

XXIII Congress of the ISTH Conference Review

Making Education Easy

July 23–28, 2011; Kyoto, Japan

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Welcome to this review of the XXIII Congress of the International Society on Thrombosis and Haemostasis (ISTH) held in Kyoto, July 23–28, 2011.

This review has been created to allow those unable to attend, but with a keen professional interest, to access a summary of some of the presentations. The conference was well organised and the quality of the presentations was uniformly high. Review and commentary has been carried out by Assoc Prof John M Carter, from the Wellington School of Medicine, University of Otago and Wellington Blood and Cancer Centre, Wellington Hospital, who attended the conference in Kyoto.

Abstracts presented at the Congress can be accessed from <http://onlinelibrary.wiley.com/doi/10.1111/jth.2011.9.issue-s2/issuetoc>.

We hope you enjoy this review of the XXIII Congress of the ISTH.

Kind regards

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Deep vein thrombosis: a United States cost model for a preventable and costly adverse event

Authors: Mahan C et al

The health burden of venous thrombosis is considerable, both in terms of patient morbidity and mortality and the costs to the health system. Of major importance is the cost of 'preventable' DVT.

Using the health economic tools of decision-tree and cost modelling, the authors researched the morbidities, their incidence rates and costs, and incidence of death. Included in the analysis were where (in- or outpatient) the DVT was acquired, recurrence rates, bleeding and other acute complications of treatment and the burden of post-thrombotic syndrome. Their estimates for the annual US cost of 'preventable' DVT ranged from \$US3.4–27 billion, with estimated US annual prophylaxis costs of \$US600 million.

Country-specific costs could be applied to the authors' model to estimate the potential savings of effective prevention and prophylaxis programmes. While the variance in the figures is significant, the savings demonstrated by this study are very large.

Session: Hemostatic Abnormalities in Thrombosis; Oral Communications [O-TU-044]

The impact of low-molecular-weight heparin prophylaxis on mortality in acutely ill medical patients: the LIFENOX study

Authors: Kakkar AJ et al, on behalf of the LIFENOX Investigators

It has been shown that appropriate prophylaxis can reduce the incidence of VTE in at-risk acute medical inpatients. This positive effect can reduce patients' morbidity, increase their quality of life and reduce health costs. However, an improved overall survival has not been clearly demonstrated for this group, largely due to the existing studies not being adequately powered.

The Lifenox study is a prospective, double-blind, randomised placebo controlled trial. The primary objective was to demonstrate increased survival of enoxaparin prophylaxis in acute medical inpatients 30 days after randomisation. The intervention arm delivered enoxaparin (40mg once daily for 6–14 days) and graduated compression stockings (GCS). The control arm was GCS plus placebo enoxaparin.

The primary outcome measures were all-cause mortality and haemorrhage at day 30.

8307 patients were included in the intention-to-treat analysis, with a mean age of 65.4 years. 37% had acute decompensated heart failure, 64% severe infection with added risk factors and 6% had active cancer. At day 30, all-cause mortality was the same in the enoxaparin plus GCS arm and the placebo plus GCS arm (4.9% vs. 4.8% $p=0.83$). There was no difference in bleeding between the two arms (0.4% vs. 0.3% $p=0.35$).

While there are several studies showing the benefit of heparin prophylaxis in this patient group, with the endpoint measured often being subclinical DVT detection, there are little high quality data on the use of GCS alone. The present study suggests that the simple intervention of GCS may produce equivalent practical clinical outcomes to pharmaceutical prophylaxis.

Session: Late Breaking Clinical Trials; Oral Communications [O-MO-036]

A randomized controlled trial comparing aspirin with dalteparin for the prevention of venous thromboembolism following total hip arthroplasty

Authors: Anderson DR et al

Surgery to the hip, especially total hip arthroplasty (THA), carries a significant risk of VTE. The current guidelines from the American College of Chest Physicians [Chest 2008;133(6 Suppl):381s-453s] give a grade 1A recommendation that thromboprophylaxis for this surgery should be with low-molecular-weight heparin (LMWH) for 35 days and that the sole use of aspirin is advised against.

This multicentre (12) Canadian study on elective THA patients delivered LMWH (SC dalteparin 5000U daily) to all patients for 10 days. They were then randomised to a further 28 days of LMWH or aspirin (85mg daily) delivered in a double-blind fashion. The primary endpoint was the development of confirmed symptomatic DVT within 90 days of surgery. The design was a noninferiority study with a target size of 2222. The study was halted at 786 patients, as the target of noninferiority had been achieved. Symptomatic VTE occurred in 1.3% of the LMWH arm compared with 0.3% of the aspirin arm. Aspirin was noninferior ($p < 0.0001$) but not superior ($p = 0.22$), and clinically important bleeding was the same in each arm (1.3% vs. 0.5% $p = NS$).

Compliance with prophylaxis guidelines after THA has been very variable. Audit studies demonstrate this in many countries and for a variety of reasons. This study is not compliant with the American guidelines cited above, but it does deliver an obligatory 10 days of LMWH postoperatively. Further verification of these results is desirable, but the cheap and convenient use of aspirin for 28 days is attractive and may result in a higher rate of compliance for this extended prophylaxis.

Session: Thrombotic Disorders: Clinical Trials I; Oral Communications [O-TU-130]

Extended follow-up of the multi-center prospective cohort that derived the “Men Continue and Herdoo2” clinical decision rule identifying low risk unprovoked patients

Authors: Rodger MA et al

In patients with a first idiopathic proximal vein DVT or PE, the decision of how long to remain on anticoagulants is controversial. The extremes of opinion range from 3 months to lifelong treatment with warfarin. In 2008, Rodger et al [CMAJ 2008;179(5):417-26] published the ‘Men continue and HERDOO2’ clinical-decision tool. In this study, men had a thrombosis recurrence rate of 13.7% per annum. Women with < 2 of the following: hyperpigmentation, oedema or redness of either leg, D-dimer $> 250 \mu\text{g/L}$ (on warfarin), BMI $> 30 \text{ kg/m}^2$ or age > 65 years, had a recurrence rate of 1.6%. Women with > 2 risk factors had a recurrence rate of 14.1%. The mean follow-up time in this report was 18 months.

The current report presents a mean 3.9 years of follow-up on 664 patients prospectively enrolled (11 centres) with a first unprovoked VTE. Men had an annual risk of recurrent VTE of 8.5% (95% CI 7.1, 10.1), high-risk women 6.4% (4.5, 8.7) and low-risk women 1.3% (0.6, 2.2). As would be expected with a longer follow-up period, the recurrence rates have fallen compared with the original study. However, one may still conclude that it may be less risky to stop anticoagulation than to continue (and be exposed to the risk of bleeding) for low-risk women. For the other two groups, decision making remains difficult and is probably best individualised. It is of note that in this study, follow-up venous ultrasound was not predictive of recurrence and that the technique had poor interobserver reliability. Skin hyperpigmentation on the other hand was useful with good concordance between observers. In this study, clots associated with air travel or hormone therapy alone were considered idiopathic and included in the analysis.

Session: Thrombotic Disorders: Clinical I; Oral Communications [O-MO-090]

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VTE Venous Thrombo Embolism, which is a combination of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)
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References. 1. Clexane and Clexane Forte Approved Data Sheet April 2010
2. www.medsafe.govt.nz. Please refer to the data sheet before prescribing. PP1436 NZ.ENO.11.08.001

SANOFI

Age-adjusted D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded

Authors: Douma RA et al

The use of the Well's clinical scoring criteria combined with D-dimer testing has provided an efficient tool for safely excluding DVT or PE in patients presenting in the ambulatory care setting. One limitation of the Well's score plus D-dimer algorithm has been uncertainty as to the effect of increasing age on the validity of the D-dimer assay. In the older patient, the D-dimer assay has had a lower specificity leading to a reduced ability to exclude VTE in the older patient (age >50 years).

The reported study has used an age-corrected D-dimer assay (patient's age \times 10 μ g/L) to evaluate patients aged >50 years presenting with a low or intermediate Well's score. The formula (using four different sensitive D-dimer assays) was studied in four separate cohorts of outpatients presenting with suspected DVT. Compared with using an upper D-dimer cutoff of 500 μ g/L, the age-adjusted formula allowed an extra 10–15% of all patients to have VTE safely excluded (patients aged >70 years: 20–28%).

The incidence of VTE disease rises steeply with increasing age. The ability to safely exclude a thrombus in this group using clinical scoring and an age-adjusted D-dimer will greatly increase clinical efficiency and reduce the demand for radiographic evaluation saving expensive resources.

Session: VTE: Laboratory Tests I; Oral Communications [O-TU-134]

Reasons for failure to remove inferior vena cava filters (IVCF): 2 year retrospective study in a tertiary care and trauma centre

Authors: Peterson EA et al

The use of inferior vena cava filters (IVCFs) appears to be increasing, despite a paucity of controlled trial evidence of their value. With the introduction of removable filters, the risks of increased lower limb thrombosis and other complications can be reduced. However, it is of concern that many filters are not retrieved.

The Vancouver General Hospital placed 151 retrievable filters over the 2007–8 period. A retrospective study ascertained the outcome of this intervention. Filters were inserted for the following reasons: acute (<3 months) VTE (76%), malignancy (36%) and trauma (21%). In 72%, there was a contraindication to anticoagulation. Retrieval was attempted in only 56% of patients (successful in 87% of attempts). 107 patients had a retrieval plan, and this was implemented in 78 of them, with a 90% success rate. Of the 44 patients without a removal plan, removal was attempted in six and was successful in only three patients.

The authors conclude that IVCF removal is suboptimal, and suggest that this will be improved if there is a clear prospective removal plan for each patient in whom a filter is placed. If this was combined with a more critical evaluation of the need for initial filter placement, there would be fewer patients with potentially troublesome filters left *in situ*. The involvement of a dedicated hospital thrombosis service may help optimise the use of this device.

Session: Intravascular Devices and Thrombosis; Poster Presentation [P-MO-428]

Dabigatran or warfarin for extended maintenance therapy of venous thromboembolism

Authors: Schulman S et al

There are several new oral anticoagulants entering clinical practice, and potentially they are able to replace warfarin for full anticoagulation and LMWH for prophylaxis. Dabigatran, a direct thrombin inhibitor, is one such agent that has the advantage of, in appropriate patients, being delivered as a standard-dose oral agent with no need for monitoring. It is registered for use in atrial fibrillation and for orthopaedic surgery prophylaxis. Several studies have reported its use in VTE.

In the Re-Cover study [[N Engl J Med 2009;361\(24\):2342–52](#)], Schulman and coworkers have shown that a fixed dose of dabigatran is as effective as warfarin for the treatment of acute VTE. In the present study, the two agents were compared for the secondary prophylaxis of VTE. Patients aged >18 years who had completed 3–12 months of anticoagulant therapy for acute VTE (DVT or PE) received either dabigatran (150mg twice daily) or warfarin (INR 2–3) in a double-blind, prospective fashion for an additional 6–36 months. The primary outcome measure was recurrent VTE or VTE death. The safety outcomes were bleeding, acute coronary syndrome and other adverse events.

Recurrent VTE occurred in 1.8% of 1430 dabigatran recipients and 1.3% of 1426 warfarin recipients, with major bleed rates of 0.9% vs. 1.8% and all bleed rates of 19% vs. 26% in the two groups, respectively. Acute coronary events were more common in the dabigatran group (0.9% vs. 0.2%; $p=0.02$), but there was no difference between the two groups in overall death rate or other side effects. The conclusion was that dabigatran is as effective as warfarin in secondary prophylaxis of VTE with a reduced risk of bleeding.

The difference in the coronary syndrome events is a finding common to several studies comparing dabigatran with warfarin, and the reason for this is uncertain. Whether there is a subtle difference in the degree of anticoagulation between the two agents, at the prescribed dose, to explain this is uncertain, but this simple explanation would also explain the difference in bleeding complications. Consistent with the simple hypothesis that the degree of anticoagulation may be significant is the observation that in the Magellan study, comparing enoxaparin with rivaroxaban, the latter drug was more efficacious at thrombosis prevention, but at the price of increased bleeding.

Session: Thrombotic Disorders: Clinical Trials II; Oral Communications [O-TH-033]

Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis

Authors: Carrier M et al

In any individual patient with a DVT, the ability to accurately predict the risk of clot recurrence, after stopping anticoagulation, would be very valuable. Some clinicians are using follow-up compression ultrasonography to guide ongoing therapy, i.e. if a residual vein obstruction (RVO) is detected, anticoagulation is continued for a longer period. The utility of this approach is controversial. The multivariate analysis of variables in the 'Men continue and HERDOO2' study (see p2) did not find this approach useful.

Carrier and coworkers performed a systematic literature search (Medline, Embase and Cochrane Registry) to determine whether RVO, determined at the time of stopping anticoagulation, was associated with an increased risk of recurrent VTE. Fourteen studies met selection criteria. When all patients with VTE were analysed, there was an association of RVO and recurrent VTE (odds ratio 1.5 [95% CI 1.1, 2.0]). However, importantly in the unprovoked VTE subgroup, RVO was not associated with a significantly increased risk of recurrent VTE (odds ratio 1.24 [95% CI 0.9, 1.7]) leading the authors to conclude that further prospective studies are needed to determine the role of RVO in the significant number of patients with unprovoked DVT. Until such studies are done, it could be argued that follow-up ultrasonography should not be done on these patients.

Session: Deep Vein Thrombosis and Pulmonary Embolism; Poster Presentation [P-MO-283]

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The optimal duration of anticoagulant therapy in patients with cancer-related deep vein thrombosis: the advantage of using residual vein thrombosis (the Cancer-Dacus study)

Authors: Malato A & Siragusa S

Further information on residual vein obstruction (RVO) in patients with provoked clots is provided by the Cancer-Dacus study. 347 patients with active cancer and a first episode of DVT received 6 months of low-molecular-weight heparin (LMWH) in standard fashion. At completion of this therapy, those patients with a negative RVO study had their anticoagulation stopped (105 patients; 30.3%), and in this group, a further thrombotic event occurred in only 2.8% of patients. 242 patients (69.7%) had evidence of RVO at the completion of 6 months of LMWH. This group was randomised to either continue or discontinue anticoagulation. Recurrent thrombosis was common in both of these groups; 14.2% and 21.9%, respectively. This is the first study to evaluate a marker of continuing thrombosis in cancer patients, and the results allow the clinician to identify a group of patients (RVO-negative) in whom anticoagulation can be safely stopped after 6 months of therapy.

Session: VTE: Risk Factors I; Oral Communications [O-MO-038]

Prevalence of chronic thrombo-embolic pulmonary hypertension after acute pulmonary embolism: a prospective multicenter study

Authors: Sanchez O et al

Chronic pulmonary hypertension is a well-recognised complication of pulmonary embolism (CTEPH), but most clinicians make the diagnosis infrequently. It is likely that its true incidence is higher than currently recognised.

Sanchez and coworkers prospectively studied 261 patients with acute PE. At 1 year, 149 patients were still alive and 11 (7.3%) had suspected pulmonary hypertension based on Doppler ultrasound examination. Eight of these patients had right heart catheterisation, and the diagnosis was confirmed in seven (4.7%). The affected patients were of older age (75 vs. 61 years), were more likely to have had multiple previous embolic events (67% vs. 22%) and a larger proximal vein thrombosis (72% vs. 31%). This study does demonstrate a significantly higher incidence of CTEPH than is often perceived. It also gives data to clarify the features of patients most at risk, i.e. older patients with a large PE and with a history of embolic events. The most prominent symptom in the affected patients was breathlessness.

Given the above data, it would be useful if it was possible to reliably exclude the diagnosis of CTEPH with simple noninvasive techniques. In the following study, the Dutch workers have tested a noninvasive algorithm that reliably excluded CTEPH after acute PE.

Session: VTE: Epidemiology; Oral Communications [O-MO-092]



Assoc Prof John Carter

MNZM BMedSc MB ChB (Otago) FRACP FRCPA (Haematology) is a clinical haematologist who holds joint appointments in Wellington with the University of Otago and the Wellington Hospital Blood and Cancer Centre, where he is Clinical Leader. He was responsible for establishing the Wellington bone marrow transplant programme 20 years ago, and more recently led the reorganisation of the national Blood Transfusion service. His current research interests include stem-cell transplants and the use of dendritic cells to target immunotherapy.

A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism

Authors: Klok FA et al

Consecutive patients with confirmed CTEPH (n=82) were compared with 160 consecutive patients in whom this diagnosis had been excluded. In the involved group, ECG criteria of right ventricular hypertrophy was found in 77% vs. 11% of the control group (odds ratio 26 [95% CI 13, 53]). Similarly, elevated N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) was found in the hypertensive patients. Using these parameters as a diagnostic model, a sensitivity of 94% (95% CI 86, 98) and specificity of 65% (56, 72) was demonstrated. Assuming a disease prevalence of up to 10%, the negative predictive value of this model was very high (99% [95% CI 97, 100]).

These two studies suggest a significant incidence of CTEPH after PE, but evaluation with simple noninvasive tests can exclude this complication with a high degree of certainty.

Session: VTE: Risk Factors I; Oral Communications [O-MO-040]

Idrabiotaparinux for acute symptomatic pulmonary embolism

Authors: Buller HR et al

There are currently a number of new anticoagulants available or being evaluated in clinical trials. Compared with warfarin, they have the advantage of not needing to be dose adjusted by regular blood testing and appear to have fewer drug or diet interactions. On the other hand, they may be difficult to reverse, their effects difficult to quantify in unstable patients or they may have, as yet, undetected side effects.

Buller and coworkers reported the results of a novel oral agent, idrabiotaparinux, that inhibits activated factor X.

In a prospective, randomised, double blind, noninferiority study, patients with acute PE were treated with enoxaparin followed either by standard warfarin or weekly SC idrabiotaparinux for 3–6 months. The study demonstrated noninferiority for the test drug, with recurrence rates for warfarin and idrabiotaparinux being 2.7% vs. 2.1% and bleeding occurring in 6.6% and 4.5%, respectively.

This drug is given once weekly subcutaneously and has an extremely long antithrombotic effect in patients. While the commercial future of this particular agent is uncertain, it is an example of the rapidly expanding range of novel anticoagulant agents being developed and tested. The result of these developments will be that significant changes will occur in anticoagulant prescribing. The optimal decision making for their use will pose challenges for clinicians, as full clinical evaluation and comparisons between agents will be time consuming and complex.

Session: Late Breaking Clinical Trials; Oral Communications [O-MO-033]