Thrombosis & Haemostasis Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ABR = annualised bleeding rate; **CLIA** = chemiluminescent immunoassay; **DVT** = deep vein thrombosis; **eGFR** = estimated glomerular filtration rate; **ELISA** = enzyme-linked immunosorbent assay; **FVIII** = coagulation factor VIII; **HHT** = hereditary haemorrhagic telangiectasia; **HIPA** = heparin-induced platelet activation assay; **HIT** = heparin-induced thrombocytopenia; **LMWH** = low-molecular-weight heparin; **PaGIA** = particle-gel immunoassay; **PE** = pulmonary embolism; **VTE** = venous thromboembolism.

Welcome to the latest issue of Thrombosis & Haemostasis Research Review.

Results from the pivotal, international, phase 3 XTEND-1 trial of efanesoctocog alfa in *The New England Journal of Medicine* demonstrate efficacy for severe haemophilia A, providing superior bleed prevention versus prestudy coagulation factor VIII (FVIII) prophylaxis. This novel agent enables once-weekly dosing without compromising FVIII activity levels by overcoming the interaction with endogenous von Willebrand factor, a major therapeutic advance that led to the US Food and Drug Administration approval of efanesoctocog alfa for this indication. In other research, aspirin may be a suitable thromboembolism prophylactic for nonelective orthopaedic trauma patients treated with or without surgery, with the PREVENT-CLOT trial finding a comparable efficacy for mortality prevention versus enoxaparin; a prospective pilot study from the Concord Repatriation General Hospital in Sydney reports the feasibility of tinzaparin for venous thromboembolism (VTE) in patients with renal impairment; and the ONKOTEV-2 validation study finds that the novel assessment model provides a meaningful estimation of cancer-associated thrombosis risk. Finally, the online TORADI-HIT machine-learning model may help with the clinical diagnosis of heparin-induced thrombocytopenia (HIT), pending further evaluation.

We hope you enjoy this update in Thrombosis & Haemostasis research, and look forward to receiving any feedback you may have.

Kind Regards,

Dr Bronwyn Thorp
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Efanesoctocog alfa prophylaxis for patients with severe haemophilia A

Authors: von Drygalski A et al., for the XTEND-1 Trial Group

Summary: Results from the pivotal international phase 3 XTEND-1 trial published in *The New England Journal of Medicine* demonstrate efficacy for the investigational agent efanesoctocog alfa – a novel class of FVIII replacement - in haemophilia A, eliciting significantly improved bleeding prevention versus other prophylactic therapies and durably normalising FVIII activity with once-weekly dosing. The one year, open label nonrandomised study, enrolled 159 patients at least 12 years of age with previously treated severe haemophilia A (< 1 international unit (IU)/dL [<1% FVIII coagulant activity] endogenous FVIII activity) in two parallel arms to assess prophylactic once-weekly (n=133; 50 IU/kg) and on-demand (n=26) treatment strategies. In the prophylactic trial arm, the median annualised bleeding rate (ABR) on treatment was 0 and the mean intrapatient reduction in ABR versus prestudy recombinant and/or plasma-derived FVIII agent treatment was 77% (0.69 vs 2.96; $p<0.001$). Significant improvements in physical health, pain intensity and joint health were also reported. A single on-demand injection treatment was sufficient to resolve almost all (97%) bleeds (most found in the on-demand treatment arm). FVIII activity levels were maintained at normal or close to normal for most of the week (mean FVIII activity > 40 IU/dL). Treatment was reported to be tolerable with an acceptable safety profile and no patients developed FVIII inhibitors.

Comment: Efanesoctocog alfa is a novel recombinant FVIII therapy. It adds a region of Von Willebrand factor and extra peptides to an Fc fusion protein, allowing it to break through the Von Willebrand factor "ceiling", which limits the half-life of current therapies. This paper, published in *NEJM*, presents data from XTEND-1, an open label, non-randomised trial of efanesoctocog alfa in severe haemophilia A patients. The key aspect of the trial was an intra-patient comparison of efanesoctocog alfa prophylaxis versus prior standard of care prophylaxis. Once weekly prophylaxis with efanesoctocog alfa provided effective bleeding prevention with a median ABR of 0 and a clinically relevant reduction (77%) in mean ABR. In addition, it performed well for management of bleeding episodes as nearly 97% resolved with a single dose. Near-normal mean factor levels (>40%) were maintained for the majority of the week with a mean trough level of 15%. This suggests the potential to fully prevent haemarthroses. Efanesoctocog alfa presents an opportunity for good clinical outcomes and quality of life with once-a-week dosing. Further studies are required to asses long-term safety and efficacy.

Reference: N Engl J Med 2023;388(4):310-18
Abstract

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Aspirin or low-molecular-weight heparin for thromboprophylaxis after a fracture

Authors: The Major Extremity Trauma Research Consortium (METRC)

Summary: Aspirin may be an easy and cheap alternative to low-molecular-weight heparin (LMWH) for thromboembolism prophylaxis in adult orthopaedic trauma patients with pelvic, hip or extremity fractures according to results from the North American PREVENT-CLOT trial. In a cohort of 12,211 patients (mean age 44.6 years; 0.7% history of VTE; 2.5% history of cancer) treated surgically for an extremity fracture proximal to the metatarsals or carpals or hospitalised for a pelvic or acetabular fracture and randomised to enoxaparin (30 mg twice daily; n=6,110) or aspirin thromboprophylaxis (81 mg twice daily; n=6,101) the trial found that aspirin was non-inferior for prevention of all-cause mortality at three months (0.73% vs 0.78%; *p* for non-inferiority<0.001). The study cohort received a median of eight in-hospital doses and 21-days post discharge prophylaxis. A slight increased risk of deep vein thrombosis (DVT) in the aspirin arm (2.51% vs 1.71%) was driven by below-the-knee clots but comparable rates of pulmonary embolism (PE), bleeding complications and other serious adverse events were found between trial cohorts.

Comment: The strength of this paper is its large size of over 12,000 participants. Patients with pelvic fractures, or those who had undergone surgery for an extremity fracture, were randomised to receive aspirin or LMWH as VTE prophylaxis, with duration as per local protocols. Up to two doses of LMWH were given prior to randomisation. The paper demonstrated non-inferiority of aspirin for all cause death by 90 days, proximal DVT, PE and major bleeding. However, there were more symptomatic DVTs in the aspirin arm overall, due to increased rates of below knee DVTs. This is similar to findings from previous studies of aspirin prophylaxis post arthroplasty. It should be noted that the median age in this study was under 50, bringing into question its applicability to an elderly population.

Reference: N Engl J Med 2023;388(3):203-13
Abstract

A machine-learning model for reducing misdiagnosis in heparin-induced thrombocytopenia: a prospective, multicentre, observational study

Authors: Nilius H et al.

Summary: Henning Nilius and colleagues harnessed artificial intelligence to derive a novel diagnostic instrument, named TORADI-HIT, with the aim of improved accuracy of HIT diagnosis. The prospective cohort study, funded jointly by the Swiss National Science Foundation and the International Society on Thrombosis and Haemostasis, enrolled a multicentre cohort of almost 14 hundred patients with suspected HIT (8.5% diagnosed with HIT by the reference standard washed platelet heparin-induced platelet activation assay [HIPA]). Machine-learning algorithms were employed to create five prediction models that integrated diverse clinical and laboratory data across three immunoassay platforms (chemiluminescent immunoassay [CLIA], particle-gel immunoassay [PaGIA] and enzyme-linked immunosorbent assay [ELISA]). Complex interactions between six variables – platelet count nadir, C-reactive protein, type of immunoassay, numeric immunoassay test result, timing of thrombocytopenia and other possible causes of thrombocytopenia – were evaluated utilising either a support vector machine or a gradient boosting machine according to immunoassay type. TORADI-HIT demonstrated a high diagnostic accuracy (area under the receiver operating characteristic, 0.99 for each model) and significantly reduced misdiagnoses compared to the currently used 4Ts score plus immunoassay diagnostic algorithm with improvements of between 50% to 66.7% in the rate of false-negatives and 30% to 68.5% for false-positives. An exception was noted for the algorithm based on CLIA results where an increase in false-positives was found. The authors stated that TORADI-HIT is undergoing further evaluation in a wider range of patient populations.

Comment: This paper details the development, validation and implementation of a machine learning-led model for HIT diagnosis. A prospective cohort study was conducted in 1,393 Swiss suspected HIT cases, using HIPA (washed platelet heparin induced platelet activation) assay as the diagnostic gold standard. Diagnostic algorithms were then developed for use with the three most commonly used immunoassays - PaGIA, CLIA and ELISA - and validated against the study data set. The best performing algorithms for each immunoassay were found to substantially out- perform the combination of 4T score and immunoassay, other than for an increased false positive rate (by 29%) when used with CLIA. The composite TORADI-HIT prediction tool is now accessible online and incorporates C-reactive protein and use of unfractionated heparin as variables. This paper suggests it may provide a practical aid to the timely and accurate diagnosis of HIT.

Reference: EClinicalMedicine 2022;55:101745
Abstract

Thrombosis in multiple myeloma: Risk estimation by induction regimen and association with overall survival

Authors: Charalampous C et al.

Summary: This Mayo Clinic study retrospectively analysed the incidence of thromboembolism and impact on clinical outcomes in patients newly diagnosed with multiple myeloma commencing induction regimens containing the immunomodulatory drug lenalidomide. In a cohort of 672 patients 12.4% experienced a thrombotic episode in the 12 months after diagnosis, most commonly DVT (8.3%) followed by PE with or without DVT (3.4%), and stroke (0.6%). With a thromboembolism incidence rate of one in five patients (21.1%) the triplet induction regimen KRd (carfilzomib, lenalidomide, and dexamethasone) was associated with the greatest risk of thromboembolism, conferring a more than doubled likelihood of a clot versus other induction regimens (odds ratio 2.6; $p<0.01$). An elevated risk of thrombosis was also observed with quadruplet regimens and the triplet bortezomib, lenalidomide plus dexamethasone. Thrombosis was associated with inferior long-term outcomes with a halving of median overall survival, from 11 to 5.5 years ($p<0.01$) and a hazard ratio of greater than two on both univariate and multivariable analyses adjusted for relevant confounding factors. The authors noted that this excess thromboembolism risk was observed despite nearly universal aspirin thromboprophylaxis, emphasising the great unmet need in this population.

Comment: This retrospective cohort study reviewed incidence of thrombosis in the year post myeloma diagnosis. The takeaway message was the significantly higher risk of thrombosis with carfilzomib-lenalidomide versus other regimes (odds ratio 2.6) with no other identified confounders between treatment groups. Thrombosis was associated with increased mortality, even after adjusting for high-risk disease features (hazard ratio 2.61). This association was not seen in earlier trials and may relate to improved disease-related early mortality over time. Interestingly, the observed deaths were disease-related. Thrombosis rates were high (12.4%) despite high rates of prophylaxis (95.2%). There was no difference between rates of thrombosis with low-dose and high-dose aspirin prophylaxis. Further comparisons between thromboprophylaxis regimes were not possible in this study.

Reference: Am J Hematol 2023;98(3):413-20
Abstract

Traumatic coagulopathy in the older patient

Authors: Curry N et al.

Summary: Analysis of coagulation profiles from the Activation of Coagulation and Inflammation in Trauma-2 (ACIT-2) observational, multicentre study was undertaken to delineate whether severe injury coagulation profiles vary by age and therefore, if age-specific trauma haemorrhage therapy may be required. Analysis was based on 1,576 patients at least 16 years of age admitted to one of six European hospitals through the emergency department or via London's air ambulance and recruited to the study within two hours of injury. Results showed that patterns of post-trauma coagulation were broadly consistent regardless of age, characterised by low procoagulant factor levels (including fibrinogen), high activated protein C levels and hyperfibrinolysis, with evidence of coagulopathy across age cohorts. The magnitude of the coagulation response immediately following major trauma differed by age, with an exaggerated response in patients with advanced age compared to younger patients with an injury of comparable severity.

Comment: This paper is based on data from the ongoing ACIT-2 research study. It compares extensive laboratory data for three age cohorts of trauma patients including a cohort >65 years. In patients with severe injury and shock the same pattern of relative hypofibrinogenaemia, hyperfibrinolysis (although not evidenced on thromboelastography and rotational thromboelastometry), and hypercoagulability (including loss of FVII and activated protein C) was observed. However, the older cohort had significantly higher levels of fibrinogen and fibrinolysis, including in a linear regression model. Standard thresholds for fibrinogen replacements were found to be less sensitive predictors for bleeding in the older cohort. This data suggests a different approach for replacement of fibrinogen and/or use of antifibrinolytics in this cohort may be required. However, potential confounders are that it was not possible to determine whether tranexamic acid was given prior to testing and there were more cases of isolated traumatic brain injury in the older cohort.

Reference: J Thromb Haemost 2023;21(2):215-26
Abstract

Tinzaparin for venous thromboembolism in patients with renal impairment

Authors: Yeung J et al.

Summary: A single-centre, prospective pilot study from the Concord Repatriation General Hospital in Sydney reports the feasibility of tinzaparin anticoagulation in patients with renal insufficiency. A total of 20 patients with kidney disease (estimated glomerular filtration rate [eGFR] 20–50 mL/min) with a range of indications for anticoagulation therapy received subcutaneous tinzaparin infusions (175 units/kg daily) prior to transition to oral anticoagulant. Tinzaparin was cleared with no accumulation out to two weeks by plasma anti-Xa assay. There were five cases of bleeding complications, two of which were major, and four deaths, all of which the study authors credited to comorbidities. The publication stated that adverse outcomes were comparable to trials of tinzaparin in cancer-associated VTE.

Comment: This paper from Vivien Chen's group at Concorde hospital describes a pilot program to trial the use of tinzaparin therapeutic anticoagulation in patients with renal disease. Twenty patients with creatinine clearance 20 to 50 mL/min were included and weight-based dosing was used with no dose adjustment for renal impairment. The important takeaway is that there was no accumulation up to day 14 and no correlation of anti-Xa levels with renal function. The bleeding rate was high (two major and three minor), as expected in this high-risk group, as was the case with mortality (four deaths, none attributable to bleeding). Ideally a larger study including more patients with more severe renal impairment (eGFR 20-30 mL/min) will follow. This data suggests that tinzaparin is a viable alternative anticoagulant in selected patients with renal disease, particularly for cancer-associated thrombosis, and calls for greater access in Australia.

Reference: Intern Med J 2023;53(1):68-73
Abstract

Validation of the ONKOTEV risk prediction model for venous thromboembolism in outpatients with cancer

Authors: Cella C et al.

Summary: The European ONKOTEV-2 validation study has corroborated the clinical utility of the previously developed four-level ONKOTEV risk assessment model for prediction of VTE risk in patients with cancer. A total of 425 adult patients (median age 61 years) with a solid malignancy with/without metastasis - most commonly breast, oesophageal, colon or lung tumours – initiating a new treatment regimen were enrolled into the noninterventional prognostic study, evaluated for VTE risk in the absence of anticoagulation therapy using four variables (a Khorana score of >2, metastatic disease, vascular or lymphatic compression and a previous VTE event) at baseline and followed for up to two years. Suspected thromboembolic events were assessed by objective imaging assessment. At presentation the bulk of the patient population had an ONKOTEV score of 2 or less, more than half with a score of 1, and only a minority (2.6%) had a score of 3 or 4. There were a total of 54 VTE events (DVT and/or PE) over the study period for a cumulative incidence of 12.7%. At six months the cumulative incidence of VTE in patients with an ONKOTEV score of 0, 1, 2 and > 2 were 2.6%, 9.1%, 32.3% and 19.3%, respectively. Assessment of each of the variables in the ONKOTEV model for association with VTE risk confirmed metastatic disease and macroscopic vascular or lymphatic compression as elevating risk and found a non-significant trend with Khorana score > 2 but did not find an independent association between previous VTE and future risk. The authors concluded that ONKOTEV provides a meaningful estimation of cancer-associated thrombosis risk.

Comment: Multiple risk assessment models for venous thromboembolism in cancer outpatients have been developed. More recently these have added different variables to the validated Khorana score to better stratify patients. This paper describes the validation of the previously published ONTOKEV risk assessment model in an independent prospective cohort. This has a four-level scoring system, incorporates Khorana score over 2, and adds vascular or lymphatic compression, metastatic disease and previous VTE. The cumulative incidence function of the high-risk score was relatively high at six and 12 months, demonstrating better discrimination than other similar recent risk assessment model validations. Previous VTE was not found to be independently associated with VTE in this cohort. Further validation in different populations is required, but this paper suggests potential for the use of this risk assessment model in clinical practice.

Reference: JAMA Netw Open 2023;6(2):e230010
Abstract

Nitrous oxide abuse leading to extreme homocysteine levels and thrombosis in young adults

Authors: Caris M et al.

Summary: This case series from the OLVG Hospital in Amsterdam, the Netherlands reports an association between nitrous oxide abuse and thromboembolism. In 326 cases of nitrous oxide abuse-related hospitalisations in an almost seven-year period up to May 2021 the incidence of severe thrombotic events was 5% (n=17). This cohort were characterised by excessive recreational nitrous oxide use with between 400 and 6000g inhaled per day, equating to roughly 50-750 balloons, and were predominantly young adult males. Thrombotic events consisted of both venous (70%) and arterial (30%) thrombosis including portal vein thrombosis, cerebral vein thrombosis, acute coronary syndrome, femoral artery thrombosis and middle cerebral artery thrombosis. In half of these patients at least one neurologic symptom manifested prior to the thrombotic event, all of which were attributable to nitrous oxide misuse. Extremely high serum homocysteine concentrations were noted in all patients with thrombosis with a median concentration more than 125-times higher than reference and concentrations up to 1500-times higher observed (median 125 µmol/L; range, 22-253 µmol/L vs reference <15 µmol/L), supporting the hypothesised link between hyperhomocysteinemia and thrombosis and indicating that B vitamin supplementation may be of benefit.

Comment: This paper details the emergent risk of thromboembolism with recreational nitrous oxide use. It is a series of 17 cases of thrombosis in patients with a history of excessive nitrous oxide use. Thromboses included arterial (acute coronary syndrome and stroke) and venous in unusual sites (cerebral venous sinus thrombosis and splanchic thrombosis). Patients were predominately young (median age 26) with few other risk factors. Neurological symptoms attributable to excessive nitrous oxide preceded thrombosis in 50%. Hyperhomocysteinemia was relatively common in the patients with thrombosis and in those with neurological sequelae without thrombosis, with extremely high levels in some cases. This paper calls for increased awareness and suggests a re-examination of the role of homocysteine in thrombosis.

Reference: J Thromb Haemost 2023;21(2):276-83
Abstract

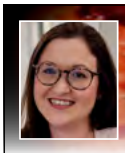
Safety, tolerability, and effectiveness of anticoagulation and antiplatelet therapy in hereditary haemorrhagic telangiectasia

Authors: Virk Z et al.

Summary: Zane Virk and colleagues retrospectively evaluated outcomes in a cohort of patients with hereditary haemorrhagic telangiectasia (HHT) who underwent anti-thrombotic treatment in a real-world setting. Data from 119 patients treated with one or more antiplatelet and/or anticoagulant medications in a 27-year period up to February 2022 at a Mass General Brigham affiliated hospital were obtained from electronic health care records. Premature treatment discontinuation was very common (44%), predominantly due to bleeding-related adverse events such as worsening epistaxis or gastrointestinal bleeding and this rate was not improved by initiation with reduced dose therapy. Bleeding complications necessitated dose-reductions in an additional 6% of the cohort, corresponding to half of patients receiving reduced dose or prematurely ceasing treatment due to bleeding. Previous gastrointestinal bleeding was the only factor found to elevate the likelihood of antithrombotic discontinuation in multivariable logistic regression modelling analysis (odds ratio 3.25; p=0.001). Treatment-related bleeding increased morbidity with greater haematological support and hospitalisations required after, versus before, antithrombotic therapy initiation. The rate of thrombosis while undergoing antithrombotic therapy was 15% and included stroke, VTE and acute coronary syndrome, amongst others.

Comment: This is a large cohort study of patients with HHT on antithrombotic therapies and highlights the difficulties of anticoagulation in this population. Therapy was tolerated very poorly with increased rates of bleeding leading to discontinuation or dose reduction in 50% of patients (59/119). This resulted in high rates of recurrent thrombosis (15%). An important finding was that the rates of reduction or discontinuation were not any greater with the use of direct-acting oral anticoagulants (DOACs), than with heparins, vitamin K antagonists or even single-agent antiplatelets. Initiation on reduced intensity therapy also did not result in improved tolerance. Selection bias due to choice of therapy likely plays a role. Anti-angiogenic and anti-fibrinolytic therapies were only used in 9%, but seemed to be an effective adjunct.

Reference: J Thromb Haemost 2023;21(1):26-36
Abstract



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Independent commentary by Dr Bronwyn Thorp

Dr Bronwyn Thorp is a staff specialist haematologist at St Vincents Hospital Sydney, a VMO at the Northern Beaches Hospital and a laboratory haematologist at Clinical Labs. She has a particular interest in perioperative management of bleeding as well as point of care haemostatic testing.

36-month clinical outcomes of patients with venous thromboembolism: GARFIELD-VTE

Authors: Turpie A et al., on behalf of the GARFIELD-VTE investigators

Summary: GARFIELD-VTE (Global Anticoagulant Registry in the FIELD – Venous Thromboembolic Events), a non-interventional prospective registry, aims to delineate the effectiveness of real-world treatment strategies for VTE for the prevention of death and acute and long-term adverse sequelae. This report in *Thrombosis Research* provides three-year outcomes in a cohort of over 10 thousand patients with objectively confirmed VTE enrolled prior to 2017. Acute DVT without concurrent PE was the most common VTE diagnosis, found in over 60% of the study population. Almost all patients (98.1%) received anticoagulant therapy ± other therapeutic modalities with a variable duration of anticoagulation (most at least three months and more than half at least 12 months). The 12-month incidence of all-cause mortality was 6.5 per 100 patient-years, recurrent VTE 5.4 per 100 patient-years and major bleeding 2.7 per 100 patient-years. The incidence of all three outcomes declined over the next two years. Parenteral therapy or oral anticoagulants were superior to no anticoagulation for prevention of recurrent VTE but parental therapy had increased rates of deaths and major bleeds compared to oral anticoagulants. Cancer was by far the most common cause of mortality, accounting for almost half of all deaths at three-years, followed by cardiac and VTE (8.1% and 3.2%, respectively).

Comment: GARFIELD-VTE is a large international prospective registry of VTE. Many findings have already been published from this dataset. This paper reviews outcomes at 36-month follow-up. The most notable observations are the poor outcomes in the first-year post diagnosis, particularly the first month, as well as the high rates of continued anticoagulation. Incidence of recurrent VTE, major bleeding, all-cause mortality as well as new cancer, stroke and myocardial infarction were all highest at 12 months. Forty-two percent of patients were still on anticoagulation at 36 months. This is not in accordance with guidelines, but is reflective of a trend towards longer anticoagulation. Rates of bleeding and all-cause mortality were highest in patients who received parental anticoagulation, likely due to overrepresentation of patients with malignancy in this group.

Reference: Thromb Res 2023;222:31-9
Abstract

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