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What Did We Learn from New Oral Anticoagulant Treatment?[¶]

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Abstract

Orally active direct inhibitors of thrombin and factor Xa have now been approved for treatment or prevention of deep vein thrombosis, and stroke associated with atrial fibrillation. The factor Xa inhibitor, rivaroxaban, has shown promising results in the treatment of acute coronary syndrome but is not yet approved for that indication. These agents share a rapid onset and are cleared with half lives of approximately 10 hours. At present there is no approved antidote for either class of anticoagulant, making the treatment of life-threatening bleeding episodes problematic. These agents have fewer drug interactions than warfarin, have a predictable clearance, and hence do not require monitoring. Patients with renal insufficiency have delayed clearance and hence may have elevated levels of the drug leading to increased risk of bleeding.

Keywords

direct thrombin inhibitor; direct factor Xa inhibitor; stroke; heart attack; deep vein thrombosis; atrial fibrillation

A long term goal in anticoagulant management has been to obtain orally active anticoagulants with predictable pharmacodynamics (thereby avoiding the need for monitoring) whose function was minimally perturbed by diet, antibiotics or common drugs frequently used by the elderly. The advent of the new orally active anticoagulants appears to have addressed many of these issues with comparable or improved safety and efficacy. Areas where these drugs show comparable or superior efficacy and/or safety to warfarin or heparin are in the prevention of deep vein thrombosis following knee or hip replacement and in the prevention of stroke associated with non valvular atrial fibrillation. Areas currently under investigation are the potential use of these agents to prevent stroke and myocardial infarction in patients with acute coronary syndromes. For purposes of this brief review, rivaroxaban (Xarelto[®]), a factor Xa inhibitor, and dabigatran (Pradaxa[®]), a thrombin inhibitor, will be discussed and compared because these two drugs have the most available clinical data (Figure 1).

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As the population ages, the need for anticoagulant treatment increases. For chronic treatment with orally active agents, the only available agent has been warfarin or closely related vitamin K antagonists. As the understanding of the structure and function of the coagulation enzymes increased and with the improvement in medicinal chemistry, it has now been possible to identify orally active anticoagulants with a great deal of specificity for individual coagulation factors. Initial studies have focused primarily on thrombin and factor Xa as targets for anticoagulation. A host of agents are now available to regulate coagulation at various steps (Figure 1).

Some of these new agents are also extremely effective in acute high risk for thrombosis surgical situations which historically have depended primarily on heparin, or some smaller fractions of heparin, to reduce thrombotic risk (Table 1). The heparins all function indirectly through conformational modification of antithrombin to convert it to a much more efficient inhibitor of the coagulation factors [1] and [2]. In contrast, the orally active direct inhibitors do not use antithrombin as a component of their anticoagulant function. Thrombin inhibition by the heparin-antithrombin complex is rapid with free thrombin but slow when thrombin is bound to clots. In contrast, direct thrombin inhibitors like dabigatran inhibit both free and clot bound thrombin [3]. The latter may be quite important in situations in which the thrombus has begun to form prior to drug administration, for instance, following surgery. A parallel situation exists with factor Xa. Free factor Xa is rapidly inhibited by the heparin-antithrombin complex, but once factor Xa is incorporated into the prothrombin activation complex, it is quite resistant to inhibition [4]. One can easily imagine that in situations in which platelets activate and assemble the prothrombin activation complex, the ability to inhibit the complex is important in preventing further thrombus growth.

Warfarin has many drawbacks making it difficult to control, in part because warfarin effectiveness is determined by the levels of vitamin K. Factors influencing nutritional vitamin K levels include major diet and antibiotic use (which lowers vitamin K levels by killing intestinal bacteria). In the elderly, diets tend to vary considerably and as the immune system weakens, infections leading to antibiotic therapy are more common. In addition, routine monitoring of therapy in the elderly is often difficult, as many can no longer travel to testing centers independently. This can lead to much wider variation in the INR in real life than is seen in the more carefully controlled clinical trials. Hence it is likely that drugs not needing monitoring would perform relatively better in “real world” situations than they do in the trials.

Heparin historically has played an important role in preventing thrombosis on catheters and other artificial surfaces. Unfractionated heparin binds to many proteins, requires intravenous administration, can lead to heparin induced thrombocytopenia, and requires frequent monitoring. To address these issues, low molecular weight heparins have been developed that can be administered subcutaneously. They have less associated heparin induced thrombocytopenia (HIT) and are less variable in dosage, thereby minimizing the need for monitoring [5]. The pentasaccharide, fondaparinux, has shown superior results in prevention of thrombosis in orthopedic surgery. In clinical studies, however, it was observed that fondaparinux was not capable of preventing catheter associated thrombosis [5]. Unlike unfractionated heparin or low molecular weight heparin, which effectively accelerated the inhibition of both thrombin and factor Xa, fondaparinux lacks anti-thrombin activity, raising the question of whether direct factor Xa inhibitors might also be unable to prevent catheter induced thrombosis or thrombosis on artificial surfaces. To my knowledge, this issue has not been dealt with in detail and would need to be clarified before this class of anticoagulant could be considered for use in patients with indwelling devices.

Atrial fibrillation

Both thrombin (dabigatran) and factor Xa (rivaroxaban) are effective at reducing stroke. In the Re-LY trial, dabigatran demonstrated that it was more effective than warfarin in preventing stroke at the higher dose with comparable bleeding risk [6]. At the lower dose, dabigatran was equivalent to warfarin in preventing stroke, but had a lower bleeding risk. By examining the two doses and demonstrating these differences, it offers the possibility for patient and doctor to choose a dose appropriate for the perceived bleeding risk.

Rivaroxaban was tested in the RECORD trial [7]. They chose a higher risk population to examine and hence direct comparisons between the trials, always risky, are in this case really inappropriate. Rivaroxaban was as effective as warfarin in preventing ischemic strokes and had a lower rate of intracranial hemorrhage.

Acute coronary syndrome

One of the surprising findings is that the factor Xa inhibitor, rivaroxaban, actually decreased the risk of myocardial infarction [8] relative to warfarin, whereas the thrombin inhibitor increased this risk slightly [9]. Although the number of events are relatively small, the differences suggest that factor Xa inhibition may be more effective than thrombin inhibition in the arterial circulation, at least in the heart. That suggestion is borne out by the observation that rivaroxaban on top of clopidogrel and aspirin reduced the death rate in patients with acute coronary syndrome, whereas dabigatran did not [8]. The molecular basis for this is not known. One possible reason for the difference is that arterial thrombosis involves heavy platelet recruitment leading to massive factor V release and the factor V is at least partially activated during release [10]. Therefore, several of the early thrombin feedback loops lose any relevance. The activated factor V on the platelet surface is then poised to pick up any factor Xa and generate a potent prothrombin activation complex. The activity of this complex is dampened by direct factor Xa inhibitors but not by the thrombin inhibitors, and the platelet prothrombinase may simply produce too much thrombin for the thrombin inhibitors to control.

In the ACS setting it is interesting to note that the lowest level of rivaroxaban tested appeared to have the greatest efficacy. This suggests that on top of platelet inhibitors, only modest Xa inhibition is tolerated and effective before any benefits are offset by bleeding.

Limitations with the orally active anticoagulants

At present, there is no antidote for these new anticoagulants. To be fair, these agents are cleared with half lives in the range of 10 hours. Further, there are no effective antidotes for low molecular weight heparins. Even warfarin is difficult to reverse. Vitamin K stops the warfarin effect, but it takes over a day for sufficient new protein synthesis to partially alleviate the anticoagulant effect. Plasma infusion can be used, but this requires considerable volumes of plasma. Complexes of the vitamin K-dependent factors can also be used, but these carry a significant thrombotic risk.

The population most in need of antithrombotic therapy is the elderly. Unfortunately, most of the new drugs have a significant renal clearance and hence the drug dose is higher in patients with renal insufficiency [7] and [11]. In addition, many of these drugs are processed by the CYP-3A4 and P-glycoprotein efflux transporter [1]. Ketoconazole, itraconazole, voriconazole and related drugs may increase rivaroxaban levels, possibly leading to over anticoagulation.

Bone fragility

A number of reports have indicated that patients on warfarin have an increased risk of bone fracture [12]. This is particularly problematic in elderly patients, the target group needing anticoagulation the most. Since the new anticoagulants are not vitamin K antagonists, they are unlikely to have this effect.

Vascular calcification

Warfarin leads to vascular calcification, especially of valves [13]. This may contribute to future heart attacks or heart failure. One can easily imagine that patients treated from an early age with warfarin for prevention of thrombosis with mechanical valve replacement may suffer long term from additional vascular calcification. The new oral anticoagulants are unlikely to exhibit this effect since they will not interfere with the most likely warfarin target leading to this effect, matrix Gla protein.

Conclusions

The new oral anticoagulants offer several advantages over traditional anticoagulant therapy. They have a rapid onset and reasonably fast clearance; on the order of 12 hrs. For some situations, simply ceasing the administration of the new agent may be sufficient to allow resolution of bleeding problems. In life threatening cases, however, the lack of an approved antidote remains problematic. Perhaps one of the more interesting differences to emerge between the direct thrombin and direct factor Xa inhibitors is the incidence of arterial thrombosis. Whereas the factor Xa inhibitor seems to be superior to other anticoagulants, the thrombin inhibitors seem to elevate risk. If this trend is borne out in additional clinical studies, elucidating the underlying mechanisms responsible would contribute significantly to our understanding of the pathophysiology of the disease and perhaps suggest new and improved mechanisms to limit arterial thrombosis.

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Abbreviations

HIT	heparin induced thrombocytopenia
DVT	deep vein thrombosis
Afib	atrial fibrillation
ACS	acute coronary syndrome

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Many targets for new anticoagulants

Figure 1. Many targets for new anticoagulants. TF/VIIa, tissue factor/factor VIIa; Xa, factor Xa; IIa, thrombin. Content adapted from Weitz and Bates [19].

Table 1

Applications for orally active direct anticoagulants

	DVT PREVENTION	DVT TREATMENT	AFIB	ACS
Rivaroxaban (Xarelto®)	Approved [14]	Approved [15]	Approved [7]	Improved survival [16] Not yet approved
Dabigatran (Pradaxa®)	Approved [17]	Approved [18]	Approved [6]	No benefit Trend toward increased myocardial infarction Trial halted

DVT, deep vein thrombosis; Afib, atrial fibrillation; ACS, acute coronary syndrome.