Thrombosis & Haemostasis Research Review™

Making Education Easy

Issue 16 - 2021

In this issue:

- Mutated endothelial cells in myeloproliferative neoplasms
- Platelet-associated IgG and corticosteroid therapy in ITP
- Mutations in patients with essential thrombocythemia
- SIRT1 SNPs and corticosteroids in thrombocytopenia
- Factor VIIIa-mimetic bispecific antibody Mim8
- Anti-platelet factor 4 antibodies and SARS-CoV-2 spike protein
- Pegylated P-selectin glycoprotein ligand-1 glycomimetic
- Management of acquired haemophilia A
- Intensified antiplatelet therapy for high on-treatment platelet reactivity
- Trends in acute pulmonary embolism admission and mortality in Australia

Abbreviations used in this issue:

ADP = adenosine diphosphate; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **CT** = computed tomography; **FBE** = full blood examination; **IgG** = immunoglobulin G; **IPSET** = International Prognostic Score for Thrombosis in Essential Thrombocythemia; **ITP** = immune thrombocytopenia; **JAK** = Janus kinase; **Kd** = equilibrium dissociation constant; **LMWH** = low-molecular-weight heparin; **MPL** = myeloproliferative leukaemia gene; **OR** = odds ratio; **PCR** = polymerase chain reaction; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SNP** = single-nucleotide polymorphism; **VWF** = von Willebrand factor.

Claim CPD/CME points Click here for more info.

Like us on Facebook
facebook.com/researchreviewau/

Welcome to issue 16 of Thrombosis and Haemostasis Research Review.

First up we take a look at an excellent review on the possible role of mutated endothelial cells in myeloproliferative neoplasms. The review follows on from data reported over the past few years from experimental models implicating endothelial cells carrying the *JAK2 V617F* mutation in the development of thrombosis. Next, in a Japanese study we learn that platelet-associated IgG is a significant predictor of response to first-line corticosteroid therapy in patients with newly diagnosed immune thrombocytopenia. Other topics covered in this issue include mutations in patients with essential thrombocythemia, factor VIIIa-mimetic bispecific antibody Mim8, Anti-platelet factor 4 antibodies and SARS-CoV-2 spike protein, the management of acquired haemophilia A, and trends in acute pulmonary embolism admission and mortality in Australia.

We hope you find the selected studies interesting and we welcome your feedback.

Kind Regards,

Professor Harshal Nandurkar

harshal.nandurkar@researchreview.com.au

The possible role of mutated endothelial cells in myeloproliferative neoplasms

Authors: Farina M et al.

Summary: This review examined studies identifying endothelial cell (EC) dysregulation as a factor contributing to myeloproliferative neoplasm (MPN) disease development. The *JAK2 V617F* mutation and other myeloid-associated mutations detected in haematopoietic cells from MPN patients and in ECs and EC precursor cells, suggests a link between mutated ECs and the high incidence of vascular events in these patients. The review describes experimental strategies used to study EC biology and assesses evidence generated by these assays that implicate mutated ECs in MPN-associated abnormalities. Mutated ECs have a pro-adhesive phenotype resulting from increased endothelial P-selectin exposure, secondary to Weibel-Palade body degranulation, which is accentuated by pro-inflammatory cytokine exposure. MPN myeloproliferation also requires JAK2 V617F expression in haematopoietic stem cells and ECs, and suggests that MPN driver mutations may first appear in a common EC and haematopoietic cell precursor.

Comment: This is an excellent review that follows on from data reported over the past few years from experimental models implicating ECs carrying the *JAK2 V617F* mutation in the development of thrombosis. The contribution of ECs, independent of JAK2-related platelet events, may explain how patients with polycythaemia vera (PV) develop thrombotic episodes (e.g., splanchnic vein thrombosis) before obvious full blood examination abnormalities. It may also help our understanding how thrombotic risk will persist despite normalisation of haemoglobin. The observation that ECs and their precursors may harbour the *JAK2 V617F* mutation supports this hypothesis of direct contribution by ECs. The review raises support for the hypothesis that ECs and haematopoietic stem cells may derive from a common progenitor cell, the "haemangioblast", which results in mutated EC and myeloid cells in a subpopulation of patients with MPN. Murine gene manipulation studies have shown that *JAK2 V617F*-positive (*JAK2 V617F*+) ECs in the absence of similarly mutated haematopoietic cells is associated with a higher rate of thrombosis due to a pro-adhesive phenotype because of increased exposure to endothelial P-selectin and VWF, secondary to degranulation of Weibel-Palade bodies. In vitro studies have also confirmed that JAK2-mutated ECs respond to shear flow in a different manner than wild-type EC, leading to upregulation of EC adhesion molecules. *JAK2 V617F*+ vascular niche cells promote *JAK2 V617F*+ myeloid cell expansion, while inhibiting JAK2 wild-type haematopoiesis, thereby implicating EC-signalling events in myeloid proliferation.

Reference: Haematologica 2021;106(11):2813-2823
Abstract

Association between platelet-associated immunoglobulin G Levels and response to corticosteroid therapy in patients with newly diagnosed immune thrombocytopenia

Authors: Saburi M et al.

Summary: This Japanese, single-centre, retrospective (2010-18) study investigated the relationship between platelet-associated IgG (PA-IgG) and immature platelet fraction (IPF) levels at diagnosis and during first-line therapy (prednisolone [0.5–1.0 mg/kg/day], high-dose dexamethasone [40 mg/day] or methylprednisolone [125-1000 mg/day]) among 43 patients with immune thrombocytopenia (ITP). Median PA-IgG was 285 ng per 10^7 cells and median IPF was 15.5%; the upper limit of normal (ULN) range for PA-IgG is 0-46 ng per 10^7 cells while the ULN for IPF is 1.1-9.5%. Twenty-four patients (55.8%) responded to first-line therapy. Univariate analysis revealed no difference between responders (n = 24) and non-responders with differing corticosteroids and no difference in IPF levels (15.35% vs 16.7%). PA-IgG levels were higher in non-responders (430 vs 254.5 ng/10^7 cells; p = 0.004). Multivariate analysis indicated that PA-IgG level was independently associated with first-line response (OR 1.000; 95% CI 1.000-1.010; p = 0.029).

Comment: This retrospective study revealed PA-IgG as a significant predictor of response to first-line corticosteroid therapy in patients with newly diagnosed ITP. PA-IgG refers to IgG attached to the surface of platelets, including not only antiplatelet autoantibodies, but also Fc-RIIA (CD32)-mediated binding of immunocomplexes and nonspecific IgG. Hence, it is not specific for ITP. However, in this study, a PA-IgG cut-off of 508 ng/10^7 cells offered 47.3% sensitivity and 100% specificity for predicting response to first-line corticosteroid therapy. Corticosteroids work by reducing autoantibody production and hence this finding may reflect a threshold of platelet-bound autoantibodies that are too high to be suppressed effectively by corticosteroids. At present, its only of translational research interest as it is probably difficult to be established in routine hospital labs.

Reference: Acta Haematol. 2021;144(5):528-533
Abstract

RESEARCH REVIEW™ Australia's Leader in Specialist Publications

Comparison of the effects between MPL and JAK2V617F on thrombosis and peripheral blood cell counts in patients with essential thrombocythemia: A meta-analysis

Authors: Yang E et al.

Summary: This meta-analysis examined the effect of *MPL* and *JAK2 V617F* mutations on thrombosis risk (*MPL* n = 73; *JAK2 V617F* n = 1184) and peripheral blood cell counts (*MPL* n = 138; *JAK2 V617F* n = 3315) in patients with essential thrombocythemia based on seven studies. *MPL*+ essential thrombocythemia patients had a greater risk for thrombosis than *JAK2 V617F*+ patients (RR 1.80; 95% CI 1.08-3.01, p = 0.025). Platelet counts of *MPL*+ patients were higher than those of *JAK2 V617F*+ patients (weighted mean difference [WMD] 81.18; 95 % CI 31.77-130.60, p = 0.001), but they had lower haemoglobin (WMD -11.66; 95% CI -14.32 to -9.00, p = 0.000) and white blood cell counts (WMD -1.01; 95% CI 1.47 to -0.56; p = 0.000).

Comment: MPL mutations are noted in ~3% of patients with essential thrombocythemia. The overall numbers are small. Previous reports do show association between *MPL* mutations and higher risk of thrombosis. This is a meta-analysis of five prospective studies and two retrospective studies including a total of 3453 patients with essential thrombocythemia (138 *MPL*+ and 3315 *JAK2 V617F*+). The *MPL*+ cohort had lower haemoglobin and white blood cell counts, but higher platelets and higher risk of thrombosis. The IPSET-thrombosis algorithm for evaluating the risk of thrombosis events in essential thrombocythemia was published in 2012 and was innovative for including *JAK2* mutation status in the score determination. Based on the above meta-analysis, it is intuitive to suggest that *MPL* mutation status should be evaluated as a component of the thrombosis risk prediction algorithm.

Reference: Ann Hematol. 2021;100(11):2699-2706
Abstract

SIRT1 single-nucleotide polymorphisms are associated with corticosteroid sensitivity in primary immune thrombocytopenia patients

Authors: Wang S et al.

Summary: This Chinese study assessed the contribution of Sirtuin 1 (SIRT1) single-nucleotide polymorphisms (SNPs) rs12778366 and rs4746720 to corticosteroid sensitivity among 330 Han Chinese patients with primary ITP and 309 healthy controls. The risk of corticosteroid resistance was increased with the CC/TC genotypes of SIRT1 rs12778366 compared to the homozygous major TT genotype (OR 2.034; 95% CI 1.039-3.984, p = 0.038). In contrast, the CC/CT genotype of SIRT1 rs4746720 decreased the risk of corticosteroid resistance (OR 0.560; 95% CI 0.321-0.976, p = 0.041). The C allele substitute in SIRT1 rs12778366 was associated with corticosteroid sensitivity of ITP patients (p = 0.021).

Comment: SIRT1 is a member of the mammalian sirtuin family, a class 3 nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylase that is involved in regulating several biological processes. SIRT1 plays an important role in the anti-inflammatory effect of corticosteroids. SIRT1 deacetylation substrates include p65, p53, FOXO, and PGC1α subunit of nuclear factor-κB (NF-κB) proteins, which are central regulators of cellular metabolism, inflammation, and stress response pathways. The SIRT1 SNPs rs12778366 and rs4746720 have been implicated in various autoimmune diseases. There was no association between SIRT1 gene polymorphisms and ITP susceptibility. The mechanisms by which these polymorphisms link with corticosteroid sensitivity or resistance is not clear. However, if these results are confirmed in other ethnicities, then there may be a role for the study of these polymorphisms in planning treatment at the time of diagnosis.

Reference: Ann Hematol. 2021;100(10):2453-2462
Abstract

Thrombosis & Haemostasis Research Review™

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).

RESEARCH REVIEW™ Australia's Leader in Specialist Publications

REVOLADE®
(eltrombopag olamine)

69% of ITP patients said they would **avoid corticosteroids wherever possible**[1]

Free your ITP patients from corticosteroid cycling with REVOLADE*[2,3]

*REVOLADE is indicated for adult patients with chronic ITP who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins.[4]

FOR MORE INFORMATION ABOUT THE PBS STATUS OF THE PRODUCT PLEASE CLICK HERE.
PLEASE CLICK HERE FOR PRESCRIBING INFORMATION.

ITP: immune thrombocytopenia
References: 1. Matzdorff AC, *et al. PLoS One* 2011;6(11):e27350. **2.** Wong RSM, *et al. Blood* 2017;130(23):2527–36. **3.** Gonzalez-Lopez TJ, *et al. Am J Hematol* 2015;90(3):E40–3. **4.** REVOLADE Approved Product Information.

Novartis Pharmaceuticals Australia Pty Ltd, ABN 18 004 224 160, 54 Waterloo Road, Macquarie Park, NSW 2113. Ph (02) 9805 3555. For medical enquiries please contact 1800 671 203 or medinfo.phauno@novartis.com ®Registered trademark. Item No: AU-15889. March 2021. RVD0063.

NOVARTIS

A factor VIIIa–mimetic bispecific antibody, Mim8, ameliorates bleeding upon severe vascular challenge in hemophilia A mice

Authors: Østergaard H et al.

Summary: This laboratory-based study aimed to identify functional pairs of antibodies to the cofactor of activated factor IX (FIXa) and factor X (FX), followed by optimisation of functional and biophysical properties. The derived bispecific antibody (Mim8) generated membrane assemblies with FIXa and FX, and supported activation (apparent equilibrium dissociation constant 16 nM). The binding affinity of FIXa and FX in solution was lower (FIXa equilibrium dissociation constant 2.3 nM; FX 1.5 µM). Mim8 activity was dependent on anti-FIXa stimulatory activity, which enhanced FIXa proteolytic activity by 4 orders of magnitude. In plasma and whole blood samples from haemophilia A patients, Mim8 normalised thrombin generation and clot formation, with potencies 13- and 18-fold higher than a sequence-identical emicizumab analogue. In a haemophilia A mouse model, a similar potency difference was observed in a tail vein transection model, while in a severe tail-clip model a reduction of bleeding was observed only for Mim8. In cynomolgus monkeys, Mim8 had a half-life of 14 days.

Comment: FIXa and X concentrate on thrombogenic surfaces whereby FIXa enzymatic activity generates Xa with FVIII acting as an essential and non-redundant cofactor. At present, we have emicizumab that mimics the effect of FVIIIa by binding to activated FIXa and FX, and it has exhibited good efficacy for prophylactic treatment of haemophilia A patients with or without inhibitors. It is important to note that while emicizumab can bypass the need for FVIII, the cofactor activity of FVIIIa is considerably greater than that of emicizumab. Mim8 was assembled using monoclonal antibodies recognising FIXa and FX identified by expression cloning. The relevant biological details are that Mim8 has minimal recognition of FIX and FX in solution. In contrast, on a procoagulant surface, Mim8-FIXa-FX assembly occurred with an apparent affinity that was orders of magnitude stronger than the individual affinities in solution. An important attribute of Mim8 was its capacity for allosteric activation of FIXa, mimicking FVIIIa. The in vivo haemostatic activity of Mim8 was 18-fold superior to emicizumab.

Reference: Blood 2021;138(14):1258-1268
Abstract

Anti–platelet factor 4 antibodies causing VITT do not cross-react with SARS-CoV-2 spike protein

Authors: Greinacher A et al.

Summary: This laboratory study assessed whether antibodies induced against the anti-SARS-CoV-2 spike protein by the ChAdOx1 nCoV-19 (Vaxzevria; AstraZeneca) and the Ad26.COV2.S (Janssen) COVID-19 vaccine cause vaccine-induced immune thrombotic thrombocytopenia (VITT) by cross-reacting with anti-platelet factor 4 (PF4) antibodies through Fc-RIIa receptors. *In silico* prediction tools and 3D modelling used to compare immunogenic epitopes of PF4 and SARS-CoV-2 spike protein suggested that they share at least one similar epitope. However, no affinity-purified anti-PF4 antibodies from 14 patients with VITT cross-reacted with recombinant SARS-CoV-2 spike protein. Sera from 222 PCR-confirmed COVID-19 patients tested using PF4-heparin enzyme-linked immunosorbent assays and PF4-dependent platelet activation assays identified anti-PF4 antibodies in 8.6% of patients. However, only four patients had weak to moderate platelet activation in the presence of PF4, and none developed thrombotic complications. Among 4.5% of COVID-19 patients with thrombosis, none had PF4-dependent platelet-activating antibodies.

Comment: COVID-19 is caused by infection with the SARS-CoV-2 virus and is associated with thrombotic sequalae, whereas VITT is precipitated by vaccines encoding the SARS-CoV-2 proteins and is also associated with thrombosis. Severe COVID-19 is associated with a heightened inflammatory response, and markedly elevated levels of antibodies to the receptor binding domain and spike protein. VITT is also due to an aberrant immune response after certain vaccines. There are, however, differences in phenotype with COVID-19-related morbidity linked with age and pre-existent cardiovascular diseases manifesting with VTE and cardiac disease, while that of VITT can occur without pre-existent diseases (except probably antiphospholipid syndrome) and is associated with thrombosis in cerebral and splanchnic vascular beds. This body of work details how VITT is different from COVID-19 or SARS-CoV-2 protective immunity. Anti-PF4 antibodies isolated from VITT do not bind SARS-CoV-2 spike proteins. Moreover, anti-PF4 antibodies from COVID-19 patients do not cause heparin-dependent platelet activation, which is characteristic of VITT. Thus, the experiments demonstrate that VITT is its own disease entity, distinct from COVID-19.

Reference: Blood. 2021;138(14):1269-1277
Abstract

A PSGL-1 glycomimetic reduces thrombus burden without affecting hemostasis

Authors: Wong DJ et al.

Summary: This study reports on a pegylated glycomimetic of the N terminus of the P-selectin glycoprotein ligand-1 (PSGL-1), PEG40-GSnP-6 (P-G6), which is a highly potent P-selectin inhibitor. In vitro, P-G6 blocks human platelet-monocyte and platelet-neutrophil aggregation and in vivo inhibits microcirculatory platelet-leukocyte interactions. P-G6 reduces thrombus formation in a non-occlusive model of deep vein thrombosis and reduces leukocyte accumulation but does not disrupt haemostasis.

Comment: P-selectin is expressed on the surface of activated platelets and endothelium and binds its cognate ligand, PSGL-1, which is expressed on leukocytes and supports platelet-leukocyte aggregation and leucocyte rolling. P-selectin mediates tissue factor release, and fibrin deposition during venous thrombosis. Previous attempts to block P-selectin/PSGL-1 interaction have not lived up to their promise and these include recombinant PSGL and small molecule inhibitors. This paper describes the generation of P-G6, as the first synthetic high-affinity (Kd 22 nM) and specific P-selectin antagonist. P-G6 inhibited leukocyte/P-selectin binding in a dose-dependent manner and platelet-leukocyte aggregation in vitro and in vivo. In mice, P-G6 was able to inhibit venous thrombosis comparable with LMWH but without any bleeding effect. The half-life of P-G6 was 16 hours making once-daily treatment feasible. It's likely (though not studied in this work) that P-G6 may be effective in vaso-occlusive crises of sickle cell disease as has been noted for crizanlizumab [Adakveo®], an antibody against P-selectin.

Reference: Blood. 2021;138(13):1182-1193
Abstract

Management of acquired hemophilia A: Results from the Spanish registry

Authors: Mingot-Castellano ME et al.

Summary: This retrospective analysis of data from the Spanish Acquired Hemophilia A (AHA) registry looked at 154 patients (56.3% men; median age 74 years; idiopathic AHA 44.1%; autoimmune disorder-associated AHA 31.7%) followed for a median of 12 months. Haemostatic treatment was used in 70% of patients, 34% on antithrombotic therapy. Recombinant FVIIa was more frequently infused than activated prothrombin complex concentrate (60.3% vs 20.6%); one patient did not achieve haemorrhage control. After immunosuppressive therapy, complete remission was achieved by 84.2% of cases. Steroids alone were less effective (68.2% vs 87.2%; p = 0.049) than other strategies, with no differences among other treatments (steroids/cyclophosphamide 88.5%; steroids/calcineurin inhibitors 81.2%; rituximab-based 87.5%). Complete response was inhibited by female sex and high inhibitor levels. There were 36 deaths (23.8%), main cause of death was infection (9.9%) and haemorrhage (3.3%). Prior antithrombotic therapy was inversely associated with survival. The median age was higher in those who died (79 vs 73 years) and those dying of infection were older than others who died (85 vs 78 years).

Comment: Acquired haemophilia is uncommon, but it needs to be recognised promptly and treatment initiated. Access to recombinant FVIIa as well as early introduction of immunosuppressive therapies have considerably improved diagnosis. This report is of interest as it is real-world registry data of a significant number of patients with a median follow-up of 12 months. Take-home messages are that acquired haemophilia A is probably underdiagnosed in Spain as the incidence per population was lower than noted in Western countries. Underlying aetiologies and residual FVIII levels were similar to those reported in other series. One surprising variation was that the Spanish cohort had one-third of patients on antithrombotic therapy at the time of diagnosis and antithrombotic therapy before AHA diagnosis was associated with mortality during follow-up, also among those patients <75 years. The reason to stress on this point is that bleeding is common in older age groups with antithrombotic treatments and hence a diagnosis of acquired haemophilia may not be suspected in those presenting with bleeding as the principal symptom. The use of FVIIa, activated prothrombin complex concentrate and choice of immunosuppression was comparable with experience from other countries.

Reference: Blood Adv. 2021;5(19):3821-3829
Abstract

RACP MyCPD Program participants can claim **one credit per hour** (maximum of 60 credits per year in Category One – Educational Activities) **for reading and evaluating Research Reviews.**

Please CLICK HERE to download CPD Information

RESEARCH REVIEW™
Australia's Leader in Specialist Publications

Intensified antiplatelet therapy in patients after percutaneous coronary intervention with high on-treatment platelet reactivity: The OPTImal Management of Antithrombotic Agents (OPTIMA)-2 Trial

Authors: Ying L et al.

Summary: This 12-month randomised study tested intensified therapy for 1 month with aspirin 100 mg once daily plus clopidogrel 150 mg once daily, clopidogrel 75 once daily plus cilostazol 100 mg twice daily, ticagrelor 90 mg twice daily, or clopidogrel 75 mg once daily (standard therapy [STD]) in 434 patients experiencing high on-treatment platelet reactivity (HOPR) after 5 days of standard dual antiplatelet therapy (DAPT) post-percutaneous coronary intervention (PCI), followed by standard DAPT for a further 11 months. After 1 month, fewer patients with persistent HOPR were in the intensified therapy groups versus those receiving standard therapy with clopidogrel 75 mg once daily. Patients receiving intensified therapy had fewer major adverse cardiovascular events (MACE) at 1 and 12 months with no increase in bleeding.

Comment: We need 'personalised' antiplatelet therapy, so that intensive treatment can be directed towards those in most need. In this study, light transmission aggregometry with ADP as an agonist was used to categorise high platelet reactivity. The platelet reactivity levels were lower in patients randomised to any intensified antiplatelet treatment compared with standard therapy at 1 month. The 1-month residual HOPR rate was 18.0% in the combined intensified treatment group, 22.1% in the clopidogrel 150 mg group, 22.7% in the clopidogrel + cilostazol group and 9.1% in the ticagrelor group respectively, compared with 57.1% in the STD group ($p < 0.001$ for each comparison). At 12 months, compared with the STD group, the combined intensified treatment group had significantly reduced MACE (12.3% vs. 22.7%; HR 0.50). The price to pay with intensive antiplatelet therapy is bleeding; here, no significant differences in bleeding rate were observed overall or for pairwise comparisons with the STD group ($p > 0.05$ for all). Prior trials with intensification of antiplatelet treatments (e.g., PLATO with ticagrelor) demonstrated higher rates of bleeding. One explanation provided was that patients in this study presented a significantly higher residual platelet reactivity of 28% including those on ticagrelor (compared to ~10% on previous studies with ticagrelor). Another advantage with this trail is that the decision to intensify treatment was taken within the first week, which may enable a larger number of patients to be treated with less intense treatment during the first month.

Reference: Br J Haematol. 2021;Oct 5 [Epub ahead of print]
Abstract

Trends in acute pulmonary embolism admission rates and mortality outcomes in Australia, 2002–2003 to 2017–2018: A retrospective cohort study

Authors: Hoskin S et al.

Summary: This Australian retrospective population-linkage study sought to determine admission rates of acute pulmonary embolism (PE) and assess temporal trends in short- and medium-term mortality. All 61,607 PE admissions in New South Wales (NSW) between 2002 and 2018 were included (mean 3624 admissions/annum; 50.42 admissions/100,000 people/annum). The admission rate was higher among females versus males (54.85 vs 44.91 admissions/100,000 people/annum) and remained stable throughout the study. The main cohort, with index PE admission, included 46,382 people (mean age 64.6; 44.4% male). Cumulative mortality rates were in-hospital 3.7%, 30-day 5.6%, 3-month 9.6%, and 1-year 16.8%. After adjustment for age, gender, and relevant confounders, there was a reduction in mortality risk between 2002 and 2017 in-hospital (OR 0.34; 95% CI 0.25-0.46), at 30-days (OR 0.58; 95% CI 0.46-0.73), and at 1-year (HR 0.74; 95% CI 0.66-0.84; all $p < 0.001$). Survival improvements were observed in both genders and were greater among females.

Comment: This study is noteworthy at it encapsulates the Australian experience with PE management in 2017 compared with outcomes in 2002. The data is from NSW residents and not wider Australia. Male 1-year mortality rate did not improve between 2002 and 2017 (18.3 vs 18.3%), while it improved for females (16.2 vs 14.4%). Male gender was not an independent predictor of in-hospital mortality (OR 1.10; 95% CI 0.99-1.22), but was an adverse independent predictor of mortality at all other studied time points. Interestingly, weekend admission was a predictor of in-hospital (OR 1.16; 95% CI 1.03-1.31; $p = 0.01$) and 1-year mortality. Most in-hospital deaths were attributed to the acute PE event (74.0%), while non-cardiovascular causes accounted for 18.3% of in-hospital deaths, with malignancy (6.8%) and sepsis (3.6%) the leading causes. For patients who survived to discharge, 28.0% of deaths were due to cardiovascular causes, with 4.4% due to a recurrent fatal PE event. Non-cardiovascular causes accounted for 72.0% of deaths that occurred after discharge, with malignancy the leading cause-specific death (34.7%). Significant improvements in in-hospital and 30-day mortality following acute PE since 2002 was postulated to be due to advances in diagnostic technology (easier access to CT pulmonary angiogram), validated prognostic risk scores, and greater management options including thrombolysis, embolectomy, and availability of direct-acting anticoagulants.

Reference: Thromb Haemost. 2021;121(9):1237-1245
Abstract

REVOLADE®
(eltrombopag olamine)

It's time to look beyond immunosuppression for sustained response*[1–3]

*Achieving median platelet counts of ≥50 x 10⁹/L in adult patients with ITP throughout 250 weeks of treatment[1-3]

The only oral TPO-RA approved for second-line treatment of chronic ITP in Australia[1,4]

Available in 25 mg and 50 mg tablets[1]

Tablets displayed are not actual size.

FOR MORE INFORMATION ABOUT THE PBS STATUS OF THE PRODUCT PLEASE CLICK HERE.
PLEASE CLICK HERE FOR PRESCRIBING INFORMATION.

ITP: immune thrombocytopenia
References: 1. REVOLADE Approved Product Information. **2.** Wong RSM, *et al. Blood* 2017;130(23):2527–36. **3.** Cheng G *et al. Lancet* 2011;377(9763):393–402. **4.** Romiplostim Approved Product Information.

Novartis Pharmaceuticals Australia Pty Ltd, ABN 18 004 224 160, 54 Waterloo Road, Macquarie Park, NSW 2113. Ph (02) 9805 3555. For medical enquiries please contact 1800 671 203 or medinfo.phauno@novartis.com ®Registered trademark. Item No: AU-15889. March 2021. RVD0063.

NOVARTIS

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au.
Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists. **Privacy Policy:** Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.
Research Review publications are intended for Australian health professionals.

RESEARCH REVIEW™ Australia's Leader in Specialist Publications

© 2021 RESEARCH REVIEW