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

ROBERT F. JAMES, M.D.,¹ VIKTORAS PALYS, M.D.,² JASON R. LOMBOY, B.A.,¹
J. RICHARD LAMM JR., B.S.,¹ AND SCOTT D. SIMON, M.D.²

¹Division of Neurosurgery, Department of Surgery, East Carolina University Brody School of Medicine, Greenville, North Carolina; and ²Department of Neurosurgery, Virginia Commonwealth University School of Medicine, Richmond, Virginia

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.

(<http://thejns.org/doi/abs/10.3171/2013.2.FOCUS1328>)

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-

FIG. 1. The clotting cascade including common anticoagulant medications and their site of action. vit = vitamin.

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.⁷ 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.⁷⁵ 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.⁷ International normalized ratio levels greater than 4.0 have been reported to be associated with significantly increased risk for ICH.²¹ 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.²³ 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.^{12,54,75} These medi-

cations include dabigatran (a direct thrombin inhibitor), and rivaroxaban and apixaban, direct inhibitors of factor Xa.¹² 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.^{15,29,52}

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]).¹⁵ 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

Anticoagulant- and antiplatelet-related intracerebral hemorrhage

and apixaban were both found to demonstrate statistically significant reductions in hemorrhagic stroke compared with warfarin.^{29,52} 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.⁷⁷ 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.³³ 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 deficient in factor IX, requires large volume infusion, and can lead to complications such as pulmonary edema and delayed reversal of INR.⁴¹ 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.^{39,78} 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.^{49,68,72,76} 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.⁷² 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.⁵⁵ 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.³² 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.¹⁶ 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.¹⁶ 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, 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.⁴¹ 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.²⁰ 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.⁷³ 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.⁵⁴

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*

Generic Name (trade name)	Mechanism of Action	Recommended Dosing	Pharmacokinetics/ Metabolism/Excretion	Laboratory Monitoring of Effect	Emergency Reversal Options	Additional Notes
injectable (IV/SQ) unfractionated heparin ⁷	binds antithrombin III; at low doses, inactivates factor Xa, inhibits conversion of pro-thrombin to thrombin; at higher doses, inactivates factors IX, X, XI, XII, thrombin, inhibits conversion of fibrinogen to fibrin; also inactivates activation of factor VIII	IV: varies; SQ for DVT prophylaxis: 5000 u SQ BID or TID	metabolism: partial liver, partial renal excretion; elimination: 60–90 min, longer at higher doses	aPTT, antifactor Xa (aPTT reference ranges vary btwn hospitals)	w/in 4 hrs of dosing: 1 mg protamine sulfate for 100 u heparin administered	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
enoxaparin (Lovenox) ⁷	LMWH; binds to antithrombin, increasing its ability to inhibit activated coagulation factors w/in intrinsic & common pathways (Xa), no effect on extrinsic pathway	DVT prophylaxis: 1 mg/kg SQ BID or 1.5 mg/kg SQ QD	metabolism: liver desulfation, depolymerization, renal excretion; elimination: 4.5 hrs (single dose), 7 hrs (repeated dosing)	antifactor Xa assay	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	
fondaparinux (Arixtra) ⁷	inhibits factor Xa	DVT treatment: 5–10 mg weight-based SQ QD; prevention: 2.5 mg SQ QD	renal excretion elimination T _{1/2} : 17–21 hrs; contraindicated in patients w/ severe renal impairment	antifactor Xa assay	no specific antidote; consider rVIIa 90 µg/kg; ⁴ hemodialysis reduces by about 20%; protamine no effect	synthetic 5-saccharide analog of active pentasaccharide sequence found in heparin & LMWHs
lepirudin (Refludan) ⁷	direct thrombin inhibitor (binds to catalytic & exosite I of thrombin)	HIT: 0.4 mg/kg IV over 20 sec, then 0.15 mg/kg/hr IV up to 10 days	renal excretion T _{1/2} : 1.3 hrs	daily monitoring of aPTT; goal 1.5–2.5x median of laboratory's normal aPTT range	no specific antidote; consider FFP & cryoprecipitate ¹⁶	approved in US for treatment in heparin-induced thrombocytopenia
argatroban (Acova) ⁷	direct thrombin inhibitor (reversibly binds to catalytic site of thrombin)	initial 2 µg/kg/min IV over 1–3 hrs until steady state	metabolism: hepatic CYP enzymes; biliary excretion T _{1/2} : 40–50 min	aPTT: maintain 1.5–3x baseline value; can also elevate PT making transitioning to warfarin difficult to monitor	no specific antidote; consider FFP & cryoprecipitate ¹⁶	
oral warfarin (Coumadin) ⁷	inhibits hepatic production of vitamin K-dependent coagulation factors (II, VII, IX, & X; & anticoagulant proteins C & S)	2–5 mg/day for 2–4 days; INR adjusted dosing thereafter 1–10 mg/day	99% bound to plasma proteins (albumin); CYP2C9 hepatic metabolism plasma T _{1/2} : 25–60 hrs (mean 40 hrs); induction of hepatic enzymes including CYP2C9 can increase metabolic clearance	INR 2–3; difficult to keep in therapeutic range because of many drug & diet interactions & patient genetic variability	1 of the following fast-acting agents: PCC (25–100 U/kg) or FFP (15 ml/kg) & vitamin K 5–10 mg IV	medical usage began in 1950s, originally developed as a rodenticide, safe for nursing mothers

(continued)

TABLE 1: Common anticoagulation medications* (continued)

Generic Name (trade name)	Mechanism of Action	Recommended Dosing	Pharmacokinetics/ Metabolism/Excretion	Laboratory Monitoring of Effect	Emergency Reversal Options	Additional Notes
<i>oral (continued)</i>						
dabigatran (Pradaxa) ^{7,54}	direct thrombin inhibitor	150 mg BID	80% renal excretion; plasma T _{1/2} : 12–14 hrs; caution w/ renal impairment; contrain- dicated in severe impair- ment	routine anticoagulation monitoring unneces- sary; normal aPTT indicates no dabigatran effect	consider transfusion w/ FFP, rVlla (10–90 µg/kg), & PCC; hemodialysis as last resort; ⁷⁵ PCC shown to be most effica- cious yet unproven ⁷⁹	2010 FDA approval for prevention of stroke in AF
rivaroxaban (Xarelto) ^{7,54}	factor Xa inhibitors	20 mg QD	plasma T _{1/2} : 7–11 hrs; 33% renal excretion; 67% me- tabolized by liver, inactive metabolites excreted in urine & stool	routine anticoagulation monitoring unneces- sary; normal antifactor Xa assay indicates no anticoagulation effect	PCC, FFP rVlla (10–90 µg/kg)	2011 FDA approval for pre- vention of stroke in AF & treatment of acute DVT
apixaban (Eliquis) ⁵⁴	factor Xa inhibitors	5 mg BID	metabolism: liver (75%), renal excretion (25%); elimination T _{1/2} : 8–15 hrs	routine anticoagulation monitoring unneces- sary; normal antifactor Xa assay indicates no anticoagulation effect	PCC, FFP rVlla (10–90 µg/kg)	2013 FDA approval for prevention of stroke in AF

* 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; T_{1/2} = half life; TID = three times daily; USP = United States Pharmacopeia convention.

not been consistently demonstrated for any specific drug among many reports.^{8,10,11,25,37,57,60,70} The risk for ICH appears to be dose dependent with aspirin, the most studied agent, but exists with other agents as well.^{1,6,11,36,56,59,66,67,69,71} 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.⁹ 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.^{3,40} 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.²⁴ 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.⁴⁵ 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).¹⁷

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 Along 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*

Generic Name (trade name)	Mechanism of Action (essential steps)	Recommended Dosing	Pharmacokinetics/ Metabolism/Excretion	Laboratory Monitoring of Effect	Reversal Method	Additional Notes
oral						
acetylsalicylic acid (aspirin) ⁷	irreversible COX-1 inhibition → decreased TXA ₂ pro- duction → decreased TXA ₂ receptor activation → decreased intracellular Ca ⁺⁺ level [†]	81–325 mg/day	metabolism: hepatic; excretion: urine (80%–100%), sweat, saliva, feces; elimination T1/2: 20 min (may reach 15– 30 hrs when higher doses are ingested)	arachidonic acid-based tests (VerifyNow ASA [aspirin test])	platelet transfusion (5 concentrate units), desmopressin (0.3 µg/ kg), rVlla ⁸	prevalence of clinical aspirin resistance is 5%–60% ^{26,27,65}
ticlopidine (Ticlid) ⁷	thienopyridines (prodrug [†]): selective irreversible plate- let P2Y ₁₂ receptor inhibi- tion → decreased ADP binding to P2Y ₁₂ → increased cAMP levels [†]	may use 500 mg load- ing then 250 mg BID	metabolism: hepatic; excretion: urine (60%), feces (23%); elimination T1/2: 13 hrs (after single dose), 4–5 days (after repeat dosing)	bleeding time, variability of response has not been reported	NA	effective in 96.5% of patients w/ clopidogrel resistance; frequent side effects in- cluding life-threatening neutropenia & thrombotic thrombocytopenic purpura
clopidogrel (Plavix) ⁷	thienopyridines (prodrug [†]): selective irreversible plate- let P2Y ₁₂ receptor inhibi- tion → decreased ADP binding to P2Y ₁₂ → increased cAMP levels [†]	300–600 mg (loading) followed by 75–150 mg/day	metabolism: hepatic, 15% un- dergoes metabolic activa- tion dependent on CYP2C19, remainder 85% inactivated by esterases; excretion: urine (50%), feces (46%); elimination T1/2: 6 hrs (30 min for active metabolite)	tests to identify patient's CYP2C19 genotype; P2Y ₁₂ platelet receptor cascade tests (Verify- Now P2Y ₁₂ [PRU Test])	platelet transfusion (10 concentrate units every 12 hrs for the next 48 hrs), desmopressin (0.3 µg/kg) ⁸	more potent & has a more favorable toxicity profile than ticlopidine; preva- lence of clinical clopid- ogrel resistance is 8%– 35% ^{18,26,27} ; omeprazole & esomeprazole significantly reduce the antiplatelet activity of clopidogrel
prasugrel (Effient) ⁷	thienopyridines (prodrug [†]): selective irreversible plate- let P2Y ₁₂ receptor inhibi- tion → decreased ADP binding to P2Y ₁₂ → increased cAMP levels [†]	60 mg (loading) fol- lowed by 10 mg/day (5 mg/day if weight <60 kg or age >75 yrs)	intestinal esterase plays impor- tant role; therefore drug re- quires fewer hepatic meta- bolic steps for activation; metabolism independent of CYP genotype; excretion: urine (68%), feces (27%); elimination T1/2: 2–15 hrs (active metabolite)	P2Y ₁₂ platelet receptor cascade tests (Verify- Now P2Y ₁₂ [PRU test])	platelet transfusion >6 hrs after loading dose or >4 hrs after mainten- ance dose; active me- tabolite not removed by dialysis	faster & more predictable action (than clopidogrel); CYP2C19 polymorphism is less important for meta- bolic activation
ticagrelor (Brilinta) ⁷	cyclopentyltriazolopyrimidine: reversible allosteric (non- competitive) platelet P2Y ₁₂ receptor antagonist → decreased ADP binding to P2Y ₁₂ → increased cAMP level [†]	180 mg (loading) fol- lowed by 90 mg BID	does not require metabolic ac- tivation (independent of CYP genotype); metabo- lism: hepatic; excretion (ticagrelor): feces (58%), urine (26%); excretion (ac- tive metabolite): biliary ex- cretion, urine (<1%); elimina- tion T1/2: 7 hrs (ticagrelor), 9 hrs (active metabolite)	NA	NA, not removed by dialysis	transitioning from clopidogrel to ticagrelor resulted in ab- solute IPA increase of 26.4%; transitioning from ticagrelor to clopidogrel resulted in absolute IPA decrease of 24.5%

(continued)

TABLE 2: Common antiplatelet medications* (continued)

Generic Name (trade name)	Mechanism of Action (essential steps)	Recommended Dosing	Pharmacokinetics/ Metabolism/Excretion	Laboratory Monitoring of Effect	Reversal Method	Additional Notes
<i>oral (continued)</i>						
dipyridamole (Persantine) [†]	inhibitor of phosphodiesterases, blocker of platelet adenosine uptake → increased cAMP levels [‡]	75–100 mg q6h	metabolism: hepatic; excretion: feces; elimination T1/2: 10–12 hrs	NA	dialysis is not likely to be of benefit	Aggrenox: combination of 200 mg of extended-release dipyridamole w/ 25 mg aspirin
<i>IV</i>						
abciximab (ReoPro) [‡]	GP IIb/IIIa receptor antagonists: inhibit vWf & fibrinogen-mediated platelet aggregation	0.25 mg/kg bolus followed by 0.125 µg/kg/min	metabolism: proteolytic cleavage; elimination T1/2: 30 min	thrombin receptor activating peptide-based tests (VerifyNow IIb/IIIa test)	platelet transfusions	currently approved only for hospital administration in ACS patients undergoing PCI
eptifibatide (Integrilin) [‡]	GP IIb/IIIa receptor antagonists: inhibit vWf & fibrinogen-mediated platelet aggregation	180 µg/kg bolus followed by 2 µg/kg/min	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	thrombin receptor activating peptide-based tests (VerifyNow IIb/IIIa test)	may be removed by dialysis	currently approved only for hospital administration in ACS patients undergoing PCI
tirofiban (Aggrastat) [‡]	GP IIb/IIIa receptor antagonists: inhibit vWf & fibrinogen-mediated platelet aggregation	0.4 µg/kg/min for 30 min, then 0.1 µg/kg/min	metabolism: limited; excretion: urine (65%), feces (25%); elimination T1/2: 2 hrs, prolonged in renal insufficiency	NA	removed by dialysis	currently approved only for hospital administration in ACS patients undergoing PCI

* 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/IIIa, 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 reason 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: James, Simon. Reviewed submitted version of manuscript: 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.

Acknowledgment

The authors would like to thank Kristin J. Wainwright for her help in editing the manuscript.

References

1. Akbari SH, Reynolds MR, Kadkhodayan Y, Cross DT III, Moran CJ: Hemorrhagic complications after prasugrel (Efient) therapy for vascular neurointerventional procedures. *J Neurointerv Surg* [epub ahead of print], 2012
2. Altman R, Scazzioti A, DE Lourdes Herrera M, Gonzalez C: Recombinant factor VIIa reverses the inhibitory effect of aspirin or aspirin plus clopidogrel on in vitro thrombin generation. *J Thromb Haemost* 4:2022–2027, 2006
3. Beshay JE, Morgan H, Madden C, Yu W, Sarode R: Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. A review. *J Neurosurg* 112:307–318, 2010
4. Bijsterveld NR, Moons AH, Boekholdt SM, van Aken BE, Fennema H, Peters RJ, et al: Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 106:2550–2554, 2002
5. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, et al: Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA* 303:754–762, 2010
6. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, et al: Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke* 38:1072–1075, 2007
7. Brunton LL, Chabner BA, Knollmann BC: **Goodman & Gilman's The Pharmacological Basis of Therapeutics**, ed 12. New York: McGraw-Hill, 2011
8. Campbell PG, Sen A, Yadla S, Jabbour P, Jallo J: Emergency reversal of antiplatelet agents in patients presenting with an intracranial hemorrhage: a clinical review. *World Neurosurg* 74:279–285, 2010
9. Campbell PG, Yadla S, Sen AN, Jallo J, Jabbour P: Emergency reversal of clopidogrel in the setting of spontaneous intracerebral hemorrhage. *World Neurosurg* 76:100–104, 2011
10. Cantalapietra A, Gutierrez O, Tortosa JI, Yañez M, Dueñas M, Fernandez Fontecha E, et al: Oral anticoagulant treatment: risk factors involved in 500 intracranial hemorrhages. *J Thromb Thrombolysis* 22:113–120, 2006
11. Caso V, Paciaroni M, Venti M, Alberti A, Palmerini F, Milia P, et al: Effect of on-admission antiplatelet treatment on patients with cerebral hemorrhage. *Cerebrovasc Dis* 24:215–218, 2007
12. Cervera A, Amaro S, Chamorro A: Oral anticoagulant-associated intracerebral hemorrhage. *J Neurol* 259:212–224, 2012
13. Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, et al: Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 367:2100–2109, 2012
14. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, et al: Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 110:2361–2367, 2004
15. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al: Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361:1139–1151, 2009
16. Crowther MA, Ageno W, Schnurr T, Manfredi E, Kinnon K, Garcia D, et al: Oral vitamin K produces a normal INR within 24 hours of its administration in most patients discontinuing warfarin. *Haematologica* 90:137–139, 2005
17. de Gans K, de Haan RJ, Majoie CB, Koopman MM, Brand A, Dijkgraaf MG, et al: PATCH: platelet transfusion in cerebral haemorrhage: study protocol for a multicentre, randomised, controlled trial. *BMC Neurol* 10:19, 2010
18. Depta JP, Fowler J, Novak E, Katzan I, Bakdash S, Kottke-Marchant K, et al: Clinical outcomes using a platelet function-guided approach for secondary prevention in patients with ischemic stroke or transient ischemic attack. *Stroke* 43:2376–2381, 2012
19. Ducruet AF, Hickman ZL, Zacharia BE, Grobelsky BT, DeRosa PA, Landes E, et al: Impact of platelet transfusion on hematoma expansion in patients receiving antiplatelet agents before intracerebral hemorrhage. *Neurol Res* 32:706–710, 2010
20. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M: Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 124:1573–1579, 2011
21. Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, et al: Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med* 141:745–752, 2004
22. Ferrari E, Benhamou M, Cerboni P, Marcel B: Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol* 45:456–459, 2005

23. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J: Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. **Neurology** **63**:1059–1064, 2004
24. Flordal PA, Sahlin S: Use of desmopressin to prevent bleeding complications in patients treated with aspirin. **Br J Surg** **80**:723–724, 1993
25. Foerch C, Sitzler M, Steinmetz H, Neumann-Haefelin T: Pre-treatment with antiplatelet agents is not independently associated with unfavorable outcome in intracerebral hemorrhage. **Stroke** **37**:2165–2167, 2006
26. Fong J, Cheng-Ching E, Hussain MS, Katzan I, Gupta R: Predictors of biochemical aspirin and clopidogrel resistance in patients with ischemic stroke. **J Stroke Cerebrovasc Dis** **20**:227–230, 2011
27. Fukuoka T, Furuya D, Takeda H, Dembo T, Nagoya H, Kato Y, et al: Evaluation of clopidogrel resistance in ischemic stroke patients. **Intern Med** **50**:31–35, 2011
28. Godino C, Mendolicchio L, Figini F, Latib A, Sharp AS, Cosgrave J, et al: Comparison of VerifyNow-P2Y12 test and Flow Cytometry for monitoring individual platelet response to clopidogrel. What is the cut-off value for identifying patients who are low responders to clopidogrel therapy? **Thromb J** **7**:4, 2009
29. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al: Apixaban versus warfarin in patients with atrial fibrillation. **N Engl J Med** **365**:981–992, 2011
30. Gratz I, Koehler J, Olsen D, Afshar M, DeCastro N, Spagna PM, et al: The effect of desmopressin acetate on postoperative hemorrhage in patients receiving aspirin therapy before coronary artery bypass operations. **J Thorac Cardiovasc Surg** **104**:1417–1422, 1992
31. Grottemeyer KH, Scharafinski HW, Husstedt IW: Two-year follow-up of aspirin responder and aspirin non responder. A pilot-study including 180 post-stroke patients. **Thromb Res** **71**:397–403, 1993
32. Guest JF, Watson HG, Limaye S: Modeling the cost-effectiveness of prothrombin complex concentrate compared with fresh frozen plasma in emergency warfarin reversal in the United Kingdom. **Clin Ther** **32**:2478–2493, 2010
33. Huttner HB, Schellinger PD, Hartmann M, Köhrmann M, Juettler E, Wikner J, et al: Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. **Stroke** **37**:1465–1470, 2006
34. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. **JAMA** **293**:2126–2130, 2005
35. Jakubowski JA, Li YG, Small DS, Payne CD, Tomlin ME, Luo J, et al: A comparison of the VerifyNow P2Y12 point-of-care device and light transmission aggregometry to monitor platelet function with prasugrel and clopidogrel: an integrated analysis. **J Cardiovasc Pharmacol** **56**:29–37, 2010
36. Lacut K, Le Gal G, Seizeur R, Prat G, Mottier D, Oger E: Antiplatelet drug use preceding the onset of intracerebral hemorrhage is associated with increased mortality. **Fundam Clin Pharmacol** **21**:327–333, 2007
37. Lacut K, van der Maaten J, Le Gal G, Cornily G, Mottier D, Oger E: Antiplatelet drugs and risk of venous thromboembolism: results from the EDITH case-control study. **Haematologica** **93**:1117–1118, 2008
38. Mangiacapra F, Patti G, Peace A, Gatto L, Vizzi V, Ricottini E, et al: Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention. **Am J Cardiol** **106**:619–623, 2010
39. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al: Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. **N Engl J Med** **358**:2127–2137, 2008
40. McMillian WD, Rogers FB: Management of prehospital antiplatelet and anticoagulant therapy in traumatic head injury: a review. **J Trauma** **66**:942–950, 2009
41. Mittal MK, Rabinstein AA: Anticoagulation-related intracranial hemorrhages. **Curr Atheroscler Rep** **14**:351–359, 2012
42. Naidech AM, Bendok BR, Garg RK, Bernstein RA, Alberts MJ, Bleck TP, et al: Reduced platelet activity is associated with more intraventricular hemorrhage. **Neurosurgery** **65**:684–688, 2009
43. Naidech AM, Bernstein RA, Levasseur K, Bassin SL, Bendok BR, Batjer HH, et al: Platelet activity and outcome after intracerebral hemorrhage. **Ann Neurol** **65**:352–356, 2009
44. Naidech AM, Jovanovic B, Liebling S, Garg RK, Bassin SL, Bendok BR, et al: Reduced platelet activity is associated with early clot growth and worse 3-month outcome after intracerebral hemorrhage. **Stroke** **40**:2398–2401, 2009
45. Naidech AM, Liebling SM, Rosenberg NF, Lindholm PF, Bernstein RA, Batjer HH, et al: Early platelet transfusion improves platelet activity and may improve outcomes after intracerebral hemorrhage. **Neurocrit Care** **16**:82–87, 2012
46. Naidech AM, Rosenberg NF, Bernstein RA, Batjer HH: Aspirin use or reduced platelet activity predicts craniotomy after intracerebral hemorrhage. **Neurocrit Care** **15**:442–446, 2011
47. Nishijima DK, Zehtabchi S, Berrong J, Legome E: Utility of platelet transfusion in adult patients with traumatic intracranial hemorrhage and preinjury antiplatelet use: a systematic review. **J Trauma Acute Care Surg** **72**:1658–1663, 2012
48. Ozben S, Ozben B, Tanrikulu AM, Ozer F, Ozben T: Aspirin resistance in patients with acute ischemic stroke. **J Neurol** **258**:1979–1986, 2011
49. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H: Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. **J Thromb Haemost** **6**:622–631, 2008
50. Paniccio R, Antonucci E, Gori AM, Marcucci R, Giglioli C, Antonucci D, et al: Different methodologies for evaluating the effect of clopidogrel on platelet function in high-risk coronary artery disease patients. **J Thromb Haemost** **5**:1839–1847, 2007
51. Paniccio R, Antonucci E, Maggini N, Miranda M, Gori AM, Marcucci R, et al: Comparison of methods for monitoring residual platelet reactivity after clopidogrel by point-of-care tests on whole blood in high-risk patients. **Thromb Haemost** **104**:287–292, 2010
52. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. **N Engl J Med** **365**:883–891, 2011
53. Pleym H, Stenseth R, Wahba A, Bjella L, Tromsdal A, Karevold A, et al: Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. **Anesth Analg** **98**:578–584, 2004
54. Potpara TS, Polovina MM, Licina MM, Stojanovic RM, Prostran MS, Lip GY: Novel oral anticoagulants for stroke prevention in atrial fibrillation: focus on apixaban. **Adv Ther** **29**:491–507, 2012
55. Rolfe S, Papadopoulos S, Cabral KP: Controversies of anticoagulation reversal in life-threatening bleeds. **J Pharm Pract** **23**:217–225, 2010
56. Roquer J: Previous antiplatelet treatment and mortality in patients with intracerebral hemorrhage. **Stroke** **38**:863–864, 2007 (Letter)
57. Roquer J, Rodríguez Campello A, Gomis M, Ois A, Puente V, Munteis E: Previous antiplatelet therapy is an independent predictor of 30-day mortality after spontaneous supratentorial intracerebral hemorrhage. **J Neurol** **252**:412–416, 2005

Anticoagulant- and antiplatelet-related intracerebral hemorrhage

58. Rossen JD, Chalouhi N, Wassef SN, Thomas J, Abel TJ, Jabour PM, et al: Incidence of cerebral ischemic events after discontinuation of clopidogrel in patients with intracranial aneurysms treated with stent-assisted techniques. Clinical article. **J Neurosurg** **117**:929–933, 2012
59. Saloheimo P, Ahonen M, Juvela S, Pyhtinen J, Savolainen ER, Hillbom M: Regular aspirin-use preceding the onset of primary intracerebral hemorrhage is an independent predictor for death. **Stroke** **37**:129–133, 2006
60. Sansing LH, Messe SR, Cucchiara BL, Cohen SN, Lyden PD, Kasner SE: Prior antiplatelet use does not affect hemorrhage growth or outcome after ICH. **Neurology** **72**:1397–1402, 2009
61. Schwammenthal Y, Tsaabari R, Shenkman B, Schwartz R, Matetzky S, Lubetsky A, et al: Aspirin responsiveness in acute brain ischaemia: association with stroke severity and clinical outcome. **Cerebrovasc Dis** **25**:355–361, 2008
62. Seidel H, Rahman MM, Scharf RE: Monitoring of antiplatelet therapy. Current limitations, challenges, and perspectives. **Hamostaseologie** **31**:41–51, 2011
63. Sharma AK, Ajani AE, Hamwi SM, Maniar P, Lakhani SV, Waksman R, et al: Major noncardiac surgery following coronary stenting: when is it safe to operate? **Catheter Cardiovasc Interv** **63**:141–145, 2004
64. Sibbing D, Schulz S, Braun S, Morath T, Stegherr J, Mehilli J, et al: Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. **J Thromb Haemost** **8**:250–256, 2010
65. Snoep JD, Hovens MM, Eikenboom JC, van der Bom JG, Huisman MV: Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis. **Arch Intern Med** **167**:1593–1599, 2007
66. Sorimachi T, Fujii Y, Morita K, Tanaka R: Predictors of hematoma enlargement in patients with intracerebral hemorrhage treated with rapid administration of antifibrinolytic agents and strict blood pressure control. **J Neurosurg** **106**:250–254, 2007
67. Stetler WR, Chaudhary N, Thompson BG, Gemmete JJ, Maher CO, Pandey AS: Prasugrel is effective and safe for neuro-interventional procedures. **J Neurointerv Surg** [epub ahead of print], 2012
68. Taberner DA, Thomson JM, Poller L: Comparison of prothrombin complex concentrate and vitamin K1 in oral anticoagulant reversal. **BMJ** **2**:83–85, 1976
69. Thrift AG, McNeil JJ, Forbes A, Donnan GA: Risk of primary intracerebral haemorrhage associated with aspirin and non-steroidal anti-inflammatory drugs: case-control study. **BMJ** **318**:759–764, 1999
70. Toyoda K, Okada Y, Minematsu K, Kamouchi M, Fujimoto S, Ibayashi S, et al: Antiplatelet therapy contributes to acute deterioration of intracerebral hemorrhage. **Neurology** **65**:1000–1004, 2005
71. Tuhim S: Aspirin-use before ICH: a potentially treatable iatrogenic coagulopathy? **Stroke** **37**:4–5, 2006
72. van Aart L, Eijkhout HW, Kamphuis JS, Dam M, Schattenkerk ME, Schouten TJ, et al: Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: an open, prospective randomized controlled trial. **Thromb Res** **118**:313–320, 2006
73. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al: Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. **Thromb Haemost** **103**:1116–1127, 2010
74. Vilahur G, Choi BG, Zafar MU, Viles-Gonzalez JF, Vorchheimer DA, Fuster V, et al: Normalization of platelet reactivity in clopidogrel-treated subjects. **J Thromb Haemost** **5**:82–90, 2007
75. Watanabe M, Siddiqui FM, Qureshi AI: Incidence and management of ischemic stroke and intracerebral hemorrhage in patients on dabigatran etexilate treatment. **Neurocrit Care** **16**:203–209, 2012
76. Yasaka M, Oomura M, Ikeno K, Naritomi H, Minematsu K: Effect of prothrombin complex concentrate on INR and blood coagulation system in emergency patients treated with warfarin overdose. **Ann Hematol** **82**:121–123, 2003
77. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al: Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. **Chest** **141** (2 Suppl):e531S–e575S, 2012
78. Yuan ZH, Jiang JK, Huang WD, Pan J, Zhu JY, Wang JZ: A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute intracerebral hemorrhage without hemophilia. **J Clin Neurosci** **17**:685–693, 2010
79. Zhou W, Schwarting S, Illanes S, Liesz A, Middelhoff M, Zorn M, et al: Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. **Stroke** **42**:3594–3599, 2011

Manuscript submitted January 15, 2013.

Accepted February 21, 2013.

Please include this information when citing this paper: DOI: 10.3171/2013.2.FOCUS1328.

Address correspondence to: Robert F. James, M.D., ECU Neurosurgical and Spine Center, 2325 Stantonsburg Road, Greenville, North Carolina 27834. email: jamesro@ecu.edu.