Thrombosis & Haemostasis Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AAV5 = adeno-associated viral vector 5; **CALR** = calreticulin; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **CT** = computed tomography; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DVT** = deep vein thrombosis; **FVIII** = blood clotting factor VIII; **ITP** = immune thrombocytopenia; **IVC** = inferior vena cava; **MPN** = myeloproliferative neoplasm; **OR** = odds ratio; **PE** = pulmonary embolism; **RR** = relative risk; **TAPS** = thrombotic antiphospholipid syndrome; **VTE** = venous thromboembolism.

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

Preclinical work from a group at the South Australian Health and Medical Research Institute (SAHMRI) and SA Pathology published in *EMBO Reports* provides hope for patients with rare calreticulin (*CALR*)-driven myeloproliferative neoplasms (MPNs) reporting preliminary potential of an immunotherapeutic approach utilising a monoclonal antibody – 4D7 – targeted to a neoepitope in mutant forms of CALR. AusHealth plans to commence early phase clinical trials of 4D7 later in 2022 and these results are eagerly awaited. Based on results from BioMarin Pharmaceutical's phase 3 international GENEr8-1 trial in *The New England Journal of Medicine* that demonstrated improved endogenous clotting factor production and significantly decreased bleeding episodes in men with severe haemophilia A after a single infusion of the gene therapy valoctocogene roxaparvovec, the US Food and Drug Administration has designated it as a breakthrough therapy and regenerative medicine advanced therapy. If approved for use in this population it could substantially decrease the treatment burden associated with regular factor VIII (FVIII) infusions and improve patient outcomes. We also discuss results from the Dutch MR CLEAN-MED trial reported in *The Lancet* that elucidate the risks involved in the use of adjunctive antithrombotic medications during endovascular thrombectomy for acute ischemic stroke; look at the safety of coronavirus disease (COVID-19) vaccination in patients with immune thrombocytopenia; and finally, present results from an updated systematic review and meta-analysis that analysed the efficacy and safety of aspirin for primary cardiovascular (CV) risk prevention according to age.

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

Kind Regards,

Professor Harshal Nandurkar
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Reduced cardiovascular morbidity in patients with haemophilia

Authors: Van Der Valk P et al.

Summary: Results of a five-year multinational prospective study (NCT01303900) published in *Blood Advances* reveal a lower-than-expected CV morbidity burden in patients with haemophilia, supporting the hypothesis that haemophilia exerts a protective effect against CV disease (CVD). The study enrolled 709 male patients over the age of 30 years with any severity of haemophilia (mean age 48 years) from two Dutch and four UK haemophilia treatment centres between 2009 and 2011. The cohort was comprised predominantly of patients with haemophilia A (83.8%) with half having severe disease. At baseline patients were evaluated for five-year risk of thrombotic CV events including myocardial infarction and ischaemic heart disease, stroke or transient stroke using the QRISK2-2011 risk model. Of 579 patients with evaluable risk at baseline and follow-up data, a significantly lower five-year rate of fatal and non-fatal CV disease events was found, with a 2.4% absolute risk reduction versus the expected (4.1% vs 1.7%; relative risk [RR] 0.38; 95% confidence interval [CI], 0.18-0.80; Fisher exact test two-sided p=0.01). Subgroup analysis found a consistently lower than expected incidence of heart disease regardless of haemophilia severity with absolute risk reductions ranging from 2.6% to 4% (mild: 5% vs 1%, RR 0.20; non-severe: 4.7% vs 1.8%, RR 0.38; severe: 3.9% vs 1.3%, RR 0.33; all p<0.05).

Comment: Haemophilia is associated with bleeding morbidities. With longer survival and overall increasing incidence of CVD, this study prospectively compared the incidence of CVD in patients with haemophilia versus the predicted incidence in the wider population. Haemophilia had a significantly lower number of fatal and nonfatal CVD events than predicted (RR 0.38), corresponding with an absolute risk reduction of 2.4%. This risk reduction was seen in all types of haemophilia severities. The risk reduction was noted in all CVD risk groups: high-risk group (RR 0.42); intermediate-risk group (RR 0.43); and low-risk group (RR 0.17). This study supports the theory that very low FVIII or IX activity levels protect against thrombotic CVD. There was no statistically significant effect of severity of disease or factor level on CVD events. It is possible that lower clotting factor levels diminish pathologic clot formation at sites of unstable plaques.

Reference: Blood Adv 2022;6(3):902-08
Abstract

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Characteristics and risk factors for thrombosis in POEMS syndrome: A retrospective evaluation of 230 patients

Authors: Mellors P et al.

Summary: This Mayo Clinic study investigated factors contributing to risk for thrombotic events in patients with POEMS syndrome (named for the disorder's five major symptoms: **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal gammopathy and **S**kin abnormalities). The incidence of thrombosis in a retrospective cohort of 230 patients was 27%, with arterial events occurring at a higher rate compared to venous. One-quarter of all thromboses resulted in a stroke. Thrombocytosis, elevated haemoglobin/haematocrit, extravascular volume overload and splenomegaly were identified as risk factors for arterial thrombosis, and hyperprolactinemia was associated with increased risk for venous thrombosis. Significantly increased risk for thrombosis was observed in male patients with elevated haemoglobin or haematocrit (32% vs 5% and 42% vs 5%; respectively; both $p<0.001$). Based on these data the authors recommended prophylactic antiplatelet therapy and possibly anticoagulation for patients at risk for POEMS-associated thrombosis.

Comment: POEMS syndrome is a rare, multisystem paraneoplastic disorder driven by an aberrant plasma cell clone. Thrombocytosis and elevated vascular endothelial growth factor are recognised in POEMS, but there is no association between thrombocytosis and either ischemic stroke or thrombosis in general. The study cohort included all patients with a diagnosis of POEMS syndrome evaluated at Mayo Clinic, Rochester from June 2002 to March 2021. Rates of arterial, venous, and line-associated thromboses were 13%, 11%, and 2%, respectively for the 230 patients studied. Patients with arterial thrombosis had higher incidence of effusions and ascites. Splenomegaly was more common in patients with arterial thrombosis than in patients with no thrombosis (60% vs 39%, respectively). Another notable association was for elevated prolactin, which was more common among patients with venous thrombosis than without (71% vs 44%). Thrombosis showed a strong association with thrombocytosis and male gender with 29% of men with high platelet counts had arterial thrombosis compared with 6% of men with normal platelet count (odds ratio [OR] 6.67). Elevated sex-adjusted haemoglobin (60% vs 32%; OR 3.18) and haematocrit (58% vs 27%; OR 3.68) were more common in the thrombosis group, notably the arterial event group. Male gender, high haemoglobin or haematocrit also had strong positive correlation with the risk of arterial thrombosis. Of the 61 initial thrombotic events, there were 16 ischemic strokes, which were the most common thrombotic event, accounting for 26% of all thromboses and 53% of arterial thromboses. Deep vein thrombosis (DVT) was the most common venous thrombosis, occurring in 18 cases (69%). Most arterial and venous thromboses occurred prior to instituting POEMS directed therapy (77% and 54%). The take-home message is that consideration should be given for antiplatelet prophylaxis at a minimum for all patients at diagnosis given high overall rates of thrombosis and possibly full anticoagulation.

Reference: Blood Adv 2022;6(3):902-08
Abstract

Management strategies and clinical outcomes in patients with inferior vena cava thrombosis: Data from GARFIELD-VTE

Authors: Cohen O et al.

Summary: This population-based study extracted data from the global, prospective, observational Global Anticoagulant Registry in the FIELD - Venous Thromboembolism (GARFIELD-VTE) registry in order to elucidate optimal treatment strategies for inferior vena cava (IVC) thrombosis. Data from over seven thousand patients with objectively diagnosed venous thromboembolism (VTE) and a minimum of three-year follow-up were included in the analysis with therapeutic approaches and two-year outcomes compared between IVC thrombosis (n=100) and lower extremity DVT (n=7,629). Compared to the lower extremity DVT cohort, patients with IVC thrombosis were an average of eight-years younger at diagnosis (51.9 vs 59.8 years) and more than one-quarter had a concomitant active malignancy diagnosis, three-times more often than the comparator cohort (26% vs 8.9%). Differences in the type of anticoagulant were noted according to VTE type with IVC thromboses more often administered monotherapy with a parenteral anticoagulant (35.1% vs 15.9%) and less often a vitamin K antagonist such as warfarin, low molecular weight heparin rivaroxaban or dabigatran or a direct oral anticoagulant (25.8% vs 32% and 35.1% vs 49%, respectively). Inferior two-year outcomes were noted in patients with IVC thrombosis with significantly higher all-cause mortality (13.28 vs 4.91 per 100 person-years) and a marginally higher incidence of major bleeding (2.03 vs 1.66).

Comment: IVC thrombosis is rare and thus optimal treatment strategies and outcomes are unclear. This paper is of interest as it gives a perspective on the outcomes of IVC thrombosis in 100 patients as compared to lower extremity DVT in over 7,000 subjects. An advantage is that it is from the Garfield registry that collects data from many countries and hence the conclusions can be generalised. IVC thrombosis occurs most commonly with proximal extension of lower extremity DVT, but it may occur in isolation in patients with cancer or in those with IVC atresia or other IVC abnormalities. Heritable or acquired hypercoagulable states increase the risk of IVC thrombosis. The incidence of IVC thrombosis in the registry was 1.3% and the patients were younger. As expected, computed tomography (CT) was used more often to diagnose IVC thrombosis than lower extremity DVT (48% vs 4.3%). Active cancer or past history of cancer was more common in IVC thrombosis, while trauma and surgery were more frequent in lower extremity DVT. The use of thrombolysis and parenteral anticoagulation was more commonly used in IVC thrombosis. The incidence rates of VTE recurrence in patients with IVC thrombosis or lower extremity DVT were comparable. The incidence rate of major bleeding was slightly higher in IVC thrombosis compared to lower extremity DVT; 2.03 vs 1.66 per 100 person-years. The all-cause mortality rate was higher in patients with IVC thrombosis than in those with lower extremity DVT. IVC thrombosis patients with active cancer appear to have higher mortality than lower extremity DVT patients with active cancer. The study also demonstrated that patients with IVC thrombosis are generally treated according to international practice guidelines for VTE.

Reference: J Thromb Haemost 2022;20(2):366-74
Abstract

Targeting human CALR-mutated MPN progenitors with a neoepitope-directed monoclonal antibody

Authors: Tvorogov D et al.

Summary: This preclinical study led by researchers in South Australia in collaboration with an Austrian group, details the design and *in vitro and in vivo* assessment of 4D7, a rat anti-CALR IgG2α monoclonal antibody targeted to a neoepitope in *CALR* exon 9 conserved in both type 1 and type 2 frameshift mutations, with potential therapeutic application for myeloproliferative neoplasms (MPNs). Analysis showed that the antibody was specific for mutant CALR and prevented CALR dimerisation, inhibiting subsequent downstream signalling and megakaryocyte differentiation of mutant CALR myelofibrosis progenitors. In both patient samples and xenografted bone marrow models of mutant CALR-dependent myeloproliferation, 4D7 demonstrated inhibition of cancer cell growth and extended survival without adverse events.

Comment: Mutations within *CALR*, the second most common genetic aberration associated with primary myelofibrosis, are observed in 70% of non-*JAK2V617F* and non-myeloproliferative leukaemia cases and are found in 20%–30% of essential thrombocytopaenia. Patients with *CALR* mutations do not effectively respond to Janus kinase (JAK) inhibitor therapy. Mutant CALR protein lacks an endoplasmic reticulum retention signal and is passively secreted out of cells. Mutant CALR forms a homodimer that can bind-to and activate the TPO receptor, causing the myeloproliferative phenotype. Homodimerisation of CALR is critical for the initiation of abnormal signalling by TpoR. The monoclonal antibody 4D7 is specific for the recognition of mutant CALR peptide and inhibits TpoR activation by preventing homodimerization of mutant CALR and hence inhibits signal transduction. It has no activity for JAK2 mutation-initiated disease. This paper shows that 4D7 had strong inhibitory activity on cells that were resistant to ruxolitinib. In xenograft models, 4D7 blocked CALR-dependent proliferation and prolonged survival. Importantly, this antibody can be used in both insertion and deletion CALR mutation-positive patients and appeared to have minimal or no effects on normal cells *ex vivo*, thereby increasing its utility.

Reference: EMBO Rep 2022;23(4):e52904
Abstract

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Valoctocogene roxaparvovec gene therapy for haemophilia A

Authors: Ozelo M et al., for the GENEr8-1 Trial Group

Summary: Results from BioMarin Pharmaceutical's phase 3 international GENEr8-1 trial of valoctocogene roxaparvovec for severe haemophilia A published in *The New England Journal of Medicine* indicate that the gene therapy utilising an adeno-associated viral vector 5 (AAV5) to mediate gene transfer restored endogenous FVIII production and decreased bleeding episodes. The trial enrolled 134 adult men with residual FVIII levels ≤ 1IU/dL who had been on prophylactic replacement therapy for at least one year. Trial inclusion criteria specified that patients have no pre-existing anti-AAV5 antibodies or history of FVIII inhibitor development. Patients were administered a single infusion of valoctocogene roxaparvovec at a dose of 6 x10^{13} vector genomes/kg. The trial met its primary outcome measure to demonstrate efficacy in a modified intention-to-treat population consisting of HIV-negative participants (n=132) with mean increases in FVIII activity levels of 41.9 IU/dL at weeks 49-52 (median change 22.9 IU/dL). Valoctocogene roxaparvovec also virtually ameliorated FVIII use and significantly reduced bleeding episodes, eliciting mean reductions in the annualised rates of 98.6% and 83.8%, respectively (annualised rate of FVIII infusions at baseline vs after infusion, 135.9 vs 2 per year; annualised rate of bleeding episodes at baseline vs after infusion, 4.8 vs 0.8 per year). Serious adverse events were reported in 16.4% of the cohort. There were no cases of FVIII inhibitor development or thrombosis.

Comment: Valoctocogene roxaparvovec substantially increased FVIII activity and reduced the annualized rates of FVIII use and bleeding as compared with FVIII prophylaxis. At weeks 49 through 52, a median FVIII activity level of 5 IU/dL or higher was found in 88.1% of participants. The annualized rates of FVIII use and treated bleeding declined by 98.6% and 83.8%, respectively, after infusion. There was variability in responses with 5.3% having a median FVIII activity level greater than 150 IU/dL. During the same interval, 12 participants (9.1%) had a median FVIII activity level of less than 3 IU/dL. Overall, 90.3% of the participants in the study had either no treated bleeds or fewer treated bleeds after infusion than with FVIII prophylaxis. The expression of the transferred gene appears to decline over time. Data from phase 1-2 study shows that median FVIII activity was 60.3, 26.2, 19.9, 16.4, and 8.2 IU/dL after one, two, three, four and five years, respectively. Hypersensitivity of unknown cause occurred after infusion in 5% of participants. The most common adverse events were elevations in alanine aminotransferase levels. There was no assessment of potential vector genome integration into the host nuclear genome.

Reference: N Engl J Med 2022;386(11):1013-25
Abstract

Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial

Authors: van der Steen W et al., for the MR CLEAN-MED investigators

Summary: The use of adjunctive antithrombotic medications during endovascular thrombectomy for acute ischemic stroke doubles the odds of symptomatic intracranial haemorrhage without eliciting functional improvements according to results from the Dutch MR CLEAN-MED study reported in *The Lancet*. The trial utilised a 2 x 3 factorial design to elucidate if the addition of antithrombotic therapy to surgical clot removal elicits a clinical benefit without compromising on safety. A total of 663 adult patients who underwent thrombectomy within six hours of ischaemic stroke due to an intracranial large-vessel occlusion with no evidence of intracranial haemorrhage on imaging were enrolled from 15 Dutch centres over a three-year period spanning 2018 to 2021. Two consecutive rounds of randomisation divided patients into aspirin (300 mg bolus) or no aspirin periprocedural treatment arms followed by low-dose heparin, moderate-dose heparin (5000 IU bolus followed by 500 or 1250 IU/h for six hours, respectively) or no heparin arms, leading to a total of six trial arms. Analysis of a modified intention-to-treat population (n=628) revealed a roughly two-fold increased incidence and almost double odds of symptomatic intracranial haemorrhage in patients who received either aspirin or heparin compared to no perioperative antithrombotic (aspirin; 14% vs 7%, adjusted OR 1.95, 95% CI 1.13-3.35; heparin: 13% vs 7%, adjusted OR 1.98, 95% CI 1.14-3.46). An interim efficacy analysis conducted after the trial was terminated due to safety concerns showed a non-statistically significant trend towards inferior functional outcomes with aspirin or heparin use, as assessed using the modified Rankin Scale (adjusted OR 0.91 and adjusted OR 0.81, respectively).

Comment: Two prior observational studies found that periprocedural use of heparin was associated with good clinical outcomes and low risks of intracranial haemorrhage. But no randomised trials on treatment with periprocedural anti-thrombotics in patients treated with endovascular treatment have been done and there is a large variation in routine practice. This the first randomised controlled trial evaluating the safety and efficacy of periprocedural use of aspirin or unfractionated heparin during endovascular treatment of acute ischaemic stroke. All patients had a CT or magnetic resonance imaging scan at enrolment ruling out intracranial haemorrhage. Both aspirin and heparin were given within a few minutes of groin puncture. The unfavourable shift in the modified Rankin Scale distribution at 90 days after randomisation was significant for moderate-dose unfractionated heparin (adjusted common OR 0.42) but not for low-dose unfractionated heparin (0.86) compared with those who did not receive unfractionated heparin. Symptomatic intracranial haemorrhage occurred more often in patients allocated to receive aspirin than in those not receiving aspirin (OR 1.95), as well as in patients allocated to receive unfractionated heparin than in those not receiving unfractionated heparin (OR 1.98). In patients allocated to low-dose unfractionated heparin, there was a non-significant increase in the rate of symptomatic intracranial haemorrhage. There was higher recanalisation rates in the unfractionated heparin group, but this benefit did not outweigh the increased risk of symptomatic intracranial haemorrhage.

Reference: Lancet 2022;399(10329):1059-69
Abstract

Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome

Authors: Woller S et al.

Summary: A randomised trial - ASTRO-APS (NCT02295475) – funded by Bristol-Myers-Squibb and Pfizer Pharmaceuticals evaluated the efficacy and safety 12-months of anticoagulation therapy with apixaban versus warfarin for prevention of recurrent thrombosis in patients with thrombotic antiphospholipid syndrome (TAPS). A total of 48 patients (mean age 47.3 years; 95.8% white) who had received at least six months of therapeutic anticoagulation for secondary prevention of thrombosis were accrued, predominantly from the Intermountain Medical Centre in Utah, USA. Patients were randomised to one-year of treatment with apixaban (dosed at 2.5 mg twice daily in the first 25 patients before amendment to 5 mg twice-daily; n=23) or dose adjusted warfarin to a target international normalised ratio 2-3 (n=25). An ad hoc data and safety monitoring board review that revealed an increased incidence of stroke in the apixaban arm initiated a second protocol amendment to exclude patients with a history of arterial thrombosis from the apixaban treatment arm. Analysis of the primary efficacy outcome – the combined rate of clinically overt arterial and/or venous thromboses or vascular death – was prevented by non-converging Cox proportional hazard models. Data showing that more than one-quarter of patients in the apixaban arm experienced a stroke compared to none in the warfarin arm (n=6 vs n=0) suggests that apixaban is not an adequate substitution for warfarin in this population.

Comment: This study is worthy of discussion as there is enormous interest to test the efficacy of direct oral anticoagulants in TAPS to obviate the need to persist with warfarin. Approximately 30% of patients were triple positive. Patient enrolment underwent two protocol changes as described above. The increment in dose intensity from 2.5 mg twice daily to 5 mg twice daily was after the occurrence of three strokes in the apixaban arm. Subsequently, after three additional strokes in the apixaban cohort, patients with arterial thrombosis were excluded from the study and those on apixaban were changed to warfarin. Overall, there were six thrombotic events among patients randomised to apixaban, all of which were strokes. Two of these patients were included in the study because of a prior DVT. There were no thrombotic events in the warfarin arm. There were no venous thromboses. Not unexpectedly, patients preferred apixaban over warfarin. It is possible that there exists a subset of TAPS patients for which apixaban may be a reasonable alternative to vitamin K antagonism and ongoing studies will provide clarity.

Reference: Blood Adv 2022;6(6):1661-70
Abstract

COVID-19 vaccination in patients with immune thrombocytopenia

Authors: Visser C et al.

Summary: This Dutch multicentre observational study evaluated the safety of COVID-19 vaccination in patients with immune thrombocytopenia (ITP). Analysis was based on a cohort of patients with ITP (n=218; mean age 55 years; mean baseline platelet count, 106 x 10^9/L) from nine hospitals in the Netherlands who received a two-dose regimen of COVID-19 vaccine (predominantly with the Moderna mRNA vaccine, 92.2%) administered four weeks apart. Approximately two-thirds (62.4%) of patients had chronic disease with 29.5% undergoing treatment at the time of vaccination. The other one-third of patients were in remission. A cohort of healthy participants from the Renal patients COVID-19 VACcination Immune Response (RECOVAC IR) study (n=200; mean age 58 years; mean baseline platelet count, 256 x 10^9/L) who received two doses of the Moderna vaccine served as controls. More than half of both cohorts had decreased platelet counts following vaccination (55% vs 63%) but linear mixed-effects modelling analysis found no significant difference between groups at one and four weeks after each dose of vaccine. Disease exacerbations were reported in 13.8% of patients with ITP (n=30) and a bleeding event in 2.2% (n=5). Platelet count < 50 x 109/L, ITP treatment at time of vaccination and age were associated with increased risk for ITP exacerbation with ORs of 5.3, 3.4 and 0.96 per year, respectively. The study authors concluded that COVID-19 vaccination is safe in this population but patients with the identified risk factors should be closely monitored.

Comment: Exacerbation of thrombocytopenia in patients with ITP after COVID-19 vaccination has been described in retrospective studies, but a systematic evaluation of platelet counts over time is missing. This work systematically monitored platelet counts, bleeding events and ITP exacerbations in routine clinical practice. Both ITP and healthy controls had significantly decreased platelet counts as a result of COVID-19 vaccination. This suggests that exacerbation or development of thrombocytopenia because of COVID-19 vaccination might be unrelated to ITP, as evidenced by the fact that an interaction could not be found between platelet counts over time and whether a subject had ITP. It is important to note that almost all patients with ITP in this study received a messenger RNA vaccine, so caution is warranted when generalising these data to other vaccines.

Reference: Blood Adv 2022;6(6):1637-44
Abstract

Usefulness of a refined computed tomography imaging method to assess the prevalence of residual pulmonary thrombi in patients 1 year after acute pulmonary embolism

Authors: Nakano Y et al.

Summary: The Nagoya PE study, a Japanese prospective, observational study utilised modified multidetector computed tomography scanning as part of a multifaceted assessment protocol to investigate the burden of residual pulmonary thrombi after acute symptomatic pulmonary embolism (PE). The study enrolled 52 patients with acute PE from 46 Japanese hospitals and conducted follow-up assessments at one month, six months and one year. One-year after acute PE residual thrombi was detected in three-quarters of evaluable patients (32/43; median modified CT obstruction index, 10.7%). Chronic thromboembolic pulmonary hypertension developed in two patients (3.8%). Multivariate analysis revealed 103-fold increased odds of longer-term (one year) residual thrombi associated with residual thrombi at one month (OR 103.4; 95% CI, 4.2-2542.1). Long-term thrombotic burden was related to right ventricular overload at diagnosis (tricuspid regurgitation pressure gradient ≥60 mmHg: β=0.367, *p*=0.003; left ventricular end-diastolic dimension at diagnosis, β= –0.435, *p*=0.001).

Comment: Post-PE syndrome is defined to include persistent dyspnoea, exercise limitation, and impaired quality of life after acute PE. Persistent pulmonary thrombi are among the main components of post-PE syndrome. Detection of residual pulmonary thrombi is also dependent on the technique used (lung perfusion scans versus CT pulmonary angiogram). This study used a modified scanning protocol using fast multidetector computed tomography to detect small thrombi up to the level of the subsegmental branches of the pulmonary artery and combined it with long-term multifaceted assessment and a modified index for scoring thrombotic burden. At diagnosis of the 43 patients, 44% of the study population had BNP >100 pg/ml or NT pro-BNP >600 pg/ml. At one year, 95% of patients were continuing to receive anticoagulation therapy; among them, 95% received a direct oral anticoagulant. Compared to 79% at one month after acute symptomatic PE, 74% of study patients demonstrated residual pulmonary thrombi at one year. Approximately 26% of patients were at NYHA class 2 or higher, and 10% had a six-minute walking distance of < 330 m. Residual pulmonary thrombi at one month after acute PE evaluated by conventional CT protocol was significantly associated with residual pulmonary thrombi at one year evaluated by the modified CT scanning protocol used here. Non radiographical criteria predictive of the residual pulmonary thrombotic burden at one year were tricuspid regurgitation pressure gradient ≥60 mmHg and left ventricular end-diastolic dimension at diagnosis. This paper reports a significantly high frate of residual PE associated with symptoms. This raises consideration for a modified CT imaging protocol, as described here, to be incorporated in routine follow-up of patients with PE.

Reference: J Thromb Haemost 2022;20(4):888-98
Abstract

Efficacy and safety of aspirin for primary cardiovascular risk prevention in younger and older age

Authors: Calderone D et al.

Summary: An updated systematic review and meta-analysis of 173,810 subjects from 21 randomised studies conducted by a group from Azienda Ospedaliero-Universitaria Policlinico "G. Rodolico – San Marco" University of Catania in Italy, reports an age dependent effect of aspirin in patients without overt CVD with a benefit in mortality reduction restricted to younger patients. At a mean follow-up of 5.3 years, aspirin did not demonstrate efficacy for protection against all-cause mortality versus control (risk ratio 0.96; 95% CI, 0.92-1.00; *p*=0.057). Significant reductions in major adverse CV events including myocardial infarction and transient ischaemic attack were offset by increased risk of major bleeding, intracranial haemorrhage and gastrointestinal bleeding. When age was considered as a treatment modifier, aspirin was associated with reduced all-cause death in individuals younger than 65 years.

Comment: There is evidence that aspirin is beneficial after a CV event, but its role in primary prevention has been subject to a number of studies with conflicting results. Its use in this setting needs to be guided by evidence rather than dogmatic belief. This paper is noteworthy for the analysis of over 170,000 subjects and almost one million patient-years of follow-up over 21 trials. The main take-home points are that aspirin was not associated with significant reductions in all-cause death and CV death, while the risk of myocardial infarction was significantly reduced, mostly due to a reduction in nonfatal myocardial infarction. The reduction in CV events was modest and high numbers of patients needed to be treated to prevent one event. The protective effects were balanced by a significant increase in major bleeding, including intracranial haemorrhage and gastrointestinal bleeding. The risk to benefit balance being less favourable in older people, even though they are more likely to have unrecognized coronary artery disease. For people aged ≥65 years, if 1,000 people took aspirin for five years, it would result in three fewer myocardial infarctions and two fewer strokes but without effect on CV death and result in five additional non-cardiovascular deaths, four more intracerebral bleeds and seven more major bleeding events. For people aged <65 year, if 1,000 people took aspirin for five years, the authors predicted that this would lead to two fewer deaths, one CV and one non-CV, about three fewer myocardial infarctions, and one less stroke, but one more intracerebral bleed and nine more major bleeding events. An accompanying editorial to this paper by John Cleland aptly summarised that aspirin taken long-term may "give with one hand but take away with the other".

Reference: Thromb Haemost 2022;122(3):445-55
Abstract

Thrombosis & Haemostasis Research Review™

Independent commentary by Prof Harshal Nandurkar

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

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