Thrombosis & Haemostasis Practice Review™

Making Education Easy

Issue 1 - 2022

In this issue:

Abbreviations used in this review:

ASH = American Society of Hematology;
ATAGI = Australian Technical Advisory Group on Immunisation;
PBS = Pharmaceutical Benefits Scheme; **PE** = pulmonary embolism;
TGA = Therapeutic Goods Administration;
VTE = venous thromboembolism.

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Welcome to the first issue of Thrombosis and Haemostasis Practice Review.

This new Review covers news and issues relevant to clinical practice in thrombosis and haemostasis. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources for Haematologists, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

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Clinical Practice

ASH guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: Post discharge thromboprophylaxis

The American Society of Hematology (ASH) has added an additional recommendation in its clinical practice guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. The updated guidelines now include a conditional recommendation against outpatient anticoagulation prophylaxis in patients with COVID-19 who have been discharged but do not have suspected or confirmed venous thromboembolism (VTE).

ASH first published guidelines on the use of thromboprophylaxis in discharged patients who had recovered from COVID-19 in early 2021. The guidelines were developed by a multidisciplinary panel that also included three patient representatives.

The guideline panel agreed on two recommendations in the original ASH guideline, both of which were open for public feedback. The conditional recommendations were in favour of prophylactic-intensity anticoagulation versus intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19 who do not have confirmed or suspected VTE. These recommendations were based on very low certainty evidence and were focused on patients with COVID-19–related critical illness (i.e., requiring intensive care unit admission) and those with acute disease (i.e., admission to a COVID-19 ward without need for advanced support).

In the update, the guideline panel suggested against the routine use of post-discharge thromboprophylaxis in patients with COVID-19 who are being released from the hospital and do not have either confirmed or suspected VTE or any other indication for anticoagulation. This means that most patients should not receive prophylactic anticoagulation following discharge. However, thromboprophylaxis may be appropriate in patients at high thrombotic risk and low bleeding risk. Of note, there is a lack of prospectively validated risk assessment models to estimate bleeding and thrombotic risk in patients with COVID-19 after discharge.

Data to support this new recommendation were very uncertain for all considered outcomes. Some studies included in the review showed that prophylactic-intensity anticoagulation following discharge may reduce mortality (odds ratio [OR] 0.55; 95% CI 0.37-0.83), corresponding to five fewer deaths per 1,000 individuals. Additionally, the evidence suggested that post-discharge prophylactic-intensity anticoagulation may reduce the risk of pulmonary embolism (OR 0.76, 95% CI 0.46-1.25), VTE (OR 0.76; 95% CI 0.46-1.25), and readmission (OR 0.92, 95% CI 0.41-2.05).

The guideline notes that clinicians may consider performing an individualised assessment of a patient's thrombosis and bleeding risk before deciding on post-discharge thromboprophylaxis, and recommends engaging patients in a shared decision-making approach.

Although the power of the currently available evidence may not yet be sufficient to guide clinical practice confidently, forthcoming results from the MICHELLE and ACTIV-4c trials should provide higher quality evidence to support the recommendation. The trials evaluated the effects of post-discharge thromboprophylaxis in patients with COVID-19.

The guidelines panel will update the recommendation when these trials or other high-quality evidence is published.

Blood Adv. 2022;6(2):664–71

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Association of ChAdOx1 COVID-19 vaccine with thrombotic events

The risk of intracranial thrombosis is increased in some people following vaccination with the AstraZeneca COVID-19 vaccine (ChAdOx1), according to the results of two large UK studies.

Intracranial venous thrombosis

The first study analysed the electronic health records from December 8, 2020 to March 18, 2021 of 46 million adults aged 18 or over in England – approximately 21 million of whom were vaccinated during the study period.

After adjusting for a range of demographic characteristics and comorbidities, for people aged 70 or over the risks of arterial and venous thrombotic events were slightly lower in the 28 days following vaccination with either the Pfizer-BioNTech or AstraZeneca vaccine, compared with unvaccinated individuals.

With regards to those under age 70, the risks of arterial and venous thrombotic events were comparable to unvaccinated individuals in the 28 days following vaccination, but a small increase in the rate of intracranial venous thrombosis and thrombocytopenia was observed following the AstraZeneca vaccine.

After adjusting for a range of demographic characteristics and comorbidities this corresponded to an estimated excess risk for intracranial venous thrombosis of 0.9 to 3.0 per million and was approximately twice the rate compared to unvaccinated people. The same effect was not seen after the Pfizer-BioNTech vaccine.

Increases in intracranial venous thrombosis and thrombocytopenia after AstraZeneca COVID-19 vaccination in adults aged under 70 years were small compared with its effect in reducing COVID-19 morbidity and mortality, although more precise estimates for adults under 40 years are needed, according to the authors.

The authors also pointed out that the small increased risk of intracranial venous thrombosis and hospitalisation with thrombocytopenia after first vaccination with the AstraZeneca COVID-19 vaccine in adults under 70 years old is likely to be outweighed by the vaccine's effect in reducing COVID-19 mortality and morbidity.

Cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis is an extremely rare event, with an estimated incidence of 3-4 per million person-years in adults. The second paper aimed to investigate possible associations between COVID-19 vaccines and cerebral venous sinus thrombosis.

The authors used data from December 8, 2020 to June 30, 2021, including more than 11 million adults in England, Scotland, and Wales, and compared the rate of cerebral venous sinus thrombosis events in the 90 days prior to vaccination and the 4 weeks following a first dose of AstraZeneca or Pfizer-BioNTech COVID-19 vaccines.

A small, elevated risk of cerebral venous sinus thrombosis events in the 4-week period following vaccination with the AstraZeneca COVID-19 vaccine was identified, which equated to about a two-fold increased risk when compared to rates before vaccination. This was equivalent to one additional event per 4 million people vaccinated. There was not any increased risk for cerebral venous sinus thrombosis with the Pfizer-BioNTech vaccine.

Future COVID-19 vaccination policy

This new data may be useful in risk-benefit evaluations for vaccine-related policies, and in providing quantification of risks associated with vaccination to the general public.

The authors of the first study said that their data should aid development of future COVID-19 vaccination programmes, and that healthcare systems planning to use the AstraZeneca COVID-19 vaccine should balance the very small harms against the known benefits of the vaccine. They added that whilst for older populations who are most vulnerable to COVID-19 they found no evidence of increased risk of any event with the AstraZeneca COVID-19 vaccine, in younger individuals who have a lower morbidity and mortality due to COVID-19, other available vaccines might be prioritised, especially when the risk of COVID-19 is otherwise low.

PLoS Med. 2022;19(2):e1003926

PLoS Med. 2022;19(2):e1003927

Safety and efficiency of diagnostic strategies for ruling out pulmonary embolism in clinically relevant patient subgroups

Adapted D-dimer thresholds based on pretest probability were effective for excluding pulmonary embolism (PE) in subgroups of high-risk individuals without the use of imaging in a recently published systematic review and meta-analysis.

The effectiveness of current diagnostic strategies for suspected PE in patient subgroups defined by sex, age, cancer, and previous venous thromboembolism (VTE) has not been well-studied.

The goal of the review was to evaluate the safety and efficiency of the Wells and revised Geneva scores in combination with D-dimer tests, and also the YEARS algorithm, for ruling out acute PE in these subgroups.

A systemic review and individual patient data meta-analysis was conducted that included 16 studies and 20,553 patients, with all studies published between January 1, 1995, and January 1, 2021. The primary outcomes were the safety and efficiency of each of the three strategies.

Safety was defined as the diagnostic failure rate (predicted 3-month incidence of VTE after PE was excluded without imaging at baseline). Efficiency was defined as the proportion of patients for whom PE was ruled out based on D-dimer thresholds without imaging.

Overall, efficiency was highest in the subset of patients aged younger than 40 years (47% to 68%). Efficiency was lowest in patients aged 80 years and older (6.0% to 23%), and in patients with cancer (9.6% to 26%). Efficiency improved when D-dimer thresholds based on pretest probability were used, compared with when fixed or age-adjusted D-dimer thresholds were used.

Predicted failure rates were highest for strategies with adapted D-dimer thresholds, with failure rates ranging from 2% and 4% in the patient subgroups.

The study findings were limited by several factors including between-study differences in scoring predictors and D-dimer assays. Another limitation was that differential verification biases for classifying fatal events and PE may have contributed to overestimation of failure rates of the adapted D-dimer thresholds.

The authors concluded that these data support application of adapted D-dimer thresholds.

Ann Intern Med. 2022;175(2):244-55

Association of psoriasis with incident venous thromboembolism and peripheral vascular disease

Psoriasis, venous thromboembolism (VTE), and peripheral vascular disease have similar mechanisms involving chronic inflammation, however, the associations between psoriasis and VTE or peripheral vascular disease are unclear.

VTE and peripheral vascular disease may be slightly more likely to develop among patients with psoriasis than those without the condition, according to a new systematic review and meta-analysis.

A total of 13 cohort studies with 12,435,982 participants were included. Patients with psoriasis had a 1.26-fold risk for incident VTE (HR 1.26; 95% CI 1.08-1.48) and a 1.27-fold risk for incident peripheral vascular disease (HR 1.27; 95% CI 1.16-1.40) compared to those without psoriasis.

Subgroup analyses revealed an increased risk for VTE among participants with psoriatic arthritis (HR 1.24; 95% CI 1.01-1.53), women (HR 1.89; 95% CI 1.36-2.61), and those in Asia (HR 2.02; 95% CI 1.42-2.88) and Europe (HR 1.28; 95% CI 1.06-1.53).

The authors concluded that typical presentations of VTE and peripheral vascular disease should not be overlooked by clinicians who treat psoriatic patients. Risk factors, such as obesity, physical inactivity, smoking, and varicose veins, should be carefully followed and treated in patients with psoriasis, and medications such as hormone-related therapies should be given with caution.

JAMA Dermatol. 2022;158(1):59-67

Regulatory News

PBS listings

Eculizumab (Soliris®) and **ravulizumab** (Ultomiris®) have been listed on the PBS Section 100 Highly Specialised Drugs program for the treatment of paroxysmal nocturnal haemoglobinuria under certain conditions. Access to eculizumab under the Life Saving Drugs Program was ceased for new patients from 1 March 2022, with transition arrangements in place to facilitate access to these medicines via the PBS.

Methoxsalen (Uvadex®), delivered as part of an integrated, closed system extracorporeal photopheresis service, has been listed on the PBS for the treatment of patients with steroid dependent, steroid intolerant or steroid refractory chronic graft-versus-host disease..

Ravulizumab (Ultomiris®) has been listed on the PBS for the treatment of paroxysmal nocturnal haemoglobinuria.

TGA – new registrations

Belumosudil mesilate (Rholistiq®) is indicated for the treatment of patients with chronic graft-versus-host disease aged 12 years and older who have an inadequate response to corticosteroids.

Human fibrinogen; human thrombin (Veraseal®) is indicated as supportive treatment in adults where standard surgical techniques are insufficient, for improvement of haemostasis.

Romiplostim (NPLATE®) is now also indicated for treatment of thrombocytopenia in adult patients with primary immune thrombocytopenia who are:

- non-splenectomised and have had an inadequate response, or are intolerant, to corticosteroids and immunoglobulins;
- splenectomised and have had an inadequate response to splenectomy.

Ruxolitinib phosphate (Jakavi®) is now also indicated for the treatment of patients aged 12 years and older with acute graft-versus-host disease who have inadequate response to corticosteroids.

Read more here and here

News in Brief

ATAGI update on COVID-19 vaccination for people with immunocompromise

The Australian Technical Advisory Group on Immunisation (ATAGI) has updated its advice for COVID-19 vaccination for people who are immunocompromised. Changes as of March 2022 are listed below:

- people aged 16 years and older who have received a three-dose primary course due to severe immunocompromise are recommended to receive a booster (i.e., fourth) dose at least three months after their third dose.
- information on the Nuvaxovid COVID-19 vaccine (Novavax) has been included.
- people aged 6 to 11 years can now receive Spikevax (Moderna) at half the adult dose.

Read more here

Effects of replacement therapies with clotting factors in patients with haemophilia

This systematic review and meta-analysis compared the effects of factor replacement therapies in patients with haemophilia. Nine RCTs were included, of which six compared episodic with prophylactic treatment in patients with haemophilia A. Prophylactic treatment (at either low, intermediate, or high doses) was superior to episodic treatment for bleeding prevention, as measured by annualised bleeding rate and annualised joint bleeding rate. The bleeding rate appeared to have a dose-response relationship. However, no study compared different doses of prophylactic treatment, and all results had a very low certainty of evidence.

PLoS One. 2022;17(1):e0262273

What is the optimal management of thromboprophylaxis after liver transplantation regarding prevention of bleeding, hepatic artery or portal vein thrombosis?

This systematic review and meta-analysis of 16 studies examined the best management of thromboprophylaxis after liver transplantation regarding portal vein thrombosis or hepatic artery thrombosis and prevention of bleeding. The review found that thromboprophylaxis is not recommended for prevention of de novo portal vein thrombosis after liver transplantation in patients not at high risk, as it does not reduce the risk of thrombosis but does increase bleeding risk. Aspirin should be considered as the standard of care following liver transplantation to prevent hepatic artery thrombosis, due to showing a small but significant decrease in the incidence of thrombosis without increasing bleeding. Thromboprophylaxis should be offered to patients at risk of hepatic artery thrombosis and portal vein thrombosis post-transplantation.

Clin Transplant. 2022:e14629

COVID-19 Resources for Haematologists

Australian & New Zealand Society of Blood Transfusion Ltd
British Society for Haematology
European Hematology Association
European Society for Blood and Marrow Transplantation
International Society of Blood Transfusion

Conferences, Workshops and CPD

Please click on the links below for upcoming local and international haematology meetings, workshops and CPD.

HSANZ - Events
ALLG - Events
COMS – Conferences and Meetings on Hematology

Research Review Publications

Bone Marrow Transplant Research Review
with Dr David Routledge
https://tinyurl.com/yaxzqjg7

Haematology Research Review
with Professor Jeff Szer
https://tinyurl.com/yy537p5b

Thrombosis & Haemostasis Research Review
with Professor Harshal Nandurkar
https://tinyurl.com/y6hzrdyu

Blood 2021 Conference Review
https://tinyurl.com/72bdt2td

EHA 2021 Conference Review
https://tinyurl.com/bhyhypyh

Product Review - Emicizumab for the treatment of haemophilia A
https://tinyurl.com/79dwv9te

Product Review – Subcutaneous normal human immunoglobulin
https://tinyurl.com/bj6r56zc

Study Review – Rivaroxaban or aspirin for extended treatment of VTE
https://tinyurl.com/2p8nzcfh

Study Review – Rivaroxaban vs enoxaparin/vitamin K antagonist in VTE
https://tinyurl.com/2s3395ba

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