Thrombosis & Haemostasis Research Review™

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In this issue:

Abbreviations used in this issue:

AF = atrial fibrillation; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **CT** = computed tomography; **DVT** = deep vein thrombosis; **FVIII** = clotting factor VIII; **IL** = interleukin; **iTTP** = immune-mediated thrombotic thrombocytopenic purpura; **NOAC** = non-vitamin K antagonist oral anticoagulants; **OR** = odds ratio; **PE** = pulmonary embolism; **PT** = pulmonary thrombosis; **TTP** = thrombotic thrombocytopenic purpura; **VTE** = venous thromboembolism; **VWF** = von Willebrand factor.

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

A Canadian prospective diagnostic management study finds that utilisation of the 4D algorithm comprised of a combination of Wells clinical pretest probability and D-dimer concentration can safely reduce the use of ultrasound imaging assessment of suspected deep vein thrombosis (DVT) cases by identifying patients at low risk. This algorithm rules out a DVT diagnosis in patients with D-dimer concentrations below thresholds of 1,000 and 500 ng/mL plus a low or moderate clinical probability, respectively, and may significantly reduce both the time and cost involved in the diagnostic procedure. Results from a multicentre, prospective cohort study published in *Annals of Internal Medicine* support the use of anticoagulation in patients with isolated subsegmental pulmonary embolism (PE) without proximal DVT, finding a higher-than-expected rate of recurrent venous thromboembolism (VTE) without its use. The novel investigational fusion protein efanesoctocog alfa, a new class of clotting factor VIII (FVIII) replacement therapy independent of the von Willebrand factor (VWF)-imposed FVIII half-life ceiling, may offer a reduced dosing schedule for prophylactic treatment of severe haemophilia A with results from a phase 1 study published in *Blood Advances* reporting no safety or tolerability concerns and high sustained levels of FVIII. Further results from phase 3 testing are eagerly awaited. Finally, results from the Consortium of Leaders in the Study of Traumatic Thromboembolism (CLOTT) study group indicate that posttraumatic *de novo* pulmonary thrombosis (PT) may be a clinical entity distinct from PE and constitute the bulk of pulmonary clots in this setting.

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

Kind Regards,

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Diagnosis of deep vein thrombosis with D-dimer adjusted to clinical probability: prospective diagnostic management study

Authors: Kearon C et al.

Summary: The 4D designer D-dimer DVT diagnosis study (NCT02038530) was conducted by a research group at McMaster University, in Ontario, Canada to evaluate the safety of a novel diagnostic algorithm that restricts upfront and follow-up proximal vein ultrasonography to patients with a high clinical probability of DVT based on D-dimer concentrations in combination with clinical assessment. A total of 1,508 adult patients who presented to one of 10 University-based emergency department or outpatient clinics in Canada with clinically suspected DVT were stratified into low, moderate or high-probability groups based on Wells pretest scores. Only patients with either a high probability of DVT (Well scores ≥3) or a moderate or low-probability (Well score 1/2 or -2 to 0, respectively) in combination with D-dimer concentrations below 500 or 1000 ng/mL, respectively, underwent proximal ultrasound imaging of the symptomatic leg(s) from the common femoral vein down to the calf vein trifurcation and those with ultrasound evidence of venous segment compressibility received anticoagulant therapy. Patients outside these criteria received no further testing or treatment. One-week follow-up ultrasonography was restricted to the subgroup of patients with a D-dimer concentration above 3000 ng/mL plus a low or moderate Well score or D-dimer concentration > 1000 ng/mL plus a high Well score. This testing algorithm diagnosed DVT in 11.5% (n=173) of the cohort, 168 on ultrasound at presentation and five at one-week repeat ultrasound. At 90-day follow-up, the prevalence of confirmed symptomatic proximal DVT in the cohort of patients who did not receive anticoagulant therapy was 0.6% (8/1,275). The authors reported that compared to the traditional DVT testing strategy this algorithm reduced ultrasonography by 47% (mean scans per patients, 0.72 vs 1.36) and was safe.

Comment: Clinical evaluation, D-dimer blood testing, and ultrasound imaging are the three pillars used to diagnose lower limb DVT. DVT is considered excluded if clinical pretest probability is low and the D-dimer test is negative. Since the application of the original Wells criteria-based diagnostic strategy over 20 years ago, various modifications have been studied to improve the predictive values and avoid expensive sonography and other radiological investigations. Compared to the conventional approach, use of the above algorithm reduced the need for ultrasounds by 47%. Moreover, the application of higher D-dimer cut-offs to determine the need for repeat proximal ultrasound imaging safely reduces the need for repeat ultrasound scanning. The caveat to the global utilisation of such rules is the local ease of accessibility of D-dimers versus that of ultrasound. If DVT is to be managed by primary practitioners without referral to a hospital emergency department, it would require prompt availability of D-dimer assays. It is often quicker to get an ultrasound in the community than a D-dimer level, which requires blood to be sent to a centralised laboratory.

Reference: BMJ 2022;376: e067378
Abstract

Association of recent use of non–vitamin K antagonist oral anticoagulants with intracranial haemorrhage among patients with acute ischemic stroke treated with alteplase

Authors: Kam W et al.

Summary: Kam et al retrospectively interrogated data from the Get with The Guidelines-Stroke and Addressing Real-world Anticoagulant Management Issues in Stroke (ARAMIS) registries to assess the safety of the standard reperfusion therapy, alteplase, for acute ischemic stroke in patients who have recently taken a non-vitamin K antagonist oral anticoagulant (NOAC). Analysis was based on 163,038 patients (median age 70 years) hospitalised for an acute ischaemic stroke at a US hospital affiliated with the Get with The Guidelines–Stroke program between 2015 and 2020 who received intravenous alteplase. While rates of symptomatic intracranial haemorrhage within 36-hours of alteplase therapy were absolutely higher in the cohort of patients who had used NOAC's in the last week (n=2,207) compared to those who had not (n=160,831; 3.7% vs 3.2%) the risk did not meet statistical significance after adjustment for baseline clinical factors (adjusted odds ratio [OR] 0.88; 95% confidence interval [CI], 0.70-1.10). Secondary safety outcomes were consistent in this finding with higher crude rates of inpatient mortality in the cohort on concurrent NOAC therapy that did not reach statistical significance (6.3% vs 4.9%; adjusted OR 0.84; 95% CI, 0.69-1.01) while four of seven secondary functional outcomes including proportion of patients discharged home favoured the NOAC cohort.

Comment: The devil is in the details and in this assessment of registry data, key factors such as more precise information on the time of last NOAC dose was available in only a small number of patients. Most patients on NOACs had atrial fibrillation (AF) and the strokes were more likely to be embolic events. In the non-NOAC population, the composition of the target occlusion may be more variable, and sometimes include admixed atherosclerosis and supervening thrombosis. It's possible that recanalisation after thrombolysis may be more effective in the setting of embolic strokes. Another possibility being considered is that patients on NOACs may have low residual levels that may aid in maintaining recanalisation post thrombolysis. Even with those caveats, it is reassuring that there is at least no signal of increased intracranial haemorrhage.

Reference: JAMA 2022;327(8):760-71
Abstract

Challenging traditional paradigms in posttraumatic pulmonary thromboembolism

Authors: Knudson M et al.

Summary: Results from this prospective, observational, multicentre cohort study conducted by the Consortium of Leaders in the Study of Traumatic Thromboembolism (CLOTT) study group published in *JAMA Surgery* suggest that posttraumatic *de novo* pulmonary thrombosis (PT) may be a clinical entity distinct from PE and constitute the bulk of pulmonary clots in this setting. A total of 7,880 adult patients under 41 years of age (mean age 29.1 years) hospitalised at one of 17 US trauma centres following a traumatic injury with a moderate or high level of VTE risk in a two-year period spanning 2018 to 2020, inclusively, constituted the study cohort and were followed for 30 days or until discharge. Pulmonary clots were visualised using chest computed tomography (CT) in 157 patients (2%), three-quarters of which were deemed to be *de novo* PT (n=117; 74.5%) and the remainder embolic (n=40) based on the presence of concomitant DVT. Shock on hospitalisation was significantly more prevalent in patients with pulmonary clots or DVT compared to those without (~26% vs 6.2%). Shock on admission and major chest injury (Abbreviated Injury Score of at least three) were associated with a significantly increased likelihood of PT versus DVT or PE (OR 2.74 and OR 1.72, respectively).

Comment: This paper discusses the possibility that PT can arise *de novo* without DVT and may be a manifestation of local inflammation, rather than the traditional assumption that PE occurs due to embolism of a leg or pelvic vein thrombus. The 17 CLOTT trauma surgeons contributed to this prospective study with the main objective of defining the pathogenesis of, and risk factors for, posttraumatic PT. For the purposes of this study, pulmonary clots seen in association with any DVT that developed within the 30 days were considered PE, whereas isolated clots without known DVT were considered *de novo* PT. Risk factors independently associated with the development of PT but not DVT or PE include shock on admission (OR 2.74), major chest injury (OR 1.72) and a history of VTE (OR, 5.39). A major limitation of this study was the assumption that pulmonary clots not associated with DVT are not embolic, but only 64.2% of patients with DVT and pulmonary clot had a duplex DVT scan close to their CT with positive findings in this study. It is possible that DVT that developed before the PE was simply missed. The presence of both DVT and pulmonary clot in the same patient during hospitalisation does not prove that the pulmonary clot is embolic. Another limitation was that it was an observational study, the use of prophylactic measures, DVT screening procedures, and the treatment of any identified clots was variable across the 17 centres. The correlation of chest trauma and shock with PT raises the hypothesis that local pulmonary endothelial injury leads to *in situ* thrombosis. Virchow's Triad can be modified by retaining the components of vessel wall injury and hypercoagulability but replacing stasis with inflammation.

Reference: JAMA Surg 2022;157(2): e216356
Abstract

Risk for recurrent venous thromboembolism in patients with subsegmental pulmonary embolism managed without anticoagulation

Authors: Le Gal G et al.

Summary: This multicentre prospective cohort study (NCT01455818) was conducted to determine if patients with very small PE localised in the subsegmental pulmonary arteries (subsegmental PE) can be safely managed without anticoagulation. Primary analysis included 266 patients with newly diagnosed isolated (single or multiple) subsegmental PE, diagnosed by the presence of a subsegmental artery intraluminal filing defect on repeated bilateral ultrasonography in the absence of proximal DVT (negative leg limb ultrasonography), who were monitored for 30-days but did not receive blood thinners. The cumulative incidence of recurrent VTE at 90-days was 3.1% and was higher in patients with multiple versus isolated subsegmental PEs (5.7% vs 2.1%). The authors noted that the rate of recurrent VTE was higher than expected.

Comment: Prolific use of CT has led to the increase in the identification of acute PE, including thrombi isolated to the subsegmental pulmonary arteries. While the incidence of PE has increased, the case-fatality rate has been decreasing, suggesting overdiagnosis and increase in less severe thrombi. The clinical significance of single or multiple isolated subsegmental PE (without thrombosis in segmental or more proximal vessels) remains unknown. The American College of Chest Physicians clinical practice guidelines suggest clinical surveillance over anticoagulation in selected patients with subsegmental PE without lower-extremity DVT who have low risk for recurrent VTE (low level of evidence, grade 2C). In this prospective international multicentre cohort study, patients with single or multiple isolated subsegmental PE without proximal DVT were managed without anticoagulation to assess the rate of recurrent VTE. A significantly higher rate of recurrent VTE was noted, much more than the postulated rate of 1% at 90-days and hence, the study was terminated. The incidence of recurrence increased with age (1.8% in 65 years or younger and 5.5% in older than 65 years). These data have clinical implications that need more corroboration.

Reference: Ann Intern Med 2022;175(1):29-35
Abstract

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).

Low rates of venous thromboembolism in hospitalised COVID-19 patients: an Australian experience

Authors: Ong J et al.

Summary: This retrospective, single-centre cohort study from Peninsula Health in Melbourne, Australia, reports no cases of VTE in patients hospitalised for coronavirus disease 2019 (COVID-19) in the setting of a risk-adapted thromboprophylaxis protocol. The study cohort was comprised of 86 elderly patients (median age 77 years; 73% cognitive impairment) hospitalised between March and August 2020 with any severity of COVID-19 (34% mild, 41% moderate, 25% severe/critical disease) who received anticoagulation, predominantly with enoxaparin, as thromboprophylaxis. Patients with a pre-existing indication such as a history of VTE or AF (n=16, 18.6%) continued their premorbid anticoagulation regimen (apixaban, dabigatran, rivaroxaban, warfarin) while almost all other patients (94%) initiated dose-adjusted enoxaparin. During hospitalisation there were no cases of radiologically confirmed symptomatic DVT or PE. The in-hospital mortality rate was 24%. The authors concluded that a thromboprophylaxis strategy adapted to consider disease severity, bodyweight and renal function may have contributed to the very low rates of VTE in this study.

Comment: This is an Australian study examining the efficacy of using a risk-adapted strategy for intensity of thromboprophylaxis. Therapeutic anticoagulation was continued in patients with a pre-existing indication. All other patients without a contraindication received enoxaparin, with dose adjusted according to disease severity, weight and renal function. Dosage was not adjusted to D-dimer level. The primary outcome was symptomatic DVT or PE during hospital admission and confirmed on radiological scans. There were no routine lower limb screening ultrasound examinations. Eighty-one (94%) patients received anticoagulation, either continuation of pre-existing therapeutic anticoagulation or thromboprophylaxis. There was high level of adherence to protocols (90%). No in-hospital VTE was diagnosed. There were four bleeding events comprising of one clinically significant non-major bleed on a patient who was already on therapeutic anticoagulation for pre-existent VTE and three cases of minor bleeds. This report from an Australian context demonstrates that use of risk-adapted thromboprophylaxis according to disease severity, bodyweight and renal function in hospitalised COVID-19 patients is effective in preventing VTE.

Reference: Intern Med J 2022;52(1):37-41
Abstract

Non-vitamin K antagonists versus warfarin in patients with atrial fibrillation and bioprosthetic valves

Authors: Cardoso R et al.

Summary: This systematic review and meta-analysis aimed to indirectly compare the efficacy and safety of NOACs versus warfarin for thromboprophylaxis in patients with AF and bioprosthetic valves or valve repair. Four randomised clinical trials including 1,379 patients were identified from an online search of three databases - EMBASE, PubMed and Cochrane – and included in the pooled meta-analysis. Results showed that compared to warfarin, NOACs had a higher likelihood of preventing thromboembolic events (incidence of stroke or systemic embolism, 1.9% vs 3.7%; OR 0.43; p=0.02) and had a favourable safety profile (incidence of major bleeding, 2.8% vs 4.7%; OR 0.49; p=0.02). Comparable rates of ischaemic stroke, haemorrhagic stroke, cardiovascular death and all-cause mortality were found with either thromboprophylaxis. Based on these results use of NOACs should be prioritised in this population.

Comment: There is a paucity of randomised data to guide the optimal anticoagulation strategy in patients with AF and bioprosthetic valves. This systematic review and meta-analysis compared NOACs as a class with warfarin in patients with bioprosthetic valves or surgical valve repair. In 1,379 patients with AF and bioprosthetic valves or valve repair, stroke and systemic embolism was significantly lower in patients treated NOACs (1.9%) compared with warfarin (3.7%). The incidence of major bleeding was also significantly lower with NOACs (2.8%) compared with warfarin (4.7%). One caveat to the interpretation of the bleeding data in this study was the low rate of concomitant aspirin use in the study population (approximately 16%). It is important to note that in the 2020 American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines AHA/ACA guideline for patients with bioprosthetic valves, aspirin is recommended only in the absence of other indications for anticoagulants (class 2a).

Reference: Am J Med 2022;135(2):228-234.e1
Abstract

Microlyse: a thrombolytic agent that targets VWF for clearance of microvascular thrombosis

Authors: de Maat S et al.

Summary: de Maat and colleagues from the University Medical Centre Utrech, Utrecht University in the Netherlands have expanded on their previously published mouse model work that found a benefit to systemic plasminogen activation for thrombotic thrombocytopenic purpura (TTP). In order to activate plasminogen more specifically at target sites of microvascular occlusion the group developed a fusion protein – Microlyse - comprised of an anti-VWF nanobody bonded to the protease domain of urokinase plasminogen activator. Microlyse demonstrated specific platelet-VWF complex destruction *in vivo* and exerted its activity more rapidly compared to the bivalent antibody caplacizumab. In rodent models Microlyse attenuated thrombocytopenia without compromising haemostasis and the study authors concluded that Microlyse may be an effective treatment for TTP.

Comment: Microvascular thrombosis in TTP is driven by the interaction between platelet glycoprotein Ibα and VWF. This does not require platelet activation, coagulation system activation, or fibrin formation. The current standard of care for acute acquired TTP attacks includes plasma exchange to remove autoantibodies and restore ADAMTS13 activity. Caplacizumab is a bivalent single-chain antibody that blocks the binding of platelets to the VWF A1 domain for treatment of acquired TTP. There is evidence for activation of endogenous plasminogen in patients during TTP attack and systemic plasminogen activation is of benefit in preclinical models. The innovative therapeutic described here takes advantage of the observation that plasminogen can directly bind to VWF and that the conversion of plasminogen to plasmin localised to the sites of microvascular occlusion led to the targeted destruction of platelet-VWF complexes on activated endothelial cells. In a preclinical model of TTP, the authors confirm that this novel therapeutic 'Microlyse' (consisting of a single polypeptide composed of the enzymatic domain of urokinase plasminogen activator, fused together with a VWF-targeting V_HH through a glycine-serine linker sequence) bound to VWF and degraded platelet-VWF complexes on endothelial cells, which led to improvement in platelet counts and lactate dehydrogenase without any haemostatic defects (as studied by tail-clip bleeding). These actions of Microlyse were superior to those of caplacizumab in the model studied. Further studies are planned to optimise Microlyse activity and it may have a role in broader thrombotic conditions of stroke and myocardial infarction.

Reference: Blood 2022;139(4):597-607
Abstract

Efanesoctocog alfa for haemophilia A: results from a phase 1 repeat-dose study

Authors: Lissitchkov T et al.

Summary: Sanofi and Swedish Orphan Biovitrum AB assessed the safety of repeat dosing of the novel investigational FVIII therapy efanesoctocog alfa (BIVV001) as a once-weekly prophylactic therapy for haemophilia A. The phase 1 open-label, single-centre trial (EU Clinical Trials Register 2018-001535-51) enrolled 24 previously treated adult males with severe haemophilia A (<1 IU/dL [<1%] endogenous FVIII at screening; median 48 bleeds in the preceding year) into two cohorts. The study participants had predominantly (88%) received on-demand, versus prophylactic, FVIII treatment prior to study enrolment. After a washout and screening period all patients underwent a four-week treatment period consisting of once-weekly efanesoctocog alfa injections at doses of 50 IU/Kg (n=10; median age 35 years) or 65 IU/kg (n=14; median age 41 years) followed by a 28-day safety observation period. The study met its primary outcome to demonstrate the safety and tolerability of repeat dosing of efanesoctocog alfa with no development of anti-FVIII neutralising antibodies. While the study was not designed to assess efficacy there were no bleeds reported during the treatment period. Pharmacokinetic analysis found that efanesoctocog alfa induced high levels of FVIII activity (mean FVIII activity on day 3, 46% and 69% for cohorts 1 and 2, respectively) and this was durable with an elimination half-life longer than currently available FVIII products. The efficacy of efanesoctocog alfa is currently being assessed in two phase 3 trials (NCT04161495 and NCT04644575).

Comment: Primary prophylaxis is the standard of care in severe haemophilia A to reduce bleeding occurrence and prevent joint damage. For standard half-life factor replacement products (e.g., recombinant FVIII), this target level usually requires injections three times per week or every other day, whereas injections are given every three-five-days for extended half-life FVIII products. Although pegylation and Fc fusion techniques have increased the half-life of current extended half-life FVIII products, the interaction with VWF that stabilises and protects endogenous and exogenous FVIII from early degradation limits FVIII half-life extension to 1.5-fold to two-fold that of standard half-life products. Efanesoctocog alfa decouples FVIII from endogenous VWF. It is composed of a single recombinant FVIII protein fused to dimeric Fc, the D'D3 domain of VWF (FVIII-binding domain), and 2 XTEN polypeptides. Addition of the D'D3 domain of VWF to FVIII in efanesoctocog alfa prevents binding to endogenous VWF and removes the limit on half-life extension imposed by VWF-FVIII interaction. The Fc fusion and XTEN technologies provide further half-life extension. In this study, efanesoctocog alfa was given weekly for four weeks with evaluation of pharmacokinetics and safety. Two doses (cohort 1: 50 IU/kg) and (cohort 2: 65 IU/kg) were studied. Weekly dose was adequate to maintain FVIII level well in the prophylaxis range with mean FVIII activity in the normal to near-normal range (>40%) for three to four days postdose and >10% on day 7. No bleeds were reported during the four-week treatment period with efanesoctocog alfa and no inhibitor development to FVIII was detected up to 28-days following the final dose of efanesoctocog alfa. In addition, there were no reports of hypersensitivity, anaphylaxis or vascular thrombotic events. These results suggest that efanesoctocog alfa may offer extended bleed protection with less frequent dosing for individuals with severe haemophilia A, thereby making a significant positive impact on their lives.

Reference: Blood Adv 2022;6(4):1089-94
Abstract

Biomarker signatures in cancer patients with and without venous thromboembolism events: a substudy of CASSINI

Authors: Khorana A et al.

Summary: While the CASSINI trial (NCT02555878) did not meet its primary efficacy endpoint to demonstrate the superiority of rivaroxaban thromboprophylaxis versus placebo for the prevention of a composite outcome comprised of DVT, PE or VTE-related death at 180-days in high-risk ambulatory patients (Khorana thromboembolic risk score ≥2) with cancer undergoing systemic treatment, it did find a benefit during the intervention period (Khorana A et al *N Engl J Med* 2019;380[8]:720-28). The original trial lead author Alok Khorana and colleagues conducted a biomarker substudy to identify potential markers prognostic for VTE or death in this population. Analysis was based on the 62 patients who developed VTE within six months in CASSINI (n=38 on treatment and n=24 after treatment termination) in comparison to 62 controls matched on age, sex, cancer type, tumour stage and Khorana score. The researchers used Wilcoxon rank-sum test analysis and sparse Bayesian regression modelling to identify candidate VTE biomarkers differentially expressed between patients who developed VTE and those who didn't in baseline blood samples. Decreased levels of stromal cell–derived factor-1, thyroid-stimulating hormone, monocyte chemotactic protein 4 and increased levels of growth hormone and interleukin (IL)-1 receptor type 1 were identified as potential biomarkers for cancer-associated VTE and death.

Comment: The CASSINI study examined the effect of rivaroxaban versus placebo on VTE incidence in ambulatory cancer patients considered to be at high risk for VTE, as assessed by the Khorana score. While on treatment, rivaroxaban 10 mg once daily significantly reduced the risk of a VTE event. This report describes a substudy that utilised a case-control design to compare blood samples from the 62 patients who developed VTE during the six-month CASSINI study with 62 matched controls. Several biomarkers (as listed above) were different in the VTE and without VTE cohorts. Comparing patients who survived with those who died, 12 biomarkers had significantly different distributions at baseline with largest differences in median values included the protein ST2 (encoded by the IL-1 receptor-like 1 gene), macrophage inflammatory protein-3 α, tenascin-C, tumour necrosis factor ligand superfamily member 12 (Tweak), eotaxin-1, IL-8, and C-reactive protein. The tumour-specific biomarkers, cancer antigen, and carcinoembryonic antigen were significantly elevated for patients who died compared with those who survived. These observations will lead to a detailed analysis regarding how these signatures lead to thrombosis and also help in building better risk stratification models to personalise thromboprophylaxis.

Reference: Blood Adv 2022;6(4):1212-21
Abstract

Cardiovascular disease is a leading cause of mortality among TTP survivors in clinical remission

Authors: Sukumar S et al.

Summary: Sukumar et al provide a pooled review of mortality in survivors of immune-mediated TTP (iTTP) from two cohorts – the Ohio State University TTP/aHUS Registry (n=62) and the Johns Hopkins University TTP cohort (n=160). A total of 222 patients (median age 42 years; 70.3% female) with a diagnosis of iTTP (thrombocytopenia with a platelet count < 100 x 109/L, microangiopathic haemolytic anaemia and evidence of schistocytes in the absence of alternative thrombotic microangiopathy) were included in the study. The median follow-up was 4.5-years, corresponding to 1,318 patient-years. The mortality rate to the first iTTP episode was 4% (n=9) while survivors of the first episode had a mortality rate of 13.6% (29/213) over the follow-up period, a rate almost double that of a matched reference US population (2,228.3 vs 1,273.8 per 100,000 person-years; p=0.007). The median age at death was also significantly younger than the reference population (49 vs 78.7 years). Cardiovascular disease including sudden cardiac death, decompensated heart failure/cardiogenic shock secondary to ischaemic heart disease and stroke; and relapsed TTP were the leading causes of death, combined accounting for more than half the deaths (27.6% each). Other leading causes of death included malignancy (20.7%) and infection (13.8%). A trend towards inferior survival with lower ADAMTS13 activity during remission was reported. The authors concluded that there is an unmet need for survivorship care in this population and further study is warranted to elucidate strategies to mitigate cardiovascular disease.

Comment: There are reports of high rates of adverse health sequelae in iTTP survivors, including hypertension, obesity, stroke, cognitive impairment, mood disorders and poor quality of life. Immune-mediated TTP survivors also appear to have higher all-cause mortality than expected from an age-, race-, and sex-matched control population with five-fold increased risk of incident stroke, which was associated with ADAMTS13 activity ≤70% during remission. This multicentre cohort study evaluated cause of death in patients who survived their first iTTP episode and risk factors for earlier mortality. The mortality rate in individuals that survived a first episode of iTTP was higher than the expected mortality rate from an age-, sex-, and race-standardized reference US population (2,228.3 vs 1,273.8 per 100,000 person-years). As detailed in the abstract, among patients who survived their first iTTP episode, cardiovascular disease was the leading primary cause of death, tied with relapsed iTTP, followed by malignancy, and infection. Among patients who survived their first iTTP episode, male sex, increasing age, and number of iTTP episodes were associated with mortality. Patients who died had significantly lower median ADAMTS13 activity than survivors with a trend toward shorter survival in patients with ADAMTS13 ≤70% versus >70%. These data highlight the need to screen and aggressively manage cardiovascular risk factors in iTTP survivors, as well as the need for further investigation into the mechanisms underlying cardiovascular and other complications after iTTP and optimise treatments. It also highlights that ongoing follow-up and maintenance of registry will help us to understand the longer-term sequelae of this condition.

Reference: Blood Adv 2022;6(4):1264-70
Abstract

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