Brief Review

Impact of Non–Vitamin K Antagonist Oral Anticoagulants From a Basic Science Perspective

Maureane Hoffman, Dougald M. Monroe

Abstract—The biochemical properties of the non–vitamin K antagonist oral anticoagulants (NOACs) and their differences from the mechanism of action of vitamin K antagonists contribute to their properties as anticoagulants. These properties include as follows: (1) Inhibiting a single protease is much less effective at inhibiting coagulation than is inhibiting at multiple steps. Thus, the dose–response relationship between NOAC level and intensity of anticoagulation is shallower and more linear than that of vitamin K antagonists. This partially accounts for the greater safety of NOACs than vitamin K antagonists reported in some studies. (2) Because they are small molecules, NOACs can reach their target proteases in locations that plasma protease inhibitors, such as antithrombin, cannot. (3) NOACs compete with substrates for binding at the active site of the target protease and that binding is reversible. When the drug level falls, the drug dissociates from its target, and protease activity is restored. Thus, there is the possibility of a rebound in procoagulant activity if the drug is abruptly terminated. (4) The effects of a NOAC can be overcome by increasing the amount of substrate available for the target protease or the amount of protease produced. This property may contribute to the safety of NOACs and their potential reversibility by coagulation factor concentrates. The biochemical properties of NOACs contribute to their suitability for use in conditions that require a predictable moderate degree of anticoagulation when administered orally at a consistent dose. Their effects can be overcome by a sufficiently strong procoagulant stimulus. This characteristic likely contributes to their generally reduced risk of serious bleeding. However, they are not well suited for use in settings that require a profound degree of anticoagulation.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2017;37: 1812-1818. DOI: 10.1161/ATVBAHA.117.306995.)**

Key Words: anticoagulants ■ hemostasis ■ protease inhibitors ■ thrombosis ■ vitamin K

When a new class of drug reaches the market, clinicians need to learn how to use it. No matter how well done the clinical trials with the new drug, there is no substitute for real world experience. However, it is useful to also consider the likely consequences of the biochemical, mechanistic, and pharmacological features of new drugs and how those might be similar to or different from the existing agents.

Non–vitamin K antagonist oral anticoagulants (NOACs), also referred to as direct oral anticoagulants, have been rapidly adopted because of the well-recognized difficulties in managing anticoagulation with vitamin K antagonists (VKAs), such as warfarin. VKAs were first promoted as rodenticides, but warfarin was subsequently introduced as an anticoagulant under the trade name Coumadin.[1] It achieved wide acceptance after 1955 when it was administered as an anticoagulant to President Eisenhower after a heart attack. The first randomized clinical trial of a VKA was published in 1960, showing it to be highly effective in preventing recurrence or extension of pulmonary embolism.[2] VKAs have continued to be widely used up through the present time because until recently they were the only orally active anticoagulants available.

Clinical trials show the NOACs as a group to be at least as effective in preventing thrombosis as warfarin for most indications and less likely to be associated with serious bleeding complications.[3–5] They are also more convenient for doctor and patient—no routine monitoring and little need for dose adjustment. This is because the pharmacokinetic properties of NOACs are more predictable and there are fewer food and drug interactions than with the VKAs. Of course, the NOACs are not perfect drugs. Like all anticoagulants to date, they are associated with a risk of bleeding. They are also much more expensive than VKAs, blood levels are more difficult to assay when needed, and agents to reverse their anticoagulant effects are less readily available.[6] Their characteristics have been reviewed many times in the literature (See, for example, the following references [7–10]). There are also several ways in which the NOACs are mechanistically different from VKAs that are not so widely appreciated or discussed. The goal of this brief review is to point out some of these characteristics and highlight their potential clinical implications.

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Nonstandard Abbreviations and Acronyms	
FXa	factor Xa
NOAC	non–vitamin K antagonist oral anticoagulant
SERPIN	serine protease inhibitor
TF	tissue factor
UFH	unfractionated heparin
VKA	vitamin K antagonist

What Is So Different About NOACs?

NOACs Are Inhibitors Rather Than Inactivators

The NOACs are orally active small molecule inhibitors (<500 MW) that each has high specificity and relatively high affinity for a single coagulation protease. At the present time, there is 1 such inhibitor of thrombin on the market, dabigatran (Pradaxa, Boehringer Ingelheim) and 4 factor Xa (FXa) inhibitors (rivaroxaban [Xarelto, Bayer Pharma/Janssen Pharmaceuticals], apixaban [Eliquis, Bristol-Myers Squibb/Pfizer], edoxaban [Savaysa/Lixiana, Daiichi Sankyo], and betrixaban [Bevyxxa, Portola]). It is certainly possibly that in the future there will be direct inhibitors of other proteases as well, such as FIXa or FXIa.

The NOACs bind at the active sites of coagulation enzymes. Thus, each competes for binding at the active site with substrates of its target protease. Small molecule substrates of the coagulation proteases, such as the chromogenic substrates used in activity assays, usually bind solely at the active site. Such interactions occur in solution and fit neatly into the framework taught in undergraduate biochemistry class. NOACs are competitive inhibitors in this scenario: substrate and inhibitor bind to the same site on the enzyme, both cannot be bound simultaneously, and the presence of the inhibitor affects the Km, but not the Vmax of the reaction. Sadly for those of us who are not kineticists, the physiologically relevant reactions of the coagulation proteases are not that simple. Most of the coagulation proteases act in concert with a protein cofactor and on a cellular surface rather than in solution. The biological substrates of coagulation proteases are themselves large proteins. These macromolecular substrates bind not only at the enzyme's active site but also at additional sites (called exosites) away from the active site. They may also bind to the membrane surface on which the active complex is assembled. Many of these macromolecular substrates are also cleaved at more than 1 site. For example, prothrombin is activated by FXa in complex with its cofactor FVa (prothrombinase complex). When this complex is assembled on the surface of activated platelets, prothrombin binds and is cleaved first at Arg-271 followed by cleavage at Arg-320, without dissociating from the complex.[11] Interestingly, when prothrombinase complexes assemble on synthetic phospholipid vesicles or red blood cells, prothrombin is cleaved first at Arg-320.[12] The resulting intermediate (meizothrombin) dissociates from the surface, rebinds, and is cleaved at Arg-271 to produce thrombin. In summary, the binding and activation of prothrombin by FXa/FVa is complex, and it is influenced by the lipid surface and involves interactions with multiple sites on FXa. Therefore, it should come as no surprise that the precise kinetic effects of a small molecule FXa inhibitor on such an intricate process are also not straightforward and are beyond the scope of this review.

The fact that NOACs interact with the active site of the target protease means that binding only occurs after the zymogen form of the target protease has been activated by the coagulation reactions. By contrast, VKAs reduce the effective plasma levels of all of the vitamin K–dependent coagulation zymogens. They do this by interfering with post-translational carboxylation of specific glutamic acid residues that are critical for activity. While the proteins are synthesized, their undercarboxylated forms do not have normal activity. VKAs thereby reduce the levels of active proteases that can be produced in response to a procoagulant stimulus rather than inhibiting them after they have been activated.

The NOACs are inhibitors of coagulation factors rather than inactivators. The primary physiological regulators of factors IXa, Xa, and thrombin are the plasma serine protease inhibitors (SERPINs) antithrombin and α-1-proteinase inhibitor, with contributions from the non-SERPIN inhibitor α-2-macroglobulin. Like the NOACs, SERPINS and α-2-macroglobulin only interact with coagulation factors after they have been activated to functional proteases. However, SERPINS and α-2-macroglobulin inactivate their target proteases by formation of complexes that are essentially irreversible.[13,14] By contrast, the NOACs form reversible complexes with the active site of their target proteases.

NOACs Inhibit a Single Protease Instead of Many

By contrast to the highly specific NOACs, warfarin and other VKAs interfere with the γ carboxylation of all vitamin K–dependent coagulation factors. In effect, VKAs lower the plasma level of multiple procoagulant factors (FII, VII, IV, and X), as well as the antithrombotic factors protein C, S, and Z.[15] Because multiple factors are affected, the net effect of any given dose or plasma level of a VKA is difficult to predict. By contrast, with the direct inhibitors, the relationship between the plasma level of a direct inhibitor and the degree of protease inhibition is much more predictable.

The unpredictability of VKAs is also because of variability in absorption and metabolism of the drug, as well as variability in baseline levels of coagulation factors between individuals. Because of the many variables that can impact the degree of anticoagulation by VKAs and their narrow therapeutic window, routine laboratory monitoring is necessary. The prothrombin time has been used empirically and standardized as a measure of the overall VKA effect in an individual.[16]

The other anticoagulants backed by extensive clinical experience are unfractionated heparin (UFH) and low molecular weight heparins. Neither UFH nor low molecular weight heparins directly inhibits coagulation proteases. Both accelerate antithrombin inactivation of proteases. UFH accelerates inactivation of all of the coagulation proteases to some degree. Low molecular weight heparins primarily accelerate inactivation of Fxa but can also enhance inactivation of other factors to lesser extents. In all cases, even after the heparins are cleared from the plasma, the proteases do not dissociate from antithrombin and regain activity.

Similar to VKA's, the effect of UFH in any given individual is unpredictable. Thus, the activated partial thromboplastin time has been used empirically to monitor the net anticoagulant effect of UFH. It should be noted that the prothrombin time and activated partial thromboplastin time are prolonged to a much great degree by drugs that inhibit multiple proteases (VKAs and UFH) than by drugs that only inhibit 1 protease (NOACs, low molecular weight heparins, fondaparinux, and bivalirudin). Fondaparinux is a pentsaccharide that can be thought of as the lowest molecular weight heparin. It binds to antithrombin and enhances its ability to inhibit FXa, with little ability to enhance antithrombin inhibition of other proteases. Like other heparin-like agents, it must be administered parenterally. Bivalirudin is a specific direct inhibitor of thrombin that also must be administered parenterally. None of these specific inhibitors prolong the common prothrombin time and activated partial thromboplastin time assays to a significant and predictable degree. Thus, they all require more specialized and expensive testing to assay.

How Do NOACs Exert Antithrombotic Effects?

There exists a considerable body of evidence supporting the premise that the amount and pattern of thrombin generated in response to a procoagulant signal reflect the adequacy of hemostatic function[17–19] and the risk of thrombosis.[20] Several assays, both commercial and homemade, have been used to assess the pattern of thrombin generation in response to a procoagulant signal using platelet-rich or platelet-poor plasma. In these assays, the level of thrombin activity is assessed as the amount of a chromogenic or fluorogenic substrate that is cleaved over the course of the reactions. This can be monitored continuously by initiating the coagulation reactions in the presence of the thrombin substrate or by taking samples from the reaction mixture and transferring them into a solution of the thrombin substrate. Although thrombin generation assays are not yet practical or sufficiently standardized for routine clinical use, they have been widely used as a research tool. However, it is not clear which parameter(s) derived from thrombin generation assays best predict either hemostasis or thrombosis. At least in theory, there should be a sweet spot in the parameters of thrombin generation that reflects a state in which the risk of thrombosis is minimized while the ability to attain hemostasis is optimized.

In contrast to their effects on the prothrombin time and activated partial thromboplastin time assays, the effects of NOACs on thrombin generation can be readily demonstrated. However, they are not as predictable as one might expect. The response of thrombin generation parameters to increasing NOAC concentrations is certainly not linear and seems to show threshold effects in some cases. The points of inhibition by NOACs are often represented in a coagulation cascade model (Figure 1). Viewed in this context, it seems that both FXa and thrombin (FIIa) inhibitors should reduce the effective amount of thrombin available to clot fibrinogen. Although this view is clear and useful for illustrating the different proteases inhibited by these agents, the situation in vivo is more complex and subtle than represented in this model. A cell-based model of coagulation better represents hemostatic coagulation in vivo. In this model,

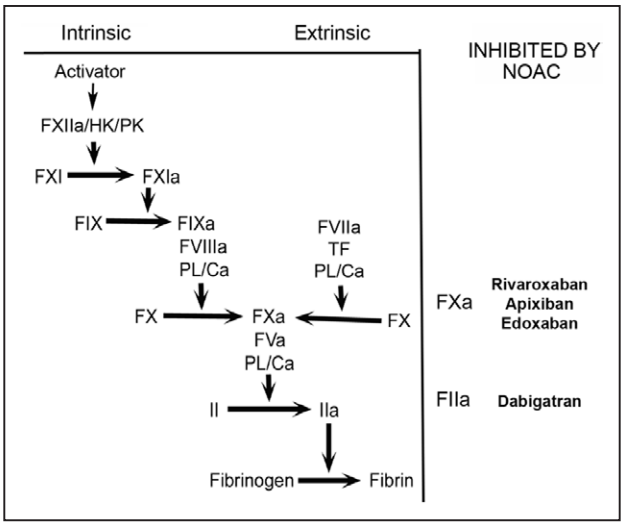

Figure 1. Targets of non–vitamin K antagonist oral anticoagulants (NOACs) in the cascade model of coagulation. FXa indicates factor Xa; HK, high-molecular weight kininogen; PK, prekallekrein; PL, phospholipid; and TF, tissue factor.

the process of thrombin generation is viewed as occurring on cell surfaces in overlapping phases (Figure 2) rather than as a continuous cascade of thrombin generation.

In a cell-based model,[22] the initiation phase of blood coagulation results in production of small amounts of thrombin on tissue factor (TF)–bearing cells. TF is normally separated

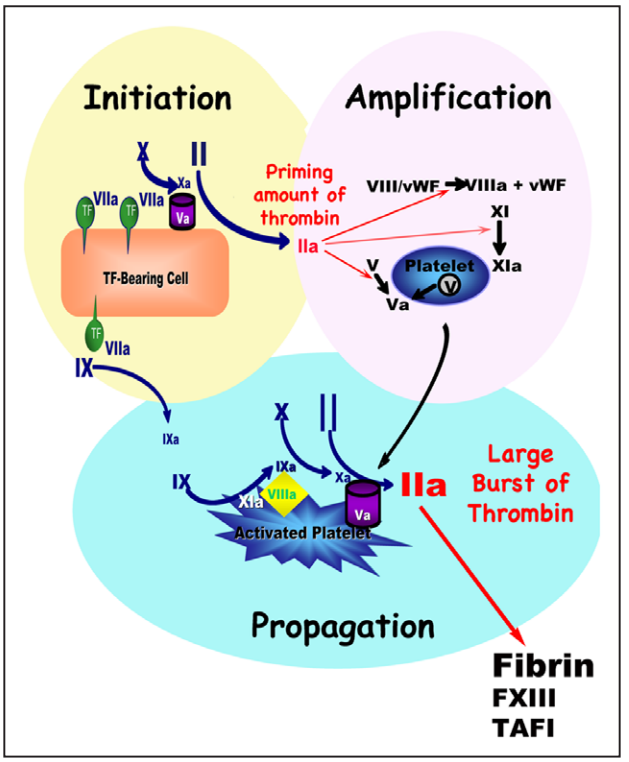

Figure 2. A cell-based model of coagulation. FXIII indicates factor XIII; TAFI, thrombin-activatable fibrinolysis inhibitor; and vWF, Von Willebrand factor. Adapted with permission from Hoffman and Cichon.[21] Copyright ©2013, John Wiley & Sons, Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

from the blood by an intact vessel wall. TF is expressed at high levels around the adventitial surface of vessels, as well as by epithelial cells, and at sites where bleeding could be catastrophic (brain, lungs).[23,24] This pattern of TF localization has been described as a hemostatic envelope to stop bleeding at sites of injury. When the vessel wall is breached, extravascular TF-bearing cells come in contact with blood components. Platelets adhere to collagen and other exposed extracellular matrix proteins near the site of injury and are partially activated.

Thrombin produced on TF-bearing cells then drives several positive feedback loops on platelet surfaces during the amplification phase of coagulation. If the procoagulant stimulus is sufficiently strong, the amplification process succeeds in setting the stage for large-scale platelet-surface thrombin generation in the propagation phase of coagulation. This burst of thrombin is necessary to stabilize the initial platelet plug in a stable fibrin clot. The hemostatic clot is further stabilized by activation of thrombin-activatable fibrinolysis inhibitor and FXIII. Active thrombin also remains bound within the fibrin clot, where it can rapidly cleave additional fibrinogen and reinforce the clot structure if it is mechanically or enzymatically disrupted.

Viewed in this way, the intrinsic and extrinsic pathways are not redundant as they seem to be in the cascade model. Instead, they carry out distinct functions on different cell surfaces—each of which depends on thrombin generation. The extrinsic pathway acts on TF-bearing cells to produce the small, but critical, amounts of thrombin needed for amplification of the initial procoagulant signal. Components of the intrinsic pathway act on the surface of activated platelets to produce large amounts of thrombin required for formation of a stable fibrin clot. Thus, there are 2 key points at which a NOAC thrombin or FXa inhibitor can act to impair clotting (Figure 3): (1) at level of thrombin-driven feedback loops—thus blocking amplification, and (2) at the level of the burst of platelet-surface thrombin generation.

Although thrombin is a critical mediator at each of these phases, NOACs that directly target thrombin are mechanistically distinct from NOACs that target thrombin production by inhibiting FXa. A direct FXa inhibitor acts to reduce the amount of thrombin generated while a direct thrombin inhibitor inhibits the thrombin after it is already formed (Figure 3).

The NOACs are small molecules and have properties that are different from the naturally occurring inhibitors of coagulation proteases. The physiological inhibitors, antithrombin and tissue factor pathway inhibitor are large proteins, ≈58 kDa and 34 to 40 kDa, respectively. Thus, antithrombin is sterically hindered from interacting with thrombin that is sequestered within a fibrin clot or bound to a cofactor, such as thrombomodulin. Likewise, FXa on a platelet surface is relatively protected from inhibition by either antithrombin or tissue factor pathway inhibitor. Thus, the plasma inhibitors are important control mechanisms that localize the coagulation reactions to specific cell surfaces and prevent thrombin generation from occurring in the fluid phase (disseminated intravascular coagulation) or spreading within the vascular tree (thrombosis). However, they allow coagulation to proceed on appropriate cell surfaces.

By contrast, NOACs can inhibit thrombin and FXa at sites on cell surfaces where they are relatively inaccessible to the plasma protease inhibitors.[25] They can also reach their target proteases within the structure of a fibrin clot. Thus, NOACs can inhibit coagulation by acting at sites where the natural inhibitors are ineffective. However, the activity of thrombin can be changed dramatically by binding to different cofactors. For example, thrombin bound to thrombomodulin on the surface of healthy endothelial cells cannot clot fibrinogen but instead can activate protein C and exert an antithrombotic effect. Dabigatran not only inhibits the procoagulant effects of thrombin but also inhibits thrombin in complex with thrombomodulin,[26] thereby reducing protein C activation and potentially exerting an unintended prothrombotic effect.

In thrombin generation assays, and likely in vivo, the rate of thrombin generation is a measure of hemostatic effectiveness. The rate of thrombin generation reflects both the number of functional FXa/Va complexes on platelets and the amount of prothrombin available as a substrate for those FXa/Va complexes. The VKAs alter thrombin generation by reducing the levels of FIX, FX, and prothrombin. The reduced levels lead to less FX available to be activated and less FIXa to active FX;

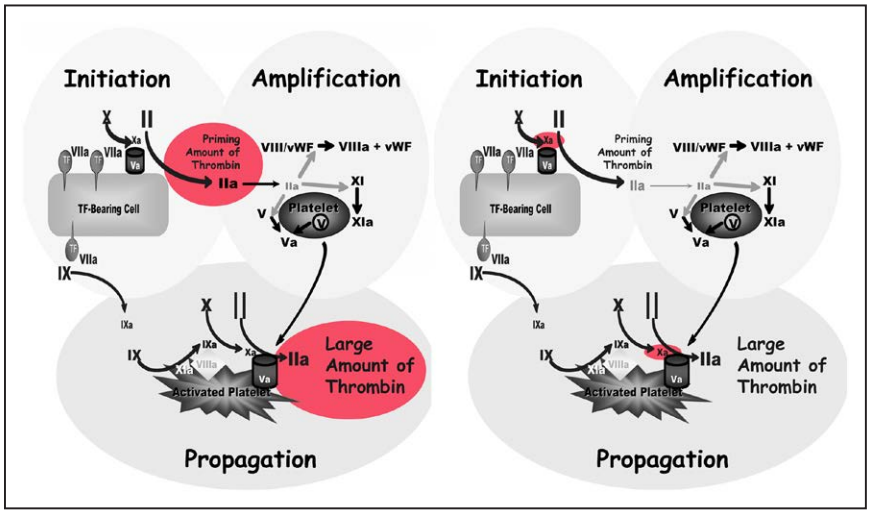

Figure 3. The targets of non–vitamin K antagonist oral anticoagulants in a cell-based model of coagulation. Factor Xa (Fxa) inhibitors (**left**) exert anticoagulant effects by preventing thrombin generation during the initiation and propagation phases. Thrombin inhibitors (**right**) directly inhibit thrombin from cleaving its protein substrates during the amplification phase and after it is formed in the propagation phase. TF indicates tissue factor; and vWF, Von Willebrand factor.

overall, this reduces the number of FXa/Va complexes. The reduced levels of prothrombin further slow the rate of thrombin generation. So overall, VKAs predominantly impact the propagation phase of thrombin generation.[27]

In our own data and that of several other workers, dabigatran and other direct thrombin inhibitors seem to have a primary effect by slowing or blocking the amplification phase of coagulation. This delays or prevents large-scale thrombin generation. In a thrombin generation assay, this is seen as a prolongation of the lag before onset of detectable thrombin generation. When the level of thrombin produced exceeds some threshold, the burst of platelet-surface thrombin generation ensues. The activity of the thrombin generated during the propagation phase is also blunted by the presence of a thrombin inhibitor. However, thrombin is generated at a sufficient rate to be detected in the thrombin generation assay. Thus, a thrombin inhibitor is most effective as an anticoagulant if it can prevent the burst of platelet surface thrombin generation from ever getting started. The in vivo reflection of this mechanism is likely that a thrombin inhibitor can prevent coagulation from even being launched at inappropriate sites, yet allow coagulation to proceed if the procoagulant stimulus is sufficiently strong.

Direct FXa inhibitors increase the lag phase to a limited extent by delaying thrombin generation during the initiation phase. However, their dominant effect is to decrease the rate of thrombin generation during propagation by inhibiting a fraction of the platelet-surface FXa/Va complexes. The effects of rivaroxaban on thrombin generation are shown in Figure 4.

Observations on the Inhibitory Properties of NOACs

NOACs Do Not Completely Inhibit the Target Protease

The ability of a strong procoagulant stimulus to overcome the anticoagulant effect of an inhibitor is inherent in its mechanism of action. The free and bound forms of a reversible inhibitor (dabigatran in this example) with its target protease (thrombin) reach a state of equilibrium. The proportion of the thrombin molecules that are in the bound (inhibited) form can be calculated from the concentrations of the reactants (thrombin and dabigatran) and the affinity of the inhibitor for its target protease. The higher the concentration of dabigatran, the greater will be the proportion of the thrombin that is inhibited. However, there will always be some thrombin molecules that are not inhibited. If more thrombin is generated, the level of free (active) thrombin will increase at any given concentration of dabigatran. Thus, the effect of the inhibitor could be overcome if the procoagulant stimulus is sufficiently strong and, therefore, the total amount of thrombin generated is sufficient to trigger the burst of platelet surface thrombin generation.

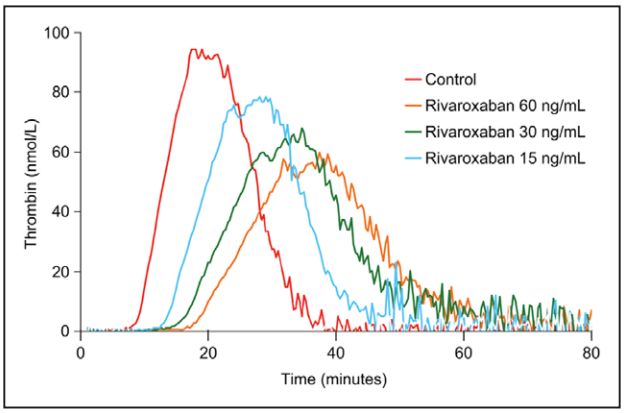

Figure 4. Effect of rivaroxaban on a thrombin generation assay. The curves represent the level of thrombin activity triggered by 0.5 pmol/L tissue factor in platelet-rich plasma at the indicated concentrations of rivaroxaban. There is a concentration-dependent decrease in the rate of thrombin generation and a less pronounced decrease in the peak thrombin level. Modified with permission from Perzborn et al.[28] Copyright ©2015, the Authors.

We speculate that this could be the reason that intracranial bleeding is reported to be lower with some NOACs than VKAs.[29–31] The brain contains extremely high levels of TF, the main initiator of coagulation. Thus, exposure of blood to brain tissues could constitute a sufficiently strong stimulus to overcome the inhibitory effect of a therapeutic level of NOAC anticoagulation.

In addition, the ability of a greater rate/amount of protease activation to overcome the effects of a NOAC likely accounts for the ability of prothrombin complex concentrates to reverse their anticoagulant effect.[32] Administration of prothrombin complex concentres raises the plasma levels of FVII, FIX, FX, and prothrombin and leads to a greater rate of FX and prothrombin activation. The increased production of FXa and thrombin would increase the amount of active thrombin available to support hemostasis.

NOAC Inhibition Is Reversible

A key biochemical property of NOACs is their reversibility. This is in contrast to the effects of VKAs, UFH, antithrombin, and other SERPINs, and α-2-macroglobulin, which are effectively not reversible. Thrombin generation assays also reveal a surprising result of the reversible nature of NOAC inhibition. Because dabigatran blocks the active site of thrombin, it blocks all active site functions, including preventing inactivation by antithrombin and other inhibitors.[33] Commonly used thrombin generation assays (left panel of Figure 5, assays conducted as in 34) show how much free, that is, active, thrombin is present at a given point in time. So the assay detects neither thrombin inactivated by antithrombin nor thrombin inhibited by dabigatran. Increasing concentrations of dabigatran markedly increase the lag time, with a less dramatic effect on the rate of thrombin generation and peak thrombin level attained. These effects are seen over a range of dabigatran concentrations attained during anticoagulant in vivo.

By contrast, a modified thrombin generation assay (right panel of Figure 5) detects thrombin that has not been permanently inactivated by antithrombin. In this assay, thrombin generation is again triggered in platelet-rich plasma containing different levels of dabigatran. Samples are removed at timed intervals and added to an assay mixture containing a chromogenic substrate for thrombin. Sampling into the assay mixture dilutes all of the plasma components. This results in

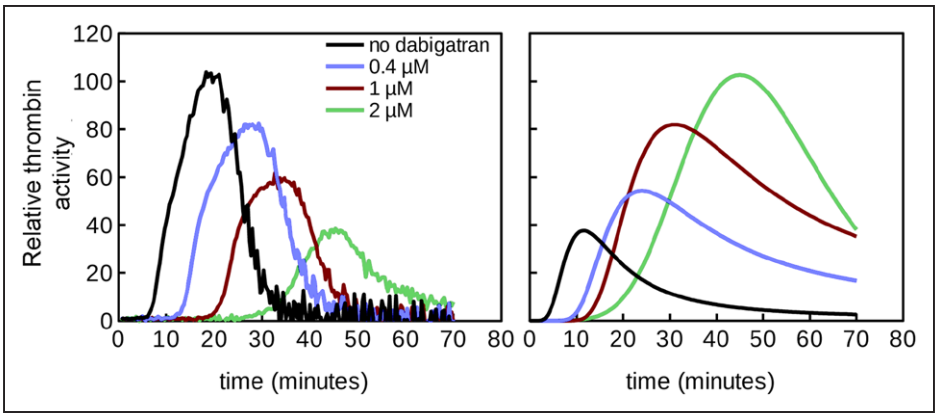

Figure 5. Dabigatran protects thrombin from inhibition by antithrombin. **Left**, Level of thrombin activity when measured in platelet-rich plasma in a thrombin generation assay at the indicated concentrations of dabigatran. **Right**, Active thrombin measured when samples are taken from the thrombin generation assay and diluted into a solution of chromogenic substrate. Under the latter conditions, the dabigatran is diluted and dissociates from thrombin to regenerate the active protease. If the inhibitor were not present (black line), some of the thrombin would be irreversibly inhibited by antithrombin. Thus, dabigatran does not reduce thrombin generation but rather inhibits the thrombin that is generated and protects it from antithrombin.

the dabigatran concentration falling to a level at which the equilibrium between free (active) thrombin and bound (inhibited) thrombin favors the free form. Thus, the activity of the thrombin that had been reversibly inhibited by dabigatran, but protected from inactivation by antithrombin, is revealed. In this modified assay, the expected increase in the lag time is seen. But one can also see an increase in the amount of thrombin that was not inactivated by antithrombin. It is clear that a large amount of thrombin has been protected from inactivation and can express its activity as the dabigatran level falls.[26]

The in vivo consequences of the reversibility of a coagulation protease inhibitor are not completely clear, but we hypothesize the following. The NOACs have short half-lives relative to VKAs. Thus, the plasma levels rise and fall between doses. This means that the extent of thrombin inhibition rises and falls. This effect is exacerbated if more than 1 doses of drug are missed. When the drug level falls, the reservoir of thrombin that has been sequestered within a fibrin/platelet clot can regain activity. Potentially, this thrombin could have procoagulant activity and contribute to rebound hypercoagulability if the dabigatran level falls sufficiently. However, this thrombin can now be inactivated by the physiological inhibitors, including antithrombin. If the fall in dabigatran levels is slow, antithrombin inactivation might prevent the accumulation of sufficient free thrombin to have any biological effect. Thus, the overall clinical effect in vivo is difficult to predict.

The same reversibility would be seen for FXa inhibitors.[25] Because much less FX (on a molar basis) is activated during hemostasis than thrombin, we would not expect as large a reservoir of FXa activity to be revealed as the levels of an FXa inhibitor fall. However, to our knowledge, the reactivation of FXa activity on platelet surfaces or within a fibrin clot has not been studied.

In summary, the biochemical properties of the new generation of reversible active site inhibitors of coagulation proteases are significantly different from the commonly used anticoagulants to which we are accustomed. The properties of the NOACs as therapeutic agents remain to be fully explored. However, a consideration of their biochemical features can help us understand their pharmacological effects and provide a rationale for therapeutic strategies using these agents.

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Highlights

- Inhibiting one protease is much less effective at inhibiting coagulation than is inhibiting at multiple steps. Thus, non–vitamin K antagonist oral anticoagulants (NOACs) are less able to achieve intensive anticoagulation than are vitamin K antagonists or heparin. The more linear relationship between drug level and inhibitory effect makes it easier to reach the sweet spot in the desired intensity of NOAC anticoagulation. This partially accounts for why the NOACs are safer than vitamin K antagonists.
- NOACs can reach their target proteases at sites that naturally occurring plasma protease inhibitors, such as antithrombin, cannot, including on the platelet surfaces and within a fibrin clot.
- NOACs are reversible inhibitors. When the drug level falls, the drug dissociates from its target and active protease is released. In addition, the presence of a NOAC prevents antithrombin from inactivating the protease. Thus, there is the possibility of a rebound in procoagulant activity if the drug is abruptly terminated.
- The effects of NOACs can be overcome by increasing the amount of protease production. At any given drug level of drug, there will be a fixed proportion of the target protease that is not inhibited. When production of the target protease is increased, the amount of active protease will also be increased. This property may contribute to the safety of NOACs and their potential reversibility by coagulation factor concentrates.

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