

## Monitoring anticoagulant therapy with new oral agents

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### Abstract

Thromboembolic disease is a major leading cause of mortality and morbidity in industrialized countries. Currently, the management of these patients is challenging due to the availability of new drugs with proven efficacy and security compared to traditional oral vitamin K antagonists. These compounds are characterized by a predictable pharmacokinetic profile for which blood monitoring is not routinely needed. Nevertheless, some data have suggested

inter-patient variability in the anticoagulant effect of these drugs, raising concerns about their effectiveness and safety. Although mass-spectrometry is the gold standard to determine drug plasma concentrations, this method is not widely available in every-day practice and some coagulation assays are commonly used to determine the anticoagulant effect of these drugs. The present review aims to summarize the current knowledge regarding the clinical question of how and when to monitor patients with new anticoagulant oral agents.

**Key words:** Anticoagulant agents; Apixaban; Dabigatran; Drug monitoring; Rivaroxaban

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**Core tip:** New oral anticoagulants are replacing oral vitamin K antagonists for some practical advantages, like unnecessary monitoring and a better pharmacokinetic profile. Nevertheless, in some circumstances, their anticoagulant activity must be monitored in order to prevent adverse outcomes. In this minireview a list of the available laboratory test are reviewed to better understand the pros and cons of each analysis.

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### INTRODUCTION

The management of thromboembolic disease has always been challenging since current treatments involve an inherent risk of bleeding that must be counterbalanced by the anticoagulant effect of each drug.

The use of vitamin K antagonists, such as warfarin, implies the monitoring of their anticoagulant effect through frequent blood tests and the education of patients about

**Table 1 Pharmacokinetic features of new oral anticoagulants<sup>[11,12]</sup>**

	Apixaban	Rivaroxaban	Dabigatran
Posology	Twice daily	Once daily	Twice daily
Oral bioavailability	45%	> 80%	6%
Half life	12 h	7-11 h	12-17 h
Excretion	25% renal	66% renal (active and inactive)	80% renal

potential drug and food interactions, making their use puzzling and difficult for many clinicians. In contrast, new agents have shown some advantages over vitamin K antagonists, since no dose adjustment and monitoring is routinely needed, as a consequence of a "more favorable pharmacokinetic profile". In addition, these new drugs, usually mentioned as new oral anticoagulants (NOACs), have demonstrated clinical efficacy and a better security profile than warfarin in various clinical trials, making attractive their use in clinical practice<sup>[1-3]</sup>.

However, recent data have emerged regarding a potential role for monitoring the anticoagulant effect of these drugs particularly in patients with specific circumstances and comorbidities in order to reduce side effects and improve efficacy<sup>[4-7]</sup>.

Some recommendations to measure the anticoagulant effect of NOACs include the following scenarios<sup>[8,9]</sup>: (1) Bleeding or recurrence of thrombosis; (2) Before surgery or any invasive procedure when the patient has taken the drug in the previous 24 h or longer if creatinine clearance is less than 50 mL/min; (3) Identification of supra or subtherapeutic levels in patients taking other drugs with potential interactions, or in patients with extreme body weight; (4) Patients with renal failure or prompt to it; (5) Reversal of anticoagulation; (6) Suspicion of drug overdose; (7) Patients with genetic mutations (e.g., rs2244613 minor allele carriers for dabigatran etexilate); and (8) Assessment of compliance.

Although it is desirable to explore the anticoagulant effect of these drugs in the aforementioned circumstances, some cons have also emerged and detractors of routine monitoring include the following reasons in their arguments<sup>[10]</sup>: (1) Lack of measures in clinical trials; (2) Wide therapeutic window of some of these agents; (3) There is no a standardized clinical method to detect the anticoagulant effect or it is not yet available; and (4) The interpretation and dose adjustments have not been established.

## PHARMACOLOGY OF NOACS

NOACs are categorized according to their site of action; apixaban and rivaroxaban act by inhibiting factor Xa, thereby decreasing the conversion of prothrombin to thrombin. On the other hand, dabigatran acts by directly inhibiting thrombin. Table 1 summarizes some pharmacokinetics features of clinical utility for these agents. Of particular interest is the renal clearance of these drugs that modifies

or prohibits their use in case of severe kidney failure.

Although it is thought that there are fewer drug interactions for NOACs than for warfarin, clinical data suggest moderate to severe drug-drug interactions when dabigatran is used in combination with verapamil, amiodarone, and dronedarone<sup>[13,14]</sup>.

Similarly, some other drugs commonly known as CYP inhibitors such as ketoconazole, itraconazole, macrolides, human immunodeficiency virus protease inhibitors can increase the serum NOACs concentration. On the other hand, some CYP inducers, such as phenytoin, phenobarbital, rifampicin and carbamazepine can decrease the anticoagulant effect of NOACs and thus are not generally recommended in these patients.

## DETERMINING ANTICOAGULATION LEVELS WITH THE NOACS

The gold standard to measure plasma drug concentrations is mass-spectrometry. Nevertheless, the availability and laboratory expertise for doing this specialized technique is not fulfilled in the majority of clinical centers. For this reason, some other test must be carried out in order to determine the anticoagulant effect of NOACs. Table 2 resumes the advantages and drawbacks of available coagulation tests that have been used to determine the anticoagulant effect of NOACs in clinical settings.

### Dabigatran

**Activated partial thromboplastin time and thrombin time:** These are very sensitive assays that do not accurately reflect plasma dabigatran concentrations. Although they are widely available, they are affected by a lot of variables such as inappropriate collection, improper handling and storage. Besides neither are strong predictors of bleeding, and patients may present any kind of hemorrhage even when the activated partial thromboplastin time and/or thrombin time are within normal range<sup>[15]</sup>.

**Diluted thrombin time:** Since assays to evaluate thrombin activity are very sensitive to determine the anticoagulant effect of dabigatran, the use of diluted plasma in conjunction with the Hemoclot thrombin inhibitor permits to easily measure dabigatran anticoagulant activity<sup>[16]</sup>.

### Ecarin clotting time and ecarin chromogenic assay:

These assays are not widely available and calibration is required to perform these tests. They use a metalloprotease called ecarin and are very specific for anti thrombin inhibitors due to the fact that prothrombin is a substrate for these analyses<sup>[17]</sup>.

### Rivaroxaban

**Prothrombin time:** The Subcommittee of Control of Anticoagulation of the Scientific and Standardization Committee recommends that this assay can determine the relative intensity of anticoagulation in patients taking

**Table 2 Available coagulation tests to determine the anticoagulant effect of oral anticoagulants**

Drug	Coagulation test	Pros	Cons
Dabigatran	aPTT	Highly available	Do not reflect the intensity of coagulation Low specificity
	TT	Highly available	It only determines the effect of dabigatran but lacks specificity
	dTT	Very accurate and precise to estimates plasma concentrations of dabigatran	Requires specific calibrators and controls in specialized laboratories with trained personal Low specificity
	ECT		Requires specific calibrators and controls in specialized laboratories with trained personal Limited standardization and validation required Low specificity Interlot variability reported
	ECA	Very accurate and precise to estimates plasma concentrations of dabigatran	Requires specific calibrators and controls in specialized laboratories with trained personal Low specificity
	DRVV-T		Requires specific calibrators and controls in specialized laboratories with trained personal Low specificity
Rivaroxaban	PT	Highly available	Do not reflect the intensity of coagulation Low specificity
Rivaroxaban and Apixaban	Chromogenic anti-Xa assays	Very accurate and precise to estimates plasma concentrations of dabigatran	Requires specific calibrators and controls in specialized laboratories with trained personal
	DRVV-T		Requires specific calibrators and controls in specialized laboratories with trained personal Low specificity

Any of these tests have been associated with clinical endpoints and data regarding their use in special populations are scarce. aPTT: Activated partial thromboplastin time; DRVV-T: Dilute Russell's viper venom time; dTT: Dilute thrombin time; ECA: Ecarin chromogenic assay; ECT: Ecarin clotting time; PT: Prothrombin time; TT: Thrombin time.

rivaroxaban but it is not useful to extrapolate plasma concentrations. Besides, it has different sensitivities according to the type of the employed reagent with high variability among laboratories<sup>[8,18]</sup>.

**Dilute Russell's viper venom time:** This is a useful test to determine the anticoagulant effect of Xa and thrombin inhibitors since Russell's viper venom contains a potent activator of factor X and II. Nevertheless, validation and calibrations are technical issues that must be explored in future trials to determine a valid cut off and their sensitivity is low<sup>[19]</sup>.

**Chromogenic anti-Xa assay:** Plasma concentrations of rivaroxaban and anti-Xa levels correlate fairly well and it is the preferred method to estimate plasma concentrations. This method is less affected by sample handling or clotting factors in patients. However, a major limitation is the standardization and the availability of laboratories with specific calibrators and controls<sup>[20]</sup>.

### Apixaban

**Dilute Russell's viper venom time:** As pointed before, this test is very useful and sensitive to determine the anticoagulant effect of apixaban, but with a low specificity.

**Chromogenic anti-Xa assay:** It is the most sensitive assay to determine the inhibition of factor Xa by apixaban and it is recommended to estimate plasma

concentrations of this drug. Nevertheless, this test is not widely available and it is time consuming<sup>[21]</sup>.

## SPECIAL CONSIDERATIONS

It is important to point out that any of these analyses have been tested in special populations such as elderly patients and children, as well as pregnant women and individuals with multiple morbidities<sup>[22,23]</sup>. Besides, some methodological issues regarding sample collection must be accomplished to avoid misinterpretations and biases. For example, plasma concentrations of the NOACs can vary among 10 to 20 times between peak and trough concentrations. Therefore, the assessment of the anti-coagulant activity of each drug should be obtained immediately prior to the next scheduled dose<sup>[22]</sup>. Furthermore there are few reports regarding a correlation between any of these tests and the efficacy and security of any NOAC and the clinical significance of these analyses must be interpreted cautiously.

## CONCLUSION

Despite of the potentials scenarios in which the role of monitoring the anticoagulant effect of NOAC can be clinically valid, it must be point out that there is no trial which has compared results of these drugs with or without coagulation monitoring and there are no guidelines to determine the steps to follow in order to improve the quality of the anticoagulation therapy.

Nevertheless, with the broad use of NOACs in clinical practice we must keep in mind the inter-patient variability of these drugs that can result in loss of efficacy and security.

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