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A Comparison of Modern Antithrombotic Agents

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When hemostatic balance is interrupted by stasis, stress, or hypercoagulabilty, patients are at risk for venous or arterial thrombosis that may require medical prophylaxis or treatment. In the low shear venous system, thrombi are composed of red blood cells trapped by fibrin and manifest clinically as deep vein thrombosis (DVT). DVTs can cause post-thrombotic syndrome (PTS) or travel to the lungs where they become lodged and present as pulmonary embolism (PE). PEs may be one of many causes of chronic pulmonary hypertension and are known together with DVTs as venous thromboembolism (VTE). In the high shear arterial circulation, thrombi are primarily platelet aggregates that impede adequate blood flow and may result in myocardial infarction (MI), ischemic stroke, or limb gangrene.[1]

If the endothelium of a blood vessel is damaged (e.g. by a cholesterol plaque), the intrinsic coagulation pathway is activated to repair the vessel. This trauma also causes the release of tissue factor, which is responsible for activation of the extrinsic pathway. These two pathways utilize different clotting factors to reach a common pathway where factor Xa converts prothrombin into thrombin, which transforms fibrinogen into fibrin.[1]

Fibrin is responsible for platelet aggregation which binds platelets together at their GPIIb-IIIa receptors. These receptors are exposed by platelet activation when thrombin binds to the platelet's protease-activated receptors (PARs) or adenosine diphosphate (ADP) binds to $P2Y_{12}$ receptors. To keep the clot in place, von Willebrand factor is produced by the damaged vessel and facilitates platelet adhesion.[2]

Both coagulation and platelet aggregation are involved in thrombosis; therefore risk factors for various thrombotic events are evaluated and anticoagulant or antiplatelet

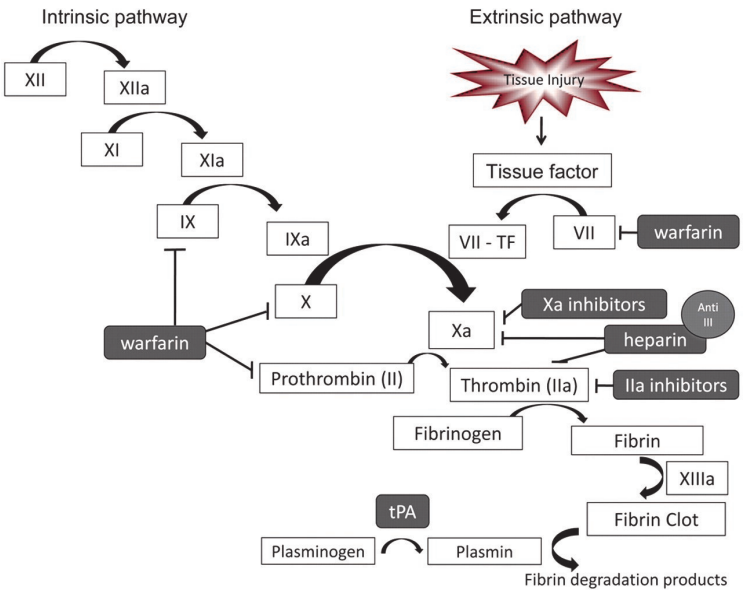

Figure 1: Clotting cascade and site of action of antithrombotic drug classes

agents are prescribed. Warfarin, heparin, heparin derivatives, aspirin, and clopidogrel have been successful in treating and preventing these types of events but are limited in their dosage forms, need for monitoring, and efficacy in certain patient populations. Patients who require rapid reversal of bleeding (i.e. trauma or emergent surgery), have a genetic predisposition to clopidogrel resistance, or indications for triple antithrombotic therapy will benefit from new options. Five oral antithrombotic agents (Table 1) have earned FDA-approval over the past four years. Prasugrel, dabigatran, rivaroxaban, ticagrelor, and apixaban each offer a unique pharmacologic profile.[1] Anticoagulation previously gained versatility with the introduction of subcutaneous

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Table 1: Recently approved oral antithrombotics

		Medication	Indications	Key Trials	Results
Anticoagulants	Factor Xa	Rivaroxaban (Xarelto)[3]	Stroke and systemic embolism prevention in nonvalvular AF DVT/PE treatment DVT/PE secondary prevention DVT prophylaxis in knee or hip replacement surgery	• ROCKET-AF • EINSTEIN DVT • EINSTEIN PE • ROCKET 1-3	Non-inferior to warfarin Non-inferior to enoxaparin-warfarin bridge Non-inferior to enoxaparin
		Apixaban (Eliquis)[4]	Stroke and systemic embolism prevention in nonvalvular AF	• ARISTOTLE • AVERROLES	Superior to warfarin Superior to aspirin
	Thrombin	Dabigatran (Pradaxa)[5]	Stroke and systemic embolism prevention in nonvalvular AF	• RE-LY • RE-ALIGN	Non-inferior and superior to warfarin Increased bleeding risk with mechanical heart valves
Antiplatelets	$P2Y_{12}$	Prasugrel (Effient)[6]	Reduction of thrombotic CV events in patients with ACS to be managed with PCI	• TRITON-TIMI 38	Superior to clopidogrel Intracranial bleeding with previous TIA
		Ticagrelor (Brilinta)[7]	Reduction of thrombotic CV events in patients with ACS	• PLATO	Superior to clopidogrel Reduces stent thrombosis

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injections; patients could use the medications at home to treat and prevent embolic events. The low molecular weight heparin enoxaparin has proven efficacy but can still increase a patient's risk for heparin-induced thrombocytopenia and fondaparinux, the original factor Xa inhibitor, is limited by its subcutaneuous route of administration.

Dabigatran was approved in 2010 for thrombus prevention in patients with nonvalvular atrial fibrillation (AF). The first approved oral anticoagulant since warfarin, the direct thrombin inhibitor demonstrated non-inferiority to warfarin for prevention of stroke and systemic embolism in patients with AF. Patients included in the approval trial scored a mean 2.1 on the $CHADS_2$ scale for stroke risk in AF and the warfarin group was within therapeutic range for 64% of the trial. Dyspepsia was reported in 35% of the dabigatran group (24% warfarin group), possibly due to its tartaric acid core.[5,9] The pharmacokinetics observed in this trial allowed for extrapolation of dosing recommendations in patients with severe renal impairment (CrCl 15-30 mL/min). Another trial evaluated patients with AF and mechanical heart valves. Results indicated an increased risk of thromboembolism and major bleeding with dabigatran when compared to warfarin.[5] Post-marketing reports to the FDA have demonstrated higher rates of gastrointestinal bleeding and intracranial hemorrhage than had been identified in clinical trials.[10]

Rivaroxaban, an oral factor Xa inhibitor, was originally approved with the sole indication of prevention of VTE in orthopedic surgery patients. Since, it has gained FDA approval for VTE treatment, recurrent VTE prevention, and stroke and systemic embolism prevention in nonvalvular atrial fibrillation (AF). The ROCKET AF trial compared the risk of stroke in patients with AF treated with rivaroxaban or warfarin; patients had a mean $CHADS_2$ score of 3.5 and the warfarin group was within therapeutic range 55% of the trial. Use is not recommended in patients with creatinine clearance below 15 mL/min.[5]

The approval of the next factor Xa inhibitor apixaban introduced a unique claim: superiority to warfarin in stroke and systemic embolism prevention in nonvalvular AF. The patients in the ARISTOTLE trial (comparing apixaban to warfarin) had a mean $CHADS_2$ score of 2.1 and the warfarin group was within the therapeutic range 62% of the trial. Limitations to this option include twice daily dosing and adjustments for weight (<60 kg) renal function (SCr>1.5), and age (>80 years).[4]

The new antiplatelet agent prasugrel was shown to be superior to clopidogrel in reducing cardiovascular (CV) events in patients with acute coronary syndrome (ACS) managed with percutaneous coronary intervention (PCI). Prasugrel is contraindicated in patients with a history of transient ischemic attack (TIA) due to an increased risk of intracranial bleeding. As a result of prasugrel's irreversible platelet inhibition and the 7-10 day lifespan of a platelet, prasugrel should be discontinued at least 7 days prior to a surgical procedure (ex. coronary artery bypass grafting).[6]

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Patients with ACS can also take ticagrelor to reduce their risk of thrombotic CV events. Results of the PLATO trial indicate that ticagrelor is superior to clopidogrel in the reduction of stent thrombosis. Patients undergoing surgery should discontinue ticagrelor therapy at least 5 days prior to the procedure.[7] Unlike clopidogrel, neither prasugrel nor ticagrelor rely on CYP2C19 activation of the drug and therefore present viable options for patients exhibiting clopidogrel resistance secondary to CYP2C19 slow metabolizer phenotypes.[6-7]

Although these agents are becoming commonly prescribed, none have the long-term safety or efficacy data of warfarin, heparin, aspirin, or clopidogrel. Therefore, they are still relatively unpredictable and have no complete antidotes for reversal in the case of bleeding. The ideal antithrombotic agent would be pharmacodynamically predictable, potent, low in price, and easy to administer. It would also have a rapid onset and offset of action,[8] such as is being investigated with the intravenous antiplatelet agent cangrelor.[1] While further research is being conducted, we can utilize these new oral agents in the specific populations they have been studied without the nuisance of monitoring.

<Click for references>

4-Factor Prothrombin Complex Concentrate for Warfarin Reversal

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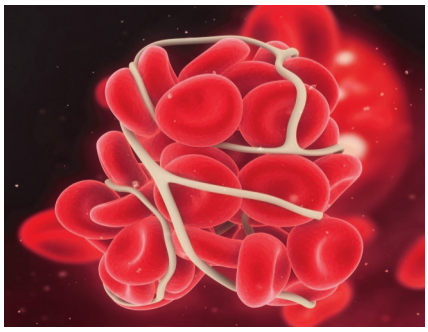
Warfarin, a vitamin K antagonist (VKA), results in the hospitalization of 1% of all patients being treated each year, and can cause fatal-bleeding in 0.3% of those treated.[1] Normally used to prevent or treat venous thrombosis, warfarin can cause major bleeding events due to its reduction of vitamin K-dependent clotting factors (VKDFs: Factors II, VII, IX, and X) and anticoagulant proteins C and S.[2] Prolonged clotting times caused by the reduced levels of coagulation factors can be devastating in patients presenting with intracerebral hemorrhage or other acute bleeds that require prompt restoration of VKDFs. Vitamin K administration is not recommended as monotherapy for these patients because VKA reversal can take several hours.[3] Administration of fresh frozen plasma (FFP) requires thawing and ABO blood typing, both of which can delay treatment. FFP has also been found to cause several transfusion-related adverse events. Clinicians need a reliable, safe, effective and timely VKA reversal agent to restore the body's ability to slow the bleeding in an attempt to improve patient outcomes. Products of prothrombin complex concentrates (PCC) can be either 3 factor (3F-PCC) or 4 factor (4F-PCC). While 3F-PCCs contain a minimal amount of factor VII and are more effective at reversing anticoagulation at lower INRs, 4F-PCC could be a potential alternative treatment because it contains sufficient amounts of all 4 factors II, VII, IX, X and has the ability to reduce INR and stop bleeding more efficiently regardless of the initial INR.[1]

A randomized, controlled study compared the safety and efficacy of 4F-PCC (Kcentra®; CSL Boehring) vs. FFP in VKA-treated patients who presented with a major bleed.[3] The open-label, non-inferiority, prospective, multinational



clinical trial consisted of 216 patients of similar baseline data and characteristics. To be included, patients were at least 18 years old, had an INR >2.0 within 3 hours of treatment, and experienced an acute major bleed (life-threatening or potentially life-threatening, associated with a fall in Hgb >2g/dL, or requiring blood transfusion). Patients were randomly assigned to receive either intravenous (IV) 4F-PCC or IV FFP; dosing was adjusted based on both baseline INR and body weight. Maximum infusion rate was 3 IU/kg/min for 4F-PCC, and 1 unit per 30 minutes for FFP. Vitamin K was given to all patients via slow IV infusion (dosing was adjusted according to 2008 ACCP guidelines or local clinical practice). Co-primary endpoints included hemostatic efficacy over 24 hours from the start of infusion and rapid INR reduction (<1.3) at 0.5 hours post-infusion. Secondary endpoints were time to INR correction and plasma levels of VKDFs and proteins C and S. Hemostatic efficacy was assessed by a blinded, independent endpoint adjudication board and classified as "excellent", "good", or "poor/none" based on hemoglobin, hematocrit, hemostatic treatments, adverse events and clinical outcomes. Hemostasis was considered effective if the rating was excellent or good over

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4-Factor Prothrombin Complex Concentrate for Warfarin Reversal

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24-hour period from the start of the infusion, and as non-effective if it was rated poor/none or patients required other hemostatic products besides the study treatment. The trial demonstrated non-inferiority of 4F-PCC to FFP, with effective hemostasis occurring in 72.4% in 4F-PCC versus 65.4% in FFP (difference 7.1% CI -5.8 - 19.9). Of the patients treated with 4F-PCC, 62.2% achieved rapid INR reduction compared to only 9.6% of those treated with FFP, showing the superiority of 4F-PCC (difference 52.6%; CI 39.4-65.9). Patients presenting with major musculoskeletal bleeding showed the highest rate of "good or excellent" hemostatic efficacy when treated with 4F-PCC compared to FFP (*P*=0.007).[3]

4F-PCC patients had higher plasma levels of coagulation factors ($p<0.05$), and an acceptable safety profile compared with FFP patients (9.7% vs 21.1% patients with related non-serious adverse events, and 1.9% vs 3.7% patients with related serious adverse events, respectively). The study was not powered to show a significant difference between treatment groups for safety outcomes.[3]

Clinical trial data has proven 4F-PCC to be a safe and effective alternative to FFP in the treatment of severe bleeds in patients currently treated with warfarin. In April 2013, The FDA approved the first 4F-PCC product (Kcentra®; CSL Boehring) for use in the United States for the urgent reversal of warfarin therapy in adult patients with acute major bleeding. In December, the indication was expanded to include urgent reversal of warfarin in adult patients needing an urgent surgery or other invasive procedure.

The most recent guidelines published by the American College of Chest Physicians recommend the use of a 4F-PCC along with slow IV injection of Vitamin K to rapidly reverse warfarin-associated major bleeding events, rather than the use of FFP.[4] Due to the greater volume requirements and increased risk for fluid overload in patients treated with FFP, patients who are at risk for fluid overload such as those suffering from heart failure, renal failure, or cirrhosis are likely to respond more positively to treatment with 4F-PCC.[3,7] A limitation to more widespread use of 4F-PCC is the significant cost difference as compared to FFP. A single course of 4F-PCC in a 175 pound patient with an INR=5 exceeds $5000.[5,6]

New data shows the use of 4F-PCC may be effective in reversing the effects of rivaroxaban,[8] a factor Xa inhibitor indicated for the treatment of deep vein thrombosis and pulmonary embolism, and the prevention of stroke.[9] More studies are required to test the safety and efficacy of 4F-PCC in the reversal of rivaroxaban before making any off-label recommendations. As the only commercially available 4F-PCC in the U.S., and considering its clinical advantages such as quick onset and acceptable safety profile, Kcentra is a viable option for patients with major acute bleeds requiring rapid reversal.

<Click for references>

Watch for economic analysis of newer anticoagulants in a future issue of The Point!

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