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What Every Emergency Physician Needs to Know About Anticoagulants and Antiplatelet Agents

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Thromboembolic disease is the third leading cause of death worldwide, accounting for more deaths than breast cancer, prostate cancer, AIDS, and road traffic accidents combined. Venous thromboembolism (VTE) is usually clinically silent, yet is the main cause of vascular illness in young people. Its incidence rises with age. Acute arterial thrombosis is the leading cause of heart attacks and strokes (~80%) in the developed world. The approach to treatment differs. The main focus for prevention and treatment of VTE is the coagulation cascade, while platelets are the primary therapeutic target in arterial thrombosis.

It is generally agreed that the ideal anticoagulant does not exist. What we seek is a drug that:

- has 100% efficacy in preventing and / or treating thromboembolism
- is free of any bleeding complications
- can be administered either by mouth or by injection
- does not require dose adjustment in any situation
- does not require monitoring of anticoagulant effect
- is cost effective
- has no unexpected toxicity
- can be quickly reversed when the patient is exsanguinating

An Old Standard: Vitamin K Antagonists

For a drug that we've been using for more than half a century, warfarin has taken quite a pounding lately.[1] Yet despite its many flaws, it is the gold standard for anticoagulation. Warfarin is a vitamin K antagonist (VKA). Vitamin K, you recall, is essential for the synthesis by the liver of extrinsic pathway Factors II, VII, IX, and X (my mnemonic: "1972," the year that George McGovern ran for president), as well as protein C and protein S. Factor VII has the shortest half-life (see Table 1) and therefore is the most depleted with warfarin therapy.[2] Some European countries use other coumarin derivatives (phenprocoumon and acenocoumarol), but all VKAs work the same.[3]

Table 1: Vitamin K-Dependant Clotting Factors[2]

Name	Function	Half-life
Protein C	Anticoagulant	8 hours
Protein S	Anticoagulant	30 hours
Factor VII	Procoagulant	7 hours
Factor IX	Procoagulant	24 hours
Factor X	Procoagulant	36 hours
Factor II	Procoagulant	50 hours

Coagulation begins almost instantly after injury to a blood vessel damages its endothelial lining. Blood is then exposed to proteins like tissue factor, which initiate blood platelet changes and fibrinogen activation. Primary hemostasis occurs when platelets form an immediate plug at the site of injury. Secondary hemostasis occurs simultaneously when the coagulation factors respond in a complex cascade to form fibrin strands, which strengthen the platelet plug.

Once the intrinsic pathway (blood stasis and contact activation)[4] and extrinsic pathway (tissue exposed after vascular damage) activate Factor X, the "coagulation cascade" truly becomes a cascade: one molecule of Factor Xa (i.e., activated Factor X) induces formation of 50 to 1000 thrombin (Factor IIa, or activated Factor II) molecules. Thrombin's primary role is converting fibrinogen to fibrin, the building block of a hemostatic plug. It also activates Factors VIII and V and their inhibitor protein C.

Regulation of the coagulation pathway can occur at each phase either through enzymatic inhibition or modulation of cofactor activity.

During the first two to three days of VKA therapy, there is a rapid increase in INR, but this reflects only a reduction of the shorter half-life of factors VII and IX (see Table 1). Clinically significant reductions of factors X and II have yet to occur. Because factor II (prothrombin) has the longest half-life, the optimal potential of VKAs to inhibit the expansion and development of the clot is determined only after the final clearance of factor II ($T_{½}$ 50 hours). This delayed effect is the principle reason there is a "bridging" with heparin therapy for four or five days – at least two half-lives – at the start of VKA therapy.

With appropriate dosing, VKAs effectively inhibit coagulation and substantially reduce the risk of stroke in atrial fibrillation and recurrence of venous thromboembolism. Yearly incidence of stroke in patients with atrial fibrillation is 5%, approximately five times higher than the population without atrial fibrillation.[5] Cardioembolism accounts for 20% of ischemic strokes. The infarct is typically larger than that in atherothrombotic stroke and the outcome is poorer.[6] The stroke rate in patients with persistent or permanent nonvalvular atrial fibrillation can be reduced by 2/3 by using oral anticoagulants.[7] (Nonvalvular atrial fibrillation is defined as absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.)

VKAs are difficult to manage. Even after patients are stabilized on an appropriate dose, monthly blood monitoring is recommended. In addition, foods rich in vitamin K (especially green, leafy vegetables like kale, collards, spinach, and turnip greens) and literally hundreds of medications[8] can cause difficulty in maintaining an appropriate INR. Several studies have shown that at any given time only about half the people taking it are appropriately anticoagulated. Oral administration of VKAs is ineffective in patients with biliary obstruction (poor absorption), and neither oral nor parenteral administrations are effective in patients with severe liver failure.

Table 2: Advantages and Disadvantages of VKAs

Advantages	**Disadvantages**
Proven high effectiveness	Monitoring of INR
Therapeutic window established	Drug interactions
Antidote(s) established	Food interactions
Long action: low thrombosis risk with poor compliance	Slow onset of action
	High bleeding risk

While the prothrombin time test is sensitive to changes in all four extrinsic pathway factors (II, VII, IX, X), the test reagent (thromboplastin) has much variability, and labs have adapted an international ratio (INR) as a more valid measurement. In most patients, the INR must be kept within a narrow range of 2.0 to 3.0 to be effective without increasing the risk of bleeding.[9] While patients with an artificial mitral

valve are at higher risk for thromboembolic events than those with valves in other locations, [10] current recommendations are an INR of 2.5 to 3.5 be maintained in all patients who have tilting-disk and bileaflet valves and probably for caged-ball valves.[11] For every one point increase in the INR, the risk of bleeding doubles.[12] Of the 50% of patients outside the normal therapeutic range, about 14% have an INR above 3.0.[13] The most worrisome side effect of warfarin is, of course, major bleeding, which varies from less than 2% a year with care in an anticoagulation clinic to 4% to 5% a year with usual medical care.[14]

Reversing the VKAs

When a VKA is withheld, it may take several days or even a week for the INR to return to baseline. This process can be shortened to approximately 24 hours with administration of vitamin K (see Table 3). This appears to be beneficial in patients with excessive INR levels.[15] Oral supplementation has slow onset of action and unpredictable response, so is not recommended as a reversal agent in the patient who is actively bleeding.[16] Subcutaneous administration is also slower and less reliable than intravenous.[17] Intravenous vitamin K is associated with a small (~3 / 100,000) risk of anaphylaxis and anaphylactoid reactions, and several deaths have been reported.[18] Newer formulations have removed the castor oil excipient and are apparently less likely to cause this reaction.[19]

Table 3: Recommended Indications for Use of Vitamin K1 as an Antidote to the VKAs

INR	Clinical condition	Dose	Alone or adjunct	Grade of evidence
>1.3	Life-threatening bleed	10 mg IV	Adjunct	1C
>1.3	Serious bleeding	10 mg IV	Adjunct	1C
>9	No significant bleeding	5 – 10 mg PO	Alone	2C
>5 to <9	No significant bleeding	<5 mg PO	Alone	2C

Another choice to reduce the bleeding complications is fresh frozen plasma (FFP), as each milliliter of FFP theoretically contains 1.0 u of each clotting factor. But the dose of FFP required is usually more than one liter which is difficult to administer quickly. One study showed a median time of 6¼ hours to transfuse an appropriate amount of FFP.[20] Add to this the 30 to 45 minutes needed to thaw FFP. In addition, there is a small risk of transfusion-transmitted infection. Recall that "normal" INR is 1.0 ± 0.2, depending on your laboratory. Transfusion of FFP will not reliably decrease the INR below about 1.7, as FFP itself has an INR of ~1.6.[21] Below that point, the patient needs a normal temperature and good perfusion to drop the INR further.[22]

In prothrombin complex concentrates (PCCs), the concentration of the vitamin K-dependent factors is approximately 25 times higher than in FFP, so the volume required for reversal is many times less that of FFP – usually about 40 ml.[23] There are controversies regarding the optimal dose of PCC. Some practitioners use a fixed dose, while others calculate the dose according to the body weight. Ideally, the dose should be adjusted to body weight as well as to the desired reduction of INR; the calculations involved are beyond the scope of this paper.

There is no doubt that PCCs work. One small study evaluated 10 hemorrhaging patients with a median INR greater than 20; following administration of PCC, the median INR was reduced to 1.1 at 30 minutes and all patients had immediate cessation of bleeding.[24] Another study reported a rapid decline in mean INR from 6.1 to 1.5 within 10 minutes after PCC administration in 20 patients with major bleeding or requiring surgery.[25] PCCs are available under many names around the world. In the USA, it is sold under the trade name Bebulin-VH®, a three-factor product. Other 4-product PCCs (e.g. Octaplex®) are available in different areas of the world.

Some studies have looked at using recombinant factor VIIa (rFVIIa). This may correct the INR, since the prothrombin time is most sensitive to reductions in factor VII, but it gives a false sense of security that the bleeding diathesis has been corrected.[26] Recall that factors IX, X, and II all have half-lives more than three times that of factor VII (see Table 1). PCC, FFP, and vitamin K correct the deficiency in all four of the vitamin K-dependent coagulation factors.

An Old Standard: The Heparins

Despite being derived from the ancient Greek word *hepar*, meaning liver, the heparins are usually extracted from porcine intestine or bovine lung tissue. Presently they are divided into unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), and heparinoids.

Heparin was discovered in 1916, although its use in humans as an anticoagulant did not start until 1935.[27] LMWHs were developed in the 1980s and are derived by polymerization from UFH and, because of several clinical advantages, have replaced UFH for most indications.[28] UFH binds to platelets, plasma proteins, macrophages, and endothelial cells, leading to a highly unpredictable anticoagulant response. LMWHs have reduced binding to these elements, leading to a more predictable dose response (although each LMWH is different). Because of the need for intravenous or subcutaneous administration, they are inconvenient and costly for out-of-hospital long-term use.

Heparin and its derivatives bind to antithrombin (AT)[29], thus indirectly inactivating Factors IIa (thrombin) and Xa; to a lesser degree, IXa, XIa, and XIIa are also inhibited.[30] The efficacy of heparins increases as selectivity for FXa increases,[31] with LMWHs superior to UFH. The two preferred routes of administration of UFH are continuous IV infusion and subcutaneous (SC) injection. When the SC route is used, the initial dose should be approximately 10% higher than the usual IV dose to overcome the reduced bioavailability associated with SC administration.[32] When heparin is given by SC injection in a dose of 35,000 U over 24 h in two divided doses, the anticoagulant effect is delayed for approximately 1 h, and the peak plasma levels occur at approximately 3 h.[33] If an immediate anticoagulant effect is required, the initial dose should be accompanied by an IV bolus injection. The apparent biological half-life of heparin increases from approximately 30 minutes following an IV bolus of 25 U/kg, to 60 minutes with an IV bolus of 100 U/kg, to 150 minutes with a bolus of 400 U/kg.[34]

Major bleeding occurs in 0.8% of patients receiving full-dose UFH, but is less frequent with low-dose subcutaneous heparin. LMWH may cause less frequent bleeding, but this finding has not been consistent across trials. Bleeding rates vary with product, indication, patient population, and dose.[35]

Reversing the Heparins

Because of UFH's relatively short half-life (roughly 60 minutes when given in therapeutic doses), discontinuing the infusion may be enough. Should bleeding be profound or continue despite discontinuation, or should an accidental overdose occur, the anticoagulant effect of heparin can be reversed with intravenous protamine,[36] which neutralizes heparin by forming a stable salt which is then removed from the body by the reticuloendothelial system. The dose used is 1 mg of IV protamine sulfate for every 100 U of heparin given in the previous 2 hours. Because protamine binds preferentially to larger heparin molecules, it is not as effective in reversing the effect of LMWHs.[37,38] Minor reactions occur in up to 16% of patients receiving protamine, and major reactions including anaphylaxis and catastrophic pulmonary vasoconstriction in up to 3%.[39]

Single Coagulation Factor Inhibitors: Direct Thrombin Inhibitors

Recall that in the final steps of the coagulation cascade, thrombin (factor IIa) converts fibrinogen to fibrin. Fibrin-bound thrombin remains active and amplifies thrombus expansion. The heparin-antithrombin complex cannot inactivate fibrin-bound thrombin, but direct thrombin inhibitors (DTIs) do not require antithrombin and can inactivate the clot-bound thrombin, as well as free thrombin and fibrin-bound thrombin.[40]

Parenteral DTIs are used during percutaneous coronary interventions (PCIs) and to treat or prevent thrombosis in patients with heparin-induced thrombocytopenia (HIT). Three DTIs are currently in clinical use – lepirudin (Refludan), bivalirudin (Angiomax), and argatroban. They differ with respect to thrombin binding sites, reversibility, pharmacology, and specific indications. They are derivatives of hirudin, originally derived from leech saliva.[41]

The first oral direct thrombin inhibitor available for clinical use was ximelagatran (Exanta®), a major advance over VKAs since it did not require anticoagulant monitoring or dose adjustments. In clinical trials for VTE prevention and treatment, ximelagatran was either more effective than or comparable to warfarin.[42] However, Phase IV (post marketing) safety monitoring revealed liver toxicity in 6% of patients and use of the drug was discontinued in 2006.[43] Clinical trials had been no longer than 12 weeks, and the problems did not emerge until patients had been taking the drug for far longer periods. Ximelagatran had very low oral bioavailability, so was formulated as a prodrug, which may have contributed to its toxicity.

The second oral thrombin inhibitor, dabigatran etexilate (Pradaxa®), was approved for marketing in the United States in 2010 with a single indication: to reduce the risk of stroke in patients with nonvalvular atrial fibrillation. Other studies have indicated possible off-label uses,[44] but thus far stroke prevention in patients with atrial fibrillation is its only approved use. Some early adaptors have tried switching patients being treated with VKA to prevent VTE with mixed results.[45]

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity, but is rapidly absorbed and converted to its active principal, dabigatran, by esterase-catalyzed hydrolysis in plasma and in the liver.

The RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy) randomized more than 18,000 patients to either open-label warfarin, with dosing adjusted to achieve a target INR of 2 to 3, or 1 of 2 blinded doses of dabigatran (110 mg or 150 mg, twice daily). Patients were followed for a median of 2 years. The primary outcome measure was the incidence of stroke or systemic embolism.[46] Both doses of dabigatran etexilate were non-inferior to warfarin in preventing stroke or systemic embolism. In patients taking 150 mg of dabigatran etexilate twice daily, the rate of the primary outcome was 1.11%, versus 1.69% in the warfarin group. Rates of major bleeding, the primary safety outcome, were 3.36% per year with warfarin, 3.11% per year with dabigatran etexilate 150 mg twice daily and 2.71% per year with dabigatran 110 mg twice daily. Both doses of dabigatran etexilate were associated with higher rates of myocardial infarction than warfarin. When presented to the FDA in 2010, only the 150mg twice-daily dose was approved. See Table 4 for direct comparison of warfarin and dabigatran.

Table 4: RE-LY Outcomes: dabigatran vs warfarin			
End points (%)	Dabigatran 150 mg bid	Warfarin (goal INR 2.0 – 3.0)	**NNT / NNH**
Primary outcomes	1.11	1.69	**172**
Myocardial infarction	0.7	0.5	**500**
Mortality	3.6	4.1	**200**
Major bleeding	3.1	3.4	**333**
Intracranial bleeding	0.3	0.7	**250**
Net clinical benefits	6.9	7.6	**143**

In the RE-COVER trial, dabigatran etexilate 150 mg twice daily was compared to warfarin for secondary prevention of VTE in patients with confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE).[47] This randomized, double-blind trial of 2564 patients established the non-inferiority of dabigatran compared to oral VKA therapy. After 6 months, recurrent VTE was found in 2.4% of patients taking dabigatran etexilate and in 2.1% of those taking warfarin. While there was no significant difference in rates of bleeding, more patients discontinued dabigatran etexilate due to adverse events compared to warfarin (9% versus 6.8%).

It has also been studied for venous thromboembolism prophylaxis among patients undergoing elective total hip replacement (RE-NOVATE trial)[48] and total knee replacement (RE-MODEL trial)[49], both of which showed it was noninferior to LMWH in the primary outcomes of VTE and all-cause mortality; rates of major bleeding and other adverse events were also similar.

So dabigatran meets two criteria of an ideal anticoagulant: no dose adjustment needed and no monitoring required. It is rapidly absorbed and converted to the active form dabigatran, reaching a serum peak in about 1 hour after oral administration, possibly eliminating the need for a "heparin bridge." In patients with normal renal function, approximately 80% is excreted in the urine, with a half-life of 12 to 17 hours, so it requires twice daily dosing.[50] Dosing adjustment is recommended in patients with renal insufficiency, but no adjustment is necessary in those with liver malfunctions. About 35% of dabigatran is bound to plasma proteins, and it has a volume of distribution (Vd) of 50 to 70 L.[51]

When first marketed, the medication guide stated, "After opening the bottle, use Pradaxa within 30 days. Safely throw away any unused Pradaxa after 30 days."[52] This was not a problem in Europe, where Pradaxa is released in blister packs and the 30-day limit did not apply, but had the potential for huge wastage in the US. Within months, this was expanded to a 60 day period of safe, effective usage.

One downside of dabigatran is that we cannot monitor anticoagulation. Both the thrombin time (TT) and ecarin clotting time (ECT) demonstrate a linear response to serum dabigatran concentrations, neither of these assays is in widespread clinical use.[53] A product called the Hemoclot Thrombin Inhibitor kit is reported to have direct correlation with dabigatran concentration, but awaits approval by the FDA.[54] INR measurement is of no value, since dabigatran works "downstream" of the VKAs; with therapeutic dabigatran concentrations, the INR might be somewhere between 1.2 and 2.0. The activated partial thromboplastin time (aPTT) measures contact activation (i.e., intrinsic pathway), so does not respond linearly to the dose or intensity of anticoagulation with dabigatran. The aPTT can, however, be used as a *qualitative* measure of effect without providing a precise degree of anticoagulation; in other words, a normal aPTT excludes significant anticoagulation in a patient taking dabigatran.[55]

Reversing the DTIs

Another downside is that there is no known effective antidote for the patient who is taking dabigatran and who presents with a bleeding complication. There are many current recommendations, but they are not based on evidence or clinical experience. They are what can be colloquially called GOBSAT recommendations (Good Old Boys Sitting Around a Table.)

The first recommendation is that, if dabigatran was consumed within two hours of presentation, activated charcoal, at standard doses, should be given per institutional protocol. This falls into the "sounds like a good idea" (plausible pseudoscience) category, but is backed by no evidence.

Vitamin K, of course, is of no use, as it acts upstream of dabigatran. While some experts recommend the use of FFP, it will not reverse the anticoagulation effect of dabigatran, as the drug will inhibit thrombin in the transfused plasma. (Remember that the prolonged clotting times in patients taking dabigatran are a reflection of thrombin **inhibition** and not a clotting factor **deficiency**). Cryoprecipitate will not work, as thrombin acts independently of the factors found in it.

While animal studies suggest that recombinant factor VIIa (rFVIIa) can reduce bleeding time and aPTT from high dose dabigatran, human evidence is mixed.[56] Administration of PCCs has improved clotting times in both animal and human models of dabigatran-induced bleeding, but they are thrombogenic and their indiscriminate use leads to ischemic events.[35] Other products used to help control bleeding (desmopressin, aprotinin, tranexamic acid and aminocaproic acid) did not help in rat models and would not be expected to help in humans.[57]

Emergency dialysis can remove up to 62% of dabigatran at 2 hours,[58] but the thought of sticking a catheter of a suitable size for dialysis in a patient who is over-anticoagulated is a frightening one. Early studies are underway for a dabigatran antidote, but final results are years away.

Obviously, the jury is still out on dabigatran. A recent on-line story on HeartWire[59] reported 260 fatal bleeds in patients taking the drug, but there is no good way to compare this to the number of fatal bleeds suffered by patients taking VKAs during the same period. Safety advisories have been issued in many countries, including Japan and New Zealand.[60]

Single Coagulation Factor Inhibitors: Indirect Factor Xa Inhibitors

Fondaparinux (Arixtra) is the only drug in this category thus far. The heparins are also indirect Factor Xa inhibitors, but differ from fondaparinux in that they also inactivate Factor IIa. In addition fondaparinux does not inhibit **bound** Factor Xa, so it cannot completely inhibit Factor Xa. It is a synthetic whose structure is based on the natural pentasaccharide contained within the heparins. It potentiates the rate of neutralization of Factor Xa by antithrombin. In numerous studies of various hypercoagulabile states, it seems to offer no advantages over the standard heparins, but is probably useful in patients who have experienced heparin-induced thrombocytopenia.[61]

Long-term use is limited by the requirement of subcutaneous injection.[62] Bleeding is the most common adverse event with fondaparinux, and major bleeding occurs at about the same rate as seen with patients treated with LMWHs. Protamine is not effective to reverse its effects. [63]

Single Coagulation Factor Inhibitors: Direct Factor Xa Inhibitors.

Direct Factor Xa inhibitors (aka "xabans") act directly upon Factor X in the coagulation cascade, without using antithrombin as a mediator. Rivaroxaban (Xarelto®) is currently available in the United States, while apixaban (Eliquis), betrixaban, edoxaban, and otamixaban are in various stages of development. All of the generic names cleverly have "xa" in them, indicating they work on activated Factor X. Unfortunately, the proprietary name for dabigatran – Pradaxa® - also contains this "xa," even though it is a direct thrombin inhibitor.

The original xabans were discovered in the 1980s when antistasin was isolated from the extracts of the Mexican leach, *Haementeria officinalis*.[64] Then another naturally occurring inhibitor, tick anticoagulant peptide (TAP) was isolated from the extract of tick *Ornithodoros moubata*.[65]

Rivaroxaban is an oral, direct, reversible, rapid, dose-dependent Factor Xa inhibitor that works in vitro on both free FXa and FXa bound to the prothrombinase complex.[66] It is rapidly absorbed, reaching peak plasma concentrations in 2.5 to 4 hours after oral administration. The half-life of FXa inhibition is 6 to 7 hours, meaning it must be dosed twice daily.[67] About 30% is excreted in the urine, while the other 70% is either metabolized by the liver or excreted in stool. Hence, patients with renal or hepatic insufficiency may be at risk for overdose.

Its indications are: 1) prophylaxis of deep vein thrombosis in patients undergoing knee or hip replacement surgery and 2) to reduce the risk of stroke in patients with nonvalvular atrial fibrillation.

The recently published The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) showed rivaroxaban was noninferior to warfarin in terms of stroke and non-central-nervous-system (CNS) embolism.[68] In November 2011, the FDA approved Xarelto® for this indication, agreeing that it was noninferior to warfarin, but declining to say it was superior to the VKAs.[69] ROCKET-AF results are summarized in Table 5.

Table 5: ROCKET-AF study: primary ischemic outcomes

Outcomes	Rivaroxaban	Warfarin	*P*	**NNT**
Primary outcomes (noninferiority)	1.71	2.16	<0.001	**222**
Non-CNS embolism	0.04	0.19	0.003	**667**
Vascular death / stroke / CNS embolism	3.11	3.63	0.034	**192**
Ischemic stroke	1.34	1.42	0.581	**1250**
Death, unknown cause	0.06	0.10	0.366	**2500**

Another direct FXa inhibitor, apixaban (Eliquis), has been approved in Europe[70] but awaits FDA approval for use in the United States for both stroke prevention and VTE. Its development for acute coronary syndromes (ACS) was dropped after an unacceptable bleeding risk was seen in the APPRAISE-2 trial.[71] The ARISTOTLE (Apixaban for Reduction In Stroke and other ThrombOemboLic Events in atrial fibrillation) trial seems to show apixaban's superiority to warfarin in preventing stroke in patients with atrial fibrillation, but with a lower rate of bleeding and other complications.[72] Final evaluation and approval are forthcoming.

Since oral Direct FXa inhibitors exert their effect at the junction of the two coagulation pathways, they prolong both the PT and aPTT in a dose-dependent manner. PT can show some linearity with select (but not all) reagents, but low dose response may be poor and the INR system is not recommended for use.[73]

The APTT is also prolonged in a dose dependent fashion, but is even less sensitive than the PT. Anti-FXa activity is also influenced by rivaroxaban, but no standard for calibration is available. The previously mentioned ECT and TT are not affected.

Reversing the Direct FXa Inhibitors

We may have an option to treat patients who present with hemorrhagic conditions while they are taking Direct FXa inhibitors. Recombinant Factor VIIa (rFVIIa) seems to partially reverse rivaroxaban in both human and rats, as measured by bleeding time, PT prolongation, and other clotting tests, but thus far only abstracts have been published.[74] PCCs were studied healthy subjects receiving rivaroxaban and showed immediate reversal of the prolonged PT that last for a minimum of 24 hours, but the study was done in healthy subjects.[75] Since it is so highly protein bound, it is not removable by dialysis.

Antiplatelet Agents (APAs)

Over the past two decades, there has been an explosion of agents to affect platelet function. Blood vessels are lined with a thin layer of endothelium that normally inhibits platelet activation by producing nitric oxide, endothelial-ADPase, and PGI2. Endothelial cells also produce von Willebrand factor (vWF) which helps endothelial cells adhere to collagen in the basement membrane. Under normal conditions, collagen is not exposed to the bloodstream and the secreted vWF is stored in granules in both endothelial cell and platelets. When the endothelial layer is injured, collagen, vWF and tissue factor from the subendothelium are exposed to the bloodstream. When the platelets contact collagen or vWF, they are activated and clump together. They are also activated by thrombin. Activated platelets assume a more spherical shape and develop pseudopods, giving them a stellate appearance.

Major antiplatelet agents are classified in Table 6. For this essay we will briefly mention aspirin and NSAIDs, but then concentrate on the adenosine diphosphate (ADP) receptor inhibitors.

Table 6: Therapeutics Agents Affecting Platelet Function	
Cyclooxygenase inhibitors	Aspirin and, to a lesser degree, NSAIDs
Adenosine diphosphate (ADP) receptor inhibitors	Clopidogrel (Plavix); Prasugrel (Effient); Ticagrelor (Brilinta); Ticlopidine (Ticlid)
Phosphodiesterase inhibitors	Cilostazol (Pletal)
Glycoprotein IIB/IIIA inhibitors (intravenous use only)	Abciximab (ReoPro); Eptifibatide (Integrilin); Tirofiban (Aggrastat)
Adenosine reuptake inhibitors	Dipyridamole (Persantine)
Thromboxane inhibitors	Ifetroban, terutroban

Aspirin (ASA) is immediately absorbed after ingestion and its effects can be seen in as little as 15 minutes. ASA irreversibly acetylates the cyclooxygenase (COX-1) enzyme, thus suppressing production of thromboxane A2 and inhibiting platelet activation and aggregation. Platelets have a life span of 8 to 10 days. Normal bone marrow releases about 10% of its platelets daily, so discontinuation of ASA for two days in a patient with a platelet count of 250,000/microL will result in production of 50,000/microL functionally adequate platelets – enough to achieve normal hemostasis. Spontaneous bleeding is rare with a functional platelet count of more than 20,000/microL, although significant bleeding can occur in trauma and surgery with counts of 20,000/microL – 50,000/microL.

Non steroidal anti-inflammatory drugs (NSAIDs) bind to COX-1 reversibly for only 6 to 8 hours. NSAID ingestion several hours prior to ASA renders ASA ineffective, as COX-1 receptors are temporarily occupied by the NSAID.[76]

Aspirin "resistance" is described in 10% to 30% of patients.[77] Several causes are proposed, including low compliance, NSAID interference with COX-1 acetylation, competitive effect of COX-1 activation, and protein glication in type 2 diabetes. Increased platelet turnover is found in several conditions, including diabetic angiopathy, peripheral arterial disease, and acute coronary syndrome. This is associated with faster reappearance of newly formed, non aspirinated platelets and can cause a condition practically corresponding to "aspirin resistance.[78]

ADP receptor inhibitors prevent binding to and activating Glycoprotein IIb/IIIa (GP IIb/IIIa), which is necessary for platelet activation. Ticlopidine (Ticlid) was the first ADP receptor inhibitor approved by the FDA and is used in patients in whom aspirin is not tolerated, or in whom dual antiplatelet therapy is desirable. But because it is reported to increase the risk of thrombotic thrombocytopenic purpura (TTP)[79] and neutropenia,[80] its use has largely been supplanted by newer drugs.

Another ADP receptor inhibitor, Clopidogrel (Plavix) is a prodrug that must be metabolized by the cytochrome P450 system into an active compound. A loading dose of 300 to 600 mg shows its effect within 2 to 4 hours, whereas a daily dose of 75 mg shows effects within 24 hours, but maximal effect is not reached for 4 to 7 days.

Clopidogrel was initially approved by the FDA in 1997, but then received new indications in 2001. CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) randomly assigned 12,562 patients who presented within 24 hours after the onset of unstable angina without ST-elevation but with dynamic EKG changes and / or troponin elevation (i.e., these were sick patients) to receive clopidogrel in addition to aspirin for 3 to 12 months. The "first primary outcome" was death from cardiovascular causes OR nonfatal myocardial infarction OR stroke. One of these outcomes occurred in 9.3% of the patients in the clopidogrel group and 11.4% of patients in the placebo group.[81] A summary table of events is shown in Table 7.

Table 7: CURE trial results[80]	**Clopidogrel (Plavix®) Events / 1000**	**Placebo Events / 1000**	**NNT**
Nonfatal myocardial infarction OR stroke OR death from cardiovascular causes	**93**	**114**	**48**
Death from cardiovascular causes	**51**	**55**	**250**
Myocardial infarction	**52**	**67**	**67**
Stroke	**12**	**14**	**500**
Nonfatal myocardial infarction, stroke, death from cardiovascular causes or refractory ischemia	**165**	**188**	**43**
Refractory ischemia	**87**	**93**	**167**
			NNH
Major bleeds	**37**	**27**	**100**
Life-threatening bleeding*	**22**	**18**	**250**

The COMMIT Trial[82] results published in 2005 showed some benefits in patients having an acute MI: patients given clopidogrel (in addition to aspirin) had a 9% relative reduction in death or reinfarction or stroke (9.2% vs. 10.1%; NNT for any primary endpoint 110; absolute reduction: 0.9%). However there

was no standardization of other care, the thrombolytic agent used was not fibrin-specific (urokinase), and there was a relatively low rate (54%) of reperfusion therapy.

The CHARISMA Trial[83] (see Table 8) from 2006 showed far less impressive results in less sick patients, possibly due to clopidogrel resistance in up to 40% of patients receiving it.[84]

Table 8: CHARISMA Trial[82]	**Clopidogrel + ASA (n=7802)**	**Placebo + ASA (n=7801)**	**p**	**NNT**
Death from any cause	371 (4.8%)	374 (4.8%)	0.90	∞
Death from CV cause	238 (3.1%)	229 (2.9%)	0.68	**500**
MI (nonfatal)	147 (1.9%)	159 (2.0%)	0.48	**1000**
Ischemic stroke (nonfatal)	132 (1.7%)	160 (2.1%)	0.10	**250**
Stroke (nonfatal)	149 (1.9%)	185 (2.4%)	0.05	**200**
Hospitalization for USA, TIA, revascularization	866 (11.1%)	957 (12.3%)	0.02	**83**

While clopidogrel therapy is recommended after placement of coronary artery stents, drug-eluting and otherwise, its discontinuation causes major increases in stent occlusion, which increases by a factor of more than 30 when clopidogrel is discontinued within 6 months of insertion of a drug-eluting stent,[85] and by a factor of approximately six when discontinued beyond 6 months.[86]

Clopidogrel resistance mainly depends upon acquired or genetic changes in the activity of the cytochrome P450 in the liver. It may occur due to changes brought about by interferences with other drugs competing with the same metabolic system, as proton pump inhibitors (with the exception of pantoprazole), frequently used for gastro-protection in patients under antithombotic agents.[87]

Prasugrel (Effient) is similar to clopidogrel in many ways – prodrug metabolized by cytochrome P450, irreversibility, onset of action. Patients receive a loading dose of 60mg followed by a daily dose of 10 mg (5 mg for patients weighing <60 kg).[88] In clinical trials, prasugrel had significantly more bleeding, both major and minor, than clopidogrel. In a head-to-head comparison to clopidogrel, 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel reached the primary efficacy end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel, and life-threatening bleeding in 1.4% vs. 0.9%. Overall mortality did not differ between the two treatment groups.[89]

Ticagrelor (Brilinta™) is the latest antiplatelet agent to be approved in the US, based primarily on the PLATO (PLATelet Inhibition and Patient Outcomes) study.[90] Ticagrelor was far superior to clopidogrel for every endpoint, but major bleeding results were virtually identical in both groups. (See Table 9 for the results.)

Table 9: **Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery (PLATO)[88]**				
N = 1261 patients	Ticagrelor	Clopidogrel	P	NNT
Primary composite end point at 12 months	10.6%	13.1%		40
Total mortality	4.7%	9.7%	<0.01	20
Cardiovascular death	4.1%	7.9%	<0.01	26
Non-cardiovascular death	0.7%	2.0%	0.07	143

Ticagrelor has faster onset than clopidogrel or prasugrel (because it is not a prodrug and does not require metabolism to work), so the current practice of giving clopidogrel 300mg (or 600mg) to emergency department patients en route to the cath lab may change. It also wears off faster, as it binds to platelets reversibly. Since it does not require metabolism to become active, ticagrelor resistance is far less likely.[91] A downside is the shorter half-life, meaning that ticagrelor will require twice-daily dosing. Another puzzling finding is that patients on combined ticagrelor-ASA therapy had better results with low-dose ASA therapy (81mg/day) vs standard ASA therapy (325mg/day). This has not been fully explained and may be an element of the trial design.[92] It may not offer enough benefits for all practitioners to switch their patients from clopidogrel, but the initial results are very promising.[93]

Reversing the APAs

The platelet count is a first line test of platelet function, and the manual count is still considered the gold standard, despite interobserver variations of 15% to 25%.[94] Although modern automated cell counters are rapid, precise, and reproducible, they tend to overestimate the platelet count in samples that contain cellular debris (e.g., thalassemia, thrombotic thrombocytopenic purpura, leukemia). In patients with large platelets, the count is underestimated.[95]

Several platelet function assays (PFA) are now available, including older methods like bleeding time and platelet aggregometry, and newer commercial products like thromboelastograph platelet mapping, PFA-100 (said to have a turnaround time of less than 10 minutes),[96] and the VerifyNow® Aspirin assay and VerifyNow® PLAVIX assay. These latter two are currently used primarily to determine resistance to ASA and clopidogrel.

While it is well known that reversing the anticoagulant effects of VKAs in patients experiencing spontaneous intracerebral hemorrhage (ICH) is beneficial,[97] the evidence for patients taking APAs is far less clear.[98] Nonetheless, most neurosurgeons and neurointensivists continue to recommend aggressive reversal of APAs in the setting of spontaneous ICH.[99]

Similarly, the evidence for reversal of APAs in patients suffering traumatic ICH is also unclear. Some studies show no difference between patients taking and not taking APAs,[100] while others show a difference in mortality as large as 30%.[101]

As far as treatment, the evidence is scanty. In the one large published study comparing patients taking APAs who had traumatic ICH and who received platelet supplementation, the mortality rates were virtually identical (17.5% in the untreated group vs 16.7% in the untreated group).[102]

Nonetheless, there are numerous recommendations about the need to transfuse platelets in these patients, either with or without a PFA.[103] A “standard” dose of platelets for an adult is transfusion of one apheresis unit or 6 units of pooled donor platelets harvested from whole blood, both containing approximately 4 to 6 x 10^{11} platelets. Transfusion of one unit of apheresis derived platelets or six units of pooled donor platelets should raise the platelet count in an adult with a body surface area of 2.0 square meters by approximately 30,000/microL at 10 minutes to one hour after transfusion, enough to prevent spontaneous bleeding. Exceptions to this rule are common and may be an indication of refractoriness to platelet transfusion.

Another common recommendation is desmopressin (d-amino d-arginin vasopressin, aka DDAVP), despite a lack of randomized controlled trials.[82] DDAVP promotes the release of vWF with subsequent increase in FVIII survival in patients with thrombocytopenia.[104] It can also be used with uremic induced

platelet dysfunction.[105] There is a case report of a patient undergoing emergent carotid endarterectomy who received a single dose of DDAVP 0.3 mcg/kg; the PFA-100 (which was consistent with therapeutic clopidogrel treatment) improved significantly, but did not return to normal, and the patient underwent an uneventful procedure.[106]

Although strictly based on opinion, I find the proposed protocol below to be easy, sensible, and potentially useful:

From Campbell et al.[81]

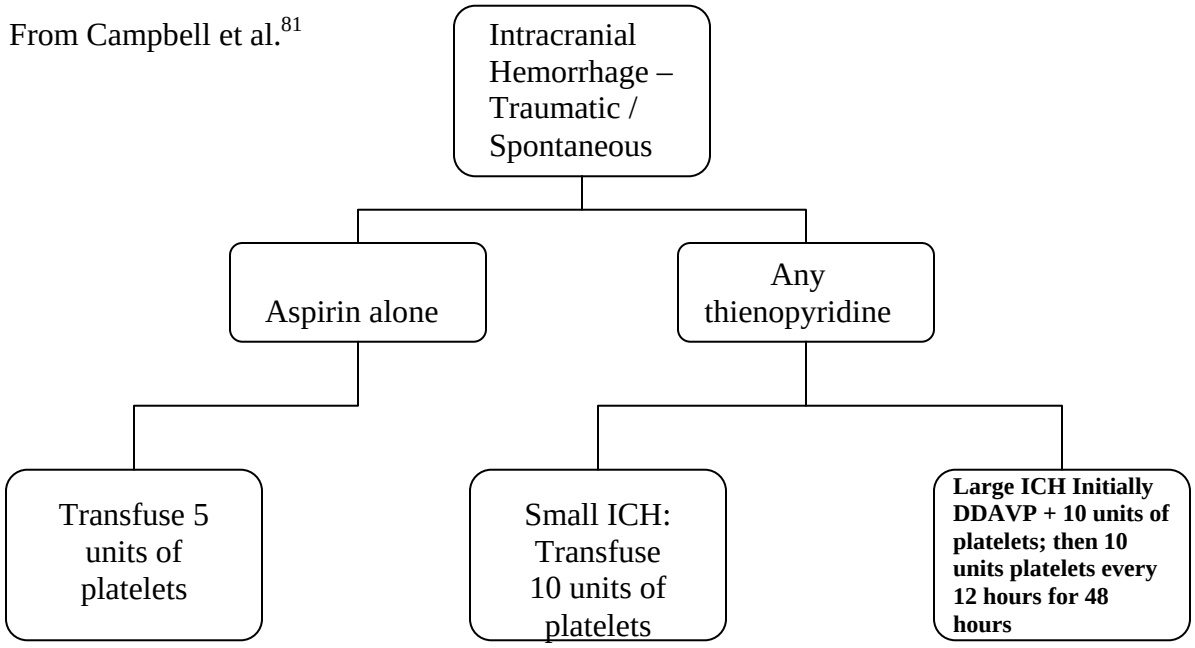

Table 10: summary of anticoagulants / antiplatelet agents and their emergency reversal			
Agent	Reversal	Lab Test	Comments
Warfarin / VKAs (Coumadin)	1. Vitamin K1, 5-10 mg IV (slow) 2. PCC 4000 IU	PT / INR	FFP 10-15 ml/kg if PCC not available
UFH (heparin)	1. Stop infusion 2. Protamine sulfate, 1 mg for each 100U of active heparin (slow)	PTT	FFP **contraindicated**
LMWH (Lovenox et al)	Protamine sulfate, 1 mg for each 1mg LMWH (partial reversal only)*	Anti-Xa assay	
DTI (Pradaxa)	1. No specific antidote 2. DDAVP 0.3 mcg/kg 3. Consider cryoprecipitate* 4. Consider rVIIa (30-90 mcg/kg)*	PTT (qualitative only)	Caution: hyponatremia, seizures, elevated ICP possible with DDAVP
Factor Xa inhibitors Arixtra	rVIIa (30-90 mcg/kg)*	Anti-Xa assay	
Aspirin	1. 1U platelet transfusion 2. Consider DDAVP (0.3 mcg/kg)* 3. Consider rVIIa (30-90 mcg/kg)*	Consider PFA-100*	Caution: hyponatremia, seizures, elevated ICP possible with DDAVP
ADP inhibitors (Plavix, Effient, Ticlid, Brilinta)	1. 2U platelet transfusion 2. Consider DDAVP (0.3 mcg/kg)* 3. Consider rVIIa (30-90 mcg/kg)*	Consider platelet aggregometry*	Caution: hyponatremia, seizures, elevated ICP possible with DDAVP
*No evidence – GOBSAT recommendation (Good Old Boys Sitting Around a Table)			

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[3] ***Warf****arin derives its name from the Wisconsin Alumni Research Foundation where much of the original research was done; its -arin ending is from coumarin, a plant molecule that produces dicoumarol. In the early 1920s, there was an outbreak of a previously unrecognized cattle disease in the northern United States and Canada. Cattle were bleeding to death after minor procedures (dehorning, castration), and on some occasions, spontaneously. Frank Schofield, a Canadian veterinary pathologist, determined in 1921 that the affected cattle were ingesting moldy silage made from sweet clover. Only spoiled sweet clover hay produced the condition. In 1929, North Dakota veterinarian L.M. Roderick demonstrated that the condition was due to a lack of functioning prothrombin. In 1933 Karl Paul Link and his lab of chemists at the University of Wisconsin set out to isolate and characterize the hemorrhagic agent from the spoiled hay. They determined that the anticoagulant was 3,3'-methylenebis-(4-hydroxycoumarin), which they named dicoumarol. They confirmed their results by synthesizing dicumarol and proving that it was identical to the naturally occurring agent. It was introduced as a rat poison in 1948, but approved for therapeutic human use in 1954; one of its first recipients was President Dwight Eisenhower, as he recovered from a heart attack in 1955.*
[4] See http://en.wikipedia.org/wiki/Coagulation#Tissue_factor_pathway_.28extrinsic.29 (accessed 12 December 2011): *The contact activation pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa. The minor role that the contact activation pathway has in initiating clot formation can be illustrated by the fact that patients with severe deficiencies of FXII, HMWK, and prekallikrein do not have a bleeding disorder. Instead, contact activation system seems to be more involved in inflammation. Patients without FXII (Hageman factor) suffer from constant infections.*
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> *"I have Protein Enzyme C and S Deficiency. I suffered 2 strokes in 1994, had blood clots go through my heart and lungs, and a Vena Cava Filter implanted. Since then, I simply took warfarin for 17 years with no negative side effects. My INRs were always between 2.5 and 3.0 with no blood clotting while on the prescribed dose of 10 mg per day. About 3 months ago, my family care Physician Assistant…received some samples for Pradaxa, she suggested that I go off the warfarin and start the Pradaxa at 150 mg twice per day. She explained all the benefits and said that it would work for me. So, I did it. Only several weeks later found to have almost a solid blood clot from my upper pelvis to my lower calf in the left leg. Blood clots hit my filter and some pieces got through to my lungs. After I got out of the hospital, she apologized and said that Pradaxa does not work on the proper clotting factors to treat Protein Enzyme C or S deficiency."*

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