Haematology RESEARCH REVIEW™

Making Education Easy

Issue 35 – 2020

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Abbreviations used in this issue

AUC = area under the receiver operating characteristic curve
DVT = deep vein thrombosis
ITP = immune thrombocytopenia
LMWH = low-molecular-weight heparin
MDS = myelodysplastic syndrome
MPN = myeloproliferative neoplasm
OR = odds ratio
PAD = peripheral arterial disease
PE = pulmonary embolism
QOL = quality of life
SVT = splanchnic vein thrombosis
VTE = venous thromboembolism

Welcome to issue 35 of Haematology Research Review.

The first paper selected for this issue reports that for thromboprophylaxis following gynaecological cancer surgery, oral apixaban is potentially safe, less painful and easier to administer than subcutaneous enoxaparin, while being similarly effective. Bodyweight-adjusted LMWH was found to be a feasible and well-tolerated thromboprophylactic option for hospitalised patients with cancer at high risk of VTE in a phase 2 trial. There is also a study reporting that the Caprini, IMPROVE and Padua VTE risk scores are no better than patient age alone for predicting VTE risk in noncritical medical inpatients. A randomised crossover study on the effect of alternate-day versus consecutive-day administration on iron absorption in women with iron-deficiency anaemia concludes this issue.

Remember, your feedback and suggestions are always welcome.

Kind regards,

Dr Paul Ockelford
paulockelford@researchreview.co.nz

Dr Laura Young
laurayoung@researchreview.co.nz

Safety and efficacy of apixaban vs enoxaparin for preventing postoperative venous thromboembolism in women undergoing surgery for gynecologic malignant neoplasm

Authors: Guntupalli SR et al.

Summary: Women scheduled for surgery for suspected or confirmed gynaecological cancer were randomised to 28 days of postoperative thromboprophylaxis with oral apixaban 2.5mg twice daily (n=204) or subcutaneous enoxaparin 40 mg/day (n=196) in this trial. No significant difference was seen between apixaban and enoxaparin recipients for major bleeding events (0.5% vs. 0.5%; OR 1.04 [95% CI 0.07, 16.76]), clinically relevant nonmajor bleeding events (5.4% vs. 9.7%; 1.88 [0.87, 4.1]), VTE events (1.0% vs. 1.5%; 1.57 [0.26, 9.50]), adverse events, medication adherence or QOL. Compared with enoxaparin, a greater proportion of apixaban recipients reported satisfaction for ease of taking the medication (98.9% vs. 58.8%; OR 0.06 [95% CI 0.01, 0.25]) and and a smaller proportion reported pain associated with taking the medication (2.1% vs. 49.2%; 9.20 [2.67, 31.82]).

Comment (PO): Ovarian cancer debulking is often prolonged and performed in patients with other thrombotic risk factors. Thrombotic rates consequently are significantly higher in women with gynaecological malignancies compared with other cancers. DVT rates of up to 25% and PE rates of up to 9% are reported postoperatively without prophylaxis. LMWH using subcutaneous enoxaparin 40mg for 28 days is recommended in the ACCP guidelines and is effective without high rates of major bleeding. This study is worth noting if apixaban is ever funded in NZ. It has consistently shown a very favourable efficacy-to-bleeding profile in a number of clinical settings. This may be related to the twice-daily dosing schedule. Randomisation occurred 8 hours after removal of the catheter in those receiving epidural anaesthesia, and both groups were given preoperative unfractionated heparin (5000U) and every 8 hours until randomisation. Patient satisfaction was higher with apixaban.

Reference: JAMA Netw Open 2020;3:e207410
Abstract

Safety and feasibility of rivaroxaban in deferred workup of patients with suspected deep vein thrombosis

Authors: Fronas SG et al.

Summary: The safety of deferring compression ultrasonography using therapeutic doses of rivaroxaban was prospectively evaluated in 624 outpatients referred to a Norwegian emergency department with suspected first or recurrent lower-extremity DVT. While awaiting compression ultrasonography, patients received rivaroxaban 15mg twice daily starting within 24 hours of presentation if their D-dimer level was ≥0.5 mg/L fibrinogen-equivalent units. DVT was diagnosed in 19.1% of the patients. There were no major bleeding events from study inclusion until confirmation of DVT with continued anticoagulation or within 48 hours following administration of the last rivaroxaban dose (primary outcome), and there were no major complications during the compression ultrasonography deferral time.

Comment (PO): The safety of deferring diagnostic scanning for 24 hours, by treating with empiric LMWH, is established practice. This well performed study in ED patients confirms that rivaroxaban can substitute LMWH in this setting, provided patients at high risk of adverse events are excluded. Exclusions are those with active bleeding, haemoglobin level <110 g/L, platelet count $<100\times10^9$/L, known renal impairment (<45 mL/min), active cancer or chemotherapy and suspected PE. Patients with comorbidities needing admission or other in-hospital treatment were also excluded. The same diagnostic strategy was applied to all patients indicating that rivaroxaban can be safely administered to those at low thrombotic risk and ultrasonography deferred in high-risk cases. The pretest probability was moderate or high in 81% of the inclusions and the overall DVT prevalence was 19%. There was a low threshold for bleed reporting, but 95% were minor, and 38% of potentially eligible patients were included, showing the strategy is feasible.

Reference: Blood Adv 2020;4:2468–76
Abstract

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Dose-adjusted enoxaparin thromboprophylaxis in hospitalized cancer patients

Authors: Zwicker JI et al.

Summary: Fifty patients with active cancer with a high VTE risk (based on Padua risk score) were randomised to enoxaparin 40 mg/day or 1 mg/kg/day during hospitalisation in this phase 2 trial. No major bleeds or symptomatic VTE events occurred in either study arm. At the time the blinded clinical assessment was completed, one incidentally identified PE had occurred in the weight-adjusted enoxaparin arm. The cumulative DVT incidence among fixed-dose enoxaparin recipients who subsequently underwent surveillance ultrasonography was 22%.

Comment (PO): Inpatient prophylaxis dosing for cancer patients is an area of unmet need. Prophylaxis studies, using fixed-dose LMWH based on general medical prophylaxis protocols, have shown higher thrombosis rates in the cancer patients compared with those without cancer, but the numbers of patients with cancer have been low. This is an interesting but small study, so conclusions are limited. It does demonstrate that weight-adjusted LMWH is well tolerated when administered to a maximum dose of 100mg for up to 14 days during hospital stay. It was not continued after discharge. Inclusion criteria were sensible and the study was double blinded. While the cumulative DVT incidence seems high, this only represents two patients with calf vein thrombi who underwent ultrasonography at day 17–25 in the fixed-dose treatment arm. The study population included 60% classified as very high or high thrombotic risk, and patients were stratified according to Khorana tumour risk.

Reference: Blood Adv 2020;4:2254–60
Abstract

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Rivaroxaban in peripheral artery disease after revascularization

Authors: Bonaca MP et al.

Summary: Patients with PAD who had undergone revascularisation received aspirin with either twice-daily rivaroxaban 2.5mg (n=3286) or placebo (n=3278) in this randomised trial. The primary efficacy outcome (composite of acute limb ischaemia, major amputation for vascular causes, MI, ischaemic stroke or death from CV causes) occurred in fewer participants from the rivaroxaban group compared with the placebo group (3-year Kaplan-Meier estimates, 17.3% vs. 19.9%; hazard ratio 0.85 [95% CI 0.76, 0.96]). The incidence of major bleeding did not differ significantly between groups according to TIMI criteria, but was significantly greater in the rivaroxaban arm according to ISTH criteria (hazard ratio 1.42 [95% CI 1.10, 1.84]).

Comment (PO): Thrombosis plays a critical role in PAD. A recent study (COMPASS; Lancet 2018) demonstrated that rivaroxaban and aspirin lowered the risk of major adverse limb events in patients with PAD by 45%. Patients needing revascularisation have a 4-fold higher risk of further ischaemic events and repeat procedure rates are high. The VOYAGER PAD study randomised patients undergoing endovascular or surgical revascularisation. The composite outcome was 15% lower at 3 years in those receiving rivaroxaban 2.5mg twice daily with aspirin compared with aspirin alone. Major bleeding was higher with rivaroxaban but neither intracerebral haemorrhage nor fatal bleeding was increased. Annualised rivaroxaban discontinuation rates were high (14%), but taken together, these two studies show that adverse CV and ischaemic limb events can be reduced with combined therapy. Unfortunately rivaroxaban 2.5mg tablets are not yet available in NZ.

Reference: N Engl J Med 2020;382:1994–2004
Abstract

Rivaroxaban or enoxaparin in nonmajor orthopedic surgery

Authors: Samama CM et al., for the PRONOMOS Investigators

Summary: Adults undergoing lower-limb nonmajor orthopaedic surgery who were at high VTE risk (based on investigator's judgment) were randomised to receive rivaroxaban (n=1809) or enoxaparin (n=1795) in this noninferiority trial. The major VTE rate (composite of symptomatic distal or proximal DVTs, PEs or VTE-related deaths) was lower in the rivaroxaban arm than in the enoxaparin arm (0.2% vs. 1.1%; risk ratio 0.25 [95% CI 0.09, 0.75; respective p values for noninferiority and superiority, <0.001 and 0.01]), with no significant difference for the incidence of major bleeding (1.1% vs. 1.0%) or nonmajor clinically relevant bleeding (0.6% vs. 0.7%).

Comment (PO): The risk of DVT in nonmajor lower-limb surgery is approximately 3%. Patient-related factors such as age, body mass index, medication and patient VTE history increase the risk. There is no consensus on appropriate prophylaxis in these patients. USA and European guidelines differ. Europe favours prophylaxis where there are one or more additional risk factors and thrombosis likelihood exceeds the bleed risk. This French double-blind, randomised, controlled trial compared rivaroxaban 10mg and enoxaparin 40mg in patients in whom immobility was 2 weeks or more. Patients were stratified for duration of immobility, and compression ultrasonography was performed at the end of the immobilisation between day 15 and 3 months. Symptomatic events were investigated at any time. Rivaroxaban was associated with a 75% lower risk of major VTE with no increase in bleeding. There were no proximal DVTs or PE events in the rivaroxaban recipients. Thromboprophylaxis should be carefully considered in those with additional risk factors.

Reference: N Engl J Med 2020;382:1916–25
Abstract

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Molecular profiling and risk classification of patients with myeloproliferative neoplasms and splanchnic vein thromboses

Authors: Debureaux P-E et al.

Summary: Risk factors for adverse haematological outcomes were identified for a retrospective cohort of 80 patients with SVT secondary to MPN; most patients were women (mean age 42 years) with polycythaemia vera. Thirteen percent of the patients met the primary outcome of evolution to myelofibrosis, acute leukaemia or death, with risk factors being *JAK2* V617F allele burden ≥50% (OR 14.7) and additional mutations in chromatin/spliceosome genes (OR 9). Compared with low-risk patients, high-risk patients (i.e. those harbouring ≥1 molecular risk factor; 29% of the cohort) had worse 10-year event-free and overall survival rates (81% vs. 100% and 89% vs. 100%, respectively [p≤0.01]). The results were confirmed in an independent validation cohort of 30 patients with SVT secondary to MPN.

Comment (LY): The role of next-generation sequencing in haematological disease is rapidly expanding. Myeloid mutations with adverse prognosis are already factored into decision making regarding the use of stem-cell transplantation in more advanced myeloproliferative disease and have been shown to be more frequent as the diseases progress. It is not surprising that the identification of these mutations in patients who have just been diagnosed is prognostically relevant. High risk defined as a high *JAK2* allele burden and/or mutations involving *TP53* /chromatin/spliceosome was almost one-third of the group and reduced survival. This confirms that the subgroup of MPN patients presenting with SVT can also undergo greater prognostic definition at the time of diagnosis.

Reference: Blood Adv 2020;4:3708–15
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.

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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.

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Positivity rate of systematic bone marrow smear in patients over 60 years old with newly diagnosed immune thrombocytopenia

Authors: Comont T et al., and the CARMEN investigators group

Summary: These authors reported on the frequency of pathological bone marrow smears and their evolution for 197 patients aged ≥60 years with ITP from the prospective CARMEN registry; the patients had isolated thrombocytopenia (mean platelet count 32.7×10⁹/L) with no clinical signs of haematological malignancy. Bone marrow smears were performed at diagnosis for 114 of the patients, with only one (a 62-year-old man) having abnormal results corresponding to MDS with multilineage dysplasia, with normal cellularity. This man partially or completely responded to ITP treatments over 5 years of follow-up, and a second bone marrow smear at 4 years returned similar findings to his first smear. There was no progression to other cytopenias or myeloid leukaemia for this man.

Comment (LY): Historically, a bone marrow biopsy was recommended at diagnosis of ITP in the older adult, due to the possibility the diagnosis may be another primary bone marrow disease, most likely myelodysplasia. This was changed in recent guidelines to be a biopsy at relapse or if treatment-refractory. This study confirms that in fact typical ITP can be diagnosed in this group, and a biopsy initially is only necessary if there are other cytopenias or risk factors such as monocytosis. This is useful confirmation of a sensible practice shift.

Reference: Blood Adv 2020;4:2136–8
Abstract

Validation of risk assessment models predicting venous thromboembolism in acutely ill medical inpatients

Authors: Moumneh T et al.

Summary: This was a retrospective analysis of a cohort of 14,660 evaluable PREVENU trial participants aged ≥40 years who had been hospitalised for ≥2 days on a medical ward. The aim was to externally assess three VTE risk scores, and compare their performance with advanced age as a standalone predictor of VTE risk. Over 3 months of follow-up, 1.8% of the patients experienced a symptomatic VTE or sudden unexplained death. The respective AUC values for the Caprini, IMPROVE and Padua risk assessment scores were 0.60, 0.63 and 0.64, with none of these performing significantly better than advanced age, for which the AUC value was 0.61.

Comment (LY): This is a very large French cohort study of medical inpatients. Decisions regarding prophylaxis in this group are difficult, as while prophylaxis is efficacious, there is also an increased risk of bleeding. Three scores were compared. The cohort is a little messy as a proportion received prophylaxis and a significant percentage of the VTE events were unexplained deaths. However, the modelling comparing the risk assessment scores showed little difference. It is discouraging that these scores, which are relatively complex, do not better discriminate and there is still work to do in this space.

Reference: J Thromb Haemost 2020;18:1398–407
Abstract

Red cell transfusion in outpatients with myelodysplastic syndromes

Authors: Stanworth SJ et al., on behalf of the REDDS Investigators

Summary: In this feasibility, exploratory trial, outpatients (including from NZ) with MDS were randomised to transfusion algorithms with a current restrictive transfusion threshold of 80 g/L (to maintain haemoglobin levels at 85–100 g/L; n=20) or a liberal threshold of 105 g/L (to maintain haemoglobin levels at 110–125 g/L; n=18). In an intent-to-treat analysis, the respective proportions compliant to transfusion thresholds in the restrictive and liberal arms were 86% and 99%, the respective mean pretransfusion haemoglobin levels were 80 and 97 g/L, and the respective on-study totals for number of red cell units transfused were 82 and 192. An exploratory analysis revealed improvements in five main QOL domains in the liberal versus restrictive arm.

Comment (LY): Haemoglobin level targets in patients who have a long-term transfusion requirement are poorly defined. In the inpatient setting, relatively restrictive targets have been shown to be noninferior and in some cases better than more liberal targets, but of course perioperative or acutely ill patients are not the same as the MDS patient in the community. This interesting multinational pilot study, which included patients in Wellington, assessed the feasibility of a blinded liberal versus restrictive strategy. Important points to note include that achieving a minimum haemoglobin level target of 80 vs. 105 g/L required almost double the number of red cell units. Patients themselves could not reliably identify which haemoglobin group they were in, but there was a trend towards improved QOL measures in the liberal group. The playoff between QOL benefits, and cost, resource and other disadvantages, like iron overload, would justify a larger study to assist in decision making regarding appropriate targets.

Reference: Br J Haematol 2020;189:279–90
Abstract

Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women

Authors: Stoffel NU et al.

Summary: Nineteen women with iron-deficiency anaemia received stable iron isotope-labelled ferrous sulfate either 100mg or 200mg administered at 8AM on days 2, 3 and 5 with the alternate dose administered on the same schedule after a 16-day incorporation period in this crossover study. For both doses, serum hepcidin level was significantly higher 3 days after administration than on days 2 and 5 ($p \leq 0.01$), and fractional iron absorption was 40–50% greater on days 2 and 5 than it was on day 3 ($p<0.001$), with no significant differences between days 2 and 5 for either of these parameters. The two doses did not differ significantly for the incidence of gastrointestinal side effects.

Comment (LY): Oral iron therapy is cheap and easily prescribed for the large group of women who are deficient in iron, but is often poorly tolerated. This interesting crossover study of iron-deficient women showed that there is an increase in serum hepcidin level (which will reduce iron absorption) and that the fractional iron absorption was lower if oral iron is given daily. Alternate daily dosing was preferable. Larger iron doses even given alternate daily have a reduced fractional absorption than the lower dose, but a higher total absorption. Overall the effects of 100mg daily or 200mg alternate daily were likely similar. Gastrointestinal side effects tended to be more common with the higher dose but without significance; overall the higher dose on an alternate daily basis seems like an appropriate strategy to maximise benefit and reduce side effects.

Reference: Haematologica 2020;105:1232–9
Abstract