



NEW DEVELOPMENTS IN ORAL ANTICOAGULATION AND REVERSAL

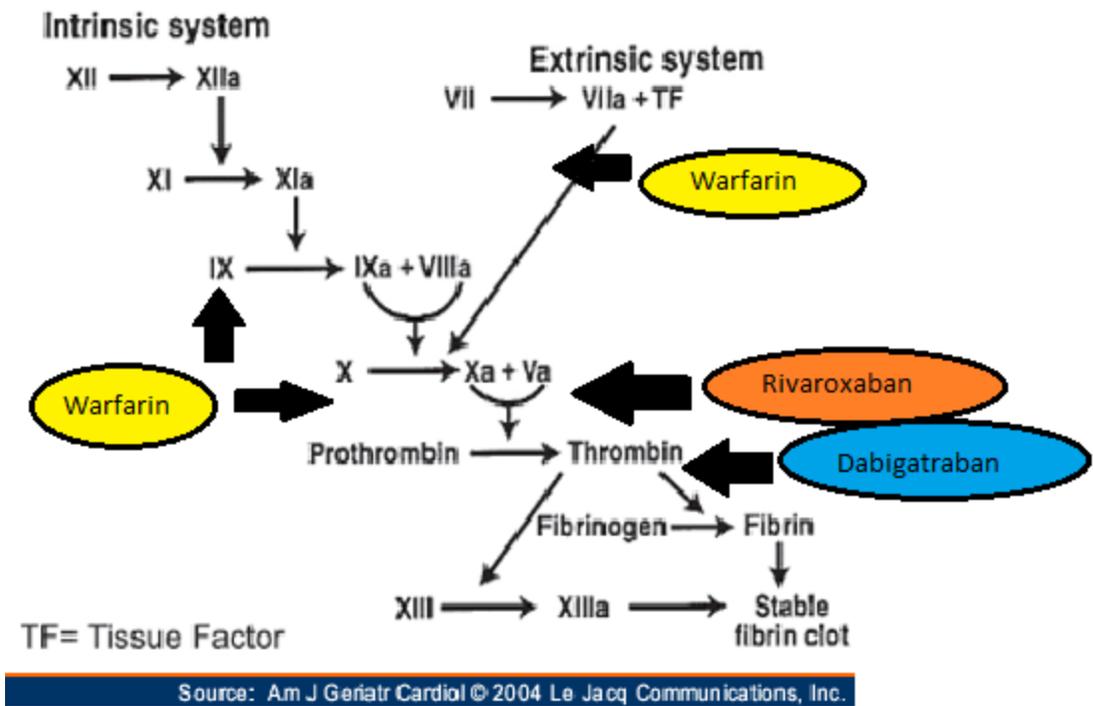
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Introduction

Since the 1940's, Warfarin was approved by the US Food and Drug administration and until recently, was the unrivaled medication for treatment of deep vein thrombosis, pulmonary embolism, and treatment of atrial fibrillation. With the introduction of a “new generation” of anticoagulants come many great advantages, but not without some considerable disadvantages as well.

Atrial fibrillation, one of the most common conditions in which warfarin is chronically prescribed, is becoming increasing more prevalent. Experts project 1 in 4 individuals will develop the condition in his or her lifetime, and will consequently have a 5 times greater risk for stroke. Due to this increase in population, combined with the challenges of maintaining therapeutic coagulation levels with Warfarin, several new drugs are slowly gaining popularity among prescribing physicians.



Types of oral anticoagulants

Warfarin (Coumadin)- Interferes with clotting by decreasing the availability of vitamin K dependent clotting factors and thrombin formation (IX, X, II, VII)

Pros:

- Inexpensive- approximately \$50/year
- Easily reversible with Vitamin K and FFP

Cons:

- Difficulty maintaining therapeutic range- (patients achieving target range approximately 60% of the time)
- Requires frequent laboratory testing and dose adjustments due to its variability.

Dabigatran (Pradaxa)- Direct thrombin inhibitor. For patients with nonvalvular atrial fibrillation, Pradaxa is currently FDA approved for stroke and systemic embolism prevention.

Pros:

- Less risk of intracranial hemorrhage than Coumadin (0.23% and 0.74% respectively).
- Laboratory testing is not required due to predictable pharmacodynamics effects
- No need for dose adjustments

Cons:

- Limited available reversal agents have been approved
- Expensive (approximately \$3200/year in prescription costs)

Rivaroxaban (Xarelto)– a direct inhibitor of activated factor Xa. Currently FDA approved for management of venous thromboembolism after orthopedic surgery and nonvalvular atrial fibrillation.

Pros:

- Fatal bleeding and intracranial hemorrhage rates are lower than Coumadin
- Superior to Lovenox in prevention of VTE after knee and hip replacement
- Similar to Pradaxa, laboratory testing not required.

Cons:

- Limited reversal agents have been approved

(See above chart for review of medication effects in reference to clotting cascade)

Reversal strategies

Prothrombin complex concentrate (PCC)– concentrated clotting factor products containing one or more clotting factors. PCC is far more concentrated than fresh frozen plasma, with 25 times more clotting factors present than in human blood. One of the newest reversal agents, PCC has several forms that are yet to be approved by the US FDA. Currently available in the United States is 3 factor PCC and activated PCC. Activated PCC (aPCC) contains the four vitamin K dependent clotting factors, thus making it a viable option for urgent Warfarin reversal. Several advantages of PCC over FFP include lack of necessity to thaw prior to administration and smaller volume

required for full reversal of anticoagulants (15 ml/kg for FFP and 1–2 ml/kg for PCC). One disadvantage of PCC is the increased likelihood of thromboembolic complications such as stroke, myocardial infarction or pulmonary embolism. While this risk is low (1.3%), this needs to be taken into consideration before correction with PCC is utilized.

Vitamin K– reverses anticoagulation effect of Warfarin by promoting hepatic production of vitamin K clotting factors. Vitamin K is typically administered in combination with another quick acting reversal agent (FFP or PCC) due to its longer duration of action.

Fresh frozen plasma (FFP)– Obtained from human blood and contains all of the clotting factors found in plasma. Each unit of FFP contains 200–250ml of product, therefore producing problems for patients with heart failure or other comorbidities where fluid overload is a concern. Studies have shown that reversal of FFP is slower and less effective at hemostasis than PCC. Other potential drawbacks from FFP include longer administration wait times due to thawing of the product, and possible transfusion reactions associated with human blood products.

Reversal strategies for different agents

Warfarin– When urgent warfarin reversal is indicated, the most effect reversal agents are FFP or PCC combined with Vitamin K administration. PCC has been shown to be more effective in reducing INR. In a recent published study, 4 units of FFP correct an INR to 2.3, whereas a dose of PCC of 25–50 IU/kg reduced the INR to 1.3. The correction time was also shorter with PCC versus FFP (41 minutes versus 115 minutes).

New generation anticoagulants (Pradaxa and Xarelto)– With the recent release of these medications by the FDA, studies are still pending for a definitive reversal agent. There currently are studies in progress that are testing the efficacy of some of the new formulations of PCC in correction of these anticoagulants, but limited data has resulted in a lack of evidence for clinical use. There have been studies that show PCC to be effective in reducing bleeding with these anticoagulants in animal studies, but human studies remain inconclusive. Hemodialysis has proven to be effective in reduction of Pradaxa because of the low protein binding. However, it has no effect in reduction of Xarelto because the drug is highly protein bound.

References:

Baumann Krueziger LM, Morton CT, Dries DJ. New anticoagulants: A concise review. *Journal of Trauma & Acute Care Surgery*. 2012; 73 (4): 983-992.

Danger, William E. Developing a management plan for oral anticoagulant reversal. *American Journal of Health-System Pharmacy*. 2013 May 15; 70 (10): S21-31.

Franchini M, Lippi G. Prothrombin complex concentrates: an update. *Blood Transfusion*. 2010 Jul; 8 (3): 149-154.

Kalus, James S. Pharmacologic interventions for reversing the effects of oral anticoagulants. *American Journal of Health-System Pharmacy*. 2013 May 15; 70 (10): S12-21.

Mitka M. New anticoagulants offer options beyond warfarin to reduce stroke risk. *JAMA: Journal of the American Medical Association*. 2012 Nov 7; 308 (17): 1727-1728.