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REVIEW

# Can drug-induced platelet dysfunction be reversed?

Suzanne Maynard[1,2,3] | Alexander P. Bye[4] | Michael J. R. Desborough[1,2,3]

[1]Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom

[2]Department of Clinical Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

[3]NHS Blood and Transplant, John Radcliffe Hospital, Oxford, United Kingdom

[4]School of Pharmacy, University of Reading, Reading, United Kingdom

**Correspondence**
Michael J. R. Desborough, Department of Clinical Haematology, Churchill Hospital, Old Road, Oxford, OX3 7LE, UK.
Email: michael.desborough@ouh.nhs.uk

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## Abstract

Antiplatelet drugs are used for treatment of arterial disease, but side effects include an increased risk of bleeding. For patients with intracerebral hemorrhage, traumatic brain injury, and lower gastrointestinal bleeding, mortality rates are higher for patients taking antiplatelet drugs. Reversing the effect of antiplatelet drugs may therefore reduce the risk of mortality and morbidity in these conditions. However, the benefits of any reversal agent must be balanced against the risk of thrombotic complications. Platelet transfusion is often used in clinical practice as a reversal agent, but the only randomized controlled trial in the setting of intracerebral hemorrhage showed an increased risk of death and disability with platelet transfusion compared with standard care. Tranexamic acid is used in a wide range of conditions to reduce bleeding. The risks and benefits of tranexamic acid appear similar in patients taking antiplatelet drugs compared with those not taking antiplatelet drugs. A feasibility trial of desmopressin to reverse the antiplatelet drug effect in intracerebral hemorrhage showed promising results, but definitive efficacy studies are needed. Lastly, unlike other antiplatelet drugs, ticagrelor binds reversibly to platelets. A reversal agent for ticagrelor, bentracimab, has been used in a single-arm clinical trial that demonstrated reversal of the antiplatelet drug effect and good hemostatic outcomes, although without a comparator arm to allow a full assessment of efficacy. This review highlights an unmet need for high-quality studies assessing the efficacy of reversal strategies for drug-induced platelet dysfunction using clinically relevant outcomes.

**KEYWORDS**
antiplatelet drugs, bentracimab, desmopressin, platelet transfusion, tranexamic acid

## Essentials

- Antiplatelet drugs may worsen severe bleeding.
- Platelet transfusion is often used but may be harmful as a reversal agent.
- Desmopressin and tranexamic acid are under investigation.
- Bentracimab is a reversal agent for ticagrelor but is not widely available.

## 1 | INTRODUCTION

Platelets play a key role in primary hemostasis as well as in the pathophysiology of thrombotic disorders [1]. Antiplatelet drugs are commonly used medications, prescribed to approximately 16% of the general UK population [2]. They are predominantly used to prevent arterial thrombosis, for instance, in secondary prevention of ischemic heart disease, transient ischemic attack, ischemic stroke, and peripheral arterial disease. Examples include aspirin, an irreversible cyclooxygenase-1 inhibitor, $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor), and, less commonly, the small-molecule protease-activated receptor (PAR) 1 inhibitor vorapaxar. Aspirin may be used in other scenarios, such as in pregnancy to reduce risk of symptoms from preeclampsia or antiphospholipid syndrome [3].

While antiplatelet drugs have proven effectiveness in these conditions, side effects of these medications include an increased propensity to hemorrhage and increased severity of hemorrhage when it does occur. Bleeding complications necessitate consideration of a role for antiplatelet reversal agents, as for anticoagulants. *In vitro* evidence supports the ability to reverse drug-induced platelet dysfunction; however, more evidence is required to support efficacy *in vivo* and to demonstrate that effective reversal translates to improvement of clinically meaningful outcomes, such as major bleeding and mortality.

This review summarizes the evidence supporting the need for reversal strategies (Table 1 [4–7]), the rationale behind the mechanistic approach (Figure), and discusses the latest strategies for antiplatelet reversal, along with current and emerging evidence for their efficacy and monitoring (Tables 2 and 3).

## 2 | ANTIPLATELET DRUGS AND MAJOR BLEEDING: RATIONALE FOR THE NEED FOR REVERSAL AGENTS

Antiplatelet drugs may increase the risk of major bleeding and are associated with increased mortality when bleeding occurs at certain anatomical sites (Table 1). It should be highlighted that where the data available for bleeding occurrence and outcomes are from observational and nonrandomized, population heterogeneity and unadjusted differences in characteristics limit interpretation.

### 2.1 | Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is responsible for approximately 3 million deaths worldwide per year, with many of the survivors left disabled and dependent on others [8]. Approximately one-quarter of patients with ICH are taking antiplatelet drugs [9], which are independently associated with a worse outcome [10]. A patient-level meta-analysis of 6 randomized trials estimated a hazard ratio for ICH of 1.42 (95% CI, 1.05-1.92) in patients taking dual antiplatelet therapy (DAPT) vs single antiplatelet therapy (SAPT) [7]. A subgroup analysis of the tranexamic acid for hyperacute intracerebral

**TABLE 1** Epidemiology of major bleeding associated with antiplatelet drugs.

| Type/site of bleeding | UK incidence and absolute risk | Proportion (%) taking antiplatelet drugs | Comparative mortality rates with antiplatelet drugs |
|---|---|---|---|
| ICH | 13,600/y<br>0.24 per 1000 patient-years on or off antiplatelets [4] | 25 | 34.8% mortality on antiplatelet drugs<br>16.6% mortality if not on antiplatelet drugs<br>Higher risk of ICH on DAPT vs SAPT (HR, 1.42; 95% CI, 1.05-1.92) [7] |
| Major trauma, including traumatic brain injury | 22,000/y<br>No absolute risk available for those taking antiplatelets vs not taking antiplatelets | Varies depending on case mix. Approximately 13.9-19.1 | Death due to head injury was similar between patients on antiplatelet drugs and those not taking antiplatelet drugs (5.4% vs 7.2%).<br>Risk of ICH higher with DAPT: 11% aspirin or clopidogrel, 28.6% DAPT |
| UGIB | 30,000/y<br>0.97 per 1000 person-years on antiplatelets vs 0.47-0.67 per 1000 person-years not taking antiplatelets [5,6] | 28 | Similar mortality outcomes in patients on antiplatelet drugs compared with those not taking antiplatelet drugs<br>Higher risk of rebleeding if antiplatelet drugs are continued after a UGIB, but lower risk of thrombotic events |
| LGIB | 21,000/y<br>0.76 per 1000 person-years on antiplatelets vs 0.33 per 1000 person-years not taking antiplatelets [5,6] | 29.5 | Mortality in 2.4% on SAPT and 7.7% on DAPT compared with 2.1% of patients not on antiplatelet drugs<br>Rebleeding in 20.1% on SAPT and 30.3% on DAPT compared with 12.8% of patients not on antiplatelet drugs |

DAPT, dual antiplatelet therapy; HR, hazard ratio; ICH, intracerebral hemorrhage; LGIB, lower gastrointestinal bleeding; SAPT, single antiplatelet therapy; UGIB, upper gastrointestinal bleeding.

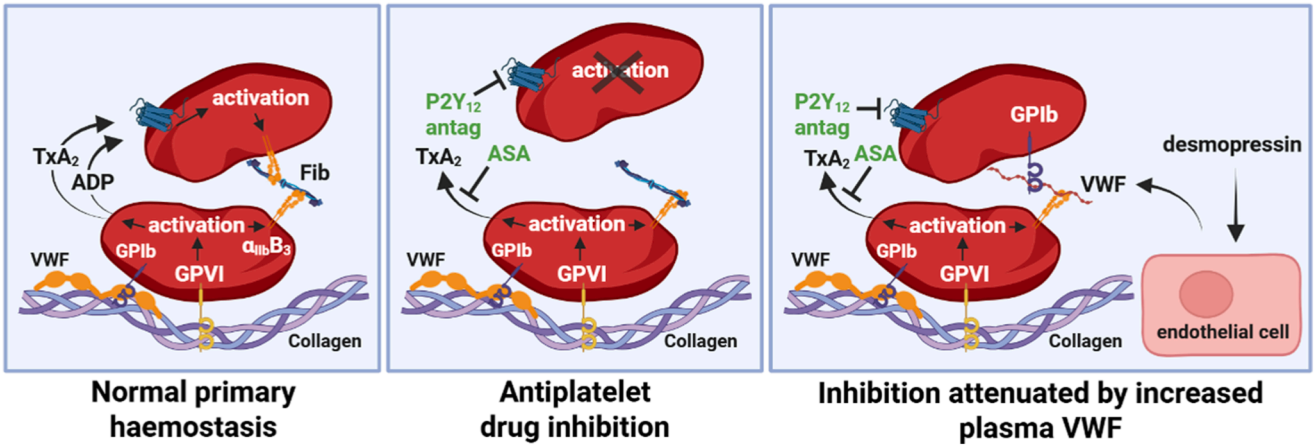


**FIGURE** Indirect attenuation of platelet inhibition via desmopressin-induced secretion of von Willebrand factor (VWF). Under normal conditions, platelet activation is initiated by the binding of glycoprotein (GP)Ib to VWF immobilized on exposed collagen and by direct collagen engagement via GPVI. This activation is amplified by secondary mediators, thromboxane $A_2$ ($TxA_2$) and adenosine diphosphate (ADP), leading to fibrinogen (Fib) binding to integrin $\alpha_{IIb}\beta_3$ (left panel). Antiplatelet drugs, such as aspirin (ASA) and $P2Y_{12}$ antagonists (antag), inhibit $TxA_2$- and ADP-mediated signaling, reducing platelet activation, impairing fibrinogen binding, and reducing clot formation (middle panel). Increasing plasma VWF by inducing release from endothelial cells with desmopressin enhances GPIb-mediated platelet function and may partially restore platelet function despite antiplatelet therapy (right panel).

haemorrhage (TICH-2) trial (a 2325-patient randomized trial comparing tranexamic acid with placebo in ICH) [11] showed that in patients with ICH, 16.6% of patients not taking antiplatelet drugs died compared with 34.8% of those taking antiplatelet drugs [12]. The combined rate of death or severe disability (modified Rankin Scale $\geq$5) was 30.1% for those not taking antiplatelet drugs compared with 51.4% for those taking antiplatelet drugs [12]. In ICH, hematoma expansion occurs relatively early; therefore, the earlier an intervention is administered, the more likely it is to have an effect [13]. For instance, in the recombinant factor VIIa for acute haemorrhagic stroke administered at earliest time (FASTEST) trial (assessing early administration of recombinant factor [F]VIIa), patients are recruited only within 2 hours of symptom onset (NCT03496883), and within 4.5 hours in ongoing the TICH-3 trial (tranexamic acid compared with placebo; ISRCTN97695350). Patients taking antiplatelet drugs appear to be at risk of hematoma expansion for up to 24 hours after stroke symptom onset [14]. There is therefore a rationale that while any reversal agent should be given as soon as possible after onset of ICH symptoms, potential reversal agents may be effective within the first 24 hours of symptom onset. Although hematoma expansion is not a validated surrogate outcome, studies demonstrating an impact on hematoma expansion may not translate into improved clinical outcomes.

## 2.2 | Traumatic brain injury

Traumatic brain injury and major trauma are both leading causes of death, with hemorrhage playing a significant role. For instance, in 2015, there were 4.7 million deaths due to road accidents worldwide [15]. A total of 30% to 40% of major trauma deaths are due to major bleeding [16]. Data on the proportion of patients taking antiplatelet drugs vary considerably across studies. However, the risk of developing intracranial hemorrhage following traumatic brain injury is higher in patients taking antiplatelet drugs than in those who are not [17]. Elderly patients with traumatic brain injury after falls are more likely to have a prolonged hospital admission or die if they are taking antiplatelet drugs [18].

## 2.3 | Acute upper gastrointestinal bleeding

Acute upper gastrointestinal bleeding (UGIB) affects approximately 47 people per 100,000 per year [5]. Approximately 28% are taking antiplatelet drugs [19], and risk of UGIB is increased on SAPT and DAPT [20]. The mechanism of bleeding includes variceal hemorrhage (patients with liver disease), ulceration, and malignancy [19]. In a UK national audit, rebleeding rates were 13% among patients receiving antiplatelet drugs and 14% among those not taking antiplatelet drugs [19]. A randomized controlled trial comparing continuation of aspirin vs stopping aspirin in patients with peptic ulcer disease found a nonstatistically significant difference in recurrent bleeding in those who continued aspirin (10.3% vs 5%), but a significantly increased overall mortality when aspirin was stopped (12.9% vs 1.3%) [21]. National guidelines for treatment of acute UGIB recommend continuing antiplatelet drugs in the event of major bleeding [22].

## 2.4 | Acute lower gastrointestinal bleeding

Acute lower gastrointestinal bleeding affects approximately 33 people per 100,000 per year [5]. Data from a UK national audit found that

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**TABLE 2** Platelet function assays.

| Assay | Mechanism | Detection of $P2Y_{12}$ inhibition | Detection of COX-1 inhibition | Specialist test or bedside? |
|---|---|---|---|---|
| **LTA** | Measures the increase in light transmission through PRP as platelets aggregate | ADP | Arachidonic acid | Specialist (lab-based) |
| **Multiplate** | Impedance aggregometry using disposable test cells with dual electrodes | ADP test | ASPI test with arachidonic acid | Specialist (lab-based) |
| **VerifyNow** | Turbidimetric-based cartridge system using fibrinogen-coated beads | $P2Y_{12}$ cartridge | Aspirin cartridge | Bedside/point-of-care |
| **TEG platelet mapping** | Measures platelet contribution to clot strength in response to agonists | ADP channel | Arachidonic acid channel | Specialist (some near-patient setups) |
| **PFA-200** | Measures the closure time of a membrane aperture under high shear using whole blood | CADP cartridge, limited sensitivity | CEPI cartridge (prolonged closure time with aspirin) | Bedside/point-of-care |
| **Impedance aggregometry** | Measures the change in electrical impedance in whole blood as platelets aggregate on electrodes | ADP | Arachidonic acid | Specialist (lab-based) |
| **Flow cytometry** | Measures activation markers (eg, P-selectin, activated GPIIb/IIIa) on the platelet surface | VASP phosphorylation assay or responses to ADP | Less commonly used for COX-1 inhibition | Specialist (lab-based) |
| **Thrombus formation under flow** | Visualizes thrombus formation under shear using microfluidic devices, often to type I collagen | Thrombus formation on type I collagen is impaired by $P2Y_{12}$ inhibition | Thrombus formation on type I collagen is impaired by COX-1 inhibition | Specialist (research/lab-based) |

ADP, adenosine diphosphate; ASPI, arachidonic acid-induced platelet aggregation; CADP, collagen and ADP; CEPI, collagen and epinephrine; COX, cyclooxygenase; GP, glycoprotein; lab, laboratory; LTA, light transmittance aggregometry; PFA-200, platelet function analyser 200; PRP, platelet rich plasma; TEG, thromboelastography; VASP, vasodilator-stimulated phosphoprotein.

**TABLE 3** Comparison of potential reversal agents for antiplatelet drugs.

| Reversal agent | Evidence base |
|---|---|
| Platelet transfusion | One randomized controlled trial in intracerebral hemorrhage showed an increased risk of death or disability with platelet transfusion.<br>*In vitro* studies suggest that 2 to 3 adult doses of platelets will reverse the antiplatelet effect of the drug. However, evidence of a clinical benefit from randomized controlled trials is lacking. |
| Tranexamic acid | Randomized controlled trial of intracerebral hemorrhage showed reduced hematoma expansion but no difference in 90-d function outcome.<br>Trials of cardiac and noncardiac surgery showed a significant reduction in the risk of hemorrhage and transfusion requirements without an increase in thrombotic events.<br>Trials of gastrointestinal hemorrhage did not include a subgroup on antiplatelet drugs. Overall, the trial showed no benefit of tranexamic acid, with an increased risk of thrombotic events and seizures.<br>Beneficial in traumatic brain injury and postpartum hemorrhage, although data on antiplatelet subgroups are lacking. |
| Desmopressin | Potential benefit in reducing blood loss and major bleeding requiring reoperation in cardiac surgery.<br>Trials are underway for intracerebral hemorrhage; data are not sufficient from randomized trials to make a strong recommendation. |
| Bentracimab | Effective for reversing ticagrelor. A single-arm trial showed that 95% of clinicians considered hemostasis as good or excellent after bentracimab use, with no comparator arm. |

29.5% were taking an antiplatelet drug, with 23.1% taking aspirin, 9.3% clopidogrel, and 3% DAPT [23]. The use of SAPT and DAPT further increased risk of bleeding [20]. Bleeding can result from various causes, including cancer, angioectasia, and diverticulitis [23]. Antiplatelet drug use is associated with worse outcomes, with rebleeding occurring in 20.1% on SAPT and 30.3% on DAPT compared with 12.8% of patients not on antiplatelet drugs. Mortality occurred in 2.4% on SAPT and 7.7% on DAPT compared with 2.1% of patients not on antiplatelet drugs [23,24]. National guidelines recommend discontinuing antiplatelet drugs if used for primary prophylaxis but continuing if used for secondary prophylaxis, weighing the risks and benefits of bleeding and thrombotic events [25].

### 2.5 | Pregnancy

In pregnancy, aspirin is often given for prevention of preeclampsia [26]. Aspirin is also used for other conditions, such as obstetric antiphospholipid syndrome [27]. A Cochrane review of 19 trials including 23,769 women found that among those taking antiplatelet drugs, there was a small increased risk of postpartum hemorrhage (defined as blood loss of 500 mL or more at delivery) with a relative risk of 1.06 (95% CI, 1.00-1.12) [28]. There was significant variation in the aspirin dose used and in the timing of when it was continued or stopped between trials included in this review. The risk of bleeding at other sites, such as gastrointestinal and ICH in pregnancy, is not well documented in the literature; however, it should be noted that the overall risk is much lower than that of the general population, where older age and comorbidity are significant independent risk factors for bleeding.

### 2.6 | Surgery

Antiplatelet drugs may also convey a higher risk of bleeding around the time of surgery. The perioperative ischemic evaluation-2 (POISE-2) trial recruited 10,010 patients undergoing elective noncardiac surgery and randomized them to aspirin or no aspirin. There was significantly more bleeding in the group of patients who took aspirin perioperatively (4.6% vs 3.8%). There was no significant difference in the rate of myocardial infarction or death (7% vs 7.1%) [29]. In a trial of patients undergoing low-to-moderate-risk noncardiac surgery who had a cardiac stent *in situ*, patients were randomized to either continue or stop aspirin for surgery. The trial was underpowered to detect differences in major bleeding but showed major bleeding occurred in 6.5% of those on aspirin and 5.2% of those not on aspirin. There was an increase in minor bleeding in patients taking aspirin (14.9%) compared with those not taking aspirin (10.1%). There was no difference in myocardial infarction, which occurred in 0.6% of patients in both trial arms [30]. Overall, while there is a small increased risk of bleeding in patients undergoing surgery who are taking antiplatelet drugs, this must be balanced against the risk of thrombotic events, particularly myocardial infarction, if the antiplatelet drugs are discontinued or reversed.

## 3 | MECHANISMS OF ACTION FOR ANTIPLATELET DRUGS: JUSTIFICATION OF TARGETS FOR REVERSAL AGENTS

Antiplatelet drugs inhibit platelet receptors or enzymes that promote platelet activation. The mechanism of action impacts the choice of assay to detect activity and the approach to reversal.

Many commonly used antiplatelet drugs, including aspirin, clopidogrel, and prasugrel, achieve irreversible inhibition via covalent modification of their molecular targets. Relevant to clinical practice, irreversible inhibition means that washout of the antiplatelet effect is often dependent on platelet turnover, which has a half-life of 7 to 10 days [31]. Reversal strategies for antiplatelet drugs with an irreversible mechanism must attenuate the antiplatelet effect via an indirect mechanism, as function cannot be restored to the drug target.

The increase in plasma von Willebrand factor (VWF) evoked by desmopressin is an example of an indirect reversal strategy (Figure). The reversibility of an antiplatelet drug, combined with the details of its cellular mechanism of action, is a key determinant of the potential for direct and indirect reversal strategies.

Aspirin is an irreversible cyclooxygenase-1 inhibitor that prevents synthesis of the platelet activator, thromboxane $A_2$ ($TxA_2$) [32,33]. Platelets synthesize $TxA_2$ in response to blood vessel damage, which activates the thromboxane receptor, a $G\alpha_q$- and $G\alpha_{13}$-coupled G protein-coupled receptor. Intracellular release of $Ca^{2+}$ leads to downstream integrin $\alpha_{IIb}\beta_3$ (glycoprotein IIB/IIIa) activation, aggregation, and formation of a stable clot [34]. Several platelet receptors couple to $G\alpha_q$, including the adenosine diphosphate (ADP) receptor $P2Y_1$, and this redundancy in activation pathways evoked by the thromboxane receptor may render indirect methods of reversal more viable.

The $P2Y_{12}$ inhibitors antagonize the $P2Y_{12}$ receptor via reversible (cangrelor and ticagrelor) or irreversible (clopidogrel and prasugrel) mechanisms [35]. $P2Y_{12}$ is a $G\alpha_i$-coupled G protein-coupled receptor. Activation by ADP inhibits adenylyl cyclase to lower cyclic adenosine monophosphate, countering $PGI_2$-mediated inhibition [33] and, via phosphoinositide 3-kinase, relieves Ras GTPase-activating protein 3 (RASA3) restraint on Rap1b, promoting integrin $\alpha_{IIb}\beta_3$ activation [36]. A few other pathways activate platelets by overcoming inhibitory signals, making $P2Y_{12}$ inhibition highly effective but at the cost of increased bleeding risk. The key role of $P2Y_{12}$ in platelet activation may render indirect reversal methods of other $P2Y_{12}$ inhibitors challenging.

Vorapaxar is a small-molecule PAR1 inhibitor that reversibly binds to the receptor, thereby preventing thrombin-mediated platelet activation [37,38]. Unlike aspirin or $P2Y_{12}$ inhibitors, PAR1 antagonism does not modulate platelet responses to other agonists such as ADP or collagen [39], which may explain its modest efficacy and the need for combination therapy. Human platelets possess a second receptor, PAR4, which provides some redundancy to thrombin-mediated platelet activation of PAR1 stimulation. The long duration of action and lack of a specific reversal agent for vorapaxar pose challenges in managing bleeding complications.

Off-target inhibition of platelet function is a feature of some drug classes, such as some tyrosine kinase inhibitors and selective serotonin reuptake inhibitors, which can increase bleeding risk [40]. The mechanism of action of these drugs is described in more detail in the Supplementary Data. Where reversal of platelet inhibition is considered clinically appropriate, *in vitro* data support efficacy of platelet transfusion [41] and increasing plasma VWF [42] for reversal of the tyrosine kinase inhibitor ibrutinib, but clinical data on the efficacy of these approaches are currently lacking.

## 4 | ASSAYS TO DETECT ANTIPLATELET EFFECTS: IMPACT ON CLINICAL DECISION MAKING

Available assays and their detection of antiplatelet effects are summarized in Table 2. Detailed mechanism of each assay is included in the Supplementary Data.

Light transmission aggregometry remains the gold standard due to its versatility and sensitivity, although its specialist, laboratory-based nature limits its integration into real-time care [43]. To support time-critical decisions, eg, surgical timing and decision to transfuse [44], whole-blood point-of-care assays such as VerifyNow (Werfen), Multiplate (Roche), thromboelastography platelet mapping, and the platelet function analyser (PFA200; Siemens) provide results within minutes, offer confirmation of treatment effect and recovery tracking after therapy interruption, and may help evaluate reversal or mitigation strategies. However, analytic heterogeneity, drug-specific dependencies, variable cutoffs, and only a modest correlation with outcomes limit routine clinical use [19–21]. For short-half-life anticoagulants (eg, direct oral anticoagulants), drug-level assays can guide reversal; by contrast, because antiplatelet effects are largely irreversible, platelet function testing may be unnecessary in the acute setting once effective reversal strategies are validated. Current guidance supports selective testing, particularly for urgent cardiac surgery after recent P2Y12 exposure [45]. Because it operates under high shear, the PFA-200 may be particularly useful for assessing desmopressin-mediated indirect reversal via VWF. Other specialist methods, including impedance aggregometry, flow cytometry, and microfluidic thrombus formation under flow, yield valuable mechanistic information but have limited immediate clinical utility due to their high demands for time, resources, and expertise. Overall, drug-induced platelet dysfunction can be detected and, in some scenarios, mitigated, but testing should be targeted, interpreted within the constraints of each platform, and used to inform rather than dictate reversal decisions.

## 5 | STRATEGIES FOR REVERSING THE ANTIPLATELET DRUG EFFECT

### 5.1 | Platelet transfusion

Platelet transfusions are derived from whole blood or apheresis from blood donors. The product is variable, with different platelet concentrations in each unit, depending on the country [46]. The supply of platelet transfusions is dependent on blood donors, and there is a risk of shortages, as was the case during the COVID-19 pandemic [47].

The rationale for platelet transfusion is that most antiplatelet drugs irreversibly inhibit platelets to which they bind [48]. Consequently, providing a source of uninhibited platelets may restore normal hemostatic effects, and there are promising *in vitro* data to support this approach [48,49]. An animal bleeding model similarly demonstrated the efficacy of platelet transfusion to reverse increased bleeding times induced by triple antiplatelet therapy with aspirin, clopidogrel, and vorapaxar [50]. When normal volunteers were given aspirin or clopidogrel for 7 days, platelet function, as measured by light transmission aggregometry (agonists were arachidonic acid for aspirin and ADP for clopidogrel), was significantly suppressed. When inhibited platelets were replaced with donor platelets *in vitro*, the platelet function was restored. For those treated

with aspirin, this occurred when approximately 20% to 30% of platelets were donated. The authors estimated that if this were to be extrapolated to *in vivo* transfusion, 2 to 3 adult doses of platelets would be required to restore platelet function. National and international guidelines, such as those from the British Society for Haematology, recommend consideration of platelet transfusion (2-3 units) on the basis of these data [51,52].

One randomized controlled trial has evaluated platelet transfusion for antiplatelet drug reversal [53]. In this trial platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH), patients with ICH who were taking aspirin or clopidogrel were randomized 1:1 to either standard care or to platelet transfusion [53]. Patients could be included if they were within 6 hours of ICH symptom onset. Patients taking aspirin received 1 adult dose of platelets, and patients taking clopidogrel received 2 adult doses. The outcome was measured using the ordinal shift of the modified Rankin Scale (a 7-point scale ranging from 0 [no symptoms] to 6 [death]). The trial demonstrated that the odds of a poor outcome (death or severe disability) were worse in patients treated with platelet transfusion compared with standard care. Mortality was 32% in those treated with platelets and 22.6% in those given standard care. The rates of death or severe disability (modified Rankin Scale $\geq$5) were 41.2% for platelet transfusion and 29% for standard care. The reason for the poorer outcomes is not clear; however, the proposed mechanisms and nature of harms associated include several interrelated biological and clinical factors. Transfused platelets can become activated and exhibit enhanced prothrombotic and proinflammatory properties, potentially exacerbating cerebral injury and promoting further vascular permeability and compromise [54]. There were a small number more thrombotic events and cases of hydrocephalus in the platelet transfusion arm compared with standard care [55]. After adjusting for perihematomal edema at baseline, post hoc analysis found an odds ratio (OR) for ICH growth >6 mL in patients receiving platelets of 2.36 (95% CI, 1.03-5.40) compared with those receiving standard of care. ICH growth >6 mL was associated with an increased risk of poor outcome (OR, 2.45; 95% CI, 1.07-5.63) compared with $\leq$6 mL growth [55]. No association with poorer outcomes was identified for shelf life or preparation type of platelets. Considering limitations of the post hoc analyses, it remains unclear whether the poorer outcomes observed in PATCH trial are explained by baseline population imbalances or by a detrimental effect of platelet transfusion.

Notably, in the PATCH trial, patients were excluded if they were due to undergo neurosurgery; therefore, it is not possible to comment on this patient group. In the PATCH trial, the majority of patients were on aspirin and were only given 1 adult dose of platelets, whereas *in vitro* data suggest that 2 to 3 adult doses of platelets would be required to normalize platelet aggregation. The allocated treatment in the PATCH trial could therefore be considered subtherapeutic. However, given the evidence of harm from platelet transfusion, higher doses of platelet transfusion are not recommended. Guidelines give no recommendation on platelet transfusion for patients with ICH who undergo neurosurgery [56].

While there are no randomized trials in surgery of platelet transfusion perioperatively there are several published case series. In one series, 181 patients undergoing urgent cardiac surgery on antiplatelet drugs were treated with 2 adult doses of platelets preoperatively. A total of 5.5% had a thrombotic event, 12.2% had major bleeding, and 6.6% required reoperation due to bleeding [57]. In a series of 14 patients undergoing urgent noncardiac surgery on DAPT who were treated with 2 adult doses of platelets preoperatively, 1 had acute coronary syndrome (7%), and 1 had a significant perioperative bleed not requiring transfusion (7%) [58]. Without a comparator group, it is difficult to assess the risks and benefits of platelet transfusions in these groups.

## 5.2 | Tranexamic acid

Tranexamic acid was first described in 1964 [59]. It is a lysine analog that inhibits fibrinolysis by blocking plasmin binding sites of fibrinogen [60]. While tranexamic acid does not reverse the effects of antiplatelet drugs, it is commonly recommended to reduce bleeding in patients taking antiplatelet drugs, with most of the direct evidence from human studies [51,52].

The evidence for the efficacy of tranexamic acid in patients taking antiplatelet drugs is mixed. In patients with ICH, a subgroup analysis of the TICH-2 trial, confined to patients taking antiplatelet drugs, showed that tranexamic acid reduced hematoma expansion for patients taking antiplatelets drugs whereas it did not for all patients [12]. Despite this, the tests for interaction were not statistically significant. Tranexamic acid did not reduce the risk of death or disability in patients on antiplatelet drugs. Of those taking antiplatelet drugs, the risk of death was 34.8% when given tranexamic acid and 34.7% when given placebo. However, in this trial, tranexamic acid was given within 8 hours of ICH symptom onset. In the ongoing TICH-3 trial (ISRCTN97695350), tranexamic acid will be given within 4.5 hours instead. The results of this will help to inform practice.

The haemorrhage alleviation with tranexamic acid - intestinal system (HALT-IT) trial randomized 12,009 patients with acute UGIB to tranexamic acid (4 g >24 hours) compared with matching placebo. This trial did not assess a subgroup of patients who were taking antiplatelet drugs. For all patients, tranexamic acid did not improve death due to bleeding (4% in both trial arms) and led to an increased risk of thrombotic events (0.8% vs 0.4%) [61].

Likewise, in postpartum hemorrhage, large randomized trials have shown the benefit of tranexamic acid in reducing bleeding in unselected patients but have not included a subgroup of patients taking antiplatelet drugs [62].

A potential concern with any prohemostatic drug would be the potential to cause thrombosis. Aside from the HALT-IT trial described above, a wide range of trials have demonstrated no thrombotic risk with tranexamic acid given around the time of surgery, including a trial administered 9 g of tranexamic acid preoperatively to patients undergoing coronary artery bypass grafting [63]. In this trial, the subgroup of patients taking antiplatelet drugs who

were treated with tranexamic acid had a significantly reduced risk of transfusion (33.9% vs 52.7%) and major bleeding requiring reoperation (1.3% vs 3.6%). There was no increased risk of the incidence of death or thrombotic events (19% in the tranexamic acid arm and 20.8% in the placebo arm), even though this patient group was high risk and the dose of tranexamic acid was substantially in excess of the standard dose that is recommended for clinical practice [64]. The lack of thrombotic risk has been confirmed in many surgical trials [65].

While large trials are confirming the efficacy of tranexamic acid for traumatic brain injury [66], major trauma [67], and postpartum hemorrhage [62], these trials did not include subgroup analysis of patients taking antiplatelet drugs.

### 5.3 | Desmopressin

Desmopressin was first described in 1967 [68] and reported as a prohemostatic agent in 1977 [69]. Desmopressin stimulates endothelial Weibel–Palade bodies to release VWF and FVIII. It may also increase the formation of procoagulant platelets [70].

Desmopressin is commonly used for treatment of mild to moderate hemophilia A [71] and von Willebrand disease [72]. It is also used for inherited platelet function disorders [73] and bleeding of unknown cause [74]. Animal bleeding models have provided direct evidence of the efficacy of desmopressin to reverse the drug-induced platelet dysfunction of aspirin [75,76] and clopidogrel [77], but failed to do so with prasugrel [78].

A meta-analysis of 10 trials of cardiac surgery in patients with platelet dysfunction or taking antiplatelet drugs, who were randomized to desmopressin or placebo, demonstrated reduced red cell transfusion requirements (mean difference, −0.65 units; 95% CI, −1.16 to −0.13 units) and a lower risk of reoperation due to bleeding (Peto OR, 0.39; 95% CI, 0.18-0.84) [79].

Key side effects of desmopressin include vasodilation (leading to tachycardia, hypotension, and facial flushing), water retention (leading to hyponatremia and, in severe cases, seizures), and concerns over a potential increased rate of thrombosis. A meta-analysis of desmopressin compared with placebo in all surgical indications and for those with platelet dysfunction did not find a difference in the risk of arterial or venous thromboembolism for patients treated with desmopressin compared with placebo [79,80].

Hypotension is considered an adverse event for many conditions but may convey benefits in some circumstances, such as intracerebral bleeding, where lowering blood pressure may improve outcomes [81].

Desmopressin improves platelet function, as measured by PFA, when used to reverse the antiplatelet drug in ICH [82]. Desmopressin has been assessed in a randomized phase 2 feasibility trial desmopressin for reversal of antiplatelet drugs in stroke due to haemorrhage (DASH-1) comparing 20 μg desmopressin intravenously with placebo in patients with ICH taking an antiplatelet drug or thought to be taking an antiplatelet drug [83]. Patients taking selective serotonin reuptake inhibitors were not excluded. Desmopressin was administered within 24 hours of symptom onset. The DASH-1 trial demonstrated that it would be feasible to conduct a definitive trial of desmopressin compared with placebo. Initial results found a lower, although not statistically significant, rate of death (19% vs 26%) and death or severe disability (modified Rankin Scale $\geq$5; 23% vs 37%) in patients treated with desmopressin compared with placebo. There was no difference in thrombotic events (4% in both trial arms) or serious adverse events (44% for those treated with desmopressin and 48% for those treated with placebo) between the desmopressin and placebo arms of the trial. More patients had mild hyponatremia (125-135 mmol/L) when treated with desmopressin than placebo (35% vs 13%), although there were no instances of moderate to severe hyponatremia. In order to assess the efficacy of desmopressin compared with placebo, a 1000-patient efficacy trial for this patient group (DASH-2) is scheduled to start in winter 2025 (NIHR208082).

Desmopressin and tranexamic acid are often given in combination. There is some biological rationale for this: desmopressin induces the release of tissue plasminogen activator, a profibrinolytic agent, from endothelial Weibel–Palade bodies, and tranexamic acid being an effective inhibitor of fibrinolysis. The DASH-2 and TICH-3 trials will include a partial factorial design to provide data on the combination of these agents in patients with ICH who are taking antiplatelet drugs.

### 5.4 | Ticagrelor reversal

While most antiplatelet drugs, including aspirin, dipyridamole, and most $P2Y_{12}$ inhibitors, bind irreversibly to platelets, ticagrelor binds reversibly [84]. Bentracimab is a neutralizing, recombinant, human immunoglobulin G1 monoclonal antibody antigen-binding fragment that binds ticagrelor and its major circulating metabolite [85]. A phase 3 single-arm trial of bentracimab for the reversal of ticagrelor in patients undergoing major surgery or with major bleeding demonstrated that the antiplatelet effect of ticagrelor (measured by VerifyNow) was rapidly reversed within 5 to 10 minutes and reversal remained for >24 hours [86]. Clinicians were asked to rate the quality of hemostasis, and 95.1% rated it as excellent. Notably, 5.3% of patients had a thrombotic event. A challenge in this case is the absence of a control arm, which makes it difficult to assess whether bentracimab leads to better outcomes than standard care. As discussed above for platelet transfusion, evidence of efficacy *in vitro* does not necessarily translate into improved outcomes compared with standard care in a randomized controlled trial. Future trials should report on clinically relevant outcomes, such as major bleeding, return to theater, thrombosis, and mortality. Strategies for reversal of antiplatelet drugs are sumarised in Table 3.

## 6 | CAN DRUG-INDUCED PLATELET DYSFUNCTION BE REVERSED?

Antiplatelet drugs are lifesaving. However, studies have shown that mortality in the setting of major bleeding is higher in patients taking

antiplatelets, providing rationale for reversal. Reversible inhibitors of platelet dysfunction (eg, ticagrelor) do have the potential to be reversed, although data from controlled trials are lacking. For irreversible inhibitors, mitigation strategies, such as platelet transfusion, tranexamic acid, and desmopressin, are needed instead of reversal. Promising *in vitro* and animal model data does not mean that patients will benefit and there is a need for robust clinical trials. The only randomized controlled trial data assessing reversal of drug-induced platelet dysfunction in ICH (where no neurosurgery is planned) suggested that platelet transfusion is harmful and should not be used. There is a lack of data in other settings, and there is a need to address this clinical question. The upcoming DASH-2 trial will give strong evidence to assess the efficacy of desmopressin in patients with ICH. The use of tranexamic acid is beneficial for the reduction of bleeding in many situations, but it is not necessarily better (or worse) for patients taking antiplatelet drugs. While point of care platelet function tests are available, their utility to guide clinical decision-making remains uncertain, and they should not be used in routine practice.

## 7 | CONCLUSION

There is rationale for the development and validation of reversal strategies for drug-induced platelet dysfunction, and efficacy is supported by *in vitro* data. However, the assumption that reversal will improve clinical outcomes is not grounded in evidence, and future trials are needed.

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### AUTHOR CONTRIBUTIONS

A.P.B. and M.J.R.D. conceived and wrote the original article. S.M. reviewed, edited, and restructured the revised version. All authors approved the final manuscript.

### RELATIONSHIP DISCLOSURE

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### ORCID

*Michael J. R. Desborough* https://orcid.org/0000-0002-1951-5616

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## SUPPLEMENTARY MATERIAL

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