Review

# Oral Anticoagulants:

## *New vs. Old*

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Oral anticoagulants are widely used for long-term prevention and treatment of venous and arterial thrombosis. Vitamin K antagonists, such as warfarin, are the only oral anticoagulants that are currently available.[1] These agents have an indirect mechanism of action. By interfering with vitamin K metabolism in the liver, vitamin K antagonists block a post-translational modification of the vitamin K-dependent clotting factors that are essential for their activity (Figure 1). Because vitamin K-dependent clotting factors are involved in the extrinsic, intrinsic and common pathways of blood coagulation, vitamin K antagonists have profound effects on thrombin generation (Figure 2).

Although vitamin K antagonists are very effective anticoagulants, they have limitations that render them difficult to administer in an optimal fashion. These limitations have prompted a search for new oral anticoagulants. This review will:

- outline the limitations of the vitamin K antagonists,
- identify the properties of an ideal oral anticoagulant,
- describe the mechanism of action of the new oral anticoagulants under development,
- highlight the results of clinical trials with the new agents and
- offer insight into the strengths and potential weaknesses of the new oral anticoagulants.

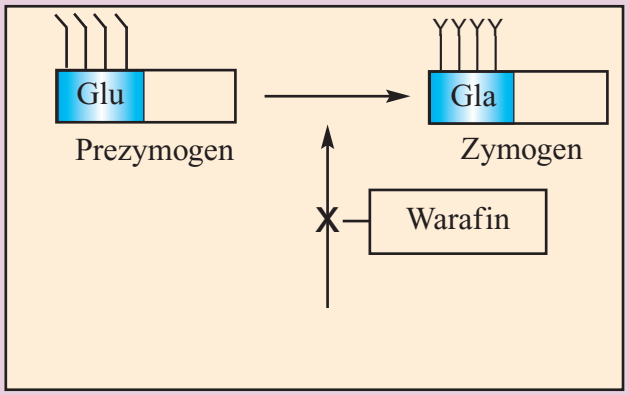


Figure 1. **Mechanisms of action of vitamin K antagonists, such as warfarin**

By interfering with the vitamin K cycle in the liver, vitamin K antagonists block the post-translational modification of the vitamin K-dependent clotting factors, factors VII, IX, X and II (prothrombin). This post-translational modification involves carboxylation of 10 to 12 Glutamic acid (Glu) residues at the N-termini of the prozymogens to yield the carboxyglutamic (Gla) domain that is capable of binding calcium. Without this modification, the clotting factors are inactive because they cannot bind to anionic phospholipid surfaces, such as the surface of activated platelets, to form the clotting factor complexes that are essential for efficient thrombin generation.

## *Limitations of vitamin K antagonists*

The limitations of the vitamin K antagonists and their consequences are outlined in Table 1. Vitamin K antagonists have a slow onset of action because they only block the modification of newly synthesized vitamin K-dependent clotting factors. In contrast, any already formed clotting factors must decay according to their natural half-lives, which range from four to six hours for

factor VII to up to 72 hours for prothrombin. To exert their antithrombotic effect, vitamin K antagonists must lower the level of prothrombin to < 25% of its normal value.[1] Because this takes four to five days to accomplish, vitamin K antagonists are often overlapped with a rapidly acting parenteral anticoagulant, such as heparin or low-molecular-weight heparin, when initiating therapy in patients with established thrombosis, or at high risk of thrombosis.

Dosing of vitamin K antagonists is problem-atic. Dietary vitamin K counteracts the effects of vitamin K antagonists, whereas excessive alcohol intake can attenuate their effect by impairing hepatic synthesis of clotting factors.[1] Common genetic polymorphisms in the isoenzymes of the cytochrome P450 system involved in the metabolism of vitamin K antagonists can render patients so sensitive to their effects that only small doses are required. In contrast, genetic variations in vitamin K epoxide reductase, the enzyme target of vitamin K antagonists, can render patients resistant to these drugs unless high doses are given.

Vitamin K antagonists have a narrow therapeutic window.[1] Thus, failure to achieve an adequate level of anticoagulation is associated with an increased risk of thrombosis, whereas overanticoagulation increases the risk of hemorrhage. Consequently, frequent coagulation monitoring is necessary to ensure that a therapeutic level of anticoagulation has been achieved. Drug-drug interactions with vitamin K antagonists are common and increase the need for monitoring, which is inconvenient for patients, as well as physicians and increases healthcare costs.

## *Properties of an ideal anticoagulant*

An ideal anticoagulant would overcome the limitations of the vitamin K antagonists and would

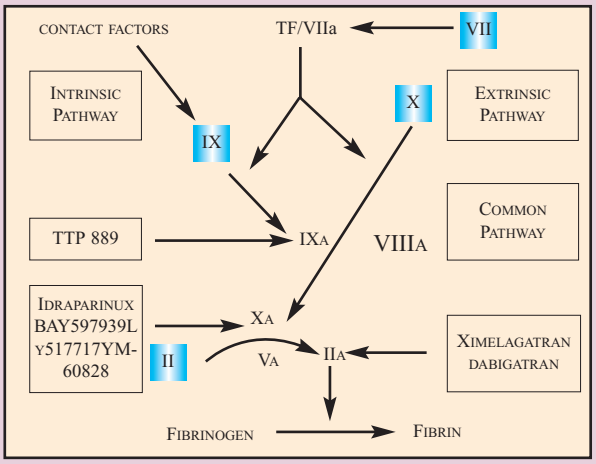


Figure 2. **Sites of action of vitamin K antagonists new oral anticoagulants**

Coagulation is initiated by the tissue factor (TF)/factor VIIa complex (extrinsic pathway), which activates factors IX and X. Factor IXa, together with its co-factor, factor VIIIa, amplifies factor X activation (intrinsic pathway).

Factor Xa, together with its cofactor factor Va, converts prothrombin (factor II) to thrombin (factor IIa); thrombin then converts fibrinogen to fibrin (common pathway). By blocking the post-translational modification of factors VII, IX, X and II (shaded in boxes), vitamin K antagonists attenuate thrombin generation by interfering with the extrinsic, intrinsic and common pathways of coagulation. New anticoagulants target single clotting enzymes, either thrombin, factor Xa or factor IXa.

**Table 1**
**Limitations of vitamin K antagonists and their consequences**

| Limitations | Consequences |
|---|---|
| Slow onset of action | • Overlap with parenteral anticoagulants is necessary when starting treatment in patients with established thrombosis, or who are at risk of thrombosis |
| Complicated dosing | • Dose is influenced by dietary vitamin K, alcohol consumption and genetic polymorphisms in cytochrome P450 isoenzymes or vitamin K epoxide reductase |
| Narrow therapeutic window | • Frequent international normalized ratio monitoring necessary to ensure therapeutic levels of anticoagulation |
| Multiple drug-drug interactions | • More frequent monitoring required when starting new drugs |

have the properties listed in Table 2. It should be available in oral form and have a sufficiently rapid onset of action, so as to obviate the need for overlap with parenteral anticoagulants. There should be no food interactions or genetic variations in metabolism, so that the drug can be given in fixed or weight-adjusted doses. The drug should produce a predictable level of anticoagulation with a wide therapeutic window and no drug-drug interactions to overcome the need for monitoring. Finally, a specific antidote should be available in case of bleeding or the need for rapid reversal. If an antidote is not available, the drug should have a relatively short half-life so that its anticoagulant effects will disappear quickly once the drug is stopped.

**Table 2**
**Properties of an ideal oral anticoagulant and their consequences**

| Properties | Consequences |
|---|---|
| Rapid onset of action | • No need to overlap with a parenteral anticoagulant |
| No food or drug interactions or genetic variations in metabolism | • Can be given in fixed or weight-adjusted doses |
| Predictable anticoagulant response and wide therapeutic window | • Little or no need for coagulation monitoring |
| Specific antidote available | • Rapid reversal possible in case of bleeding or need for urgent intervention |

## *Mechanism of action of new oral anticoagulants*

New oral anticoagulants are direct inhibitors of clotting enzymes that target various steps in the coagulation cascade, including thrombin, factor Xa or factor IXa (Figure 2). The two oral thrombin inhibitors, ximelagatran and dabigatran etexilate, are prodrugs (inactive compounds that the body converts *in vivo* to active drugs).[2] Once absorbed from the gastrointestinal tract, these prodrugs are rapidly bioconverted into their active forms. In contrast, most of the oral factor Xa inhibitors under development are active drugs, as is the factor IXa inhibitor.[3] All of the new oral anticoagulants have a rapid onset of action after oral administration with peak drug levels achieved within two to four hours. These drugs have been designed to avoid food or drug-drug interactions and to produce a predictable anticoagulant response so as to minimize or eliminate the need for coagulation monitoring. This is an important point because the new agents have variable effects on routine tests of coagulation. Consequently, if coagulation monitoring is required, routine tests will be of limited utility.

Many of the new agents are excreted via the kidneys, although some have dual renal and non-renal clearance mechanisms. Drugs that are cleared exclusively by the kidneys are likely to accumulate in patients with renal insufficiency. This may necessitate dose reductions or complete avoidance in patients with renal impairment.

The half-lives of these new agents varies from five to more than 12 hours. Consequently, some will require twice-daily dosing, whereas others can be given on a once-daily basis. No specific antidotes are available for any of the new agents. In healthy volunteers, recombinant factor VIIa reverses the anticoagulant effect of these drugs. However, it is unclear whether recombinant factor VIIa will safely restore hemostasis in

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patients with hemorrhage or in those requiring urgent surgical interventions.

## *Clinical trials with new oral anticoagulants*

Most of the new oral anticoagulants are currently in phase II clinical trials or are entering phase III evaluation. The exception is ximelagatran, which has completed phase III testing. When given at a dose of 24 mg twice-daily, ximelagatran was more effective than placebo at preventing recurrent venous thromboembolism (VTE) in patients who had already completed a six-month course of conventional anticoagulant therapy for treatment of VTE. Moreover, the risk of major bleeding was no higher with ximelagatran than it was with placebo.[4]

*All of the new oral anticoagulants have a rapid onset of action after oral administration with peak drug levels achieved within two to four hours.*

In other studies, ximelagatran was used at a dose of 36 mg, twice-daily. At this dose, monotherapy with ximelagatran was as effective and safe as enoxaparin followed by warfarin for treatment of acute VTE.[5] Ximelagatran was also as effective and safe as warfarin for stroke prevention in patients with atrial fibrillation.[6-8] However, ximelagatran was easier to administer because it was given in fixed doses without monitoring, whereas warfarin doses were adjusted to achieve an international normalized ratio of 2.0 to 3.0.

The drawback of ximelagatran is that it produces an over three-fold increase in alanine aminotransferase (ALT) in up to 7.9 % of patients who are treated for a month or longer.[9] Although usually asymptomatic and reversible whether the drug is continued or stopped, the increase in ALT is accompanied by a two-fold or greater elevation in bilirubin in about 0.4% of patients.[9] Although the risk of serious ximelagatran-induced hepatic damage is currently unknown, there was sufficient concern to warrant ximelagatran being withdrawn from the world market. Nonetheless, the clinical trial results with ximelagatran highlight the promise of new oral anticoagulants as potential replacements for vitamin K antagonists.

### • FAQs •

**1. Why is the anticoagulant response to warfarin so variable?**

- Multiple factors contribute to the variability. In addition to compliance issues, dietary vitamin K intake, excessive alcohol intake, and common genetic polymorphisms in the enzymes involved in warfarin metabolism also influence the dose response. This variability makes warfarin difficult to administer and highlights the need for new oral anticoagulants.

**2. How will the new oral anticoagulants be monitored?**

- It is likely that little or no monitoring will be required. If monitoring is needed, the test of choice will depend on the agent.

**3. When will these new anticoagulants be available?**

- Ximelagatran is currently approved for short-term indications in Argentina and many European countries. Because of its potential to cause hepatic injury, however, the drug has recently been withdrawn from the market. Other new oral anticoagulants will not be ready for approval for at least three to five years.

## Future directions

New oral anticoagulants have potential advantages over vitamin K antagonists, such as warfarin. With fixed or weight-adjusted dosing and no monitoring, the new agents will be easier to administer. Consequently, patients and physicians are likely to prefer the new agents if they prove as effective and safe as the vitamin K antagonists. However, the gain in convenience will come at the expense of new challenges.

- *Without monitoring, how will patient compliance be assessed?*

Compliance will be particularly important for drugs with short half-lives because patients may be inadequately anticoagulated if doses are missed. Careful attention to drug packaging and ongoing supervision will be required to promote compliance.

The lack of an antidote poses a problem for patients who are bleeding or for those who require urgent surgery. New anticoagulants with a short half-life will be easier to manage in this setting than those with a long half-life. Although recombinant factor VIIa may be useful, the drug is expensive and can cause thrombotic complications.

- *When monitoring of the new agents is required, how will it be done?*
- *How will we know if bleeding is due to over-anticoagulation or to an anatomical lesion, since routine testing does not accurately assess the level of anticoagulation?*
- *Will all such patients require investigations for a potential source of bleeding?*

## Take-home message

- For over 60 years, vitamin K antagonists, such as warfarin, have been the only available anticoagulants.
- Vitamin K antagonists have several limitations, including the need for routine coagulation monitoring, which is inconvenient for patients and physicians and costly for the healthcare system.
- New oral anticoagulants that target specific clotting enzymes are under development.
- The new anticoagulants will be more convenient than warfarin because they can be given in fixed doses without monitoring.
- Although not yet available for long-term use, new oral anticoagulants may be approved within two to five years.
- Eventually, head-to-head trials with the new agents will be necessary to determine whether drugs that target upstream to thrombin offer advantages over those that target thrombin directly.

These questions will need to be addressed if these new drugs come to market. Likewise, their cost-effectiveness compared to vitamin K antagonists also will require careful evaluation. Dx

References
1. Ansell J, Hirsh J, Poller L, et al: The pharmacology and management of the vitamin K antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl):204S-33S.
2. Gustafsson D: Oral direct thrombin inhibitors in clinical development. J Intern Med 2003; 254(4):322-34.
3. Weitz JI, Bates SM: New anticoagulants. J Thromb Haemost 2005; 3(8):1843-53.
4. Schulman S, Wahlander K, Lundstrom T, et al: THRIVE Treatment Study Investigators: Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med 2003; 349(18):1713-21.
5. Fiessinger JN, Huisman MV, Davidson BL, et al: THRIVE Treatment Study Investigators. JAMA 2005; 293(6):681-89.
6. Olsson SB: Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): Randomized controlled trial. Lancet 2003; 362(9397):1691-98.
7. Albers GW, Diener HC, Frison L, et al: SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: A randomized trial. JAMA 2005; 293(6):690-98.
8. Albers GW: SPORTIF Investigators. Stroke prevention in atrial fibrillation: Pooled analysis of SPORTIF III and V trials. Am J Manag Care 2004; 10(14 Suppl):S462-69.
9. Lee WM, Larrey D, Olsson R, et al: Hepatic findings in long-term clinical trials of ximelagatran. Drug Saf 2005; 28(4):351-70.