Haematology RESEARCH REVIEW™

Making Education Easy

Issue 41 – 2022

In this issue:

Abbreviations used in this issue
AAV = adeno-associated viral
DAPT = dual antiplatelet therapy
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
FVIII/FIX/FXI = factor VIII/IX/XI
ICH = intracranial haemorrhage
PE = pulmonary embolism
VTE = venous thromboembolism
VWD/VWF = von Willebrand disease/factor

Welcome to issue 41 of Haematology Research Review.

This issue begins with research reporting a higher than expected VTE recurrence rate among patients with subsegmental PE without proximal DVT who did not receive anticoagulation. DOAC use in the real-world is the focus of two research papers selected, one of which compared apixaban with rivaroxaban in the management of VTE, looking specifically at the outcomes of VTE recurrence and GI or intracranial bleeding, and the other reports on their use with concomitant antiplatelet agents for treating VTE. The issue concludes with a systematic review and meta-analysis reviewing the accuracy of diagnostic tests using different VWF antigen cutoff values and platelet-dependent VWF activity assays for diagnosing VWD.

We hope you find the selected research interesting, and we look forward to hearing from you with your comments and suggestions.

Kind regards,

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Risk for recurrent venous thromboembolism in patients with subsegmental pulmonary embolism managed without anticoagulation

Authors: Le Gal G et al., SSPE Investigators

Summary: VTE recurrence rates were investigated in a prospective cohort of 266 evaluable patients from 18 sites with subsegmental PE who did not receive anticoagulants; enrolment was stopped early due to a predefined stopping rule being met. VTE recurrence within 90 days (primary outcome) occurred in eight participants (cumulative incidence 3.1%), with incidences of 2.1% and 5.7% in participants with single and multiple isolated subsegmental PE, respectively. No fatal recurrent PEs were reported.

Comment (PO): This prospective study has evaluated subsegmental PE in symptomatic patients without proximal DVT and who were low clinical risk. Those with active cancer, pregnancy, with an oxygen requirement or in hospital at PE diagnosis were excluded. The subsegmental PE was single in 72% and D-dimer level was elevated in 95% of cases. Proximal DVT was identified in 9.6% either at baseline or on elective repeat ultrasonography performed at days 5–7. These patients received anticoagulation. Recurrent VTE occurred in 3.1% – four were PE recurrences and four were DVTs. The incidence was lower in those with single emboli (2.1%) than in those with multiple subsegmental PEs (5.7%) at diagnosis. Patients aged <65 years had a lower incidence (1.8%) than older subjects (5.5%). This study makes a case for treating most subsegmental PE, possibly with the exception of younger patients with solitary emboli for whom recurrence risk approximates 2% at 3 months. The necessity for extended treatment is less clear. Interobserver CT pulmonary angiogram variability was not evaluated.

Reference: Ann Intern Med 2022;175:29–35

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.

Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE)

Authors: Ramacciotti E et al., on behalf of the MICHELLE investigators

Summary: Patients hospitalised in Brazil with COVID-19 (52% in ICU) who were at increased risk for VTE were randomised to receive rivaroxaban 10 mg/day on discharge for 35 days (n=160) or no anticoagulation (n=160) in this open-label trial. Compared with no anticoagulation, a significantly lower proportion of rivaroxaban recipients experienced a primary efficacy event, namely symptomatic or fatal VTE, asymptomatic VTE on bilateral lower-limb venous ultrasound and CT pulmonary angiogram, symptomatic arterial thromboembolism or CV-related death (3% vs. 9%; relative risk 0.33 [95% CI 0.12, 0.90]). There were no major bleeds in either of the trial arms, and two rivaroxaban recipients experienced allergic reactions.

Comment (LY): Early in the course of the COVID-19 pandemic, high rates of VTE, notably PE, were seen. This has been managed with varying intensity of anticoagulant prophylaxis, generally with low molecular weight heparin, but a measurable incidence of postdischarge VTE remains, maximally around 2.5%. However, in previous studies of extended prophylaxis in medical patients beyond discharge, outside of the COVID situation, the benefits of use of rivaroxaban were not clear, and in one study there was more bleeding. This pragmatic trial of hospitalised COVID patients in Brazil who received standard prophylaxis rather than treatment dose in hospital, showed that there was a benefit to administration of rivaroxaban after discharge without paying the price of more bleeding. The cohort had a mean age of about 57 years, whereas the previous (non-COVID) trials were of medical inpatients who were older, which might make a difference to bleeding risk. Use of postdischarge prophylactic rivaroxaban seems a sensible adjunct for hospitalised COVID patients in NZ who don't have bleeding risk factors.

Reference: Lancet 2022;399:50–9
Abstract

Milvexian for the prevention of venous thromboembolism

Authors: Weitz JI et al., for the AXIOMATIC-TKR Investigators

Summary: This phase 2 trial randomised 1242 patients undergoing elective primary unilateral total knee replacement surgery to receive 10–14 days of postoperative anticoagulation with one of seven regimens of orally administered milvexian 25–200mg once-daily or twice-daily (pooled n=923) or enoxaparin (n=319). Rates of total VTE (proximal and/or distal DVT, nonfatal PE or death) in four milvexian trial arms (200mg once daily and 50mg, 100mg and 200mg twice daily) were significantly lower compared with the enoxaparin arm (7%, 11%, 9% and 8%, respectively, vs. 21% [all p≤0.01]). In addition, the rate of VTE in the pooled twice-daily milvexian cohort was significantly lower than the prespecified benchmark of 30% (12% [p<0.001]). Any-severity bleeding occurred in 4% of patients in the pooled milvexian arms and also in the enoxaparin arm. The rate of severe adverse events in the pooled milvexian cohort was half that of the enoxaparin arm (2% vs. 4%).

Comment (PO): Elective knee arthroplasty is a useful model for dose-finding studies evaluating new anticoagulants. It has previously been used to study subcutaneous prophylaxis with an antisense oligonucleotide, which reduces FXI levels, and an intravenous FXI directed antibody (abelacimab), which was superior to enoxaparin in this patient group. FXI is regarded as a useful target for anticoagulating patients, as it is important in thrombus growth but plays a lesser role in stopping bleeding. Milvexian is a rapidly absorbed oral inhibitor of activated FXI with a half-life of 12 hours. It significantly reduced VTE in this study in a dose-dependent manner. Daily doses of 100mg or more also significantly reduced thrombosis compared with the standard comparator. There was a low rate of clinically relevant bleeding despite prolonging the activated partial thromboplastin time. This is further proof of principle and opens the way for studies to prevent arterial thrombosis. The study was open-label, but endpoint assessment was blinded.

Reference: N Engl J Med 2021;385:2161–72
Abstract

Dual antiplatelet therapy after PCI in patients at high bleeding risk

Authors: Valgimigli M et al., for the MASTER DAPT Investigators

Summary: The MASTER DAPT trial investigated the efficacy of DAPT in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent. Patients considered to be at high risk for bleeding (n=4434) received 1 month of DAPT after PCI (percutaneous coronary intervention) before being randomised to single antiplatelet therapy or continued DAPT for ≥2 more months; a single third-generation sirolimus-eluting stent was used. PCI for acute coronary syndrome was performed in 48.3% of participants, and 36.4% were receiving concomitant anticoagulants. One month of DAPT was noninferior to 3 months of DAPT, both for net adverse clinical events (7.5% vs. 7.7% [p<0.001 for noninferiority]) and major cardiac and cerebral events (6.1% vs. 5.9% [p<0.001 for noninferiority]), and resulted in a lower incidence of major or clinically relevant nonmajor bleeding (6.5% vs. 9.4% [p<0.001]).

Comment (LY): Drug-eluting stents in the coronary arteries are preferred as the restenosis risk is considerably less. However, the anti-inflammatory effects impair the rate of endothelialisation, potentially with higher rates of early rethrombosis, so prolonged dual antiplatelet use has been recommended. The more modern versions of these devices have changed the drug-eluting properties to reduce the latter effect. Encouragingly the authors of this large study of patients most often with stable coronary disease found that a shorter duration was noninferior. There is a thoughtful editorial attached to the paper that makes the point that the findings are specific to the stent used in the study, and that the noninferiority analysis was complex. Additionally, there was a substudy of patients requiring oral anticoagulants who received less dual and longer monoplatelet therapy, and are currently included in the analysis with a substudy to follow. Nevertheless, it is encouraging that bleeding risks may be reduced in the future while still allowing the benefits of drug-eluting stents.

Reference: N Engl J Med 2021;385:1643–55
Abstract

Multiyear factor VIII expression after AAV gene transfer for hemophilia A

Authors: George LA et al.

Summary: Eighteen men with haemophilia A received infusions of an AAV (adeno-associated viral) vector, SPK-8011, for hepatocyte FVIII expression in this phase 1–2 trial. Four cohorts received doses ranging from 5×10^{11} to 2×10^{12} vector genomes per kilogram of bodyweight, with some participants also receiving glucocorticoids within 52 weeks to either prevent or treat a presumed AAV capsid immune response. Eight men experienced 33 treatment-related adverse events over a median 36.6 months, 17 of which were vector-related (one serious) and 16 glucocorticoid-related. FVIII expression was completely lost in two participants due to an anti-AAV capsid cellular immune response insensitive to immune suppression, but the remaining participants had maintained FVIII expression, with 12 of these participants followed for >2 years, during which there was no apparent decrease in FVIII activity. Median annualised bleeding rate fell from 8.5 events per year before vector administration to 0.3 events per year after vector administration.

Comment (PO): There are a number of ongoing clinical trials of gene therapy for severe haemophilia A using recombinant AAV vectors to target hepatic FVIII expression with the goal of a one-time disease altering therapy. In those with Christmas disease (FIX deficiency), durable transgene FIX expression for >8 years has been realised but there has been loss of expression over time in those with haemophilia A, due to a cellular immune response against the AAV capsid. In this study, there were no major safety concerns, but elevated alanine aminotransferase levels, consistent with a cellular immune response against SPK-8011, occurred in 22% of subjects. Stable FVIII activity was achieved in most individuals but lost in two of 18 due to immune rejection. Sustained, stable and predictable FVIII levels in all vector recipients therefore remains an unrealised goal for haemophilia A gene therapy. Long-term FVIII expression >10% is achievable and prevents joint bleeding. The altered bleeding phenotype is similar to that seen with emicizumab prophylaxis.

Reference: N Engl J Med 2021;385:1961–73
Abstract

Risk for recurrent venous thromboembolism and bleeding with apixaban compared with rivaroxaban

Authors: Dawwas GK et al.

Summary: These researchers reported on the use of apixaban versus rivaroxaban for a retrospective real-world cohort of US patients with VTE, among whom 18,618 new apixaban users and 18,618 propensity score-matched new rivaroxaban users were included in the analyses. After medians of 102 and 105 days of follow-up for apixaban and rivaroxaban users, respectively, the recurrent VTE rate was lower in the apixaban group than in the rivaroxaban group (hazard ratio 0.77 [95% CI 0.69, 0.87]), as was the bleeding rate (0.60 [0.53, 0.69]). For apixaban versus rivaroxaban, the respective 2- and 6-month absolute reductions in the likelihood of VTE recurrence were 0.006 and 0.011, and the respective absolute reductions in the likelihood of GI and intracranial bleeding over these timeframes were 0.011 and 0.015.

Comment (LY): The randomised trials of DOACs in atrial fibrillation suggested that apixaban (treatment dosage of 5mg twice daily) may have an advantage in that there was less bleeding than rivaroxaban (treatment dosage 20mg once daily). However, the findings could be complicated due to confounding, and no head-to-head randomised trials have been published. This large analysis of a matched cohort population of 37,000 VTE patients registered with an American private insurer suggests again that there is an advantage to apixaban with less bleeding and recurrent VTE. As it is nonrandomised, it is still possible that selection bias may play a role. The COBRA study is an international investigator-initiated study that is randomised in VTE patients between apixaban and rivaroxaban (no pharma funding). This should answer the question, if recruitment is adequate. Apixaban remains unfunded in NZ, which is a shame, as there is likely to be a role in patients requiring DOACs with significant renal impairment or higher bleeding risk.

Reference: Ann Intern Med 2022;175:20–8
Abstract

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Effectiveness and safety of direct oral anticoagulants with antiplatelet agents in patients with venous thromboembolism

Authors: Douros A et al.

Summary: This study evaluated concomitant DOAC and antiplatelet (aspirin, clopidogrel, ticagrelor, prasugrel, dipyridamole) use by comparing two population-based cohorts of real-world patients with VTE, one of which had concomitant DOAC and antiplatelet use (n=2289) and the other had concomitant vitamin K antagonist and antiplatelet use (n=2682). There was no significant difference between the DOAC plus antiplatelet versus vitamin K antagonist plus antiplatelet group for major bleeding risk (hazard ratio 0.81 [95% CI 0.46, 1.45]), all-cause mortality (1.25 [0.87, 1.79]) and VTE recurrence (0.96 [0.40, 2.27]).

Comment (PO): Patients with VTE also often have CV disease requiring treatment. Approximately 10% of patients presenting with a new VTE are already on antiplatelet therapy. There is a knowledge gap concerning DOAC combination therapy with antiplatelet medication. This study addressed the issue by comparing warfarin with DOACs using real-world endpoints. A majority of patients were using rivaroxaban, which is one of the funded DOACs in NZ and the agent with the least favourable relative bleeding profile. Overall, there were no surprises as there were no major differences in either effectiveness or safety of the DOACs as a group compared with warfarin. Despite the potential limitations of the source information, the conclusions are likely generalisable to the relevant NZ population. The evidence is most robust for major bleeding and overall mortality, which are the primary endpoints of interest.

Reference: Res Pract Thromb Haemost 2022; 6:e12643
Abstract

Incidence and mortality rates of intracranial hemorrhage in hemophilia

Authors: Zwagemaker A-F et al.

Summary: This systematic review and meta-analysis included 45 studies (n=54,470) reporting on ICH incidence and mortality in patients with haemophilia across three age groups over 809,151 person-years of follow-up and 5326 live births of patients with haemophilia. For all ages, the respective pooled ICH incidence and mortality rates were 2.3 and 0.8 per 1000 person-years, in children and young adults, they were 7.4 and 0.5 per 1000 person-years, and for neonates, the pooled cumulative ICH incidence was 21% per 100 live births. A classification of spontaneous was reported for 35–58% of ICH cases.

Comment (LY): While treatment for haemophilia has improved dramatically over several decades, the feared complication of ICH remains much more common than for the general population. The highest risk period is in neonates. Assisted vaginal delivery is a particular risk in this setting, and the choice of elective caesarean section is hotly debated in this area, as the mother may also have bleeding risks. Of course, one-third of severe haemophilia cases are new mutations, so the diagnosis may not be known in advance of birth. In children and adults, ICH remains more common in early childhood, and is reduced by around half with regular prophylaxis, which raises questions over the age to commence. Finally, the benefits of a product such as emicizumab (for severe haemophilia A), which maintains a stable level approximately equivalent to an FVIII of 10%, will be seen over the coming years. For severe FIX deficiency, the extended half-life products may also reduce the risks with higher trough levels in the coming years.

Reference: Blood 2021;138:2853–73
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.
For full bio CLICK HERE

Targeted SERPIN (TaSER): a dual-action antithrombotic agent that targets platelets for SERPIN delivery

Authors: Sanrattana W et al.

Summary: These researchers evaluated the antithrombotic properties of a targeted SERPIN (serine protease inhibitor) fusion protein (TaSER) that interferes with platelet-driven thrombin formation. A range of *in vitro* experimental investigations revealed that TaSER was able to: i) bind to platelets, inhibiting thrombin activity on the platelet surface; ii) block VWF binding and disassemble platelet agglutinates; iii) delay tissue factor-triggered thrombin generation and ATP secretion in platelet-rich plasma, in a targeted manner; iv) interfere with platelet adhesion and aggregate formation secondary to blockade of GPIbα; and v) limit thrombus formation via targeted inhibition of platelet-dependent thrombin activity.

Comment (PO): This is futuristic stuff and conceptually very exciting. In the search for newer anticoagulants, both coagulation proteins and platelets are potential targets independent of the cause of the thrombotic event. Novel strategies use a similar sophisticated approach of combining dual-action molecules. One portion is designed to target the drug to a specific location, such as exposed collagen, an activated platelet receptor or a platelet surface. The other is functionally active as an antithrombotic. TaSER uses a nanoantibody, derived from llamas, to bind the platelet receptor Gp1bα, which prevents VWF-platelet interaction. This is combined with a SERPIN engineered to inhibit thrombin (>95%) *in vitro*. The technology used in this approach can be modified to inhibit a variety of targets relevant to both venous and arterial thrombosis. Antiphospholipid syndromes and thrombotic thrombocytopenic purpura spring to mind. To date, the evaluation is *in vitro* only, so future development has a number of hurdles before clinical applications are realised.

Reference: J Thromb Haemost 2022;20:353–65
Abstract

von Willebrand factor levels in the diagnosis of von Willebrand disease

Authors: Kalot MA et al.

Summary: This was a systematic review with meta-analysis of 21 studies that evaluated the accuracy of diagnostic tests using different cutoff values of VWF antigen and platelet-dependent VWF activity assays for diagnosing VWD. There was low-certainty evidence for a net health benefit from reconsidering the VWD diagnosis when VWF levels have normalised with age, rather than removing the diagnosis of VWD. For diagnosing type 1 VWD, *VWF* sequence variants were detected in 75–82% of patients with VWF antigen levels <0.30 IU/mL, and in 44–60% of those with levels 0.30–0.50 IU/mL. For a platelet-dependent VWF activity-VWF antigen ratio of <0.7 for detecting type 2 VWD, the respective sensitivity and specificity values were 0.90 and 0.91 (moderate certainty in the test accuracy results). It was found that VWF antigen and platelet-dependent activity are continuous variables associated with increased bleeding risk as the levels decrease.

Comment (LY): VWD is the most common bleeding disorder and is autosomally inherited. It is well recognised that lower levels, below 30%, correlate best with demonstrable genetic defects. However, at the more mild end of the spectrum, there is cross over between lower FVIII and VWF levels due to blood group O and inherited *VWF* gene mutations. This analysis of prior studies confirms that genetic mutations are more prevalent at levels below 30%, but still present in around half of patients between 30% and 50%, making the point that in association with an abnormal bleeding phenotype, the diagnosis is still valid. It is common for milder disease to improve with age. The analysis found that this phenomenon has not been shown to definitively result in less bleeding, so that while treatment may be modified, the diagnosis should still be retained.

Reference: Blood Adv 2022;6:62–71
Abstract