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Laboratory Monitoring of DOACs? Merits & Pitfalls (Review Article with Latest Updates)

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Abstract: ***Background: DOACs are considered to be more effective and safer than warfarin, and offers several advantages such as predictable pharmacokinetics, allowing for standardized dosing without monitoring, a lack of food interactions and fewer drug interactions. This study's objective was to systematically review and summarize current evidence regarding laboratorymeasurement of the anticoagulant activity of dabigatran, rivaroxaban, and apixaban. Discussion: For Dibigatran, normal TT excludes clinically relevant drug levels and normal APTT excludes excess drug levels. The best monitoring tests for Dabigatran at therapeutic plasma concentration is Dilute TT, ECA & ACT. Rivaroxaban & Apixaban at therapeutic drug concentration can be best monitored by Anti-Xa assay & normal level excludes clinically relevant drug. Summary: Dabigatran, rivaroxaban, and apixaban exhibit variable effects on coagulation assays & same drug level affects differently in different persons. Studying pharmacokinetics, bioavailability half life and time dependent trough & peak plasma concentration of drugs aids in monitoring & interpretation of test results. Still research studies are required to gather thorough information on the relationshipbetween drug levels and clinical outcomes.***

Keywords: Direct thrombin inhibitors, Dabigatran, Rivaroxaban, Activated clotting time, APTT

Abbrevations: ACT = activated clotting time, ECT = ecarin clotting time, TT = thrombin time

1. DOACs - Updates

In 2010 a new category of anticoagulant drugs were developed & so initially these are called as "New oral anticoagulant agents" (NOACs), but now this term is replaced by DOACs ("direct oral anticoagulants")[1.]

Table I: Classification & Monitoring [2,3,4,5]

Anticoagulants drugs	MOA	Monitored
1) DOACs a) Dabigatran b) Rivaroxaban and Apixaban, Edoxaban	 DTI/ FIIa/Prothrombin FXa Inhibitor	 1) Anti IIa 2) TCT 3) ECT Anti Xa assay
2) SC c) LMWH d) Fondaparinux	 F Xa Inhibitor >FIIa F Xa Inhibitor	 Anti Xa assay Anti Xa assay
3) IV route e) Argatroban & Bivalirudin	 F IIa inhibitors	 1) APTT 2) ACT 3) ECT 4)Anti Xa
4) SC/IV f) UFH g) Danaproid	 F IIa = Xa F Xa	 1) APTT 2) Anti- IIa 3) Anti- XaAnti Xa assay

Action	Drug	Screening	Therapeutic monitoring
Anti-Vitamin K ⇒	Warfarin Syntrom ⇒	PT/INR ⇒	(PT/INR)
Anti-FII/FX ⇒	UHF ⇒	APTT ⇒	(APTT) Anti-FXa assay
Anti-FII/FX ⇒	LMWH Fondaparinux ⇒	None ⇒	Anti-FXa assay
Anti-FIIa ⇒	Dabigatran ⇒	APTT ⇒	dTT/ECT
Anti-FXa ⇒	Rivaroxaban ⇒	PT?	Anti-FXa assay calibrated aginst the specific drug
	Apixaban		
	Edoxaban		
	Betrixaban*		
	Darexaban*		
	Otamixaban*		
	Letaxaban*		
	Eribaxaban*		

Renal function (CrCl, ml/min	Estimated half-life(h)	Low bleeding risk (h)	High bleeding risk (h)
Dabigatran			
≥80	13	24	48
≥50 to <80	15	24-48	48-72
≥30 to <50	18	48-72	96
≥30	9	24	48
<30		48	72

Renal clearence

DOACs are better than traditional anticoagulants like LMWH, which has to be given. Sc, and for warfarin dosage has to monitored frequently and dose adjustment is needed. [2,4,5, 6,7]

Table 2: Comparison of DabigatranVsRivaroxaban

	Dabigatran	Rivaroxaban
Dosage	Taken orally, 150 mg od, 220 mg od,110 mg bd and 150 mg bd	Are 10 mg od and 20 mg od (15 mg bd for first 3 weeks of treatment of DVT
GFR & half life	GFR > 80 ml/min half life = 13 hours DTI (factor IIa) inhibitor	If GFR < 15 ml/min, it is contraindicated, if GFR=50ml/min, no dose adjustment. For bleeding patients, dialysis is not useful because rivaroxaban is protein-bound.Half life – 9 hours
Indications	Prophylaxis and Rx of VTE in major surgeries Treatment of Acute DVT and to prevent stroke and Emboli in AF, ACS	Rivaroxaban – No dose adjustment for patients > 75 years **Indications** **AF with risk of STROKE** - 20 mg/OD (recommended max dose) **Rx of Acute DVT /VTE**, start with 15 mg for first 3 weeks and then 20 mg. **VTE prophylaxis**: Hip and knee replacement surgery, 10 mg/OD and first dose is given 6-10 hours after surgery
Drug interaction	Tacrolimus, Ketoconazole, Ritonavir ↑ drug	Ketoconazole, ritonavir increases drug
Monitoring	**APTT** APTT – can be used to determine the relative intensity of dabigatran and it is usually prolonged by therapeutic doses of dabigatran, even at trough level. However, PTT cannot determine the drug level. The APTT dose-response curve relating dabigatran concentration and prolongation of APTT is curvilinear,flattening at higher concentrations (Lisenfeld et al, 2006; Van Ryn et al, 2010). This effect, coupled with the lack of specificity of APTT for the presence of drug, indicates that the APTT is unsuitable for quantification of drug. **ECT** – Linear dose response to therapeutic concentration **PT, APTT** - Insensitive (normal range does not exclude dabigatran) **Hemoclot Thrombin inhibitor assay** – sensitive for monitoring Dabigatran level/conc **ACT** – Non-sensitive Drug level can be determined by HPLC tandem mass spectrometry	ISI/INR system, derived from patients receiving vitamin K antagonists, is not valid for patients receiving other anticoagulants PT – is widely used, correlates well with the drug levels, results vary with the type of thromboplastin Conventional INR is used, for VKA is not suitable. Rivaroxaban INR= (PT Test⁄PT control) $^{\text{- ISI rivaroxaban}}$ Very much similar to liver ISI. FXa chromogenic assays and rivaroxaban standards are required and Xa assay is useful patients with in bleeding or the risk of bleeding. **PT is** sensitive to measure the intensity of rivaroxaban but it shouldn't be used to measure drug level. **ECT** – not effected by rivaroxaban Anti-factor Xa assays are sensitive to rivaroxaban (Samama et al, 2010) and can be measured by HPLC tandem mass spectrometry.

- Thrombophilia testing is best avoided during therapy with DTIs, but if activated protein C resistance (APCR) testing isbeing performed to exclude FV Leiden; genetic testing is preferred because it would not be affected by the presence of DTIs.
- Factor Xa-based assays of antithrombin are preferred over thrombin-based assays. Chromogenic or antigen assays are preferable to clot-based assays of protein C and protein S in the presence of DTIs.
- Fibrinogen should be determined using assays in which dabigatran has minimal influence.
- Clotting factor assays performed in the presence of dabigatran should include multiple test plasma dilutionsand an assessment of parallelism.

Table 3: Effect of DOAC on special coagulation tests[3,6,7,8]

Factors	Dabigatran effect and corrective measures	Rivaroxaban effect and corrective measures
Factors 2, 5, 7, 8, 9, 10, 11 Correction	Underestimated by clot-based assays (Factor 2 severly affected) Chromogenic factor VIII assay can be done	Underestimated Higher test dilution is less affected
APCR	Elevated ratio, false normal APCR in Factor V ladein mutation Genetic studies	Elevated ratio
AT	Overestimation Xa based assays	Overestimation IIa based assays
PC	Overestimation Advised chromogenic assays	Overestimation
PS	Overestimation Advised free PS Ag assay	Overestimation
Coagulation inhibitor	False positive Bethesda > 0.2mg/l	
DRVVT	False positive at 0.05 mg/	False prolongation
Thrombin	TT is very sensitive to the presence of dabigatran	Rivaroxaban has no effect on TT

Time	with greater than 10-fold prolongation at peak levels (Van Ryn et al, 2010). Normal TT excludes clinically relevant dabigatran (sensitive Van Ryn 2010).	
DDimer	↓by all anticoagulants but D-dimer assay will be normal	↓by all anticoagulants but D-dimer assay will be normal

Dilute thrombin-based assays, ecarin-based assays or chromogenic anti-IIa assays (in the absence of heparin) are suitable for determination of plasma concentrations of dabigatran. PT and APTT should not be used to measure the plasma concentration of dabigatran. Clotting factor assays performed in the presence of dabigatran should include multiple test plasma dilutions and an assessment of parallelism. Specific reversal agents for dabigatran isIdarucizumab 5g.

Patients taking dabigatran or rivaroxabancould have a prolonged APTT and/or PT and those on dabigatrana falsely low fibrinogen and the results might mimic DIC. (c/fPLTcount& D dimer level is normal in this drug intake). Clopidogrel (antiplatelet agent) ADP receptor antagonist half-life 7-8 hours, TIA, stroke, MI – to reduce ischemic attacks CAD, stenting or angioplasty. Monitor verify now system [9]

Golden words[3,4,5,7,8]

- Thrombophilia testing is best avoided during therapy withDTIs, but if APCR testing isbeing performed to exclude FV Leiden, genetic testing is preferred because it would not be affected by the presence of DTIs.
- Factor Xa-based assays of antithrombin are preferred over thrombin-based assays.
- Chromogenic or antigen assays are preferable to clot-basedassays of protein C and protein S in the presence of DTIs.
- The APTT can be used with most reagents for a crude estimate of the relative intensity ofanticoagulation due to dabigatran but some patients with therapeutic concentrations will have a normal APTT.
- The APTT cannot be used to determine the drug concentration.
- A normal thrombin time suggests the level of dabigatran is likely to be very low.
- Fibrinogen should be determined using assays in which dabigatran has minimal influence.
- Clotting factor assays performed in the presence of dabigatran should include multiple test plasma dilutions and an assessment of parallelism.
- Anti-Xa chromogenic assays should be used to determine plasma concentration of direct FXa inhibitors. Product-specific calibrator should be used and result should be expressed in mass concentration.

For Dibigatran, normal TT excludes clinically relevant drug levels and normal APTT excludes excess drug levels. The best monitoring tests for Dabigatran at therapeutic plasma concentration is Dilute TT, ECA & ACT. Rivaroxaban & Apixaban at therapeutic drug concentration can be best monitored by Anti-Xa assay & normal level excludes clinically relevant drug.

Table IV: Summarizing the monitoring of DOACs at various drug concentration in plasma

	Clinical Objective					
	Determine If Clinically Relevant Below On-Therapy Drug Levels Are Present		Estimate Drug Levels Within On-Therapy Range		Determine If Above On-Therapy Drug Levels Are Present	
Drug	Suggested Test	Interpretation	Suggested Test	Interpretation	Suggested Test	Interpretation
Dabigatran	TT	Normal TT likely excludes clinically relevant drug levels	Dilute TT, ECA, ECT	–	APTT, dilute TT, ECA, ECT	Normal APTT likely excludes excess drug levels; only dilute TT, ECA, and ECT are suitable for quantitation
Rivaroxaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa	–	Anti-Xa, PT	Normal PT likely excludes excess drug levels; only anti-Xa is suitable for quantitation
Apixaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa	–	Anti-Xa	–

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