM)**: Until recently, reversal strategies for the direct oral anticoagulants have been lacking. This interim analysis shows that idarucizumab reverses the anticoagulant effect of dabigatran within minutes, with complete correction of the ecarin clotting time in all 90 patients. It should be noted that one-quarter of patients in this group had a normal dilute thrombin time at study entry, indicating very little or no circulating dabigatran – this group of patients was therefore unlikely to have benefited from the addition of the reversal agent to standard of care. The five thrombotic events are more likely related to the underlying hypercoagulability of the patients as opposed to any direct thrombotic effect from the idarucizumab; however, the lack of a control group makes this difficult to ascertain. The issue of 'rebound' is interesting, with two patients having dabigatran concentrations well above the therapeutic range at 4 hours after treatment, despite initial complete reversal. The final results of the study are awaited with interest.

***Late Breaking Abstract Session: Thrombosis and Anticoagulation; LB005***



**Independent commentary by Eileen Merriman,** a haematologist and Lead Thrombosis Clinician at North Shore Hospital, NZ. She trained in haematology in Christchurch, New Zealand and spent a year as a thrombosis/research fellow at Monash Medical Centre in Melbourne. Her interests include distal DVT, antiphospholipid syndrome and myeloproliferative disorders. She is currently conducting a multicentre Australasian trial for management of distal DVT (TWISTER trial).

**Independent commentary by Dr Paul Ockelford,** a haematologist and Clinical Associate Professor at the University of Auckland School of Medicine and Director of both the Adult Haemophilia Centre and Thrombosis Unit at Auckland City Hospital.

**For full bio CLICK HERE.**

## Anticoagulant therapy for symptomatic distal deep vein thrombosis: the CACTUS randomized placebo-controlled trial

**Authors**: Righini M et al.

**Summary**: Patients with a first distal DVT were randomised to receive SC nadroparin 170 UI/kg (n=126) or placebo (n=133) once daily for 42 days in the CACTUS trial; four nadroparin and three placebo recipients withdrew or were lost to follow-up. No significant differences were seen between the nadroparin and placebo arms for symptomatic proximal DVT or PE events by day 42 in intent-to-treat and per-protocol analyses (primary outcome; 3.3% vs. 5.4% [p=0.54] and 3.6 vs. 5.6% [p=0.55], respectively), and nadroparin was associated with a significantly greater major or clinically relevant nonmajor bleed rate in the intent-to-treat analysis (4.1% vs. 0.0% [p=0.03]).

**Comment (EM)**: Treatment of isolated symptomatic distal DVT is controversial. This trial showed that in patients with absence of risk factors such as immobilisation, malignancy or pregnancy, the VTE recurrence risk was not significantly different between groups receiving nadroparin/elastic compression stockings versus placebo/elastic compression stockings; however, rates of major or clinically relevant nonmajor bleeding were significantly higher in the nadroparin group. The risk-benefit appears to favour observation in this low-risk group. Time to resolution of symptoms was not reported. It may still be that a shorter duration of treatment, such as 10–14 days of intermediate-dose LMWH, could still be beneficial to shorten the duration of symptoms.

***Therapeutic management of venous thrombosis; AS137***

## Diagnosing small clots: SSPE

**Presenter**: Carrier M

**Summary/comment (EM)**: The introduction of multiple-detector CTPA has improved the sensitivity of diagnosis of PE, thereby increasing rates of diagnosis of subsegmental PE. The age-adjusted incidence of PE has increased by 80% since CTPA was introduced. However, mortality due to PE has not changed and the age-adjusted case fatality of PE has reduced, suggesting that the extra PEs found are less lethal. The PIOPED study showed that 17% of those with a low-probability VQ scan had subsegmental PE on CTPA compared with only 1% of patients with high probability VQ scans, yet the 3-month thromboembolic risk was similar by either strategy. There is also a high rate of interobserver variability for CTPA showing subsegmental PE (50%), therefore it is important that all diagnoses of subsegmental PE should be reviewed by an experienced chest radiologist. Management studies have shown it is safe to manage subsegmental PE patients with a strategy of serial bilateral leg ultrasound, with anticoagulation withheld in the absence of lower-limb DVT. No VTE recurrences have been reported using this strategy. A prospective study to investigate this is ongoing (NCT01455818) and will provide useful information to help guide management.

***SSC Subcommittee Sessions: Predictive and Diagnostic Variables in Thrombotic Disease***

## Pulmonary embolism: who to thrombolyse? Who to discharge?

**Presenter**: Meyer G

**Summary/comment (EM)**: Traditionally all patients with a diagnosis of PE were admitted to hospital for treatment. However, there is a group of low-risk patients who can likely be managed safely as outpatients. Selection of appropriate candidates for ambulatory treatment of PE can be aided by using risk scores such as the Hestia or simplified PESI (PE Severity Index) scores, taking into account factors such as haemodynamic instability, active bleeding/high risk of bleeding, liver impairment and hypoxia. Patients with low Hestia or simplified PESI scores have been shown to have low rates of VTE recurrence, major bleeding and death at 3 months (1.8% mortality with low simplified PESI, 25% mortality with high simplified PESI). This indicates that outpatient treatment in selected patients is probably safe, although it should be noted that most cohort studies were conducted in specific settings including dedicated thrombosis clinics with the ability to closely follow patients. Conversely, patients with haemodynamic instability and low-risk factors for bleeding clearly benefit from thrombolysis, with a reduction in the all-cause case-fatality rate from 47% to 15% in one study. However, those with submassive PE (haemodynamically stable with right ventricular dysfunction) have not shown a convincing benefit with thrombolytic therapy when compared with standard therapy, with no difference in mortality and a 4-fold increase in nonintracranial haemorrhage bleeding. It may be that a select group of patients with submassive PE with lower bleeding risk could still benefit from safer thrombolytic regimens, such as lower dose tenecteplase. Prospective, large-scale studies are required in this group.

***State of the Art 1: Controversies in VTE Management***

## World Thrombosis Day

A WTD (World Thrombosis Day) symposium entitled 'From global conversation to global catalyst' began with opening remarks from the Chair of the Steering Committee, Gary Raskob. The aim of the WTD is for global awareness of thrombosis in general and venous thrombosis in particular, as the latter has no other 'champion'.

The Global Burden of Diseases, Injuries and Risk Factors GBD Study 2010 (Lancet 2012;380[9859]:2095-128) documented that ischaemic heart disease and stroke combined contribute to 25% of deaths annually worldwide but did not report on VTE as a cause of death and disability. This prompted a systematic review of the literature on the global disease burden caused by VTE in low-, middle- and high-income countries, published as 'Thrombosis: a major contributor to the global disease burden' by the ISTH Steering Committee for the WTD (J Thromb Haemost 2014;12[10]:1580–90). They established an incidence of venous thrombotic events of 0.75–2.69 per 1000 across a range of ethnicities in different countries increasing to 2–7 per 1000 in those aged >70 years. A surprising finding was that hospital-associated VTE was the leading cause of DALYs (disability-adjusted life-years) in low- and middle-income countries. In high-income countries it is the second commonest cause of DALYs contributing more life-years lost than hospital-acquired pneumonia, catheter-related sepsis and adverse drug events combined.

VTE-related deaths in the European Union have been estimated to exceed 500,000 (Cohen AT et al., Thromb Haemost 2007;98[4]:756-64), and in the US there are an average 547,000 hospitalisations with a diagnosis of VTE each year (Yusuf, MMWR 2012;61[22]:401–4). As approximately 60% of these are hospital-acquired, a substantial proportion of the morbidity and mortality is preventable.

A recent international survey (accepted for publication in J Thromb Haemost) indicated high public awareness for well publicised disorders (85–90% for hypertension, MI, AIDS and stroke) but less awareness (44–54%) for PE and DVT. Risk factors for these conditions were even more poorly understood (16% for cancer association; 25% for hospital stay and 35% for surgery). In the UK, under the NICE initiatives 95% of adults now admitted to hospital get assessed for VTE risk/prophylaxis, which is thought to have contributed to an observed 9% reduction in death from hospital-acquired VTE (Dr Beverley Hunt, meeting moderator).

The first WTD (October 13, 2014) resulted in a successful social media campaign on many continents with 10.5 million twitter impressions in the US and five campaign awards for the novel use of social media marketing. A panel of physicians representing Thailand, Argentina, Singapore and Greece outlined their initiatives with local newspaper, radio and television exposure. They reported a "surprising degree of interest", but importantly stressed the aim was "awareness, not panic". WTD 2015 will focus on hospital associated VTE, a preventable disorder.

Paul Ockelford



## Bridging anticoagulation in patients who require temporary interruption of warfarin therapy for an elective invasive procedure or surgery (the BRIDGE trial)

**Authors**: Douketis J et al., and on behalf of for the BRIDGE Study Investigators

**Summary**: The BRIDGE study randomised 1884 adults with nonvalvular/valvular AF or atrial flutter who interrupted warfarin to receive SC dalteparin 100 IU/kg as bridging anticoagulation or placebo twice daily for 3 days preprocedure and 5–9 days postprocedure resuming 12–24 hours after minor procedures and 48–72 hours after major procedures. Follow-up was 30 ±7 days postprocedure, and the respective adherence rates for pre- and postprocedure periods were 81.0% and 94.5%. The results for the primary outcomes of ATE and major bleeding, and secondary outcomes of minor bleeding, death, MI and VTE, were presented at the Congress.

**Comment (PO)**: The double blinded randomised BRIDGE trial was designed to determine if bridging anticoagulation with LMWH is necessary in patients undergoing a surgical procedure (most low risk). It excluded mechanical heart valves. Patients had a mean $CHADS_2$ score of 2.3 and 20% continued aspirin throughout. Warfarin was stopped 5 days before and resumed 24 hours after the procedure. Bridging was with dalteparin (100 IU/kg twice daily) given days –3 to –1 then for 5–10 days postoperatively starting at 24–72 hours. In 1884 patients, arterial thrombotic event rates within 30 days were 0.4% in nonbridged participants and 0.3% in bridged participants (p=0.01 for noninferiority), and the major bleed rates were 1.3% and 3.2%, respectively (relative risk 0.41 [p=0.005 for superiority]). These results support observational studies that have suggested that the higher bleeding risk associated with perioperative LMWH bridging is not offset by reduced ATE events. Continued aspirin use did not contribute to bleeding.

***Late Breaking Abstract Session: Thrombosis and Anticoagulation; LB002***

## Additional catheter-directed thrombolysis for high proximal deep vein thrombosis; 5 year results of a randomized controlled trial (the CaVenT study)

**Authors**: Haig Y et al., and on behalf of CaVenT Study Group

**Summary**: The CaVenT study randomised patients with a first, objectively verified DVT affecting their upper femoral and/or iliac vein to receive conventional therapy with or without CDT. A preliminary analysis at 60 months follow-up showed that compared with the control group (evaluable n=89), CDT recipients (evaluable n=87) had a significantly lower of incidence of PTS (43% vs. 71% [p<0.001]), and the respective numbers of participants with severe PTS were 1 and 4.

**Comment (PO)**: High proximal (upper femoral/iliac vein) DVT is associated with a high risk of PTS. A previous Cochrane review of 17 studies (2014) has shown that thrombolysis in this setting increases vein patency and reduces PTS. Patients with a first high DVT were randomised in this multicentre Norwegian trial to receive either conventional (LMWH/warfarin plus compression stockings) alone or additional CDT with alteplase via popliteal vein infusion. PTS (Villalta scale) was assessed at 60 months. A total of 209 patients, aged 18–75 years, with symptoms <21 days were randomised. Half had pelvic vein involvement. At 5 years the PTS rates in 176 assessable subjects were 42.5% (CDT) and 70.8% for an absolute risk reduction of 28.3% and a number needed to treat of 4 (p<0.001) favouring the use of thrombolysis. The majority of patients in both groups had mild PTS, but moderate PTS was four-fold higher in those treated conventionally.

***Therapeutic management of venous thrombosis; AS136***

## Additional data from the TITAN trial with the anti-VWF nanobody caplacizumab in the treatment of acquired TTP

**Authors**: Peyvandi F et al.

**Summary**: TITAN trial participants with acquired TTP were randomised to receive a single intravenous bolus injection of caplacizumab (n=36) or placebo (n=39) prior to their first on-study plasma exchange, and subsequent SC caplacizumab 10mg or placebo daily after each plasma exchange session and for 30 days following their last plasma exchange. Caplacizumab recipients had a significantly quicker median time to platelet response than placebo recipients (2.97 vs. 4.79 days; hazard ratio 2.2). At the time of reporting, the relevance of this endpoint in terms of more rapid curtailment of tissue ischaemia was being evaluated and analyses of other further plasma exchange and 1-month outcomes were being undertaken.

**Comment (PO)**: Caplacizumab is an anti-vWF nanobody under development for treating acquired TTP. It binds to the vWF A1 domain preventing the vWF-mediated platelet aggregation, which is the hallmark of TTP. Caplacizumab has been evaluated in addition to standard of care plasma exchange with immunosuppressants in this study, for which the primary endpoint was the time to platelet count increasing to ≥150,000/µL and sustained for 48 hours. Either caplacizumab or placebo was given intravenously prior to the first plasma exchange then daily SC caplacizumab/placebo after each plasma exchange and for 30 days after the last plasma exchange. There were 75 subjects. Caplacizumab reduced the time to platelet normalisation by 39% for an overall hazard ratio of 2.2 (95% CI 1.3, 3.8; p=005). Consistent with the platelet normalisation at twice the rate relative to placebo, caplacizumab treatment reduced the number of plasma exchange days and reduced biomarkers of organ damage more rapidly.

***Late Breaking Abstract Session: Bleeding disorders, TTP; LB006***

## A subcutaneously administered investigational RNAi therapeutic (ALN-AT3) targeting antithrombin for treatment of hemophilia: interim phase 1 study results in patients with hemophilia A or B

**Authors**: Sorensen B et al., and on behalf of ALN-AT3 Investigators

**Summary**: Healthy volunteers received SC ALN-AT3 30 µg/kg (n=3) or placebo (n=1) in part A of this phase 1 study. The respective maximum and mean antithrombin knockdown values were 28% and 19% (p<0.01), which resulted in a ≤152% increase in peak thrombin generation with a mean 138% maximum increase (p<0.01); the antithrombin knockdown was stable and durable for >60 days. Five mild adverse events occurred, but none were serious and there were no injection-site reactions. Parts B and C of the trial are enrolling patients with moderate or severe haemophilia A or B to receive ascending ALN-AT3 doses with weekly and monthly dosing. At the time of reporting, three participants had received three weekly doses of ALN-AT3 15 and 45 µg/kg, resulting in up to around 80% antithrombin knockdown with increased thrombin generation and improved whole blood clot formation, and good tolerability. Updated results from parts B and C of the trial were presented at the Congress.

**Comment (PO)**: When a thrombophilic trait such as antithrombin deficiency is co-inherited with haemophilia, the bleeding disorder is milder. RNA interference is a biological process in which RNA molecules inhibit gene expression. ALN-AT3 is an SC RNA interference therapeutic agent targeting antithrombin with the aim of restoring the haemostatic balance. It has been evaluated in ascending doses in haemophilia (n=12) to assess safety, tolerability, antithrombin knockdown and thrombin generation. Antithrombin knockdown up to 86% lasted >2 months after the last dose, with mean increases of 350% in thrombin generation. A reduced bleeding frequency was observed at higher antithrombin knockdown levels with a maximum bleed-free interval of 114 days. Treatment was well tolerated. This exciting therapeutic has the potential for infrequent SC dosing in haemophilia with/without inhibitors. Phase 3 studies are due to start mid-2016.

***Oral Presentations: Hemophilia – novel treatments; OR213***