The role of anticoagulants, antiplatelet agents, and their reversal strategies in the management of intracerebral hemorrhage

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New anticoagulant and antiplatelet medications have been approved and are prescribed with increased frequency. Intracranial hemorrhage is associated with the use of these medications. Therefore, neurosurgeons need to be aware of these new medications, how they are different from their predecessors, and the strategies for the urgent reversal of their effects. Utilization of intraluminal stents by endovascular neurosurgeons has resulted in the need to have a thorough understanding of antiplatelet agents. Increased use of dabigatran, rivaroxaban, and apixaban as oral anticoagulants for the treatment of atrial fibrillation and acute deep venous thrombosis has increased despite the lack of known antidotes to these medications.

KEY WORDS • intracerebral hemorrhage • warfarin • oral anticoagulants • antiplatelet

Nontraumatic spontaneous ICH may occur in patients taking antiplatelet and/or anticoagulant medications and is associated with worse outcomes and increased mortality.8,10,11,21,23,25,36,57,60,70 Difficulty or delay in the reversal of the effects of anticoagulant medications can result in hematoma expansion or delayed surgical evacuation. By comparison, reversal of antiplatelet medication in a similar setting still has unproven benefit. Recently, FDA-approved oral antiplatelet and anticoagulant medications have found increased usage, but introduce new challenges into the emergency management of antiplatelet- and anticoagulant-related ICH. In this paper we review the relevant literature on antiplatelet- and anticoagulant-related ICH to familiarize practicing neurosurgeons with the medications now available, and to provide strategies for the emergency reversal of these medications, some of which have no direct antidote.

Abbreviations used in this paper: AF = atrial fibrillation; DVT = deep venous thrombosis; FFP = fresh-frozen plasma; ICH = intracerebral hemorrhage; INR = international normalized ratio; PCC = prothrombin complex concentrate; rVIIa = recombinant factor VIIa.

Anticoagulant-Related ICH

Anticoagulation medications are important treatments for numerous medical conditions including DVT, pulmonary embolism, and nonvalvular AF. Unfortunately, these medications are associated with an increased risk of ICH. Often the cause of the hemorrhage is directly related to a supratherapeutic effect of the anticoagulant. In other situations therapeutic levels can exacerbate an ICH of an alternate origin (such as trauma or cerebral aneurysm rupture).

All of the anticoagulant medications alter the coagulation cascade at various points along the extrinsic, intrinsic, or common pathways with an ultimate goal of reduced fibrin formation (Fig. 1). Because of the frequency that neurosurgeons are consulted to aid in the management of patients with anticoagulant-related ICH, neurosurgeons should at least maintain a cursory understanding of these pathways and how they relate to the various anticoagulant medications.

Injectable anticoagulants (unfractionated heparin and enoxaparin) are most commonly used during admission to a medical facility, whereas the most commonly pre-

Abbreviations used in this paper: AF = atrial fibrillation; DVT = deep venous thrombosis; FFP = fresh-frozen plasma; ICH = intracerebral hemorrhage; INR = international normalized ratio; PCC = prothrombin complex concentrate; rVIIa = recombinant factor VIIa.
scribed outpatient anticoagulant is warfarin. Warfarin’s immediate predecessor was designed as a rodenticide; in the 1950s, warfarin began common usage as a medical anticoagulation therapy. Warfarin is a vitamin K antagonist and prevents the hepatic formation of the vitamin K–dependent clotting factors (II, VII, IX, and X). Numerous randomized trials and meta-analyses have confirmed warfarin is highly effective at reducing the risk of stroke from AF. However, genetic polymorphisms, several common medications, as well as changes in a patient’s diet can drastically alter the anticoagulation effect, which is compounded by warfarin’s relatively narrow therapeutic window. As a result, frequent drug monitoring with a prothrombin time and the INR is required. Even with frequent drug monitoring, high INR levels are frequently encountered in the outpatient setting and medication adjustments must be made. The most frequently recommended INR level for the treatment of AF is between 2 and 3. Even in the setting of strict INR monitoring during clinical trials, it can be difficult to maintain patients in this narrow therapeutic window, and subtherapeutic and supratherapeutic levels are common. International normalized ratio levels greater than 4.0 have been reported to be associated with significantly increased risk for ICH. Warfarin-related ICH patients have a significantly increased risk of hematoma expansion (OR 6.2, 95% CI 1.7–22.9) compared with ICH patients not receiving anticoagulant therapy. After decades in which warfarin was the only oral anticoagulation therapy available to patients, new oral medications have recently gained approval by the FDA (www.fda.gov) that have much similar stroke protection, more reliable dose-response relationships, and do not require blood-level monitoring. These medications include dabigatran (a direct thrombin inhibitor), and rivaroxaban and apixaban, direct inhibitors of factor Xa. Many cardiologists and neurologists have been increasingly prescribing these medications over the last few years. However, this enthusiasm has been tempered by the lack of an antidote and fear of being unable to safely manage patients taking these new medications who experience anticoagulant-related ICH. The silver lining to these uncertainties is that the incidence of major hemorrhage in Phase III clinical trials for these new oral anticoagulants is lower than that of warfarin.

A prospective randomized, open-label trial (Randomized Evaluation of Long-Term Anticoagulation Therapy, or RE-LY) compared 2 blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) with open-label adjusted dose warfarin (INR target 2.0–3.0) in 18,113 patients. Dabigatran 150 mg twice daily was found to be significantly better than warfarin at preventing stroke or systemic embolism, and dabigatran 110 mg twice daily was demonstrated as noninferior to warfarin. Both doses of dabigatran were found to produce a significant reduction in the rates of ICH and hemorrhagic stroke compared with warfarin (dabigatran 0.12%, 0.10% vs warfarin 0.38% per year; RR 0.31 and 0.26; p < 0.01 [both]). Only the 150-mg dose tested in the study is available in the US. Similar results were found in other prospective randomized, double-blind Phase III clinical trials including the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, in which rivaroxaban...
and apixaban were both found to demonstrate statistically significant reductions in hemorrhagic stroke compared with warfarin. Recently, the American College of Chest Physicians published their newest recommendations for antithrombotic therapy for atrial fibrillation; they are now suggesting dabigatran 150 mg twice daily rather than warfarin when oral anticoagulant therapy is recommended. As these newer oral anticoagulants are increasingly prescribed more frequently, we hope a real-world decrease in the frequency of anticoagulant-related ICH will follow. Nevertheless, there will be patients with anticoagulant-related ICH who need emergency attention and immediate reversal of the anticoagulating effects.

Hematoma expansion is common in the setting of anticoagulant-related ICH, leading to more deaths. Correcting the INR to 1.3 or less within 2 hours has been shown to decrease hematoma expansion. Advances and improvements have been made in methods for reversal of warfarin (a summary of common anticoagulants and their reversal methods can be found in Table 1). The first consideration for emergency management of anticoagulant-related ICH is to stop the anticoagulant agent. Blood pressure should be controlled, although there is little evidence to support a specific blood pressure goal. The authors’ preference is to maintain the systolic blood pressure below 160 mm Hg. Medical management of elevated intracranial pressure should be initiated immediately. Fast-acting agents for reversal of anticoagulation by factor replacement include FFP, PCC, and rVIIa. Of these, FFP (the historical standard of care) is relatively ineffective in factor IX, requires large volume infusion, and can lead to complications such as pulmonary edema and delayed reversal of INR. Recombinant factor VIIa is effective for immediate INR reversal and prevention of hematoma expansion, but is associated with increased thrombotic complications such as myocardial infarction, pulmonary embolism, and DVT. Recombinant factor VIIa has not been shown to improve survival or functional outcome and is generally not recommended for reversal in anticoagulant-related ICH. Prothrombin complex concentrate is increasing in popularity as a low-volume, rapid-reversal agent, and has been reported as superior to FFP in several studies. Individualized dosing of PCC may be the most effective method of reversal. In 1 study, individualized dosing of PCC based on the patient’s body weight and initial INR was superior at reaching the target INR 15 minutes after dosing compared with the standard dosage of PCC. Similar data has led to support for PCC as the standard of care at many institutions.

Prothrombin complex concentrate formulations vary worldwide, with the US receiving FDA approval for “3-factor” PCC (II, IX, X) whereas many clinical studies conducted outside the US involve “4-factor” PCC, which includes factor VII. It is unclear whether the difference in these preparations is significant and any review of the literature on this topic needs to have this critique in mind. Even though PCC formulations have variable amounts of factor VII, PCC replaces multiple factors compared with rVIIa, and is cost effective when compared with FFP for serious bleeding. When reversing warfarin one must remember that treatment with a fast-acting agent alone is not enough for a sustained reversal effect. It is necessary to also administer vitamin K (orally or intravenously) to maintain INR reversal. In emergency situations, vitamin K should not be used alone, but should be used in conjunction with faster-acting agents because vitamin K can take up to 24 hours to achieve INR correction. Additionally, intravenous (versus oral) vitamin K is associated with a low risk of anaphylaxis, but generally remains the preferred route of administration.

New oral anticoagulants (dabigatran, rivaroxaban, and apixaban) have recently been approved by the FDA for use in patients with AF for the prevention of stroke and for the treatment of acute DVT (rivaroxaban). The advantages of these medications include a more reliable anticoagulant effect, decreased risk of associated ICH, and no need for monitoring of therapeutic levels. The biggest disadvantage of these medications is the lack of an antidote. For recent dosing or recent overdose, consider oral activated charcoal to help absorb the drug and reduce the bioavailability. Strategies for reversal may include FFP, PCC, and/or rVIIa administration, but current studies show that for dabigatran these methods may be ineffective and only moderately effective with rivaroxaban. Current evidence is too weak to support a specific reversal protocol for any of these medications; thus, supportive care is essential for ICH related to these medications. As dabigatran is cleared by renal excretion, optimizing renal function is necessary. Hemodialysis has been suggested as an emergency means of removal of dabigatran, and may be the most effective means in patients with impaired creatinine clearance. With dabigatran, a normal activated partial thromboplastin time suggests no active anticoagulation effect and can be used to guide reversal therapy or timing of surgical intervention. For rivaroxaban and apixaban, emergency reversal with PCC is likely the most effective option as both are Xa inhibitors and PCC is more likely to be effective with these medications than with dabigatran (a direct thrombin inhibitor; Fig. 1). Confirmation of normal antifactor Xa assay activity is useful in showing that rivaroxaban and apixaban are no longer causing an anticoagulation effect.

In the case of anticoagulant-related ICH, warfarin remains the most commonly prescribed oral anticoagulant, but due to improved dose response, larger therapeutic windows, and reduced risk of ICH, newer oral agents such as dabigatran, rivaroxaban, and apixaban are being used with increasing frequency. Having a basic appreciation for the pharmacokinetics of these medications, including possible reversal strategies in the setting of ICH, are essential for patient safety. Although there are no specific antidotes to the newer oral anticoagulants, reversal strategies do exist and may be implemented in emergency situations. Additional research studies evaluating the best methods for reversal of these medications are ongoing and much needed.

**Antiplatelet-Related ICH**

Antiplatelet medication has been shown to be a risk factor for spontaneous ICH as well as increased ICH volume and increased mortality, but the exact increase has
TABLE 1: Common anticoagulation medications*

<table>
<thead>
<tr>
<th>Generic Name (trade name)</th>
<th>Mechanism of Action</th>
<th>Recommended Dosing</th>
<th>Pharmacokinetics/ Metabolism/Excretion</th>
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<td>injectable (IV/SQ)</td>
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<td>unfractionated heparin</td>
<td>binds antithrombin III; at low doses, inactivates factor Xa, inhibits conversion of prothrombin to thrombin; at higher doses, inactivates factors IX, X, XI, XII, thrombin, inhibits conversion of fibrinogen to fibrin; also inactivates activation of factor VIII</td>
<td>IV: varies; SQ for DVT prophylaxis: 5000 u SQ BID or TID</td>
<td>metabolism: partial liver, partial renal excretion; elimination: 60–90 min, longer at higher doses</td>
<td>aPTT, antifactor Xa (aPTT reference ranges vary between hospitals)</td>
<td>within 4 hrs of dosing: 1 mg protamine sulfate for 100 u heparin administered</td>
<td>in 2009, a new USP unit dose was correlated to international unit dose; this results in a 10% reduction in effectiveness of new dosing units</td>
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<tr>
<td>enoxaparin (Lovenox)</td>
<td>LMWH; binds to antithrombin, increasing its ability to inhibit activated coagulation factors within intrinsic &amp; common pathways (Xa), no effect on extrinsic pathway</td>
<td>DVT prophylaxis: 1 mg/kg SQ BID or 1.5 mg/kg SQ QD</td>
<td>metabolism: liver desulfation, depolymerization, renal excretion; elimination: 4.5 hrs (single dose), 7 hrs (repeated dosing)</td>
<td>antifactor Xa assay</td>
<td>protamine sulfate (1 mg/ 1 mg enoxaparin given last 8 hrs) can be used although it will only partially (~60%) reverse effects of enoxaparin; consider rVIIa</td>
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<td>fondaparinux (Arixtra)</td>
<td>inhibits factor Xa</td>
<td>DVT treatment: 5–10 mg weight-based SQ QD; prevention: 2.5 mg SQ QD</td>
<td>renal excretion elimination T1/2: 17–21 hrs; contraindicated in patients w/ severe renal impairment</td>
<td>antifactor Xa assay</td>
<td>no specific antidote; consider rVIIa 90 μg/kg; hemodialysis reduces by about 20%, protamine no effect</td>
<td>synthetic 5-saccharide analog of active pentasaccharide sequence found in heparin &amp; LMWHs</td>
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<tr>
<td>lepirudin (Refludan)</td>
<td>direct thrombin inhibitor (binds to catalytic &amp; exosite I of thrombin)</td>
<td>HIT: 0.4 mg/kg IV over 20 sec, then 0.15 mg/kg/hr IV up to 10 days</td>
<td>renal excretion T1/2: 1.3 hrs</td>
<td>daily monitoring of aPTT; goal 1.5–2.5x median of laboratory’s normal aPTT range</td>
<td>no specific antidote; consider FFP &amp; cryoprecipitate</td>
<td>approved in US for treatment in heparin-induced thrombocytopenia</td>
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<tr>
<td>argatroban (Acova)</td>
<td>direct thrombin inhibitor (reversibly binds to catalytic site of thrombin)</td>
<td>initial 2 μg/kg/min IV over 1–3 hrs until steady state</td>
<td>metabolism: hepatic CYP enzymes; biliary excretion T1/2: 40–50 min</td>
<td>aPTT: maintain 1.5–3x baseline value; can also elevate PT making transitioning to warfarin difficult to monitor</td>
<td>no specific antidote; consider FFP &amp; cryoprecipitate</td>
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<td>oral</td>
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<td>warfarin (Coumadin)</td>
<td>inhibits hepatic production of vitamin K–dependent coagulation factors (II, VII, IX, X, &amp; anticoagulant proteins C &amp; S)</td>
<td>2–5 mg/day for 2–4 days; INR adjusted dosing thereafter 1–10 mg/day</td>
<td>99% bound to plasma proteins (albumin); CYP2C9 hepatic metabolism plasma T1/2: 25–60 hrs (mean 40 hrs); induction of hepatic enzymes including CYP2C9 can increase metabolic clearance</td>
<td>INR 2–3; difficult to keep in therapeutic range because of many drug &amp; diet interactions &amp; patient genetic variability</td>
<td>1 of the following fast-acting agents: PCC (25–100 UI/kg) or FFP (15 ml/kg) &amp; vitamin K 5–10 mg IV</td>
<td>medical usage began in 1950s, originally developed as a rodenticide, safe for nursing mothers</td>
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(continued)
TABLE 1: Common anticoagulation medications* (continued)

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<tr>
<td>dabigatran (Pradaxa)</td>
<td>direct thrombin inhibitor</td>
<td>150 mg BID</td>
<td>80% renal excretion; plasma T1/2: 12–14 hrs; caution w/ renal impairment; contraindicated in severe impairment</td>
<td>routine anticoagulation monitoring unnecessary; normal aPTT indicates no dabigatran effect</td>
<td>consider transfusion w/ FFP, rVIIa (10–90 μg/kg), PCC; hemodialysis as last resort; PCC shown to be most efficacious yet unproven</td>
<td>2010 FDA approval for prevention of stroke in AF</td>
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<tr>
<td>rivaroxaban (Xarelto)</td>
<td>factor Xa inhibitors</td>
<td>20 mg QD</td>
<td>plasma T1/2: 7–11 hrs; 33% renal excretion; 67% metabolized by liver, inactive metabolites excreted in urine &amp; stool</td>
<td>routine anticoagulation monitoring unnecessary; normal antifactor Xa assay indicates no anticoagulation effect</td>
<td>PCC, FFP rVIIa (10–90 μg/kg)</td>
<td>2011 FDA approval for prevention of stroke in AF &amp; treatment of acute DVT</td>
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<tr>
<td>apixaban (Eliquis)</td>
<td>factor Xa inhibitors</td>
<td>5 mg BID</td>
<td>metabolism: liver (75%), renal excretion (25%); elimination T1/2: 8–15 hrs</td>
<td>routine anticoagulation monitoring unnecessary; normal antifactor Xa assay indicates no anticoagulation effect</td>
<td>PCC, FFP rVIIa (10–90 μg/kg)</td>
<td>2013 FDA approval for prevention of stroke in AF</td>
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* aPTT = activated partial thromboplastin time; BID = twice daily; CYP = cytochrome P450 isoenzyme; HIT = heparin-induced thrombocytopenia; IV = intravenous; LMWH = low-molecular-weight heparin; PT = prothrombin time; QD = each day; SQ = subcutaneous; T1/2 = half life; TID = three times daily; USP = United States Pharmacopeia convention.
not been consistently demonstrated for any specific drug among many reports.3,10,11,25,37,50,70 The risk for ICH appears to be dose dependent with aspirin, the most studied agent, but exists with other agents as well.1,8,11,36,59,66,67,69 Naidech et al.42–44 demonstrated that increased platelet inhibition (as measured with VerifyNow ASA and P2Y12 tests [Accumetrics, Inc.] for aspirin and clopidogrel, respectively), correlated with increased ICH volume growth at 12 hours, volume of intraventricular hemorrhage, increased chance of death at 14 days, and poor outcome at 3 months. Additionally, Naidech et al.46 demonstrated that the chance of undergoing a craniotomy for ICH, when controlling for size of hemorrhage and location, was increased with pre-event aspirin use and platelet inhibition as determined by VerifyNow ASA. In a retrospective comparison of patients presenting with ICH on aspirin or Plavix (clopidogrel), Campbell et al.7 noted larger ICH size and decreased chance of discharge to home in the clopidogrel group. They also noted increased mortality, but this failed to reach statistical significance.

Given the likely association between antiplatelet use, ICH volume, intraventricular hemorrhage, and death, 1 possible strategy for reducing hematoma growth and mortality is to reverse the effect of antiplatelet medications by administering a platelet transfusion.3–60 A platelet transfusion of 10–12.5 units of platelets has been shown to restore normal platelet function in patients on aspirin and clopidogrel.74 Desmopressin has been known to increase platelet reactivity in patients treated with aspirin by releasing a greater number of von Willibrand multimers.74 The role of intravenous desmopressin in decreasing bleeding during cardiac surgery is controversial, whereas rVIIa has shown promise preclinically as a possible agent.2,30,53

Some authors have described variations of platelet reversal regimens as standard at their centers.3,45 Naidech et al.8 evaluated this hypothesis by treating 45 patients with spontaneous ICH and an assay consistent with platelet inhibition, with a platelet transfusion within 12 hours of admission. Transfusion resulted in a decrease of platelet inhibition out of therapeutic range for most patients, although the dose of platelets was not standardized. Within their cohort, they identified 32 patients with a high degree of platelet inhibition, and within this subset, those who received a transfusion within 12 hours had less hematoma growth and a better outcome than those who received a transfusion after 12 hours.

The limited positive outcome of antiplatelet reversal is counterbalanced by many studies showing no benefit. Ducruet et al.19 compared the clinical course and outcomes in 35 patients presenting with ICH on antiplatelet therapy reversed with platelet transfusion, to 31 patients without platelet transfusion, and found no difference in hematoma growth or outcome. Nishijima et al.47 performed a retrospective meta-analysis of ICH secondary to trauma in patients receiving antiplatelet medication before injury. These authors identified 635 studied patients in 5 retrospective reviews in which 3 studies revealed no benefit, 1 revealed higher mortality in the transfusion cohort, and 1 demonstrated decreased mortality with transfusion (although there were 92 patients in the transfusion arm and 19 in the no-transfusion arm).47 Another literature review by Campbell et al.8 also found no clear evidence of benefit with platelet transfusion, but suggested the following protocol as a starting point for further investigation: 1) for a patient with ICH on aspirin alone, transfuse 1 pack of platelets; 2) for a patient with a small ICH on clopidogrel or a combination of therapies, administer 2 units of platelets; 3) for patients with large ICH on clopidogrel or multiple agents, administer desmopressin 3 mcg/kg intravenously and 1 pack of platelets every 12 hours for 48 hours. There is a randomized trial currently underway to evaluate antiplatelet agent reversal in ICH (Platelet Transfusion in Cerebral Hemorrhage [PATCH] trial).77

One limitation of testing strategies that use platelet assays is the variability in the types of assays available. As described in Table 2, platelet activity and levels of inhibition can be measured by many different types of platelet function assays. There are multiple laboratory and point-of-care testing systems available and results are reported in units of time, change in light transmission, platelet count, surface area covered, and flow cytometry.62 On many of these systems, high platelet inhibition has been associated with bleeding events and low platelet inhibition with in-stent thrombosis after coronary artery stenting.5,64 Moreover, aspirin and clopidogrel resistance has been associated with poor outcome in patients with stroke.31,61 Nonetheless, multiple comparison studies have been unable to establish a correlation between the results of the various testing systems.28,35,38,48,50,51 Furthermore, point-of-care testing tends to have greater inaccuracy than hematology lab testing.62 There is currently no established standard to define inappropriate platelet activity.62

The impact of these limitations is illustrated in multiple studies that have attempted to use platelet assay–guided therapy protocols to tailor patient medical regimens with poor results. Collet et al.13 randomized patients undergoing coronary artery stenting into 2 groups, 1 receiving antiplatelet medication without monitoring and 1 with monitoring utilizing the VerifyNow P2Y12 assay with medication adjustments made as necessary. At 1 year there was no difference between the 2 groups in any of the outcome measures, including death, myocardial infarction, stroke, urgent revascularization, or major bleeding event.13 Among similar lines, Depta et al.18 retrospectively reviewed patients with ischemic stroke who were subsequently placed on antiplatelet therapy, comparing patients given antiplatelet medication without testing to those followed by platelet aggregometry with appropriate dose adjustments. The authors describe a higher rate of death, ischemic events, and bleeding in the patients followed by aggregometry who subsequently received dose increases.18

Stopping antiplatelet medication is not without risk. Withdrawal of antiplatelet agents before elective surgery has been shown to be a risk factor for heart attack and death.14 Cessation of antiplatelet therapy for those with cardiac stents is associated with a high rate of stent thrombosis and infarction, especially for drug-eluting stents.22,34,63 Patients with intracranial stents are at increased risk of stroke and transient ischemic attack with early withdrawal of an antiplatelet agent or resistance.58
### TABLE 2: Common antiplatelet medications

<table>
<thead>
<tr>
<th>Generic Name (trade name)</th>
<th>Mechanism of Action (essential steps)</th>
<th>Recommended Dosing</th>
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<tr>
<td>acetylsalicylic acid (aspirin)</td>
<td>irreversible COX-1 inhibition → decreased TXA2 production → decreased TXA2 receptor activation → decreased intracellular Ca²⁺ levels†</td>
<td>81–325 mg/day</td>
<td>metabolism: hepatic; excretion: urine (80%–100%), sweat, saliva, feces; elimination T1/2: 20 min (may reach 15–30 hrs when higher doses are ingested)</td>
<td>arachidonic acid-based tests (VerifyNow ASA [aspirin test])</td>
<td>platelet transfusion (5 concentrate units), desmopressin (0.3 μg/kg), rVIIa⁸</td>
<td>prevalence of clinical aspirin resistance is 5%–60%²⁶,²⁷,⁶⁵</td>
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<td>ticlopidine (Ticlid)</td>
<td>thienopyridines (prodrugs‡): selective irreversible platelet P2Y12 receptor inhibition → decreased ADP binding to P2Y12 → increased cAMP levels †</td>
<td>may use 500 mg loading then 250 mg BID</td>
<td>metabolism: hepatic; excretion: urine (60%), feces (23%); elimination T1/2: 13 hrs (after single dose), 4–5 days (after repeat dosing)</td>
<td>bleeding time, variability of response has not been reported</td>
<td>NA</td>
<td>effective in 96.5% of patients w/ clopidogrel resistance; frequent side effects including life-threatening neutropenia &amp; thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>clopidogrel (Plavix)</td>
<td>thienopyridines (prodrugs‡): selective irreversible platelet P2Y12 receptor inhibition → decreased ADP binding to P2Y12 → increased cAMP levels †</td>
<td>300–600 mg (loading) followed by 75–150 mg/day</td>
<td>metabolism: hepatic, 15% undergoes metabolic activation (dependent on CYP2C19), remainder 85% inactivated by esterases; excretion: urine (50%), feces (46%); elimination T1/2: 6 hrs (30 min for active metabolite)</td>
<td>tests to identify patient’s CYP2C19 genotype; P2Y12 platelet receptor cascade tests (VerifyNow P2Y12 [PRU Test])</td>
<td>platelet transfusion (10 concentrate units every 12 hrs for the next 48 hrs), desmopressin (0.3 μg/kg)⁹</td>
<td>more potent &amp; has a more favorable toxicity profile than ticlopidine; prevalence of clinical clopidogrel resistance is 8%–35%;²⁶,²⁷,⁶⁵ omeprazole &amp; esomeprazole significantly reduce the antiplatelet activity of clopidogrel</td>
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<tr>
<td>prasugrel (Effient)</td>
<td>thienopyridines (prodrugs‡): selective irreversible platelet P2Y12 receptor inhibition → decreased ADP binding to P2Y12 → increased cAMP levels †</td>
<td>60 mg (loading) followed by 10 mg/day (5 mg/day if weight &lt;60 kg or age &gt;75 yrs)</td>
<td>intestinal esterase plays important role; therefore drug requires fewer hepatic metabolic steps for activation; metabolism independent of CYP genotype; excretion: urine (68%), feces (27%); elimination T1/2: 2–15 hrs (active metabolite)</td>
<td>P2Y12 platelet receptor cascade tests (VerifyNow P2Y12 [PRU test])</td>
<td>platelet transfusion &gt;6 hrs after loading dose or &gt;4 hrs after maintenance dose; active metabolite not removed by dialysis</td>
<td>faster &amp; more predictable action (than clopidogrel); CYP2C19 polymorphism is less important for metabolic activation</td>
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<tr>
<td>ticagrelor (Brilinta)</td>
<td>cyclopentyltriazenopyrimidine: reversible allosteric (non-competitive) platelet P2Y12 receptor antagonist → decreased ADP binding to P2Y12 → increased cAMP levels †</td>
<td>180 mg (loading) followed by 90 mg BID</td>
<td>does not require metabolic activation (independent of CYP genotype); metabolism: hepatic; excretion (ticagrelor): feces (58%), urine (26%); excretion (active metabolite): biliary excretion, urine (&lt;1%); elimination T1/2: 7 hrs (ticagrelor), 9 hrs (active metabolite)</td>
<td>P2Y12 platelet receptor cascade tests (VerifyNow P2Y12 [PRU test])</td>
<td>NA</td>
<td>NA, not removed by dialysis</td>
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(continued)
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<tr>
<td>dipyridamole (Persantine)$^7$</td>
<td>inhibitor of phosphodiesterases, blocker of platelet adenosine uptake → increased cAMP levels†</td>
<td>75–100 mg q6h</td>
<td>metabolism: hepatic; excretion: feces; elimination T1/2: 10–12 hrs</td>
<td>NA</td>
<td>dialysis is not likely to be of benefit</td>
<td>Aggrenox: combination of 200 mg of extended-release dipyridamole w/ 25 mg aspirin</td>
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<td>IV</td>
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<tr>
<td>abciximab (ReoPro)$^7$</td>
<td>GP Iib/IIa receptor antagonists: inhibit vWF &amp; fibrinogen-mediated platelet aggregation</td>
<td>0.25 mg/kg bolus followed by 0.125 µg/kg/min</td>
<td>metabolism: proteolytic cleavage; elimination T1/2: 30 min</td>
<td>thrombin receptor activating peptide-based tests (VerifyNow Iib/IIa test)</td>
<td>platelet transfusions</td>
<td>currently approved only for hospital administration in ACS patients undergoing PCI</td>
</tr>
<tr>
<td>eptifibatide (Integrilin)$^7$</td>
<td>GP Iib/IIa receptor antagonists: inhibit vWF &amp; fibrinogen-mediated platelet aggregation</td>
<td>180 µg/kg bolus followed by 2 µg/kg/min</td>
<td>metabolism: renal clearance 50% total body clearance; majority excreted unchanged, deaminated form (metabolites detected in urine but not in plasma); excretion: urine; elimination T1/2: 2.5 hrs; prolonged in renal insufficiency</td>
<td>thrombin receptor activating peptide-based tests (VerifyNow Iib/IIa test)</td>
<td>may be removed by dialysis</td>
<td>currently approved only for hospital administration in ACS patients undergoing PCI</td>
</tr>
<tr>
<td>tirofiban (Aggrastat)$^7$</td>
<td>GP Iib/IIa receptor antagonists: inhibit vWF &amp; fibrinogen-mediated platelet aggregation</td>
<td>0.4 µg/kg/min for 30 min, then 0.1 µg/kg/min</td>
<td>metabolism: limited; excretion: urine (65%), feces (25%); elimination T1/2: 2 hrs, prolonged in renal insufficiency</td>
<td>NA</td>
<td>removed by dialysis</td>
<td>currently approved only for hospital administration in ACS patients undergoing PCI</td>
</tr>
</tbody>
</table>

* ACS = acute coronary syndrome; ADP = adenosine diphosphate; cAMP = cyclic adenosine monophosphate; COX = cyclooxygenase; GP = glycoprotein; IPA = inhibition of platelet aggregation; NA = not available; P2Y = family of G protein–coupled purinergic receptors; PCI = percutaneous coronary intervention; TXA2 = thromboxane A2; vWf = von Willebrand factor.
† Physiologically, the net effect of increased intracellular Ca$^{++}$ and decreased cAMP is to activate glycoprotein Iib/IIa, which binds soluble adhesive substrates (including vWF and fibrinogen), leading to platelet anchoring to foreign surfaces and platelet aggregation into platelet-rich “white” thrombus.
‡ Require hepatic biotransformation into active metabolites.
Anticoagulant- and antiplatelet-related intracerebral hemorrhage

When considering antiplatelet-related ICH, determining the exact role that antiplatelet agents play in ICH formation, growth, and outcome as well as the role for antiplatelet reversal in patients with ICH requires significantly more clinical data. Currently, there is no well-supported algorithm for treating these patients. The decision to stop all antiplatelet medication needs to be carefully considered, weighing the size and morbidity of the ICH against the reasons the agents were initiated. The value of platelet function assays in patients presenting with ICH is uncertain at this time. Reversing antiplatelet medication with transfusion, desmopressin, or other factors is not currently supported by strong clinical data and should be considered investigational at this juncture.

Conclusions

Anticoagulant- and antiplatelet-related ICH involve the risks of hematoma expansion and poor outcome. Reversal of antiplatelet medications is an option to prevent worsening of the ICH, but the effectiveness for improved clinical outcomes remains unproven. Reversal of warfarin to prevent enlargement of the ICH is recommended. Physicians should consider utilizing PCC over FFP in addition to vitamin K for the reversal of warfarin anticoagulation. Dabigatran reversal may benefit from PCC but the evidence is weak and efforts should be directed toward improving renal clearance with consideration of hemodialysis in emergency situations. Rivaroxaban and apixaban are more likely to benefit from PCC administration than dabigatran but are unlikely to benefit from hemodialysis.

Disclosure

Dr. James is an investor/stockholder in Remedy Pharmaceuticals, Inc.

Author contributions to the study and manuscript preparation include the following. Conception and design: James. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: James, Simon. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors: James. Administrative/technical/material support: James. Study supervision: James. Table creation: Palys, Lomboy. Figure preparation: Lamm.

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