Thrombosis & Haemostasis Research Review™

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Issue 17 - 2021

In this issue:

Abbreviations used in this issue:

ATRA = all-trans retinoic acid; **BRVO** = branch retinal vein occlusion; **CAR** = chimeric antigen receptor; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **CRVO** = central retinal vein occlusion; **DVT** = deep vein thrombosis; **FVII/IX** = factor VII/IX; **HR** = hazard ratio; **ICANS** = immune effector cell–associated neurotoxicity syndrome; **IRT** = item response theory; **ITP** = immune thrombocytopenia; **LD-RTX** = low-dose rituximab; **OR** = odds ratio; **PE** = pulmonary embolism; **PROMIS** = Patient-Reported Outcomes Measurement Information System; **PROs** = patient-related outcomes; **SARS-CoV-2** = severe acute respiratory distress syndrome coronavirus 2; **VITT** = vaccine-induced immune thrombocytopenia and thrombosis; **VTE** = venous thromboembolism.

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Welcome to issue 17 of Thrombosis and Haemostasis Research Review.

In our final edition for this year, we look at the clinical features of vaccine-induced immune thrombocytopenia related to the AstraZeneca severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) vaccine as reported in *The New England Journal of Medicine*, the incidence and risk factors associated with bleeding and thrombosis following chimeric antigen receptor (CAR) T cell therapy and a pre-defined sub-analysis of the phase 3 CARAVAGGIO trial reveals that oral apixaban is non-inferior to subcutaneous dalteparin for both incidental and symptomatic venous thromboembolism (VTE) due to cancer without compromising on risk for bleeding. An exploratory substudy of the MARINER trial concludes that extended thromboprophylaxis with rivaroxaban after hospital discharge has a favourable risk: benefit profile in elderly, acutely unwell patients and may result in wider utilisation of direct-acting oral anticoagulants in this population, especially given the lack of increased bleeding risk. Finally, results from the NuProtect study find that simoctocog alfa has lower immunogenicity than other recombinant factor VIII (FVIII) products in previously untreated patients with severe haemophilia A, indicating it may be suitable for paediatric use and a microsimulation study from the US finds gene therapy for severe haemophilia B cost-effective compared to on-demand factor IX (FIX) replacement and primary FIX prophylaxis.

We hope you find these and the other selected studies interesting, wish you a happy and safe holiday period and look forward to sharing more editions of Thrombosis & Haemostasis Research Review with you in 2022.

Kind Regards,

Professor Harshal Nandurkar

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Clinical features of vaccine-induced immune thrombocytopenia and thrombosis

Authors: Pavord S et al.

Summary: This prospective cohort study from the UK reports clinical features, outcomes and prognostic factors for the first 220 cases of definite or probable vaccine-induced immune thrombocytopenia and thrombosis (VITT) seen in the country in the *New England Journal of Medicine*. VITT, also called vaccine-induced prothrombotic immune thrombocytopenia or thrombosis with thrombocytopenia syndrome, is a novel and rare but severe syndrome of thrombosis and thrombocytopenia associated with the adenovirus vector ChAdOx1 nCov-19 (AstraZeneca) vaccine encoding spike proteins 1-4 of SARS-CoV-2. A panel of expert haematologists identified 220 cases of definite/probable VITT (n=170 and n=50, respectively; probable diagnoses mostly due to missing data) in patients who presented to any UK hospital in a just over two-month period between March 22 and June 6, 2021 with thrombosis, thrombocytopenia, elevated D-dimer levels and antibodies to PF4 following SARS-CoV-2 vaccination. The median age of the cohort was 48 years (range, 18-79), presentation to hospital was at a median of 14 days after first AstraZeneca vaccine dose (range, 5-48 days) and the cohort was roughly half male (54% female). The authors estimated an approximate incidence of VITT of ≥ 1:100,000 and ≥ 1:50,000 in people ≥ 50 years of age and < 50 years of age, respectively. The mortality rate was 22%. Significantly elevated odds of death were found with cerebral venous sinus thrombosis, decreased platelet count, increased D-dimer levels and decreased fibrinogen levels (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.4-5.2; OR 1.7 per every 50% decrease in baseline platelet count; OR 1.2 for every increase of 10,000 fibrinogen-equivalent units in the baseline D-dimer level and OR 1.7 for every 50% decrease in the baseline fibrinogen level, respectively). Baseline platelet count and intercranial haemorrhage were both identified as independent risk factors for death. In patients with platelet counts < 30,000/mm^3 plus intracranial haemorrhage the mortality rate was close to three-quarters (73%).

Comment: The interest in this paper is that it is one of the largest cohorts of VITTs reported and this report is limited to the UK, there is the possibility that access to care was similar for all. It is interesting to note the overall mortality rate of 22%. Our experience in Australia is that VITT mortality was much lower and the recently announced MRFF trial in local VITT (Huyen Tran and colleagues) will shed more light. Another take-home point here is that while thrombocytopenia, hypofibrinogenemia and elevated D-dimers are recognised parameters in making a VITT diagnosis, this paper quantifies a mortality risk to the severity of these parameters.

Reference: N Engl J Med 2021;385(18):1680-89
Abstract

Independent commentary by Prof Harshal Nandurkar, who 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).

Incidence and risk factors associated with bleeding and thrombosis following chimeric antigen receptor T-cell therapy

Authors: Johnsrud A et al.

Summary: Retrospective analysis of a single-centre cohort of patients in the US who received CAR T cell therapy for lymphoma or leukaemia has found a clinically significant bleeding rate of 9%. Patients (n=127) who underwent CAR T cell therapy, predominantly axicabtagene ciloleucel (70%), following lymphodepleting chemotherapy with cyclophosphamide/fludarabine for relapsed/refractory large B-cell lymphoma or B-cell acute lymphoblastic leukaemia between 2017 and 2020 were included in the study. The cohort were heavily pre-treated with a median of three prior lines of therapy including an autologous stem cell transplant. Rates of clinically significant bleeding and thrombosis (≥ grade 2 according to modified World Health Organization bleeding criteria and ≥ grade 2 using Common Terminology Criteria for Adverse Events or requiring intervention, respectively) within three-months of CAR T cell infusion were 9.4% and 6.3% with median onset of 17.5 and 29 days, respectively. Bleeding events included gross haematuria, soft tissue bleeding, subdural hematoma, gastrointestinal haemorrhage and haemoptysis. Signs of disseminated intravascular coagulation were observed with bleeding. Significantly higher rates of clinically significant bleeding were found in patients with grade ≥ 3 immune effector cell–associated neurotoxicity syndrome (ICANS; 50% vs 15%; p=0.01), thrombosis (50% vs 16%; p=0.04), prolongation of prothrombin time, hypofibrinogenemia or elevated D-dimer. The authors concluded that close monitoring for up to one month after CAR T cell infusion is necessary for patients with low baseline platelet counts and high-grade ICANS.

Comment: In this study both bleeding (9.4%) and thrombotic (6.3%) events were reported in the first three months after CAR T cell therapy. All bleeding events occurred within the first 30 days after CAR T infusion, and more than 50% occurred after patients were discharged, illustrating the importance of close follow-up. Although several baseline characteristics were associated with bleeding risk on univariate analysis (age, low baseline platelet count, and high tumour burden, as indicated by elevated LDH and history of bleeding), low baseline platelet count was the only factor predictive of increased bleeding risk on multivariate analysis. Cytokine release syndrome was not associated with increased bleeding risk but severe ICANS demonstrated this association, suggesting that patients with low baseline platelets and grade 3 or higher ICANS should be particularly closely monitored with complete blood count and fibrinogen levels, even after hospital discharge until one month after CAR T therapy. Support with blood products including platelet and/or cryoprecipitate and fresh-frozen plasma infusions, was sufficient to resolve their active haemorrhage. The thrombotic events observed were attributable more to concurrent risk factors (older age, active malignancy, chemotherapy, and hospitalization) than to direct toxicity of CAR T therapy and anticoagulation could be given safely.

Reference: Blood Adv 2021;5(21):4465-75
Abstract

Validation of PROMIS Profile-29 in adults with haemophilia in the Netherlands

Authors: van Balen E et al.

Summary: Erna van Balen and colleagues from Leiden University Medical Centre conducted a cross-sectional study to validate the Dutch-Flemish version of the Patient-Reported Outcomes Measurement Information System (PROMIS) Profile-29 questionnaire in Dutch haemophilia patients. A total of 700 adult males with mild to severe congenital haemophilia A or B with levels of factor VIII or IX <0.40 IU/ml were accrued to the study from six Dutch haemophilia treatment centres. Confirmatory factor analysis revealed a sufficient structural validity, internal consistency and construct validity of each subscale of the PROMIS Profile-29 in correlation to the corresponding RAND-36 measure of health-related quality of life and the Haemophilia Activities List domains. The PROMIS Profile-29 was found to be an accurate method to evaluate patient-related outcomes (PROs) in haemophilia.

Comment: PROs are any aspect of a patient's health that comes directly from the patient without interpretation of the patient's responses by a physician or anyone else. These assessments are an important tool to gauge the impact of interventions in quality of life. There have been several haemophilia-specific PRO assessment tools. Proifile-29 question set is based on Item Response Theory (IRT), which has several advantages over other generic instruments. First, instruments using IRT-based scoring take the difficulty of items into account, thereby providing more valid and reliable scores. IRT-based item banks, consisting of large sets of questions, can be used as short forms of any length (consisting of the best performing items from an item bank) or as computerised adaptive tests. PROMIS, developed in the United States, is the most extensively validated measurement system of item banks in the world. As a generic tool, PROMIS Profile-29 has the advantage of making results comparable across diseases and the general population. In this paper, the PROMIS Profile-29 set was validated in a Dutch haemophilia cohort. Responses were analysed from 770 participants (out of the 1,746 invited to participate). Structural validity, internal consistency and construct validity was observed of the PROMIS Profile-29 subscales of physical function, depression and sleep disturbance. Construct validity was also sufficient for anxiety, fatigue and pain intensity. This study is notable as it can create a platform for comparison of outcomes between haemophilia cohorts of most countries and can identify gaps in service or lessons to be learnt from those doing better.

Reference: J Thromb Haemost 2021;19(11):2687-701
Abstract

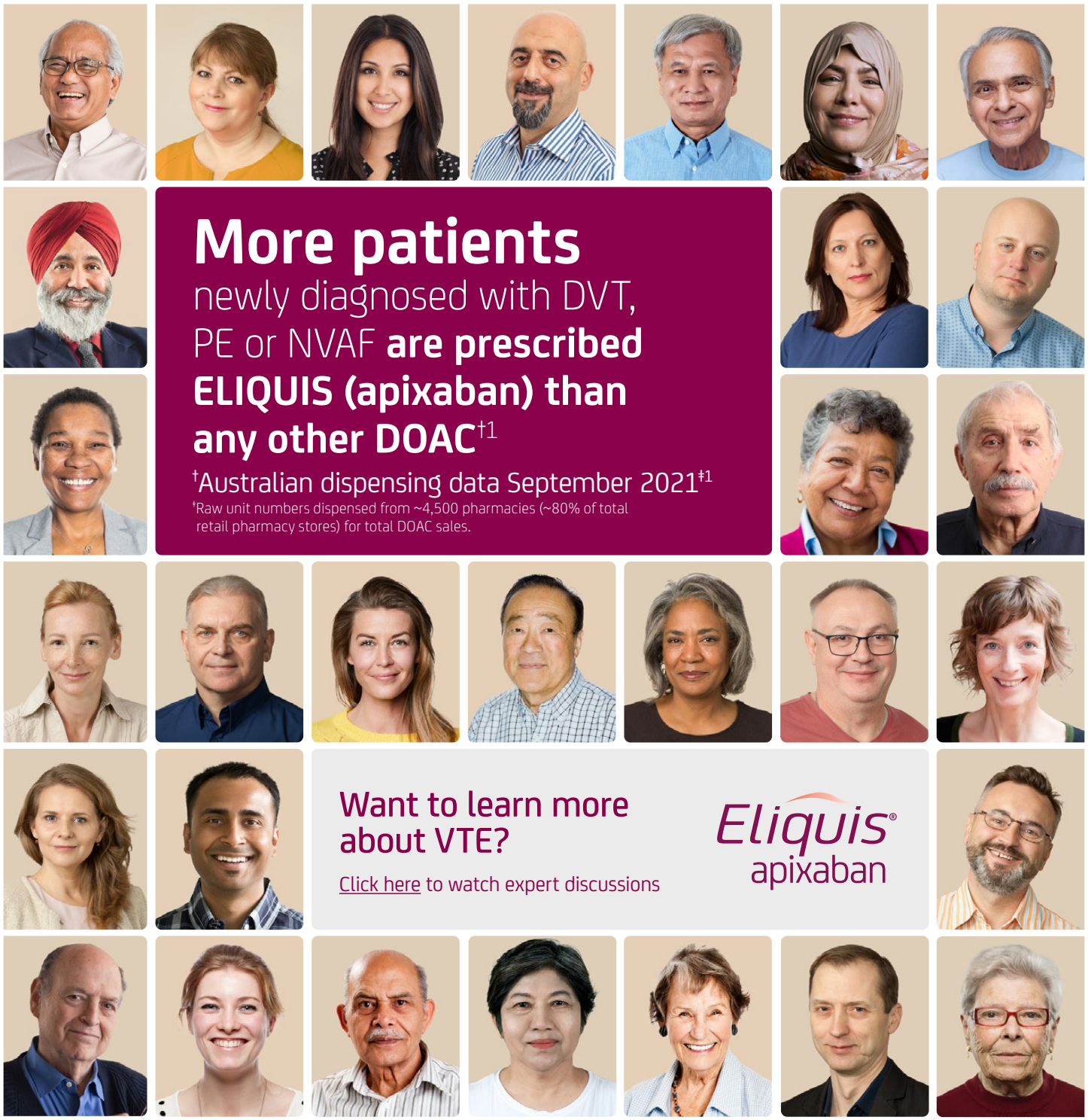
Clinical characteristics and outcomes of incidental venous thromboembolism in cancer patients: Insights from the Caravaggio study

Authors: Giustozzi M et al.

Summary: Data from the Italian phase 3 CARAVAGGIO trial (NCT03045406) demonstrated a non-inferior efficacy of oral apixaban to subcutaneous dalteparin for cancer-related VTE (Agnelli G et al. *N Engl J Med.* 2020;382[17]:1599-1607). This predefined sub-analysis of the trial in *Journal of Thrombosis & Hemostasis* assessed clinical outcomes and efficacy of the two anticoagulants according to type of VTE – incidental or symptomatic. Per the study protocol, most of the study population (80% of N=1,155) consisted of patients with symptomatic VTE with the proportion of patients with incidental VTE (detected on imaging for other indication without clinical suspicion of acute proximal deep vein thrombosis [DVT] or pulmonary embolism [PE]) capped at 20%. Three-quarters of patients with incidental VTE experienced PE ± DVT as their index VTE event, significantly more than patients with symptomatic VTE (76.5% vs 499%) who were more likely to experience DVT as their primary event (50.1% vs 23.5%). A greater proportion of patients with incidental VTE had no impact on daily functioning (Eastern Cooperative Oncology Group performance score of 0, 41.3% vs 28.2%). Greater rates of colorectal cancer were seen in the presence of incidental VTE and haematological malignancies in the presence of symptomatic VTE. Rates of recurrent VTE (composite of proximal DVT of the lower or upper limbs plus PE) over six-months were numerically lower in patients with incidental versus symptomatic VTE but did not reach statistical significance (4.3% vs 7.4%). Risk of major bleeding events and all-cause mortality were comparable between patients with incidental and symptomatic VTE (5.2% vs 3.6% and 26.5% vs 24.5%, respectively; neither statistically significant). Apixaban maintained a non-inferior efficacy to dalteparin for the primary outcome measure of recurrent VTE in both incidental and symptomatic VTE (hazard ratio [HR] 0.41; 95% CI, 0.11-1.56 and HR 0.73; 95% CI, 0.45-1.19) without increasing the risk for major bleeding (HR 0.96; 95% CI, 0.31-2.96 and HR 0.93; 95% CI, 0.47-1.83; p for interaction 0.96).

Comment: The approach to the management of incidentally detected cancer-associated VTE is less straightforward. This paper is a predefined sub-analysis of the CARAVEGGIO study to investigate the clinical features and outcomes of incidental and symptomatic VTE in patients with cancer and the relative efficacy and safety of apixaban and dalteparin in patients with incidental and symptomatic VTE. The inclusion of incidental VTE was limited to 20% of the total enrolment as a predefined criterion. The principal take home messages were that despite anticoagulation, cancer patients with incidental VTE have a considerable rate of recurrent VTE (4.3%) though the six-month risk of recurrent VTE is numerically lower compared to patients with symptomatic VTE (7.4%). Another important point was that the rate of major bleeding was numerically higher in patients with incidental VTE (5.2%) than patients with symptomatic VTE (3.7%). As an explanation, here was a higher proportion of patients with colorectal cancer in patients with incidental VTE and it is well recognised that luminal cancers have a higher association with bleeding on anticoagulation. The risk of all-cause mortality was similar between patients with symptomatic and incidental VTE. This finding is consistent with previous studies and indicates that there is not a difference in terms of prognosis between these two groups of patients. These observations justify the recommendations by several guidelines to manage incidental VTEs with adequate anticoagulation.

Reference: J Thromb Haemost 2021;19(11):2751-59
Abstract



PBS Information: Authority required (STREAMLINED). Refer to PBS Schedule for full authority information.
PBS codes: NVAF – 4269 and DVT/PE initial treatment – 4098 (DVT); 5098 (PE). Other PBS codes differ – please refer to PBS Schedule.

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DOAC, direct-acting oral anticoagulant; DVT, deep vein thrombosis; NVAF, non-valvular atrial fibrillation; PE, pulmonary embolism; VTE, venous thromboembolism.
Reference: 1. NostraData Pty Ltd Hawthorn, Vic. Data on file September 2021. ©2021. Bristol Myers Squibb Australia Pty Ltd. ABN 33 004 333 322. Level 2, 4 Nexus Court, Mulgrave, Vic 3170. Pfizer Australia Pty Ltd. 151 Clarence Street, Sydney, NSW 2000.
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Rivaroxaban for extended thromboprophylaxis in acutely ill medical patients 75 years of age or older

Authors: Ageno W et al.

Summary: Ageno et al conducted an exploratory substudy of data from the MARINER trial (NCT02111564) to ascertain if extended thromboprophylaxis with rivaroxaban has a favourable risk: benefit profile in elderly, acutely unwell patients. The international Janssen Research & Development sponsored double blind phase 3 trial assessed a 45-day post-hospitalisation treatment with oral rivaroxaban versus placebo in patients at high-risk for VTE (modified International Medical Prevention Registry on Venous Thromboembolism score ≥ 4 or 2-3 plus a plasma D-dimer level of more than twice the upper limit of the normal range) with the primary outcome measure a composite of symptomatic VTE or VTE-related death. A total of 12,019 patients hospitalised for heart failure, respiratory insufficiency, stroke or infectious or inflammatory disease for between three and 10 consecutive days were randomised to rivaroxaban or placebo on discharge with overall results finding lower rates of the primary outcome with rivaroxaban that did not translate into a significantly reduced risk (0.83% vs 1.10%; HR 0.76; 95% CI, 0.52-1.09; p=0.014). While older patients (≥75 years of age) experienced two-fold higher rates of the primary outcome than younger patients, consistent with the overall results, rates of symptomatic VTE or VTE-related death were numerically, but not significantly, lower with rivaroxaban prophylaxis versus placebo regardless of age (≥ 75: 1.2% vs 1.6%, HR 0.73, 95% CI 0.43-1.22; < 75: 0.6% vs 0.8%, HR 0.78, 95% CI 0.46-1.32). Both age groups had a low incidence of major bleeding events, the primary safety outcome measure, that was not significantly higher in rivaroxaban versus placebo arms (≥ 75: 0.3% vs 0.1%; HR 3.45; 95% CI, 0.72-16.61; < 75; 0.3% vs 0.2%; HR 1.44; 95% CI, 0.55-3.77).

Comment: Acutely ill medical patients are at increased risk for VTE as in-patients and after discharge. International guidelines recommend pharmacologic prophylaxis during hospitalisation for an acute medical illness, but not after hospital discharge because of the uncertain benefit of extended treatment. Advanced age, especially ≥75 years is an independent risk factors for VTE in acutely ill medical patients, but advanced age is also associated with an increased bleeding risk. MARINER was a randomised, double-blind trial that compared once-daily oral rivaroxaban 10 mg (7.5 mg if creatinine clearance was between 30 and 49 ml/minute) with placebo for 45 days and conducted at 671 centres in 36 countries. The primary hypothesis of the MARINER study was that rivaroxaban was superior to placebo for the prevention of the composite outcome of symptomatic VTE and VTE-related death. The incidence of VTE and death was higher in patients aged ≥75 years, while efficacy with rivaroxaban was consistent across all age groups and incidence of major bleeding was low with rivaroxaban as compared to placebo in both age groups. These data could lead to wider utilisation of direct-acting oral anticoagulants (DOACs) in acutely ill medical patients, particularly patients aged ≥75 years, post discharge to prevent VTE without fear of increased bleeding risk.

Reference: J Thromb Haemost 2021;19(11):2772-80
Abstract

Association of prehospital antiplatelet therapy with survival in patients hospitalized with COVID-19

Authors: Chow J et al.

Summary: This propensity score-matched analysis based on a large US observational cohort study reports a protective effect for pre-hospital antiplatelet therapy against coronavirus disease 2019 (COVID-19)-related mortality. From over 30,000 adult patients (n=34,675) aged over 50 years hospitalised for COVID-19 between February to September 2020, 17,347 were propensity-score matched and included in the analysis. Compared to patients who did not receive pre-hospitalisation antiplatelet therapy (n=10,566) those who received antiplatelet treatment had a lower incidence of in-hospital mortality that conferred a 19% reduced risk of death (18.9% vs 21.5%; HR 0.81; 95% CI, 0.76-0.87; p<0.005). The authors noted that prospective trial data is required to fully elucidate the benefit of antiplatelet therapy for COVID-19.

Comment: COVID-19 is not only a respiratory disease but also a disease characterized by endothelial cell dysfunction. Patients with severe COVID-19 are now well known to have hypercoagulability and an increased risk for VTE and arterial thrombosis. Anticoagulation (standard or intermediate-dose) prophylaxis is now widely used. Unusual features such as increased megakaryocytes in multiple organs on autopsy in COVID-19 patients, and also the high rate of thromboembolic events, raises the hypothesis that there may be a role for antiplatelet therapy in the management of COVID-19. Aspirin was the most common antiplatelet agent administered (83.9%), followed by clopidogrel (8.2%), ticagrelor (0.3%) and prasugrel (0.1%). The independent variables in the propensity score model included age, gender, body mass index, race, chronic kidney disease, asthma, chronic obstructive pulmonary disease, heart disease, hypertension, diabetes, prior stroke and prior PE. A 2.6% absolute reduction in mortality was noted with antiplatelet therapy. With the exception of epistaxis, this study did not find an increased risk of serious haemorrhagic complications such as cerebral, gastrointestinal, and pulmonary haemorrhage. This study suggests that antiplatelet drugs are associated with a modest reduction in mortality in an older, diverse patient population with relatively high rates of baseline cardiovascular comorbidities.

Reference: J Thromb Haemost 2021;19(11):2814-24
Abstract

Simoctocog alfa (Nuwiq) in previously untreated patients with severe haemophilia A

Authors: Liesner R et al.

Summary: Final results of the NuProtect study (NCT01712438), published in *Thrombosis and Haemostasis*, demonstrate that simoctocog alfa (Nuwiq®; Octapharma) treatment elicits low rates of inhibitor development in previously untreated patients with severe haemophilia A, indicating it may be suitable for paediatric patients. The trial enrolled 108 (median age 12 months) male treatment-naïve patients with severe haemophilia A (blood clotting protein FVIII coagulant activity < 1%; no prior exposure to FVIII concentrates or blood products) from centres across North America and Europe with a 100-exposure day or maximum five-year follow-up. An immunogenetic response was reported in just over one-quarter of evaluable patients (28/105) with high-titre inhibition in 16.2% (≥ 5 BU/mL). In almost half of participants who had a low-titre inhibitor response, antibodies spontaneously reduced to undetectable levels. Development of treatment inhibitor antibodies was restricted to patients with null *F8* mutations. The authors noted that the rate of inhibitor development was lower compared to that published for hamster-cell-derived recombinant FVIII product therapy. An extension phase study (NCT01992549) is now underway to evaluate long-term inhibitor development in patients who completed NuProtect

Comment: Inhibitors typically develop in up to 40% of patients and are widely considered the most serious treatment-related complication of haemophilia A. Remaining free from inhibitors is important to enable effective FVIII treatment for bleeding events or surgery, as well as to remain eligible for potential future treatment options such as gene therapy. Simoctocog alfa is manufactured using a human cell line without chemical modification or protein fusion, with the aim of reducing inhibitor development by replicating the native human FVIII protein and avoiding incorporation of potentially immunogenic elements of animal cell origin. Simoctocog alfa retains a high binding affinity for von Willebrand factor. These properties of simoctocog alfa may lower its immunogenic potential by shielding potentially antigenic epitopes from recognition by the immune system. Patients received simoctocog alfa for prophylaxis or on-demand treatment, as well as for the treatment of breakthrough bleeding episodes during prophylaxis and to cover surgical procedures. The primary endpoint of the study was the incidence of anti-FVIII inhibitors after simoctocog alfa administration. Patients with large *F8* deletions (n=5) had the highest inhibitor incidence (80%). Patients with a family history of inhibitors (n=13) had a higher incidence of inhibitors (46.2%), compared with those without. In comparison, recently published reports show that with turoctocog alfa (NovoEight), 25 (43.1%) developed inhibitors of which 16 (27.6%) were high-titre and in another study with single-chain rFVIII (Afstyla), 52% developed inhibitors of which 26% were high-titre. Thus, the overall risk of inhibitor development was lower with simoctocog as compared to other recombinant FVIII products.

Reference: Thromb Haemost 2021;121(11):1400-08
Abstract

Real-life management of central and branch retinal vein occlusion: A seven-year follow-up study

Authors: Arrigo A et al.

Summary: Interventional, retrospective analysis of long-term outcomes after intravitreal treatment for retinal vein occlusion from a single Italian centre (Department of Ophthalmology, IRCCS San Raffaele Hospital, University Vita-Salute in Milan, Italy) reveals significant improvements in visual acuity and central macular thickness. Analysis was based on 313 eyes that underwent anti-vascular endothelial growth factor (VEGF)/dexamethasone treatment for central or branch retinal vein occlusion (CRVO, n=178; BRVO, n=135). The mean number of treatments was 10.7 for CRVO and 9.8 for BRVO. At a mean follow-up of almost four-years (maximum seven years) eyes with either type of vein occlusion had logarithm of the minimum angle of resolution (LogMAR) improvements of approximately 0.2 (CRVO, 0.57 to 0.41 LogMAR; BRVO, 0.53 to 0.30 LogMAR; both p<0.01) and central macular thickness reductions of 137 µm (both 585.54 to 447.88 µm; p<0.01). Maximal improvements were observed at one- and two-years for CRVO and BRVO, respectively after which improvements were maintained until the end of follow-up. Significantly worse outcomes were reported in cases of ischemia.

Comment: This study analysed the seven-year follow-up real-life outcomes of eyes affected by BRVO and CRVO treated in an Italian referral centre and demonstrates significant improvement in the parameters of visual acuity and central macular thickness with eyes affected by both CRVO and BRVO with both anti-VEGF and dexamethasone. It is recognised that ischemic CRVO has been reported to fare badly both under anti-VEGF and dexamethasone treatments and that observation was also confirmed here. They observed that CRVO needed higher number of treatments throughout the follow-up if compared with BRVO.

Reference: Thromb Haemost 2021;121(10):1361-66
Abstract

The cost-effectiveness of gene therapy for severe haemophilia B: a microsimulation study from the United States perspective

Authors: Bolous N et al.

Summary: According to results of a microsimulation study from a US third-party payer perspective published in *Blood* adeno-associated virus–mediated FIX deficiency-Padua gene therapy for severe haemophilia B is more cost-effective than on-demand FIX replacement and primary FIX prophylaxis. Researchers from St Jude Children's Research Hospital in Tennessee, USA created a Markov model with a time horizon spanning from 18 years of age to death with a quality-adjusted life-year threshold of US$150,000. Compared to either standard or extended half-life FIX products gene therapy was more cost-effective and this remained true in a hypothetical situation where factor concentration price was discounted to 20%. Over 90% (92/102) of one-way sensitivity analyses were consistent in this finding.

Comment: The cost-effectiveness of on-demand, prophylactic coagulation factor support versus gene transfer treatment options remains poorly described. This report is a comprehensive, cost-effectiveness analysis by comparing the cost and potential cost-effectiveness of adeno-associated virus-FIX–Padua gene therapy for severe haemophilia B (<1% factor activity) versus those of on-demand and prophylactic factor replacement therapies. The long-term effectiveness of gene therapy was varied in eight different scenarios with different peak levels of FIX and different decrement patterns. It is too complicated to detail the economic analysis in this commentary. But is suffices to say that at least in the health system economy of the USA, adeno-associated virus-mediated gene therapy for severe haemophilia B seemed dominant over prophylaxis and on-demand factor replacement therapies across the drivers of time horizon (18 years till death), gene therapy durability, price of gene therapy and the unit cost of factor concentrates. It will be interesting to do a similar analysis in the Australian health system; the cost of health encounters is different here than in the USA, but it is likely that gene therapy will give similar cost effectiveness and increased quality of life.

Reference: Blood 2021;138(18):1677-90
Abstract

All-trans retinoic acid plus low-dose rituximab vs low-dose rituximab in corticosteroid-resistant or relapsed ITP

Authors: Wu Y et al.

Summary: Adding all-trans retinoic acid (ATRA) to a low-dose rituximab (LD-RTX) treatment regimen improves response rate and is more durable than LD-RTX monotherapy for corticosteroid-resistant or relapsed immune thrombocytopenia (ITP) according to a Chinese phase 2 trial sponsored by Peking University People's Hospital. The trial assessed the combination on the hypothesis that agents with differing mechanisms of action may act synergistically by dual targeting of platelet production and destruction. A total of 168 patients with confirmed ITP and a platelet count < $30x10^9$/L after an inadequate response to front-line corticosteroids were enrolled from centres across China and randomised 2:1 to LD-RTX ± ATRA. At one-year, combination therapy resulted in a 20% higher overall response and six-month sustained response rate (80% vs 59%; between group difference of 0.22; 95% CI, 0.07-0.36 and 61% vs 41%; between group difference 0.20; 95% CI, 0.04-0.35). Dry skin, headache and dizziness were adverse events reported in the combination arm.

Comment: The key points are that the combination of ATRA and LD-RTX could achieve an 80% overall response rate and a 61% sustained response rate. Thus, the combination of ATRA plus LD-RTX regimen is a promising treatment option for corticosteroid-resistant or relapsed ITP. It has been demonstrated that the efficacy of ATRA in ITP is due to its effects on inducing megakaryocyte differentiation and maturation, as well as its immunomodulatory effects. There are other earlier studies showing superiority of ATRA over danazol and prednisolone. RTX was given at a fixed dose of 100 mg weekly for six weeks. For the combination group, ATRA was given concomitantly orally at 20 mg/m^2 daily for 12 weeks. The treatment period lasted for 12 weeks for patients in the combination group and for six weeks for patients in the monotherapy group. Adding ATRA to the LD-RTX regimen improved the 12-month remission rate from 13% to 29%. ATRA-related adverse events primarily included dry skin and headache or dizziness, and the manifestations were mild and did not require additional treatment. There will be more studies to follow in other centres to confirm these observations.

Reference: Blood 2021; Oct 19 [Epub ahead of print]
Abstract

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