Thrombosis & Haemostasis Research Review™

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Issue 8 - 2016

In this issue:

Abbreviations used in this issue:

APS = antiphospholipid syndrome; **BBB** = blood-brain barrier; **CNS** = central nervous system; **EAE** = experimental autoimmune encephalitis; **FFP** = fresh frozen plasma **FVIII** = factor VIII; **FVL** = factor V Leiden mutation; **FXa** = factor Xa; **ICH** = intracranial haemorrhage; **INCH** = intracranial haemorrhage related to vitamin K antagonists; **INR** = international normalised ratio; **PC** = protein C; **PCC** = prothrombin complex concentrate; **PE**= pulmonary embolism; **TM** = thrombomodulin; **tPA** = tissue-type plasminogen activator; **VTE** = venous thromboembolism; **VWF** = von Willebrand factor.

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Welcome to the 8th issue of Thrombosis and Haemostasis Research Review

A study in this issue reports on a rapid pro-haemostatic agent to reverse the effects of direct oral anticoagulants. This group used an experimental mouse model to show that a variant coagulation factor, FXa(I16L), rapidly restores haemostasis in the presence of the anticoagulant effects of FXa inhibitors. A multicentre, prospective, open-label study evaluated the anti-factor Xa activity of andexanet alfa, a recombinant modified human factor Xa decoy protein. The researchers concluded andexanet alfa substantially reduced anti-factor Xa activity in patients with acute major bleeding associated with factor Xa inhibitors, with effective haemostasis occurring in 79%.

A population-based study in Norway investigated the association between plasma D-dimer levels measured at incident VTE diagnosis and the risk of cancer within the subsequent two years. The authors reported D-dimer levels were higher in patients who developed cancer than those who did not. An Italian study reported pulmonary embolism was identified in nearly one of every six patients hospitalised for a first episode of syncope. This work suggests that a diagnostic workup for PE should be strongly encouraged in all patients admitted with a first episode of syncope (provided they are not anticoagulated), including those in whom there is an apparent explanation for the episode of syncope. Another paper in this issue assessed hereditary risk factors for thrombophilia and probability of VTE during pregnancy and puerperium. This study, for the first time, provides estimates of the absolute risk of thrombosis according to age and thrombophilic defects, allowing for an individualised risk assessment as a basis for prophylactic treatment decisions.

I hope you enjoy the selection in this issue and I welcome your comments and feedback.

Kind Regards,

Professor Harshal Nandurkar

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Efficacy and safety of rVIII-SingleChain: Results of a phase 1/3 multicenter clinical trial in severe hemophilia A

Authors: Mahlangu J, et al

Summary: Study participants with severe haemophilia A were treated with rVIII-SingleChain, prophylactically (n=146) or on-demand (n=27). The authors reported haemostatic efficacy was rated by the investigator as excellent or good in 93.8% of the 835 bleeds treated and assessed. Across all prophylaxis regimens, the median annualised spontaneous bleeding rate was 0.00 and the median overall annualised bleeding rate was 1.14. Surgical haemostasis was also rated as excellent/good in 100% of major surgeries by the investigator. The authors noted no participant developed FVIII inhibitors.

Comment: The plasma half-life of most currently available factor VIII (FVIII) products means patients are required to inject FVIII every other day or 3 times a week, resulting in poor compliance. Several new recombinant FVIII products with extended half-life have been tested. Modifications such as (glycol) pegylation and Fc fusion have prolonged the half-life of rFVIII, this extension is limited to only 1.5 to 1.7 times the normal half-life of endogenous FVIII largely due to the dependence of FVIII on the half-life of von Willebrand factor (VWF) in the circulation. rVIII-SingleChain demonstrated excellent efficacy for prophylactic treatment with 43% of patients having no treated bleeds during the study. The overall median consumption for subjects on rVIII-SingleChain prophylaxis was 4283 IU/kg per year, which is comparable to that of the recently approved long-acting efmoroctocog alfa where a median consumption of 4118.4 IU/kg per year. The increased binding affinity of rVIII-SingleChain for VWF translates into a favorable PK profile of rVIII-SingleChain when compared with octocog alfa (Advate).

Reference: Blood 2016 Aug 4;128(5):630-7

Abstract

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Andexanet alfa for acute major bleeding associated with factor Xa inhibitors

Authors: Connolly SJ, et al

Summary: This multicentre, prospective, open-label study evaluated the anti-factor Xa activity of andexanet alfa (andexanet), a recombinant modified human factor Xa decoy protein. Patients (n=67) who had acute major bleeding within 18 hours after the administration of a factor Xa inhibitor received a bolus of andexanet followed by a 2-hour infusion of the drug. Most of the patients had substantial cardiovascular disease and bleeding was predominantly gastrointestinal or intracranial. After the bolus administration, the median anti-factor Xa activity decreased by 89% from baseline among patients receiving rivaroxaban and by 93% among patients receiving apixaban. Four hours after the end of the infusion, there was a relative decrease from baseline of 39% in anti-factor Xa activity among patients receiving rivaroxaban and of 30% among those receiving apixaban. Clinical haemostasis was adjudicated as excellent or good in 37 of 47 patients (79%) in the efficacy analysis (twelve hours after the andexanet infusion). Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up.

Comment: Following the earlier report of efficacy of Xa-inhibitor reversal in normal volunteers, this report demonstrates biochemical reversal and haemostatic improvement in patients with major bleeding. Thrombotic events were also noted with the use of idarucizumab for dabigatran reversal (in 10% of 51 patients) and may reflect that these patients have a baseline prothrombotic state needing effective anticoagulation.

Reference: N Engl J Med 2016 Sep 22;375(12):1131-41
Abstract

Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): A randomised trial

Authors: Steiner T, et al

Summary: The prospective, randomised, open-label, blinded-endpoint trial included patients (n=50) with intracranial haemorrhage (ICH) related to vitamin K antagonists who presented within 12 hours after symptom onset with an international normalised ratio (INR) of at least 2·0. Patients were randomly assigned (1:1) to 20 mL/kg of intravenous fresh frozen plasma (FFP) or 30 IU/kg of intravenous four-factor prothrombin complex concentrate (PCC) within 1 h after initial cerebral CT scan. Two (9%) of 23 patients in the FFP group versus 18 (67%) of 27 in the PCC group reached the primary endpoint of INR 1·2 or lower within 3 hours of treatment initiation. Thirteen patients died: eight (35%) of 23 in the FFP group (five from haematoma expansion) and five (19%) of 27 in the PCC group (none from haematoma expansion). Three thromboembolic events occurred within 3 days (one in the FFP group and two in the PCC group), and six after day 12 (one and five).

Comment: This is the first randomised controlled trial to compare anticoagulation reversal with FFP or PCC in patients with ICH specifically. In addition to showing more rapid INR normalisation in patients treated with PCC, faster anticoagulation reversal was associated with reduced early intracranial haematoma expansion. The study is limited by the small patient population and number of recruiting centres. One recruiting centre enrolled a large percentage of patients, which could limit the generalisability of these findings. Small sample size prevented drawing meaningful clinical conclusions about differences in survival or recovery.

Reference: Lancet Neurol 2016 May;15(6):566-73
Abstract

Prevalence of pulmonary embolism among patients hospitalized for syncope

Authors: Prandoni P, et al

Summary: This team performed a systematic workup for pulmonary embolism (PE) in 560 patients admitted to 11 hospitals in Italy for a first episode of syncope, regardless of whether there were alternative explanations for the syncope. They ruled out a diagnosis of PE in 330 of the 560 patients (58.9%) on the basis of the combination of a low pretest clinical probability of PE and negative D-dimer assay. Among the remaining 230 patients, PE was identified in 97 (42.2%). In the entire cohort, the prevalence of PE was 17.3%.

Comment: There was unexpectedly high prevalence of PE amongst patients with syncope. Pulmonary embolism was identified in 45 of the 355 patients (12.7%) who had an alternative explanation for syncope and in 52 of the 205 patients (25.4%) who did not have any other clinical explanation. This work suggests that a diagnostic workup for PE should be strongly encouraged in all patients admitted with a first episode of syncope (provided they are not anticoagulated), including those in whom there is an apparent explanation for the episode of syncope. Limitations of the study include its restriction to only include patients in the hospital setting.

Reference: N Engl J Med 2016 Oct 20;375(16):1524-1531
Abstract

A rapid pro-hemostatic approach to overcome direct oral anticoagulants

Authors: Thalji NK, et al

Summary: This group developed a variant coagulation factor, FXa(I16L), with an impaired active site function, resistant to active site inhibitors and longer plasma half-life than native FXa, which rapidly restores haemostasis in the presence of the anticoagulant effects of FXa inhibitors. FXa(I16L) mechanism of action is the active site inhibitor hindering antithrombin-dependent FXa. FXa(I16L) was able to rescue thrombin generation after rivaroxaban challenge; 300-fold more efficient than andexanet. FXa(I16L) was effective in reducing bleeding by dabigatran.

Comment: This is a unique FXa variant that bypasses the bleeding effect of both rivaraoxaban and dabigatran partly drug-binding (for rivaraoxaban) and predominantly by local pro-haemostatic effect (for both rivaroxaban and dabigatran).

Reference: Nat Med 2016 Aug;22(8):924-32
Abstract

Hyperfibrinolysis increases blood–brain barrier permeability by a plasmin- and bradykinin-dependent mechanism

Authors: Marcos-Contreras OA, et al

Summary: These researchers developed an experimental model of hyperfibrinolysis in mice by hydrodynamic transfection of a plasmid encoding for tissue-type plasminogen activator (tPA). They found the hyperfibrinolytic mice presented a significant increase in blood-brain barrier (BBB) permeability. This effect was dependent on plasmin-mediated generation of bradykinin and subsequent activation of bradykinin B2 receptors and prevented by icatibant (a clinically available B2 receptor antagonist).

Comment: This is exciting work that elucidates the mechanism of BBB leakage after thrombolysis and clearly demonstrates that this is due to bradykinin formation. As a potential therapeutic approach, icatibant can be used to prevent BBB leakage and brain consequences. Tranexamic acid, a lysine analog inhibitor of plasmin activation best known for its role in treating and preventing haemorrhage, has been used to treat angioedema since the 1970s and this work provides an explanation for its effect.

Reference: Blood 2016 Nov 17;128(20):2423-2434
Abstract

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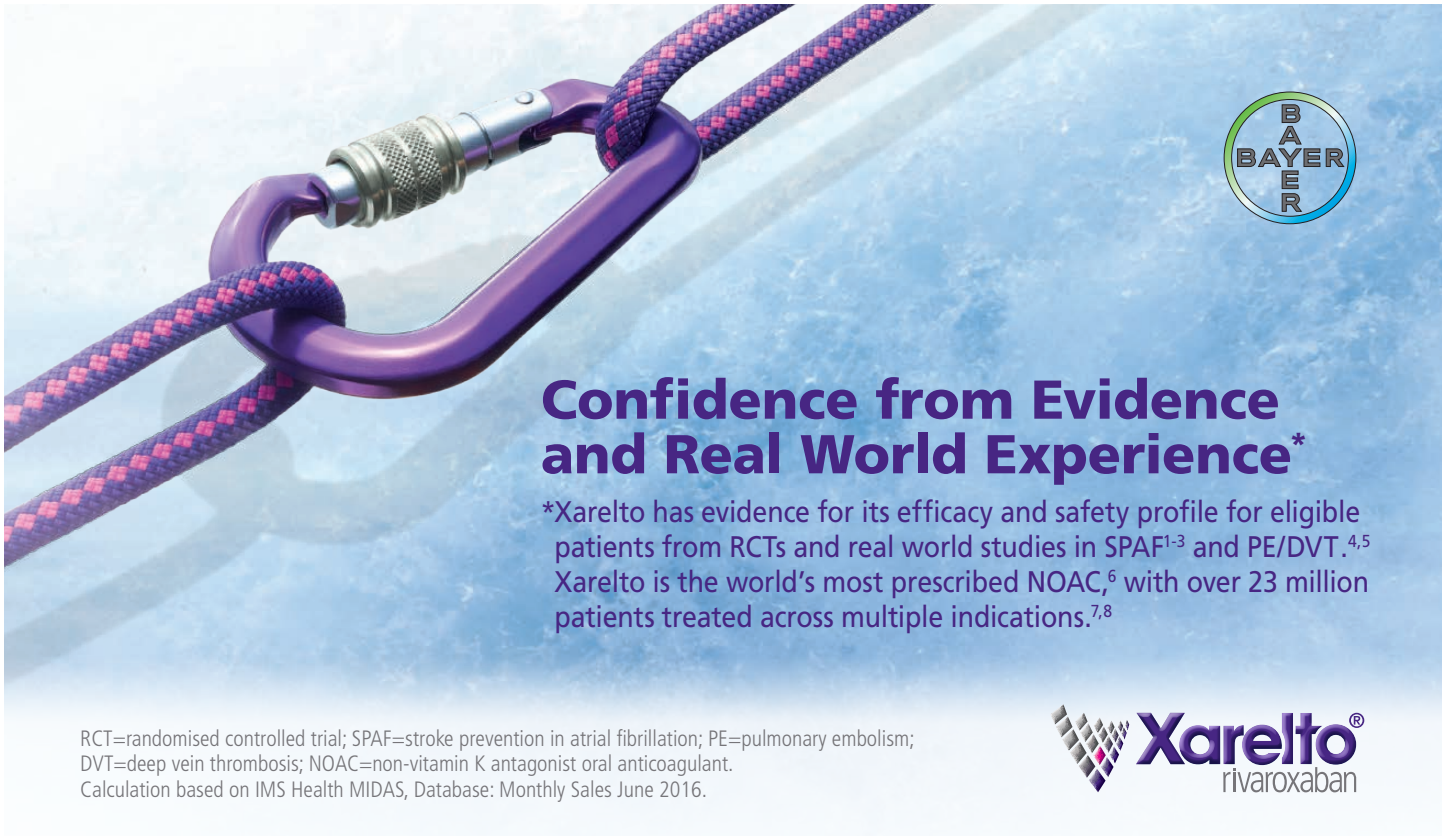
Independent commentary by Prof Harshal Nandurkar, Head of the Australian Centre for Blood Diseases and Director of Clinical Haematology, Alfred Health. Current President of the Australasian Society of Thrombosis and Haemostasis.



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RCT=randomised controlled trial; SPAF=stroke prevention in atrial fibrillation; PE=pulmonary embolism; DVT=deep vein thrombosis; NOAC=non-vitamin K antagonist oral anticoagulant.
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References: 1. Patel MR *et al. N Engl J Med* 2011;365:883–91. **2.** Camm J *et al. Eur Heart J.* 2015 Sep 1. pii: ehv466. [Epub ahead of print]. **3.** Tamayo S *et al. Clin Cardiol* 2015;38:63–8. **4.** Prins MH *et al. Thrombosis J* 2013;11(1):21. **5.** Beyer-Westendorf J *et al. Blood* 2014;124:955–62. **6.** IMS Health MIDAS, Database: Monthly Sales June 2015. **7.** Calculation based on IMS Health MIDAS, Database: Monthly Sales June 2016. **8.** Xarelto® (rivaroxaban) Product Information, 01 June 2016.

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Thrombomodulin-dependent protein C activation is required for mitochondrial function and myelination in the central nervous system

Authors: Wolter J, et al

Summary: The objective of this study was to explore the role of thrombomodulin (TM)-dependent activated protein C (PC) generation in immunological and non-immunological demyelinating disease models. Myelination and reactive oxygen species generation were evaluated in mice with genetically reduced TM-mediated PC activation and in wild-type mice under control conditions or following induction of experimental autoimmune encephalitis (EAE). Non-immunological demyelination was also analysed in the cuprizone-diet model. The authors reported impaired TM-dependent activated PC generation disturbs myelination and mitochondrial function at baseline and is linked with increased mitochondrial reactive oxygen species and aggravates EAE. Reducing mitochondrial reactive oxygen species, restoring activated PC plasma levels or injecting soluble TM ameliorates EAE in mice with genetically reduced TM-mediated protein C activation. Soluble TM additionally conveyed protection in wild type-EAE mice. The authors also reported soluble TM dampened demyelination in the cuprizone-diet model.

Comment: This report identifies a previously unknown mitochondria- and myelin-stabilising effect of the TM-PC system. In addition, the authors point towards solulin, a soluble TM variant that conveys strong protection from EAE and could be of therapeutic potential in human disease.

Reference: J Thromb Haemost 2016 Nov;14(11):2212-2226
Abstract

Rivaroxaban limits complement activation compared with warfarin in antiphospholipid syndrome patients with venous thromboembolism

Authors: Arachchillage DR, et al

Summary: The study cohort included 111 antiphospholipid syndrome (APS) patients with previous venous thromboembolism (VTE), on warfarin in the RAPS (Rivaroxaban in Antiphospholipid Syndrome) trial. Fifty-six patients remained on warfarin and 55 switched to rivaroxaban. Fifty-five normal controls were also studied. Blood samples were taken at baseline and at day 42 after randomisation and markers of complement activation assessed (C3a, C5a, terminal complement complex [SC5b-9] and Bb fragment). The team concluded APS patients had significantly higher complement activation markers compared with normal controls at both time-points irrespective of the anticoagulant. There were no differences between the two patient groups at baseline, or patients remaining on warfarin at day 42. In 55 patients randomised to rivaroxaban, C3a, C5a and SC5b-9 were lower at day 42 but levels of Bb fragment were unchanged. The team also reported there were no correlations between rivaroxaban levels and complement activation markers.

Comment: Warfarin is the conventionally preferred anticoagulant in APS thrombosis. This report describes novel actions of rivaroxaban in suppressing complement inhibition. The mechanism is not known but possibly via Xa. Since complement components such as C5a are proinflammatory contributing to the APS phenotype, the complement-inhibitory activities of rivaroxaban (and possibly other Xa-inhibitors) makes it a preference over warfarin.

Reference: J Thromb Haemost 2016 Nov;14(11):2177-2186
Abstract

D-dimer measured at first venous thromboembolism is associated with future risk of cancer

Authors: Gran OV, et al

Summary: The authors investigated the association between plasma D-dimer levels measured at incident VTE diagnosis and the risk of cancer within the subsequent two years in a cohort of 422 VTE patients recruited from the general population in Norway. Of the 422 first lifetime VTE events, 239 were DVTs and 183 PEs. Fifty-nine cancers were diagnosed during a median follow-up of 4.7 years; 28 cancer diagnoses within one year following a VTE diagnosis, and 34 within two years. The authors reported D-dimer levels were higher in patients who developed cancer than those who did not. In patients who developed cancer within one year, the most common cancer sites were those of the lung (29%) prostate (21%), and haematological cancers (14%).

Comment: Cancer cells possess strong procoagulant properties that can induce local activation of the coagulation system. Fibrin formation is necessary for tumour growth, spread and tumour-induced angiogenesis, and fibrin degradation products possess potent angiogenic properties. This study reports that patients with the highest D-dimer levels had a higher incidence of cancer and also advanced/metastatic cancer at diagnosis. Possibly D-dimer level at the time of VTE diagnosis should be considered in the decision algorithm whether to screen for cancer.

Reference: Haematologica 2016 Dec;101(12):e473-e475
Abstract

Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium

Authors: Gerhardt A, et al

Summary: This team aimed to estimate the individual probability of gestational VTE associated with thrombophilia. The study cohort consisted of 243 women with first VTE during pregnancy and the puerperium, and 243 age-matched normal women. They reported in women ≥35 years [<35 years], the individual probability of gestational VTE was: 0.7% [0.5%] for heterozygous factor V Leiden mutation (FVL); 3.4% [2.2%], for homozygous FVL; 0.6% [0.4%], for heterozygous prothrombin G20210A; 8.2% [5.5%] for compound heterozygotes for FVL and prothrombin G20210A; 9.0% [6.1%] for antithrombin deficiency; 1.1% [0.7%] for protein C deficiency; and 1.0% [0.7%] for protein S deficiency. The team concluded results were independent of a positive family history of VTE.

Comment: This study, for the first time, provides estimates of the absolute risk of thrombosis according to age and thrombophilic defects, allowing for an individualised risk assessment as a basis for prophylactic treatment decisions. The age stratification takes into account the demographic changes in the society with increasing rates of childbearing women ≥35 years of age and these data should influence individual decisions regarding thromboprophylaxis.

Reference: Blood 2016 Sep 9. pii: blood-2016-03-703728
Abstract

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