Haematology RESEARCH REVIEW™

Making Education Easy

Issue 33 – 2020

In this issue:

Abbreviations used in this issue

APS/CAPS = (catastrophic) antiphospholipid syndrome
ATE/VTE = arterial/venous thromboembolism
DVT = deep vein thrombosis
LMWH = low-molecular-weight heparin
MPN = myeloproliferative neoplasm
OR = odds ratio
PTS = post-thrombotic syndrome
RCT = randomised controlled trial
THJR/TKR = total hip joint/knee replacement

Welcome to issue 33 of Haematology Research Review.

We begin with one of several systematic reviews/meta-analyses included in this issue: it concluded that there is a lack of hard evidence supporting ruxolitinib for preventing thrombosis in polycythaemia vera. The CACTUS-PTS study reports long-term follow-up for PTS (post-thrombotic syndrome) for the CACTUS trial, which compared nadroparin with placebo after calf vein thrombosis. Also included is a JAMA paper that reported on the efficacy of the factor-XIa inhibitor osocimab for VTE prevention in patients who had undergone TKR (total knee replacement). This issue concludes with research reporting no benefit of adding ultrasound-accelerated catheter-directed thrombolysis to standard care for PTS prevention after acute iliofemoral DVT.

We hope you enjoy the selection, and we look forward to receiving your comments and feedback.

Kind regards,

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Dr Laura Young laurayoung@researchreview.co.nz

Ruxolitinib for the prevention of thrombosis in polycythemia vera

Authors: Masciulli A et al.

Summary: This was a systematic review and meta-analysis of data from four RCTs (n=663) comparing ruxolitinib with best available therapy as second-line prevention of thrombosis in patients with polycythaemia vera. The respective estimated incidences of thrombosis associated with ruxolitinib and best available therapy were 3.09% and 5.51% (risk ratio 0.56). Although ruxolitinib was associated with a consistently lower number of thrombotic events compared with best available therapy, the overall difference did not reach statistical significance (p=0.098).

Comment (PO): The natural history of primary polycythaemia vera is associated with arterial and venous thrombosis, myelofibrosis and increased risk of leukaemia. In high-risk patients, hydroxycarbamide (hydroxyurea) is used to decrease the thrombosis risk. Ruxolitinib has been recommended (European LeukemiaNet) as second line in those resistant or intolerant of hydroxycarbamide to maintain target haematocrit levels, but the benefit for decreasing CV events is uncertain. In this analysis, half of the patients (n=331) received ruxolitinib. Only one of the four RCTs was double blinded and the median follow-up was 1 year, ranging 0.3–2.6 years. The main risk factors of age and thrombosis history were generally balanced. There were 16 thromboses on ruxolitinib (4.8%) and 22 (6.6%) for those treated with best available therapy. The findings suggest a benefit for ruxolitinib in preventing thrombosis in polycythaemia vera, but the absolute event rate is low and follow-up duration is short, which limits the data quality.

Reference: Blood Adv 2020;4:380–6

Abstract

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Arterial thrombosis in Philadelphia-negative myeloproliferative neoplasms predicts second cancer

Authors: De Stefano V et al.

Summary: This research included 647 case patients with carcinoma, nonmelanoma skin cancer, haematological second cancer and melanoma diagnosed concurrently or after a diagnosis of Philadelphia-negative MPN, each matched to ≤3 controls with no history of cancer. No significant difference was seen between cases and controls for the frequency of thrombotic events prior to the MPN diagnosis (p=0.462), but there were more thrombotic events among cases after the MPN and before the second cancer compared with controls (11.6% vs. 8.1% [p=0.013]) driven by a greater proportion of ATEs (6.2% vs. 3.7% [p=0.015]). An independent association was seen between the occurrence of ATE and the likelihood of carcinoma (adjusted OR 1.97 [95% CI 1.14, 3.41]).

Comment (PO): Unprovoked VTE may precede malignancy, but an association between ATE and cancer has only recently been appreciated. In MPNs, the ATE rate approximates 2.5-fold that of VTE (16% vs. 6%). This appears to be relevant for second cancers in MPN patients. Thrombosis frequency prior to MPN diagnosis was similar (20%) in each cohort, but the ATE rate was significantly higher (6.2% cancer cases vs. 3.7% controls [p=0.015]) after the MPN diagnosis and before the second cancer was recognised. The cumulative ATE incidence, but not VTE, was also higher in the cases with second cancers. In contrast, second cancers in MPN with VTE are similar to the general population with unprovoked VTE. Low-dose aspirin prophylaxis lowered the risk (OR 0.47) of ovarian, endometrial or breast cancer, but not colorectal, skin or haematological malignancies. Approximately 70% of both cases and controls used hydroxycarbamide. There were no differences for ATE and VTE rates in either cohort when on hydroxycarbamide, but in the absence of myelosuppression with hydroxycarbamide, ATE was significantly higher in cases with second cancers.

Reference: Blood 2020;135:381–6
Abstract

Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS

Authors: Chaturvedi S et al.

Summary: Using animal studies demonstrating a role of complement in APS-related clinical events as a basis, these researchers used the modified Ham assay (complement-dependent cell killing) and cell-surface deposition of C5b-9 to test the association of complement activation with thrombotic events in APS. Serum samples returned positive modified Ham results (with corresponding C5b-9 deposition) in 85.7% of CAPS (catastrophic APS) samples, 35.6% of APS samples (including 68.5% of those collected within 1 year of thrombosis) and 6.8% of systemic lupus erythematosus samples. A positive modified Ham assay was associated with recurrent thrombosis and also with triple positivity for lupus anticoagulant, anticardiolipin and anti-β2GPI antibodies. C5b-9 deposition was induced by patient-derived anti-β2GPI antibodies, and this was completely blocked by an anti-C5 monoclonal antibody, but not by a factor D inhibitor. Patients with CAPS were found to have higher rates of rare germline variants in their complement regulatory genes than those with APS, those with systemic lupus erythematosus and normal controls (60% vs. 21.8%, 28.6% and 23.3%, respectively), with mutations occurring at a rate similar to that of patients with atypical haemolytic uraemic syndrome (51.5%).

Comment (PO): APS is an acquired thrombophilia for which anti-B2GP1 antibodies are thought to be the primarily pathogenic antibody. The catastrophic form (CAPS) of APS represents ~1% of cases, but the mortality is >40%. Anti-β2GP1 IgG from patients with thrombotic APS causes deposition of the C5b-9 membrane attack complex on vascular cell surfaces, indicating that complement activation via the classical pathway is a critical characteristic of pathogenetic antiphospholipid antibodies. Based on similarities between CAPS and atypical haemolytic uraemic syndrome (a complement-mediated microangiopathy), and the HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, which can be associated with germline complement gene mutations, these authors are postulating a 'two-hit' mechanism for APS and CAPS. APS is postulated to need a single amplifying trigger while CAPS will occur in patients with inherited complement mutations experiencing the same trigger. Complement gene mutations have been found in 60% of patients with CAPS. The role of complement inhibitor therapy in these difficult patients is awaited with interest.

Reference: Blood 2020;135:239–51
Abstract

Long-term risk of postthrombotic syndrome after symptomatic distal deep vein thrombosis

Authors: Galanaud J-P et al.

Summary: Data after a median follow-up period of 6 years were reported for the double-blind CACTUS trial, which compared 6 weeks of subcutaneous nadroparin 171 IU/kg/day with placebo in patients with a first symptomatic isolated distal DVT. Among participants assessed for PTS (n=178), this occurred in 30%, and was moderate or severe in 24% of these cases. There was no significant difference between the nadroparin and placebo arms for the prevalence of PTS (29% vs. 32% [p=0.6]), although the rate was lower for nadroparin recipients in the subgroup with no evidence of primary chronic venous insufficiency (9% vs. 24% [p=0.04]). There was also no significant difference between the nadroparin and placebo arms for the VTE recurrence rate during follow-up (8% vs. 14% [p=0.2]).

Comment (PO): Calf vein thrombosis comprises up to half of all DVTs, but the risk of PTS and the impact of anticoagulation treatment on this risk remains uncertain. CACTUS-PTS is the long-term follow-up of patients enrolled in the CACTUS study who had a first symptomatic calf vein thrombosis treated either with compression stockings alone or in combination with the LMWH nadroparin. PTS developed in about one third of the patients and impacted on quality of life. Perhaps surprisingly, anticoagulation did not appear to reduce PTS in the population overall, but did reduce the risk in those without pre-existing chronic venous insufficiency. Six weeks of nadroparin reduced the thrombosis recurrence rate (8% vs. 14%), but this was not significant.

Reference: J Thromb Haemost; Published online Jan 3, 2020
Abstract

Clinical effectiveness and safety of aspirin for venous thromboembolism prophylaxis after total hip and knee replacement

Authors: Matharu GS et al.

Summary: There were 13 RCTs (n=6060), with evidence ranging from low to high quality, assessing aspirin for VTE prophylaxis following THJR/TKR included in this systematic review and meta-analysis. There was no significant difference between aspirin and other anticoagulants for the risk of VTE, DVT or pulmonary embolism after THJR/TKR (respective relative risks 1.12 [95% CI 0.78, 1.62], 1.04 [0.72, 1.51] and 1.01 [0.68, 1.48]), or for the adverse events of major bleeding, wound haematoma and wound infection; these findings persisted when THJRs and TKRs were evaluated separately. Furthermore, there was no significant difference between aspirin and LMWH or rivaroxaban for VTE risk (respective relative risks 0.76 [95% CI 0.37, 1.56] and 1.52 [0.56, 4.12]).

Comment (PO): This is the first analysis to include the largest trial (N Engl J Med 2018;378:699–707) in this controversial area. Rivaroxaban 10mg was prescribed for 5 days then aspirin 81mg or rivaroxaban 10mg (in a double-blind RCT) for an additional 9 days (TKR) or 30 days (THJR). DVT rates were 0.64% and 0.7%; bleed rates also did not differ significantly (0.47% and 0.29%). While the authors conclude that available evidence suggests aspirin monotherapy (various doses in different studies) is not significantly different from other agents for arthroplasty prophylaxis, the variable trial quality and the potential for bias are acknowledged. A large US trial (NCT02810704) will randomise 25,000 subjects having undergone TKR/THJR to either aspirin, warfarin or rivaroxaban, excluding dabigatran/LMWH. This may add to the confusion…, or not! Meantime, the large Canadian trial provides the best available evidence.

Reference: JAMA Intern Med; Published online Feb 3, 2020
Abstract

Effect of osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty

Authors: Weitz JI et al.

Summary: The phase 2 open-label FOXTROT noninferiority trial randomised adults undergoing unilateral TKR to receive a single intravenous postoperative dose of osocimab 0.3 mg/kg (n=107), 0.6 mg/kg (n=65), 1.2 mg/kg (n=108) or 1.8 mg/kg (n=106), preoperative doses of osocimab 0.3 mg/kg (n=109) or 1.8 mg/kg (n=108), subcutaneous enoxaparin 40mg once daily (n=105) or oral apixaban 2.5mg twice daily (n=105) for ≥10 days or until venography; 600 of the randomised participants were included in the primary per-protocol analysis. The respective VTE incidences during postoperative days 10–13 (primary outcome) were 23.7%, 15.7%, 16.5% and 17.9% for the postoperative osocimab 0.3, 0.6, 1.2 and 1.8 mg/kg groups, 29.9% and 11.3% for the preoperative osocimab 0.3 and 1.8 mg/kg groups, and 26.3% and 14.5% for the enoxaparin and apixaban groups. When compared with enoxaparin, postoperative osocimab 0.6, 1.2 and 1.8 mg/kg met the noninferiority criterion (respective risk differences, 10.6% [one-sided 95% CI –1.2%, ∞], 9.9% [–0.9%, ∞] and 8.4% [–2.6%, ∞]), whereas preoperative osocimab 1.8 mg/kg was superior (15.1% [95% CI 4.9%, 25.2%]). The respective major or clinically relevant nonmajor bleeding rates among osocimab, enoxaparin and apixaban recipients were 4.7%, 5.9% and 2%.

Comment (LY): In recent years, the contact system of coagulation has come back to the attention of companies developing novel anticoagulants, due to the possibility of reduced thrombosis without an increase in bleeding. This novel antibody targeting factor-XIa is explored in a large dose-finding phase 2 study of VTE prevention after knee arthroplasty, compared with two comparators (apixaban and enoxaparin). While the novel agent had efficacy, rates of bleeding were appreciable and similar to enoxaparin for higher doses. Factor-XI is at the junction of the contact system and physiological pathways, and bleeding in patients with hereditary deficiency varies hugely from minimal symptoms to bleeding, especially with surgery and trauma. It is unclear based on the data presented if osocimab would be preferred, particularly to apixaban with its low rates of bleeding complications, but further larger studies will be of interest.

Reference: JAMA 2020;323:130–9
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.

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.

Diagnostic high-throughput sequencing of 2396 patients with bleeding, thrombotic, and platelet disorders

Authors: Downes K et al.

Summary: These researchers used a high-throughput sequencing panel test of diagnostic-grade genes known to harbour variants associated with rare bleeding, thrombotic and platelet disorders to sequence 2396 index patients. The overall molecular diagnostic rate, determined by the clinical phenotype, was 49.2% for patients with thrombotic, coagulation, platelet count and function disorders, whereas the rate was 3.2% for those with unexplained bleeding disorders characterised by normal haemostasis test results. A multidisciplinary team classified 745 unique variants (including copy number and intronic variants) as pathogenic, likely pathogenic or variants of uncertain significance. Of these variants, 50.9% were novel, and 41 unique variants were identified in seven genes recently implicated in bleeding, thrombotic and platelet disorders. Twenty-nine patients who had evidence of oligogenic inheritance were identified on inspection of canonical haemostasis pathways.

Comment (LY): Next-generation sequencing of DNA for genetic diagnosis is likely to be commonplace in the future, but has not been routine for diagnosis of genetic variants associated with bleeding and thrombosis. Instead, where the clinical suspicion of these diseases is present, a laborious set of functional and specific gene tests are undertaken at considerable expense, with frequently low diagnostic yield. This platform established in Cambridge, UK, has been used to screen around 2500 patients with potential disorders of haemostasis. Almost 50% of patients had a diagnosis, including 3% of those thorny patients with a bleeding history but no demonstrable defects on extensive coagulation and platelet testing. Hopefully laboratories in NZ will be able to work towards a change/introduction of these diagnostic techniques.

Reference: Blood 2019;134:2082–91
Abstract

Treatment efficacy for adult persistent immune thrombocytopenia

Authors: Puavilai T et al.

Summary: This was a systematic review, with 12 RCTs (n=1313) of second-line drugs in adults with persistent immune thrombocytopenia, reporting the outcome of platelet response, platelet count, any bleeding or serious adverse events, included in a network meta-analysis. Compared with placebo, eltrombopag and romiplostim were the best agents for platelet response, with eltrombopag having a nonsignificant advantage (risk ratio 1.10 [95% CI 0.46, 2.67]). Eltrombopag was also superior to rituximab with and without recombinant human thrombopoietin (respective risk ratios 4.18 [95% CI 1.21, 14.49] and 4.56 [1.89, 10.96]) as was romiplostim (3.79 [1.02, 14.09] and 4.13 [1.56, 10.94]). Romiplostim was best for the outcome of platelet count, followed by eltrombopag, rituximab plus recombinant human thrombopoietin and then rituximab alone. The lowest bleeding risk was seen with rituximab, followed by eltrombopag and romiplostim. The treatment associated with the highest risk of serious adverse events was rituximab plus recombinant human thrombopoietin, followed by rituximab alone, eltrombopag and romiplostim. Romiplostim had the best balance between short-term efficacy and serious adverse events, followed by eltrombopag.

Comment (LY): Immune thrombocytopenia that relapses early after steroid response or is refractory remains troublesome. In the NZ climate, treaters are still directed to splenectomy as second line, but international guidelines now reserve surgery for patients who have failed other lines of therapy over several months. This analysis attempts to compare second-line medical therapies. The thrombopoietin receptor agonists eltrombopag and romiplostim were preferred to rituximab, for which a significant relapse rate is recognised. This analysis reflects the latest ASH guidelines in terms of prioritisation of therapies.

Reference: Br J Haematol 2020;188:450–9
Abstract

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Clinical outcomes under hydroxyurea treatment in polycythemia vera

Authors: Ferrari A et al.

Summary: This systematic review included a meta-analysis of data from 3236 participants from 16 studies (2008–2018) reporting the absolute risks of events among patients receiving hydroxycarbamide for polycythaemia vera. The thrombosis and acute myeloid leukaemia incidences remained stable over time, whereas mortality and myelofibrosis incidences varied according to duration of follow-up. The respective yearly thrombosis rates for the median participant ages of 60, 70 and 80 years were 1.9%, 3.6% and 6.8%. A history of a CV complication predicted for a higher incidence of arterial events. The incidence of leukaemic transformation was 0.4% persons per year. The transformation to myelofibrosis and mortality incidences were significantly dependent on age and follow-up duration. The respective 5- and 10-year myelofibrosis rates were 5.0% and 33.7%, and the respective 5- and 10-year overall mortality rates were 12.6% and 56.2%.

Comment (LY): Hydroxycarbamide has been the standard of care for high-risk polycythaemia vera for many years. However, when counselling patients, it would be helpful to have some accurate estimates for outcomes of interest such as thrombosis, transformation and death. This meta-analysis from the prominent Italian group is designed to provide this. Of note, thrombosis incidence remains higher than expected, and myelofibrosis transformation increases steeply from 5 to 10 years after diagnosis. Improving these outcomes remains the goal of newly developing strategies for polycythaemia vera therapy.

Reference: Haematologica 2019;104:2391–9
Abstract

Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA)

Authors: Notten P et al.

Summary: Adults with a first-time acute iliofemoral DVT and symptoms for ≤14 days were randomised to either standard treatment with (evaluable n=77) or without (evaluable n=75) additional ultrasound-accelerated catheter-directed thrombolysis, and were followed for a median of 12.0 months. There was no significant difference between the intervention and standard treatment only groups for the primary endpoint of PTS at 12 months (29% vs. 35%; OR 0.75 [95% CI 0.38, 1.50]). Four participants in the intervention arm experienced a major bleed, compared with none in the standard treatment group. There were no serious adverse events recorded, and none of the four deaths were considered to be treatment-related.

Comment (LY): The role of catheter-directed thrombolysis in acute proximal lower-limb DVT has been controversial, as several large trials have not shown a convincing benefit. It is possible that any benefit over conventional anticoagulation is diluted by including lower-risk patients, notably superficial femoral rather than iliac DVT. This multicentre study focussed on higher-risk patients with true iliofemoral DVT. There was no improvement in the primary outcome of PTS, although the authors optimistically note a weak benefit if a clot breakdown technique was used. Another important point was a significant rate of recurrent stent thrombosis while on anticoagulants; aggressive anticoagulation is needed in this group. This trial again supports the use of this technique only in patients with very severe symptoms/limb-threatening signs and low bleeding risk.

Reference: Lancet Haematol 2020;7:E40–9
Abstract