Haematology Research Review™

Making Education Easy

Issue 24 - 2017

In this issue:

Abbreviations used in this issue
DVT = deep vein thrombosis
FVIII = factor VIII
LMWH = low-molecular-weight heparin
OR = odds ratio
RBC = red blood cell
VTE = venous thromboembolism

Welcome to issue 24 of Haematology Research Review.

This issue begins with a study that set out to validate the HERDOO2 rule for identifying patients who can safely discontinue anticoagulants after short-term treatment for a first unprovoked VTE. There is also a meta-analysis and case presentation discussing the risk of VTE during pregnancy in the presence of essential thrombocythaemia. Other research published in N Engl J Med reports that use of rivaroxaban (10mg or 20mg) significantly lowers the risk of VTE recurrence compared with aspirin, without increasing the risk of bleeding, in patients with VTE in equipoise for continued anticoagulation. The issue concludes with a meta-analysis of trials assessing the role of desmopressin for reducing perioperative allogeneic RBC transfusion and bleeding in patients with platelet dysfunction.

We hope you are enjoying these regular updates in haematology research, and we appreciate receiving your feedback and suggestions.

Kind regards,

Dr Paul Ockelford
paulockelford@researchreview.co.nz

Dr Laura Young
laurayoung@researchreview.co.nz

Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis

Authors: Rodger MA et al., for the REVERSE II Study Investigators

Summary: The HERDOO2 rule (hyperpigmentation, oedema or redness in either leg, D-dimer level ≥250 µg/L, body mass index ≥30 kg/m^2 or age ≥65 years) was validated in a prospective cohort of women with a first unprovoked VTE treated with 5–12 months of short-term anticoagulation therapy. There were 631 women classified as low risk of recurrent VTE (0–1 HERDOO2 criteria), of whom 591 discontinued anticoagulants, 323 high-risk women (≥2 HERDOO2 criteria) and men who discontinued anticoagulants and 1802 who continued anticoagulants according to clinician and patient discretion. Recurrent symptomatic VTE within 1 year occurred at rates of 3.0% per patient-year in low-risk women, 8.1% per patient-year in high-risk women and men who discontinued anticoagulants and 1.6% per patient-year in high-risk women and men who continued anticoagulants.

Comment (LY): Selection of patients at the highest risk of recurrence after a spontaneous VTE is appealing, as lower risk patients may not need to take the inherent risks associated with anticoagulation. These Canadian investigators were unable to stratify men who were at highest risk, but were able to elucidate a scoring system for women, which was validated in this large international study. Some interesting points arose from the larger numbers enrolled. While premenopausal women with or without hormone therapy at the time of diagnosis who were low risk on the scoring system had a low recurrence risk, postmenopausal women even with low-risk scores had a higher risk, suggesting more work is needed for stratifying this group. The rates of recurrence in nonanticoagulated high-risk patients, and bleeding rates in those who remained on treatment, were as expected. This study does validate the original cohort and provides further useful statistics for patients facing this decision.

Reference: BMJ 2017;356:j1065
Abstract

Risk of venous thromboembolism in pregnant women with essential thrombocythemia

Authors: Skeith L et al.

Summary: This was a systematic review and meta-analysis of 21 trials covering 756 pregnancies in women with essential thrombocythaemia. The absolute VTE risk in the *ante partum* period (2.5%) was not above the threshold for a clear indication of LMWH prophylaxis or below the threshold for withholding LMWH, but the risk *post partum* (4.4%) exceeded the threshold for consideration of LMWH prophylaxis. The authors also discussed the use of LMWH prophylaxis during pregnancy for the case of a 28-year-old woman with JAK2-positive essential thrombocythaemia and no personal or family history of VTE who was on current treatment with aspirin and hydroxyurea for a history of problematic erythromelalgia.

Comment (LY): Approximately one in every six patients with essential thrombocythaemia will be a woman of childbearing age. Pregnancy therefore is a question to consider on occasion. Many studies in the area are naturally small case series, therefore a meta-analysis is of value. A total of 756 pregnancies could be evaluated with higher rates of VTE than pregnancies without the disorder; *post partum* prophylaxis appears to be justified and *ante partum* prophylaxis should be considered in women with risk factors. What is striking is the lack of quality evidence in this area – the benefits of disease control with interferon, and reduced platelet activation with aspirin in terms of both pregnancy complications and VTE remain unclear. This is an area for further research.

Reference: Blood 2017;129(8):934–9
Abstract

Eltrombopag added to standard immunosuppression for aplastic anemia

Authors: Townsley DM et al.

Summary: Consecutive patients with severe aplastic anaemia (n=92) were enrolled in three consecutive cohorts differing according to time of initiation and duration of eltrombopag, combined with immunosuppressive therapy, in this prospective phase 1–2 study. Cohort one received eltrombopag from day 14 to 6 months, cohort 2 from day 14 to 3 months, and cohort 3 from day 1 to 6 months. The respective complete response rates in cohorts 1–3 were 33%, 26% and 58%, and the respective 6-month overall response rates were 80%, 87% and 94%; these combined rates were higher than reported for a historical cohort (complete response rate 10% and overall response rate 66%). The survival rate at median follow-up of 2 years was 97%; the only death was related to a nonhaematological cause. There were marked increases in bone marrow cellularity, $CD34^+$ cell number and frequency of early haematopoietic progenitors. Relapse and clonal evolution rates were similar to historical values. Two participants developed severe rashes leading to early eltrombopag discontinuation.

Comment (LY): Stimulation of the thrombopoietin receptor c-mpl by agonists such as eltrombopag has been a major advance for chronic immune thrombocytopenia. However, the receptor has other important roles in haematopoiesis and importantly is found on stem cells. Aplastic anaemia is a devastating immune disorder associated with an empty bone marrow and in severe cases poor survival if treatment responses don't occur. Bone-marrow transplant for those of a suitable age with a donor is the only curative option; however, many are left with immune suppression as their only therapy. This study has built on the original work by the investigators showing a benefit for eltrombopag in patients who had failed immune suppression. Here the additive benefits of both therapies are shown with impressive results compared with historical controls. This is a very encouraging development with low additional toxicity.

Reference: N Engl J Med 2017;376(16):1540–50
Abstract

Nonneutralizing antibodies against factor VIII and risk of inhibitor development in severe hemophilia A

Authors: Cannavò A et al.

Summary: These researchers analysed plasma samples from 237 SIPPET trial participants for the presence of anti-FVIII non-neutralising antibodies prior to FVIII concentrate exposure. Non-neutralising antibodies were detected in 7.6% of the participants at screening with a clear age gradient. The respective cumulative incidences of inhibitor development were 45.4% and 34.0% for participants with and without non-neutralising antibodies. Cox regression analyses revealed that compared with participants without non-neutralising antibodies at screening, those with non-neutralising antibodies were significantly more likely to develop inhibitors (hazard ratio 1.83 [95% CI 0.84, 3.99]), particularly high-titre inhibitors (2.74 [1.23, 6.12]); these associations persisted after adjustment.

Comment (LY): Alloantibodies against infused FVIII products are a devastating, expensive complication of severe haemophilia A, resulting in some cases in prolonged immune tolerisation or worse, lifelong requirement for bypassing agents. While predictive factors are known, thus far this has not been used in an effective way to prevent inhibitor development. The SIPPET study was a brave randomised study of plasma-derived versus recombinant FVIII, which confirmed that inhibitors are significantly less by a factor of 1.8 in those who receive plasma-derived products. In this additional study, they have shown that the presence of non-neutralising antibodies against FVIII detected before therapy starts does predict an increased risk of inhibitor development. This is important, and if the detection of these antibodies in the laboratory can be simplified, further use in algorithms to try and modify the rate of inhibitors in these patients is likely to be valuable.

Reference: Blood 2017;129(10):1245–50
Abstract

Using iron studies to predict *HFE* mutations in New Zealand: implications for laboratory testing

Authors: O'Toole R et al.

Summary: These researchers compared biochemical markers of iron overloading in 2388 NZ patients genotyped for C282Y, H63D and S65C during 2007–2013. Test ordering patterns revealed that an elevated serum ferritin level alone triggered *HFE* genotype testing in 62% of the patients, and a C-reactive protein level was obtained to rule out an acute phase reaction in only 11% of these patients. There was only a low association between serum ferritin level and significant *HFE* genotype. However, transferrin saturation values of ≥45% predicted hereditary haemochromatosis mutations with the greatest sensitivity and specificity. A serum ferritin level of >1000 µg/L was found in one C282Y homozygote who had a transferrin saturation of <45%.

Comment (LY): Hereditary haemochromatosis is a relatively common genetic disorder, which historically had devastating consequences; however, in the modern era where the genetic tests are readily available, up to 30% of patients who are homozygous for C282Y in the *HFE* gene may not even develop the clinical syndrome. Where family members are affected, genetic screening as an initial diagnostic strategy is completely appropriate. As a population strategy, use of iron studies as a screening test is still cheaper and more efficient; however, hyperferritinaemia due to inflammation, fatty liver or alcohol is very common. This interesting audit from colleagues in Wellington showed that the pickup overall was fairly low – just 17% of patients screened for *HFE* mutations had a significant result. Most patients had iron tests before screening, but the majority were screened with a ferritin only and not a full iron profile. The authors conclude that screening makes sense if the ferritin level exceeds 1000 µg/L (who are most at risk of complications if the diagnosis is hereditary haemochromatosis) or if the ferritin level is increased with an increase in iron saturation of >45%. When considering further costly tests, considering the basics initially still makes good sense.

Reference: Intern Med J 2017;47(4):447–54
Abstract

New Zealand Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our **CPD page**.

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.**

Thromboprophylaxis after knee arthroscopy and lower-leg casting

Authors: van Adrichem RA et al., for the POT-KAST and POT-CAST Group

Summary: POT-KAST (evaluable n=1451) and POT-CAST (evaluable n=1435) were parallel open-label trials that randomised patients undergoing knee arthroscopy (POT-KAST) or who required casting of the lower leg (POT-CAST) to receive or not receive anticoagulation prophylaxis with LMWH for 8 days after knee arthroscopy or during the full period of immobilisation due to casting. There was no significant difference between the LMWH and control arms for the 3-month VTE rate in the respective POT-KAST and POT-CAST trials (0.7% vs. 0.4%; relative risk 1.6 [95% CI 0.4, 6.8] and 1.4% vs. 1.8%; 0.8 [0.3, 1.7]). Bleeding events had occurred in 0.1% of each group in POT-KAST and in none of the POT-CAST participants at 3 months. The most common adverse event was infection in both trials.

Comment (PO): Arthroscopic surgery and lower-limb immobilisation in a plaster cast are regarded as risk factors for DVT. Previously, small studies have suggested a benefit of DVT prophylaxis in these patients, but the absolute need for thrombosis prevention has been controversial and the precise DVT risk with a lower-limb cast is uncertain. In this large nonblinded trial, the rate of symptomatic events in the controls was low, 0.4% (arthroscopy) and 1.8% (limb immobilisation), with no benefit demonstrated with prophylactic-dose LMWH. Outcome adjudication was blinded. Patients developing thrombotic events had additional risk factors such as older age, hormone use or a family history of VTE. This suggests that prevention regimens are still likely to be needed in higher risk patients, perhaps using anticoagulants at doses that are higher than usually 'recommended' for prophylaxis.

Reference: N Engl J Med 2017;376(6):515–25
Abstract

CLICK HERE
to read previous issues of Haematology Research Review

Rivaroxaban or aspirin for extended treatment of venous thromboembolism

Authors: Weitz JI et al., for the EINSTEIN CHOICE Investigators

Summary: These researchers randomised 3365 patients with VTE to receive rivaroxaban 20mg or 10mg or aspirin 100mg once daily for ≥12 months (median 351 days) in this phase 3 trial; all study participants had completed 6–12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. Compared with aspirin, rivaroxaban at the 20mg and 10mg doses was associated with significantly lower rates of symptomatic recurrent fatal or nonfatal VTE (primary efficacy outcome; 1.5% and 1.2%, respectively, vs. 4.4%; hazard ratios 0.34 [95% CI 0.20, 0.59] and 0.26 [0.14, 0.47]) and similar rates of major bleeding (0.5% and 0.4% vs. 0.3%), clinically relevant nonmajor bleeding (2.7% and 2.0% vs. 1.8%) and any adverse event.

Comment (PO): In patients with spontaneous VTE, the rates of recurrence off treatment, after an initial 3–6 months of primary anticoagulation, approaches 50% at 10 years. The dilemma with extending treatment in this population has previously been to balance the competing bleeding risks (with warfarin) against the benefits of effective (>90%) thrombosis prevention. Aspirin has been attractive in lower risk patients by decreasing recurrences by 30–35% compared with not extending treatment. Now we have a 'choice'. Rivaroxaban at standard 20mg or prophylactic (10mg) dosing reduces the risk of repeat events by ~70% compared with low-dose aspirin without any additional bleeding. The benefits are seen in both provoked and spontaneous VTE, but the study power is insufficient to confirm that 10mg dosing is noninferior. Subjects were those in whom the decision to extend treatment was not clear cut, so high-risk patients were excluded. Furthermore, the extended treatment was limited to an additional 12 months. Rivaroxaban is registered but unfunded in NZ.

Reference: N Engl J Med 2017;376(13):1211–22
Abstract

Testosterone treatment and risk of venous thromboembolism

Authors: Martinez C et al.

Summary: This UK population-based research explored the risk of VTE associated with testosterone use in 19,215 men with confirmed VTE and 909,530 age-matched controls. Testosterone exposure was categorised as current treatment for <6 months, current treatment for >6 months, recent (but not current) treatment and no treatment for ≥2 years. Compared with no testosterone treatment, there was no significant increase in VTE for any current testosterone treatment (rate ratio 1.25 [95% CI 0.94, 1.66]); however, VTE was increased during the first 6 months of testosterone treatment (1.63 [1.12, 2.37]), but not for >6 months of treatment (1.00 [0.68, 1.47]) or after treatment cessation (0.68 [0.43, 1.07]). The rate ratios for VTE during the first 6 months of testosterone treatment were 1.52 (95% CI 0.94, 2.46) and 1.88 (1.02, 3.45) for men with and without pathological hypogonadism, and they were 1.41 (0.82, 2.41) and 1.91 (1.13, 3.23) for men with and without a known VTE risk factor.

Comment (PO): This is a large and well-done population-based case-control study with 50 matched controls for every VTE case. The adjusted rate ratio (1.25) for VTE, current versus no testosterone, approaches significance, but is significant within the first 6 treatment months (rate ratio 1.63) returning to baseline beyond 6 months (rate ratio 1.0). Testosterone therapy therefore should be regarded as a mild precipitating VTE factor in men starting treatment within 6 months but not in those on longer term replacement. For men who are chronic users, the history of testosterone use does not influence the need for long-term anticoagulation for spontaneous VTE. What is a little more problematic is how those on testosterone replacement for <6 months, with an otherwise unprovoked event, should be treated. Is the testosterone a transient risk factor in this setting? There is no evidence base for this decision, which in part will be driven by the thrombotic burden, any sequelae and patient preference.

Reference: BMJ 2016;355:i5968
Abstract

Association of antithrombotic drug use with subdural hematoma risk

Authors: Gaist D et al.

Summary: This case-control study investigated the association between antithrombotic drug use and subdural haematoma risk in 10,010 adults with a first ever subdural haematoma in 2000–2015 and 400,380 matched controls from the general population; 47.3% of the patients with subdural haematoma were receiving antithrombotics. A logistic regression analysis showed that the risk of subdural haematoma was increased by current use of low-dose aspirin (adjusted OR 1.24 [95% CI 1.15, 1.33]), clopidogrel (1.87 [1.57, 2.24]), direct oral anticoagulants (1.73 [1.31, 2.28]) and vitamin K antagonists (3.69 [3.38, 4.03]). The risk of subdural haematoma was highest when a vitamin K antagonist was used with either clopidogrel (adjusted OR 7.93 [95% CI 4.49, 14.02]) or low-dose aspirin (4.00 [3.40, 4.70]).

Comment (PO): This observational study from Denmark, which included more than 10,000 patients with subdural haematoma, shows that aspirin monotherapy is associated with the lowest bleed risk (OR 1.2), clopidogrel or a direct oral anticoagulant with a moderate risk (ORs 1.8 and 1.7, respectively) and warfarin with the highest risk (OR 3.6). Not surprisingly, combinations of more than one antithrombotic drug are associated with a substantially higher risk of subdural haematoma. This is particularly marked for combined therapy with clopidogrel and warfarin (OR 7.93). Antithrombotic drug use is associated with higher relative risks of subdural haematoma in women, and fatal subdural haematoma is more likely to be associated with antithrombotic therapy than nonfatal bleeds. The incidence of subdural haematoma, particularly among older patients (75–89 years), increased over the 16-year study period, consistent with the trend towards more aggressive anticoagulation in older individuals.

Reference: JAMA 2017;317(8):836–46
Abstract

Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents

Authors: Desborough MJR et al.

Summary: This systematic review and meta-analysis of ten randomised controlled trials (n=596) investigated the role of desmopressin (DDAVP) for perioperative allogeneic RBC transfusion and bleeding in patients with platelet dysfunction; all included trials were conducted in cardiac surgery settings, and the reported evidence was graded very low to moderate. Antiplatelet agents were the cause of platelet dysfunction in six trials and cardiopulmonary bypass was responsible in four. Use of desmopressin was associated with fewer RBCs transfused (mean difference –0.65 units [95% CI –1.16, –0.13]), less blood loss (–253.93mL [–408.01, –99.85]) and a lower risk of re-operation due to bleeding (OR 0.39 [0.18, 0.84]).

Comment (PO): Antiplatelet drugs are used in approximately 6% of individuals in developed countries, but optimal perioperative management is unresolved. This meta-analysis compares desmopressin and placebo in patients undergoing cardiac surgery. Although the vasopressin analogue reduced RBC transfusions, blood loss and the risk of reoperation due to bleeding, all the trials are small and the desmopressin was used prophylactically rather than for active bleeding. Most of the studies used aspirin monotherapy. Although desmopressin is recommended in some guidelines for bleeding in patients with platelet dysfunction and antiplatelet agents, the size of the benefit and the risks of thrombotic events and other side effects remain uncertain. Any additional benefit of antifibrinolytic medication is also unclear. Further information is needed on the use of desmopressin with or without tranexamic acid to prevent and manage bleeding in patients on antiplatelet medication undergoing different surgical procedures. Current protocols are largely pragmatic rather than evidence-based.

Reference: J Thromb Haemost 2017;15(2):263–72
Abstract

CONGRATULATIONS TO **Dr Robin Rund**
who won an iPad mini 3 by taking part in our recent subscriptions update promotion. Robin is an Anaesthetist at the Bay of Plenty District Health Board.