Thrombosis & Haemostasis Research Review™

Making Education Easy

Issue 22 - 2022

In this issue:

Abbreviations used in this issue:

AF = atrial fibrillation; **APC** = activated protein C; **APS** = antiphospholipid syndrome; **ATE** = arterial thromboembolism; **BTK** = Bruton's tyrosine kinase; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **DOAC** = direct-acting oral anticoagulant; **EPCR** = endothelial cell protein C receptor; **ET** = essential thrombocythemia; **FXI** = coagulation factor XI; **HR** = hazard ratio; **HU** = hydroxyurea; **IFN** = interferon; **IL** = interleukin; **ITP** = immune thrombocytopenia; **LA** = lupus anticoagulant; **OR** = odds ratio; **PV** = polycythemia vera; **VTE** = venous thromboembolism.

Welcome to the latest issue of Thrombosis & Haemostasis Research Review.

Positive preliminary results from a phase 1/2 dose-finding study of the experimental oral Bruton's tyrosine kinase (BTK) inhibitor rilzabrutinib, reported in the *New England Journal of Medicine* by David Kuter and colleagues at the Massachusetts General Hospital and Harvard Medical School, both in Boston, USA, indicate that it rapidly and durably increases platelet counts in heavily pre-treated patients with relapsed/refractory immune thrombocytopenia (ITP). Further results from placebo-controlled trials are eagerly awaited. Data from Bayer's phase 3 PACIFIC-AF trial in *The Lancet* demonstrates that in patients with atrial fibrillation (AF) at risk of stroke the oral, small-molecule inhibitor of coagulation factor XIa (FXIa) asundexian was effective for pathologic thrombi prevention and had a more favourable safety profile than apixaban with lower rates of non-major bleeding. Population-based studies from Sweden and Denmark report increased risk of venous thromboembolism (VTE) in men with prostate cancer, and high risks of arterial thromboembolism (ATE), VTE and bleeding in first-time nephrotic syndrome, respectively. The ongoing adaptive platform trial REMAP-CAP provides some insight into the efficacy of antiplatelet therapy for critically ill patients with coronavirus disease 2019 (COVID-19), finding no acute benefit in terms of reducing organ support-free days but a signal of favourable 90-day survival. Further elucidation to determine which patients derive enough benefit to outweigh the increased risk of major bleeding is required.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Professor Harshal Nandurkar
harshal.nandurkar@researchreview.com.au

Risk of venous thromboembolism in men with prostate cancer compared with men in the general population

Authors: Balabanova Y et al.

Summary: A nationwide population-based cohort study in Sweden published in the *British Medical Journal Open* reports that in the five years following a prostate cancer diagnosis the risk of VTE is 50% higher compared to age-matched men without prostate cancer. A total of 92,105 men diagnosed with prostate cancer between 2007 and 2017 were identified from the Nationwide Prostate Cancer Database Sweden and matched by birth year and region of residence to five control men without prostate cancer (n=466,241). Higher rates of first VTE were found in the cohort of men with prostate cancer (3.21% vs 2.1%; crude incidence rates of 6.54 vs 4.27 per 1,000 person-years at a median follow-up of 4.5 years). Adjusted Cox regression analysis revealed an almost 50% increased risk of both deep vein thrombosis and pulmonary embolism in men with prostate cancer compared to controls (hazard ratio [HR] 1.48 and HR 1.47).

Comment: Prostate cancer is the most commonly diagnosed cancer in middle aged and older men worldwide. The survival rates are high and there is a large at-risk population underscoring the importance of understanding the magnitude of VTE in this cancer. The strengths are that health data capture in Sweden is amongst the most comprehensive and hence, this study is an excellent indicator of VTE risk in prostate cancer in more than 90,000 subjects compared with over 450,000 controls. For each man with prostate cancer, the investigators identified their matched men from the general population. Over half of men (52%) in the prostate cancer cohort had T2 stage disease; 17% had metastases; and the median prostate specific antigen was 9 mg/L (IQR 5–20) at the time of the cancer diagnosis. The focus on one specific cancer type, the near absence of any loss to follow-up and the inclusion of patients with VTE who were either hospitalised or managed on an outpatient basis are also strengths. A weakness of this study was that it did not exclude for the development of other cancers in the comparison cohort. Some in the comparison cohort may have developed another cancer during follow-up, thereby increasing their risk of developing a VTE and diluting the relative risk estimates observed.

Reference: BMJ Open 2022;12(5):e055485

Abstract

Rilzabrutinib, an oral BTK inhibitor, in immune thrombocytopenia

Authors: Kuter D et al.

Summary: Results from an international, adaptive, open-label, dose-finding, phase 1–2 clinical trial sponsored by Principia Biopharma, a Sanofi Company (NCT03395210), in the *New England Journal of Medicine* demonstrate that rilzabrutinib is tolerable and elicits rapid and durable increases in platelet counts in patients with relapsing immune thrombocytopenia (ITP). A total of 60 adult patients with heavily pre-treated refractory or relapsed primary or secondary ITP and platelet counts <30,000/μL (median baseline platelet count, 15 x10^3/mm^3, median 6.3 years disease duration; median of four previous therapies) with no available and approved therapeutic options were accrued from sites across the US, Australia and several European countries. Patients underwent 24 weeks of oral rilzabrutinib therapy with doses starting at between 400 mg once daily to 400 mg twice daily and intrapatient dose escalation as necessary. The primary efficacy outcome measure of a platelet response – defined as at least two consecutive platelet counts of ≥ 50,000/μL plus an increase of ≥20,000/μL without the use of rescue medication – was achieved in 40% of patients at the end of the treatment period (median 167.5 days) with a median time to response of 11.5 days. The higher dose of rilzabrutinib 400 mg twice daily was determined to be the optimal dose for further testing. Treatment-related adverse events were mild (grade 1-2) and transient. No bleeding or thrombotic events of greater severity than grade 2 were reported.

Comment: The rationale for the use of a BTK inhibitor is that BTK is widely expressed in many cells and plays a critical role in B-cell maturation, antibody production and phagocytosis of platelets via Fcγ receptor– mediated pathway in macrophages. The covalent binding of rilzabrutinib contributes to long BTK-target engagement and durable inhibition with limited drug exposure. This results in rapid systemic clearance, which reduces the potential for off-target toxic effects. Moreover, the high specificity of rilzabrutinib is thought to decrease the risk of off-target toxic effects (e.g., AF) by means of the phosphatidylinositol 3-kinase–AKT signalling pathway, which is associated with other BTK inhibitors. Another significant advantage is that rilzabrutinib use did not alter platelet aggregation in healthy volunteers or in patients with ITP and hence, there is less risk of bleeding that is a feature of other BTK inhibitors. Intrapatient dose escalation was allowed every 28 days, according to the investigator's judgment. The treatment protocol was for 24 weeks with a further four weeks of safety monitoring. At enrolment, patients had to have platelet counts less than 30×10^3 per cubic millimetre on two occasions no less than seven days apart within the 15 days before trial entry. The primary end points were safety and platelet response. There were a number of secondary end points including the percentage of weeks with a platelet count of at least 30×10^3 per cubic millimetre. The primary end point was met in 40% of the cohort with the dose of 400 mg twice a day as the most effective. Rescue medication was used in seven patients (12%). The most common treatment-related adverse events of any grade were diarrhea (in 32% of the patients), nausea (30%), and fatigue (10%). There was improvement in ITP–specific bleeding scores. A randomised, double-blind, phase 3 trial comparing rilzabrutinib with placebo is underway.

Reference: N Engl J Med 2022;386(15):1421-31
Abstract

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

Authors: Piccini J et al., on behalf of the PACIFIC-AF Investigators

Summary: Bayer's phase 3 PACIFIC-AF trial (NCT04218266) evaluated the bleeding risk with anticoagulation with asundexian versus apixaban in patients with AF. Patients (n=753; median age 73.7 years) at least 45 years of age with documented electrocardiogram evidence of AF (CHA_2DS_2-VASc score ≥ 2 or ≥ 3 for males and females, respectively) with an indication for oral anticoagulation treatment, either treatment-naïve or currently on a non-vitamin K antagonist oral anticoagulant (NOAC), were enrolled from sites across Europe, Canada and Japan. Patients were randomised to anticoagulation treatment with asundexian at a dose of 20 or 50 mg/day (n=249 and n=254, respectively) or apixaban 5 mg twice daily (n=250). The trial demonstrated superior haemostasis-sparing with asundexian versus apixaban with lower International Society on Thrombosis and Haemostasis major and clinically relevant non-major bleeding rates (ratios of incidence proportions 0.50 and 0.16 for asundexian 20 mg and 50 mg, and 0.33 for pooled asundexian [four events] vs six events in the apixaban arm). Comparable rates of adverse events were reported in the three trial arms (47% vs 47% vs 49%). Very high rates of *in vivo* FXIa inhibition were reported at trough and peak concentrations – 81%/90% for 20 mg/day asundexian and 92%/94% for asundexian 50 mg/day, respectively.

Comment: Commonly used direct-acting oral anticoagulants (DOACs) target Xa or thrombin. As these coagulation factors are critical in haemostasis, their inhibition is likely to lead to bleeding side effects. Congenital FXI deficiency causes a marked prolongation of the aPTT but it is associated with a mild bleeding disorder. Bleeding in FXI deficiency usually follows trauma to certain tissues (oropharynx or urinary tract). Bleeding into the central nervous system, gastrointestinal tract, joints and muscles are not features of FXI deficiency, and spontaneous bleeding is rare. Thus, targeting XIa will uncouple desired antithrombotic effects from deleterious anti-haemostatic effects. PACIFIC-AF, a phase 2 double-blind randomised trial was powered to assess bleeding in patients with AF receiving 12-week courses of the FXIa inhibitor asundexian or the FXa inhibitor apixaban. The primary endpoint was a composite of major or clinically relevant non-major bleeding. Trough concentrations of asundexian demonstrated substantial inhibition of FXIa activity (by 80%–90%). These findings provide rationale for larger clinical outcome studies with asundexian. The limitations of this study are that it was not powered to test differences in rates of thrombosis between groups. The number of bleeding events was only half of the anticipated number (10 compared with 20 events) and no major bleeding events were observed. Therefore, although asundexian is likely to have caused less bleeding than apixaban, the results did not allow the magnitude of the effect to be accurately determined.

Reference: Lancet 2022;399(10333):1383-90
Abstract

Risk of arterial thromboembolism, venous thromboembolism, and bleeding in patients with nephrotic syndrome

Authors: Vestergaard S et al.

Summary: A population-based cohort study from Denmark reports a high absolute risk of ATE, VTE and bleeding in adults with first-time nephrotic syndrome. Analysis included all patients diagnosed with first-time nephrotic syndrome in the 24-year period preceding 2018 (n=3,967), age- and sex- matched to 10 general population members each. The one-year risk of ATE, VTE and bleeding were 4.2%, 2.8% and 5.2%, respectively. Cox modelling revealed a three-fold increased hazard of ATE, seven-fold increased risk of VTE and four-fold increased hazard of bleeding in patients with nephrotic syndrome compared to adults without nephrotic syndrome after adjustment for confounding factors (HR 3.11, 95% confidence interval [CI], 2.60-3.73; HR 7.11, 95% CI 5.49-9.19 and HR 4.02, 95% CI 3.40-4.75).

Comment: VTE is a well-recognised complication of nephrotic syndrome, but the risk of ATE and bleeding in patients with nephrotic syndrome needs more assessment. The aetiology is multifactorial. Hyperlipidaemia, an imbalance in pro- and anti-thrombotic factors, impaired thrombolytic activity, treatment with steroids, underlying cancer and other factors related to nephrotic syndrome may contribute to an increased risk of both ATE and VTE. This cohort study was based on data from nationwide population-based registries in Denmark. Thoroughness of Danish registries is a key strength. 3,967 adults with first-time nephrotic syndrome during 1995-2018 were matched to 39,670 individuals from the general population. Key observations were that adults with nephrotic syndrome have high 10-year risk of ATE (14.0%), VTE (7.7%), and bleeding (17.0%). The 10-year risk was highest for ischemic stroke (8.1%), myocardial infarction (6.0%), and gastrointestinal bleeding (8.2%). The rate of ATE, VTE, and bleeding is higher in patients with nephrotic syndrome than in the general population. There were some differences based on renal pathology: Generally, patients with membranous nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis and other histopathology had the highest risk of ATE, VTE and bleeding as compared to the group with minimal change disease. The risk of ATE in patients with nephrotic syndrome increased markedly with lower estimated globular filtration rate, with a three-fold higher risk of ATE in patients with chronic kidney disease stage 5 (29.0%) compared to those with chronic kidney disease stages 1-2 (8.8%). Such an association with estimated globular filtration rate was less prominent for the risk of VTE.

Reference: Am J Med 2022;135(5):615-25.e9
Abstract

Effect of antiplatelet therapy on survival and organ support–free days in critically ill patients with COVID-19.

A randomised clinical trial

Authors: REMAP-CAP Writing Committee for the REMAP-CAP Investigators

Summary: This publication in *JAMA* reports results for the antiplatelet domain of the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP; NCT02735707) in critically ill patients hospitalised with COVID-19. Trial inclusion criteria restricted entry to adult patients admitted to the intensive care unit within 48 hours of hospital admission with COVID-related community-acquired pneumonia and radiological evidence of new onset consolidation requiring organ support with ventilation and/or vasopressor or inotrope infusion. A total of 1,557 critically ill patients were enrolled between October 2020 and June 2021 and administered up to 14 days of antiplatelet therapy with either aspirin (n=565), site-preferred P2Y12 inhibitor (n=455) or no antiplatelet therapy (n=529); all on a background of anticoagulation thromboprophylaxis. The primary efficacy outcome measure was organ support-free days (days alive and not requiring respiratory or cardiovascular organ support) up to day 21. Bayesian cumulative logistic modelling found comparable median organ support-free days between pooled antiplatelet arms versus no antiplatelet therapy that did not meet the prespecified threshold to demonstrate efficacy (7 vs 7 days; odds ratio [OR] 1.02; 95% CI, 0.86-1.23; 95.7% posterior probability of futility). A significantly higher rate of major bleeding was found in the antiplatelet pooled cohort with an almost three-fold increased likelihood versus control (2.1% vs 0.4%; adjusted OR 2.97; 95% CI, 1.23-8.28; 99.4% probability of harm).

Comment: Pathophysiology of COVID-19 is marked for the presence of acute endothelial dysfunction and coagulopathy, platelets that are hyperreactive to activation stimuli and with phenotypic changes indicative of abnormal platelet-leukocyte interactions. This led to several trials of antiplatelet therapies. Confounding factors have been variability of COVID-19 severity and the concomitant use of anticoagulation at various intensities. Large trials include the RECOVERY platform that covered over 14,000 patients randomised to receive aspirin plus usual care or just usual care, showing similar mortality (17% in both groups) with increased bleeding in the aspirin cohort (*Lancet* 2022;399[10320]:143-51). The CTIV-4a trial that included ~500 non–critically ill patients hospitalised for COVID-19, randomly allocated to receive therapeutic heparin alone or therapeutic heparin plus a P2Y12 inhibitor (63% ticagrelor and 37% clopidogrel) was terminated as there was no difference in the primary end point of organ support-free days (*JAMA*. 2022; 327[3]:227-36). In the REMAP-CAP study critically ill patients with COVID-19 who were receiving anticoagulation therapy were randomly allocated to receive aspirin (at doses between 75 mg and 100 mg; n=565), a P2Y12 inhibitor (clopidogrel, 75 mg; ticagrelor, 60 mg; or prasugrel, 60 mg; n=455), or control (n=529). The primary end point was organ support–free days through day 21, and decisions regarding antiplatelet therapy after 14 days were at the discretion of treating clinicians. This trial did not show any difference in organ support-free days, but there was a signal in critically ill patients of a 97% probability that antiplatelet therapy improved survival to hospital discharge, with an adjusted absolute reduction in mortality of 5%. The trade-off was that major bleeding occurred more frequently in patients randomised to antiplatelet therapy.

Reference: JAMA 2022;327(13):1247-59
Abstract

Predictors of bleeding in patients receiving direct oral anticoagulants

Authors: Chua G et al.

Summary: Chua et al report results from a single-centre retrospective medical chart review examining factors prognostic for clinically significant bleeding events in patients treated with DOACs. Analysis was based on 203 patients admitted to the general medical unit of Eastern Health in Victoria, Australia over a two-year period with up to 12 months follow-up. Concurrent antiplatelet medication with DOACs increased the likelihood of clinically significant bleeding events and major bleeding events by more than three-fold on multivariable analysis after adjustment for confounding factors (OR 3.6; 95% CI, 1.4-9.6; p=0.01 and OR 4.9; 95% CI, 1.1-21.4; p=0.04). A high rate of non-indicated antiplatelet use was noted.

Comment: This is a retrospective evaluation of the risks of combined use of DOACs and antiplatelet drugs from Eastern Health service in Melbourne. This data confirms the previously recognised risk of increased bleeding with the conjoint use of DOACs with antiplatelet therapies. An important observation that reflects on our empirical practice is that while almost 20% of patients were on antiplatelet drugs, only 7.7% fitted in with the current guidelines for their use.

Reference: Intern Med J 2022;52(4):581-89
Abstract

Haemorrhage in patients with polycythemia vera receiving aspirin with an anticoagulant: a prospective, observational study

Authors: Zwicker J et al.

Summary: The US, non-interventional, observational REVEAL (NCT02252159) study enrolled patients with polycythemia vera (PV) to examine disease progression and treatment outcomes in a real-world setting. Zwicker et al report an analysis of the safety of combined aspirin primary thromboprophylaxis with anticoagulation in a cohort of 1,602 adult patients (median age 67 years; 45.85 women) diagnosed with overt clinical PV undergoing aspirin ± anticoagulant therapy in a community or academic medical centre with a median 2.4-year follow-up. Analysis found a significantly higher rate of haemorrhage and severe haemorrhage in the 6.4% of the cohort who received combination aspirin/ anticoagulant (1.4 vs 6.75 events per 100 patient-years and 1.46 vs 0.49 events per 100 patient-years, respectively). Cox proportional hazards model estimated that combining aspirin with an anticoagulant conferred a five-fold increased risk of haemorrhage and a more than seven-fold increased risk of severe haemorrhage compared to aspirin alone (HR 5.83 and HR 7.49; both p<0.001). The magnitude of risk was comparable whether aspirin was combined with warfarin or DOACs. The risk of haemorrhage was doubled during periods of haemocytosis (HR 2.25).

Comment: Aspirin is used as primary thromboprophylaxis and it is often combined with anticoagulants during management of acute thrombotic events. Due to the high rates of recurrent thrombotic events, aspirin is often continued along with therapeutic anticoagulation, but the relative safety of combined anticoagulant-antiplatelet therapy is not established in PV. This is a multicentre, non-interventional, prospective, observational study of patients with PV. Increased incidence was reported with aspirin and the use of aspirin plus anticoagulant was associated with a greater than five-fold increased risk of haemorrhage compared with aspirin alone. The most common sites were gastrointestinal (43.5%), cutaneous (27.5%), central nervous system (14.5%) and genitourinary (10.1%). The most common sites of severe haemorrhage were gastrointestinal (44%) and central nervous system (36%). These included five fatal events (four as central nervous system bleeds). Thrombocytopenia (platelet count <100×109/L) was not statistically associated with an increased risk of haemorrhage but thrombocytosis was associated with an increased risk of any haemorrhage (HR 2.25). The efficacy of combined treatment was not established as the use of aspirin with an anticoagulant was not associated with a lower rate of thrombosis compared with aspirin alone.

Reference: Haematologica 2022;107(5):1106-10
Abstract

Thrombosis & Haemostasis Research Review™

Independent commentary by Prof Harshal Nandurkar

Prof Harshal Nandurkar, is the Director of the Alfred Cancer Program and Clinical Haematology, Head of the Australian Centre for Blood Diseases. He is the past President of the Thrombosis and Haemostasis Society of Australia and NZ and past Vice President of the International Union of Angiology (Australian Chapter).

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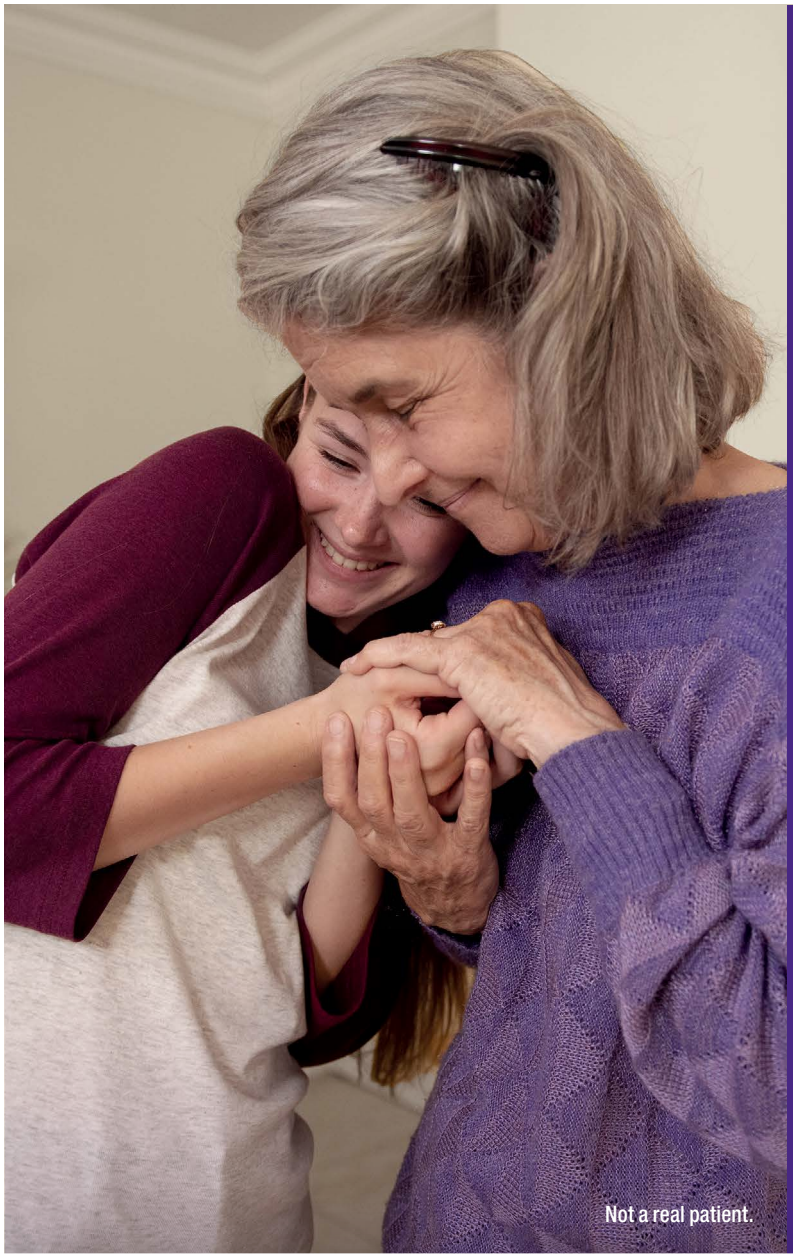

PI UPDATED
JUNE 2020

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Xarelto (rivaroxaban) has the lowest approved CrCl cut-off in Australia compared to other NOACS*[1–3]

*Use with caution in patients with CrCl 15–29 mL/min. Contraindicated in patients with CrCl <15 mL/min.[1]

Xarelto® rivaroxaban

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Minimum Product Information. Xarelto® (rivaroxaban) INDICATIONS: Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks); 10 mg tablet once daily. Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke; 20 mg tablet once daily (15 mg for patients with CrCl 15-49 mL/min). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and pulmonary embolism (PE); 15 mg tablet twice daily for 3 weeks, followed by 20 mg tablet once daily. Following completion of six to twelve months therapy, based on an individual assessment of the risk of recurrent DVT or PE against the risk for bleeding, dose reduction to 10 mg Xarelto once daily may be considered. In combination with aspirin, for the prevention of major cardiovascular events (composite of stroke, myocardial infarction and cardiovascular death) in patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD); 2.5 mg tablet twice daily in combination with 100 mg aspirin. Xarelto 15 mg and 20 mg tablets should be taken with food. Xarelto 2.5 mg and 10 mg may be taken with or without food. Tablets may be crushed and administered orally (mixed with water or applesauce) or given through gastric tubes. See full PI for details. **CONTRAINDICATIONS:** Hypersensitivity to rivaroxaban or to any of the excipients, clinically significant active bleeding, lesions at increased risk of clinically significant bleeding and patients with spontaneous impairment of haemostasis, significant hepatic disease which is associated with coagulopathy, dialysis or severe renal impairment with a creatinine clearance < 15 mL/min, concomitant treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein, Pregnancy, Lactation. **PRECAUTIONS:** Increased bleeding risk such as general haemorrhagic risk (see PI for list), bronchiectasis or history of pulmonary bleeding, renal impairment, hepatic impairment, surgery and interventions, spinal/epidural anaesthesia or puncture, patients with prosthetic heart valves (not recommended), patients with antiphospholipid syndrome, haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy, lactose intolerance. **INTERACTIONS WITH OTHER MEDICINES:** Care to be taken if concomitantly used with medicines affecting haemostasis; concomitant administration with NSAIDs, platelet aggregation inhibitors, Selective Serotonin Reuptake Inhibitors, Selective Norepinephrine Reuptake Inhibitors, other anticoagulants. **ADVERSE EFFECTS:** Please refer to PI for a complete list. Very common and common adverse reactions (≥ 1%) include post procedural haemorrhage, increased transaminases, gingival bleeding, constipation, diarrhoea, nausea, pyrexia, oedema peripheral, contusion, pain in extremity, headache, dizziness, haematuria, menorrhagia, epistaxis, haematoma, anaemia, rectal haemorrhage, fatigue and ecchymosis, haemoptysis, pruritus, conjunctival haemorrhage, abdominal pain, dyspepsia, gastrointestinal haemorrhage, syncope, hypotension, increased gamma-glutamyltransferase, tachycardia, vomiting, asthenia, wound haemorrhage, subcutaneous haematoma and rash. **DOSAGE AND ADMINISTRATION:** see INDICATIONS above. **BASED ON PI DATED:** 02 JUN 2020. **REFERENCES: 1.** XARELTO (rivaroxaban). Product Information. 02 June 2020. **2.** Pradaxa (dabigatran) Product Information. 15 March 2021. **3.** Eliquis (apixaban) Product Information. 23 June 2020. Further information available from Bayer Australia Ltd. ABN 22 000 138 714, 875 Pacific Highway, Pymble NSW 2073. Xarelto® is a registered trademark of Bayer Group, Germany. PP-XAR-AU-1403-1. SSW. XAR-003004-00/G. February 2022.

BAYER

A randomised phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia

Authors: Mascarenhas J et al.

Summary: Results from the phase 3 Myeloproliferative Disorders Research Consortium 112 trial (NCT01259856) indicate that hydroxyurea (HU) and pegylated interferon-α (IFN- α) have comparable efficacy for high-risk myeloproliferative neoplasms, reducing thrombotic events and disease progression. The trial enrolled 168 treatment-naïve patients diagnosed with high-risk PV (n=87) or essential thrombocythemia (ET; n=81) from sites in North America and Europe. Most patients were classified as high-risk due to advanced age or a history of thrombosis. Patients were randomised to 81 weeks of front-line treatment with either HU 500 mg twice daily or subcutaneous IFN- α initiated at 45 µg/week and titrated up to 180 µg/week. At 12-month assessment just over one-third of patients in each trial arm achieved a complete response (37% vs 35%; *p*=0.80), with comparable efficacy between treatments in both types of myeloproliferative neoplasms (ET, 45% vs 44%; PV, 30% vs 28%). The authors reported a greater efficacy for blood count normalising and reducing driver mutation burden (*JAK2*V617F) with IFN- α but also a higher rate of grade 3/4 adverse events (46% vs 28%).

Comment: IFN-α and HU are the most frequently used medications in normalising blood counts in ET and PV but their relative superiority has not been established. The study cohort included 168 patients of which 86 patients assigned to HU (44 PV and 42 ET) and 82 patients assigned to IFN-α (43 PV and 39 ET). The genetic mutational profile was *JAK2*V617F (91%), *CALR* (8%), *MPL* (3%), *TET2* (24%) and *ASXL1* (9%). The take home message is that there was no significant difference in the effectiveness of HU or IFN-α in normalising blood counts. Normalisation of splenomegaly was noted in 11% receiving HU compared with 17% receiving IFN-α. Reductions in *JAK2*V617F variant allele frequency from baseline was -5.3% for HU and -10.7% for IFN-α. There were also reductions in *CALR* and *TET2* variant allele frequencies for HU and IFN-α. The cumulative incidence of thrombosis was 2% for both HU and IFN-α at 24 months. Grade 3/4 treatment-related adverse events were more frequent with IFN-α. The conclusion was that both agents were effective in normalising blood counts and limiting the number of thrombotic events in patients with high-risk ET/PV.

Reference: Blood 2022;139(19):2931-41
Abstract

Lupus anticoagulant test persistence over time and its associations with future thrombotic events

Authors: Colling M et al.

Summary: LATS (Lupus Anticoagulant and Thrombosis Study) is an ongoing Austrian prospective observational cohort study that aims to explicate the prevalence and prognostic implications of a negative lupus anticoagulant (LA) test in patients persistently positive for LA. Analysis of a cohort of 164 patients (median age 41 years; 84% female) with an almost ten-year follow-up found that approximately three-quarters (72%) of patients were consistently LA positive with the other quarter (28%) testing LA negative at least once but most (68%) subsequently testing positive again. The overall 10-year incidence of ATE was 14% (12% in patients with stable LA status at 1.5 years and 0% in patients with ≥ one negative LA test), VTE was 20% (18% vs 17%), overall thrombosis 34% (31% vs 18%) and mortality 14% (12% vs 17%). Multistate time-to-event modelling analysis with multivariable adjustment found no association between an LA negative test with risk of thrombosis (ATE, VTE or total thrombosis) or death and this finding was consistent on sensitivity analyses.

Comment: This is an interesting study that may guide our clinical practice in how to deal with patients who were LA positive at initial presentation and then become LA negative, at least once, during a long follow-up period. In this report, the period of observation was considerable at a median of 9.2 years. LA was the first antibody described in antiphospholipid syndrome (APS) and later additional antibodies, most notably anticardiolipin antibodies and anti–glycoprotein-I antibodies (aβ2GPI) were identified. Of these, LA has positivity having the strongest association with APS-defining events (arterial and venous thrombotic events and/or pregnancy complications). Persistence of positive serology, defined currently as 12 weeks, is associated with thrombotic risk. But there is limited prospective data on the variability of APL over time and on the clinical implications of this variability, specifically if it is predictive of future thrombotic events or mortality. This data in this report is from a single-centre, biobank-based prospective observational cohort study that enrolled adult patients who repeatedly test positive for LA, with or without history of thrombosis or pregnancy complications. Clinical and laboratory follow-up was every six months for the first five years and annually thereafter. An important finding was that the cohort with one LA negative test, 68% subsequently developed an LA positive result in a median time of one year. A negative LA test did not change the prospective risk of arterial and venous thrombosis, or mortality. The authors also showed that a negative LA test did not predict loss of anticardiolipin antibodies or anti–glycoprotein-I antibodies IgM or IgG.

Reference: Blood Adv 2022;6(10):2957-66
Abstract

Selective inhibition of activated protein C anticoagulant activity protects against haemophilic arthropathy in mice

Authors: Magisetty J et al.

Summary: This preclinical murine-based work from a group at the University of Texas Health Science Centre at Tyler in Texas, USA, aimed to investigate what functions of activated protein C (APC) – anticoagulant action or signalling – contributes to haemophilic arthropathy in haemophilia. *In vivo* studies in a mouse model of haemophilia A (FVIII-/-) haemophilic arthropathy using anti- endothelial cell protein C receptor (EPCR) monoclonal antibodies with APC anticoagulant blocking activity ± APC signalling blocking activity (MPC1609 & MAPC1591 antibodies) the authors showed that selective inhibition of APC anticoagulation only with signalling function maintained improved haemophilic arthropathy. Both antibodies demonstrated comparable APC anticoagulant inhibition and restoration of acute blood clotting function after injury.

Comment: Patients with haemophilia with factor V–Leiden mutation, which confers partial resistance to the cleavage by APC, have reduced severity of bleeding. This has led to an interest in blocking APC to mitigate the consequences of joint bleeding. Data that lays more foundation to this hypothesis is the earlier work by these authors showing that EPCR blocking antibody blocks the binding of both protein C and APC to the EPCR and thus prevents generation of APC as well as APC-mediated cytoprotective signalling (EPCR presents protein C to thrombin for optimal conversion to APC). APOC has dual actions: an anticoagulant effect via proteolysis of factor Va and also a cytoprotective role. It is preferable for the cytoprotective activity to be retained while the anticoagulant activity is inhibited. The authors thus use two antibodies to block APC: the MPC1609 monoclonal antibody that inhibits anticoagulant plus signalling properties of APC, or the MAPC1591 antibody that only blocks the anticoagulant activity of APC. At near saturating concentrations, no significant differences were observed between the two antibodies in inhibiting APC anticoagulant activity. While MPC1609 fully attenuated APC's anti-inflammatory effect as measured by its ability to suppress interleukin (IL)-1b–induced expression of IL-6. In contrast, MAPC1591 did not show this effect. The importance of this observation is that haemophilic arthropathy shows features of inflammation and suppressing inflammation (as APC does) has been previously shown to reduce joint damage. The authors demonstrated that administration of MAPC1591, and not MPC1609, reduces joint bleeding, joint oedema and synovitis in haemophilia A mice following needle puncture joint injury. This is achieved by MAPC1591 by reducing chondrocyte apoptosis, cartilage degeneration, and blocking joint bleed–induced elevated IL-6 expression and vascular leakage in the synovium. It is also important to note that this protective effect could be potentially achieved for both haemophilia A and B.

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Abstract

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