Haematology RESEARCH REVIEW™

Making Education Easy

Issue 38 – 2021

In this issue:

Abbreviations used in this issue

DOAC = direct oral anticoagulant
ELISA = enzyme-linked immunosorbent assay
FVIII = factor VIII
HIT = heparin-induced thrombocytopenia
MI = myocardial infarction
PE = pulmonary embolism
PF4 = platelet factor-4
RR = risk ratio
SVT = splanchnic vein thrombosis
VTE = venous thromboembolism

Welcome to issue 38 of Haematology Research Review.

A paper from JAMA introduces the selected research for this issue, with a noninferiority trial of a restrictive versus liberal transfusion strategy for patients with acute MI and anaemia. This is followed by an analysis of data pooled from the HAVEN 1–4 studies to report on the long-term efficacy, safety and pharmacokinetics of emicizumab for haemophilia A prophylaxis. Thrombotic complications of vaccines for COVID-19 are the subject of two papers, including one from the N Engl J Med describing the clinical and laboratory characteristics of 11 patients who developed thrombosis or thrombocytopenia following vaccination. The issue concludes with a systematic review and meta-analysis investigating the impact of thrombolysis on survival in intermediate-risk patients with PE.

We hope you find the research selected for this issue interesting, and we invite you to send us your comments and feedback.

Kind regards,

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Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia

Authors: Ducrocq G et al., for the REALITY Investigators

Summary: The open-label, noninferiority REALITY trial randomised patients with MI and a haemoglobin level of 7–10 g/dL to a transfusion strategy that was restrictive (triggered by haemoglobin level ≤8 g/dL; evaluable n=342) or liberal (triggered by haemoglobin level ≤10 g/dL; evaluable n=324); 35.7% and 99.7% of the respective restrictive and liberal strategy groups received transfusions. The 30-day major adverse cardiovascular event rate (composite of all-cause death, stroke, MI recurrence and emergency revascularisation due to ischaemia) did not differ significantly between the restrictive versus liberal strategy arms (11.0% vs. 14.0%; relative risk 0.79 [1-sided 97.5% CI 0.00, 1.19, which met the noninferiority criterion]). The proportions of participants from the respective restrictive and liberal strategy arms who died from any cause were 5.6% and 7.7%, the proportions who experienced recurrent MI were 2.1% and 3.1%, the proportions who required emergency revascularisation due to ischaemia were 1.5% and 1.9%, and the proportion who experienced a nonfatal ischaemic stroke was 0.6% in both groups.

Comment (LY): MI patients have been the last bastion of liberal transfusion strategies based on data showing worse outcomes with anaemia and the instinctive belief that a struggling myocardium must need a higher haemoglobin and oxygen carrying capacity. This trial appears to go some way to disproving this hypothesis. The mean haemoglobin level in both groups was around 90 g/L at randomisation. Almost two-thirds of the restrictive group did not get transfused versus virtually all the liberal group and more than twice the number of units was given to the liberal arm. The study was powered for noninferiority of the restrictive arm, not superiority; noninferiority was convincingly demonstrated, but there were numerically more adverse cardiac/ischaemic events and deaths in the liberal arm, suggesting a restrictive strategy may be better in this group. Other advantages are avoiding the risks of transfusion and of course the cost, suggesting this study should be taken up by coronary-care units.

Reference: JAMA 2021;325:552–60
Abstract

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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. **For full bio CLICK HERE**

Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies

Authors: Callaghan MU et al.

Summary: These researchers pooled data from 401 paediatric and adult patients with haemophilia A, with/without FVIII inhibitors, from the phase 3 HAVEN 1, HAVEN 2, HAVEN 3 and HAVEN 4 studies to explore the long-term efficacy, safety and pharmacokinetic profiles of prophylactic emicizumab. A model-based treated annualised bleeding rate was 1.4 during a median efficacy period of 120.4 weeks. When 24-week treatment intervals were analysed, the annualised bleeding rate declined and then stabilised at <1, with a rate of 0.7 at weeks 121–144. No treated bleeds were recorded in 82.4% of participants, 97.6% had ≤3 treated bleeds and 94.1% had no treated target joint bleeds. A substantial reduction in bleeding into target joints was also apparent. Emicizumab was well tolerated, with no participants discontinuing due to adverse events except for five previously reported. The data cutoff for this analysis encompassed MI and a venous device occlusion, along with the previously described three thrombotic microangiopathies and two thromboembolic events (all associated with activated prothrombin complex concentrate use).

Comment (PO): Emicizumab is a bispecific antibody that mimics activity of FVIII in the tenase complex of the coagulation cascade. It is not influenced by antibodies against FVIII in those with haemophilia and inhibitors, the half-life is long enabling weekly to 4-weekly administration, and subcutaneous administration avoids the need for the intravenous access needed for factor replacement therapy. It has been evaluated in the sponsored series of HAVEN prophylaxis trials in 400 patients, both adult and paediatric, with and without FVIII inhibitors. The reduction in annualised bleeding rate has been spectacular compared to alternative FVIII prophylaxis in the noninhibitor group, and bypass therapy in those with inhibitors. Significant benefit is confirmed in this 2-year follow-up with no new safety concerns and neutralising drug antibodies <1%. An unexpected time-related reduction in annualised bleeding rate is seen reducing to one event by 2 years. NZ inhibitor haemophilia patients are benefitting from this breakthrough therapy via special authority funding.

Reference: Blood 2021;137:2231–42
Abstract

Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination

Authors: Greinacher A et al.

Summary: This paper reported on 11 patients (median age 36 years; nine female) who developed thrombosis or thrombocytopenia after receiving the ChAdOx1 nCov-19 vaccine against SARS-COV-2 (AstraZeneca). One of the patients presented with fatal intracranial haemorrhage. All the other patients presented with ≥1 thrombotic events 5–16 days after receiving the vaccine, including nine with cerebral venous thrombosis, three with SVT, three with PE and four with other thromboses, and six of these patients died. Five patients also had disseminated intravascular coagulation. None of the patients had previously received heparin before the onset of symptoms. The researchers also tested samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events. A screening PF4-heparin immunoassay was positive in 28 of these patients, and all of these also tested positive on the platelet-activation assay in the presence of PF4, independent of heparin. Inhibition of platelet activation was seen for high heparin, Fc receptor-blocking monoclonal antibody and immune globulin levels. PF4-dependent platelet activation was confirmed in further studies with PF4 or PF4-heparin affinity purified antibodies in two patients.

Comment (LY): This unexpected severe (but fortunately reasonably rare) complication of some COVID vaccines appears to be due to cross-reactivity of the role of PF4 in the immune response to infection, where it is involved in response to pathogens when platelet activation is triggered, e.g. severe bacterial infection. In a reaction analogous to HIT, post-vaccination development of high titres of these antibodies causes platelet activation and thrombin generation with thrombosis, which was initially reported as predominantly cerebral sinus thrombosis. Since then other thrombotic events including arterial thrombosis have been described. As well as diagnostic criteria (onset within 30 days of vaccination, platelets less than normal range, high D-dimer level, thrombosis), a positive ELISA for PF4 antibodies is noted. Key management points are the use of intravenous immune globulin and non-heparin anticoagulants. For the NZ audience, it is important to note this disorder has not so far been reported with the Pfizer COVID vaccine.

Reference: N Engl J Med; Published online April 9, 2021
Abstract

Long-term risk of recurrent venous thromboembolism after a first contraceptive-related event

Authors: Aziz D et al.

Summary: These researchers analysed data from the REVERSE cohort study with the primary aim of exploring the long-term recurrent VTE risk in women receiving versus not receiving combined oral contraceptives at the time of a first VTE. Compared with women not receiving combined oral contraceptives, those who were had a lower VTE recurrence risk (1.1% vs. 3.2% per patient-year; hazard ratio 0.37 [95% CI 0.1, 1.0]), including those who were high risk according to HERDOO2 score (3.5% vs. 6.1%; 0.6 [0.1, 2.5]).

Comment (PO): VTE is characterised as provoked or unprovoked to determine anticoagulant treatment duration. Hormone therapy is defined as a minor transient risk factor (ISTH 2016). Reported risks of recurrence following hormone-associated thromboses have been inconsistent and evaluated independently of clinically predicted recurrence risks. The recurrence rate in the study cohort (n=322) was 16.1% over mean 5.7 years of follow-up. There is conceptual support for the role of age and other HER2DOO risk factors influencing recurrence with combined oral contraceptive use. Recurrence is lower among combined oral contraceptive users and women <50 years of age. The risk of recurrent events may not always be low enough to stop therapy based on this variable alone, especially in those with a high-risk HER2DOO score. There were only 50 women on combined oral contraceptives at onset of the index VTE, so the significance of combined oral contraceptive duration, pill type and generation of progestin remains uncertain, leaving scope for larger prospective studies.

Reference: J Thromb Haemost 2021;19:1526–32
Abstract

Adverse events associated with the addition of aspirin to direct oral anticoagulant therapy without a clear indication

Authors: Schaefer JK et al.

Summary: This registry-based cohort study evaluated adverse outcomes associated with adding aspirin to DOAC therapy in patients with atrial fibrillation or VTE and no clear indication for aspirin use; 1047 patients receiving aspirin plus a DOAC were propensity-score matched with 1047 receiving a DOAC only. During mean follow-up of 20.9 months, aspirin plus DOAC recipients had more nonmajor bleeding events than those receiving DOAC monotherapy (26.1 vs. 21.7 per 100 patient-years [p=0.02]) and they also had more hospital admissions (9.1 vs. 6.5 per 100 patient-years [p=0.02]), but there was no significant between-group difference for thrombotic event rate (2.5 vs. 2.3 events per 100 patient-years) or major bleeding.

Comment (LY): It is relatively common to identify an indication for anticoagulants in patients who are already on antiplatelet therapy. It is important to carefully consider whether both medicines are required. The combination appears to provide relatively minimal benefit and has the disadvantage of increased bleeding; in general, more than 12 months after cardiac stenting, the DOAC alone can be used, and if both agents are needed then consider a proton pump inhibitor.

Reference: JAMA Intern Med; Published online April 19, 2021
Abstract

Anticoagulant therapy for splanchnic vein thrombosis

Authors: Valeriani E et al.

Summary: This systematic review and meta-analysis included 97 observational and randomised controlled studies (n=7969) reporting radiological or clinical outcomes in patients with SVT. The respective rates of SVT recanalisation, SVT progression, recurrent VTE, major bleeding and overall mortality among anticoagulant recipients were 58%, 5%, 11%, 9% and 11%, and the corresponding rates in anticoagulant nonrecipients were 22%, 15%, 14%, 16% and 25%. Compared with no treatment, receipt of anticoagulant therapy was associated with greater risks of recanalisation (RR 2.39 [95% CI 1.66, 3.44]) and lower risks of thrombosis progression (0.24 [0.13, 0.42]), major bleeding (0.73 [0.58, 0.92]) and overall mortality (0.45 [0.33, 0.60]).

Comment (PO): This analysis is helpful indicating an overall benefit for treating SVT with anticoagulants. Although recurrent VTE rates following anticoagulant treatment are similar to those who were not treated, anticoagulation significantly improves vascular recanalisation and reductions in major bleeding and mortality. The problem with this sort of analysis, based on a large number of patients, is that most studies are observational and retrospective. This is reflected in the significant heterogeneity of the patients reported and potential for bias. There are different underlying risk factors, different veins are involved and type and duration of anticoagulation are uncontrolled. While the effects of anticoagulation on clinical and radiological outcomes appear to be consistent across patient subgroups, including those with cirrhosis, benefits for specific risk groups such as myeloproliferative neoplasm or cancer cannot be determined. The reason for withholding anticoagulation was nonrandomised except in one randomised controlled trial. DOACs were used in 13% of the patients reported.

Reference: Blood 2021;137:1233–40
Abstract

Frequency of positive anti-PF4/polyanion antibody tests after COVID-19 vaccination with ChAdOx1 nCoV-19 and BNT162b2

Authors: Thiele T et al.

Summary: Patients who have developed vaccine-induced immune thrombotic thrombocytopenia after receiving the ChAdOx1 nCoV-19 (AstraZeneca) vaccine against SARS-COV-2 have tested strongly positive in PF4/polyanion enzyme immunoassays, and serum-induced platelet activation is maximal in the presence of PF4. The frequency of anti-PF4/polyanion antibodies was therefore measured in healthy volunteers who had received the ChAdOx1 nCoV-19 (n=138) or BNT162b2 (BioNTech/Pfizer; n=143) vaccine; whether PF4/polyanion EIA-positive sera exhibit platelet-activating properties after vaccination was investigated. Positivity for anti-PF4/polyanion antibodies was seen in 19 of the participants (6.8%) after vaccination, including 5.6% and 8.0% for BNT162b2 and ChAdOx1 nCoV-19 vaccine recipients, respectively. Optical densities were mostly 0.5–1.0 units (reference range <0.50) and no induction of platelet activation in the presence of PF4 was seen in any of the PF4/polyanion EIA-positive samples.

Comment (LY): The development of anti-PF4 antibodies is described with inflammation, e.g. following trauma, as well as with heparin exposure in the mechanism of HIT. The anti-PF4 antibodies noted with the reported vaccine-induced immune thrombotic thrombocytopenia described above were unexpected. In blood donors, the percentage of these antibodies found in sera is small, from 0 to 6% depending on the type of ELISA used. This study explored whether the rate of antibody formation was higher in unselected patients receiving COVID vaccination with the AstraZeneca product, which has been implicated in vaccine-induced immune thrombotic thrombocytopenia, and the Pfizer product (used in NZ), which has not. This study showed a low rate of seroconversion with vaccination, which occurred for both vaccines, although at a higher frequency for the AstraZeneca product. None of these antibodies had the strength to activate functional assays, and of the samples where prevaccination sera were available (57%), nearly two-thirds were positive even before the vaccine was administered. A high rate of antibody formation with vaccination does not appear to be the case, and as with HIT, presumably a perfect storm of events is needed for the development of thrombosis with thrombocytopenia syndrome/vaccine-induced immune thrombotic thrombocytopenia.

Reference: Blood; Published online May 14, 2021
Abstract

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Cytoreductive treatment in patients with CALR-mutated essential thrombocythaemia

Authors: Alvarez-Larrán A et al., on behalf of the MPN Spanish Group (GEMFIN)

Summary: The criteria for initiating cytoreduction and response to conventional therapies were assessed in 1446 Spanish registrants with essential thrombocythaemia, of whom 267 had *CALR* mutation. Among low-risk patients, those with *CALR* mutation had a shorter time from diagnosis to cytoreduction than those with *MPL*, *JAK2*V617F and triple-negative genotypes (2.8 vs. 3.2, 7.4 and 12.5 years, respectively [p<0.0001]). Cytoreductive treatment was received by 76% of the patients, including hydroxycarbamide (hydroxyurea; n=977), anagrelide (n=113) and others (n=14). The estimated cumulative 12-month complete haematological response rate for the *CALR* and *JAK2*V617F genotypes were 40% and 67%, respectively, and the respective median times to complete haematological response for the *JAK2*V617F, triple-negative, *MPL* and *CALR* genotypes were 192, 343, 433 and 705 days (p<0.0001). *CALR*-mutated patients had significantly shorter complete haematological response duration than the other patients. Among *CALR*-positive patients, hydroxycarbamide and anagrelide had similar efficacies with respect to response rate and duration. The respective proportions of *JAK2*V617F, *CALR*, *MPL* and triple-negative patients who developed hydroxycarbamide resistance or intolerance were 5%, 23%, 27% and 15% (p<0.0001).

Comment (PO): Cytoreduction and target blood count values were developed before the driver mutation role of *CALR* was identified. This large registry series suggests that conventional suppressive agents are less effective in *CALR*-mutated essential thrombocythaemia than in other genotypes. Response rates, time to response and response duration are inferior in those who are *CALR*-positive. Based on current treatment recommendations, *CALR*-mutated patients need cytoreduction sooner and are more likely to develop hydroxycarbamide resistance. Responses to hydroxycarbamide and anagrelide are comparable. Clinical outcomes including thrombosis and bleeding rates are not included in this analysis. In contrast to hydroxycarbamide or anagrelide with <50% response rates, complete responses around 75–80% are reported for pegylated interferon, supporting the recommendation for use in younger patients (ELN guidelines). The authors speculate that target blood values in this patient subgroup might need redefining.

Reference: Br J Haematol 2021;192:988–96
Abstract

Reduced expression of annexin A2 is associated with impaired cell surface fibrinolysis and venous thromboembolism

Authors: Fassel H et al.

Summary: A2 protein expression and function were evaluated in 115 adults with VTE and 87 healthy controls in this research. With peripheral blood mononuclear cells used as a surrogate for endothelial cells, a mean 41% decrease was seen in cell surface tissue plasminogen activator-dependent fibrinolytic activity in participants with positive personal and family histories of VTE without inherited thrombophilias. There were average decreases of 70% and 30% for A2 protein and mRNA levels, respectively, but neither of these reductions correlated with anticoagulant therapy. There was also no correlation between either cell A2 protein or cell surface plasmin generation and plasma-based clot lysis time.

Comment (LY): Historically there was interest in reduced fibrinolytic capacity contributing to hereditary thrombophilia, but there was no definitive abnormality identified in a way that was of clinical use, so it went out of fashion. Annexin A2 is important in animal models as a cell surface-mediated modulator of fibrinolysis. In this novel study, individuals with thrombosis and a family history of thrombophilia had reduced cell-based fibrinolytic activity, which correlated with both reduced annexin A2 protein function and reduced mRNA expression. To explore this interesting hypothesis in larger populations including normal controls, a more straightforward assay model would need to be developed. This may be another contributor to the significant percentage of individuals who don't have an identifiable thrombophilia.

Reference: Blood 2021;137:2221–30
Abstract

The net benefit of thrombolysis in the management of intermediate risk pulmonary embolism

Authors: Alcedo PE et al.

Summary: This was a systematic review with meta-analysis of 11 studies (n=1855) reporting on intermediate-risk patients with PE treated with thrombolysis; there were variable risks of bias among the study items. None of the included studies reported on overall survival; however, the pooled RR with thrombolysis for all-cause mortality was 0.68 (95% CI 0.40, 1.16), the RR for PE recurrence was 0.56 (0.23, 1.37), and the respective RRs for overall bleeding, major bleeding and stroke were 2.72 (1.58, 4.69), 2.17 (1.03, 4.55) and 2.22 (0.17, 28.73).

Comment (PO): Thrombolysis improves survival in patients with massive PE provided there are no high bleeding risk contraindications. The net benefit is less clear in those without hypotension. Intermediate risk or submassive PE is defined as acute PE with right ventricular dysfunction or damage without hypotension (blood pressure >90mm Hg). This meta-analysis (11 studies) included only intermediate-risk PE patients. All studies reported on all-cause mortality and overall bleeding, but fewer on major bleeding (n=8), recurrent PE (n=6) and stroke (n=2). No information was reported about overall survival in the intermediate-risk PE subgroup in any study. These observations broadly support the widespread use of anticoagulant-based treatment for patients with submassive PE, but analyses of this sort cannot evaluate differences in thrombolytic agents, dosages or potential benefits due to the mode of administration, such as catheter-directed thrombolysis.

Reference: eJHaem 2020;1:457–66
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. **For full bio CLICK HERE**