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

We begin this issue with results from the European NOAH trial of early anticoagulation initiation in patients at risk for stroke with subclinical atrial fibrillation (AF) detected by cardiac implanted devices. Data from ADVANCE IV may lead to a novel therapeutic option for adult patients with primary immune thrombocytopenia (ITP), with the first-in-class neonatal Fc receptor antagonist efgartigimod demonstrating superior efficacy to placebo. Next, intravenous tenecteplase may be an alternative front-line thrombolytic with an easier mode of administration for early thrombolysis in patients with large vessel occlusion stroke, with non-inferiority versus alteplase exhibited in a prespecified secondary analysis of the ACT trial. Other included research in this issue suggests that Asian patients with AF receive suboptimal thromboembolic risk management; the CLOT study reports that the utility of a prognostic model to mitigate hospital-acquired venous thromboembolism (HA-VTE) in paediatric patients is thwarted by reluctance to initiate thromboprophylaxis even in cases identified to be at elevated risk; and a meta-analysis finds that non-vitamin K antagonist oral anticoagulants (NOACs) are more effective and safer than warfarin in elderly patients with AF. Finally, more than 12 months of immune checkpoint inhibitor (ICI) therapy for cancer is linked to an elevated risk of arterial thromboembolic events in a Chinese single-centre retrospective study.

We hope you enjoy this update in Thrombosis & Haemostasis research, and we welcome your comments and feedback.

Kind Regards,

Dr Sara Ng

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Abbreviations used in this issue:

AF = atrial fibrillation; **AHRE** = atrial high-rate episode; **CaHUS** = complement-mediated atypical haemolytic uremic syndrome; **ESKD** = end-stage kidney disease; **HA-VTE** = hospital-acquired venous thromboembolism; **ICI** = immune checkpoint inhibitor; **IDDVT** = isolated distal deep vein thrombosis; **ITP** = immune thrombocytopenia; **NOAC** = non-vitamin K antagonist oral anticoagulant; **SCD** = sickle cell disease; **VTE** = venous thromboembolism.

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Independent commentary by Dr Sara Ng

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Anticoagulation with edoxaban in patients with atrial high-rate episodes

Authors: Kirchhof P et al., for the NOAH-AFNET 6 Investigators

Summary: The European NOAH trial evaluated whether early initiation of oral anticoagulation in patients at risk for stroke with subclinical AF (also called atrial high-rate episodes [AHRE]) detected by cardiac implanted devices may be an optimal antithrombotic strategy given the associated risk of bleeding complications. A cohort of 2,536 older adults implanted with a pacemaker, defibrillator or cardiac resynchronisation device for any indication at least two months prior who had experienced at least one atrial tachyarrhythmia episode with an atrial rate of ≥170 beats per minute that lasted at least six minutes were enrolled into the prospective, parallel-group, double-blind, randomised, multi-centre trial initiated by the European Society of Cardiology and AFNET (mean age, 78 years; median duration of atrial tachyarrhythmia episode/s, 2.8 hours). Patients were randomised to receive the non-vitamin K antagonist oral anticoagulant (NOAC) edoxaban at the therapeutic dose approved for stroke prevention in non-valvular AF (60 or 30 mg once daily dependent on renal function, body weight and concomitant use of glycoprotein-P inhibitors), or placebo. An informal assessment at a median follow-up approaching two years found no significant difference in the composite primary outcome of cardiovascular death, stroke or systemic embolism (3.2% vs 4% per patient-year), and the trial was terminated early. Further analysis revealed no benefit to early edoxaban initiation with regard to stoke prevention (incidence of ~ 1% per patient-year in both trial arms) but a substantial compromise in safety (composite outcomes of death or major bleeding, 5.9% vs 4.5% per patient-year). Finally, less than one-fifth of the study population developed clinically overt AF as diagnosed by electrocardiogram.

Comment: AHREs are associated with an increased risk of stroke, however this risk is significantly lower than the risk of stroke with clinical AF. In this double-blinded randomised control trial of 2,536 patients aged over 65 years with at least one additional risk factor for stroke, prophylactic anticoagulation with edoxaban in patients with AHREs did not appear to significantly reduce the risk of major cardiovascular events. There was a higher incidence of major bleeding and a composite outcome including death and the trial was terminated early after a median follow-up of 21 months on the basis of safety concerns and futility for efficacy.

Reference: N Engl J Med. 2023;389(13):1167-79
Abstract

Efficacy and safety of the neonatal Fc receptor inhibitor efgartigimod in adults with primary immune thrombocytopenia (ADVANCE IV): a multicentre, randomised, placebo-controlled, phase 3 trial

Authors: Broome C et al., with the ADVANCE Investigator Study Group

Summary: Data from the phase 3 ADVANCE IV trial demonstrates superior efficacy for the first-in-class neonatal Fc receptor antagonist efgartigimod versus placebo in adult patients with primary ITP, providing support for this novel treatment targeting the autoantibody-based pathophysiology of disease to reduce total IgG levels. A total of 131 previously treated adult patients with chronic or persistent primary ITP (mean platelet count < 30,000) with the diagnosis supported by a response to a prior ITP therapeutic (other than thrombopoietin receptor agonists) were enrolled from sites across Asia, Europe and North America and allocated to 24-weeks of treatment with intravenous efgartigimod (n=86) or placebo (n=45) in the third- or later-line setting. The study population had a median age of 47 years, a mean time since diagnosis of over ten years, most patients had chronic disease (90%) and had received three or more previous therapies most commonly corticosteroids, thrombopoietin receptor agonists and intravenous Ig or anti-D Ig. At the time of trial enrolment half of patients were on concurrent immune thrombocytopenia therapy. With more than four-times as many patients with chronic ITP achieving a sustained platelet count response with efgartigimod versus placebo (≥ 50 x 10^9 for at least four of the six weeks between week 19 and 24; 22% vs 5%; p=0.032), the trial met the primary outcome measure. This finding was consistent across other secondary efficacy outcomes, with statistically significant improvements found in extent of disease control - as defined by cumulative number of weeks with normalised platelet counts – with efgartigimod compared to placebo in the chronic ITP cohort, regardless of number of prior therapies, and a clinically relevant and durable platelet count response in the overall study population. The side effect profile for efgartigimod was similar to placebo, with adverse events predominantly mild or moderate (headache, 16% vs 13%; haematuria, 16% in both arms; petechiae, 15% vs 27%) and a comparable incidence of bleeding events. The open-label extension study is ongoing and the ADVANCE SC+ trial is assessing a subcutaneous formulation of efgartigimod in IPT.

Comment: A total of 131 adult patients with chronic or persistent primary ITP were included in this study (median time since diagnosis of 10.6 years with two-thirds of patients having received at least three previous lines of treatment for ITP). The use of efgartigimod in this cohort of patients was associated with a higher rate of sustained platelet count response compared to placebo (22% vs 5%). Efgartigimod appears to be an effective treatment for chronic ITP in patients who have had multiple previous lines of ITP therapy.

Reference: Lancet. 2023;402(10413):1648-59
Abstract

Patterns of oral anticoagulant use and outcomes in Asian patients with atrial fibrillation

Authors: Romiti G et al.

Summary: A post-hoc analysis from the GLORIA-AF registry reports the antithrombotic prescription pattern and outcomes in self-reported Asian patients with AF, predominantly living in Asia. Analysis was undertaken of over 34 thousand adult patients with newly diagnosed nonvalvular AF at risk for stroke (CHA_2DS_2-VASc score ≥ 1) included in the phase 2/3 Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry in the roughly five-year period spanning late 2011 to the end of 2016. Logistic regression analysis found a significantly reduced odds of oral anticoagulation prescription in Asian patients (including Chinese, Japanese, Korean and other) versus non-Asian patients (oral anticoagulant, odds ratio 0.23; NOAC, odds ratio, 0.66). Within the Asian subgroup Japanese patients were more likely to be prescribed an antithrombotic. Cox regression modelling analysis further revealed elevated risks of anticoagulation discontinuation, thromboembolism and intracranial haemorrhage in Asian patients but reduced probability of death, major adverse cardiovascular events and major bleeding.

Comment: The GLORIA-AF registry is a global, prospective registry on long-term oral anti-thrombotic treatment in patients with AF with 6,900 Asian patients (20% of the 34,421 registered patients). The prescription of oral anticoagulant therapy was found to be lower in this Asian cohort of patients with a higher rate of oral anticoagulant discontinuation, lower risk of all-cause mortality and major adverse cardiovascular events and non-intracranial major bleeding. The higher risks of thromboembolism and intracranial haemorrhage could be attributed to suboptimal thromboembolic risk management, such as latter adoption of non-vitamin K anticoagulants in Asia (higher percentage of patients prescribed antiplatelet agents overall), longer time-to-treatment initiation times as well as more frequent uses of lower-dose NOAC amongst Asian patients, despite not meeting dose-reduction criteria.

Reference: EClinicalMedicine. 2023:63:102039
Abstract

Model-guided decision-making for thromboprophylaxis and hospital-acquired thromboembolic events among hospitalized children and adolescents

Authors: Walker S et al.

Summary: The CLOT (Children's Likelihood of Thrombosis) randomised clinical trial evaluated whether an automated prognostic model embedded in the electronic medical record can assist clinicians recognise and ameliorate hospital-acquired venous thromboembolism (HA-VTE) rates in paediatric patients. Children and adolescents admitted as inpatients at the Monroe Carell Jr Children's Hospital at Vanderbilt in Tennessee between November 2020 and January 2022, inclusively (n=17,427; median age 1.7 years) were enrolled into the trial and were randomised to undergo daily automatic assessment of HA-VTE risk plus clinician review in cases of elevated risk (predicted probability ≥2.5%), or usual care. The model recommended thromboprophylaxis initiation in 287 patients (1.6% of study cohort), but this advice was followed in only one-quarter of cases. The incidence of HA-VTE development was comparable between trial arms (0.9% vs 0.7%; p=0.10). Anticoagulation was reported to be safe with low rates of minor bleeding (4.1%) and no major bleeding events. A high discrimination accuracy was reported for the prognostic model (C statistic, 0.799).

Comment: Although the rates of VTEs in hospitalised children are increasing, paediatric clinicians are still hesitant to adopt pharmacological prophylaxis for concerns of increased bleeding risk. The CLOT trial was an unblinded, randomised clinical trial to determine whether the use of a validated HA-VTE prognostic model could reduce inpatient rates of HA-VTE. The incorporation of this model into clinical practice did not decrease HA-VTE rates. However, only 25% of recommendations to initiate thromboprophylaxis in paediatric patients with an elevated risk were accepted by the primary clinical teams for concerns of increased risk of bleeding. There were no increased episodes of severe bleeding in patients that did receive pharmacological thromboprophylaxis in the trial.

Reference: JAMA Netw Open. 2023;6(10):e2337789
Abstract

Efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients (≥80 years of age) with atrial fibrillation

Authors: Kang F et al.

Summary: This systematic review and meta-analysis aimed to delineate the relative safety and efficacy of NOACs versus vitamin K antagonists in elderly patients with AF. The researchers identified 15 studies including over 15 thousand patients at least 80 years of age treated for AF with a NOAC or warfarin from a search of five online databases with a cut-off date of October 2022. Meta-analysis found that NOACs outperformed warfarin for both efficacy outcomes (stroke and systemic embolism, odds ratio 0.8; all-cause mortality, odds ratio 0.61) and had a safer profile (major bleeding, odds ratio 0.76, intracranial haemorrhage, odds ratio 0.57).

Comment: Elderly patients have a high risk of stroke and bleeding, with age being a component in both the CHA2DS2-VASc score and the HAS-BLED score. This meta-analysis included 70,446 very elderly patients (age ≥ 80 years) with AF on oral anticoagulant treatment. The pooled analysis of all included studies showed a better efficacy of NOACs compared to warfarin in stroke and systemic embolism and all-cause mortality, as well as a better safety profile with lower risks of major bleeding and intracranial haemorrhage. This study demonstrates that the use of DOAC in very elderly patients with AF is more effective and safer than warfarin.

Reference: Intern Med J. 2023;53(9):1524-32
Abstract

Safety and efficacy of tenecteplase compared with alteplase in patients with large vessel occlusion stroke

Authors: Bala F et al.

Summary: A prespecified secondary analysis of the ACT randomised clinical trial is consistent with the previously published overall trial results in finding intravenous tenecteplase non-inferior to alteplase for early thrombolysis in patients with large vessel occlusion stroke, indicating it may be an alternative front-line thrombolytic in this setting. Briefly, a cohort of over 15 hundred adult patients who experienced an acute ischemic stroke and were candidates for endovascular therapy were enrolled into the Canadian multicentre trial and randomised to receive tenecteplase (0.25 mg/kg) or alteplase (0.9 mg/kg) within 4.5 hours of symptom onset. Subgroup analysis in the one-third of patients with large vessel occlusion stroke (intracranial internal carotid artery, M1 or M2-middle cerebral artery or basilar occlusions) found efficacy to be non-inferior with tenecteplase versus alteplase, with no significant between-group difference in the proportion of patients attaining a modified Rankin Score of 0-1 or 0-2 at three months (32.7% vs 29.6% and 49% vs 51%, respectively; both $p>0.05$). Safety outcomes were also similar with symptomatic intracranial haemorrhage and mortality in 6.1% and 19.9% of patients in the tenecteplase arm and 4.3% and 18.1% of patients in the alteplase arm, respectively. In patients who underwent thrombectomy, successful reperfusion rates at first and final angiogram were also comparable between trial arms.

Comment: Tenecteplase is a modified molecule of alteplase which results in greater fibrin specificity, higher resistance to plasminogen activator inhibitor and prolonged half-life, allowing for bolus administration. In 520 patients that presented with large vessel occlusion stroke, successful repercussion rates were similar between intravenous alteplase and tenecteplase with comparable rates of functional independence (modified Rankin Score 0-1, 29.6% vs 32.7%). There were also no significant differences in rates of symptomatic intracerebral haemorrhage or mortality between the two groups. The comparable safety and efficacy of tenecteplase to alteplase would make it an attractive first-line thrombolytic agent for the treatment of acute LVO ischaemic strokes given the ease of bolus administration.

Reference: JAMA Neurol. 2023;80(8):824-32
Abstract

Association of immune checkpoint inhibitors therapy with arterial thromboembolic events in cancer patients

Authors: Zhu J et al.

Summary: A retrospective cohort study from Chongqing University Cancer Hospital in China provides real-world evidence of an elevated risk of arterial thromboembolic events linked to more than one year of immune checkpoint inhibitor (ICI) treatment for malignancy. Analysis included data from over 50 thousand patients who received radiotherapy and or chemotherapy ± an antibody targeted to programmed death-(ligand) 1 (PD-[L]1; n=2,877; 32.5%) for a malignant tumour - most commonly of the lung, uterus, colorectum or liver – in the four-year period spanning 2018 to 2021. The mean age of the study cohort was 58.7 years, metastatic disease was present in 38.7% of patients and a substantial proportion of patients had underlying cardiovascular disease or risk factors for such (including hypertension, hyperlipidaemia, peripheral arterial atherosclerosis, diabetes and chronic ischemic heart disease). Propensity score-matched analysis considering sex, age, cancer type and stage, other cardiotoxic anticancer therapies and history of cardiovascular diseases and risk factors revealed that compared to patients treated without ICI therapy, those treated with it had a doubled risk of arterial thromboembolic events including acute coronary syndrome, stroke/transient ischemic attack, and peripheral arterial thromboembolism (relative risk, 2.01). A statistically significant elevated risk of arterial thromboembolic events was further clarified on Kaplan-Meier-based cumulative hazard curves to be associated with one year or more of ICI therapy with magnitude of risk increasing with duration of therapy (one-, two-, three- and four-year follow-ups, risk ratios 1.41, 1.84, 1.90 and 1.97, respectively). The delayed risk may be attributable to the long-term progressive aetiology of atherosclerosis. Factors identified on logistic regression analysis as independently associated with elevated risk for arterial thromboembolic events included age, diabetes mellitus, hypertension, peripheral arterial atherosclerosis, AF, chronic ischemic heart disease, distant metastatic disease and cycles of ICIs use.

Comment: Age, diabetes mellitus, hypertension, peripheral arterial atherosclerosis, AF, ischaemic heart disease, distant metastases and the number of cycles of ICIs use are independent risk factors associated with increased arterial thrombotic events in cancer patients treated with ICIs. The risk of arterial thrombotic events is substantially increased from one year with a risk ratio of 1.41 to 1.97 at one- to four-years post ICI treatment.

Reference: Cancer Med. 2023;12(18):18531-41
Abstract

Atypical hemolytic uremic syndrome in the era of terminal complement inhibition

Authors: Brocklebank V et al., for the NRCTC aHUS Research Consortium

Summary: An observational cohort study from the UK details outcomes in a real-world genotype-matched cohort of patients with suspected complement-mediated atypical hemolytic uremic syndrome (CaHUS) treated with/without eculizumab for native kidney disease. A cohort of 522 adult patients with CaHUS with inherited or acquired complement abnormalities (*CFH, CFI, CD46, CFB* or *C3* mutations; or factor H autoantibodies, respectively) referred to the National Renal Complement Therapeutics Centre (NRCTC) between 1995 and 2019 and treated with/without eculizumab (n=243/279) were included in the study. In both cohorts an inherited complement abnormality was more common than an acquired one and CaHUS-associated gene mutations were predominantly heterozygous with incidence rates of homozygous mutations ranging from 1.4% to 8.3% (in *CFI* and *CD46*, respectively). The concurrent presence of inherited and acquired complement abnormalities was rare. The Kaplan-Meier estimated five-year cumulative end-stage kidney disease (ESKD)-free survival rate was more than doubled in the eculizumab treated cohort versus the control cohort with a statistically significant hazard ratio of 4.95 on Cox proportional hazard regression modelling (39.5% vs 85.5%). Subgroup analysis by genetic groups revealed that eculizumab conferred significant prolongation of ESKD-free survival in patients with *CFH, C3* and *CFI* mutations but not in patients with *CD46* mutations or patients with factor H autoantibodies. Multivariable analysis identified lower serum creatinine, a lower platelet count and younger age at presentation as favourably associated with response to eculizumab with higher ESKD-free survival rate, higher proportion of patients achieving an estimated glomerular filtration rate >60 ml/min and a higher renal response at six months. Relapses after eculizumab withdrawal occurred exclusively in patients with rare genetic variants (relapse rate, 1 per 9.5 and 1 per 10.8 person-years for patients with a pathogenic mutation and for patients with a variant of uncertain significance, respectively vs 0 in patients without a rare genetic variant), suggesting that lifelong treatment is unnecessary in most patients. The study authors also reported a lack of responsive to eculizumab in patients with biallelic pathogenic mutations in RNA-processing genes such as *EXOSC3*.

Comment: The outcome of eculizumab in patients with CaHUS is associated with the underlying genotype. Patients with *CFH*, *CFI* and *C3*-mutated CaHUS have significantly increased ESKD-free survival when treated with eculizumab compared to a genotype-matched historical CaHUS patient cohort. ESKD-free survival in patients with *CD46* mutations did not appear significantly different between eculizumab and control groups, providing some reassurance if eculizumab therapy is withdrawn in these patients. Lower serum creatinine, lower platelet count, younger age and shorter time between presentation and first dose of eculizumab were associated with estimated glomerular filtration rate >60 ml/min at six months.

Reference: Blood. 2023;142(16):1371-86
Abstract

Comparison of thromboembolism outcomes in patients with sickle cell disease prescribed hormonal contraception

Authors: Bala N et al.

Summary: Retrospective analysis of 12 years of US administrative claims data was undertaken to compare thromboembolism outcomes in patients with sickle cell disease (SCD) prescribed a combined hormonal contraceptive or a progestin-only contraceptive. Data on 7,173 patients aged 12-44 years old who initiated either hormonal contraception (combined hormonal contraceptive, 44.6%; progestin-only contraceptive, 55.4%) between 2006 and 2018 were extracted from the Centres for Medicare and Medicaid Services Medicaid Analytic eXtract database. The patient cohort was mostly Black and younger than 35 years with a haemoglobin SS genotype. Combined oral contraceptive pills and progestin-only depot medroxyprogesterone acetate were the most commonly prescribed contraceptives, together accounting for over 70% of prescriptions, while intrauterine device and implants were used in 9.9% and 5.4% of patients, respectively. At baseline, users of progestin-only contraceptive were older, had more severe SCD and were more likely to be smokers or have hypertension compared to users of combined hormonal contraceptives. The incidence of thromboembolism in the first year of contraceptive use was found to be 1.8%, with venous thromboembolic events accounting for 90% of events (pulmonary embolism, 49.2%; deep vein thrombosis 40.5%) and arterial events such as stroke or myocardial infarction less common. No significant difference in the rate of thromboembolic events was found between the two types of hormonal contraceptive in either unadjusted or adjusted analyses. A non-significant trend towards higher risk of thromboembolism with more severe SCD was reported in both contraceptive cohorts. Analysis of events across formulations of contraceptives revealed an elevated risk of thromboembolism associated with transdermal patch versus combined oral contraceptive pill (hazard ratio 2.39).

Comment: In a cohort of 7,173 patients with SCD aged between 12 and 44 years, 1.8% presented with a new diagnosis of thromboembolism within one year of first identified contraceptive prescription, the most common being pulmonary embolism and deep vein thrombosis. There was no statistically significant difference in the thromboembolism event rate between SCD patients prescribed combined hormonal contraceptives and SCD patients prescribed progestin-only contraceptives. Those who presented with thromboembolism were older, had severe sickle cell disease (defined as ≥3 inpatient admissions during a 1-year time period), obesity, diabetes and hypertension.

Reference: Blood Adv. 2023;7(20):6140-50
Abstract

Incidence of bleeding and recurrence in isolated distal deep vein thrombosis

Authors: Jørgensen C et al.

Summary: Findings from the Venous Thrombosis Registry in Østfold Hospital (TROLL) in Norway include a high long-term risk of venous thromboembolism (VTE) recurrence after a first incidence of isolated distal deep vein thrombosis (IDDVT) despite anticoagulation. The study population included 475 patients diagnosed with IDDVT not attributable to cancer between 2005 and 2020 (median age, 59 years, approximately one-third of whom had unprovoked IDDVT. The cumulative incidence of recurrent VTE (mostly pulmonary embolisms and proximal deep vein thromboses) at one-year was 5.6% and rose to 14.7% and 27.2% at five- and ten-years, respectively. Rates of major bleeding during anticoagulation treatment were low (1.5% at three months).

Comment: Four hundred and seventy-five patients with IDDVT were identified in TROLL between January 2005 and May 2020. Of these, 36.8% were classified as unprovoked IDDVT and were associated with a higher risk of VTE recurrence than provoked IDDVT. Unprovoked IDDVT are associated with a one-, five- and 10-year cumulative incidence of recurrent VTE of 9.2%, 20.1% and 40.1% respectively. The 10-year cumulative incidence of recurrent VTE in patients with IDDVT is comparable with the risk of recurrence described in studies of unprovoked overall VTE. The high recurrence rate, with a high proportion of pulmonary embolisms and proximal deep vein thromboses (62%), raises the question of whether longer-term anticoagulation should be considered in those patients with unprovoked IDDVT.

Reference: J Thromb Haemost. 2023;21(10):2824-32
Abstract