Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

and middle-income countries are not taking it.[11] This suggests that strategies to initiate and maintain these drugs need to be as simple as possible. Such strategies might also have a role in high-income countries where the main alternative strategy (titrate treatment against risk factor levels) can result in undertreatment in practice.[11] Cost-effectiveness analysis suggests that a fixed-dose combination strategy is potentially cost-effective compared with treatment titration in a high-income setting.[12]

Although a polypill strategy might sit uncomfortably with precision medicine, there is now a substantial evidence base that such an approach is effective at reducing cardiovascular disease. Guideline writers and policy makers should consider how to incorporate this evidence base into guidelines and policies.

JM declares fees for academic advisory board membership for the Bristol-Myers Squibb–Pfizer-funded GUARD-AF trial of screening for atrial fibrillation, for Pfizer-sponsored education sessions on detection and diagnosis of atrial fibrillation, and for advice on a heart failure app for Omron. RJM declares working with Omron on the development and evaluation of a blood pressure telemonitoring system for which consultancy and licensing fees are paid to his institution.

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Cerebral venous sinus thrombosis after vaccination: the UK experience

An important but rare complication of COVID-19 vaccination is vaccine-induced immune thrombotic thrombocytopenia (VITT) associated with the adenovirus vector vaccines, Ad26.COV2.S (Johnson & Johnson) and ChAdOx1 (Oxford–AstraZeneca).[1–5] VITT occurs more commonly in women younger than 50 years who present within 5–24 days of vaccination with thrombosis in unusual sites—the majority with cerebral venous sinus thrombosis.[1,6] Thrombocytopenia, elevated D-dimer, decreased fibrinogen, and positive antibodies against platelet factor 4 (PF4) are commonly observed.[1–6] Recommended treatments for VITT, based on similarities with autoimmune heparin-induced thrombocytopenia (HIT),[7] include non-heparin anticoagulation, intravenous immunoglobulin, and avoidance of platelet transfusions.[1] Mortality associated with VITT is approximately 40%.[1]

In *The Lancet*, Richard Perry and colleagues[8] report on the largest series to date of patients with VITT-associated cerebral venous sinus thrombosis. In this multicentre cohort study, cerebral venous sinus thrombosis following COVID-19 vaccination was defined as VITT-associated if platelet count nadir was less than 150×10^9 per L and, if measured, D-dimer concentration was greater than 2000 µg/L. Between April 1 and May 20, 2021, the study enrolled 70 patients with VITT-associated cerebral venous sinus thrombosis and 25 patients with cerebral venous sinus thrombosis that did not meet criteria for VITT from 43 hospitals in the UK, as well as a large historical cohort of patients with cerebral venous sinus thrombosis.

All cases of VITT-associated cerebral venous sinus thrombosis occurred after a first dose of the ChAdOx1 vaccine. 56 (97%) of 58 patients with VITT for whom


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anti-PF4 antibody tests were available tested positive using an ELISA. Compared with those without VITT, patients with VITT were younger (median age 47 years [IQR 32–55] *vs* 57 years [41–62]; p=0·0045), were more likely to be female (39 [56%] of 70 *vs* 11 [44%] of 25), had more intracranial veins thrombosed (median 3 [IQR 2–4] *vs* 2 [2–3]; p=0·041), and had an increased likelihood of concurrent extracranial thrombosis (31 [44%] of 70 *vs* one [4%] of 25; p=0·0003). The primary outcome of death or dependency on others at the end of hospital admission occurred more frequently in patients with VITT-associated cerebral venous sinus thrombosis than in the non-VITT control group (33 [47%] of 70 *vs* four [16%] of 25; p=0·0061). The proportion of patients with VITT who were dead or dependent at discharge was lower in those who received a non-heparin anticoagulant (18 [36%] of 50 *vs* 15 [75%] of 20; p=0·0031) or intravenous immunoglobulin (22 [40%] of 55 *vs* 11 [73%] of 15; p=0·022) compared with those who did not receive these treatments.

Perry and colleagues' study[8] proposes new diagnostic criteria for VITT based on patients whom the authors suspected of being misclassified according to existing criteria.[1,2,9,10] One patient in the non-VITT group had an elevated D-dimer (4985 µg/L) and positive anti-PF4 antibodies on two different ELISAs yet a platelet nadir of 158×10^9 per L. Two patients with clinical features highly suspicious for VITT were assigned to the non-VITT group on the basis of D-dimer concentrations less than 2000 µg/L, including one with positive HIT antibody testing. Perry and colleagues[8] propose dividing cases of cerebral venous sinus thrombosis following COVID-19 vaccination into possible, probable, and definite VITT-associated cerebral venous sinus thrombosis, allowing for inclusion of atypical presentations with normal platelet counts, normal D-dimer, or negative HIT antibody testing.

The utility of the proposed criteria is yet to be determined. The patient with a platelet nadir of 158×10^9 per L would be, to our knowledge, the first reported instance of VITT with a normal platelet count, yet comparisons of presenting versus prevaccination platelet counts were not available in this study. Based on HIT paradigms, a relative decline in platelet count from baseline, rather than absolute thrombocytopenia, is likely to be a uniformly distinguishing feature of VITT. The exact rate and degree of platelet decline in VITT following COVID-19 vaccination are unknown[1,5,6] and represent an area of active investigation. Although rare false negatives might occur, ELISA testing in VITT is generally very reliable[11,12] and it is unclear if patients with negative ELISA tests for anti-PF4 antibodies and functional HIT testing could still be classified as having VITT. A third of patients in Perry and colleagues' study[8] had anti-PF4 antibody testing using a chemiluminescent immunoassay; such immunoassays have poor sensitivity for VITT compared with ELISA testing[11,12] and could explain some of the negative test results.

An important consideration is that 19 (20%) of 95 study patients did not have anti-PF4 antibody testing available.[8] Additional patients in the VITT group could have had negative anti-PF4 antibody testing, and additional patients in the non-VITT group could have had positive testing, and it is possible that a spectrum of VITT might exist, similar to HIT.[13] Other limitations of the study include the small sample size, reflecting the rarity of cerebral venous sinus thrombosis, and a potential confounding bias due to age-based vaccine distribution policies, which might have contributed to the older age of the VITT and non-VITT groups compared with the historical cohort of patients with cerebral venous sinus thrombosis (median age 37 years).

The analysis by Perry and colleagues[8] represents a landmark study, which is, to our knowledge, the largest thus far of VITT-associated cerebral venous sinus thrombosis, and the first to directly compare the clinical, laboratory, and radiographic features of VITT-associated and non-VITT-associated cerebral venous sinus thrombosis. The poor outcomes of VITT-associated cerebral venous sinus thrombosis highlight the need for accurate diagnostic tools to guide early recognition of this highly morbid condition. Additional studies are warranted to further guide treatment and management of VITT with the hope of improving outcomes for patients with this rare complication.

E-JL serves on the advisory board for Principia Biopharma unrelated to the topic of this Comment. AIL declares no competing interests.

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CD3xCD20 bispecific T-cell redirectors for relapsed or refractory B-cell lymphoma

The treatment options for patients with relapsed or refractory B-cell non-Hodgkin lymphoma who do not respond to traditional treatment are rapidly evolving. In addition to chimeric antigen receptor T-cell (CAR-T) therapy, antibody–drug conjugates, and targeted therapies such as Bruton's tyrosine kinase inhibitors and PI3 kinase inhibitors, bispecific T-cell redirectors have shown promising activity in this setting. Although not yet approved for non-Hodgkin lymphoma, bispecific T-cell redirecting technology is under investigation for several haematological and solid malignancies.[1,2] Blinatumomab, the first bispecific T-cell engager, targeted CD19 and was initially tested in patients with relapsed or refractory B-cell non-Hodgkin lymphoma before being approved for acute lymphoblastic leukaemia.[3] Further development of blinatumomab for non-Hodgkin lymphoma was hindered by the need for continuous infusion for weeks or months and severe neurological toxicity at higher doses. The next generation of bispecific T-cell redirectors for non-Hodgkin lymphoma target CD20 (ie, epcoritamab, mosunetuzumab, glofitamab, odronextamab, plamotamab) and have defined pharmacokinetic properties and longer half-lives, enabling intermittent dosing and potentially subcutaneous administration, fewer serious toxic effects, and encouraging overall (39–96%) and complete (19–77%) response rates.[4]

In *The Lancet*, Martin Hutchings and colleagues[5] report the results of the phase 1 dose-escalation part of an ongoing trial of the CD3xCD20 bispecific T-cell redirector, epcoritamab, in patients with CD20+ relapsed or refractory B-cell non-Hodgkin lymphoma (NCT03625037). Subcutaneous epcoritamab was given weekly in the first two 28-day cycles, every 2 weeks in cycles 3–6, and every 4 weeks thereafter. With a half-life of 8·8 days, less frequent dosing than that in the study might be feasible and logistically preferable, and is worth investigating. Patients could continue treatment until progression or intolerance; however, studying a fixed duration of therapy for patients with a complete response should be a priority in future studies. 68 patients were treated: 46 with diffuse large B-cell lymphoma, 12 with follicular lymphoma, and ten with other histologies. The median age was 68 years. Patients were heavily pretreated with a median of three previous lines of therapy (five for patients with follicular lymphoma); 85% were refractory to the last line of therapy, 88% were refractory to anti-CD20 antibodies, and 9% did not respond to CAR-T therapy.

Epcoritamab was well tolerated with no dose-limiting toxic effects up to the maximum tested dose of 60 mg. Grade 1–2 cytokine release syndrome occurred in 59% of patients, almost exclusively during cycle 1 with no incidents of grade 3 or higher cytokine release syndrome. Four patients developed transient neurological complications, including grade 1 partial seizure, grade 1 agraphia, grade 3 hypersomnia, and grade 3 confusion; however, immune effector cell-associated neurotoxicity syndrome (ICANS) grading was not used, limiting cross-product or cross-trial comparisons (grade 1 partial seizure would be considered grade 3 ICANS).[6] Fever was the only serious treatment-related adverse event

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