Haematology RESEARCH REVIEW™

Making Education Easy

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In this issue:

Abbreviations used in this issue
AIHA = autoimmune haemolytic anaemia
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
ICH = intracerebral haemorrhage
LMWH = low-molecular-weight heparin
PE = pulmonary embolism
RCT = randomised controlled trial
TTP = thrombotic thrombocytopenic purpura
VAS = visual analogue scale
VTE = venous thromboembolism

Welcome to this issue of Haematology Research Review.

This issue begins with research from N Engl J Med reporting that dabigatran was not better than aspirin for preventing recurrent stroke in patients with a recent history of embolic stroke of undetermined source. A paper summarising the latest evidence-based guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of VTE is also included. Another study published in N Engl J Med found that patients with factor Xa inhibitor-associated acute major bleeding experienced markedly reduced anti-factor Xa activity when they received andexanet alfa. This issue concludes with a systematic review that reported individual patient-identifiable risk factors associated with any VTE outcome following temporary lower-limb immobilisation as a result of injury.

We hope you enjoy this selection of haematology research, and we invite you to send us your comments and feedback.

Kind regards,

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Dabigatran for prevention of stroke after embolic stroke of undetermined source

Authors: Diener H-C et al., for the RE-SPECT ESUS Steering Committee and Investigators

Summary: Patients who had experienced an embolic stroke of undetermined source were randomised to receive dabigatran 110mg or 150mg twice daily (n=2695) or aspirin 100mg once daily (n=2695) and were followed for a median of 19 months in this trial. The recurrent stroke rate (primary outcome) did not differ significantly between dabigatran versus aspirin recipients (4.1% vs. 4.8% per year; hazard ratio 0.85 [95% CI 0.69, 1.03]), nor did the rates of ischaemic stroke (4.0% vs. 4.7% per year; 0.84 [0.68, 1.03]) and major bleeding (1.7% vs. 1.4% per year; 1.19 [0.85, 1.66]). The respective clinically relevant nonmajor bleeding rates in the dabigatran and aspirin arms were 1.6% and 0.9% per year.

Comment (LY): We now know that aspirin has minimal efficacy in preventing stroke in atrial fibrillation. In contrast, the DOAC dabigatran is very effective. You might think therefore that in stroke with no recognised cause such as vascular disease, dabigatran would be a better choice, on the basis of a percentage of undiagnosed atrial fibrillation as a cause. This interesting pharma-sponsored study explored this question, and in fact dabigatran, dosed according to renal function/age, was no better. Even the subgroup of patients with patent foramen ovale showed no benefit. This demonstrates that sometimes intuitive therapeutic strategies are not correct and that randomised trials are important.

Reference: N Engl J Med 2019;380:1906–17
Abstract

Independent commentary by Dr Laura Young

Laura is a haematologist specialising in thrombosis and haemostasis. Having trained at the University of Auckland, School of Medicine, she completed her training in haematology in Auckland, and then completed a period of research at the University of Auckland as part of a PhD focusing on coagulation inhibitors. She is now employed at Auckland Hospital as part of the Thrombosis Unit and Haemophilia Centre, and is involved in hospital based clinical trials and also preclinical research at the University of Auckland. She also has a part time lecturing position in the Department of Molecular Medicine and Pathology at the University School of Medicine.

Low-dose rituximab in autoimmune hemolytic anemia

Authors: Fattizzo B et al.

Summary: The authors of this letter provided data on a prospective evaluation of 20 patients with AIHI treated 10 years prior with fixed doses of rituximab 100 mg/week for 4 weeks with short-course prednisolone, along with an additional 34 consecutive patients who had been treated since. Over median follow-up of 53 months, the overall response rate was >80% within the first 3 years, with the complete response rate increasing from 46% at 2 months to >60% at 6 months. When analysed by AIHA type, response rates were greater for warm AIHA (overall response rate >90% at all timepoints assessed; 24-month complete response rate 100%) than for cold agglutinin disease and atypical and mixed AIHA types (p=0.05). Responses lasted for a median of 15 months. The relapse rate was 62%, but the response rate on retreatment with low-dose rituximab was 64%. A multivariable analysis revealed that the only significant predictor of longer relapse-free survival was the presence of warm AIHA. There were no grade 3–4 adverse events, and serum IgA, IgG and IgM levels at month 112 were comparable with baseline levels.

Comment (LY): Since the initial report 10 years ago, the use of rituximab in AIHA has become standard therapy. The lower rituximab dose of 100mg weekly rather than the full 375 mg/m^2 is appealing, as it seems logical that less B-cell depletion may have efficacy in autoimmune disease compared with lymphoma. This longer-term follow-up confirms efficacy in warm AIHI, and also clearly demonstrates that cold agglutinin disease and rarer mixed variants are different and require the higher doses. It is useful to confirm the efficacy of retreatment in this cohort who can then be successfully managed with lower cumulative doses.

Reference: Blood 2019;133:996–8
Abstract

Haematological management of major bleeding associated with direct oral anticoagulants – UK experience

Authors: Green L et al.

Summary: These researchers analysed 3 years of UK hospital data on 421 episodes of haematologically managed DOAC-related major bleeding, of which 67%, 21%, 11% and 1% were associated with use of rivaroxaban, apixaban, dabigatran and edoxaban, respectively. During the study period, the proportions of DOAC prescriptions and major bleeds associated with DOAC use both increased. Patients presenting with gastrointestinal bleeds accounted for 44% of the episodes recorded, while those presenting with ICHs accounted for 37%. It was rare for DOAC concentrations to be recorded. Compared with no prothrombin complex concentrate, patients treated with low-dose (≤25 IU/kg) prothrombin-complex concentrate showed a trend for lower mortality (hazard ratio 0.15 [95% CI 0.02, 1.19]), but this was not seen for higher doses.

Comment (LY): This is a real-world observational cohort of bleed management in the DOAC era, primarily of rivaroxaban and apixaban. Intracranial bleeds were common, affecting more than one-third of patients. Unsurprisingly the mortality of patients with intracranial bleeds was high at around 20%, which is probably similar to warfarin cohorts although these were not included in this study. Antidotes appeared later in the study so don't feature prominently, leaving prothrombin complex concentrate (analogous to prothrombinex in NZ) as the main additional therapeutic option. It is hard to draw any conclusions about the benefits of these, but it is interesting that monitoring of DOAC concentrations was not undertaken particularly frequently. There remain gaps in our approach to the treatment of Xa inhibitor bleeds, as andexanet is not currently available in NZ. The strategies used in this cohort are similar to NZ practice.

Reference: Br J Haematol 2019;185:514–22
Abstract

New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism

Authors: Tran HA et al.

Summary: The new evidence-based guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of DVT and PE provide the following main recommendations: i) VTE diagnoses should be established with imaging, although VTE may be excluded using clinical prediction rules combined with D-dimer testing; ii) proximal DVT or PE secondary to major surgery or trauma that is no longer present should be treated with 3 months of anticoagulant therapy; iii) unprovoked or transient (nonsurgical) risk factor-associated proximal DVT or PE should be treated with 3–6 months of anticoagulant therapy; iv) recurrent proximal DVT or PE provoked by active cancer or antiphospholipid syndrome should be treated with extended anticoagulation; v) distal DVT due to a major provoking factor that is no longer present should be treated with 6 weeks of anticoagulant therapy; vi) therapeutic or low-dose DOACs can be prescribed in patients continuing extended anticoagulant therapy – this is preferred over warfarin in the absence of contraindications; vii) there is no indication for routine thrombophilia testing; and viii) thrombolysis or a suitable alternative is indicated for massive (haemodynamically unstable) PE.

Comment (LY): The THANZ guideline, to which I contributed, is intended as an overview of best practice for VTE treaters in Australasia. It places emphasis on continuing treatment long term in patients with unprovoked VTE who do not have an increased risk of bleeding, due to the well-recognised VTE recurrence risk, and encourage the use of DOACs in preference to warfarin in most patients. Dose-reduced extended treatment strategies with Xa inhibitors have really revolutionised the management in this setting, as the low risk of bleeding and good efficacy in preventing recurrence really provide the best of both worlds for many patients. Xa inhibitors can frequently be used upfront without initial LMWH, which is convenient. Some patients will prefer dabigatran due to the availability of an antidote, although the need for this is relatively uncommon in the VTE population.

Reference: Med J Aust 2019;210:227–35
Abstract

Characterization and treatment of congenital thrombotic thrombocytopenic purpura

Authors: Alwan F et al.

Summary: These researchers reviewed 73 cases of congenital TTP diagnosed in the UK over 15 years. At the time of review, 93% of the patients were alive. Homozygous mutations were identified in 36% of the patients, and 64% had compound heterozygous mutations. Presentation peaked twice, once at a median age of 3.5 years and again at a median age of 31 years; 69% of adult presentations were associated with pregnancy. Genetic mutations varied according to age of onset, with prespacer mutations significantly associated with childhood onset. Treatments included fresh-frozen plasma and intermediate purity factor VIII concentrate. Prophylactic therapy was associated with resolution in 88% of patients with normal blood counts, but with headaches, lethargy or abdominal pain. Weekly or fortnightly fresh-frozen plasma infusions were required for the 70% of patients with an insufficient response to the most commonly used every-third-week regimen. Patients who received prophylactic therapy had a significant reduction in stroke incidence (p=0.04). End-organ damage was seen in 75% of patients who had a late diagnosis of congenital TTP.

Comment (LY): Congenital variants of TTP were identified many years after the autoimmune disorder was described, but unusually large von Willebrand multimers were first described in patients with the congenital condition, followed by the identification of the ADAMTS-13 metalloprotease, which was absent, in 1981. The congenital disease is also rare and distinguished from the autoimmune disorder by the presence of autoantibodies and the clinical history. Neonatal and pregnancy-related presentations are most common. This important cohort analysis from the UK highlights the importance of prophylactic treatment. Stroke occurred in almost 20% of patients, and even relatively nonspecific symptoms such as headache and fatigue may respond to replacement therapy, even with a normal platelet count or thrombocytopenia without other features of haemolysis.

Reference: Blood 2019;133:1644–51
Abstract

Adjunctive intermittent pneumatic compression for venous thromboprophylaxis

Authors: Arabi YM et al., for the Saudi Critical Care Trials Group

Summary: Patients aged ≥14 years who had been admitted to an ICU ≤48 hours prior were randomised to receive unfractionated heparin or LMWH thromboprophylaxis with (n=991) or without (n=1012) intermittent pneumatic compression for a median of 22 hours each day for a median of 7 days. There was no significant difference between the pneumatic compression and control arms for incident proximal lower-limb DVT after day 3 out to day 28, ICU discharge, death or attainment of full mobility (primary outcome; 3.9% vs. 4.2% [p=0.74]), PE or any lower-limb DVT (10.4% vs. 9.4%) or the 90-day all-cause mortality rate (26.1% vs. 26.7%).

Comment (PO): PREVENT is a well performed investigator-driven study randomising patients from four different countries and 20 trial sites. Trial design is consequently pragmatic with different intermittent compression devices used, although the majority (~80%) were knee-length sleeves. Adherence to protocol was very good, and the potential for bias is low, with the use of graduated compression stockings excluded. The result challenges the advantage of intermittent compression devices over pharmacological prophylaxis in the ICU population. Unlike the CLOT3 study in stroke, skin injury with intermittent compression devices was not increased in this younger population. Sample size was calculated on an expected baseline 7% thrombosis rate, but 4% was observed. This reduced study power. The population of critically ill trauma patients (8%) was also low, so a benefit for this group cannot be excluded.

Reference: N Engl J Med 2019;380:1305–15
Abstract

Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors

Authors: Connolly SJ et al. for the ANNEXA-4 Investigators

Summary: These authors reported on 352 patients with acute major bleeding ≤18 hours after receiving a factor Xa inhibitor, treated with a bolus of andexanet alfa followed by a 2-hour infusion; most of the patients had substantial cardiovascular disease. ICH occurred in 64% of the patients and 26% had a gastrointestinal bleed. Among apixaban recipients, median antifactor Xa activity decreased from 149.7 to 11.1 ng/mL after the andexanet alfa bolus, and among rivaroxaban recipients, it decreased from 211.8 to 14.2 ng/mL. Among evaluable patients, 82% experienced excellent or good haemostasis. The 30-day mortality rate was 14% and the thrombotic event rate was 10%. Decreased anti-factor Xa activity did not significantly predict haemostatic efficacy overall, but it was modestly predictive for patients who experienced ICH.

Comment (PO): This is the final report of the single-group cohort study of andexanet alfa in patients with major bleeding on an Xa inhibitor. The 352 patients were enrolled over 3 years from 63 centres for an average of two patients per trial centre annually. The population was elderly, with 80% on treatment for atrial fibrillation. Most were treated with apixaban (55%) or rivaroxaban (36%). Two thirds had ICH. The majority of the thrombotic events and deaths were in those for whom resumption of anticoagulation was either delayed or not possible. The reduction in anti-Xa activity was not a robust predictor of clinical effectiveness. A phase 4 RCT (NCT03661528) in patients (n≈440) with ICH, comparing andexanet with usual standard of care, began January 2019. This is a prospective randomised open-label study using blinded endpoints (PROBE) in patients presenting within 12 hours of symptom onset and within 15 hours of Xa inhibitor ingestion.

Reference: N Engl J Med 2019;380:1326–35
Abstract

Independent commentary by Dr Paul Ockelford

Paul Ockelford is a haematologist and Clinical Associate Professor, University of Auckland School of Medicine and Director of both the Adult Haemophilia Centre and Thrombosis Unit at Auckland City Hospital. Paul has particular expertise in haemostasis and thrombosis and consults on a wide range of haematological disorders. He maintains an active research programme in the treatment of venous thromboembolism. Paul is a former chair of the New Zealand Subcommittee on Thrombosis and Haemostasis. He serves on the Medical Advisory panel of the New Zealand Haemophilia Foundation and the National Haemophilia Management Group. Paul acts as a reviewer for a number of medical journals and is an Investigator for a number of international clinical thrombosis trials. He is a former Chairman of the New Zealand Medical Association.

Direct oral anticoagulants in patients with venous thromboembolism and thrombophilia

Authors: Elsebaie MAT et al.

Summary: This systematic review and meta-analysis included phase 2–3 RCTs comparing rivaroxaban (four RCTs), dabigatran (three RCTs) or edoxaban (one RCT) with vitamin K antagonists in patients with VTE, including 1994 with thrombophilia; there were no evaluable trial data regarding apixaban use in this setting. Among participants with thrombophilia-associated VTE, no significant difference was detected between DOAC and vitamin K antagonist recipients for VTE recurrence (relative risk 0.70 [95% CI 0.34, 1.44]) or major/clinically relevant nonmajor bleeding (0.92 [0.62, 1.36]); similar results were seen for patients without known thrombophilia (1.02 [0.80, 1.30] and 0.72 [0.57, 0.90], respectively).

Comment (PO): DOACs are effective in cancer thrombosis, so it would be surprising if they did not work in thrombophilia. This analysis suggests they are as good as warfarin for the acute treatment and secondary prevention of VTE in patients with thrombophilia. Patients were not routinely screened for laboratory thrombophilia markers in the studies analysed. Nevertheless, there are no safety concerns with DOACs in the low-risk inherited heterozygous thrombophilias, factor V Leiden or the prothrombin variant. There were 171 patients with antithrombin, protein C or protein S deficiency. Only one of 92 DOAC-treated patients experienced recurrence but the severity of the phenotypes is unknown. DOACs also seem safe in lower risk antiphospholipid syndrome but are probably best avoided in high-risk triple positive cases, primarily because of a high risk of arterial thrombotic events.

Reference: J Thromb Haemost 2019;17:645–56
Abstract

Effect of anticoagulant treatment on pain in distal deep vein thrombosis

Authors: Righini M et al.

Summary: This ancillary analysis of the Cactus RCT sought to determine if pain could be reduced by LMWHs in patients with distal DVT; 132 participants had been randomised to receive nadroparin and 122 had been randomised to receive placebo. Mean pain VAS scores at study inclusion, week 1 and week 6 were 4.6, 2.1 and 0.4, respectively. No significant difference was seen between nadroparin versus placebo recipients for reduction from study inclusion in mean VAS score at week 1 (–2.6 vs. –2.3) or at week 6 (–4.4 vs. –4.0). There was an association detected between compression stocking use and reduction in pain.

Comment (PO): Isolated distal DVT involving the deep calf and/or the muscular calf veins accounts for approximately 50% of all lower limb thromboses. It may be spontaneous or provoked. The optimal management still remains uncertain after the double-blinded Cactus trial showed that full-dose LMWH therapy was not superior to placebo and caused more bleeding. Pain was not part of the main study outcome, and data were missing for approximately 10% of the 252 treated subjects. This analysis does however suggest that LMWH is no better than placebo for pain control. Three patients on placebo and six on LMWH used NSAIDs. Muscular thrombosis was not more painful than thrombi involving the posterior or peroneal veins. Graduated knee length (grade 2) compression stockings, especially in the first week, did reduce pain. These observations support the ACCP guidelines recommending that low-risk patients with symptomatic calf DVT can be managed with serial ultrasound scans without anticoagulation.

Reference: J Thromb Haemost 2019;17:507–10
Abstract

Individual risk factors predictive of venous thromboembolism in patients with temporary lower limb immobilization due to injury

Authors: Horner D et al.

Summary: This was a systematic review of 15 studies (n=80,678) reporting on individual patient-identifiable risk factors associated with any VTE outcome following lower-limb immobilisation; all included studies were assessed to be at moderate or serious risk of bias. The only individual risk factors that were reproducibly associated with increased symptomatic and/or asymptomatic VTE were higher age and injury type. Within the studies, several risk factors in current use in scoring tools did not seem to be robustly evaluated for subsequent association with VTE.

Comment (PO): Symptomatic VTE following temporary immobilisation is approximately 2%, but the benefit-risk ratio of thromboprophylaxis is unclear. This is a thoughtful attempt to look at the risk factors reported to increase the risk of both asymptomatic and symptomatic VTE in this patient cohort, and compare these with risk prediction models. Unfortunately, the potential risk of bias in all studies is significant, raising questions over the reliability of individual patient risk factors as predictors of VTE. The evidence base is therefore weak with a significant potential to be inaccurate. Although age >55 years, BMI >35 kg/m^2 and extent of immobilisation, as a surrogate for injury severity, were associated with greater risk, we need to be aware that the evidence supporting these factors is limited when it comes to considering thrombosis prophylaxis.

Reference: J Thromb Haemost 2019;17:329–44
Abstract