Haematology Research Review™

Making Education Easy

Issue 23 - 2017

In this issue:

Abbreviations used in this issue

AF = atrial fibrillation
APTT = activated partial thromboplastin time
CVT = cerebral venous thrombosis
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
FVL = factor V Leiden
ICH = intracerebral haemorrhage
LMWH = low-molecular-weight heparin
PE = pulmonary embolism
PT = prothrombin time
TTP = thrombocytopenic purpura
VTE = venous thromboembolism

Welcome to issue 23 of Haematology Research Review.

Highlights for this issue include a trial reporting that nadroparin is no better than placebo for reducing the risk of proximal extension or VTE events in low-risk outpatients with a first acute symptomatic DVT in the calf. Other research assessed hereditary risk factors for thrombophilia and the probability of VTE during pregnancy and puerperium and, for the first time, provided estimates of the absolute thrombosis risk according to age and thrombophilic defects. Research published in N Engl J Med found no difference in post-transfusion mortality among hospitalised patients transfused with red blood cells that had been stored for short versus long periods. This issue concludes with a study of ruxolitinib for polycythaemia vera without splenomegaly, with the results suggesting it could be considered as standard of care for patients not responding adequately to hydroxyurea.

We hope you are finding these regular updates in haematology research helpful in your everyday practice. Please don't hesitate to email us your comments and suggestions.

Kind regards,

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Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation

Authors: Pennlert J et al.

Summary: Associations between timing of antithrombotic treatment and the competing risks of severe thrombotic and haemorrhagic events were explored in a cohort of 2619 Swedish registry patients with AF and ICH; follow-up was 5759 person-years. Anticoagulated high-risk patients had lower risks of vascular death and nonfatal stroke with no significant increase in severe haemorrhage risk, with the greatest benefit apparent when treatment was started 7–8 weeks after ICH. Compared with no antithrombotic treatment, anticoagulation started 8 weeks after ICH was associated with a lower risk of vascular death or stroke recurrence within 3 years in high-risk women and men (17% vs. 28.6% and 14.3% vs. 23.6%, respectively; lower limit of 95% CI for each difference, >0%).

Comment (PO): International guidelines highlight the lack of evidence as to whether and when to re-introduce anticoagulants after an ICH. Observational studies have suggested there is a significant decrease in all-cause mortality and ischaemic stroke by recommencing anticoagulant therapy, with the ICH itself being a recognised independent risk factor for thromboembolic events in AF. The main finding from this nationwide Swedish registry of ICH in AF is that restarting warfarin is associated with a significant reduction in thromboembolic events at 3 years and does not increase bleeding events. This appears to be true for both genders with both high- and low-risk profiles. In absolute terms the time-dependent benefits are greater for those at higher risk. Optimal timing appears to be 7–8 weeks after the ICH. Antiplatelet therapy adds no benefit and may be harmful. We cannot extrapolate the data to newer oral anticoagulants. APACHE-AF using apixaban is a randomised controlled trial currently underway to evaluate this.

Reference: Stroke 2017;48(2):314–20
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**

Venous thrombotic recurrence after cerebral venous thrombosis

Authors: Palazzo P et al.

Summary: The rate of thrombosis recurrence over long-term follow-up and its predictors were investigated in 187 consecutive patients with CVT. A cause was identified for 73% of patients, 20% had coagulation abnormalities and 9% had *JAK2* mutations. Mean oral anticoagulant treatment duration was 14 months. The annual mortality rate was 2.5%, with an in-hospital mortality rate of 2%. During median follow-up of 73 months, six patients experienced CVT recurrence, and 19 experienced symptomatic extracranial venous thrombotic events, with respective 1-, 2-, 5- and 10-year cumulative venous thrombotic recurrence rates of 3%, 8%, 12% and 18%. Independent predictors of recurrence were prior venous thrombotic event (hazard ratio 2.8 [p=0.018]), presence of cancer or malignant haemopathy (3.2 [p=0.039]) and unknown cause of CVT (2.81 [p=0.024]).

Comment (PO): CVT is uncommon (3–4 per million per year), and usually occurs in patients aged <40 years, in those with a thrombophilia marker or in women during pregnancy (12 per 100,000 deliveries) or on contraceptives. Recurrence risks estimated from the ISCVT (International Study on Cardiovascular and Dural Sinus Thrombosis) are quoted at 2% (CVT) and 3% (extracerebral), but are largely unknown, as are the risk factors for recurrence. The usual treatment duration is 6 months in the absence of an ongoing risk factor. This prospective study shows the cumulative recurrence risk increasing over time and approximating 18% at 10 years, which is lower than the spontaneous VTE (DVT/PE) recurrence rate of 40–50% over a similar time period. Myeloproliferative neoplasms and male gender were associated with increased recurrence in ISCVT, but here previous VTE, cancer and myeloproliferative neoplasms as well as unknown cause (idiopathic) are highlighted. Women taking hormonal therapy at the time of the CVT had a lower recurrence than those women not using hormones at diagnosis.

Reference: Stroke 2017;48(2):321–6
Abstract

Safety of pregnancy after cerebral venous thrombosis

Authors: Aguiar de Sousa D et al.

Summary: This systematic review included 13 observational studies reporting data on CVTs and other VTEs associated with pregnancy or puerperium in women with a history of CVT. There were 9 CVTs per 1000 pregnancies and 27 noncerebral VTEs per 1000 pregnancies. The spontaneous abortion rate was 17.7%. There were limited data on the risk of CVT/extracerebral VTE according to antithrombotic prophylaxis. There was no significant difference in miscarriage rates between women who received antithrombotic therapy versus those who did not (11.3% vs. 18.8% [p=0.34]).

Comment (PO): CVT accounts for 25–50% of all pregnancy-related strokes, but the recurrence of CVT in pregnancy is poorly evaluated. This analysis included 13 qualifying observational studies of which eight had long-term follow-up of patients with CVT. The absolute recurrent CVT rate in pregnancy is low (~9 per 1000 [95% CI 3, 33]) but is increased 80-fold relative to the general pregnancy population (0.116 per 1000). The rate of noncerebral VTE was also increased (27 per 1000). There were 33 spontaneous terminations in 186 pregnancies for a crude risk rate of 18%, which is similar to the baseline rate (~10–15%). Sample sizes, duration of follow-up and use of prophylaxis were variable, consistent with this type of analysis, so there is little to take from this in terms of optimal pregnancy prophylaxis for this group of women.

Reference: Stroke 2016;47(3):713–8
Abstract

Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS)

Authors: Righini M et al.

Summary: Low-risk outpatients with a first acute symptomatic DVT in the calf were randomised to receive subcutaneous nadroparin 171 UI/kg (n=122) or placebo (n=130) once daily for 6 weeks, along with use of compression stockings, and were followed for 90 days; enrolment was terminated early due to study drug expiration and slow recruitment. There was no significant difference between the nadroparin versus placebo group for the composite primary outcome of extension of calf DVT to proximal veins, contralateral proximal DVT or symptomatic PE by day 42 (3% vs. 5% [p=0.54]), but bleeding was significantly greater among nadroparin recipients (4% vs. 0% [p=0.0255]). One nadroparin recipient died from metastatic pancreatic cancer and another developed type 2 heparin-induced thrombocytopenia.

Comment (PO): Should we treat isolated calf vein thrombosis? This study is the first randomised placebo-controlled study that suggests there is no therapeutic benefit and possible harm due to increased bleeding when therapeutic-dose LMWH (nadroparin) is used to treat low-risk patients with isolated calf vein thrombosis. About half of the patients in each arm had muscular vein thrombosis, with the remainder involving the posterior tibial or peroneal vessels. We actually know relatively little about risks for proximal propagation in this setting, which has been estimated to be up to ~10% at 1 week in these patients. The study obviously excluded high-risk patients (malignancy, inpatients, limb immobility, etc), but the slow recruitment to the study suggests other selection biases, presumably because physicians were reluctant to refer their patients. The jury is still out. In my experience patients prefer to be treated rather than leave a clot untreated and there does seem to be an improvement in pain symptoms with short-course LMWH.

Reference: Lancet Haematol 2016;3(12):e556–62
Abstract

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

Authors: Gerhardt A et al.

Summary: This research team aimed to estimate the individual probability of gestational VTE associated with thrombophilia. The study cohort consisted of 243 women with a first VTE during pregnancy and the puerperium, and 243 age-matched control women. Women aged ≥35 years and <35 years had respective individual probabilities of gestational VTE of: i) 0.7% and 0.5% for heterozygous *FVL* mutation; ii) 3.4% and 2.2% for homozygous *FVL*; iii) 0.6% and 0.4% for heterozygous prothrombin G20210A; iv) 8.2% and 5.5% for compound heterozygotes for *FVL* and prothrombin G20210A; v) 9.0% and 6.1% for antithrombin deficiency; vi) 1.1% and 0.7% for protein C deficiency; and vii) 1.0% and 0.7% for protein S deficiency – these findings were independent of a VTE family history.

Comment (PO): This case-control study indicates that unselected women, without a family history of VTE, who are homozygous for *FVL*, compound heterozygotes (*FVL*/prothrombin mutation) or with severe antithrombin deficiency have a high pregnancy-associated VTE risk. This risk is higher than the risk level of 3% that triggers anticoagulation in the general nonpregnant population during transient risk exposure. There is a recommendation to *"consider routine antenatal prophylaxis"* even with a negative family history. Consistent with local practice heterozygous *FVL* or prothrombin gene mutations are low risk, unless associated with a family or personal history. The point is made that much of the risk assessment in pregnancy derives from family studies with thrombophilia, which overestimates the risk for unselected women, particularly those with mild inhibitor deficiencies. A strength of this analysis is that it provides absolute risk estimates for age (above and below 35 years) and the severity of the deficiency in those without a family thrombotic history.

Reference: Blood 2016;128(19):2343–9
Abstract

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Effect of short-term vs. long-term blood storage on mortality after transfusion

Authors: Heddle NM et al.

Summary: Hospitalised patients with type A or O blood needing red blood cell transfusions were randomised to receive blood that had been stored for a short duration (mean 13.0 days; n=6936) or long duration (mean 23.6 days; n=13,922). There was no significant difference between the short- versus long-term blood storage groups for the primary outcome of in-hospital mortality (9.1% vs. 8.7%; odds ratio 1.05 [95% CI 0.95, 1.16]); similar results were seen when the analysis was expanded to include patients with any blood type (n=24,736; 9.1% vs. 8.8%; 1.04 [0.95, 1.14]), and in three prespecified high-risk subgroups, namely cardiovascular surgery patients, intensive care unit patients, and cancer patients.

Comment (LY): The idea that blood that has been stored for longer periods may be harmful seems to some extent logical, and was backed up by animal models, *in vitro* data and retrospective studies. Potentially increased endothelial 'stickiness', 2,3-DPG and/or nitric oxide accumulation have all been described. However, prospective studies have never shown a convincing difference in outcome, and this idea has been finally put to bed with the massive INFORM study of adult general hospital patients, which included 10 times the number of patients as the next largest study. It was multicentre, international and with a pragmatic protocol including limited electronic data collection. The storage length was almost double between the two groups when blood groups A and O were considered. No difference in mortality was shown. Prescribers of blood can be confident that storage time is not relevant even in higher risk adult populations.

Reference: N Engl J Med 2016;375(20):1937–45
Abstract

Efficacy of a rituximab regimen based on B cell depletion in thrombotic thrombocytopenic purpura with suboptimal response to standard treatment

Authors: Benhamou Y et al., French Reference Center for Thrombotic Microangiopathies

Summary: Twenty-four patients with TTP who had responded suboptimally to a plasma exchange-based regimen received two rituximab 375 mg/m^2 infusions within 4 days, with a third dose 15 days after the first infusion if peripheral B-cells remained detectable, in this phase 2 research. There were three deaths after the first rituximab infusion. Among survivors, the B-cell-driven treatment resulted in accelerated remission and ADAMTS13 activity recovery, secondary to rapid anti-ADAMTS13 depletion in a manner, similar to that seen with the standard schedule of four rituximab infusions. One-year relapse-free survival was comparable with that in participants from a previous study.

Comment (LY): TTP is a rare disease with significant potential mortality in which absence of the von Willebrand cleaving enzyme results in microthrombosis associated with haemolytic anaemia and thrombocytopenia, as well as brain and renal damage. Plasma exchange and steroids are the mainstay of management; however, B-cell depletion with rituximab has a role in slow responders/refractory patients, consistent with the autoimmune nature of the disease. This interesting multicentre study showed that at least one if not two doses of rituximab could be dropped from the standard regimen, based on demonstration of B-cell depletion, without adversely affecting outcome when compared with historical controls. The timing of maximum benefit of rituximab is still unclear, as is whether lymphoma type dosing (as used here) is required. Nevertheless, this interesting strategy is worth considering for the TTP patient requiring an escalation of therapy.

Reference: Am J Hematol 2016;91(12):1246–51
Abstract

A randomized and double-blind controlled trial evaluating the safety and efficacy of rituximab for warm auto-immune hemolytic anemia in adults (the RAIHA study)

Authors: Michel M et al.

Summary: Thirty-two adults with warm autoimmune haemolytic anaemia previously treated with <6 weeks of corticosteroids received prednisone 1 mg/kg/day for 2 weeks and then tapered; eligible participants also received two rituximab 1000mg or placebo infusions 2 weeks apart. There were 27 evaluable participants with ≥1 year of follow-up data. Compared with placebo, rituximab recipients had a significantly greater 1-year overall response rate (75% [11 complete responses, 1 partial response] vs. 31% [5 complete responses]; p=0.032), and at 2 years there were ten complete responses among rituximab recipients compared with three among placebo recipients (p=0.011). There were two severe infections in the rituximab arm and six in the placebo arm (p=0.39). There had been no deaths among rituximab recipients at 2 years, compared with six in the placebo group (p=0.017).

Comment (LY): Continuing the theme of rituximab in autoimmune disease, warm autoimmune haemolytic anaemia frequently responds to steroid therapy, but relapses are common. In this study, which excluded secondary patients, the addition of rituximab to a relatively rapid steroid taper using a rheumatological rituximab dosing schedule of 2 × 1g doses increased the complete response rate significantly at both 1 and 2 years. Although this was a national multicentre study, the numbers were small, and the total number of patients screened or excluded was not provided. Nevertheless, it encourages the early consideration of rituximab if initial responses are not adequate or steroids are relatively contraindicated, and hopefully will be pursued in larger studies.

Reference: Am J Hematol 2017;92(1):23–7
Abstract

Poor comparability of coagulation screening test with specific measurement in patients receiving direct oral anticoagulants

Authors: Testa S et al.

Summary: This multicentre study evaluated relationships and responsiveness of PT (prothrombin time) and APTT (activated partial thromboplastin time) versus DOAC plasma concentrations measured with specific coagulation tests performed with different platforms in patients with AF, including 240 dabigatran recipients, 264 rivaroxaban recipients and 131 apixaban recipients. For dabigatran, the range of r values for correlations between APTT and diluted thrombin time was 0.62–0.80, and for rivaroxaban and apixaban, the respective ranges of r values for correlations between the anti-FXa assay and PT were 0.73–0.91 and 0.54–0.81. Despite these significant correlations, responsiveness of both PT and APTT was relatively poor. A considerable proportion of patients exhibited discrepancies between global testing and DOAC plasma concentrations, depending on the platform and drug, with values of 6–62%.

Comment (LY): When considering emergency treatment of patients receiving DOACs, it would be convenient to be able to rely on standard readily available coagulation tests, analogous with INR (international normalised ratio) for warfarin therapy. Unfortunately however, this large real-world study confirms this is not the case. When comparing the APTT and PT to a drug concentration based on a commercially available calibrated assay (performed at the same centre), a significant number of patients with residual drug concentrations that would be considered clinically relevant had normal coagulation results. This was particularly true for apixaban, which has long been recognised to have a blunted effect on the PT. Really calibrated assays of drug concentrations should be readily available. The reversal agent for dabigatran, idarucizumab, does not have adverse clinical consequences if it is given to patients with low or no concentrations, so perhaps an argument could be made for use independent of the APTT (disregarding the cost, which is a relevant consideration in our practice in NZ). In contrast however, andexanet, in clinical trials to reverse Xa inhibitors outside of NZ, appears to have a higher rate of thrombotic events, so that accurate estimation of drug concentrations on an urgent basis is likely to be important.

Reference: J Thromb Haemost 2016;14(11):2194–201
Abstract

Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2)

Authors: Passamonti F et al.

Summary: Adults with polycythaemia vera, no palpable splenomegaly and hydroxyurea resistance or intolerance were stratified according to hydroxyurea therapy status and randomised to receive open-label oral ruxolitinib 10mg twice daily (n=74) or best available therapy (n=75) in this phase 3b study. Compared with best available therapy, ruxolitinib was associated with a significantly greater proportion of participants achieving haematocrit control at week 28 (primary endpoint; 62% vs. 19%; odds ratio 7.28 [95% CI 3.43, 15.45]). Haematological adverse event rates in the respective ruxolitinib and best available therapy arms were 14% and 3% for any-grade anaemia, 3% and 8% for any-grade thrombocytopenia, 0% and 1% for grade 3–4 anaemia, and 0% and 4% for grade 3–4 thrombocytopenia; respective grade 3–4 nonhaematological adverse event rates were 7% and 4% for hypertension and 0% and 3% for pruritus; respective serious adverse event rates were 0% and 2% for thrombocytopenia and 3% and 0% for angina pectoris. There were two deaths, both in the best available therapy arm.

Comment (LY): The idea of JAK (Janus kinase) inhibition for diseases driven by the *JAK2* V617F mutation is an appealing targeted therapy. Initial successful studies in myelofibrosis are now followed by polycythaemia vera, a myeloproliferative neoplasm almost exclusively associated with the *JAK2* mutation. The first study in hydroxyurea-resistant or -intolerant patients included those with splenomegaly, as spleen reduction was a significant benefit in the myelofibrosis studies. This follow-up study included patients without splenomegaly, and again showed improved reduction in haematocrit relative to hydroxyurea or alternatives. The accompanying editorial challenges the choice of the control group given the absence of proven benefits of hydroxyurea over standard venesection to maintain haematocrit, although presumably the study intended to target the group who are most likely to be offered such an expensive therapy. Given the cost, in the NZ market the absence of evidence of improved outcomes such as survival are likely to limit its use in polycythaemia vera at this stage.

Reference: Lancet Oncol 2017;18(1):88–99
Abstract

Independent commentary by Dr Laura Young, a haematologist specialising in thrombosis and haemostasis at Auckland Hospital as part of the Thrombosis Unit and Haemophilia Centre. She also has a part-time lecturing position in the Department of Molecular Medicine and Pathology at the University School of Medicine. **For full bio CLICK HERE.**

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. He serves on the Medical Advisory panel of the New Zealand Haemophilia Foundation and the National Haemophilia Management Group. **For full bio CLICK HERE.**