Anticoagulation Monitoring for Perioperative Physicians

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Anticoagulants form one arm of antithrombotic therapy, the other being antiplatelet agents.[1] The common mechanism of action of these medications is preventing fibrin formation by inhibiting one or more steps along the coagulation cascade. Although warfarin and heparin were the mainstay oral and parenteral anticoagulants of the 20th century, today's perioperative clinicians are faced with other unique classes of agents. Specifically, direct oral anticoagulants are now available to inhibit factor Xa or thrombin. This presents a challenge in monitoring since the effects of these newer agents on standard testing do not always reflect the degree of anticoagulation being achieved within the patient.

This focused review will detail the most common coagulation tests used to assess the level of patient anticoagulation. These will be organized into tests obtained from the central laboratory which are often ordered pre- or postoperatively, and those that are considered point-of-care and typically used in the operating room or at the intensive care unit bedside (see table 1). Finally, some unique monitoring considerations when transitioning between classes of agents will be considered.

Central Laboratory Coagulation Testing

Drug-specific testing to determine clearance kinetics of certain anticoagulants may have a role in elective and controlled settings, yet such tests are often limited by poor availability and long turnaround times. In contrast, urgent or emergency interventions require perioperative physicians to determine whether an anticoagulant effect is present very quickly. Doing so with traditional coagulation tests has become more complicated over the past decade with the introduction direct oral anticoagulants, including direct thrombin inhibitors (DTIs) like dabigatran, and factor Xa inhibitors like apixaban, rivaroxaban, and edoxaban. These agents have variable effects on traditional coagulation testing.[2] Nevertheless, central laboratory tests are often the first-line assays obtained and understanding an anticoagulant's site of action is important when considering how the medication affects them. An overview of the coagulation cascade with relevant targets of anticoagulation therapy is presented in figure 1. Although the division of the coagulation cascade into three pathways—extrinsic, intrinsic, and common—is a nonphysiologic delineation, it can be helpful in the interpretation of hemostasis tests, especially when trying to understand whether a specific inhibitor (*i.e.*, anticoagulant) is present.

When reviewing laboratory-based coagulation tests it is important to consider whether the assay is clot-based or chromogenic. Most standard coagulation tests, like the prothrombin time (PT) and activated partial thromboplastin time (PTT), are clot-based assays, often referred to as one-stage assays. Clot-based assays are sensitive to the effects of other components responsible for fibrin formation in the plasma, as the reaction time is dependent on multiple steps that ultimately result in clotting. Prolongation may reflect deficiencies of involved clotting factors or the presence of factor inhibitors.[3] In contrast, chromogenic assays use specific factor substrates bound to a chromophore and release a colored compound when cleaved that is proportional to the amount of factor present. Chromogenic assays are thus less sensitive to low levels of other coagulation factors or to the presence of certain nonspecific inhibitors, such as a lupus anticoagulant.[4] The basic principles of clot-based testing and chromogenic testing are illustrated in figure 2. Coagulation factors, such as factor VIII, factor IX, factor X, and factor XIII, as well as antithrombin (AT), plasminogen, and protein C, can be measured *via* chromogenic assays. Specific assays also exist for anticoagulants such as heparin, apixaban, and rivaroxaban. The major limitation of chromogenic tests for monitoring factor Xa inhibitors is the need for comparison to a drug-specific standard curve to generate a result, thereby necessitating laboratory awareness of which anticoagulant the patient is on.[5] In addition, chromogenic assays are affected by the opacity of the sample, so samples that are icteric, lipemic, and/or hemolyzed may generate inaccurate results.

PT and International Normalized Ratio

The development of the PT is widely credited to Professor Armand Quick (the "Quick time") in 1935,[6] making it one of the oldest coagulation tests still in use. It is a clot-based assay to which thromboplastin (tissue factor, phospholipid, and calcium) is added to citrated platelet-poor plasma. Decreased levels of prothrombin, factor V, factor VII, factor X, and fibrinogen (*i.e.*, the extrinsic and common pathways) will result in PT prolongation. The ability to detect decreased factors can depend on the type of thromboplastin used, but in general, PT is most sensitive to low levels of factor VII and factor X.[3] Since

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Table 1. Common Anticoagulants and Monitoring Assays

		Parenteral Agents			Oral Agents	
		Heparins	**DTIs**	**VKAs**	**DTIs**	**Factor Xa Inhibitors**
Central Laboratory Tests	**PT/INR**	Possible Interference	Possible Interference	**Quantitative**	Possible Interference	Possible Interference
	PTT	**Semi-Quantitative** *sensitive to Factor VIII & acute phase reactants*	**Semi-Quantitative** *poor correlation with drug levels*	Possible Interference	**Exclusionary** *lab reagent dependent*	Possible Interference
	TT / diluteTT	***Exclusionary*** *normal values can exclude presence of unfractionated, but not low molecular weight, heparin*	**Exclusionary (TT)** **Quantitative (diluteTT)** *sensitive to fibrinogen levels*	-	**Exclusionary (TT)** **Quantitative (diluteTT)** *sensitive to fibrinogen levels*	-
	Ecarin Assays	-	**Quantitative** *Limited availability*	-	**Quantitative** *Limited availability*	-
	Chromogenic Anti-Xa Assay	**Quantitative**	-	-	-	**Quantitative** *(with special calibrators)* **Exclusionary** *(using heparin calibrator)*
Point of Care Tests	**Activated Clotting Times**	**Semi-Quantitative** *high dose monitoring; multiple confounders*	**Semi-Quantitative** *non-linear relationship at high doses*	Possible Interference	Possible Interference	Possible Interference
	Viscoelastic Testing	**Exclusionary** *limited evidence for dosing heparin therapy*	*modified reagents are currently under investigation*	Possible Interference	Possible Interference	*modified reagents are currently under investigation*

Tests are designated as either "Quantitative" (*green*) or "Semi-Quantitative" (*yellow*) for a specific agent if an actual drug level or some ordinal magnitude of clinical effect can be determined. The "Exclusionary" designation was given if normal values of the test would rule out clinically significant effects of the anticoagulant. When interpreting the test, clinicians should be aware of the agents labeled "Possible Interference" (*red boxes*), which can interfere with the interpretation of the actual drug level being measured. Ecarin assays include the ecarin clotting time and ecarin chromogenic assay. A *dash* (–) indicates that agent had no effect on the test or that the test is not generally utilized in the presence of the listed agent.

diluteTT, dilute thrombin time; DTIs, direct thrombin inhibitors; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time; VKAs, vitamin K antagonists

multiple thromboplastin reagents exist, the international normalized ratio (INR) was developed to standardize the measurement between different labs. $INR = (PT_{sample} / PT_{control})^{ISI}$, where ISI (international sensitivity index) is calculated based upon a reference thromboplastin. It should be noted that the INR is not a linear scale; the magnitude of difference between 2.0 and 3.0 is not the same as that between 3.0 and 4.0.[7]

Since several factors affecting the PT are vitamin K–dependent (prothrombin, factor VII, factor X), it is not surprising that it is the monitoring test of choice for vitamin K antagonists (VKAs) such as warfarin, phenprocoumon, and acenocoumarol. As can be inferred from figure 1, therapeutic doses of heparin can also prolong the PT, although many commercially available reagents include a heparin neutralizer to prevent this interference. The effect of direct oral anticoagulants on the PT are variable based upon the specific component reagents used. Although oral factor Xa inhibitors generally prolong the PT more than DTIs,[2] the test is not recommended to exclude clinically relevant drug levels of either type of agent.[8]

(Activated) PTT

Like PT, PTT is a clot-based assay using platelet-poor plasma that has been incubated with a surface activator such as kaolin, silica, ellagic acid, or celite.[3] As the name suggests, this is an incomplete thromboplastin devoid of tissue factor. The activator binds to factor XII and generates factor XIIa, which cleaves factor XI to factor XIa, but further continuation of the cascade cannot occur in the absence of calcium. The reaction time of PTT begins with the addition of calcium, allowing for continuation of the cascade, and concludes with fibrin clot formation. The PTT reflects activities of factors involved in the intrinsic and common pathways of coagulation (fig. 1), although it is particularly sensitive to levels of factor VIII. The PTT reagents can be formulated to be either more or less sensitive to the lupus anticoagulant as well. Unlike the INR for the PT, no standardized measurement exists between different laboratories, so values cannot be transposed across institutions.

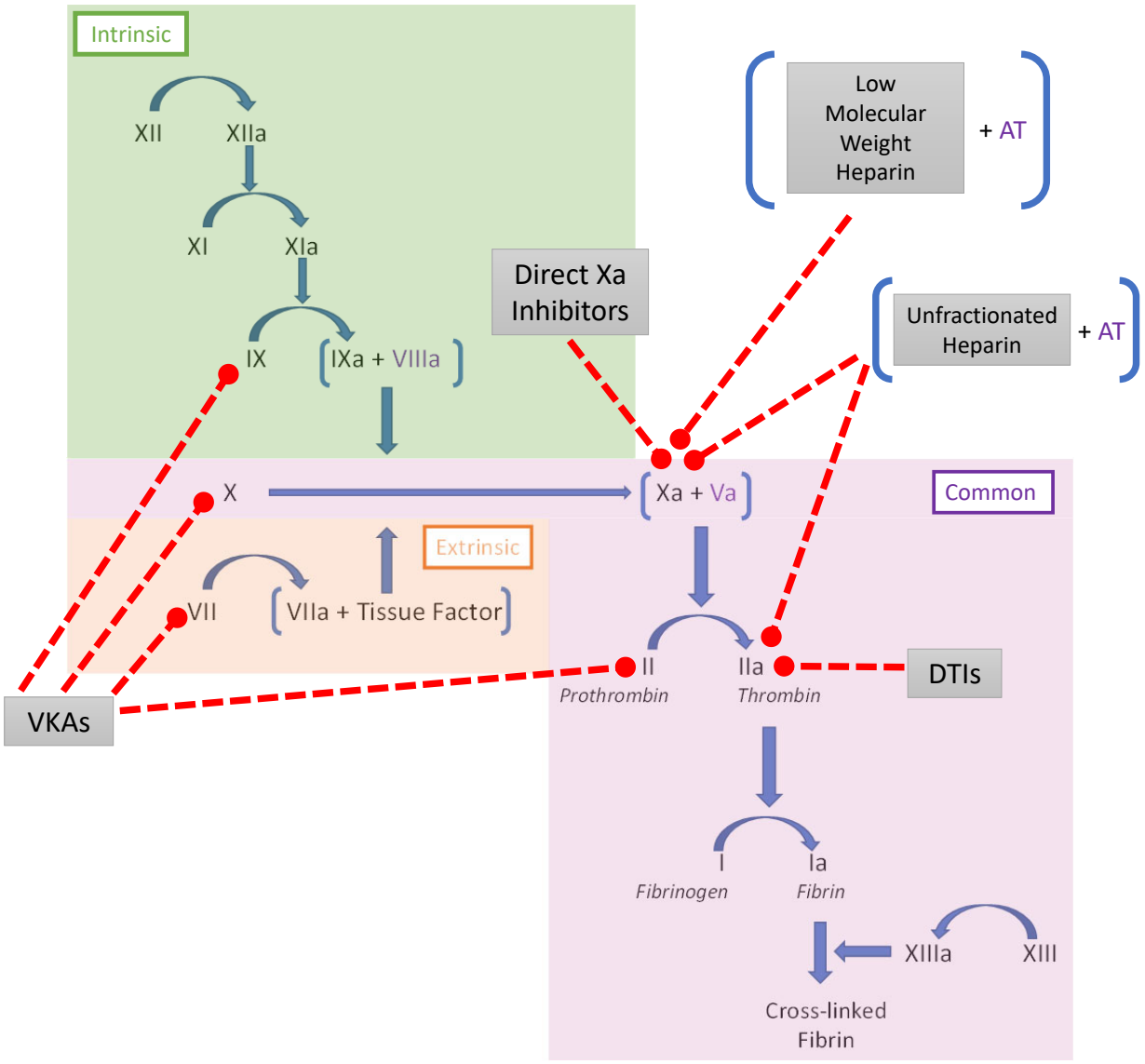

Fig. 1. Coagulation cascade with common anticoagulant agent targets. The intrinsic (*green*), extrinsic (*yellow*), and common (*purple*) pathways of the coagulation cascade are highlighted. The targets of anticoagulant agents (*gray boxes*) and denoted by *red dashed lines with boxed ends*. In general, tests using activators to stimulate the cascade at, or proximal to, the drug target will be affected by the drug. Coagulation factors are shown in roman numerals. AT, antithrombin; DTIs, direct thrombin inhibitors; VKAs, vitamin K antagonists.

The PTT historically has been used to monitor heparin therapy. The common practice of assuming an adequate heparin level when the PTT is 1.5 to 2.5 times the laboratory "normal" value is based upon a 1972 observational study of only 254 patients.[9] Unfortunately, the PTT's relationship with the amount of heparin present can be altered by a number of biologic variables. The presence of acute phase reactants, especially factor VIII and fibrinogen, can essentially "normalize" the PTT despite high levels of heparin present. Conversely, some antiphospholipid antibodies (*i.e.,* lupus anticoagulants) can result in an elevated PTT despite minimal heparin being present.[10] Because of this inconsistent relationship, both the College of American Pathologists (Washington, D.C.) and the American College of Chest Physicians (Glenview, Illinois) recommend that individual institutions set PTT goals based upon heparin levels measured by their own clinical laboratories using some other means.[11,12] More recently, the parenteral DTIs bivalirudin and argatroban have also been monitored using PTTs, with many institutional protocols utilizing a target

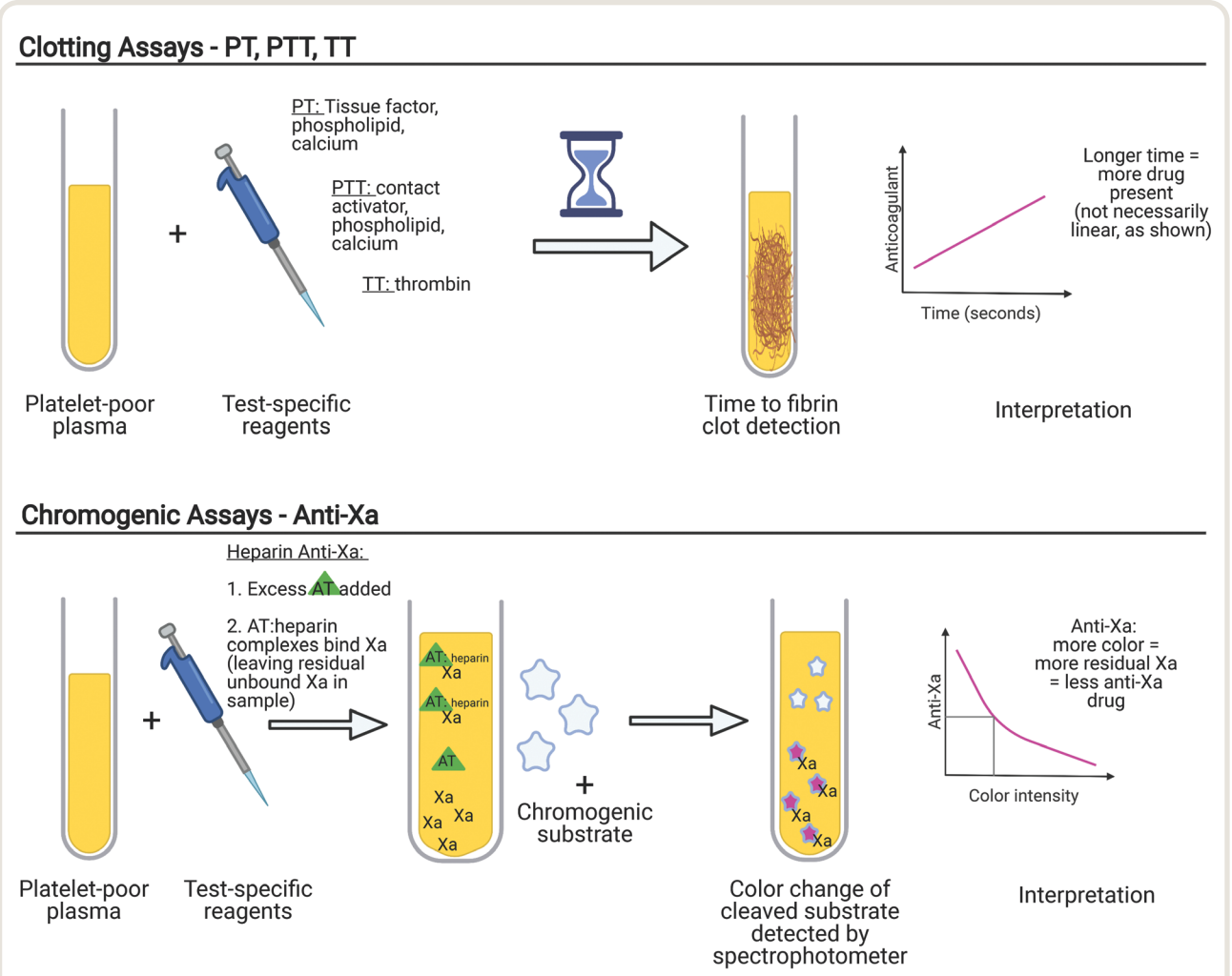

Fig. 2. Comparison of clotting assays and chromogenic assays. Both laboratory clotting assays and chromogenic assays utilize platelet-poor plasma, which requires centrifugation of whole-blood samples. Test specific reagents are then added. In clot-based assays, the time to fibrin formation, which may be detected by mechanical, turbidimetric, or other means, is measured and compared to a standard nomogram. In chromogenic assays, factor Xa cleaves a chromogenic substrate; the more factor Xa that is inhibited, the less substrate is cleaved, creating less color to be detected by a spectrophotometer. The interpretation of a drug level is inverse to the amount of color intensity. AT, antithrombin; PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time.

of 1.5 to 2.5 times the control PTT, similar to heparin.[13,14] However, correlation of PTT prolongation with levels of parenteral DTIs measured using tandem mass spectrometry has been noted to be quite poor.[15] It is worth noting that while a normal PTT would typically exclude clinically relevant levels of dabigatran, it does not rule out clinically relevant levels of the oral factor Xa inhibitors.[8]

Thrombin Time

The thrombin time (TT) involves adding thrombin, from either human or bovine sources, to platelet-poor plasma and measuring the time to fibrin clot formation.[3] The Clauss assay is actually a modified TT that uses high concentrations of thrombin and dilute patient plasma; the time to clot formation is inversely related to fibrinogen concentration. The standard TT is very sensitive to any type of thrombin inhibition and may have a role in ruling out significant DTI levels in the perioperative period. A normal TT can exclude the presence of clinically relevant concentrations of DTIs or unfractionated heparin, but not low-molecular-weight heparin since factor X is not involved in the assay (see fig. 1).[16] Decreased levels of fibrinogen, hypoalbuminemia, or high levels of fibrin degredation products can prolong the TT. Thus, an elevated TT does not confirm the presence of a DTI. More quantitative assessment of DTI levels can be made with a plasma-diluted TT for which commercial kits are available. The dilute TT essentially dilutes the patient sample to one-fourth or one-fifth of the standard

TT, decreasing the sensitivity of the test to DTI presence. The dilute TT has been found to correlate with DTI levels much better than the PTT.[15]

Ecarin Clotting Time and Ecarin Chromogenic Assay

Ecarin is derived from the venom of the snake *Echis carinatus* and converts prothrombin (factor II) into meizothrombin, which is still able to convert fibrinogen to fibrin, but has only about 10% of thrombin's procoagulant activity.[17] Although heparins do not affect meizothrombin, both oral and parenteral DTIs do. The testing advantage of using ecarin for DTI monitoring is that, unlike the PTT, there is a linear relationship between the amount of meizothrombin inhibited and the quantity of DTI present throughout a wide range of drug concentrations. Ecarin can be utilized in a clot-based assay or a chromogenic one.[18] The major advantage of the ecarin chromogenic assay is that it is not affected by patient fibrinogen levels. Unfortunately, neither ecarin test is widely available. However, some point-of-care assays for viscoelastic testing are in development.

Anti-Xa Assay

Anti-Xa tests are functional assays that measure the inhibitory activity against factor Xa in platelet-poor plasma. Its use is increasingly widespread for monitoring anticoagulation with unfractionated heparin, which has both anti-Xa and anti-IIa activity, or low-molecular-weight heparin, which has primarily anti-Xa activity. In the test, platelet-poor plasma is incubated with a fixed amount of exogenous factor Xa and then residual factor Xa activity, which is inversely proportional to the amount of anticoagulant in the patient sample, is measured. This is most commonly performed using a factor Xa–specific chromogenic substrate. The result is quantified by comparison to a standard curve generated using dilutions of the specific anticoagulant (unfractionated or low-molecular-weight heparin) and normal plasma.

Chromogenic anti-Xa tests for heparins are similar to the drug-specific anti-Xa tests used to measure fondaparinux, apixaban, or rivaroxaban, with the major difference being the use of drug-specific calibration standards to generate the standard curve for derivation of the patient level. It is important to note that an uncalibrated (or heparin-calibrated) anti-Xa assay cannot be used quantify levels of other factor Xa inhibitor drugs like apixaban or rivaroxaban, as the standard curve used to determine drug level in each anti-Xa assay is generated using dilutions of the specific anticoagulant or calibrator. It is thus imperative that clinical laboratories know what specific anti-Xa drug a patient is on, and that clinicians understand what anti-Xa testing is available at their center. In the absence of drug-specific anti-Xa test availability, a heparin-calibrated anti-Xa assay may be helpful in determining whether an anticoagulant effect is present in a patient on a direct oral anticoagulant in an emergency situation. For example, we previously reported on the excellent positive correlation between heparin-calibrated anti-Xa test results with apixaban- or rivaroxaban-calibrated anti-Xa test results in patients at our institution taking apixaban or rivaroxaban, respectively (apixaban: n = 103; R^2=0.9662; $P < 0.0001$; rivaroxaban: n = 99; $R^2 = 0.9755$; $P < 0.0001$).[19] However, each laboratory needs to validate this approach since reagents can differ between institutions.[20] Perioperative physicians should familiarize themselves with the anti-Xa testing platforms available at their centers, including whether generalizable cutoff values for a *stat* heparin-calibrated anti-Xa assay may be used to exclude significant drug effects from factor Xa inhibitors like apixaban or rivaroxaban. The construction of linear regression equations can be used to predict levels of apixaban or rivaroxaban from heparin-calibrated anti-Xa curves. In particular, derived cutoffs predicting drug concentrations of 50 ng/ml and 30 ng/ml are useful for considering the administration of reversal agents for actively bleeding and for urgent/emergent high-risk surgical procedures, respectively.[21,22]

Similar to anti-Xa assays, there are antiprotease anti-IIa assays that use a chromogenic substrate for specific determination of thrombin inhibition of anticoagulants, including heparin. As previously noted, unfractionated heparin has significant anti-IIa activity in addition to anti-Xa activity, while low-molecular-weight heparin does not. Thus, anti-IIa assays may be useful in the setting of unfractionated heparin monitoring in patients with recent oral anti-Xa inhibitor exposure, which would greatly impact anti-Xa assays.[23] Direct thrombin inhibitors could also be measured using anti-IIa assays, although drug-specific tests based on the dilute TT are much more common in current practice.

Point-of-Care Testing

Point-of-care testing for anticoagulation monitoring is generally used when rapid turnaround times are required for dynamic situations that can occur in the operating room or interventional suite. These tests use whole blood, eliminating the need for centrifugation of samples to generate platelet-poor plasma, which alone generally requires 10 to 20 min. The increased speed and simplicity of collection comes at the cost of introducing other blood elements that can affect coagulation measurements, primarily erythrocytes and platelets. Several different point-of-care devices exist for obtaining PT/INR and PTT results; although, it should be noted that these instruments have greater imprecision and may show significant bias compared to their central laboratory counterparts.[24,25] The British Society for Haematology (London, United Kingdom) recommends that institutions assess point-of-care INR and PTT results for comparability with central laboratory results and develop algorithms for confirmation of supratherapeutic levels.[26] For these reasons, utilization of point-of-care PT/INR and PTT is highly institution dependent and their advantages in the perioperative setting are unclear. However, two coagulation assays that are utilized almost exclusively as point-of-care tests are activated clotting times and viscoelastic tests.

Activated Clotting Time

The activated clotting time first reported by Paul Hattersley in 1966 was a celite-activated whole-blood clotting assay that used the operator's eyes to detect the first sign of clot formation.[27] Modern devices now utilize a wide variety of activators including celite, kaolin, and glass, among other agents. Clot is no longer detected by the naked eye, but *via* mechanical, optical, and electrochemical means.[28] No definitive standard for activated clotting time measurement exists and, given the wide array of activators found in the many available devices, comparison of values between institutions is problematic. Reported correlation coefficients of heparinized samples between different devices generally range between 0.7 and 0.9, with differences up to 70 s as the level of anticoagulation increases.[29–31] It is therefore not surprising that target activated clotting time values for initiating cardiopulmonary bypass (CPB) can vary from fewer than 350 s to more than 500 s among cardiac surgical centers.[32] Nevertheless, since other coagulation tests such as the PTT become unclottable with high levels of systemic heparinization, the activated clotting time is the *de facto* anticoagulation monitor during the conduct of CPB. Anticoagulation guidelines from the Society of Thoracic Surgeons (Chicago, Illinois) and the Society of Cardiovascular Anesthesiologists (East Dundee, Illinois) suggest maintaining an activated clotting time more than 480 s, but acknowledge that "… this minimum threshold value is an approximation and may vary based on the bias of the instrument being used."[33] In cardiac catheterization and electrophysiology laboratories, the activated clotting time is also generally utilized for its rapid results. Interventional cardiology guidelines often quantify the degree of desired anticoagulation by activated clotting time values.[34,35]

Like the PTT, the activated clotting time begins by stimulating the intrinsic pathway to form a clot. Also like the PTT, it can be prolonged by antiphospholipid antibodies and hypofibrinogenemia. Because it is a whole-blood assay, the activated clotting time is also sensitive to platelet count, hemodilution, and temperature. It is well known that activated clotting time values diverge from heparin levels during the conduct of CPB,[36] leading society guidelines to recommend either monitoring actual heparin levels or redosing heparin at fixed intervals during prolonged CPB use.[33] One point-of-care system, the Hepcon Hemostasis Management System Plus (Medtronic, Ireland) can provide heparin levels by utilizing protamine titration in its "heparin assay" cartridge. The measurement resolution of heparin is 0.4 to 0.7 U/ml depending on the cartridge range, so precision is limited. Assuming the device is used correctly, the Hepcon system generally is within ±1 U/ml compared with heparin levels measured by anti-Xa assays.[37] However, in situations requiring very high levels of heparin such as CPB, which are generally 2 to 6 U/ml, this limited precision may still alert clinicians to the need for additional heparin when the activated clotting time becomes uninformative because of the aforementioned factors.[38]

In addition to heparin, activated clotting time has been used to monitor bivalirudin for (in order of increasing degree of anticoagulation) extracorporeal membrane oxygenation (ECMO), percutaneous coronary interventions, and cardiac surgery with CPB.[39–42] Clinicians should be aware that the linearity of the relationship between activated clotting times and bivalirudin concentration begins to flatten out (*i.e.,* test values change little with increasing doses) at concentrations above 12 μg/ml. This is within the target concentration of 10 to 15 μg/ml for CPB,[43] so activated clotting time values greater than 400 s may reflect bivalirudin concentrations that are almost twice as high as expected. The other parenteral DTI, argatroban, has even less of a linear relationship with the activated clotting time.[44] Case reports of argatroban for CPB in cardiac surgery have reported thrombotic complications as well as catastrophic bleeding using activated clotting time targets of 200 to 400 s.[45] Lower levels of argatroban anticoagulation, such as those used with ECMO, are typically monitored *via* PTTs *versus* activated clotting times.[46]

Viscoelastic Tests

The two major platforms for viscoelastic testing are thromboelastography (Thromboelastograph [TEG®]; Haemonetics, USA) and thromboelastometry (ROTEM; Instrumentation Laboratory, USA). More recently the ClotPro device (Enicor; GMbH, Munich, Germany), which has specific direct oral anticoagulant assays available, and the Quantra analyzer (Hemosonics LLC, USA), which utilizes soundwaves to detect clotting, have also become available. All viscoelastic testing devices utilize whole blood to measure the time it takes to form a clot, as well as provide information on clot strength and breakdown. There is no "definitive standard" for viscoelastic testing, however, and activators and assessment of clotting parameters vary widely. The basic principles, reagents, and measuring methodologies of the various devices have been reviewed elsewhere.[47] Viscoelastic testing devices are widely used to diagnose coagulopathy and guide resuscitation with hemostatic blood products,[48] but their roles in anticoagulation monitoring is less established. While all platforms provide some measure of clot initiation, much like the PTT, the sensitivity for detecting the presence of anticoagulant medication is dependent upon the type and concentration of activator used. Results are therefore not portable across different devices.

The kaolin TEG® R (start of test to initial fibrin formation) and K (initial clot formation to 20 mm amplitude) times are sensitive to the presence of heparin, which has led some investigators to use them to titrate unfractionated heparin in ECMO patients.[49,50] The ROTEM INTEM test, which activates the intrinsic pathway using ellagic acid, has shown correlation with obtained PTT and activated

clotting time values, although not with TEG® R times, in heparinized ECMO patients.[51] The value of adding viscoelastic testing to existing anticoagulation assessment is currently unclear, however. A recent meta-analysis of TEG® and ROTEM in ECMO patients concluded that their routine use did not improve bleeding or thrombotic outcomes, although they may improve the detection of surgical bleeding.[52]

One of the problems is that viscoelastic testing platforms may be too sensitive for heparin titration. Tracings for many anticoagulated patients may simply be a "flat line," which may not represent the desired anticoagulation level as measured by more conventional tests such as the activated clotting time or PTT.[53] Viscoelastic testing devices are much better at detecting the presence of small amounts of residual heparin when heparin reversal is desired. Both TEG® and ROTEM offer the addition of heparinase to the standard tests, which has been used to guide administration of additional protamine in cardiac surgery.[54–56] Viscoelastic testing devices have not been utilized to guide VKA dosing, but clinicians should be aware that clotting times of both TEG® and ROTEM can be prolonged in patients with INR greater than 2.0.[57] Dabigatran has a similar effect.[58,59]

Monitoring of newer anticoagulants with viscoelastic testing is still an area of active research. The addition of ecarin and thrombin to standard viscoelastic measurements has been explored as a means of assessing levels of parenteral DTIs,[60,61] but these techniques are not yet used clinically. More recently, commercially produced reagents for the ROTEM and TEG® 6S platforms have been utilized to provide qualitative assessment of direct oral anticoagulant effects.[62,63] Similarly, the ecarin clotting assay and the Russel viper venom test have been used on the ClotPro platform to assess plasma concentrations of dabigatran and factor Xa inhibitors, respectively.[64,65] These may eventually allow perioperative physicians to follow reversal of oral DTIs and factor Xa inhibitors, as doing so with currently available testing options is not recommended.[66]

Monitoring during Anticoagulation Transitions

Perioperative clinicians are most likely to encounter monitoring difficulties in patients being transitioned from an oral factor Xa inhibitor or DTI to heparin. While large trials have shown that "bridging therapy" for patients on warfarin or direct oral anticoagulants is not needed before

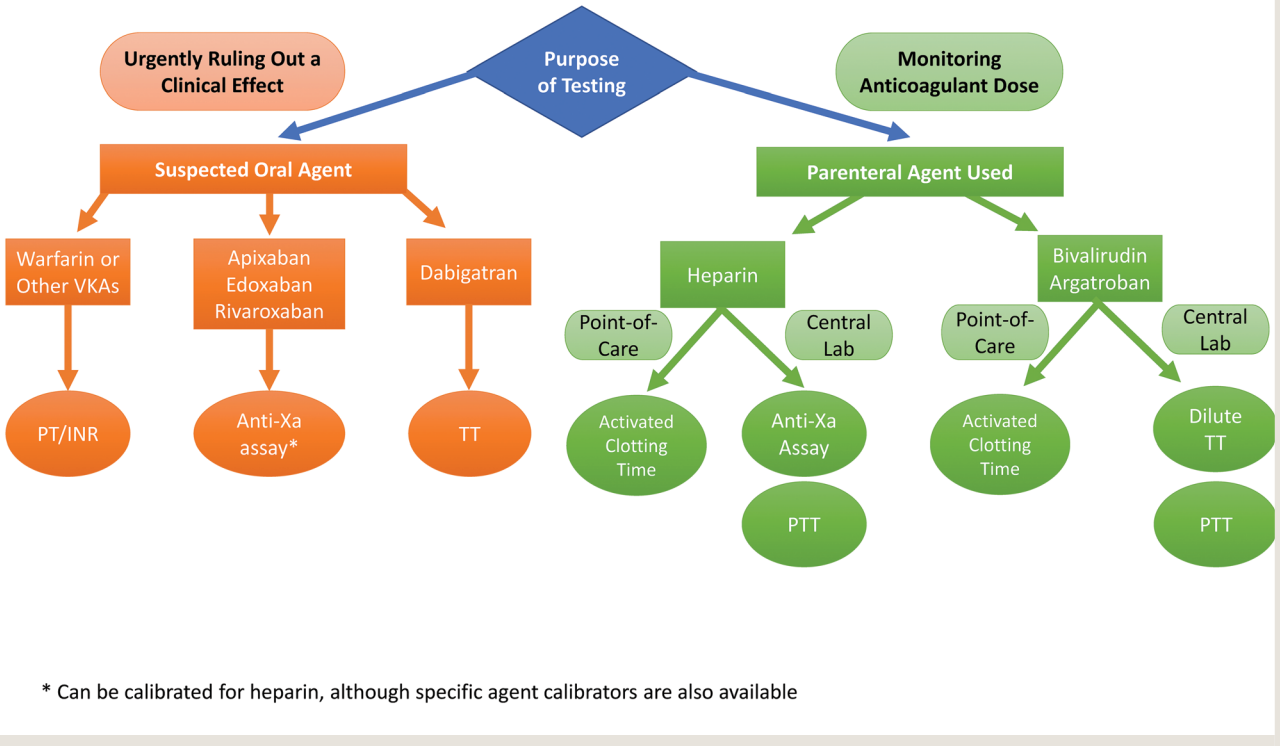

Fig. 3. Basic decision tree for anticoagulation assessment. For perioperative purposes, the need to obtain anticoagulation assessment is either for urgently ruling out a clinical effect of a patient's home medication (almost always oral agents) or for obtaining a measure of drug level for purposes of dose adjustment (almost always parenteral agents). A normal value of tests in the *orange circles* effectively rules out clinical effects of the listed agents. Tests in the *green circles* provide at least a semiquantitative assessment of how much anticoagulant is present. Table 1 should be referenced for potential confounders. Dilute TT, dilute thrombin time; PTT, activated partial thromboplastin time; TT, thrombin time; VKAs, vitamin K antagonists.

elective surgery,[67,68] heparin may still be required either as a primary therapy or prophylaxis for extracorporeal support. The half-life of direct oral anticoagulants ranges from 8 to 14 h and residual effects may be picked up by laboratory testing even at low drug concentrations. For patients on oral factor Xa inhibitors, anti-Xa levels for unfractionated heparin monitoring will be additive, leading to supratherapeutic measurements despite subtherapeutic levels of heparin.[69] In this particular situation, the PTT may offer better guidance. On the other hand, when transitioning from an oral or parenteral DTI, anti-Xa levels are better indicative of heparin levels than the PTT given the DTI interference in PTT measurements.[70] The role of using agents to neutralize direct oral anticoagulants for purposes of laboratory testing is still being explored.[71] Guidelines from the International Council for Standardization in Hematology recommend alternative monitoring tests for the first 24 to 36 h as the patient is being transitioned to unfractionated heparin.[2]

Residual testing effects of oral anticoagulants also needs to be considered for procedural anticoagulation if activated clotting time monitoring is planned. Although baseline values will be higher, administration of heparin in the presence of VKAs will increase the activated clotting time in a relatively linear manner. This is not necessarily true of direct oral anticoagulants, where most studies have been done in the atrial ablation patients with target activate clotting times of 300 to 350 s.[72] While dabigatran behaves similarly to VKAs (*i.e.,* additive), the effects of oral factor Xa inhibitors, particularly edoxaban, tend to have a blunting effect on the activated clotting time, demonstrating less of an increase for any given amount of heparin administered.[73]

Conclusions

Clinicians encounter anticoagulated patients in all phases of the perioperative period. Whether it is for preoperative reversal considerations, intraoperative dosing, or postoperative prophylaxis, monitoring the effects of therapy is a requirement. There are more anticoagulants and more testing platforms available today than ever before. Figure 3 shows a basic decision tree of which tests could be appropriate to order based upon anticoagulant and clinical situation. It could easily be adjusted for institution-specific assays.

Newer assays such as the chromogenic anti-Xa level are slowly replacing traditional lab tests such as the PTT, yet even these newer tests have limitations. Even when stopped for surgery, DTIs and factor Xa inhibitors can influence point-of-care tests such as the activated clotting time, which may have implications for procedural management. Anticoagulants are some of the most dangerous medications prescribed, yet development and widespread availability of tests to monitor their effects in a clinically relevant timeframe have lagged behind. Additional research on the clinical utility of anticoagulation testing using various lab-based and point-of-care platforms is urgently needed.

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Competing Interests

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