Review Article

A Practical Guide to Ordering and Interpreting Coagulation Tests for Patients on Direct Oral Anticoagulants in Singapore*

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Abstract

Introduction: Direct oral anticoagulants (DOACs) are establishing themselves as principle choices for the treatment of a variety of thrombotic disorders. DOACs are also known to affect common coagulation tests which are routinely performed for patients in clinical practice. An understanding of their varied effects is crucial for the appropriate ordering of coagulation tests and their interpretation. Materials and Methods: Laboratories in public and private healthcare institutions and commercial sectors were surveyed on coagulation tests offered and their methods. A Medline and bibliography search, including a search on search engines, was performed for publications reporting the effects of dabigatran, apixaban and rivaroxaban on these coagulation tests. These papers were reviewed and summarised for consensus recommendations. Results: Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are variably affected by the DOACs and dependent of the coagulation assays used. Clinicians must know which laboratory has performed these tests to logically interpret test results. A normal PT or aPTT does not exclude the presence of residual DOACs effect. The thrombin time is sensitive to dabigatran but not apixaban or rivaroxaban. Specialised coagulation tests such as thrombophilia tests are also variably affected by the DOACs. All laboratories in Singapore however, employ similar test methods permitting a common set of recommendations for specialised coagulation testing. Conclusion: Knowledge of the effects of DOACs on coagulation testing is essential to determine the appropriateness of performing such tests and interpreting them coherently. Practical recommendations which are tests and location-specific are set out in this paper.

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Key words: Apixaban, Dabigatran, Laboratory testing, Rivaroxaban

Introduction

Direct oral anticoagulants (DOACs) describe 2 classes of oral anticoagulants that target thrombin (oral direct thrombin inhibitors) (DTI) and factor Xa (anti-FXa), both of which have been rapidly changing the anticoagulation landscape. Their adoption as viable alternatives to conventional vitamin K antagonist such as warfarin have been fomented by clinical trial data indicating at least equivalence in efficacy and safety when compared to standard anticoagulants for a variety of indications.[1-10] The added benefits of fixed dosing as well as the limited drug and food interactions without the need for routine monitoring has contributed to an increasing number of patients taking these anticoagulants.[11] There are currently 3 DOACs registered in Singapore for a variety of indications as listed in Table 1. Dabigatran, a DTI, binds competitively and reversibly to the active site on free- and clot-bound thrombin.[12] Rivaroxaban and apixaban are competitive anti-FXa that bind to both free- and clot-bound factor Xa.[12]

As DOACs primarily interrupt thrombus formation via the inhibition of downstream coagulation proteins, they can potentially interfere with many commonly available

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Table 1. DOACs Approved in Singapore and Their Indications

Drug	Class	Approved Indications
Dabigatran (Boehringer Ingelheim, Germany)	Direct thrombin inhibitor	1. VTE prophylaxis in major orthopaedic surgery. 2. Treatment of acute DVT and PE. 3. Prevention of recurrent DVT and PE 4. Stroke and systemic embolism prevention in non-valvular atrial fibrillation.
Apixaban (Pfizer/Bristol Myers Squibb, USA)	Factor Xa inhibitor	1. VTE prophylaxis in major orthopaedic surgery. 2. Treatment of acute DVT and PE. 3. Prevention of recurrent DVT and PE. 4. Stroke and systemic embolism prevention in non-valvular atrial fibrillation.
Rivaroxaban (Bayer Pharma AG, Germany)	Factor Xa inhibitor	1. VTE prophylaxis in major orthopaedic surgery. 2. Treatment of acute DVT and PE. 3. Prevention of recurrent DVT and PE. 4. Stroke and systemic embolism prevention in non-valvular atrial fibrillation. 5. Prevention of cardiovascular deaths after acute coronary syndrome.

DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism

routine and specialised coagulation assays and influence their interpretation.[13] The degree of interference is dependent on the DOACs used and their plasma levels at the time of sample collection. Interference is also governed by the test methods and sensitivity of the assays used in individual laboratories.[14] Since the information provided on the patient to clinical laboratories is generally scanty, laboratories cannot assist clinicians with interpretation of test results. Clinicians therefore need to be aware of the influences of DOACs on coagulation testing in order to make informed choices when considering the appropriateness of tests for their patients and permit accurate interpretation. More importantly, this knowledge needs to be up-to-date and specific to the institution or laboratories that perform these tests. Currently, most laboratories in Singapore do not publish their laboratory-specific guides on this matter nor have the effective means of communicating this with their doctor-clients. This paper aims to address this gap in information on coagulation testing for patients taking DOACs in Singapore and is intended to provide a clinician-centric and laboratory-specific guide for our clinicians.

Materials and Methods

The test methodology and reagents used for routine and specialised coagulation tests by the major haematology laboratories in Singapore in 2015 were surveyed by contacting each laboratory individually. Laboratories that participated in this survey were: Singapore General Hospital (SGH), Tan Tock Seng Hospital (TTSH), National University Hospital (NUH), Changi General Hospital (CGH), Khoo Teck Puat Hospital (KTPH), KK Women's and Children's Hospital (KKWCH), Ng Teng Fong Hospital (NTFH), Sengkang Hospital (SKH), Parkway Laboratory Services (PLS), Mount Alvernia Hospital (MAH), Quest Laboratory, Innovative Diagnostics and Raffles Diagnostics. Coagulation tests offered and methods used in laboratories at SingHealth and National Healthcare Group polyclinics were also determined.

The effects of dabigatran, rivaroxaban and apixaban on each laboratory's routine and specialised coagulation tests were obtained by reviewing product inserts and through a literature search performed on Medline and search engines including Google. The key words "dabigatran", "rivaroxaban", "apixaban", "coagulation", "laboratory", "test", "assay" as well as names of individual tests were used during the search. Relevant papers which reported the effects of the DOACs on tests and assays used in our hospitals were subjected to further review and summarised. The bibliographies of selected papers were also searched for papers that may have eluded the Medline search. Information gathered was reviewed by all authors for their concordance of DOACs' effects on the tests in question. Unpublished validation studies of local laboratories were used to supplement published findings if available.

The tests categorised as routine were the prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), fibrinogen and D-dimers. These tests are performed by general haematology or core laboratories with high through-puts and mostly available around the clock in the major hospitals. The listed tests are offered by all the surveyed laboratories. Specialised coagulation tests, on the other hand, are performed in a limited number of institutions and mostly available during office hours with batched testing. These included testing for lupus anticoagulants, clotting factors and von Willebrand factor assays, normal plasma mixing studies, and thrombophilia markers (protein C, protein S, antithrombin, activated protein C resistance). Currently, only the laboratories in SGH, TTSH and NUH perform these specialised coagulation tests. Requests for these tests made through other laboratories are usually outsourced to these 3 laboratories.

Table 2. Routine Coagulation Tests and Reagents Used in Hospitals and Laboratories in Singapore

Test	Activator	Hospital/Laboratory
Prothrombin time (PT)	Dade Innovin	SGH,CGH, KTPH, PLS, QL, ID, RD, SKH
	Neoplastin C1 Plus	NUH, TTSH, NTFH, KKH, SHP, NHGP
	Thromborel S	MAH
Activated partial thromboplastin time (aPTT)	Actin FSL	SGH,CGH, KTPH, PLS, QL, ID, RD, MAH, SKH
	STA Cephascreen	NUH, TTSH, NTFH, KKH
Thrombin clotting time	Thromboclotin	SGH,CGH, KTPH, PLS, QL, ID, MAH, SKH
	STA Thrombin	NUH, TTSH, NTFH, KKH

CGH: Changi General Hospital; ID: Innovative Diagnostics; KKWCH: KK Women's and Children's Hospital; KTPH: Khoo Teck Puat Hospital; MAH: Mount Alvernia Hospital; NHGP: National Healthcare Group Polyclinics; NTFH: Ng Teng Fong Hospital; NUH: National University Hospital; PLS: Parkway Laboratory Services; QL: Quest Laboratory; RD: Raffles Diagnostics; SGH: Singapore General Hospital; SHP: Singhealth Polyclinics; SKH: Sengkang Hospital; TTSH: Tan Tock Seng Hospital

The summary recommendations in this paper were reviewed and affirmed by all authors with confirmation by individual laboratories for accuracy.

Results

Routine Coagulation Tests

The assays used by the various laboratories in Singapore for routine coagulation tests are shown in Table 2. For PT testing, the 3 reagents used are Innovin (Siemens Healthcare Diagnostics, Marburg, Germany), Thromborel S (Siemens Healthcare Diagnostics, Marburg, Germany) and Neoplastin C1 Plus (Diagnostica Stago S.A.S, Paris, France). These reagents were used on corresponding instruments from the same manufacturers. The number of papers that reported the effects of DOACs using at least 1 of these reagents were: dabigatran – 10,[15-24] rivaroxaban – 8,[17,19,21,25-29] apixaban – 3.[27,30,31] Dabigatran has minimal effect on PT irrespective of the reagents used. In contrast, rivaroxaban and apixaban prolong the PT test, but this effect is, however, dependent on the reagents employed. In fact, the test is more sensitive with the thromboplastin reagent Neoplastin C1 Plus, while with Thromborel S, it is least sensitive. For practical purposes, the interpretation of PT in the presence of DOACs based on the published literature and our clinical experiences are summarised as a decision tree (Fig. 1). Current PT reagents are less sensitive to apixaban as compared to rivaroxaban. In general, a normal PT result does not exclude the presence of residual anticoagulant effect for any of the DOACs.

Point-of-care (POC) PT monitoring devices such as the Coaguchek XS are affected by increasing doses of rivaroxaban and apixaban since its prothrombin time detection is also dependent on the human recombinant thromboplastin. This effect is more pronounced and linear with rivaroxaban than apixaban. Dabigatran, on the other hand, has limited effect on POC PT test results.[32] Currently, POC PT testing using the Coaguchek XS is offered by the major hospitals and all polyclinics in Singapore for the monitoring of patients on warfarin.

For aPTT testing, Actin FSL (Siemens Healthcare Diagnostics, Marburg, Germany) and STA Cephascreen (Diagnostica Stago S.A.S, Paris, France) are the 2 test reagents used in Singapore on corresponding instruments from the same manufacturers. The number of published papers that reported the effects of the DOACs by using at least 1 of these reagents were: dabigatran – 7,[15,17-20,23,33] rivaroxaban – 4,[17,19,21,25] apixaban – 3,[25,30,31]. In contrast to the PT assay, dabigatran prolonged aPTT in a more pronounced manner than the anti-Xa inhibitors. aPTT tests are generally insensitive to apixaban. The interpretation of aPTT for patients taking DOACs is summarised as a decision tree in Figure 2. As in the case of PT testing, a normal aPTT result does not exclude the presence of residual anticoagulant effect for any of the DOACs.

The thrombin clotting time (TCT) assay which is also commonly known as the thrombin time, directly measures the activity of thrombin in the plasma. It is therefore prolonged by the DTI, dabigatran.[20,23,34] A sharp linear dose-response curve is observed with increasing concentrations.[35] However, the maximal clotting limits is reached with relatively low dabigatran concentration making the TCT unsuitable for quantifying dabigatran concentration.[23,36] Slight differences in sensitivities between different instrument/reagent combinations among the labs in Singapore do not affect the generalisability of TCT results obtained. The TCT is best used to exclude the presence of dabigatran and a normal TCT in any of our institutions will indicate the absence of dabigatran in the test sample. Rivaroxaban and apixaban, which are anti-FXa, do not affect the TCT.

Assays used for fibrinogen testing in Singapore are not affected by any of the DOACs.[21] Their results may be

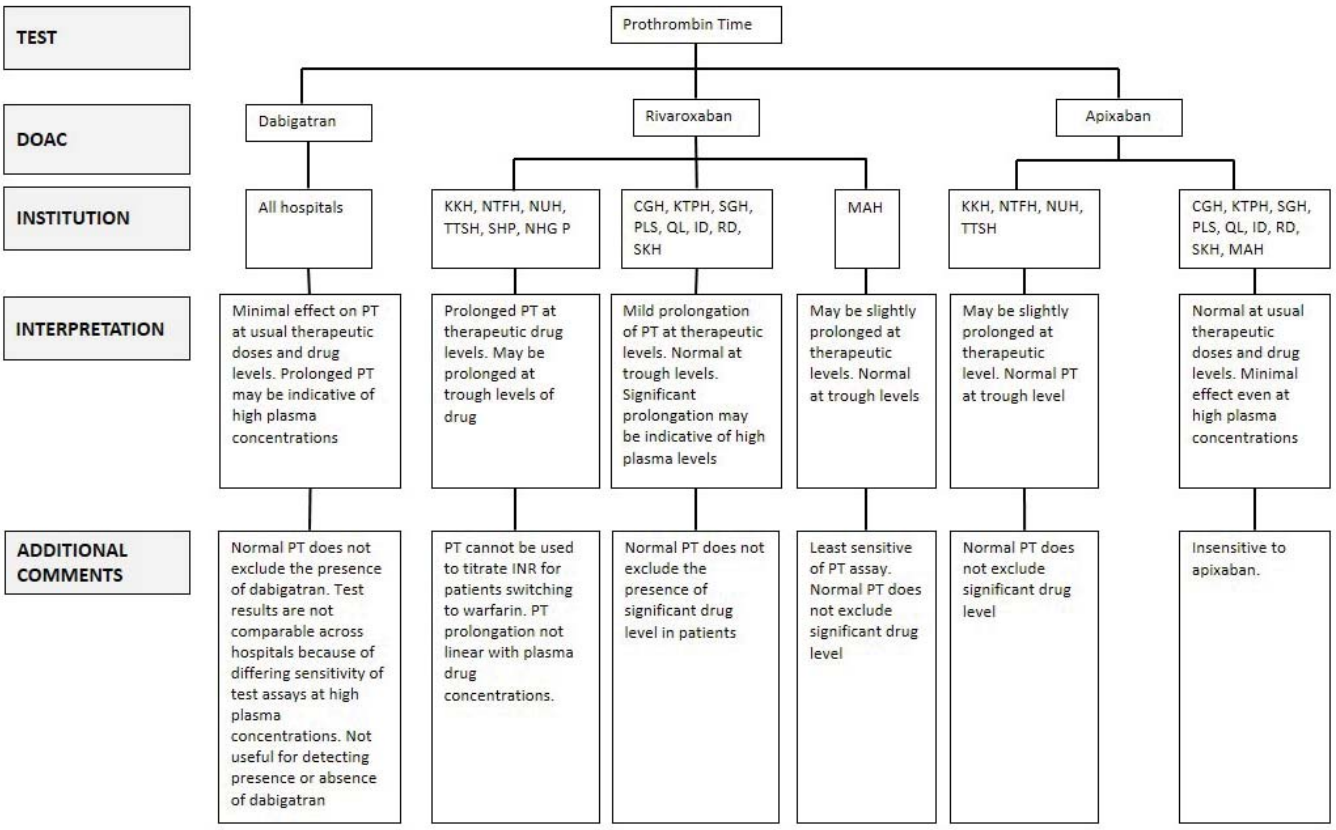

Fig. 1. Decision tree for interpreting prothrombin time in Singapore hospitals.
CGH: Changi General Hospital; DOAC: Direct oral anticoagulant; ID: Innovative Diagnostics; KKWCH: KK Women's and Children's Hospital; KTPH: Khoo Teck Puat Hospital; MAH: Mount Alvernia Hospital; NHGP: National Healthcare Group Polyclinics; NTFH: Ng Teng Fong Hospital; NUH: National University Hospital; PLS: Parkway Laboratory Services; PT: Prothrombin time; QL: Quest Laboratory; RD: Raffles Diagnostics; SGH: Singapore General Hospital; SHP: Singhealth Polyclinics; SKH: Sengkang Hospital; TTSH: Tan Tock Seng Hospital

interpreted independent of the use of DOACs. DOACs will also not interfere with D-dimer testing which is measured by immunoturbidity methods.

Specialised Coagulation Tests

The effect of DOACs on these specialised tests is generally determined by whether the assays are clot-based or chromogenic and whether thrombin or factor Xa is a substrate in the assays.[33,37-40] Specialised laboratories performing these tests in Singapore currently use a common platform with similar methods. The impact of DOACs on these tests are therefore generalisable to all institutions with no requirement for distinction between laboratories or instruments, unlike in the case of some routine tests as discussed earlier. Table 3 summarises the influence of DOACs on specialised testing, the types of common assays used in our laboratories in Singapore, and our recommendations in respect to the appropriateness of ordering these tests when a patient is taking a DOAC.

Discussion

This paper represents the collaborative effort of our Thrombosis Haemostasis Workgroup to address the current issues related to the interpretation of coagulation tests for the increasing number of patients taking DOACs in Singapore. By consolidating our current understanding of the effects of DOACs on coagulation tests into a practical reference document that is geared for both private and public institutions as well as community practice in Singapore, we hope to achieve a number of objectives. Firstly, the potential influence of DOACs on coagulation testing is currently not common knowledge to many generalist clinicians. This paper therefore serves to highlight this aspect of management and raise awareness among clinicians who should be mindful of such potential pitfalls. Awareness must however be accompanied by the availability of a handy resource for clinicians to check and interpret coagulation tests that are ordered for their patients. It is our intention for this paper to serve as this resource. Accurate interpretation

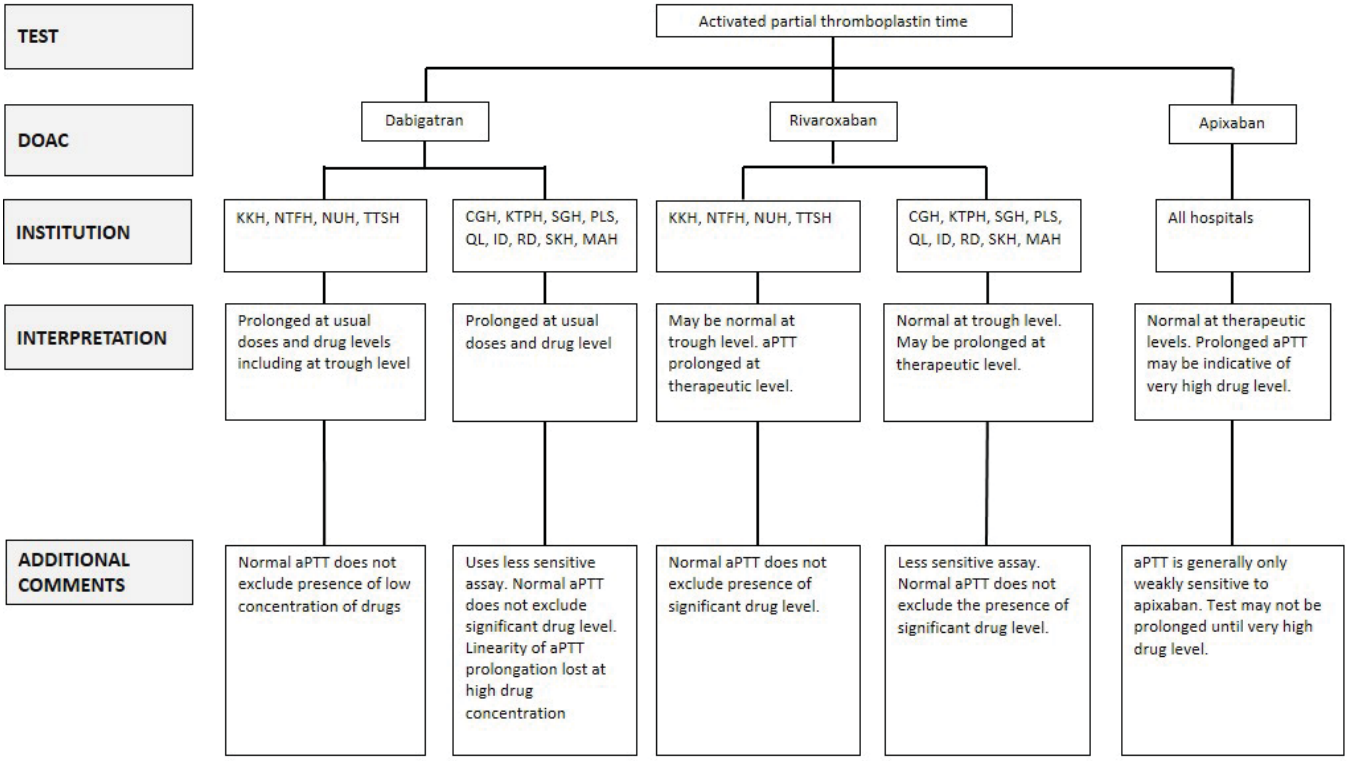

Fig. 2. Decision tree for interpreting activated partial thromboplastin time in Singapore hospitals.
aPTT: Activated partial thromboplastin time; CGH: Changi General Hospital; DOAC: Direct oral anticoagulant; ID: Innovative Diagnostics; KKWCH: KK Women's and Children's Hospital; KTPH: Khoo Teck Puat Hospital; MAH: Mount Alvernia Hospital; NHGP: National Healthcare Group Polyclinics; NTFH: Ng Teng Fong Hospital; NUH: National University Hospital; PLS: Parkway Laboratory Services; QL: Quest Laboratory; RD: Raffles Diagnostics; SGH: Singapore General Hospital; SHP: Singhealth Polyclinics; SKH: Sengkang Hospital; TTSH: Tan Tock Seng Hospital

of coagulation test results in patients on DOACs can have important implications in the management of patients especially those who are acutely ill. Key information must be available for accurate interpretation, such as the DOAC used, time of last dose, concomitant use of other drugs that might interfere with the DOAC pharmacokinetics and/or pharmacodynamics, and any comorbidities that could interfere with baseline routine coagulation tests such as the PT and APTT.

Another objective of this paper is to provide counsel on the appropriateness of performing specialised coagulation tests when a patient is taking DOACs. Our recommendation on the validity of these tests is intended to reduce false negative or false positive results which may be erroneously used to guide treatment decisions with unintended consequences. These tests are also costly to repeat and may unnecessarily increase the workload of hospital laboratories.

These recommendations however have a number of limitations. Most published papers report results of tests performed on specimens derived from normal plasma which have been spiked in the laboratory with NOACs. While this provides consistency for test specimens to be processed in different laboratories and on different machines as well as reagents, the effects on actual patient specimens are less well characterised in published literature. Secondly, while we have chosen to only include studies that best match the instruments, reagents and test environment in Singapore, there are limitations to the degree of similarity as no 2 laboratories are alike. The replicability of the published test results cannot be absolutely assured in our laboratories. Additionally, there is currently a dearth of local laboratory data on the interference of DOACs with coagulation testing. Lastly, the summary recommendations represent the line of best fit when consolidating information from various papers. There will therefore be outliers who do not conform to our current interpretation of the reported findings in this aspect. Our paper also does not cover the subject of monitoring DOAC levels which has previously been addressed by our group.[41]

Ultimately, the best recommendations on the interpretation of coagulation tests for patients taking DOACs will have to come from each individual laboratory's own validation studies and experience with a cohort of local Singapore patients. Currently, such a tedious and costly exercise is

DABIGATRAN

	Lupus anticoagulant testing			One-stage factor assays	Mixing studies	Thrombophilia screening				Other tests	
ASSAY	Dilute Russell's viper venom time (dRVVT)	PTT-LA	Phospholipid-corrected silica clotting time (Staclot LA)			Antithrombin	Protein S	Protein C	Activated Protein C (APC) Ratio	vWF:Ag, vWF:RCo	Platelet function tests
EFFECT	• Falsely prolonged • dRVVT ratio cutoff exceeded even at sub-therapeutic levels.	• Prolonged. • Phospholipid correction may be incomplete. • May result in false positive LA.		• Falsely reduced • Significant effects on factors II and V at therapeutic levels. • Significant effects on factors VIII, IX, XI and XII at trough levels.	• Incomplete correction • May suggest false presence of factor inhibitor at peak levels.	• Thrombin-based; falsely elevated AT activity in thrombin-based assays • Significant effects at therapeutic levels.	• Functional assay: clot-based; falsely elevated even at sub-therapeutic levels. • Total/free assays: antigen-based; no effect	Chromogenic; not affected.	Falsely elevated beyond trough levels.	Not affected	
RECOMMENDATIONS	Do not test when patient is on drug.			Do not test when patient is on drug. If testing must be done, recommended to do so at trough levels.	If testing must be done, recommended to do so at trough levels.	If testing must be done, recommended to so do at trough levels.	Do not test for clot-based functional Protein S when patient is on drug. May test for Protein S antigen.	May test.	Do not test when patient is on drug.	May test.	

RIVAROXABAN

	Lupus anticoagulant testing			One-stage factor assays	Mixing studies	Thrombophilia screening				Other tests	
ASSAY	Dilute Russell's viper venom time (dRVVT)	PTT-LA	Phospholipid-corrected silica clotting time (Staclot LA)			Antithrombin	Protein S	Protein C	Activated Protein C (APC) Ratio	vWF:Ag, vWF:RCo	Platelet function tests
EFFECT	• Falsely prolonged • dRVVT ratio cutoff exceeded even at sub-therapeutic levels.	Likely not affected.		• Falsely reduced factors II, V, VII and X, but might still be within normal range • Significantly reduce factors VIII and IX at therapeutic levels • Falsely reduced XI and XII levels • Chromogenic assays are also affected	Likely to be incompletely corrected	Thrombin-based; not affected	• Functional assay: clot-based; falsely elevated even at sub-therapeutic levels. • Total/free assays: antigen-based; no effect	Chromogenic; not affected.	Falsely elevated beyond peak levels.	Not affected	
RECOMMENDATIONS	Do not test when patient is on drug.			Do not test factors II, V, VII and X when patient is on drug. If testing for factors VIII, IX, XI and XII must be done, recommended to do so at trough levels.	If testing must be done, recommended to do so at trough levels.	May test.	Do not test for clot-based functional Protein S when patient is on drug. May test for Protein S antigen.	May test.	If testing must be done, recommended to do so at trough levels.	May test.	

APIXABAN

	Lupus anticoagulant testing			One-stage factor assays	Mixing studies	Thrombophilia screen				Others	
ASSAY	Dilute Russell's viper venom time (dRVVT)	PTT-LA	Phospholipid-corrected silica clotting time (Staclot LA)			Antithrombin	Protein S	Protein C	Activated Protein C (APC) Ratio	vWF:Ag, vWF:RCo	Platelet function tests
EFFECT	Falsely prolonged but dRVVT ratio only exceeded cutoff at supra-therapeutic levels.	Likely not affected.		Falsely reduced significant beyond peak levels.	Likely to be incompletely corrected	Thrombin-based; not affected	• Functional assay: clot-based; falsely elevated even at sub-therapeutic levels. • Total/free assays: antigen-based; no effect	Chromogenic; not affected.	Likely to be falsely elevated beyond peak levels.	Not affected	
RECOMMENDATIONS	If testing must be done, recommended to do at trough levels.			If testing must be done, recommended to do so at trough levels.	If testing must be done, recommended to do so at trough levels.	May test.	Do not test for clot-based functional Protein S when patient is on drug. May test for Protein S antigen.	May test.	If testing must be done, recommended to do so at trough levels.	May test.	

Table 3. Effects of NOACs on specialised coagulation testing.
LA: Lupus anticoagulant; PTT: Partial thromboplastin time; vWF: von Willebrand factor

not possible for the majority of busy service laboratories in Singapore. While this current collaborative effort to guide coagulation testing has its limitations, it will go some distance in putting sense to a confusing and relatively new area of testing. Widespread availability of specific tests for measurement of drug levels of the DOACs with rapid turnaround times will eventually resolve the current dilemma confronting our clinicians, especially in emergency situations or whenever the safety and efficacy of the DOACs are in question. Laboratories in Singapore should therefore prioritise the introduction of such tests for improving the care of patients who are taking DOACs. Our workgroup will also need to be mindful of providing updates to this paper when more local data and experiences become available in future. In the interim, this represents our best effort which we hope will benefit clinicians prescribing and managing patients taking DOACs.

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